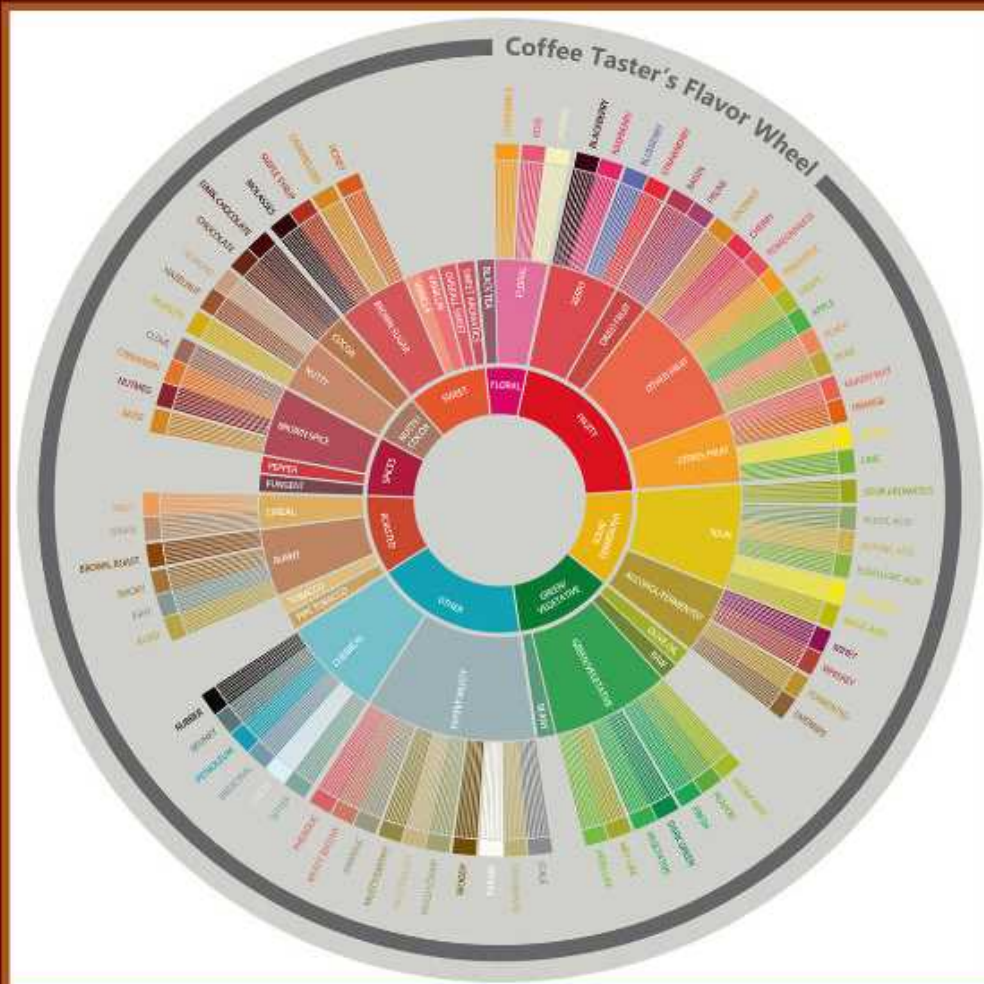




FLAVOR

FROM FOOD TO BEHAVIORS, WELLBEING AND HEALTH

SECOND EDITION

Edited by
ELISABETH GUICHARD
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Flavor

**From Food to Behaviors, Wellbeing and
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Second Edition**

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PUBLISHING**

An imprint of Elsevier

Retention and release of aroma and taste compounds, influence on perception

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1.1 Introduction

During eating, food is subjected to mastication and salivation to form a bolus, which is then swallowed for further digestion. Aroma and taste compounds are released from food bolus during the masticatory and post-swallowing steps. Aroma compounds are transferred from food to saliva, then to the air phase in the oral cavity and transported to the nasal cavity via the respiratory flow in order to reach the olfactory receptors and be perceived. Taste compounds are delivered to the receptors located on the tongue in order to be perceived. This chapter will present an overview of the different aroma and taste compounds, their dynamic release from the food matrix into the saliva and the oronasal cavity, taking into account the in-mouth physiological process, and the influence on flavor perception.

1.2 Aroma and taste compounds

In this part, we will give an overview of the physicochemical and sensory properties of the aroma and taste compounds responsible for perception.

1.2.1 Physicochemical properties of aroma compounds

Aroma compounds are present in very low amount in food (<1%). They are small molecules characterized by low molecular weight (<400 Da) and a high vapor pressure, which allow them to be easily released in the gas phase, in order to be perceived by the olfactory receptors. In food, more than 15,000 volatile compounds have been identified, as reported in the database on volatile compounds in food (<http://www.vcf-online.nl/VcfHome.cfm>). Not all the volatile compounds are odorant. Around 3500 compounds can be perceived by the nose (odor threshold) and described with various odorant notes in the Flavorbase (<http://www.levffingwell.com/flavbase.htm>). Odor

thresholds and odor qualities depend on structural parameters such as chain length, unsaturation degree, double bonds position, functional groups position, molecular characteristics, and stereochemistry of molecules. Odor thresholds vary in a wide range and can be lower than 1 ng/L. It is still difficult to predict odor properties by structural parameters (Tromelin, 2016). For example, 2-methoxy-3,5-dimethylpyrazine (earthy smelling) has an odor threshold in air of 0.001 ng/L, whereas a similar compound, 3-methoxy-2,5-dimethylpyrazine (pea-like smelling) has an odor thresholds of 56 ng/L (Molyneux and Schieberle, 2007).

In a recent meta-analysis of 5642 publications on food aroma from 1980 to 2013 and 949 other documents, a list of the 226 main key food odorants was made based on their odor activity value ($OAV > 1$) measured in a total of 119 publications dealing with 227 food samples (Dunkel et al., 2014). The most frequently occurring key odorants in foods are methional (53.7% of samples, boiled potatoes odor), 2- and 3-methyl butanal (50.7%, malty), butane-2,3-dione (41.9%, buttery), (E,E)-2,4-decadienal (41.4%, fried, fatty), and furaneol (40.5%, caramel), followed by sotolon (seasoning), 1-octene-3-one (mushroom), acetic acid (vinegar), acetaldehyde (fruity, fresh), ethyl 2- and 3-methylbutanoate (fruity), (E)-2-nonenal (cardboard like), vanillin (vanilla like), 2-acetyl-1-pyrroline (roasted, popcorn), 2- and 3-methylbutanoic acid (sweaty), and butanoic acid (sweaty).

Aroma compounds belong to different chemical classes, mainly alcohols, acids and esters, phenolic compounds, carbonyl compounds, sulfur and nitrogen aliphatic compounds, heterocyclic aroma compounds, terpenes, and norisoprenoids.

1.2.1.1 Alcohols

Alcohols are important flavor compounds, which are widely present in foods and mainly in fruits. Unsaturated alcohols have a greater impact on food flavor than saturated alcohols. For example, C6 alcohols, such as *cis*-3-hexenol and *cis*-6-hexenol (leaf alcohol), are formed in plants as a result of enzymatic oxidation of linoleic and linolenic acid by lipoxygenases and hydroperoxide lyases (Jelen and Wasowocz, 2012) and are responsible for freshly cut grass aroma. Terpene alcohols such as linalool, nerol, geraniol, alpha-terpineol present fruity and floral notes, which are characteristic, for example, of Muscat grape aroma and phenyl ethanol, with a typical rose aroma. Alcohols are also precursors for synthesis of aldehydes and esters.

1.2.1.2 Carbonyl compounds

Another important chemical class is the carbonyl compounds, aldehydes and ketones, which are responsible for various typical odorant notes such as the apple like odor of acetaldehyde, almond odor of benzaldehyde, vanilla odor of vanillin, raspberry aroma of 4-hydroxyphenyl-2-butanone, also called raspberry ketone. There are also important aroma compounds in dairy products (Le Quéré and Molimard, 2002), with the butter aroma of diacetyl (2,3-butanedione) and acetoin (3-hydroxy-2-butanone), blue-cheese aroma of 2-nonanone and 2-heptanone.

1.2.1.3 Esters and lactones

Esters and lactones present mainly fruity notes such as, for example, the banana aroma of isoamyl acetate, apple aroma of butyl acetate, peach aroma of gamma-decalactone, and coconut aroma of gamma-nonolactone. Esters with low molecular weight are mainly present in fruits, flowers, and **fermented beverages**; most of them are formed from acids and alcohols. Unsaturated esters have lower thresholds than saturated ones.

1.2.1.4 Hydrocarbons

Among the hydrocarbons, aliphatic hydrocarbons are not or little odorant but terpenes are important aroma compounds in essential oils, i.e., limonene, which is the main compound in orange juice. Sesquiterpene hydrocarbons have lower impact than monoterpenes due to their higher detection thresholds. Other terpene derivatives present low thresholds and specific odor notes such as damascenone (plum) or beta-ionone (violet).

1.2.1.5 Sulfur and nitrogen compounds

Sulfur and nitrogen compounds are present in very low amount and possess very low thresholds. Sulfur compounds contain thiols, thioesters, sulfides, polysulfides, dithiazins, oxathiazines, thiophenes, and thiazoles. They are mainly present in vegetables as, for example, dimethyl sulfide responsible for cabbage aroma. They are also responsible for off-flavor such as the “rotten egg” aroma of hydrogen sulfide. Thiols are present in **fermented foods**, drinks, cheese, and wine. Methanethiol, a product of degradation of methionine, has a cabbage like odor and is abundant in Camembert cheese. Thiols can react with other volatile compounds and form thioesters (Engel, 1999).

Of all the aliphatic nitrogen containing compounds, amines, isothiocyanates, and aminophenols are the most important for aroma. Amines have a strong ammonia like aroma. They are Strecker degradation products and their odor depends on the pH.

Isothiocyanates have both nitrogen and sulfur elements, and they contribute to pungent notes in vegetables (Burdock and Fenaroli, 2010).

1.2.1.6 Heterocyclic compounds

Heterocyclic aroma compounds contain sulfur, nitrogen, or oxygen atoms in a ring, such as thiophenes, pyrrolines, thiazoles, furanones, pyrenes, pyrazines, or pyridines. They are formed from simple precursors at high temperature, mostly by Maillard reaction. Heterocycles containing hydrogen are the main compounds of caramel aroma (Paravisini et al., 2015). Alkylpyrazines detected in coffee, cocoa, peanuts, chips have roasted, nutlike aromas (Baltes and Boehmann, 1987).

1.2.2 Physicochemical properties of taste compounds

Taste compounds belong to different chemical classes such as organic acids, carbohydrates, mineral salts, amino acids, peptides, proteins, **nucleotides**, and some phenolic

or heteroatomic compounds. They present great differences in detection thresholds. They are detected by the taste buds, located mainly on the surface of the tongue within taste papillae and are responsible for the five basic tastes: sweet, salty, sour, bitter, and umami.

1.2.2.1 Mineral salts

Sodium chloride is mainly responsible for salty taste in food, but other salts such as potassium or calcium chloride are perceived salty to a lower extent. However, they also present bitter notes, as was observed for calcium and magnesium salts in goat cheese (Engel et al., 2000).

1.2.2.2 Organic acids

Acid perception is due to the presence of hydronium ions from organic acids. Citric and malic acids are mainly responsible for acid taste in fruits and vegetables, tartaric acid in grapes, acetic acid in vinegar, and lactic acid in dairy products. Some alpha and beta acids are also responsible for bitter notes (Chen and Lin, 2004).

1.2.2.3 Amino acids

Amino acids are involved in different taste perceptions. Sweet taste has been associated with glycine in crab and with methionine in sea urchin (Salles et al., 2012). L-amino acids (L-leucine, L-isoleucine, L-valine, L-arginine, L-methionine, L-phenylalanine, L-tyrosine, L-tryptophan, L-histidine) present a bitter taste, but more polar ones (L-glycine, L-alanine, L-serine, L-threonine, L-lysine, L-proline) present a sweet taste as D-amino acids (Kato et al., 1989). Amino acids with a lateral acid function such as L-glutamic and L-aspartic acids are responsible for acid taste. Their sodium salts are responsible for umami taste. Sodium glutamate present in some foods at a concentration higher than its detection threshold (300 mg/L) mainly contributes to umami taste.

Biogen amines obtained by decarboxylation of amino acids may also present a bitter taste.

1.2.2.4 Nucleotides

Two types of ribonucleotides present in foods are responsible for umami taste, inosine monophosphate in animal products and guanosine monophosphate in vegetal products (Ninomiya, 2002). They are also used as food additives and are known to act in synergy with sodium glutamate.

1.2.2.5 Mono- and disaccharides

Sweetness perception is mainly due to the presence of mono- and disaccharides and mainly sucrose (composed of glucose and fructose). The other disaccharides are perceived less sweet than sucrose. Lactose (derived from galactose and glucose) is the most abundant in milk but with a sweetening power four times lower than sucrose. Maltose (two units of glucose) is produced in mouth from starch by the action of

amylase during mastication and trehalose (two units of glucose joined by a one to one alpha bond) produced by the action of different microorganisms present in saliva. They are two times less sweet than sucrose (Laffitte et al., 2016). The monosaccharides glucose and fructose naturally occurring in fruits are also perceived less sweet than sucrose.

1.2.2.6 Terpenoids

Some terpenoids are perceived sweet. Rebaudioside and stevioside, extracted from the leaves of *Stevia rebaudiana*, are perceived 300 to 450 times sweeter than sucrose (Lindley, 2012). They can be used as food additive but their safety is still under debate. Mogrosides constitute a family of terpenes extracted from a Chinese plant and present a strong licorice after-taste with a cooling taste which limits their potential use as sweetener.

1.2.2.7 Peptides

The taste of peptides depends on their structure and their physicochemical properties. Bitter peptides contain a great number of bitter amino acids. Their detection thresholds vary as a function of their chain length and the order of amino acids. As an example Pro-Gly-Arg and Arg-Pro-Gly have detection thresholds in water of, respectively, 25 mmol/L and 0.8 mmol/L (Laffitte et al., 2016). Cyclic dipeptides named dicyclopiperazines are perceived more bitter than their linear homologs. In cheese, bitter peptides are formed from casein degradation. Other tastes are covered by small peptides. As examples, acid peptides contain glutamic or aspartic acids, and arginyl dipeptides were found as salt taste enhancing molecules.

1.2.2.8 Proteins

In general, molecules with a high molecular weight have no taste. However, a limited number of proteins elicit a strong sweet taste among which thaumatin, constituent of the berries of an African plant (Masuda et al., 2011), has received approval to be used as sweetener in foodstuff, due to its high sweetness potency (1600 times higher than sucrose). Another small (6.4 kDa) sweet protein, brazzein, is approximately 2000 times sweeter than sucrose (Poirier et al., 2012), with a taste more similar to sucrose than thaumatin.

1.2.2.9 Other compounds

Artificial sweet-testing molecules have been generated through chemical synthesis as sucrose replacer to answer to health problems associated to diabetes. They are often used in mixture. Saccharin also known as o-benzoic sulfimide was the first artificial sweetener discovered. It can be used as sweetener at low concentration but it elicits a strong bitter taste at high concentration (Cohen, 1986). Cyclamate has a sweet taste similar to sucrose with a weak metallic and salty aftertaste (Schiffman and Gatlin, 1993). Acesulfame K is an intense sweetener often used in association to mask the

unpleasant aftertaste of other sweeteners (Schiffman and Gatlin, 1993). Aspartame is a synthetic peptide (Asp-Phe-O-Methyl) known to synergize with other sweeteners and thus mainly used in mixture with acesulfame K and saccharin. Sucralose is approximately 600 times sweeter than sucrose and its use is approved in all major countries.

1.3 Influence of food ingredients and food structure on the release of flavor compounds during the in-mouth process in relation with perception

Flavor perception is a dynamic process, which begins as food is put in the mouth, then mixed with saliva, broken with the teeth in the case of firm foods, forming a bolus easy to swallow. After swallowing, some flavor compounds remain on the oral mucosa, leading to aftertaste. In order to understand the relationships between flavor release and flavor perception, there is a need to follow the release at these different steps, in a dynamic process.

1.3.1 Retention and release of aroma compounds

In foods, aroma compounds are solubilized in the different phases according to their hydrophobic properties and are more or less retained by the macromolecules, such as proteins and polysides. Their release in the nasal cavity depends both on the composition of the food matrix and on its structural organization.

A food matrix is composed of macromolecules able to modify the release of aroma compounds in the nasal cavity due to specific interaction, described first in simple systems, then in real foods.

1.3.1.1 Effect of food ingredients on aroma retention and release in simple model systems

Most of the literature on the interactions between aroma compounds and food matrix relates to simple systems composed of lipids, proteins, and carbohydrates, alone or in mixture but other constituents such as polyphenols, melanoidins, artificial sweeteners, alcohol, and salt also affect aroma release from water solution.

1.3.1.1.1 Lipids

In systems containing lipids, aroma compounds are partitioned between the lipid and the aqueous phases, following the physical laws of partition. The release of aroma compounds from model systems containing lipids depends on the nature of both the aroma compound and the lipid. Most of the aroma compounds are more soluble in oil than in water. These compounds are considered as hydrophobic ($\log P > 1$) and are thus less released in the vapor phase from oil than from water (lower air/oil than air/water partition coefficient). The release of the most hydrophobic aroma compounds also depends on the level and nature of the lipid. As an example, ethyl hexanoate ($\log$

$P = 2.83$) is more soluble in sunflower oil than in olive oil (Roudnitzky et al., 2003). This was explained by the higher amount of unsaturated fatty acids in sunflower oil (C18:2) which leads to a higher solubility of aroma compounds (Guichard, 2002). Aroma compounds are also more soluble in short chain than in long chain saturated triglycerides (Maier, 1975). As aroma compounds are only soluble in liquid fat, a high amount of solid fat reduced their solubility and thus increased their release in the vapor phase (Roudnitzky et al., 2003).

1.3.1.1.2 Proteins

Food proteins are known to bind aroma compounds (Tromelin et al., 2006) by different mechanisms which depend both on protein structure and nature of aroma compound (Heng et al., 2004; Semenova et al., 2002). Most of the studies related to aroma-protein interactions have been done using milk proteins among which β -lactoglobulin has been the subject of many studies (Hansen, 1997; Lubbers et al., 1998; O'Neill, 1996) and only few studies are related to caseins (Voilley et al., 1991) even if they are among the most abundant milk proteins. β -Lactoglobulin is able to bind aroma compounds by hydrophobic interactions. Within the same chemical class of aroma compounds, the strength of the interaction increased with the chain length (Jouenne and Crouzet, 2000; O'Neill and Kinsella, 1987; Sostmann et al., 1997). The pH, temperature, and ionic strength affected the strength of the binding by modifying the structure of the protein (Jouenne and Crouzet, 2000; Tavel et al., 2010; Tromelin et al., 2006). These interactions reduced the release of aroma compounds in the air phase and thus aroma perception (Andriot et al., 2000). The interactions between milk proteins and aroma compounds mainly involved hydrogen bonding or hydrophobic effect (Tromelin et al., 2006). However, aldehydes and sulfur compounds interact with proteins by irreversible binding as was demonstrated between trans-2-hexenal and whey proteins with the formation of fluorescent compounds (Meynier et al., 2004).

Proteins of leguminous plants are one of the most promising materials for formulating new forms of food products. These proteins are isolated from soy, peas, and beans and used as functional additives. Nonspecific van der Waals binding was attributed for hydrocarbons whereas hydrogen binding and dipole forces have been suggested for esters, ketones, aldehydes, and alcohols (Zhou and Cadwallader, 2006), covalent binding was demonstrated between pea protein isolates and octanal or dibutyle disulfide (Wang and Arntfield, 2016). The role of the protein structure in binding and release of aroma was investigated in the case of hexyl acetate and revealed that the native leguminous molecules possess the higher binding affinity for this compound (Semenova et al., 2002).

1.3.1.1.3 Carbohydrates

Carbohydrate compounds can be classified into three categories according to their molecular weight: simple sugars such as glucose and sucrose (mono- and disaccharides), oligosaccharides (2–10 monosaccharides) such as oligofructose and polysaccharides (>10 monosaccharides) such as starch (Delarue and Giampaoli, 2006). Their addition in foods influenced both taste, especially sweetness, and texture perception. Their

impact on aroma release was quite difficult to predict, since they are able to induce both retention and release effects, depending on the intrinsic properties of the food matrix such as the type of carbohydrates, their concentration (Nawar, 1971), and also on the properties of aroma compounds such as steric hindrance, polarity, and relative volatility, as already reviewed (Goubet et al., 1998). Among the carbohydrates, starch was able to interact with aroma compounds, mainly by the formation of inclusion complexes with amylose (Biais et al., 2006), which also modified the rheological properties of starch (Heinemann et al., 2005). The addition of pectin induced a small retention of aroma compounds, mainly due to the formation of a macromolecular network (Rega et al., 2002), which limited the diffusion of small molecules. In the case of carrageenan, a small retention was observed for esters and a salting out effect for alcohols (Bylaite et al., 2004).

1.3.1.1.4 Other effects

Other ingredients from the food matrix influenced aroma release. An increased amount of salt induced an increase in the air/water partitioning of most of the aroma compounds, due to a salting out effect, explained by a reduction of the available solvent in the liquid phase. This effect was more marked for hydrophobic compounds, less soluble in water (Lauverjat et al., 2009). Addition of ethanol decreased the partition coefficient of various classes of volatile compounds by increasing their solubility (Voilley et al., 1991). Other nonvolatile compounds such as polyphenols, melanoidins, artificial sweeteners also impacted aroma release and perception.

1.3.1.2 *Effect of food ingredients on aroma retention and release in real foods*

Foods cannot only be represented by simple systems containing one macromolecule. The interactions between aroma compounds and macromolecules have to take account of the multiphasic systems comprising water, lipids, and proteins or/and carbohydrates, in the presence of other ingredients.

Food systems containing lipids can be considered as oil-in-water or water-in-oil emulsions. The volatility of aroma compounds in emulsions depends on the amount of fat but also on the type of fat (Relkin et al., 2004). An increase in fat content decreased the release of the more hydrophobic compounds; this effect was higher than that of proteins or polysides (Kopjar et al., 2010; Seuvre et al., 2000). Moreover, the effect of protein varied according to the amount of lipids in ice cream (Ayed et al., 2018); an increase in protein content induced a decrease of aroma release but this effect was significant only at a low fat level. An addition of monoglycerides in emulsions induced a decrease in air/emulsion partition coefficient of the aroma compounds (Mao et al., 2014). The presence of proteins (beta-lactoglobulin or sodium caseinate) as emulsifiers at the oil/water interface increased the resistance to transfer of hydrophobic aroma compounds from oil to water and thus induced a decrease in their release in the air phase (Harvey et al., 1995; Rogacheva et al., 1999). An addition of polyphenols in olive oil emulsions stabilized by beta-lactoglobulin modified the structure of the interface, improving the dispersion degree (Genovese et al., 2015a) and increasing

the release of the more volatile compounds (Genovese et al., 2015b). This was explained by interaction between polyphenols and whey proteins, which reduced the binding between aroma and proteins by a competition effect. These results are of great interest in the formulation of healthier foods with addition of polyphenols and providing a good aroma perception.

The addition of salt (NaCl) modified the structure of the food matrix. As an example, beta-lactoglobulin was mainly present in its dimeric form in the presence of NaCl because of a modification of electrostatic forces (Sakurai et al., 2001), leading to an increase in the binding of 2-octanone (Jouenne and Crouzet, 1997). A higher NaCl content increased the strength of iota-carrageenan gels and the self-diffusion of ethyl butanoate (Gostan et al., 2004), which was explained by the greater size of the open space located between the gel chains, resulting in fewer obstacles to the free diffusion of solutes. In model cheeses, the addition of salt modified the texture by decreasing water activity, increasing firmness, and thereby increasing the release of aroma compounds, this effect being significant at a low level of fat (20%) and not at a higher fat level (40%) (Saint-Eve et al., 2009).

Hydroalcoholic systems, such as wine, have been extensively studied. They are complex matrices, in which ethanol, polyphenols, and polysaccharides are able to interact individually with aroma compounds. When present in mixtures, tannins generally enhanced the release of aroma compounds while fructose induced a retention effect, these effects being modulated by ethanol (Villamor et al., 2013). The effect of increasing levels of polysaccharides in a model wine containing tannins differed according to the type of polysaccharide. At low concentration, arabinogalactan induced an increase in aroma release whatever the aroma compound (salting out effect), whereas at concentration higher than 1 g/L a retention was observed for the more hydrophobic aroma compounds, suggesting intermolecular binding which was no more observed at a concentration of 5 g/L, due to saturation of the binding sites (Mitropoulou et al., 2011).

1.3.1.3 Effect of food structure and texture

The effect of matrix structure and texture on the release properties of aroma compounds has been reviewed in model gels (Lubbers, 2006) and in dairy products (Gierczynski et al., 2011). In multiphase systems, the composition and nature of proteins and lipids induced different microstructures, which exerted different effects on the retention and release properties of aroma compounds. It was thus difficult to dissociate the effect of composition from the effect of texture. Different studies have tried to demonstrate the effect of texture and/or microstructure at the same food composition. By modifying the energy of emulsification, emulsions were realized with different droplet sizes (Charles et al., 2000). With an increase in emulsion droplet size, an increase in the release of hydrophilic compounds and a decrease of hydrophobic compounds were observed. This was explained by differences in aroma compounds mass transfer in relation to the modification of the surface area and thus the exchanges between the oil and water phase. In yogurts realized with the same protein concentration, a mechanical treatment was applied to decrease the viscosity (Saint-Eve et al., 2006).

It was observed that this induced decrease in viscosity resulted in an increase in aroma release and thus in the intensity of aroma perception. Moreover, in the same study, the nature of protein-induced differences in microstructure affecting aroma release parameters, caseinate enriched yogurts had a higher viscosity than whey-protein enriched yogurts, which decreased the release of aroma compounds in the air phase. In model cheeses, a modification of the protein structure by acidification with chymosin was shown to induce an increase in viscosity and thus a greater and faster release of all aroma compounds (Gierczynski et al., 2007). Similar observation was made with real cheeses varying in firmness (Repoux et al., 2012). The release rate of ethyl propanoate and nonan-2-one during the in-mouth breakdown increased with the firmness of the cheeses, due to a greater amount of particles formed at the beginning of the chewing process in the case of firm cheeses, which led to an increase in the exchange area. After swallowing, the release of the most hydrophobic compound, nonan-2-one decreased more slowly than that of ethyl propanoate due to its greater solubility in the lipid film remaining in the mouth, leading to a higher in-mouth remanence and thus a longer sensory persistence (Guichard et al., 2017).

NaCl also modified the structure of the food matrix; for example, a higher NaCl content increased the strength of iota-carrageenan gels and the self-diffusion of ethyl butanoate (Gostan et al., 2004), which was explained by the greater size of the open space located between the gel chains, resulting in fewer obstacles to the free diffusion of solutes.

Hydrocolloid mixtures such as the one used for confectionery gels contain typically a polysaccharide-protein mix such as pectin, starch, or gelatin (Burey et al., 2009). Phase separation of these mixtures leads to a continuous phase rich in one hydrocolloid which embeds the other one.

While aroma release from one specific hydrocolloid matrix is rather well understood, there is still limited understanding of aroma distribution and release from more complex mix of hydrocolloid matrices (Savary et al., 2007; Taylor et al., 2001).

Taylor et al. (2001) have investigated the correlation between aroma release and phase separated gels *in vivo*, and no significant difference in time to maximum intensity or maximum intensity of release was observed between the gels with different microstructures. More recently, Su et al. (2021) observed that gelatine-starch biphasic gel with diverse microstructures and textures has no significant effect on aroma release *in vivo*. Nevertheless, they observed a significant impact on aroma distribution and release when sucrose was added to the mixture. The microstructure was affected, and it significantly affected the behavior of the more hydrophobic compounds.

Another microstructure modification was performed by Chiu et al. (2015) who added gas bubble to a soft gel. These authors showed that increased aeration resulted in an increase of total aroma release of 1-octen-3-ol. Air inclusions lead to bigger surface area, consequently accelerating mass transfer of volatiles at the food-saliva interface. Su et al. (2021) showed that this phenomenon is different for different groups of aroma compounds. Air inclusion affects more the balance of some aldehydes in the final product. Nevertheless, this air inclusion seems to be an efficient strategy to compensate the reduction in aroma in such complex mixture without compromising on perceived flavor.

Volatile release can be related to gel strength; Frank et al. (2015) showed a flavor intensity increase in an agar gel while its strength attributes decreased. Therefore, a lower oral processing was required in a soft gel releasing more volatiles and increasing perceived flavor. Malone and Appelqvist (2003) showed that gelled particles based on starch break down when exposed to amylase contained in saliva, and this accelerates the release rate of volatile compounds, combined with fracture properties.

1.3.2 Retention and release of taste compounds

The mobility properties of small molecules govern their release in the mouth during the in-mouth process when consuming a food, whether within the same phase or during a transition between phases. In the case of sodium, the main factors affecting sodium migration during the food oral processing are the concentration gradient of sodium and the resistance to sodium migration. The resistance to sodium diffusion is governed by the tortuosity and sieving effects of the food matrix, whereas the resistance to the convective transport of sodium is reflected by the velocity of the serum flow during the food matrix compression (Kuo and Lee, 2014a,b). These two phenomena, diffusion and convection, are exacerbated with increased surface area, as a result of the matrix fragmentation during the mastication.

The release of salt from lipoprotein model matrices varying in composition into artificial saliva was studied by measuring apparent diffusion coefficients of sodium chloride (Floury et al., 2009, 2010). The authors reported that the variation of the diffusion coefficient according to the cheese matrix composition was linked to their structural and textural properties. Diffusion coefficients decreased strongly when the dry matter content decreased. This was explained by the lower protein concentration in the matrix facilitating the diffusion of the solutes. The authors also observed that the diffusion coefficient increased with the pH at renneting and with the initial salt concentration probably due to changes in the structure and microstructure of the matrix.

The influence of microstructure on sodium release was confirmed by a study on model solid lipoprotein colloids varying in composition and structure (Kuo and Lee, 2017). The authors showed that sodium release can be controlled via the convective transfer or diffusive transfer mechanisms by controlling the porosity and particle size of fat, respectively.

1.3.2.1 Effect of food structure and texture

In semisolid and solid products, flavor compounds can be entrapped either in the lipophilic or the hydrophilic phase. Compounds can be trapped in a hard hydrophilic phase (gel) and that prevents their solubility to saliva. An increase in their release can be observed when the matrix is softening, melting, or dissolving which happens during chewing (de Roos, 2003).

The impact of air inclusion in gels on saltiness and sweetness was demonstrated by Goh et al. (2010). These authors showed that with high gel aeration the salty and sweet perception was maintained while tastant concentrations were decreased. Likewise, Chiu et al. (2015) observed similar properties on soft gel in saltiness perception. Air

inclusions create a greater surface area, consequently increasing the mass transfer of tastant to saliva which results in higher perception.

1.3.3 Dynamic release and dynamic perception

1.3.3.1 Dynamic aroma release and perception

In order to follow the release of aroma compounds in the nasal cavity as close as possible to the olfactory receptors, different technologies have been developed using atmospheric pressure chemical ionization mass spectrometry (Taylor et al., 2000) or proton transfer reaction mass spectrometry (Lindinger et al., 1998). More recently the coupling with a time-of-flight analyser (PTR-ToF-MS) guarantees high mass resolution up to the third decimal, allowing to assign a formula to most mass peaks (Romano et al., 2014).

Only few papers reported simultaneously dynamic release and dynamic perception.

The relationship between perceived aroma by sensory scaling and time intensity was studied in gelatin-sucrose model gels (Baek et al., 1999). By increasing gelatin concentration, sensory flavor perception decreased with both methods; however, no significant differences were observed in the maximum in-nose aroma concentration, but only a decrease in the rate of aroma release, suggesting that the rate of release correlate better with sensory perception than the total amount of aroma release.

The effect of candy texture and eating technique (melting or chewing) was studied on the dynamics of in vivo aroma release followed by PTR-MS and temporal dominance of sensations (TDS) using a trained panel (Délérès et al., 2011). Relationships between the dynamics of release and perception have been established between dominance duration and time to reach maximal intensity. Similar approaches were conducted on fruit yogurt (Mesurolle et al., 2013) and Espresso coffee (Barron et al., 2012), highlighting also the difficulty to find clear relationships between the two analyses. In fact, data from PTR-MS measure the amount of aroma released whereas TDS measures the dominant sensation. Moreover, each sensory attribute can be issued from several aroma compounds and each ion detected by PTR-MS may come from different molecules.

In biscuits, no significant correlation was found between anethole in vivo release and perception, due to a high effect of textural properties on flavor perception and of the existence of aroma-sweetness interactions (Burse et al., 2009).

1.3.3.2 Dynamic release of taste compounds and perception

Fewer studies were carried out on taste compounds release compared to the numerous studies reporting kinetics of volatile compound release. During the in-mouth process, tastants are progressively dissolved in saliva, while food is broken down and transformed into a bolus under the combined action of saliva and chewing (Salles et al., 2011). These phenomena control the delivery of tastants to the receptors located on the tongue, which is one of the key factors determining the perceived taste of foods. The sampling of saliva at different times of mastication using adsorbents or by direct

spitting out of saliva in tubes followed by HPLC analysis is the more common approach though mini conductimetry sensor located in the mouth has been used for a continuous and real-time measure of the change in conductivity (Davidson et al., 1998; Emorine et al., 2012).

As for volatile compounds, the patterns of temporal taste compounds release and temporal taste perception depend on both the composition of the food matrix (food ingredients) and the oral physiology characteristics of the consumers (Lawrence et al., 2012a,b; Salles et al., 2011).

The tastants are retained in food through physicochemical interactions and are progressively released in the mouth under the combined action of mastication and saliva. Important differences were observed according to the nature of the macromolecules constituting the food matrix. The nature of the nonvolatile compound seems less critical since, for a given subject, the shape of the release curves were found similar for most of the 12 compounds tested, the observed differences being due only to differences in concentration (Pionnier et al., 2004). However, as for flavor, the direct relationships between taste compound release kinetics and temporal taste perception are complex. In model cheeses the increase of fat content was related to a global decrease of sodium release and an increase of saltiness perception (Phan et al., 2008). However, these effects varied according to the salt concentration (Lawrence et al., 2012a). At low salt concentration, no effect of fat was observed for sodium release while saltiness perception was more intense when the fat level was low. At medium salt concentration, no effect was observed. Conversely, at high salt concentration the saltiness perception was less intense when the fat content was lower while sodium release was the lowest at high fat content.

The water content of food also influenced the released salt concentration and saltiness perception. As an example, in cheese products, a high amount of water increased sodium release due to its solvating capacity whereas a low water content associated to a high salt concentration increased saltiness perception (Jack et al., 1995; Pflaum et al., 2013). This phenomenon seems to be mainly observed at the beginning of chewing (Phan et al., 2008). Moreover, in model cheeses, saltiness perception was rather well correlated with salt released in saliva and sodium mobility (Boisard et al., 2014). Such effects of water were also reported for breads (Pflaum et al., 2013). The structure and texture of breads were also reported as important factors for salt release and saltiness perception (Le Bleis et al., 2013; Panouillé et al., 2014; Pflaum et al., 2013).

The most recent works on the release in the mouth of taste compounds and their perception are focused on salt because of the health recommendations considering the structural and microstructure aspects of the food matrix (Kuo and Lee, 2017). As example, the structure of solid lipoprotein colloid (SLC) gels obtained by heat-induced gelation of emulsions was studied by ultrasmall-angle X-ray scattering in order to better understand mechanisms involved in sodium release (Kuo et al., 2016). The gyration radius of the fat globule of SLC gels with 3.5% NaCl was found negatively correlated with the C_{max} (the maximum concentration of released sodium and the AUC area under the curve of sodium release vs. time plot). An explanation is that, at the same total fat content, smaller fat globules implied a gel network with

a higher number of dispersed fat particles. As fat interfered with the protein network, the higher number of dispersed fat particles could lead to a greater extent of breakdown resulting in more total surface area for the broken gels thus favoring the enhanced release of sodium from the gel when compressed. This phenomenon was not observed at a lower NaCl concentration (1.5%), because of lower forces in interprotein interaction. Thus, stronger interaction made the initiation of break upon compression more likely to occur at the protein-fat interface which dominated the breakdown properties of the SLC gels with 3.5% NaCl. With the same kind of solid lipoprotein colloid foods, the saltiness perception was correlated positively with fracturable but not crumbly attributes. It was thus postulated that for the fat-containing SLCs, moderate breakdown property would favor sodium release. When the SLC breaks down relatively fast, the crumbled gel particles require less chewing work, and thus, may lead to lower sodium release and saltiness perception (Kuo and Lee, 2017). It has been reported that overall sodium mobility decreased with increasing protein and fat levels in lipoprotein matrices, influencing saltiness perception (Boisard et al., 2014; Okada and Lee, 2017). As an example, increasing protein or fat content contributed to a more ordered environment, contributing to a higher bound sodium fraction (Okada and Lee, 2017).

1.4 Influence of oral physiology on in vivo release and perception

When eating foods, not only the food composition and structure influence in-mouth flavor release, but the food matrix properties and the overall oral processing are interactive. This interaction leads to different flavor release profiles reflecting interindividual variabilities. Various oral parameters such as mastication, salivary flow rate and composition, swallowing, oral volumes, mouth coating, mucous adhesion, and breath air flow for volatile compounds may influence the availability of flavor compounds for receptors differently according to individuals and thus influence flavor perception.

1.4.1 Influence of oral physiology on in vivo aroma compound release and perception

Real-time in vivo methods have been used extensively to study the impact of the composition and/or texture of a food product on aroma release during chewing (Boland et al., 2006; Gierczynski et al., 2007; Mestres et al., 2005, 2006). A general tendency is that higher hardness induced a greater chewing activity associated with higher salivation, leading to a greater exchange area and a higher amount of aroma released (Gierczynski et al., 2007). An addition of salt in model cheeses induced a greater salivation, an increase in the number of swallowing events and chewing duration which increased the total amount of release of hydrophobic aroma compounds in the nasal cavity (Boisard et al., 2013).

However different behaviors were observed between subjects explained by different chewing strategies (Yven et al., 2012). The relationships between oral physiology (respiration, salivation, mastication) and aroma release have been studied for subjects consuming different foods (Gierczynski et al., 2008; Pionnier et al., 2004; Repoux et al., 2012). Subjects with a high amount of aroma release had also high values of respiratory rate, number of chews, and muscle activity (Pionnier et al., 2004). A greater respiratory rate contributed to bringing more volatiles to the upper airways, and consequently more volatiles were present in the expired air of the subjects. A high muscle activity induced a better degradation of the bolus. Consequently, the food surface in contact with the vapor phase increased and thus the transfer of aroma compounds from the matrix to the vapor phase was higher. A statistical multi-block PLS approach was successfully used to better understand the relative impacts of different physiological parameters on aroma release (Feron et al., 2014). The main impact of masticatory behavior was observed but other significant effects could be highlighted. Bolus rheology mainly influenced aroma release from firmer cheeses. The persistence of aroma release in the breath was mainly explained by higher bolus spreadability and bolus moistening, which resulted in a higher amount of product remaining in the mouth. The composition of stimulated saliva influenced the amount of aroma release, with a lower release for subjects with a higher amount of salivary proteins.

1.4.2 Influence of oral physiology on in vivo taste compound release and perception

The composition of the food matrix indirectly influences taste compound release by changes in their textural properties inducing changes in the physiological behavior of individuals during eating. As already mentioned, hard food products generally requested a higher chewing time. During the complex food oral processing, the physicochemical properties of the food are modified and the perception of flavor and texture is affected. Fragmentation increased the surface exposed to saliva and thus facilitated the dissolution of taste compounds in saliva and influenced taste perception while the bolus is progressively built from food particles and saliva. The mastication pattern and saliva characteristics may vary considerably between individuals. These physiological variations are an important source of inter-individual variability for temporal taste release and perception. As an example, in model cheeses, an important release rate of sodium was correlated with a high salivary flow rate, and important bite force and chewing work while salivary flow rate and chewing efficiency influenced the speed of perception, not the saltiness intensity (Phan et al., 2008). More generally, it has been reported that sodium release was rather related to mechanical chewing activity while saltiness temporal perception was rather related to the salivary flow rate (Lawrence et al., 2012b).

Even if mastication and salivary properties are the major two oral parameters related to taste compound release in mouth, other physiological parameters were shown to influence taste release and perception. Some common food macromolecules such as

polysaccharides have mucoadhesive properties which may influence the delivery of active components (Cook et al., 2017), and thus contribute to modulate the organoleptic properties of food by retaining taste or aroma molecules. As an example, some polysaccharides, common in food composition, were found to influence salt release in the oral cavity during eating. The mucoadhesive properties of carboxymethyl cellulose can modify retention, release, and perception of sodium over time. This explains the retention of sodium ions in the mouth being prolonged due to the mucoadhesive nature of the polysaccharide (Cook et al., 2018b). Therefore, the perception of the retained sodium was diminished due to the anion effect. It was reported also that, more generally, the perception of tastants and aroma over time can change depending on the mucoadhesive polysaccharide used (Cook et al., 2018a).

1.5 Simulation of oral processing using different devices

Sensory perception of flavor release during eating is highly dependent upon mouth parameters. Major limitations have been reported during *in vivo* flavor release studies, such as marked intra- and interindividual variability. To overcome these limitations, some artificial devices have been developed to mimic the human mastication of food samples. Although there are many devices dedicated to the simulation of chewing, in this part we will focus on those allowing the simulation of flavor release in oral conditions.

One of the simplest artificial mouths was developed by van Ruth and Roozen (2000) and consisted of a jacketed reactor equipped with a plunger that performs simultaneous vertical and rotational movements to simulate compression and shearing simulating chewing movements. This artificial mouth was tested on several model and real foods to mimic the release of key aroma compounds, showing a good similarity with *in vivo* data. The reactor developed by Rabe et al. (2002) allowed to control saliva and air flows and was successfully used for liquid model systems and beverages (Rabe et al., 2004). The Retronasal Aroma Simulator (Roberts and Acree, 1995) with a relatively high volume (1L) allowed for a precise control of shear rate and was successively used to follow aroma release from different products (orange juice, chocolate, ice cream, and cookies) in comparison with *in vivo* release (Deibler et al., 2001).

However, the models described above poorly represented a limited number of oral functions which are far from an actual oral environment.

The artificial mouth developed by Salles et al. (2007) reproduced most of the functions of the human mouth. The active cell comprises several mobile parts that can accurately reproduce shear and compression strengths and tongue functions in real-time, according to data previously collected *in vivo*. The mechanical functionalities of the system were validated using peanuts, with a fair degree of consistency with the human data. Flavor release can be monitored online using either APCI-MS or chemical sensors, or offline using HPLC for nonvolatile compounds (Mielle et al., 2010). This device thus has the advantage of allowing *in vitro* studies under oral conditions on flavor release and bolus formation from solid matrices. Flavored lipoprotein matrices varying

in fat content were chewed using this device where each oral parameter was controlled and decoupled. Each controlled oral parameter had significantly different influences on the release of aroma compounds according to their physicochemical characteristics. In particular, it was reported that biting and shearing forces influenced differently the release of aroma compounds according to their characteristics. The salivary flow rate primarily influenced the more hydrophobic compounds. Moreover, significant interactions were also observed between shear angle, salivary flow rate, and fat content, according to the physicochemical properties of the volatile compounds (Tarrega et al., 2019).

The relationships between the properties of extruded pea-based snack boluses and the multiscale structure of said foods were in vitro determined using the same device, allowing control of the flow rate of artificial salivary fluid and chewing time (Kristiawan et al., 2021). The structure of the extruded pea snacks was characterized by their density and protein solubility in dithioerythritol, which reflected the amount of protein aggregates cross-linked by disulfide bonds. Thus, a phenomenological model of oral breakdown of extruded pea snacks was established by linking the evolution of salivary absorption capacity and that of consistency of bolus in function of the snack density and the quantity of disulfide bonds protein aggregates created during the extrusion process. The use of the artificial chewer allowed control of the main mechanisms pertaining to the formation of extruded pea flour boluses: fragmentation and saliva absorption. Between these two mechanisms, saliva absorption governed the evolution of bolus shear viscosity, which is an essential property for food swallowing and for consumer acceptability. Thus, such an in vitro approach, extended to in vitro flavor release, could be applied to a large range of solid foods, for modeling food oral processing phenomena and used for reverse engineering to design foods with a targeted structure.

The tongue plays a crucial role throughout food oral processing, in particular, transporting food to the molar or cheek teeth, compressing or squeezing food against the hard palate, mixing food particles with saliva, and transporting bolus to the pharynx. It plays a major role in food oral processing and flavor release for soft or semisolid foods, which are not chewed. Very simple artificial tongues were designed using soft polymers such as silicone rubber (Ishihara et al., 2014) or sonagel (Gao et al., 2014). They were mainly used to simulate tongue compression of gels, between a soft material and a hard plate to study gel fracture (Kohyama et al., 2019).

The effects of tongue pressure and mastication on the release of volatile compounds in the mouth were evaluated using a model mouth with an artificial tongue (Benjamin et al., 2012). A range of tongue intraoral pressures was applied for various periods while monitoring the released volatile compounds online using a proton transfer reaction mass spectrometer. A clear peak was observed after each cycle, following a different pattern according to the physicochemical properties of the volatile compounds and the mechanical parameters applied to the artificial tongue.

Another oral function that has been tentatively simulated is swallowing. To simulate the dynamic conditions of volatile compound release from liquid foods after swallowing, a model artificial throat was designed (Weel et al., 2004). However, this simple model system cannot fully simulate the events that occur in the human throat as the

in vitro volatile compound release pattern was found much lower than that observed in vivo. Later, a pharyngeal peristalsis simulator was developed and enabled to demonstrate that during swallowing, the thickness and the composition (rate of dilution) of bolus coatings may be highly influenced both by the rheological properties of the bolus and by the physiological properties of the pharyngeal mucous membrane (Mathieu et al., 2018). This is a very interesting model to study the mechanical interactions between the food bolus and the lubricated and deformable pharyngeal mucous membranes. However, no flavor release experiments were conducted with this device yet.

1.6 Conclusion

In conclusion, flavor molecules belong to different chemical classes and possess various sensory properties. They are present in the foods, but in order to reach the sensory receptors they have to be released in the saliva during the eating process and for aroma compounds in the air phase from the oral to the nasal cavity. In-mouth flavor compound release and flavor perception are very complex phenomena, which are not well understood yet. The properties of the food matrix and oral physiological characteristics and their interactions are the main drivers for inter-individual variability. The development of mechanistic models allowed a better understanding of the release of aroma and taste compounds during the eating process. However, the release behavior does not always explain sensory perception, due to other physiological mechanisms at the central and peripheral levels. These aspects will be described in detail in the following chapters.

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Woodhead Publishing is an imprint of Elsevier
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, OX5 1GB, United Kingdom

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ISBN: 978-0-323-89903-1

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Publisher: Nikki P. Levy
Acquisitions Editor: Megan Ball
Editorial Project Manager: Lena Sparks
Production Project Manager: Nirmala Arumugam
Cover Designer: Matthew Limbert



Typeset by TNQ Technologies

Flavors mothers taught us in the womb and in milk

2

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2.1 Introduction

Among the transitions that characterize mammalian development, birth certainly is the most noteworthy in its suddenness and abruptness. It is also the most biologically challenging when one considers the high rates of neonatal mortality in any mammalian species. The natural history of mammals has selected physiological and behavioral strategies to overcome early critical challenges, based on the articulated means and skills of mothers and infants. Maternal females provide indeed passive (physiological) and active (behavioral) assistance to anticipate, guide, and optimize their offspring's competence to attend to them, survive, grow, and learn the early ways of life. Such maternal assistance combines, among other means (1) the generation of cues that are readily accessible to their offspring and that operate as sensory bridges over environmental transitions of development, and (2) the shaping of offspring able to perceive these cues across developmental stages.

Developmental discontinuities of the mammalian life cycle—here, birth—are in fact replete with overt and covert continuities mediated by mothers, which offspring can detect through all sense modalities. Such continuities result from the relative permanence of mothers as sources of sensory cues for their developing offspring, and from their formative effect on the structures/functions of offspring's sensory, motor, and integrative systems. First, the *species-specific prenatal environment*, definable as the set of stimuli to which all fetuses of a given species are inevitably exposed, canalizes offspring's initial sensory and cognitive aptitudes. They all perceive tactile cues of body containment, kinesthetic cues associated with movement regularities, sound cues related to vascular noises and vocality (Salk, 1962; De Casper and Sigafos, 1983), and possibly flavor cues caused by materno-fetal metabolism. Second, *local* or *individual-specific properties* of the fetal environment constitute an additional source of offspring selective reactivity. For example, maternal idiosyncrasies in kinesthetic or tactile stimulations (e.g., Scafidi et al., 1990), in flavors—odorants or tastants—transferred into the amnion as a function of mother's habits (diet, smoke, drugs, cosmetics; e.g., Schaal et al., 1995a, 1998), and in voice, language or particular soundscape (e.g., De Casper and Fifer, 1980; De Casper and Spence, 1986; Hepper, 1988a; Fifer and Moon, 1995). A third way through which prenatal experience might impinge on neonatal expectations is through *nonspecific properties* of the

environment, such as its average sensory intensity, complexity, or variability. Thus, for example, fetal encoding of high-level intensity or of low sensory variability in the uterine environment may orient later preferences toward high-intensity stimuli (or higher tolerance for high-level intensities) or toward changing stimuli (or less tolerance for variability and novelty).

Sensory continuities across developmental discontinuities embrace a basic principle of psychobiological development, namely that *earlier steps in ontogeny prepare the neural/behavioral organization of the next steps*. Accordingly, prenatal experience prepares offspring responsiveness to the environment immediately after birth and possibly at differed stages in later development (e.g., weaning, motor autonomy, social diversification). Beyond mammals, this conditioning of sensorimotor and neurocognitive abilities by embryonic/fetal ecology goes on in the entire animal kingdom, and is the most basic and universal mode of maternal influence, often defined as *maternal effects* (e.g., Mousseau and Fox, 1998; Wolf and Wade, 2009). One way, and probably the main way of action of these maternal effects, is the construction of the early niches in which the offspring's sensory/perceptual phenotype is shaped, leading to offspring's initial sensory selectivity or biases. Hence, certain stimuli among the sensory flow received postnatally are more salient or more significant in terms of valence than others to the newborns' senses because they have been experienced formerly (e.g., Alberts, 1987; Smotherman and Robinson, 1987, 1995). Such sensory biases have been characterized in relation to given sounds, visual objects, odorants, tastants, tactile or kinaesthetic cues, the perception of which is often termed "innate" in the soft (etymological) sense. When presented with such stimuli, neonatal and juvenile organisms respond generally by distress cessation, attention, positive orientation and coordinated approach responses, facilitated ingestion and, in the longer run, metabolic optimization, adapted growth, and cognitive integration.

This chapter focuses on the role of flavors in perinatal adaptive responsiveness of mammals, including humans. Specifically, it will address mechanisms by which flavor experience gained in the amniotic environment prepares neonates' and infants' selective responsiveness to the postnatal odor and flavor environment, especially in the context of colostrum and milk ingestion, and its consequences for engaging nonmilk food acceptance in later life. Although mainly based on human studies, comparative results obtained with murine, rabbit, porcine, ovine, or caprine perinates will also be mentioned at places to highlight the generality of the phenomena involved in the expression of adaptive responses at birth and beyond.

2.2 Biological fluids that spontaneously attract neonates

2.2.1 Colostrum and milk odors

That newly born mammals respond to the odor of conspecific milk by attention (arousal, orienting of autonomic nervous system), attraction (orientation and approach

movements), and appetite (readiness to ingest) has been known for centuries, being part of ancestral wisdom in breeders and pastoralists all over the world. Experiments in the past decades confirmed indeed that volatile compounds carried in colostrum and milk evoke attention and appetitive responses in mammalian newborns, such as lambs (Schaal & Orgeur, unpublished data), rabbit pups (Keil et al., 1990; Coureaud and Schaal, 2000), and neonatal rats¹ (Lau and Henning, 1985) and mice. In the laboratory mouse, pups differentiate indeed lactating from nonlactating dams by their sole odor, and they are more attracted to abdominal areas of lactating females comprising nipples (relative to other furry areas), hence emitting mammary skin secretions and milk, which are olfactorily attractive to pups (Al Ain et al., 2013a,b; Klaey-Tassone et al., 2019, 2021a; reviewed in Patris et al., 2012).

Human infants display as well attraction behavior or increased mouthing to the odor of human milk or mammary secretions (namely secretions from areolar Montgomery's glands containing milk; Schaal et al., 2019) obtained either from their own mother (Marlier and Schaal, 1997; Hym et al., 2020) or from an unfamiliar lactating woman (Soussignan et al., 1997; Marlier and Schaal, 2005; Doucet et al., 2009). The odor of human colostrum appears even more attractive to 2-day-old infants than the odor of mature milk collected on postpartum day 30 (Klaey-Tassone et al., 2021b). Maternal milk odor was also shown to elicit increased sucking responses in infants born at or before term (Bingham et al., 2003a; Mizuno and Ueda, 2004; Khakpour et al., 2022), with patterns and extractive efficiency of sucking that differ from those elicited by bovine milk-based formulas (in term-born infants, Mizuno and Ueda, 2004).

Finally, discriminative psychophysiological and brain responses were found toward the odor of human or maternal colostrum/milk as compared to various control stimuli. Relative to unscented and odorless controls, human milk engages neurovegetative responses involving parasympathetic mechanisms (e.g., heart-rate (HR) deceleration in sleeping infants; Soussignan et al., 1997; Klaey-Tassone et al., 2021c; attenuated HR increase in preterm infants exposed to painful procedures: Neshat et al., 2016; Kim and Choi, 2022; Lin et al., 2022). When delivered orthonasally on a glass stick, secretions from areolar glands of Montgomery, which are partially made of lacteal secretions, increase inspiratory response in newborns (Doucet et al., 2009). Breast milk odor is also reported to stabilize respiratory activity in preterm infants by reducing the frequency of apneic episodes (Lee and Ra, 2021), normalizing the level of oxygen saturation (Neshat et al., 2016), and attenuating salivary cortisol (Maayan-Metzger et al., 2018).

Cerebral electric or hemodynamic responses to the delivery of lacteal or breast odors were measured relying on near-infrared spectroscopy (NIRS), electroencephalography (EEG), or functional magnetic resonance imaging (fMRI). Following neonates' inhalation of breastmilk odor, NIRS studies report a significant cortical appeal of oxyhemoglobin to orbitofrontal and temporal regions underlain by chemosensory, salience, and reward networks (Bartocci et al., 2000; Aoyama et al., 2010;

¹ The body of work done on rat pups' responses to milk is important to understand the development of early regulation of ingestion. However, this research did not evaluate neonatal responses to *conspecific rat milk*, but to modified versions of bovine milk. Although it helps understanding functional development of appetite and satiation, it is not an ideal source to discuss issues about transnatal chemosensory continuity.

Frie et al., 2020; Muelbert et al., 2021). The level, timing, and lateralization of this milk odor—induced brain activation depends however on the neonate's gestational age (Frie et al., 2020), sex (Frie et al., 2020; Muelbert et al., 2021), feeding experience (Aoyama et al., 2010), postnatal age at testing (Bartocci et al., 2000), lactational age of milk (Bartocci et al., 2000), mode of stimulus administration (Muelbert et al., 2021), nature/intensity of reference stimulations (Bartocci et al., 2000; Aoyama et al., 2010; Frie et al., 2020), and probably infant arousal and prandial state at testing, which were variably addressed in the above studies. EEG studies of infant brain reactivity to milk odor remain rare and indicate that the milk odor—induced EEG pattern differs from that evoked by orange or farnesol odors; in addition, these studies being run on older babies (3–4 months: Yasumatsu et al., 1994, p. 5.3 months: Gellrich et al., 2021), their relevance to analyze neonatal brain reactivity is limited. Finally, fMRI studies on neonatal olfaction demonstrate that, from the very first postnatal days, arbitrarily selected odor stimuli activate the brain network typically involved in odor processing in adults (i.e., piriform and orbitofrontal cortices, and insula) (e.g., Arichi et al., 2013; Adam-Darque et al., 2018). One of them (Arichi et al., 2013) exposed sedated breast-fed preterm neonates to the odor of formula, but surprisingly not to human milk odor.

To sum up, psychophysiological and electrophysiological studies tend to confirm behavioral studies showing that neonates detect the odor of milk and respond to it discriminatively. Nonetheless, the methodological variability of electrophysiological investigations and the rather narrow range of stimuli used as references do not yet allow conclusions about the functional specificity of milk odor at the neonatal brain level. Otherwise, there is ample psychopharmacological evidence that brain neurochemistry reacts to the odor of milk in engaging the cerebral reward system. The endogenous opioid system has been particularly investigated in early development as several opioid receptor subtypes (μ , κ , and δ) were localized in the brain and spinal cord of perinatal rats (Robinson and Mendez-Gallardo, 2010). In particular, orally administered milk reduces the withdrawal response of 10-day-old pups to a painful stimulus; as it is blocked by opioid antagonists (naloxone, naltrexone), this effect was ascribed to the opioid system, and as it is already present in newly born pups, prior experience with milk was not required, suggesting that some inherent property of milk can engage the opioid system right at birth. Orally administered milk selectively engages the κ -opioid system to modulate sensation and behavior in neonate rats (Blass et al., 1991; Robinson et al., 1993; Mendez-Gallardo and Robinson, 2013). Whether milk flavor induces similar κ -opioid modulation of sensation in human infants remains to be ascertained.

2.2.2 Amniotic fluid odor

Experiments on the odor of amniotic fluid (AF) afford evidence similar to colostrum/milk of behavioral interest and attractiveness for neonates. This was first assessed in the rat (Teicher and Blass, 1976, 1977) where newborn pups express searching and oral grasping of a lactating rat's nipple. When the odor cues emanating from such nipples are removed by washing, pups refuse to orally seize them. But when AF is applied to such washed nipples, normal oral seizing performance is restored, leading to assume

that some odor cues in AF govern nipple attachment in rat pups. Amniotic odor traces are in fact spread onto the nipples by rat dams when they self-lick during parturition (Roth and Rosenblatt, 1966) and by newborns themselves when searching a nipple to suck. Similar positive responses to the odors of AF (or placenta) were shown to occur in all mammalian newborns studied so far, including mice (Hepper, 1987; Kodama, 1990, 2002; Logan et al., 2012; Al Aïn et al., 2013a,b; reviewed in Patris et al., 2012), rats (Kodama and Smotherman, 1997; Arias and Chotro, 2007; Mendez-Gallardo and Robinson 2013), rabbits (Coureaud et al., 2002), lambs (Schaal et al., 1995a), and piglets (Parfet and Gonyou, 1991). Human infants also react positively to the odor of any sample of human AF or of their own AF presented as single stimuli (Soussignan et al., 1997) or in paired-choice tests (Schaal et al., 1995b, 1998). The attentional, attractive, and appetitive potency of AF is corroborated by numerous behavioral studies (Varendi et al., 1996; Faas et al., 2013; Contreras et al., 2013). AF odor is also potentially impactful in buffering distress induced by pain in infants born preterm (Alemdar and Ozdemir, 2017; Akcan and Polat, 2016; but see De Clifford-Faugère et al., 2020).

The effects of AF odor on the autonomous or central nervous systems have been less studied than those of milk. A pharmacological approach in the rat found that AF (taken from another conceptus) administered orally engages the opioid system of fetuses externalized from the amnion, resulting in diminished face wiping responses to an aversive chemotactile stimulus (lemon flavor) (Korthank and Robinson, 1998). The application of a selective κ -opioid antagonist or agonist indicates that the κ -opioid system is involved in attenuating the fetal response to the noxious stimulus. But this “sedating” effect of AF varies as a function of the gestational age when AF was collected: it follows administration of AF from gestational day 20 (of a 21-day gestation) but not before, indicating that the sensory effects of AF on the fetus changes with advancing gestation.

In sum, AF and colostrum/milk, all fluids that convey odor cues which normally reach nasal chemoreceptors at the fetal or neonatal stages, are immediately salient to newborn organisms in that they elicit from the very first postnatal presentation motivated orientation, attraction and positive contact, and prefeeding behavior. In addition, the developmental pattern of AF-induced opioid effects may be linked to similar effects of milk (Teschemacher et al., 1997), supporting the hypothesis that AF and milk share functional continuity.

2.3 Behavioral evidence of “transnatal chemosensory continuity” and a working hypothesis

Sensory continuities between consecutive ecological niches in which early development takes place can be assessed through different, complementary ways, including measurement of neonatal responsiveness, sensory analysis by adult noses, and physicochemical or chemical analyses. The first approach relies directly on the behavior of the most concerned organisms, *viz.* mammalian newborns that must undergo the

transition in real, and which are, in principle, tailored to perceive the chemosensory thread linking the ecological succession. Studying the responses of newborns appears empirically the strongest to substantiate whether stimuli from previous and later niches are processed as same, and hence perceptually “continuous,” or as different, and hence perceptually “discontinuous.” A second, more approximative, approach is to require sensory description by adult human judges to compare the odors/flavors of the developmentally ordered sequence of the biological matrices to which newborns are exposed. A third approach relies on instrumental chemical analyses of odor active compounds to which the fetus and newborn are exposed (see below in [Section 2.4](#)).

2.3.1 Neonatal responsiveness

Newborn organisms can be “asked” to compare the sensory, motivational, or hedonic value of the flavors of the prenatal and postnatal biological fluids. Adapted choice tests induce them to choose which among the odors of their own AF or of their mother’s colostrum/milk are most attractive or aversive. When 2-day-old breastfed human infants are exposed to such choice between these biological substrates presented simultaneously, they (as a group) do not appear to differentiate AF from colostrum in terms of head orientation ([Marlier et al., 1998a](#)). Thus, the paired-choice paradigm does not evidence differential responsiveness between amniotic and milk fluids. Such nondifferential response to apparently distinct flavor stimuli may be explained in terms of (i) nondetection, (ii) nondiscrimination, or (iii) positive sensory discrimination, but without hedonic or motivational differentiation. Aforementioned choice tests opposing AF or milk odors against a scentless control stimulus exclude that infants were unable to detect their respective odor: newborns were indeed clearly attracted to AF or milk odors when presented against water. However, the other two alternative explanations have not yet been addressed properly, and the double-choice preference paradigm is not the most adequate to do it. A more critical empirical check, awaiting realisation, would consist in applying a habituation-dishabituation paradigm. But regardless of the perceptual processes underlying the observed phenomenon, we tentatively hypothesize that 2-day-old breastfed newborns sense the odors of AF and colostrum as equivalent in perceptual and/or motivational terms, as shown by their attraction behavior. Other approaches focusing on different response systems [elicitation of differential respiratory reactivity or activation of oro-facial effectors ([Soussignan et al., 1997](#))] lead to the same assumption that newborns express equal attention or interest for the odors of both perinatal fluids.

The perceptual equivalence of both perinatal substrates implies that human newborns can assess the qualitative and/or quantitative chemosensory distance between them. Deriving a single category from different versions of a stimulus has been termed *perceptual equivalence categorization* ([Bornstein, 1984](#)), and such neonatal abilities have already been shown in the olfactory domain ([Engen and Lipsitt, 1965](#)). Neonatal ability to extract perceptual invariants from qualitatively distinct odor mixtures received another confirmation with other chemostimuli. For example, newborns are able to generalize the chemosensory features of their familiar formula to a similar, but qualitatively different (for adults), formula they had never been exposed to earlier ([Soussignan et al., 1999](#)).

This nondifferential orientation to the odors of AF versus colostrum is not exclusive to human infants. There is in fact no reason why mammalian newborns should differ in this respect, as converging physiological and neurosensory underpinnings are at work in the perinatal adaptation to the birth and first sucking transitions (see below). Other mammalian newborns investigated so far are indeed in line with the responses of human neonates when exposed to choice tests pairing the odors of prenatal and postnatal substrata. For example, when given a choice test pairing the odors of placenta and of conspecific milk in a two-sided arena, newborn rabbits orient randomly to either compartment (Coureaud et al., 2002). Suckling-naïve lambs display undifferentiated searching movements toward a cloth soaked with their own AF presented in the same time as a cloth impregnated with their mother's colostrum (Schaal & Orgeur, unpublished results). Newly born piglets exposed to a three-choice test contrasting water (as a control), colostrum, and birth fluids exhibit higher, but equal, durations of nosing toward the two latter stimuli (Parfet and Gonyou, 1991). Finally, before any postnatal suckling experience, AF or murine milk odors smeared on the nipple of a nonlactating dam induce undifferentiated rates of mouse pups' oral grasping (Al Aïn et al., 2012; Logan et al., 2012). Thus, in the same way as their human counterparts, mammalian newborns from various species display equivalent odor-based interest or attraction to their AF and mother's milk.

2.3.2 Adult sensory evaluation

The second way to assess chemosensory similarity between the odors of perinatal fluids relies on the expert nose of human adults. For them, human AF has a characteristic odor quality bearing unpleasantness of moderate intensity (Soussignan et al., 1997). However, when new parents are required to describe the odor of the AF of their offspring in the days following delivery it elicits aversion-free reminiscence of the preparturient mother's body, the newly born infant or the delivery experience (Schaal and Marlier, 1998). Samples of AF evoked individually variable odor differences, based on descriptors referring to other body secretions or excretions, i.e., "urinous," "sperm-like," "sweaty," or "salivary" qualities, or based on extraneous odor notes, such as "fruity-spicy," "milky," "cheesy," "mushroomy," or "algal" (Schaal and Marlier, 1998). Similar descriptions are evoked by a panel of trained "noses" reacting to AF odor, in terms of "fatty," "rancid," "sweaty/cheesy," "fishy," "ruinous," "metallic," "hay-," "blood-," and "raw meat-like" descriptors (Hartmann et al., 2014).

Human milk was investigated more in terms of its taste than odor contribution to the flavor perception reported by adult judges (e.g., McDaniel et al., 1989). Nevertheless, when required to smell human (mature) milk, such judges evaluated its odor as weak in intensity and as conveying "hay-like," "metallic," "sweet," "fatty," and "cooked-milk-like" (Spitzer and Buettner, 2010) or "neutral," "creamy," and "sweet" smell or flavor (Mastorakou et al., 2019). Such perceptual analyses of mammary secretions by adult judges did not intend to compare the odor properties of milk with those of human AF, generally leaving aside the lactation stage. The odor or flavor properties of colostrum were thus not directly assessed by adult judges (although recent research indicates notable variations in the amount of odour-active compounds in colostrum, transitional

and mature milks; [Muelbert et al., 2021a](#)). So far, one can assert that sensory analyses of milk agree to the very low subjective odor intensity of freshly collected human milk, and they point to some shared odor qualities with AF.

In sum, behavioral responsiveness to AF and milk odors in newborns, along with hints of sensory analytic research on AF and milk odors by adult judges, lead to the general hypothesis that mammalian perinates may be exposed to a relative continuity in the chemosensory properties that may prevail in their late prenatal and early postnatal ecologies. This transnatal chemosensory continuity hypothesis has two facets. First, it implies that the neonate's ability to detect and process odor information in utero and *ex utero*, viz. in liquid and aerial conditions of reception, is sufficiently stable and that the perinatal brain is able to keep corresponding percepts in memory in its transition from the fetal to neonatal stage, and perhaps beyond. This point has been discussed at length in previous reviews (e.g., [Smotherman and Robinson, 1987, 1995](#); [Robinson and Mendez-Gallardo, 2010](#); [Schaal, 1988a,b, 2015](#); [Schaal and Orgeur, 1992](#); [Schaal et al., 1995c, 2020](#)). Second, the above hypothesis implies that a chemical overlap occurs, at least partially, between the late amniotic niche and the early postnatal niche, especially with colostrum (and perhaps other biological matrices encountered in the suckling context). This relative chemoecological continuity is discussed hereafter.

2.4 Physiological bases for transnatal chemosensory continuity

As highlighted in the previous sections, mammalian neonates respond positively to perinatal fluids when exposed to them concurrently. This non-differential behavior toward amniotic and mammary fluids may be first explained in terms of chemosensory similarity. In late pregnancy and early lactation, the amniotic and mammary compartments are indeed permeated by the same inputs of chemosensorily active metabolites reflecting the mother's normal physiology. The most obvious, and most studied, pathway to the compositional and chemosensory overlap between AF and colostrum/milk is the simultaneous transfer of odor-active compounds conveyed by the mother's diet. The effectivity of this transfer was evidenced by a perceptible alteration of the odors of AF or of the entire conceptus, or by a measurable change in the responsiveness of newborns or weanlings.

Odor-active compounds from the pregnant human mother's diet can resist maternal, placental, and fetal metabolisms and reach, at least in part, the AF or taint the newborn's body surface (e.g., [Snell, 1973](#); [Hauser et al., 1985](#); [Mennella et al., 1995](#); [Korman et al., 2001](#)). Such transfer of odorants from the mother's ingesta to the fetal environment modifies the flavor quality of AF and ensuing response of human newborns to the diluted pure odorant (e.g., garlic: [Hepper, 1995](#); anise: [Schaal et al., 2000](#); carrot: [Mennella et al., 2001](#); alcohol: [Faas et al., 2013](#)). The same process of mother-to-foetus dietary flavor transfer is attested in other placental mammals, such as the *mouse* ([Todrank et al., 2010](#)), *rat* ([Gaztagnaga et al., 2015](#); [Sreng et al.,](#)

2017), *rabbit* (Bilko et al., 1994; Coureaud et al., 2002), *sheep* (Schaal et al., 1994a; Nolte et al., 1995; Simitzis et al., 2008; Cais-Sokolińska et al., 2011; Lévy et al., 2020), *goat* (Hai et al., 2012, 2013), *pig* (Bolhuis et al., 2009; Oostindjer et al., 2009, 2010, 2011; Figueroa et al., 2013, 2019; Blavi et al., 2016; Charal et al., 2016), *dog* (Hepper and Wells, 2006; Wells and Hepper, 2006), and *cat* (Wyrwicka, 1978; Becques et al., 2010; Hepper et al., 2012).

The parallel transfer of dietary flavor cues operates from postparturient lactating female's blood to her colostrum/milk, as shown in various mammalian species by measuring behavioral outcomes in terms of flavor preferences in weanlings or even adults. This was first demonstrated by Le Magnen and Tallon (1968) who compared the intake of citral-odorized versus control foods in rat weanlings after they were exposed to their lactating mother injected (or not, for the control group) with citral for the first 10 or 30 days following birth. While the control group preferred the citral-free diet, rat pups exposed to citral in milk developed a preference for the citral diet. This discovery was then largely confirmed and refined by later studies applying spontaneous ingestion of flavors instead of injection. Thus, the milk-mediated effect of maternal dietary flavors on offspring behavior and preferences was documented in the *rat* (e.g., Galef and Henderson, 1972; Capretta and Rawls, 1974; Wuensch, 1975), *mouse* (Mainardi et al., 1989), *rabbit* (Bilko et al., 1994), *pig* (Oostindjer et al., 2010, 2011; Wang et al., 2014; Charal et al., 2016; Moon, 2017; Val-Laillet et al., 2018), *sheep* (Nolte and Provenza, 1992; Schaal and Orgeur, 1992; Schaal et al., 1994a). And the cause of the phenomenon was systematically traced in the flavor- and odor-active metabolites ingested in species of interest to dairy productions (e.g., *sheep*: Moio et al., 1996; *cow* Babcock, 1923a,b, 1925, 1927; Urbach, 1990; Bendall, 2001; Rossetti et al., 2010; Lejonklev et al., 2016; Yayota et al., 2013; Clarke et al., 2020).

Comparable evidence in humans relies on the fact that, in many cultures around the world, folk-knowledge and healthcare providers prevent the chemosensory alteration of mother's milk in proscribing the ingestion of strongly flavored foodstuffs (e.g., Brassicaceae, Alliaceae, Asparagaceae vegetables, Rutaceae fruits, various spices, cheeses, etc.; e.g., Lust et al., 1996; Jeong et al., 2017). Experiments by Mennella and Beauchamp (1991a,b, 1996, 1999) and many others (Desage et al., 1996a; Hausner et al., 2008; Kirsch et al., 2013; Denzer et al., 2015; Scheffler et al., 2016, 2019; Qin et al., 2020; Debong et al., 2021) provide evidence that complex aromas from various foods (e.g., garlic, vanilla, alcohol, carrot, cumin, curry) or pure odor-active compounds easily pass into milk (reviewed in Loos et al., 2019; Spahn et al., 2019; Debong and Loos, 2020). By sampling milk regularly after human mothers' ingestion of garlic capsules and presenting these samples to adult judges for intensity and quality rating, these studies revealed milk odor changes, the intensity of which is perceptible to adults and culminates at about 2–3 h after ingestion (Hausner et al., 2008). These diet-induced odor changes of milk are detectable to human nurslings themselves, as they measurably modify their sucking pattern at the breast and amount of milk consumed (Mennella and Beauchamp, 1991a; Mennella, 2001).

Physiological pathways additional to diet can influence the odor profile of perinatal fluids. Odorants inhaled or applied on skin by pregnant or lactating women can be

transferred in brief delay into her blood and then into AF and colostrum/milk. For example, inhaled or eructed compounds of the mother's diet (Dougherty et al., 1962), and inhaled perfumes or cosmetics (Jirowetz et al., 1991; Lang et al., 2016; Belavvia et al., 2019; Hsieh et al., 2019), or combusting tobacco or other fumes (Lambers and Clark, 1996; Svensson, 1997; Karmowski et al., 1998) attain the mammary compartment (see below). Further, perfumes or cosmetic products applied directly on lactating mothers' skin are also easily transferred into milk (e.g., Rimkus and Wolf, 1996; Liebl et al., 2000). Expectedly, mothers' reports of frequency of perfume use correlate with the concentration of fragrance compounds (musk ketones, musk xylene) in their milk (Lignell et al., 2008). Even, inhalatory and potentially percutaneous exposure of lactating women to synthetic musks through the detergents used for laundry can result in detectable amounts in milk (Lignell et al., 2008). So far, inhalatory/percutaneous passage of odor-active compounds into AF is less documented, but there is no *a priori* reason against it as these pathways easily connect with systemic circulation (Hu et al., 2010).

Metabolic processes linked with maternal physical activity might also simultaneously influence the composition of amniotic and lacteal fluids (Wallace and Rabin, 1991; Duffy, 1997; Carey et al., 1997). Lactic acid is the most studied metabolic marker of physical activity, but it is likely that other impactful odor cues fluctuate as a function of maternal activities. Such exercise-induced changes in milk composition are detected by nurslings who express increasing refusal of maternal milk as a function of the intensity of her physical activity (Wallace et al., 1992; Wright et al., 2002). In the same vein, stress can transitorily alter the chemosensory properties of the prenatal environment, either by acute transfer of stress-related odoriferous metabolites from mother to fetus, by accumulation of metabolic byproducts due to reduced placental clearance of AF, or by the direct release of chemostimuli by the fetus (e.g., micturition) in response to acute maternal or fetal stress (Zimmer et al., 1993). In this way, compounds bearing chemosensory impact might be transferred from the fetal compartment to the mother's bloodstream where they may collect in colostrum. Such reciprocal transfer of flavor-active compounds from the fetus to the mother may contribute to an olfactory match of both perinatal fluids (e.g., through fetomaternal passage of odor-active compounds resulting from fetal and maternal immunogenetic metabolism; Beauchamp et al., 1994, 1995; Yamazaki et al., 2000).

2.5 Chemical evidence for transnatal chemosensory continuity

The chemoecological match between both perinatal fluids (AF vs. colostrum/milk) has attracted too little research by chemists. While AF and colostrum/milk have received separate (bio)chemical scrutiny, often for topics related with other issues such as nutrition, environmental contamination, pharmacokinetics of drugs or validation of markers of genetic defects, their chemical and chemosensory properties have been rarely assessed for their impact on fetal olfaction or taste, and related issues on flavor

programming. A major difficulty for both behaviourists and chemists is that the composition of AF and milk are variable between individuals and within individuals along pregnancy and lactation (Pham et al., 2020; Samuel et al., 2020), respectively, making their composition difficult to capture and generalize (e.g., Ng et al., 1982; Gurekian, 2005; Velika et al., 2018). Lacteal secretions are also compositionally variable depending on maternal chronobiology and sampling time within a feed (Samuel et al., 2020; Hahn-Holbrook et al., 2019). The chemosensory consequences of these normal compositional changes of AF and colostrum/milk on the fetus and neonate, respectively, have rarely been addressed. At least regarding colostrum/milk, sensory evidence indicates that offspring vary in their responses to milks sampled at different lactation stages in both murine and human neonates (e.g., Al Ain et al., 2012; Klaey-Tassone et al., 2021b). For example, the milk odor from postpartum day 2 is preferred by 2-day-old neonates over the odor of milk from day 30 (Klaey-Tassone et al., 2021b), pointing to chemosensory variations that render colostrum versus mature milk discriminable to neonates. The chemical correlates or causes underlying these chemosensory variations remain to be explored (see Muelbert et al., 2021a, for evidence of changing amounts of odorants as a function of lactational age in preterm colostrum and milk).

2.5.1 Odor-active compounds in AF

Regarding AF, early gas chromatographic-mass spectrometric (GC–MS) investigations of solvent-extracted volatiles evidenced as much as 390 compounds in pooled samples (obtained through amniocentesis from 10 concepti aged 18 gestational weeks), and about 120 compounds in individual samples (Antoshechkin et al., 1989). For example, vaginally-sampled AF extracted in dichloromethane evidenced fatty acids (i.e., 2,2-dimethyl-3-hydroxybutanoic, 2-oxo-isocaproic, tetradecanoic, hexadecanoic, oleic acids) and 7-methyl indole, a compound known for its persistent animal note (Rognon and Chastrette, 1992). In another study, Rietdorf (2002) extracted amniotic solutes with various solvents among which a hexane extract provided 35 compounds, dominated by 30 medium- and long-chained fatty acids. A similar approach by Contreras et al. (2013) based on amniotic samples collected from vaginal and caesarean deliveries identified eight fatty acids among the 30 identified earlier by Rietdorf (2002). However, it may be noted that AF taken during vaginal deliveries may be contaminated by blood and vaginal fluids, resulting in a chemical profile that differs from that of “pure” AF sampled within the amniotic sac (although this mixture constitutes the normal olfactory scene of the nascent infant). Finally, a small-scale study analyzed AF (samples from two individuals) and compared it with infants’ head odor (from two babies aged 1–2 days, and three aged 3–5 days), which is originally soaked with AF (Uebi et al., 2019). It identified 21 and 31 components at respective ages, among which 15 were common to AF and newborns’ head smears. Human newborns—and probably all mammalian newly born offspring—may thus carry AF odor into their postnatal niche, where it may be released from the skin or hair for some days and label accordingly the surfaces which they come into contact with (mother’s breast or body, nest or sleeping environment).

2.5.2 Odor-active compounds in lacteal secretions

Chemical analyses of human (mature) milk using various milk collection and extraction methods also led to identification of certain number of odor-active compounds. The results of these studies varied considerably as a function of timing of sampling, method and duration of conservation, and finally extraction and analytic techniques (Spitzer et al., 2010; Loos et al., 2019). Chemicals detected included, among others, carbonyls, aldehydes, fatty acids, esters, terpenoids, ketones, and lactones (e.g., Stafford et al., 1976; Shimoda et al., 2000; Buettner, 2007; Pellizzari et al., 1982; Hausner et al., 2009; Loos et al., 2019; Muelbert et al., 2019, 2021). For example, an aroma extract dilution assay of fresh human milk evidenced high flavor dilution factors for (Z)-hept-4-enal (fishy odor), (E)-4,5-epoxy-(E)-dec-2-enal (metallic note), 3-hydroxy-4,5-dimethyl-2(5H)-furanone (savory note), phenylacetic acid (honey odor), vanillin, and unknown compounds bearing musky notes (Spitzer and Buettner, 2010). Analyses of colostrum are rather rare (Bingham et al., 2003b; Muelbert et al., 2021a), although required to evaluate the degree of its chemical similarity with AF. Bingham et al. (2003b), applying GC-olfactometry on milk samples from four mothers of preterm infants of imprecise lactational age, found four odor-active compounds common to all samples (E-2 nonenal, 1-octen-3-one, furaneol, maltol, and 2-nonanone). Muelbert et al. (2021) performed headspace solid-phase microextraction of GC-MS on colostrum (postpartum days 3–5), transitional (day 10) and mature (4 months) milks of mothers after preterm delivery; in total, 40 odorants (prevalently fatty acids and their esters, aldehydes, ketones, terpenoids, alcohols, and other VOCs) were identified, some of which varied in amount as a function of lactational timing. For example, octanoic and decanoic methyl esters, conveying, respectively, green-herbal-orange and fruitlike qualities, increased between 3 and 5 day-colostrum. Among these odor-active compounds of human colostrum/milk, it is currently not known which ones are dependent on the environment (chemosphere, diet) and which ones constitute the species-specific invariant core of the milk olfactome or flavourome.

Taken together, the above chemical analyses reveal that human AF and milk convey mixtures of odor-active compounds. Similar results, especially for milk, can be found for other mammals, the most studied being those yielding milk for the dairy industry (e.g., Moio et al., 1993, 1996; Toso et al., 2002; Ritea de Cassia et al., 2019; Clarke et al., 2020). But the fraction of compounds overlapping in AF and colostrum/milk, which underlies the expected molecular basis for a transnatal chemosensory continuity, remains unknown.

Although it is assumed that the qualitative perception of individual odor-active compounds does not directly translate into the complexities of odor mixture perception, the simultaneous transfer of dominant dietary aromas into both perinatal compartments constitutes a *first way* to empirically assess the evidence of a relative chemical/chemosensory convergence in perinatal fluids. Some rare GC-MS analyses followed the transfer of dietary odor “markers” into both AF and milk after their ingestion or intravenous injection. For example, when ewes were fed a cumin-odorized diet, or were injected with cumin extract during the last days of gestation, several key odorants from cumin could be traced in both maternal and fetal bloodstreams, and in fetal urine,

AF, and milk (Schaal et al., 1995c; Desage et al., 1996a). A similar experiment with cumín ingestion in human mothers indicated that some of the characteristic odor markers of cumín pass at trace levels into AF sampled at vaginal births, but with individual variations in the transferred compounds (Desage et al., 1996b; Schaal, 2005). In addition, participant mothers in this experiment reported that a characteristic cumín scent was detectable on the skin of their palms and forearms, indicating that dietary odorants can also be emitted into sweat or sebum. This suggests an additional locus for the externalization of chemosensory cues: the maternal body surface to which fetuses will be, and newborns are, obviously exposed, and perhaps for longer times than only breast-feeds. Other diet-induced alterations of the sensory profile of milk have been followed up, sometimes along with their transfer kinetics (Mennella and Beauchamp, 1991a,b; Bingham et al., 2003b; Hausner et al., 2008; Kirsch et al., 2012, 2013; Sandgruber and Büttner, 2012).

A *second way* to substantiate compositional resemblance between perinatal fluids is to compare their odor profiles in samples collected from same women outside of any experimental manipulation of the environment. An early GC study characterised solvent-extracted volatile compounds common to AF and milk sampled in the same individuals (Stafford et al., 1976). Although it has limited value for the perinatal period because the milk was from postpartum day 30, it found nevertheless volatile compounds shared between AF and mature milk. Analyses targeted on given chemical classes demonstrated that volatile compounds bearing potent olfactory impact distribute in parallel into amniotic and lacteal fluids, as is the case of volatile amines carrying strong animal or fishy odors (Lichtenberger et al., 1991) or organic acids (Nichols et al., 1978; Ng et al., 1982; Shimoda et al., 2000; Rognon and Chastrette, 1992). More recently, Contreras et al. (2013) identified eight saturated and unsaturated fatty acids (i.e., lauric, myristic, palmitic, palmitoleic, stearic; oleic, elaidic, and linoleic acids) that were common to the AF, colostrum, and milk from the same 12 healthy donors (see below).

A *third way* consists in profiling highly odor-active compounds in one fluid, say AF, and then in tracing them in the other fluids, say colostrum/milk. This strategy has been applied in a set of studies who characterized compounds bearing strong odor impact in “pure” AF, i.e., collected by amniocentesis before Cesarean sections (Doucet et al., 2010; Hartmann et al., 2012, 2014). It consisted in finding the odor qualities in AF samples which are most intense to an adult panel, then in targeting the compounds carrying these odor qualities during GC-olfactometry (GC-O) runs, and finally in identifying the GC peaks matching with the most powerful odor perceptions. Odor qualities of strong intensity in AF were reported to be metallic-like, raw meat-like, and fatty, while weaker odor qualities were described as rancid, fishy, sweaty, and hay-like. AF constituents bearing these dominant odor qualities were identified as the steroids androstenone (5 α -androst-16-en-3-one) and androstadienone (4,16-androstadien-3-one) conveying sweaty-urinous notes, methional resembling cooked potato odor, and 4-ethyl octanoic acid releasing a goaty smell. Some compounds conveying strong odor impact (in adults) were found as well as in human colostrum and milk (and, in certain cases, axillary sweat), such as odorous steroids (androstenone, AND), aliphatic acids (3-hydroxy-3-methylhexanoic acid, HMHA; 3-methylhex-2-enoic acid, 3M2H)

and sulfur compounds (3-methyl-3-sulfanylhexasan-1-ol, MMH; 3-sulfanylhexasan-1-ol, MH), often in bound form. Due to their cooccurrence in AF and colostrum/milk, these powerful odorants were thought to be odorant candidates underlying perinatal odor continuity in humans and were brought under newborn infants' noses in standardized assays (see below).

2.5.3 From chemical analyses of AF and milk to behavioral assays with human newborns

Following the identification of given odor-active compounds in human perinatal fluids, several studies attempted to evaluate their behavioral effects on neonates. One study mentioned above by [Contreras et al. \(2013\)](#) investigated the differential behavioral activity of the eight fatty acids found in human AF, colostrum, and milk ([Contreras et al., 2013](#); [Gutierrez-Garcia et al., 2017](#)). First, the mixture of these eight fatty acids was found to elicit in 1-day-old neonates' "positive actions" of similar duration than fresh AF odor and of longer duration than centrifugated AF and the scentless control ([Contreras et al., 2013](#)). Second, among these eight compounds, as well as the odorous and nonodorous control stimuli, neonates (aged <24 h) appeared to display more "attraction" (in terms of longer oral and nasal "positive responses") toward the odor of myristic acid, which was therefore claimed a "seemingly ... primary intra-uterine signal for the subsequent recognition of similar substances after birth" ([Gutierrez-Garcia et al., 2017](#), p. 36). However, apart from conceptual issues, these studies relied on poorly defined response variables in neonate infants, the behavioral state of which during testing was not adequately controlled.

Following the identification of AND, MMH, MH, HMHA, and 3M2H in human AF and colostrum (see above), these odor-active compounds were delivered separately to 3-day-old sleeping neonates at physiologically relevant concentrations and against several reference stimuli (water, vanillin, and the familiar formula/breast milk; [Loos et al., 2014, 2017](#)). Cephalic and orofacial responses indicated neonatal detection of AND, MH, HMHA, and 3M2H. The newborn's sex-modulated responsiveness to AND and MMH, while the feeding mode (formula vs. breastmilk) had no impact. Interestingly, the concentrations of AND needed to elicit responses were lower by a factor 1000 in newborns than in adult males ([Loos et al., 2014](#)), indicating greater sensitivity of neonates.

But, beyond mere detection, the aforementioned odorants elicited in neonates longer negative facio-cephalic and/or shorter positive oro-facio-cephalic actions compared with water. This suggests that these compounds were rather unpleasant to them. This surprising result contrasts with previous studies showing that mammalian neonates evince positive, or less negative, responses to prenatally or perinatally experienced odors. Several mechanisms may explain such negative responses to odorants encountered in perinatal fluids ([Loos et al., 2014](#)). *First*, neonates may perceive odorants differently when they are delivered in pure form or in mixture. AF and colostrum/milk convey indeed mixtures of compounds among which our target odorants may be blended, attenuated or masked. In pure form, they may thus be perceived as novel

odors, therefore eliciting negative responses. *Secondly*, these pure odorants may carry trigeminal effects (e.g., Boyle et al., 2006), which are known to elicit defensive responses in neonates. *Thirdly*, odorants become salient as a function of their association with rewarding events. While some odorants are stable in AF or milk as they derive from tonic processes inducing weak variations, others occur as part of phasic processes inducing fast and ample variations. One may speculate that the fetal brain can monitor odorants transferred from maternal meals, the concentration of which peaks in contingency with rewarding events, such as those produced by the central sensing of nutrients (e.g., Lewis et al., 1978; Natale et al., 1978). Odorants which are not synchronized with rewarding events, such as those mentioned above, may be swamped by adaptation or habituation and may therefore not engage perceptual saliency in fetuses, an additional reason why they may be perceived as novel by neonates, and hence as rather negative.

Negative hedonic responses of human newborns to the odor of pure compounds isolated from perinatal fluids (e.g., AND, MMH, MH, HMHA, and 3M2H) raise two paradoxes. The *first paradox* is that AF and milk mixtures, which contain the odorants tested above, are attractive to neonates, whereas these pure odorants are not attractive on their own. The analogy is not infrequent of mixtures conveying attractive odors despite their content in foul-smelling compounds (e.g., indole in jasmine odor). Thus, minute amounts of aversive compounds (such as AND) may not be detrimental to the attractiveness of complex mixtures of other odor-active molecules (such as AF or milk). The *second paradox* relates to the newborns' attraction toward mother's body areas from where the aforementioned unpleasant odorants are naturally emitted. But, again, their sensory contribution is embedded in molecular interactions within complex mixtures. Such aversive odorants may have a "function" in the perceptual processing of whole mixtures: mixing positively and negatively valenced components lead to a "contrast effect" inducing higher sensory salience and positive affective valence of the entire mixture (Grabenhorst et al., 2007). Odorant mixtures conveying such contrast effects were found to engage more intensely brain mechanisms involved in attentional capture and enhancement (Grabenhorst et al., 2011). Thus, in our perinatal context, one may speculate that negatively valenced compounds may contribute to infant perception of odor mixtures by kindling attentional brain processes and making odor signatures carried in AF, milk, or axillary sweat more conspicuous and therefore more easily learnable. This hypothesis awaits further investigation.

To sum up, results obtained so far suggest that the chemical core underlying the transnatal chemosensory continuity phenomenon may not be based on a solo or duo of molecules. Although experimentally concentrated "pure" compounds ingested by pregnant women (e.g., garlic, anise, ethanol) distribute in parallel into amniotic and mammary compartments and do subsequently result in differentiated responses for that single odorant (e.g., Hepper, 1995; Schaal et al., 2000), this may not always be the rule under normal life circumstances (but see below, the research on alcohol or nicotine; e.g., Spear and Molina, 2005; Mantella et al., 2013). The maternal chemosphere—depending on her genetic make-up, diet, atmosphere, skincare products, metabolic consequences of stress, activity or illness—is generally constituted of complex mixtures, forming perceptual "bouquets" that distribute into the different

biological (circulatory, amniotic, mammary, dermal, etc.) compartments of the body. How and when these amniotic or lacteal bouquets are created, how they do fluctuate with the incoming flux of novel chemical mixtures, and how they are stabilized over time to impinge on fetuses' and infants' developing chemosensation needs further scrutiny.

In that line, most odor-active compounds reported above in AF could occur in parallel with other dietary inputs and their metabolites. Accordingly, considerable odor and flavor variability may be expected in AF from different individuals. But this was not the case in [Hartmann et al. \(2014\)](#) study who detected the same set of compounds in AF samples, perhaps due to similar diet in postparturient women in a German hospital. The visual comparison of GC profiles of AF samples from a sample of French mothers ([Schaal et al., 1995c](#)) suggested as well shallow qualitative differences, although with quantitative variations. The issue of odor-active amniotic and lacteal constituents originating in the maternal diet awaits thus to be revisited with correlational (monitoring the spontaneous spectrum of foods consumed by the mother in the days prior to birth), experimental (proposing contrasted diets during the days prior to AF sampling), or intercultural (e.g., [Muelbert et al., 2021a](#)) approaches.

2.6 The transnatal olfactory continuity hypothesis and ensuing predictions

If the hypothesis of transnatal chemosensory continuity is biologically valid, it should raise number of testable predictions. Ten of such predictions are outlined below along with their empirical test, when available.

2.6.1 *Newborns should respond selectively to the odors of familiar AF or milk*

The transnatal chemosensory continuity hypothesis implies that newborns differentiate the individual signature of their own AF or their own mother's milk from the homologous fluids from other females. Mammalian infants of various species orient to any sample of homospecific AF ([Teicher and Blass, 1977](#); [Schaal et al., 1995a, 1998](#)). But, when given a choice between their own AF and the AF from another conceptus, neonates orient selectively toward the more familiar AF, as verified in murine ([Hepper, 1987](#)), ovine ([Vince and Billing, 1986](#); [Schaal et al., 1995b](#)), porcine ([Figuerola et al., 2013](#)), and human newborns ([Schaal et al., 1998](#)).

Such selective responsiveness has also been assessed for the odor of maternal colostrum/milk. The odor of any human milk (i.e., not from their own mother) is effective in activating neonates or is preferred over other substrates (e.g., [Cakirli and Acikgoz, 2021](#); [Marlier and Schaal, 2005](#)). But when their own mother's milk is presented against milk from another woman in the same lactational stage, breastfed infants aged 4 days orient longer to the former ([Marlier and Schaal, 1997](#)). Own mother's milk odor appears also more effective in soothing neonates than an alien mother's

milk odor (Cakirli and Acikgoz, 2021). Previous studies collecting the entire secretion of the breast of lactating women (milk + areolar secretions) provide converging results on discrimination between own versus other mother's milks, although after several days following birth (day 2–10: Schaal et al., 1980; day 6: Macfarlane, 1975; week 6: Russell, 1976). Similar discriminative responses of newborns toward own mother's versus another mother's milk were found in lambs, with generally more pronounced responses in favor of mother's milk (Ward and Vince, 1984).

Thus, newborns from at least some mammalian species react by selective attraction to their prenatal or postnatal fluids. They may respond to the odor properties of AF and milk at both species-specific and individual-specific levels, implying that these fluids convey individual odor signatures nested in supra-individual odor signatures. The developmental dynamics of these neonatal responses remains poorly understood. Although discrimination between familiar and nonfamiliar breast odor signatures is effective after several days (Macfarlane, 1975; Russell, 1976; Schaal et al., 1980), only slight evidence exists for ingestively naïve newborns. One study found indeed infants' attraction to their own mother's colostrum within 30 min after birth, the rate of appetitive mouthing depending on the duration of exposure to the breast or skin before the test (Mizuno et al., 2004), implying some degree of postnatal learning.

2.6.2 *Transnatal chemosensory continuity should be maximal in the first postnatal days*

It is likely that the olfactory similarity between AF and lacteal secretions is maximal right after birth, when both fluids are under concomitant influence of the same causes of variation. Recall that colostrum is already secreted in the mammae in the last days or weeks of pregnancy, being therefore named precolostrum or “prepartum mammary secretion” (Neville, 1995). By the end of gestation, exogenous odorants collect thus in colostrum in the same time as in AF. Accordingly, a higher degree of chemical overlap should occur between both perinatal fluids in the first postnatal days, implying that they should be less differentiable to newly born organisms. With advancing lactation during the first postpartum days, and especially after the engagement of stage II of lactation, AF may be expected to be increasingly discriminable from lacteal secretions.

This prediction was examined in several ways. A first study assessed whether human infants differentiate the odor of their late-pregnancy AF from the changing odor of their mother's lacteal secretion over the first five postnatal days, encompassing the period when lactation stage II sets on. While colostrum tends to be compositionally stable over the first 2 days, it enters in a transition on day 3–5, and then galactopoiesis increasingly replaces it (Patton et al., 1986). Between postnatal days 1 and 5, five groups of infants were exposed to a paired-choice test between their own AF and their mother's colostrum or milk of the day (Marlier et al., 1997). Two phases occurred in the neonates' responsiveness: between days 1–3, they did not olfactorily differentiate either substrates, but by day 4 they displayed increasingly longer head turning toward their mother's milk odor than to the odor of AF. Shifting from nondifferentiation of AF versus colostrum to a period of clear differentiation, this result is in line with the progressive change in the infant's appeal to milk odor as a function of exposure.

A second way to assess prediction 2 was to expose mouse and human newborns to milks sampled at different lactation stages. Before any postnatal suckling experience, AF and murine milk were olfactorily attractive to mouse pups (Al Aïn et al., 2013a,b). But as colostrum and milk composition changes along early lactation, attractiveness of their odor should fluctuate as well for newborns. This was investigated in mouse pups aged 2, 6, and 15 days exposed to milk samples collected from females in varying lactation stages (Al Aïn et al., 2012, 2015). The pups were assayed in tests opposing two by two milk samples collected at lactation days 2 (L2), 6 (L6), and 15 (L15) (which were all attractive relative to water). Two and 6-day-old pups responded similarly to the odors of L2 and L6 milks, but significantly less to the odor of L15 milk. In contrast, 15-day-old pups explored as much L15 milk odor as the odors of both L2 and L6 milks. Thus, neonatal pups preferred the odor of early-lactation milk, while older pups responded nonselectively. In a functionally similar experiment, 2-day-old human newborns showed a preference for the odor of human colostrum over the paired odor of mature milk (sampled at 30 days postpartum; Klaey-Tassone et al., 2021b).

In sum, colostrum may convey unique chemosensory properties for newborn mammals, which may derive from its relative resemblance with AF (although such attraction might also reside in so far unknown compounds that bear intrinsic signal value).

2.6.3 *Transnatal chemosensory continuity cannot happen with artificial formulas*

Since antiquity, but increasingly since the eighteenth century, human societies have adopted various substitutes of human milk to feed their infants, consisting in non-human milks or artificial formulas (e.g., Halcrow, 2019; Herrscher and Séguy, 2019). When imposed since birth, which is the case of about 20% of infants (in France, Spain or the US; Victora et al., 2016), artificial formulas expose infants to a palette of flavors that, in principle, is not aligned with the flavor palette experienced in the womb or in colostrum/milk (Hausner et al., 2006; Jiang et al., 1999; Biolatto et al., 2007; Muelbert et al., 2021b; Zhang et al., 2022). Indeed, the degree of chemosensory continuity between AF and artificial formulas (of bovine or vegetal origin) can logically not rival with that between AF and colostrum/milk of a same mother. Accordingly, formula-fed newborns should not only be able to differentiate the odors of their AF and of their formula, but they should be more attracted to AF odor than to that of any formula.

This prediction was addressed in exposing 2-day-old (formula-fed) infants to a choice test pairing the odors of cow milk-based formula and of their own AF (Marlier et al., 1998b). These infants discriminated both stimuli in displaying more head orientation to AF odor relative to the formula odor (which was not aversive on its own, as it elicited attraction against a control stimulus). Thus, in contrast with their 2-day-old breast-fed counterparts who responded equivalently to AF and colostrum odors, formula-fed infants preferred their familiar AF to the cow milk-based formula with which they were hitherto deeply familiarized as it led them to satiation several times prior to the test.

There are so far very few chemoanalytic comparisons of different types of milks offered to human neonates (Bingham et al., 2003b; Muelbert et al., 2021b). One of them compared the odor or flavor emanating from milk of women having delivered prematurely and different types of formulas or fortified breastmilk. It found a unique, rapidly evolving, compositional profile in odor-active volatiles of milk in the first days following delivery (Muelbert et al., 2021b).

2.6.4 Newborns should prefer conspecific milk over other learned odorants

Keeping with aforementioned result (i.e., preference for AF vs. familiar formula in formula-fed infants), one may predict that newborns fed exclusively formula should prefer the odor of colostrum/human milk relative to formula, and even to their familiar formula. Or at least they should display equivalent attraction to colostrum/milk and their own formula. The main reason for their preference of human colostrum/milk is that its odor properties align more with their prenatal odor experience. This was assessed in a series of tests comparing differential responses of breastfed and formula-fed infants (Marlier and Schaal, 2005):

In a first test, opposing nonfamiliar human milk (from a woman in similar lactational stage as their own mother) with a nonfamiliar formula odor, *breastfed* newborns (aged 4 days) responded by positive head orientation and more mouthing to the former odor. In these conditions, the preference for milk is interpretable in terms of a greater resemblance of any human milk with their own mother's breastmilk. A second test, exposing *formula-fed* infants to the odor of (nonfamiliar) human milk versus an unfamiliar formula odor, led to the same result of greater preference for conspecific milk over the formula. Applying here the previous way of interpretation, these infants should have preferred their habitual formula to human milk; however, their actual response was inverse in that they preferred the odor of human milk despite they had never ingested it since birth. Thus, a third test consisted then in exposing *formula-fed* infants to milk sampled in a nonfamiliar mother and their familiar cow milk-based formula. In this latter configuration, the infants displayed more oral wanting responses toward the unfamiliar human milk odor than to their familiar formula odor. Thus, as in the previous test, chemostimuli conveyed by untried human milk appeared more rewarding to human newborns than nonspecific volatiles from their habitual formula to which they were conditioned by smelling, sucking, and satiating at least 20 to 25 times before being tested.

It may be concluded that human colostrum/milk carries volatile compounds that are attractive and appetitive to human newborns. One possibility, in line with the above prediction, is that the odor cues infants detect in conspecific colostrum/milk may recall them similar cues experienced in the womb, which are memorized for at least several postnatal days and are apparently not forgotten under the pressure of later odor experiences met in substitutive formulas. A subsequent study indicated that neonatal responsiveness to conspecific colostrum/milk odor is not perturbed or erased by a newly learned odorant associated with breastfeeding. When tested for their preference

between the odor of human colostrum/milk and a chamomile scent applied on the breast at each feed since birth, 3-day-old breastfed newborns displayed indeed equivalent orientation to either stimulus (Delaunay-El Allam et al., 2006). Thus, the attractive potency of conspecific colostrum/milk odor appears to be stable, not easily overcome by an arbitrary odor although learned in strongly reinforcing conditions.

2.6.5 In utero odor exposure should lead to preference for the same odor ex utero

As noted above, AF odor remains salient after birth, in aerial conditions of stimulation: mammalian newborns show clear attention and attraction toward it (e.g., rat: Teicher and Blass, 1977; Hepper, 1988b; sheep: Schaal et al., 1995a). Human infants also remain enticed by the effluvium of human AF for some days after their birth (Schaal et al., 1995b; Faas et al., 2013). When facing the choice between their own AF odor and an alien AF odor, they clearly prefer the most familiar one (Schaal et al., 1998). Thus, late-gestation fetuses detect and encode the idiosyncratic mixture of odorants diluted in their liquid environment, and neonates remember and use it. This transnatal stability in fetal odor memories was further assessed experimentally in manipulating the chemical composition of AF or colostrum/milk, the outcome being that neonatal sensing and preferences can rely on simple compounds the quality of which may have dominated in the prenatal environment.

This was first demonstrated by injecting concentrated odor solutions into the amnion and thereafter testing fetuses in utero (Smotherman and Robinson, 1987) or postnatally as newborns, weanlings, or even adults (Stickrod et al., 1982; Smotherman, 1982a,b; Pedersen and Blass, 1982). For example, rats exposed to lemon odor as fetuses suck preferentially nipples coated with lemon odor, and their attraction toward these lemon-scented nipples is even stronger when their mother stimulated them during nursing (Pedersen and Blass, 1982). In a second wave of investigations, AF composition was manipulated more ecologically by altering the diet of pregnant females. In this way, rat pups born to females that had consumed garlic, orange, or ethanol at the end of gestation evinced a preference for that same flavor at postnatal day 12 (e.g., Hepper, 1988b; Chotro and Molina, 1990; Spear and Molina, 2005). The same result was reached with newborn rabbits exposed to various odor mixtures (cumin, juniper, thyme) transferred into the fetal compartment from the mother's diet (Bilko et al., 1994; Altbäcker et al., 1995; Semke et al., 1995; Hudson et al., 1999; Coureaud et al., 2002).

Finally, human infants born to mothers having consumed garlic or anise-flavored foodstuffs during late pregnancy displayed longer head orientation, more appetitive oral actions, and less facial distaste when reexposed to garlic paste or pure, diluted anethole (an impactful odorant from anise seeds), respectively, 20 and 3 h after birth (as compared to infants born to mothers who did not consume garlic or anise) (Hepper, 1995; Schaal et al., 2000). This positive head orientation response to anise in the anise-exposed group persisted for at least 4 days after birth (Schaal et al., 2000), showing that, in primate infants as well, experience with odorants or flavorants fosters stable

memories after birth. This postnatal bearing of prenatal exposure to a given odor cue prevailing in utero is effective with a variety of flavors ingested by the mother. It was also found with carrot flavor ([Mennella et al., 2001](#)), in comparing responsiveness to it in groups of infants born to either mothers drinking carrot juice during the third gestational trimester (4 days/week for three consecutive weeks) or mothers drinking water in the same conditions. Infant testing was run at about 5–6 months when habituated to nonmilk food since 1 month, consisting in offering a cereal food-base wetted with water or with carrot juice. When orally presented carrot-flavored cereals (as compared to the plain ones), the infants exposed to the carrot flavor in utero expressed less negative facial configurations, tended to consume more carrot-flavored cereals, and their mother reported their infant's higher enjoyment toward them. This result expands the memory span of a flavor received in utero up to 5–6 months after birth. A later study, confirmed such long-term memory for a prenatally experienced flavor. [Hepper et al. \(2013\)](#) compared the responses of 8–9 year-old children to a smashed potato-base flavored or not with garlic as a function of their exposure to garlic flavor during the last month of pregnancy. As compared to those who were not exposed to garlic in utero, the garlic-exposed children consumed more garlic-flavored food. As these infants were all fed formula since birth and mothers of both groups did not report differential garlic exposure between birth and testing, the authors assume that the preference of 8–9-year-olds originates in prenatal experience only.

However, reexposure through colostrum/milk to the flavor experienced in utero may reinforce a flavor memory engaged prenatally, and thus settle the chemosensory continuity effect across birth. This postnatal confirmation of the prenatal exposure has generally been found in several mammals (e.g., rat: [Pedersen and Blass, 1982](#); dog: [Hepper and Wells, 2006](#); cat: [Becques et al., 2010](#); [Hepper et al., 2012](#); Pig: [Oostindjer et al., 2011](#); but see [Hai et al., 2016](#) in goats).

Above studies consisted in asking pregnant and/or lactating mothers to ingest in habitually concentrated target foods bearing a specific odor quality. But effects of perinatal olfactory experience were also evidenced in conditions of spontaneous food intake. Several studies required mothers to report their daily consumption of given foods or beverages during pregnancy and breastfeeding, then assessing these exposure records with infant reactivity to related odors. The case of alcohol is interesting in this context. For example, 1–2 or 7–14-day-old infants' appetitive responsiveness to the odor of alcohol was traced to their mother's alcohol consumption during gestation ([Faas et al., 2000, 2015](#)); in this study, increased gestational exposure to alcohol results in heightened neonates' reactivity to alcohol odor, with facial signs of intensified appetite and of reduced aversion. However, a later study indicates that gestational alcohol intake does not associate linearly with neonatal responsiveness to alcohol odor as infant of low drinkers (<20 g alcohol at a time, i.e., <2 standard drinks) exhibit aversive facial responses, while those of moderate and high drinkers (20–40 and >60 g alcohol/occasion, representing <3 and >4 drinks) express appetitive responses to alcohol odor ([Anunziata et al., 2020](#)). This raises the issue of frequency and level of fetal exposure to a given flavor in determining postbirth hedonic appraisal of this same flavor or odor.

A further study (Wagner et al., 2019) monitored (using food diaries) French mothers' food intake during pregnancy and lactation as well as their infant's intake of nonmilk foods at onset of diversification. These diaries allowed inferring the rate of flavor exposures infants underwent during the last gestational trimester and during lactation and weaning, up to 1 year of age. Exposure to eight categories of foods was extracted from these diaries, targeting items conveying aromas rated by children and adults as either pleasant (apple, strawberry/peach, apricot or vanilla) or unpleasant (fish, butyric cheeses, sulfurous cheeses/vegetables, and green vegetables). Eight odorants were retained for their dominant impact in the flavors of these selected foodstuffs (respectively, commercial mixtures imitating apple, strawberry, peach/apricot, or vanilla aromas; and the pure odorants trimethylamine, butyric acid, dimethyl disulfide (DMDS), and 2-isobutyl-3-methoxypyrazine). At ages 8 and 12 months, the infants' responses to these odorants were assessed in the lab, measuring their like/dislike responses (mouthing duration) toward bottles odorized accordingly versus control bottles. At 8 months, the infants' liking for the unpleasant odors of 2-isobutyl-3-methoxypyrazine or DMDS correlated positively with the gestational and/or lactational intake of the green veg or cheese conveying them. Infants of mothers who reported eating more fish during the breastfeeding period also tended to display higher liking of trimethylamine. But no further correlations were found between the infants' liking of the other pleasant or unpleasant odorants (at ages 8 and 12 months) and perinatal exposure to the foods bearing them. This study highlights how, in realistic conditions of odor exposure, perinatal exposure to given food odors can increase subsequent liking (or reduce subsequent disliking) for certain odors at least until age 8 months. The exposure effect was not systematic for all odorants and it did not generalize between odorants, suggesting that all flavorants are not equally palatable to weanling infants. This observation raises also issues about individually variable rates (i) of degradation of dietary odorants by maternal + placental + infant metabolisms, (ii) of placental + mammary transfer rates of odor/flavor agents, (iii) of variable solvent properties of AF versus milk for odor-active compounds, (iv) and/or of heterogeneous exposure effects during early phases of chemosensory ontogeny.

In sum, prenatal and perinatal exposure to given odorants can attenuate or reverse aversive reactions that are otherwise typical of nonexposed or lowly exposed individuals. The fact that, in realistic studies, exposure effects are mainly evidenced for aversive odorants suggests that they operate mainly in reducing neophobia or in attenuating intrinsic aversion of given flavors/odors. This was indeed found in mice and rats (Nolte and Mason, 1995; Kamenetzky et al., 2018), as well as in lambs and kids who display reduced aversion to aversive odorants experienced in utero (e.g., Schaal et al., 1995b; Simitzis et al., 2008; Hai et al., 2012, 2013, 2016). The frequency and amount of exposure to an odorant or flavorant necessary to reverse an initial aversion into an appetitive response is poorly understood, and may depend on its nature, developmental timing, and associated stimuli.

2.6.6 In utero odor exposure should induce selective response to the same odor in milk

Following up the previous prediction, newborns should be able to pick up an odor cue that is common to biological substrates experienced in different developmental niches. In other words, sensing an odorant in the AF should lead to a preference for this same odorant in the developmentally next matrix, i.e., colostrum/milk.

This idea was tested in neonatal rabbits born to dams fed either a standard diet or a diet added with cumin odor. On the day of birth, before any suckling, the pups were presented three glass rods dipped either into milk from a cumin-fed dam, milk from a standard-fed dam, or water (the control stimulus). The response criterion was searching and oral grasping of the glass rod. Pups exposed to either treatment were reactive to both milks relative to the control, but those exposed to cumin in utero grasped the rod conveying milk from cumin-eating dams more frequently than the one carrying milk from standard-diet dams, and conversely for the pups prenatally exposed to the standard diet (Coureaud et al., 2002).

In sum, exposure to a given odor in the amniotic context can lead to later positive response to that same odor in the milk context, apparently without distraction by the alteration of the context. This result emphasizes the functionality of a transnatal continuity in chemosensation despite the drastic changes in physical conditions in which chemostimuli are detected (aquatic vs. aerial) and in the nature of the matrices by which they are conveyed (AF vs. colostrum/milk).

2.6.7 Disruption of transnatal olfactory continuity affects neonatal behavior and physiology

If the hypothesis of neonatal perception of a chemosensory similarity between AF and colostrum/milk has adaptive value, its perturbation should provoke measurable behavioral and/or physiological consequences. The effects of experimental violations of the transnatal olfactory continuity have been assessed in different ways in various mammals.

A first study relied on newborn rats delivered 1 day before term. Their viability during the first postnatal hour is then strongly compromised when separated from the dam. Following the idea that separated pups' survival may depend on their odor atmosphere, Smotherman et al. (1987) compared survival in four groups of preterm pups isolated in warmed containers saturated with the odors of AF, DMDS (a compound from rat saliva considered as a predisposed chemosignal; Pedersen and Blass, 1981), mint (an unfamiliar stimulus), or no added odor as the control condition. After the 1-h post-birth separation challenge, the pup survival rate was 90% in the AF group, 80% in the DMDS group, and 75% in the control group, proportions which did not differ significantly. But the presence of mint odor-induced considerable mortality (50%) as compared with the AF condition. This contrasted effect of AF versus mint odors was interpreted as resulting from exposure to olfactory continuity (AF–AF) versus discontinuity (AF–mint) in the perinatal succession of environments: olfactory continuity favored indeed

adaptive responses leading to higher survival. AF and mint mediated differential effects on the pups: while familiar AF activated their general motor activity, novel mint odor depressed it. Thus, the olfactory alignment of the postnatal atmosphere with the prenatal “atmosphere” facilitates adaptive responses in rats born in atypical preterm conditions.

Observational evidence suggests that similar effects of transnatal chemosensory continuity may occur in human infants: when the AF odor impregnating the infant’s body is eliminated by immediately postnatal washing, newborn infants’ thermoregulation and movements leading to suck the breast are notably delayed (e.g., [Righard and Alade, 1990](#); [Sobel et al., 2011](#)). Otherwise, the odor of AF has the property to attenuate responses that are potentially costly in term, and even more in preterm, neonates, such as high arousal reactivity (motor hyperactivity or crying) elicited by separation- or pain-induced distress (e.g., [Varendi et al., 1998](#) [Akcan and Polat, 2016](#); [Alemdar and Özdemir, 2017](#); [Alemdar and Tüfekci, 2017](#)). Beyond exposing the newly born infant to AF odor, other maternal odor sources that convey common odorous biological substrates (such as maternal milk or skin secretions) can also optimize infant behavioral responsiveness and physiological adaptation (e.g., [Davidson et al., 2019](#); [Park and Im, 2020](#); [Akkoca et al., 2022](#)).

Consequences of perinatal odor continuity disruption were also studied in the context of the first feeds during which colostrum is taken in. This was shown in the European rabbit by cross-fostering pups born to dams exposed to contrasted diets during gestation ([Coureaud et al., 2002](#)). Immediately after delivery, litters were fostered by half under dams eating the same diet as their biological mother (forming the “continuous odor” group), the other half being given to females eating an olfactorily distinct diet (forming the “discontinuous odor” group). Both groups of pups were followed-up for suckling success and amount of milk ingested during the first 3 days (note that during the first 3 postnatal days rabbits suckle their offspring only once a day). The continuous odor group had higher sucking success at the first 2 nursing episodes than the discontinuous odor group. In addition, pups in the discontinuous odor group that succeeded in getting to nipples ingested less milk than the successful pups in the continuous odor group. Thus, when the olfactory properties of milk (or of the dam’s otherwise skin secretions?) are aligned with the olfactory experience acquired in utero the initial sucking performance is optimized.

A final example stems from a human study, where breast- and bottle-fed infants can be objectively considered as respectively exposed to relatively continuous (chemosensory AF-colostrum match) versus discontinuous (AF-formula mismatch) perinatal odor environments. Both groups of infants underwent testing where they were simultaneously exposed to their own AF odor and the odor of their familiar feed (either human colostrum/milk or formula) to examine their relative reactivity toward them ([Marlier et al., 1998b](#)). As already mentioned in the above Prediction 2, the breast-fed newborns responded equivalently to both perinatal odors on day 2, shifting into a clear preference for milk over AF on day 4. In the homologous test series pairing

their AF odor with their formula milk odor, bottle-fed infants differentiated them at 2 days of age, with a preference for AF odor; at the same test on day 4, these bottle-fed infants still preferred the AF odor over the formula odor. In other words, when facing both odorous matrixes experienced prenatally and postnatally, breastfed (“continuous”) infants developed a preference for the postnatal matrix in a short delay, while bottle-fed (“discontinuous”) infants did not follow that same pattern within the same delay, in that they remained attracted to the odor memorized in the prenatal environment (and vraisemblably reencountered in the postnatal environment right after birth).

The differential pattern of preference acquisition for the postnatal odor matrix between these two categories of infants may be explained by multiple, nonexclusive processes. *First*, exclusively bottle-fed infants experience an abrupt odor discontinuity between AF and formula, while breastfeedlings experience a very progressive discontinuity in the chemosensory properties of AF and colostrum, and then milk. This difference in the pace of transition between salient properties of perinatal olfactory environments may differentially affect the engagement of neonatal learning. *Secondly*, colostrum/milk may contain odorant factors that are inherently attractive to newborns, and which could accelerate the learning of cooccurring odor cues. Such chemosignals were evidenced in other mammals where they are potent in releasing attraction toward nipples and in engaging sucking (e.g., [Pedersen and Blass, 1981](#); [Hudson and Distel, 1983](#); [Schaal et al., 2003](#); [Schaal, 2010](#); [Schaal and Al Aïn, 2014](#)) and subsequent conditioning and very long-term memory (e.g., [Delaunay-El Allam et al., 2010](#)). *Thirdly*, apart from predisposed chemosignals, milk additionally carries particular bioactive substances that modulate neonatal biology (e.g., immunomodulation and gastrointestinal wellbeing: [Donnet-Hughes et al., 2000](#); [Siggers et al., 2013](#); hypoalgesia, nociception, motor accalmly: [Blass, 1990, 2015](#)), and increase their conditionability to cooccurring odor cues. Often more concentrated in colostrum than in milk, such bioactive compounds bearing sedative and/or promnesic effects comprise, among others, endorphins ([Zanardo et al., 2001](#)), β -casomorphins ([Brantl and Teschemacher, 1979](#); [Sakaguchi et al., 2006](#); [Jarmołowska et al., 2007](#)), colostrinin ([Popik et al., 1999](#); [Stewart and Banks, 2006](#)) and glutamic acid or glutamine ([Agostini et al., 2000](#)). Glutamate was indeed found to promote rapid flavor learning in adult organisms (e.g., [Ackroff and Sclafani, 2016](#)), as well as in perinatal organisms (e.g., [Guzman-Pino et al., 2019](#)). *Fourthly*, neonatal exposure to conspecific versus heterospecific (or artificial) milks may engage formative processes in neurological, endocrine, or metabolic systems in atypical directions. In that line, one may mention the fact that newborn rats fed a cow-based formula display altered terminal fields of the cranial nerve VII (involved in taste processing) in the first-order central taste relay ([Lasiter and Diaz, 1992](#); [Lomanowska and Melo, 2016](#)). Thus, being fed an evolutionarily expected (conspecific) versus nonexpected (heterospecific or artificial) milk may orient the development of neonatal brain structures involved in chemosensory processing.

2.6.8 Reverse transnatal chemosensory continuity: fetal responsiveness to milk

The direction of predictions might be reversed in examining fetal responses to chemostimuli from the postnatal niche. Mammalian fetuses have indeed sufficiently mature olfactory (and gustatory) structures to detect flavors and motor abilities to react to them (e.g., [Smotherman and Robinson, 1987](#); [Schaal, 2015](#)). Late-gestation fetuses should thus already be able to react to the chemosensory properties of the evolutionarily next-vital substrate: colostrum/milk. Such anticipatory responsiveness of fetuses to postnatal stimuli may in fact be highly adaptive as the timing of gestational term is heterogeneous as a function of materno-foetal or environmental conditions (e.g., [Barnett and Little, 1968](#); [Barreca and Schaller, 2020](#)). In humans, for example, the gestational age at delivery designated as “full-term” ranges indeed over a span of 41 days (from 37 weeks 0 days and 41 weeks 6 days; [Spong, 2013](#)). In shorter-gestation species, such as the mouse, the term of typical gestation length ranges over 2 days (19–20 days; [Barnett and Little, 1968](#)), and hours can then make a difference in the viability of early born neonates. Thus, mammalian fetuses should be ready to fully react to postnatal stimuli at least from the lowest limit of the full-term gestational window.

For obvious ethical reasons, experiments delivering postnatal stimuli to fetuses in utero could only be run with non-human models, e.g., in rat and ovine fetuses. The oral infusion of a minute amount of milk (in fact, bovine “light cream”) to rat fetuses provoked indeed heart-rate and behavior changes that resemble arousal change, as attested by body extension and active mouthing typically expressed by sucking newborns ([Smotherman and Robinson, 1992a,b,c](#); [Robinson and Smotherman, 1994](#)). Fetal infusion of milk also altered the fetal perioral tactile reactivity in terms of attenuation of the avoidance response (facial wiping) released by irritation ([Smotherman and Robinson, 1992b](#)). This milk-induced attenuation in fetal responsiveness to a noxious stimulus is reversible by naloxone, indicating opioidergic mediation in brain integration ([Robinson et al., 1993](#)). Thus, from late fetal stage, the oronasal perception of milk is functionally linked with appetitive processing mediated, at least in part, by opioidergic pathways. These milk-induced behavioral and physiological changes seem to be selective, as they were induced only by raw (bovine) milk, but not by sucrose, lactose, corn oil, or a cow milk-based formula designed for human newborns ([Smotherman and Robinson, 1994](#)). It may be noted however that, for practical reasons, these studies did not use rat milk which would have been the biological stimulus to consider ([Lomanowska and Melo, 2016](#)). Nevertheless, it suggests that mammalian milks convey common sensory and (bio)chemical features that can impinge on the fetuses of different species.

Experiments using homospecific and heterospecific milks conducted with fetal lambs revealed an even narrower selectivity of oral chemoreceptors than observed in rat fetuses. While ovine fetuses do not react to an oral infusion of mature bovine milk, they mouth and swallow actively after infusions of ovine colostrum or mature milk. Fetal lambs additionally discriminate ovine colostrum from mature ovine milk in that they reduce oral muscle activity to the oral administration of the former only ([Robinson et al., 1995](#)). The peculiar properties of conspecific colostrum that elicit

this selective response are unknown, but chemosensors detecting them are already functional before direct experience with them, suggesting that the amniotic-colostral chemosensory similarity functions in anticipation at least in ovine fetuses.

Such anticipatory response to colostrum in rat and ovine fetuses may be advantageously translated to the case of prematurely born human infants. As term-born human neonates increase mouthing in response to the odors of human milk (see above), such odors were credited to also favor the engagement of nonnutritive sucking in prematurely born infants who are often sucking-deprived because they need to be tube-fed. Several studies of tube-fed preterm infants confirm indeed increased nonnutritive sucking in response to the odors of pure human milk or of “fortified formula” odors delivered orthonasally (e.g., [Meza et al., 1998](#); [Bingham et al., 2003a, 2007](#); [Raimbault et al., 2006](#); [Yildiz et al., 2011](#); [Khodagholi et al., 2018](#); [Muelbert et al., 2021b](#); [Beker et al., 2019, 2021](#)). That the odor of a breastmilk-formula mixture (i.e., “fortified formula”) is more efficient than the odor of formula alone to elicit sucking in separate groups of premature infants (aged 29 and 30 gestational weeks, and tested on postnatal days 23 and 25, respectively) suggests that human milk carries singular chemosignals for premature infants ([Bingham et al., 2003a](#)). The feeding experience of tube-fed preterm infants being decoupled from oronasal chemostimulation, it implies that these infants are deprived, or significantly impoverished, of opportunities to sense their mother’s milk, to associate gastric filling with milkborne chemosensory information, and to monitor milk odor and flavor as cues to the reinforcing consequences of feeding.

Based on the logic of transnatal chemosensory continuity, one may expect that the positive effects of conspecific milk odor on the development of sucking in premature infants is degressive as a function of its chemical match with late-gestation AF. Fresh own mother’s colostrum is predictably most efficient, whereas (banked and often heated) human (i.e., not from own mother) mature milk is predictably least efficient, with intermediate potencies of human (not from own mother) colostrum, mother’s transitional milk, human transitional milk, and mother’s mature milk. Empirical elements accumulate in support of this ordering of the relative efficiency of human milk to affect infant behavior (e.g., [Heiman and Schanler, 2006](#); [Montjaux-Régis et al., 2011](#); [De Halleux et al., 2019](#); [Cakirli and Acikgoz, 2021](#)).

2.6.9 Transnatal chemoreceptive continuity in taste and oral chemesthesis

The experimental paradigms described above focus on olfaction by construction of postnatal testing that generally delivers only volatile fractions of biological substrates under the newborn’s nose. But in the normal course of events, in the fetus in utero as well as in the newborn sucking at the breast, nasal and oral chemoreceptors are costimulated. Thus, the above arguments on transnatal sensory continuity effects in nasal chemoreception may extend to oral chemoreception (gustatory and trigeminal sensations) for at least two reasons. First, the taste system is highly plastic in relation with the composition of the environment ([Hill, 2004](#)). Second, the main fluids (AF and colostrum/milk) that bathe the taste receptors pre- and postnatally are under the

common influence of the mother's environmental choices or constraints, and therefore might convey shared taste properties.

As repeatedly noted in human and nonhuman infants, early taste experience in the nursing context induces long-lasting impact on subsequent preferences. For example, as compared to newborns exposed to relatively neutral formulas, those exposed to formulas tasting bitter, sour or salty are more likely to later comply ingesting bitter-, sour-, or salt-tasting beverages or foods (e.g., [London et al., 1979](#); [Vijande et al., 1996](#); [Mennella and Beauchamp, 2002](#); [Smriga et al., 2002](#); [Mennella et al., 2004](#); reviewed in [Nehring et al., 2015](#)). Likewise, bitter or sweet compounds of the lactating mother's diet are transferred into milk (e.g., [Zhang et al., 2011](#); [Sylvetsky et al., 2015](#); [Anderson, 2018](#); [Rother et al., 2018](#); [Mastorakou et al., 2019](#)). In lactating sows, adding sucrose to the maternal diet increases the rate of lipids and lactose in milk ([Park et al., 2010](#)) and probably modifies its chemosensory properties. Otherwise, low-caloric sweeteners (acesulfame-K, sucralose) pass easily into breastmilk following intake of diet sodas, with varying kinetics between sweeteners and concentrations between individuals ([Rother et al., 2018](#)). In the same line, when ingested during pregnancy, most low-caloric sweeteners are instrumentally detectable in the cord blood and AF (e.g., [Halasa et al., 2021](#)). Intrauterine and lacteal exposures to such sweeteners have been related to biological consequences in terms of metabolic regulations, microbiota, body weight, and development of taste preferences (e.g., [Laforest-Lapointe et al., 2021](#); [Plows et al., 2022](#)). Such perinatal sweet exposure effects on sweet taste reception were found biologically plausible in the mouse, viz. pregnant-lactating dams ingesting acesulfame-K gave birth to offspring that, as adults, showed altered gustatory anatomy and increased preference for acesulfame-K and sucrose solutions ([Zhang et al., 2010, 2011](#)). Likewise, in pigs, maternal supplementation with umami tastant monosodium glutamate induced increased preference for MSG and sucrose, suggesting interactions between umami and sweet taste ([Guzman-Pino et al., 2019](#)). However, when pregnant or lactating sows were supplemented with sucrose their weanling offspring were less sensitive to sucrose than control animals, and displayed reduced appetite for it ([Figueroa et al., 2022](#)). In sum, the differed effects of early experience with different tastants in any animal model appear not so straightforward and need further investigation ([Nehring et al., 2015](#)).

In the same line, one may assume that irritants mediated by the trigeminal nerve, such as piperine or capsaicin globally, or mint in Arabic countries, would be more easily accepted in offspring of mothers who consumed such compounds during pregnancy and/or lactation (e.g., [Kurata and Nakamura, 1994](#)). For example, after lactating mothers' ingestion of a curry dish, piperine, and its derivatives collect in milk in low concentration ([N'Diaye et al., 2021](#)). So far, we have poor understanding of how neonates would respond to such spicing of breastmilk, but there is some evidence that they do (e.g., [Mennella et al., 1991a](#)). Even earlier in development, the effects of trans-placental transfer of dietary alkaloids or irritants, remains to be assessed, as well as their sensory effects on the fetus and neonate. Between culture differences and within-culture individual differences in spicy food consumption by mothers may well originate in such very early exposure to nontoxic irritants, a hypothesis that is not sufficiently considered in the development of flavor preferences (e.g., [Ludy and Mattes, 2012](#); [Spence, 2018](#); but see [Mennella, 1995](#); [Dunn and Sanchez, 2021](#)).

Beyond maternal dietary determinants of offspring taste preferences, the composition of the “milieu intérieur” created by maternal pathological conditions may also impinge on the taste propensities of offspring. This was found in a rat model mimicking the human physiological condition of gravidic vomiting in pregnant dams submitted to repeated diuretic treatment creating dehydration and mineral imbalance. This prenatal treatment resulted in an increased salt appetite in adult offspring caused by altered renal physiology (Nicolaidis et al., 1990). This phenomenon was later also well documented in human mothers afflicted with nausea/vomiting during the first trimesters of pregnancy, which provokes extracellular dehydration and increases salt appetite in the females but also in their progeny up to adulthood (Crystal and Bernstein, 1998; Leshem, 1998; see Nicolaidis, 2008).

2.6.10 Transnatal continuity in chemoreceptive aversion

Odor/flavor-mediated maternal effects were mostly studied in relation with the transmission of “positive” information to the progeny, actualized by their increased attention, attraction, or appetite toward stimuli encountered in earlier developmental niches. Various mechanisms may account for that gain in psychobiological meaning of initially neutral chemostimuli: familiarization by mere exposure or exposure repetition effects, associative conditioning through cooccurring reinforcing processes (opioid-inducing stimuli, pheromones) in AF or colostrum/milk, or more or less stable alterations of neural receptive abilities. But mothers might as well transmit “negative” chemosensory information inductive of aversion and withdrawal in the progeny. The first transmission mode of aversion resides in mothers avoiding toxic foods the odors/flavors of which will thus not be transmitted to the offspring who, in principle, will not ingest them because they will sense them as unfamiliar and, hence, unsafe (e.g., Villalba et al., 2018). When the mother is experimentally forced or deliberately chooses to ingest toxic flavors, then the progeny will develop reduced aversion to them (e.g., Nolte and Mason, 1995; Villalba et al., 2018; cf. also references in Section 2.7). A second transmission mode is aversion learning by progeny. Fetuses and neonates are indeed prone to acquire aversive olfactory responses by pairing an odorant with a noxious agent (Lithium chloride, LiCl) injected directly on them, resulting in aversive conditioning that remains active in later development (e.g., in the rat: Rudy and Cheattle, 1977; Stickrod et al., 1982). But when the same aversive treatment was applied to rat mothers in late-gestation (days 18–19) with garlic as the conditioned flavor, the weaned offspring displayed aversion to garlic, indicating that an aversive memory is transferrable to fetuses and retained up to 6 weeks post-birth (Gruest et al., 2004). This mother-to-offspring transmission of chemosensory aversion may be caused by the fetal sensing of the mother’s illness in presence of garlic, or by secondary pairing of the noxious effects of LiCl passed to the fetus in the same time as garlic. Additional mechanisms that could potentially induce perinatal learning of odors/flavors as aversive relate to altered blood flow in the uterine arteries, caused by either stress in the mother (e.g., Van de Bergh et al., 2005) or smoking (e.g., De Asis-Cruz et al., 2021) that reduce the oxygen supply to the brain which is known to cause stress in the fetus. Such adverse experience with brain oxygenation was found to operate in fetal

rats who stably acquire as aversive odors that follow a hypoxic episode (Hepper, 1991). Finally, parents' odor experience paired with electric shock inducing fear was shown to prompt their adult offspring of the next two generations to display a fear response when they were reexposed to that odor only (Dias and Ressler, 2014). These are just several ways by which parents can teach their fetal or neonatal offspring to circumvent given odors/flavors in their later life stages.

2.7 Transnatal chemosensory continuity: can it Be maladaptive?

Among the wide spectrum of odorants or tastants that can occur in the earliest niches of developing humans, the most studied are certainly ethanol and nicotine (along with caffeine, theobromine, theophylline, as well as other drugs of abuse), because of their immemorial anthropological prevalence and their potentially deleterious effects on neurological and psychobiological development. Although conveying dose-dependent toxicity and pharmacological drivers, these compounds support the transnatal chemosensory continuity hypothesis in providing some additional mechanistic insights.

The multiple and profound effects of prenatal and lactational exposure to ethanol have been reviewed in both animal and human literature (e.g., Molina et al., 1995, 1999; Spear and Molina, 2005; Chotro et al., 2007; Gaztagnaga et al., 2020; Miranda-Morales et al., 2020; Duko et al., 2022), highlighting that low-to-moderate doses of alcohol induce largely comparable effects in rodents and humans (Driscoll et al., 1990). Accordingly, some principles can be fleetingly summed up. Ethanol easily crosses the placental and mammary barriers to collect in fetal blood, AF and colostrum/milk, tainting these vital fluids with a common dominant chemostimulus. The occurrence of ethanol in the prenatal environment orients an initial sensitization of nasal and oral chemoreceptors (Eade et al., 2010) and primes motivational, associative, and reward neural circuitry to orchestrate later neonatal attraction behavior (e.g., Chotro and Arias, 2003; Youngentob and Glendinning, 2009). Ethanol reexposure through milk reinforces the psychobiological meaning of ethanol in neonates, stabilizing their attraction and appetite for ethanol odor/taste (Youngentob and Glendinning, 2009), and increasing the palatability of ethanol in later infancy, with lasting impacts still perceptible at adolescence and adulthood (e.g., Eade et al., 2009; Tang et al., 2018).

In the human case as well, ethanol ingested by pregnant mothers is rapidly transferred to the AF, with slow clearance resulting in ethanol concentration in AF exceeding that of mother's blood up to at least 3.5 h after ingestion (Brien et al., 1983). Ethanol concurrently passes into milk, its concentration peaking 30–60 min after intake, as attested by enzymatic assaying, by sensory analyses by an adult panel, and by 1-to-7 month-old infant sucking responses (Mennella and Beauchamp, 1991b; Mennella, 1997). Why ethanol-charged milk is more palatable than ethanol-free milk might be explained by multiple, nonexclusive grounds: inherent preference,

favor for a stronger flavor, favor for a novel flavor or earlier (in utero or *in lacto*) sensitization? The correlation between the magnitude of infants' hedonic/ingestive responses and the lactating mother's alcohol intake inclines toward several of these possibilities (Mennella, 1997; Anunziata et al., 2020). In any case, experience with ethanol in utero and/or *in lacto* induces sensory saliency of ethanol flavor and may create expectation-like responsiveness in the developing brain and related readiness to react positively in later developmental niches (e.g., Miranda-Morales et al., 2020). Ethanol odor can even generalize to noningestive contexts as, for example, ethanol-exposed infants interacting more with an ethanol-scented toy than with a vanilla-scented toy (Mennella and Beauchamp, 1998a).

Convergent phenomena emerge with tobacco smoke and nicotine, although underlying mechanisms may differ. Among the over 3000 volatiles constituting combusting tobacco is nicotine (along with other minor alkaloids), with its notable contribution to smoke odor and flavor, and its major impact on addictive pleasure (Mantella et al., 2013). Inhaled nicotine reaches the brain in 9–19 sec, and distributes rapidly into the adult human body (human simulation based on rabbit physiology; Benowitz, 1990). In a late-gestation primate, nicotine (and probably cooccurring chemosensory cues) passes the placenta easily after systemic injection, peaking on average 16 min after (range: 15–30 min) in fetal blood, and collecting there at higher concentration than in mother's blood for more than 2 h post-injection (Suzuki et al., 1974). Nicotine level in maternal circulation correlates highly with its level in AF (Luck et al., 1985), indicating its rapid transplacental transfer through fetal pulmonary and renal excretion or through the chorioamniotic membrane. Prenatal contact with nicotine alters chemosensory mechanisms at both neural and functional levels (in the rat fetus); these functional alterations being reinforced by reexposure to nicotine in milk (Mantella et al., 2013). Similar processes probably occur in humans. Nicotine and other combusting tobacco flavors are indeed transferred into milk (Luck and Nau, 1984) at levels that are sensible to adults (Mennella and Beauchamp, 1998b) and probably to nurslings. In the laboratory rat, experience with nicotine in utero induces a preference for ethanol odor in neonates and adolescents (Mantella et al., 2013). In the same line, in humans, multiple epidemiological studies suggest that gestational nicotine exposure contributes to nicotine consumption at adolescence and later (e.g., Kandel et al., 1994; Cornelius et al., 2000; Niaura et al., 2001; de Genna et al., 2021; reviewed in Abrous et al., 2004), and apparently more so in girls than in boys (Kandel et al., 1994).

To sum up, ethanol and/or nicotine (and accompanying flavorants) passed on to the progeny through maternal intake during pregnancy result in fetal chemosensory experience which canalizes chemosensory functionality, engenders acquired expectations in the developing brain, and mobilizes readiness to react positively to these cues in later developmental niches (e.g., Miranda-Morales et al., 2020). Mothers who drink and/or smoke during pregnancy are indeed likely to do so during the nursing period and beyond, exposing their offspring to additive experience with alcohol/tobacco cues in the nursing context and beyond, and increasing the chance that alcohol/tobacco cues become attractive or less aversive to them, increasing the chances that alcohol/tobacco use is initiated at early adolescence. *In utero* alcohol/nicotine exposure highlights well the operation of chemosensory mechanisms inducing liking and wanting

for similar experience in the next developmental niches. Transnatal chemosensory continuity of ethanol/nicotine exposure — along with neuro-pharmacological continuity — is well exemplified in sometimes extreme manifestations of neonatal withdrawal syndrome in case of discontinued perinatal exposure (e.g., Pierog et al., 1977; Robe et al., 1981; Pichini and Garcia-Algar, 2006).

The case of ethanol/nicotine emphasizes the extent to which: (i) flavorants taken in by the mother do rapidly access oral/nasal chemoreceptors of offspring, (ii) the fetus and neonate are receptive to such chemosensory exposures and integrate them at multiple levels of functioning, (iii) the fetus and neonate rely on these chemocues in their immediate or deferred developmental niches to direct their behavior, and (iv) later behavior driven by such early acquired cues can be beneficial or maladaptive. By their intrauterine containment, mammalian offspring are indeed entirely captive from the environmental choices or constraints faced primarily by their mother and secondarily their father and entire cultural group. Perinates react by opportunistic plasticity in structures and functions, which orient the early trajectory of chemosensory processing and later stimulus-seeking tendencies, in terms of greater sensitivity, higher preference, or lower aversion.

2.8 Closing comments

The empirical results summarized in this narrative review lend credit to the hypothesis of transnatal flavor continuity. The logic of developmental (chemo)sensory continuity contributes to interpretive unity of available observations in humans (e.g., Schaal et al., 2004; Dumont et al., 2018) and more generally in placental mammals (e.g., Smotherman and Robinson, 1995; Schaal et al., 2001; Robinson and Mendez-Gallardo, 2010; Mellor, 2019; Veit and Browning, 2021). This phenomenon is further generalizable to other vertebrate species, females of which compose the flavor of eggs and select the sensory ecology in which they incubate and hatch (e.g., fish: Dittman et al., 1996; Hou and Fuiman, 2020; amphibians: Crane et al., 2018; reptiles: Sneddon et al., 2001; birds: Aigueperse et al., 2013). Developmental continuity of chemosensing is further attested in various invertebrate species between life stages that are sometimes radically contrasting in anatomy, ethology, or ecology (e.g., Thorpe, 1939; Caubet et al., 1992; Gandolfi et al., 2003).

This general phenomenon of chemosensory continuity across developmental transitions of animals connects well with the framework of *developmental plasticity* or *programming*, whereby environmental and experiential inputs during early development translate genotypes into a range of variable phenotypes capable of reacting selectively to similar inputs at later life stages (e.g., West-Eberhard, 2003; Nettle and Bateson, 2015). Bateson et al. (2004) argued that the integration of cues in early development can operate as a kind of “weather forecast” for the next developmental niche. But the predictive span of this forecast is a matter of debate (Gluckman and Hanson, 2005; Wells, 2007). Do sensory cues acquired in utero or *in lacto* influence physiology and behavior only in the stage that is very next in development or over longer time

spans into childhood, adolescence and adulthood? Animal studies provide clear indications for very long-term influence of prenatal or perinatal chemosensory experience, the effects remaining empirically detectable up to adolescent and mature stages (e.g., [Blass, 1990](#); cf. references in [Section 2.7](#)). In humans, so far, evidence for remanent perinatal chemosensory experience over two, three, or more decades remains equivocal. For food flavors, experimental studies demonstrate prenatal or perinatal experience that are robust over months and years (e.g., [Mennella et al., 2001](#); [Delaunay-El Allam et al., 2010](#)), up to nearly a decade ([Hepper et al., 2013](#)), while quasi-experimental or epidemiological data suggest lifelong effects of perinatal or early postnatal experience (e.g., [Haller et al., 1999](#); [Kandel et al., 1994](#); [Cornelius et al., 2000](#); [Niaura et al., 2001](#); [Poncelet et al., 2010](#)). However, the adaptive consequences of prenatal and/or perinatal chemosensory experience are more evident in the context of transitions between consecutive stages of early development, i.e., birth to colostrum/milk intake, milk intake to weaning food, or suckling to early social diversification (e.g., [Müller-Schwarze and Müller-Schwarze, 1971](#); [Fillion and Blass, 1986](#); [Blais et al., 2006](#); [Szenczi et al., 2022](#)). Embryonic/fetal/neonatal exposure to a given chemosensory ecology will orient the development of chemosensing abilities, local chemical cues being recorded as familiar and thus operating as a base for “expectations” against which future novelty, and related aversion, is more easily surmountable. When the young organism grows into the next developmental stage, taking place in a more or less distinct sensory ecology, it will rely on this familiar odor thread to attend and approach a desired object or context among the wealth of novel ones, or to acquire it as safe (e.g., [Brake, 1981](#); [Johanson and Terry, 1988](#); [Sevi et al., 1999](#); [Kamenetzky et al., 2015](#); [Ifran et al., 2018, 2021](#)). A relative continuity of flavor cues across ecological transitions of development should satisfy these expectations, and confer a welfare and survival advantage to offspring.

The chemosensory continuity hypothesis provides heuristic guidance for future research on the earliest determinants of odor/flavor preferences. For example, one might additionally analyze the mechanisms by which chemostimuli prevailing in the prenatal and/or immediately postnatal environments are endowed with psychobiological meaning to young organisms. These stimuli may then be detected at lower thresholds, elicit more and more selective attention, and be processed faster than novel stimuli in terms of recognition, decision for choice and elicitation of selective responsiveness. The prediction pertaining to reduced threshold levels for the detection of odors encountered in utero has received some support (e.g., [Semke et al., 1995](#)). The alteration of structural and functional properties of nasal/oral chemosensory tracts by the pre/perinatal chemical ecology are partly corroborated as well (e.g., [Rangel and Leon, 1995](#); [Youngentob et al., 2007](#); [Hudson, 1999](#); [Todrank et al., 2010](#); [Zhang et al., 2010, 2011](#)). So far only documented in rodent models, such neurosensory plasticity might be difficult to substantiate in humans for obvious ethical reasons. However, brain imaging techniques have recently shown that human neonates react discriminatively to biological substrates, including colostrum or milk odors, components of which they may have encountered in utero ([Bartocci et al., 2000, 2001](#); [Aoyama et al., 2010](#)). Thus, if chemosensory continuity based on resembling flavorants occurring in AF, colostrum, or milk, and then on the body of conspecifics or in foods, it would be of interest to compare patterns of neonatal brain activation to such perinatal stimuli.

Finally, another important topic requiring further investigation in the context of the transnatal chemosensory continuity phenomenon is the welfare and survival advantage it affords to offspring. Does it just convey a short-term adaptive advantage in accommodating a bit of familiarity acquired in the prior developmental stage into the massive novelty associated with the next developmental stage or does it form “lasting impressions” (Blass, 1990) that orient offspring behavior over a lifetime? It may be recalled that the earliest transitions in mammalian development—birth, weaning, and adolescence—are characterized by high mortality. These developmental windows concentrate indeed all types of challenges and maladaptive responses to them and are costly for neonatal viability. **Primates** represent a well-documented case: specifically in humans, 27% of infants fail to survive their first year and 47% of children fail to survive to puberty in hunter-gatherer and historical societies (Volk and Atkinson, 2013). The causes of such high mortality rates are not known precisely, but the first steps in infant-mother adjustment may bear great momentum. The ability to initiate sucking is indeed variable among human mother-infant dyads, leading to delays in establishing optimal colostrum/milk transfer in some infants (e.g., Dewey et al., 2003). Other mammalian species follow the same trend. For example, rats, mice, and piglets incur high mortality, especially when colostrum intake is lacking or insufficient (Andersen et al., 2007). Thus, mammalian mother-infant dyads are exposed to strong selective pressure in the first postnatal days and weeks, and any sensory, behavioral, or cognitive means in females or newborns that can speed up neonatal colostrum/milk ingestion is beneficial. Similar reasoning can be made for weaning or adolescence, when perinatal memory traces of flavors acquired in the maternal context can orient an individual’s choices in the uncertain diversification of both alimentary and social domains. Finally, beyond the perinatal period, the developmental chemosensory continuity may be usefully translated into practise for managing the odor and flavor ecology of individuals while they go through sensitive transition periods in their lifetime (e.g., premature birth, periods of parent-infant separation, periods of solitude, adaptation to new physical or social settings).

Nevertheless, even if the model of transnatal chemosensory continuity does usefully summarize a large set of data, attention may be drawn to results that do not fit with it², leading to new hypotheses. Although the assumed chemosensory and/or motivational resemblance between both AF and colostrum/milk illuminates the majority of current data, future finer-grained studies may complexify our understanding of

² Possible exceptions are interesting to scrutinize. In certain cases, neonate organisms were found to distinguish AF and milk odors. For example, suckling-naïve rats orally grasp a nipple coated with AF or milk, but milk is grasped with shorter latency than AF, suggesting olfactory discrimination (Koffmann et al., 1998). But, the milk stimulus delivered derives from bovine milk. Thus, although it is of interest that heterospecific milk is appetitive to newly born rats, future studies should consider using the more ecological rat milk. Another study found that human newborns exposed to AF odor cry less than those exposed to the mother’s “breast odor” suggesting discrimination between AF odor and “breast odor” (Varendi et al., 1998). But the “breast odor” was here only nominal as it excluded colostrum/milk, and was probably contaminated with axillary sweat known to convey intense odor cues after stress (Atzmüller and Grammer, 2002). These infants may thus have sensed this “breast odor” as novel or aversive, and intensified their crying accordingly.

underlying mechanisms. One cannot exclude that significant chemosensory stimuli can elicit diverse reactions regulated by heterogeneous controls and which tap differentially into discrimination processes. For example, [Craig \(1918\)](#) dissociated appetitive from consummatory behaviors, the former operating before the desired object is incorporated, while the latter takes place after. Neonatal body or head orientation is a manifestation of appetitive mechanisms (sensation seeking, attention and recognition memory), whereas orofacial responses are seen as reflecting the stimulus-bound operation of a selective hedonic monitor tied to ingestion ([Soussignan et al., 1999](#); [Steiner et al., 2001](#)). Thus, preferential responsiveness derived from a paradigm assessing appetitive behavior may not necessarily predict the result of a paradigm tapping into consummatory (ingestive) processes (e.g., [Berridge, 2000](#)). Hence, it is expectable that newborn organisms in the same time move nondifferentially to certain stimuli and display discriminative oral behavior to the same stimuli.

Even though the hypothesis of developmental chemosensory continuity accounts reasonably for most of available empirical results in the handful of species studied so far, it nevertheless represents only one possible mechanism. Other mechanisms certainly operate to complement the mammalian newborns' use of the chemosensory match between the pre- and postnatal environments in their initial selective decisions. In various species, the transnatal chemoecological continuity is created by different, graded means ranging from: (1) passive, physiological creation of an overlap in the odors/flavors transferred to AF, colostrum/milk, and other secretions from maternal environment, (2) active behavior (of mother or newborn) leading to distribute familiar stimuli (e.g., prenatal fluids or a flavor that has dominated prenatally) into the postnatal environment, to (3) being exposed to the same rewards in both perinatal environments so that they become equally reinforcing without necessarily being chemosensorily similar (e.g., [Robinson and Mendez-Gallardo, 2010](#)). Finally, (4) specialized chemosignals may be available *de novo* in the postnatal niche, through colostrum/milk or other secreted matrices (saliva), wherein they can constitute unconditional stimuli boosting the learning of novel stimuli (e.g., [Galef et al., 1988](#); [Schaal and Al Aïn, 2014](#)). All these mechanisms (and probably others) work in unison, creating a chemosensory chain linking odors/flavors in the amniotic niche that match to odors/flavors in the succession of postamniotic niches. They provide the newborn organism with redundant information that ends in locating the mammae, ingesting colostrum/milk or accepting a situation without rejecting them because they are unfamiliar, and thus aversive. More generally, the novelty of any postnatal unusual situation loses its inhibitory character when replaced in the context of its functional connection (or disconnection) with the earlier odor/flavor experiences.

Acknowledgments

This chapter is dedicated to the memory of Adrien Moessinger, professor of pediatrics in Lausanne, colleague, mentor and friend, who pioneered work on the chemical and flavor ecology of fetuses and prematurely born infants. During the writing of this chapter, the author acknowledges the financial support of the French National Research Agency (ANR ANR-15-CE21-0009-01, project Milkodor), the Regional Council of Bourgogne-Franche-Comté (project EarIEat), and the European Union (Feder Fund).

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Preface

Flavor: From Food to Behaviors, Wellbeing and Health, Second Edition is an actualization of the previous one.

The first edition published in 2016 was edited by Patrick Etiévant, Elisabeth Guichard, Christian Salles and Andrée Voilley. Patrick Etiévant and Andrée Voilley are now retired and did not want to participate to this new edition. However, Elisabeth Guichard and Christian Salles, the co-editors of this second edition, want to thank Patrick Etiévant and Andrée Voilley, who have been pioneers in the field of flavor science, for the great job they conducted for the first edition and previously for the edition of the book entitled *Flavour in Food* published in 2006.

This second edition has the ambition to describe and summarize the recent progress made in the field of flavors already covered, but also to develop recent knowledge acquired in other fields not covered in the first edition. It brings together multidisciplinary fields such as chemistry and biochemistry, psychology and neurobiology, economy and sociology, to explain, in a narrative structure, how flavor compounds may modulate food intake and behavior. However, as some authors did not want to participate to this second edition, the editors decided to invite other authors to cover emerging specific scientific topics in complement to the previous ones.

The book is organized in order to present a logical story—starting with food and the formation of a food bolus, and moving on to explain how flavor compounds reach their specific receptors, generate nervous signals sent to our brain, and how the stimulation of peripheral and more central targets in the brain contributes to the emergence of a sensory image and memory interacting with the regulation of food intake and food behavior. As far as possible, the mechanisms underlying these interactions are described.

In the first part dedicated to flavor release in humans, the reader will find how flavor compounds are released from food in a physiological environment—during mastication and digestion, but also during gestation and lactation, including the metabolization of flavor compounds.

Part two analyzes the mechanisms of flavor perception from molecule to receptor and brain integration. Chapters include the most recent data published on the nervous peripheral perception of aroma and sapid compounds, providing insight into the different nervous signals that are generated and processed at different levels in the brain. Then specific chapters focus on the multimodal interactions occurring with other internal and external signals to produce a holistic sensory image of a product in the brain, memorized for further behavior.

The third part on flavor perception, preferences, and food intake covers the impact of sensory perception and characteristics on food intake, at different ages. Chapters explore topics such as the possible influence of learning and familiarity on perception and the short- and long-term impact of sensory perception on satiety.

Finally, part four considers flavor perception and physiological status. It highlights the role of contrasted physiological situations on taste and flavor perception and appreciation, including the consequences of common pathologies and the impact of oral microbiota.

We want to thank the authors of the different chapters for their fantastic job and for the constructive exchanges we had to adjust their different inputs, thus avoiding redundancies. We learned a lot reading their manuscripts, discovering recent knowledge and understanding better complex theories. We are confident that you will also on your turn appreciate the reading of this book.

The editors
Elisabeth Guichard
Christian Salles

In-mouth metabolism of flavor compounds

3

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3.1 Introduction

During food intake, the organoleptic perception experience is an important driver of food acceptability and consumption. Flavor perception plays a key role in this organoleptic experience. It is a multimodal perception corresponding to the functional integration of information from the chemical senses: olfaction, gustation, and nasal and oral somatosensory inputs. Flavor allows the organism to evaluate food quality by providing information on the chemical composition of food. However, chemical compounds that reach the chemoreceptors can be impacted by perireceptor events occurring at the olfactory level (Heydel et al., 2017) but also at the oral level (Canon et al., 2018; Muñoz-González et al., 2018). In particular, saliva contains many enzymes that can potentially metabolize flavor compounds as a function of their chemical structure (Chauncey, 1961; Schwartz et al., 2020b). Recent studies have revealed the role of the oral metabolism of flavor compounds on flavor molecules and perception (Muñoz-González et al., 2018). This topic of research is of interest in flavor science because salivary impairments that appear with age or are associated with some pathologies could impact on food enjoyment and intake leading to malnutrition (Muñoz-González et al., 2019).

The metabolization of flavor compounds in the mouth was first reported by Hussein et al. (1983). After rinsing the mouth with aroma solutions, a decrease in aroma compound concentration was observed, concomitant with the appearance of the corresponding metabolites. Later, Buettner showed that incubation of saliva with flavor molecules decreased the release of esters, aldehydes, and thiols, suggesting that salivary enzymes handle flavor compounds (Buettner, 2002a,b). More recently, the metabolization of carbonyl compounds by saliva has been reported by Muñoz-González et al. (2018, 2019) and was found to be stimulated by NADH, which strongly supports the involvement of NAD(P)H-dependent oxidoreductases. In agreement with these findings, oxidoreduction of carbonyl compounds was also observed in the presence of an oral mucosa model (Muñoz-González et al., 2022; Ployon et al., 2020). Taken together, these studies suggest the involvement of xenobiotic-metabolizing enzymes (XMEs) in the metabolization of flavor molecules. Recently, a systematic exploration of proteomes has highlighted several XMEs potentially

involved in the metabolism of aroma molecules, shedding light on potential enzymatic targets to study (Schwartz et al., 2021b). This metabolization may affect both the quantity (decrease of the initial molecule) and the quality (formation of new molecules that may be odorant) of flavor compounds reaching the olfactory receptors. From a sensory perspective, it was shown that metabolic activity in the nasal and oral cavities impacts perception (Ijichi et al., 2019; Robert-Hazotte et al., 2019) and aroma persistence (Muñoz-González et al., 2022). Beside human metabolism, several recent studies explored the influence of the oral microbiota on taste perception (Besnard et al., 2018; Cattaneo et al., 2019; Gardner et al., 2020). With regard to food aroma, some specific microorganisms of the oral flora are able to generate fragrant molecules in the mouth, thus participating in the perception of food flavors (Parker et al., 2020; Starkenmann et al., 2008). These results suggest that both human oral metabolism and microbial oral metabolism are of importance in the modulation of flavor perception.

This chapter summarizes the current knowledge on the molecular mechanisms underlying the flavor compounds metabolization in the mouth. After presenting the different reactions observed on flavor compounds in presence of saliva or oral mucosa, we introduce their impact on sensory perception. In the last part, we discuss the factors that influence the oral metabolism, e.g., the salivary antioxidant capacity.

3.2 In-mouth metabolism of flavor compounds

The presence of saliva or oral mucosa cells has been demonstrated to affect the release of several classes of aroma compounds, namely aldehydes, ketones, esters, and thiols, while some compounds remain unaffected by saliva (e.g., alcohols and pyrazines). A pioneering study using gas chromatography–mass spectrometry (GC–MS), which was conducted by Buettner in 2002, demonstrated the decrease of release of these compounds within minutes of incubation with fresh saliva, with inter-individual differences between saliva coming from different individuals (Buettner, 2002a,b). These results were later confirmed and deepened by other studies (Muñoz-González et al., 2018, 2019; Ployon et al., 2020). Interestingly, incubation of these compounds with saliva not only decreases the quantity of flavor compounds but also leads to the formation of new compounds belonging to different chemical families and having sensory properties differing from those of precursor compounds, in particular reduced detection thresholds. These compounds are presented in Table 3.1.

3.2.1 Aldehydes

Disappearance of aldehydes following saliva incubation was correlated with the appearance of their corresponding alcohols, suggesting their reduction by salivary enzymes (Buettner, 2002a). This effect was observed for short chain aliphatic aldehydes (hexanal, methional, octanal) and aromatic aldehydes (phenylacetaldehyde) in the presence of saliva (Ijichi et al., 2019; Muñoz-González et al., 2018,

Table 3.1 Flavor compounds or precursors significantly affected by the presence of saliva or oral mucosa, detected metabolites, and metabolic reactions involved.

Chemical family	Compound	Flavor properties	DT (mg/kg)	Detected metabolite	DT (mg/kg)	Reactions	References
Aldehydes	Hexanal	Grassy	0.0075	Hexanol	0.7	Reduction	(Buettner, 2002a; Ijichi et al., 2019; Muñoz-González et al., 2018) (Buettner, 2002a)
	Methional	Cooked potato	0.00004	Methionol	0.0002		
	Phenylacetaldehyde	Honey-like	0.009	Phenylethanol	0.045		(Buettner, 2002a)
	Benzaldehyde	Fruity	0.3	Benzyl alcohol	5.5		(Muñoz-González et al., 2018)
	Octanal	Green grassy	0.0007	octanol ^a	0.054		(Buettner, 2002a; Muñoz-González et al., 2018)
	Octenal	Fatty	0.003	2-octen-1-ol	0.04		(Muñoz-González et al., 2018)
				1-octanol	0.054		(Muñoz-González et al., 2018)
	Nonanal Decanal	Citrus-like Citrus-like, soapy	0.0035	nd nd		nd nd	(Buettner, 2002a) (Buettner, 2002a)
	Trans-2-hexen-1-al	Green	0.04	Hexenoic acid		Oxidation	(Ployon et al., 2020)

Continued

Table 3.1 Continued

Chemical family	Compound	Flavor properties	DT (mg/kg)	Detected metabolite	DT (mg/kg)	Reactions	References
Ketones	Pentan-2,3-dione	Toasted	0.005	2-hydroxy-pentan-3-one		Oxidation/ reduction	(Muñoz-González et al., 2018; Ployon et al., 2020)
				3-hydroxy-pentan-2-one			(Muñoz-González et al., 2018; Ployon et al., 2020)
	Butane-2,3-dione	Buttery	0.0023	3-hydroxy-butan-2-one	0.8		(Muñoz-González et al., 2018)
	1-octen-3-one	Earthy	0.000007	3-octanone	1		(Muñoz-González et al., 2018)
Esters				1-octen-3-ol	0.007	Ester hydrolysis	(Muñoz-González et al., 2018)
	Nonan-2-one	Cheesy	0.05	Nonan-2-ol	0.28		(Ployon et al., 2020)
	Decan-2-one	Fermented	0.009	Decan-2-ol	0.33		(Ployon et al., 2020)
	Ethyl butanoate	Fruity	0.001	nd			(Buettner, 2002b; Perez-Jimenez et al., 2019)
	Ethyl pentanoate	Fruity	0.094	nd			(Perez-Jimenez et al., 2019)
	Ethyl hexanoate	Fruity	0.008	Hexanoic acid ^b	0.2		(Buettner, 2002b; Perez-Jimenez et al., 2019; Ployon et al., 2020)
	Ethyl octanoate	Waxy	0.02	Octanoic acid ^b	0.5		(Buettner, 2002b; Perez-Jimenez et al., 2019)
	Ethyl decanoate	Waxy	0.02	Decanoic acid ^b	0.7		(Perez-Jimenez et al., 2019)
	Isoamyl acetate	Fruity	0.005	nd			(Perez-Jimenez et al., 2019)
	Benzyl acetate	Fruity	0.002	Benzyl alcohol	5.5		(Ijichi et al., 2019)

Thiols	Phenylethanethiol	Sulfurous		nd		Oxidation, conjugation	(Buettner, 2002b)
	3-mercapto-3-methyl-1-butanol	Catty	0.0013	nd		nd	(Buettner, 2002b)
	2-furfurylthiol	Meatlike	0.00004	Furfuryl methyl sulfide	0.00004	Methyl-conjugation	(Buettner, 2002b; Ijichi et al., 2019)
	Guaiacol	No flavor		Guaiacol	0.00075	Glycosidic bond hydrolysis	(Mayr et al., 2014) ^c
	primeveraside						
	m-cresol glucoside	no flavor		m-cresol	0.085		(Mayr et al., 2014) ^c
	Syringol glucoside	No flavor		Syringol	0.4		(Mayr et al., 2014) ^c
	Syringol gentiobioside	No flavor		Syringol	0.4		(Mayr et al., 2014) ^c
	Guaiacol glucoside	Smoky	0.07	Guaiacol	0.00075		(Parker et al., 2020) ^c
	Geranyl glucoside	Floral	1.6	Geraniol	0.004		(Parker et al., 2020) ^c
Glycoconjugates	Cyanidin 3-sambubioside	No flavor		Cyanidin 3-sambubioside glucuronide		Glucuronide conjugation	(Mallery et al., 2011)
	S-(R/S)-3-(1-hexanol)-L-cysteine	No flavor		(R/S)-3-sulfanylhexas-1-ol	0.000017	Cys-conjugate lyase	(Starkenmann et al., 2008) ^c
	S-(1-propyl)-L-cysteine	No flavor		1-propanethiol	0.00006		
	S-((R/S)-2-heptyl)-L-cysteine	No flavor		2-heptanethiol	0.003		

DT, detection threshold in water; nd, not determined.

^aFormation of metabolites improved by adding cofactor NADH.

^bMetabolites not formed in presence of an esterase inhibitor.

^cEvidences for microbial enzymes involved.

Detection threshold were extracted from Gemert, L.J., 2003. Flavour Thresholds : Compilations of Flavour Threshold Values in Water and Other Media. Utrecht, The Netherlands: Oliemans Punter. Descriptors of flavor properties were retrieved from the Good Scent Company database (<http://www.thegoodscentcompany.com>).

Muñoz-González et al., 2019). Two aldehydes with longer aliphatic chains (nonanal and decanal) were also investigated (Buettner, 2002a). However, the decreases in the levels of these aldehydes were not associated with the appearance of metabolites in the condition of measurements. This suggests that the metabolites were not detected and/or hydrophobic interactions with salivary proteins such as mucins can also occur and impact aroma release (Pages-Helary et al., 2014). Another reported case concerns trans-2-hexen-1-al. The oxidation of this compound to hexenoic acid was noted by Ployon et al. (2020) in the presence of a model of oral mucosa. More globally, Muñoz-González et al., 2018 demonstrated that metabolization phenomena were correlated with salivary protein concentration and salivary antioxidant potential. Furthermore, in this study, the addition of NADH cofactor increased the reduction of octanal to octanol by saliva. This observation strongly suggests the involvement of NAD(P)H-dependent enzyme systems. Saliva contains various oxidoreductases that could be involved in this metabolization, for example, human salivary aldehyde dehydrogenase (Giebultowicz et al., 2009).

3.2.2 Ketones

For ketones, reduction reactions were observed in the presence of saliva (Muñoz-González et al., 2018) and oral mucosa (Ployon et al., 2020). Diketones such as butan-2,3-dione and pentan-2,3-dione were reduced to the corresponding metabolites bearing one hydroxyl function (Table 3.1). The particular case of pentan-2,3-dione is interesting. This compound is metabolized into two possible products, 2-hydroxy-pentan-3-one and 3-hydroxy-pentan-2-one, and this mechanism echoes a previous similar observation (Zaccone et al., 2015). In this case, metabolic activity was observed in the presence of human bronchial/tracheal epithelial cells and was attributed to an enzyme: the dicarbonyl and xylulose reductase (DCXR) (Zaccone et al., 2015). Other candidates among salivary enzymes could exhibit these specific activities as aldo-ketoreductases or carbonyl reductases (Muñoz-González et al., 2018).

3.2.3 Esters

Buettner demonstrated the disappearance of ethyl butanoate, ethyl hexanoate, and ethyl octanoate after incubation with fresh saliva and the correlated production of the corresponding carboxylic acids (Buettner, 2002b). Additionally, it was shown that the concentration of total esters in wine headspace decreased in the presence of human saliva, suggesting that saliva contains esterases active toward flavor esters (Genovese et al., 2009). This effect was determined to be more pronounced with white wine than with red wine; thus, the authors suggested that the presence of tannins in red wine, which also trigger the trigeminal astringency sensation (Canon et al., 2021), can explain this difference due to their ability to interact with (Canon et al., 2010) and aggregate proteins (Canon et al., 2013), and inhibit enzymatic activity. In 2019, Perez-Jimenez showed the degradation of a series of esters by the enzymatic action of fresh saliva (Perez-Jimenez et al., 2019). A metabolizing effect, coinciding with

the appearance of the corresponding carboxylic acids, was shown for ethyl hexanoate, ethyl octanoate, and ethyl decanoate. This effect was inhibited in the presence of CaCl_2 , an esterase inhibitor, supporting their role in ester metabolization. Another study reported the metabolism of benzyl acetate to benzyl alcohol in the presence of saliva and nasal mucus (Ijichi et al., 2019). The conversion of ethyl hexanoate to hexanoic acid was also shown in the presence of an oral mucosa model (Ployon et al., 2020). Different human esterases could be involved in these metabolic phenomena (carboxyl esterases, paraoxonases, carbonic anhydrases) as well as esterases from the oral microbiota.

3.2.4 Thiols

Concerning thiol-type aroma molecules, a prior study has shown their decrease in the presence of saliva (Buettner, 2002b). One should have in mind that thiols have particularly low detection thresholds and thus have a strong contribution to perception. Various oxidoreductases present in saliva can potentially oxidize thiols (Schwartz et al., 2020b). In addition, it has been suggested that salivary peroxidases may also be involved (lactoperoxidase and myeloperoxidase) (Buettner, 2002b). Sulfur-containing aroma molecules, such as disulfide compounds, could be substrates for thiol-transferases, such as glutaredoxin or glutathione transferase omega (Board et al., 2000; Schwartz et al., 2020a). In a recent study, the in-mouth metabolization of 2-furfuryl thiol to furfuryl methyl sulfide was reported (Ijichi et al., 2019). This reaction could result from the activity of a methyltransferase (e.g., TPMT, which is known to be active on various thiols) as suggested by Ijichi and coworkers in the same study.

3.3 In-mouth generation of flavor compounds by biotransformation of their precursors

Two other classes of compounds have been reported as metabolized in-mouth: cysteine conjugates and glycoside conjugates. For these two classes of compounds, the precursors are not sensorially active per se. However, the compounds formed after metabolization in the mouth are sensorially active. The enzymes that are expected to catalyze these reactions are glycosidases and cysteine-thiol lyases, that are typical of some bacteria present in the oral cavity and recently reviewed (Schwartz et al., 2021a).

3.3.1 Glycoconjugates

Glycoside conjugates constitute a class of compounds commonly found in various plant-derived foods and exposed to metabolization by microbial salivary enzymes. This metabolization generally involves the hydrolysis of the sugar group by glycosidases. Glycosylated phenols or polyphenols, such as flavonoids and anthocyanins can be hydrolyzed to aglycones that have sensory properties (Walle et al., 2005).

These properties are observed for the phenol glycosides present in certain wines with a smoky taste produced from berries harvested near burnt forests (Mayr et al., 2014). Metabolization by glycosidases releases free phenols (guaiacol, cresol, and syringol), which have “smoky”-type sensory properties. Other enzymatic products with odorant properties resulting from the deglycosylation of their precursors have been identified, such as terpenes, benzene derivatives, and alcohols (Muñoz-González et al., 2015). In saliva, a bacterial origin of glycosidase activity has been suggested, although it is significant only after several days of reaction (Muñoz-González et al., 2015). The existence of human glycosidase activity in saliva (Stradwick et al., 2017) and the oral epithelium (Mallery et al., 2011; Walle et al., 2005) should also be further investigated. This activity is believed to come from human beta-glucosidase (encoded by GBA3), which is present in the mouth (Ghosh et al., 2012) and is known to participate in the *in vivo* metabolism of certain glycosylated derivatives (Nemeth et al., 2003).

3.3.2 Cysteine conjugates

Cysteine conjugates are compounds typically found in garlic and onion but also in some white wines, such as Sauvignon Blanc (Tominaga et al., 1998). The metabolism of cysteine conjugates leads to the production of compounds with a free thiol function, which are therefore very fragrant (Starkenmann et al., 2008). In the latter study, a contribution of the oral microbiota to this metabolization was demonstrated, notably by the enzymatic action of the anaerobic bacterium *Fusobacterium nucleatum*. The formation of sulfur compounds after metabolization in the presence of saliva was also shown in cabbage extracts (Frank et al., 2018). The enzymes responsible for this activity are probably cysteine-conjugate beta lyase (CCBL) enzymes capable of catalyzing the dissociation of the C-S bond between the C $_{\beta}$ and S $_{\gamma}$ atoms of cysteine, thereby generating free thiols and pyruvate as coproducts. CCBLs catalyze the beta-elimination of cysteine conjugates having an electrophilic group on the sulfur atom, utilizing the pyridoxal phosphate cofactor converted to pyridoxamine phosphate for catalysis (Cooper and Pinto, 2006). CCBLs are typical of some anaerobes of the oral cavity such as *Fusobacterium nucleatum* (Basic et al., 2017) but could also be of human origin. Indeed, the presence of human transaminases has been identified in saliva (Sivadasan et al., 2015), and these enzymes also exhibit cysteine-thiol lyase activity (Cooper and Pinto, 2006).

3.4 Oral metabolism and links with perception

While early experiments on the metabolism of flavor molecules were conducted using saliva samples or oral mucosa models, a few recent *ex vivo* studies have confirmed that these reactions also take place in the oral cavity.

In 2019, Ijichi et al. showed that the metabolic activity of flavor compounds in the oral and nasal cavities impacted their perception in individuals. In the oral sphere, these reactions were detected on saliva samples but also in a cohort of individuals

by PTR-MS approach. Among the molecules metabolized in the mouth, 2-furfuryl-thiol was methylated to furfuryl methyl sulfide and hexanal was reduced to hexanol. Interestingly in this study, the concentrations of metabolites measured were above the known perception thresholds of the molecules involved, suggesting that the perceived flavor in this case corresponds to the sum of the flavor molecules and their metabolites. In addition, inter-individual differences in metabolism were detected among the participants of the study, suggesting that the oral metabolism is subject to inter-individual variation.

A second very recent study explored the mechanisms of aroma persistence and highlighted two factors influencing it (Muñoz-González et al., 2022). Some compounds are essentially subject to retention by the mucosal pellicle, a thin layer of protein anchored to the surface of the oral epithelium. These molecules, such as linalool or 2-nonanone, interact via hydrophobic effects with the mucosal pellicle. The second factor concerns the metabolism of certain flavor compounds. Indeed, Muñoz-González et al. (2022) showed that some compounds such as hexan-2,3-dione and octanal are subject to metabolism by an oral mucosal model as well as incubation with saliva. Furthermore, in this same study, these reactions were also detected in a cohort of individuals by a PTR-MS approach. Interestingly, the compounds subject to metabolism showed a reduced aromatic persistence, which was significantly perceived compared to molecules such as linalool or 2-nonanone, which are not metabolized orally. These results suggest that the metabolism of flavor compounds influences aroma persistence.

A third study explored the mechanism of flavor generation in-mouth formed upon hydrolysis of geranyl glucoside and guaiacyl glucoside, two glycoside precursors notably found in wine (Parker et al., 2020). Parker et al. demonstrated that these precursors were hydrolyzed to odorant aglycone compounds in mouth due to the activity of oral microbiota. In particular, a range of sensory phenotypes was observed and using sensory analysis and metagenomic screening, it was found to be related to the retronasal detection thresholds but not to the microbial communities present in mouth, although these are responsible for the hydrolysis of glucosides in saliva (Parker et al., 2020).

These results suggest that the oral metabolism involving human enzymes as well as oral microbiota could be an important factor influencing flavor perception and more work is needed to improve our knowledge of all these mechanisms.

3.5 Modulation of flavor perception by the salivary antioxidant capacity

Among the numerous factors that can modulate oral metabolism, the salivary total antioxidant capacity (TAC) appears as one of the most important. Salivary TAC is defined as the sum of the molecular entities that aim at limiting generation of reactive oxygen species in saliva. It comprises various molecules including antioxidant compounds as well as enzymes that maintain the salivary redox (Schwartz et al., 2020b). Several

studies have explored the role of salivary antioxidant capacity on flavor perception. As presented above, flavor molecules are subject to oral and nasal metabolism, and these reactions affect both the quality and the quantity of flavor compounds reaching the chemosensory receptors. Previous works have suggested that these reactions may be modulated by salivary TAC (Muñoz-González et al., 2018; Piombino et al., 2014). Additionally, all the enzyme activities depending on a redox cofactor will be regulated by the concentration of this latter one. In addition to the aroma release, the taste perception is also modulated by the TAC. Indeed, a positive correlation between salivary TAC and patients' taste disorder was shown (Zhu et al., 2021). Increased TAC was associated with increased catalase and superoxide dismutase activities (Walliczek-Dworschak et al., 2017). As recently demonstrated, nasal and oral metabolism of aroma compounds impact aroma perception (Heydel et al., 2019; Ijichi et al., 2019). Several studies have explored the impact of salivary TAC on the perception and release of aroma compounds in addition to the role in fatty acid perception.

3.5.1 Modulation of the aroma release

Studies carried out on both normal subjects (Muñoz-González et al., 2018) and on specific populations including obese (Piombino et al., 2014), elderly (Muñoz-González et al., 2021), or the elderly suffering from hyposalivation (Muñoz-González et al., 2019) have observed a negative correlation between salivary TAC and aroma release in the presence of the subjects' saliva. This effect was dependent on the structure of the aroma compounds and related to the chemical reactivity of the molecules. The studied alcohols were not metabolized while some ketones and aldehydes were strongly affected (Muñoz-González et al., 2018). To explain this, Muñoz et al. suggested that the decreased release of specific aroma compounds results from their metabolism by salivary xenobiotic-metabolizing enzymes (XMEs). XMEs are involved in the clearance and neutralization of xenobiotics, including aroma compounds. This effect is achieved through two enzymatic steps involving different classes of XMEs. Phase I enzymes catalyze the biotransformation of compounds into less reactive metabolites. Phase II enzymes promote the biotransformation of compounds that are naturally functionalized or phase I metabolites by catalyzing their conjugation with hydrophilic moieties (e.g., glutathione). This step leads to hydrophilic conjugates of the initial molecules, including glutathione conjugates of flavor compounds such as cinnamaldehyde (Schwartz et al., 2020a). Some of these enzymes use NAD(P)H as cofactor (Muñoz-González et al., 2018). Salivary TAC provides information on the redox status and indirectly on the equilibrium of the $[NAD(P)^+]/[NAD(P)H]$ ratio and thus on the level of activity of these enzymes. Indeed, addition of NADH to the saliva was found to increase the enzymatic degradation of octanal into octanol (Muñoz-González et al., 2018). This phenomenon has also been observed in the presence of oral epithelial cells (Ployon et al., 2020). Specific diets, such as those rich in coffee or broccoli, have been reported to increase the secretion of XME, including glutathione transferases, resulting in a higher metabolic activity at the salivary level (Sreerama et al., 1995). This mechanism is believed to impact perception by modulating the quality and quantity of flavor compounds (Canon et al., 2018).

3.5.2 *Metallic taste perception*

In addition to these mechanisms, lipid oxidation can occur in the oral cavity. This leads to the formation of volatile carbonyl compounds that exhibit a metallic aroma note and as a result contribute to the perception of a metallic taste. Metallic taste is actually more a flavor, as it probably results from the cerebral integration of different senses leading to a multimodal perception. Oxidation of lipids, especially polyunsaturated fatty acids, is highly increased in the presence of Fe^{2+} ions and to a lesser extent by Fe^{3+} (Omur-Ozbek et al., 2012). This oxidation is precluded in the presence of molecules that are able to chelate Fe^{2+} ions, and only partially reduced in the presence of the free radical scavenger vitamin C (Omur-Ozbek et al., 2012). Indeed, vitamin C can also reduce Fe^{3+} to Fe^{2+} , which will participate to the formation of ROS via autooxidation or the Fenton reaction (Halliwell and Gutteridge, 1990). However, no correlation between the salivary TAC, metallic taste perception, and the production of aldehydes and ketones resulting from lipid oxidation has been observed (Omur-Ozbek et al., 2012).

3.5.3 *Fat perception*

Concerning fat perception, Poette et al. have reported a positive correlation between the detection threshold of nonesterified fatty acids without noseclip and the antioxidant status of saliva, whereas there is no correlation with nose-clip (Poette et al., 2014). This suggests that the oral metabolism or the oxidation of nonesterified fatty acids leads to the release of aroma compounds involved in fat perception. Thus, as for metallic taste, fat perception appears to be a multimodal perception involving both the perception of aroma compound release in the oral cavity, trigeminal perception (mechanoreceptors involved in the perception of texture), and potentially taste chemoreceptors dedicated to the detection of free fatty acids such as the CD36 receptors located in the taste buds (Besnard et al., 2018).

3.6 Conclusions

Flavor is the main sensation felt during eating and enables tasting and evaluating the quality of the ingested food. Oral metabolism of flavor compounds is an emerging topic of research that opens new perspectives in the field of flavor research. Pioneer studies have shown that the oral metabolism reactions lead to new molecules with their own sensory properties and these studies seem to indicate that perception of a flavor could actually correspond not only to the sum of flavor molecules but rather to the sum of flavor molecules plus their metabolites that are generated in-mouth. At the origin of the metabolism reactions are found human detoxification enzymes present in saliva or tissues of the oral epithelium as well as oral microbial enzymes exhibiting very specific reactivities such as glycosidase or cysteine-thiol lyase activities. Interindividual variations have been observed through several independent studies and suggest existence of factors modulating this metabolism such as the

salivary antioxidant capacity, which is dependent on the individual physiological status. Other parameters probably exist such as the level expression of enzymes and polymorphism as well as composition of the bacterial communities. In the future, more studies are warranted to improve our understanding of flavor compounds metabolism occurring in the oral cavity and its impact on food perception.

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Taste and trigeminal perception; from detection to integration

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4.1 Introduction

The sense of taste is essential for the evaluation of food quality. It allows at the level of the oral cavity to evaluate the caloric content of the consumed food, to detect the presence of salt, and protect us against the ingestion of toxic molecules. Our gustatory system allows the perception of different food constituents as alkali metallic salts (salty), acids (sour), sugars (sweet), and bitter compounds. Umami is a different taste arising from the perception of amino acids, such as L-glutamate, and 5'-ribonucleotides. Other taste qualities are still matter of debate including fat taste corresponding to the taste of fatty acids (Khan and Besnard, 2009), metallic taste and the kokumi taste which is related to mouthfulness, thickness, and long-tasting savory sensations (Maruyama et al., 2012). This last taste sensation does not refer to an independent taste quality but corresponds more to a reinforcement of other taste qualities. Another class of compounds present in many foods or aromatic spices are named trigeminal stimuli. These chemical compounds present in the mustard oil, chilli peppers, or horseradish are responsible for pungency. Other trigeminal stimuli such as menthol or eucalyptol are also responsible for cooling sensations. Astringency is another trigeminal sensation described as a dry mouthfeel that is generated by particular foods (unripe fruits) or drinks (tea or red wine), which are rich in polyphenolic compounds such as tannins. The objective of this chapter is to review first the different molecules responsible for each basic taste with, additionally, a short overview on trigeminal molecules. A second objective is to describe the physiology of taste at both the peripheral and central levels, and the final one is to present taste-taste interactions. Physiological mechanisms involved for each basic taste at the peripheral level are presented in Fig. 4.1. Several examples are presented in this chapter but not exhaustively. Complementary examples can be found in the following book chapters (Behrens and Meyerhof, 2017; Laffitte et al., 2017; Thomas-Danguin et al., 2017).

4.2 Tasting molecules

4.2.1 Bitter molecules

More than tens of thousands of different molecules are probably responsible for bitter taste. The response to bitter molecules is generally challenging, unlike some foods as

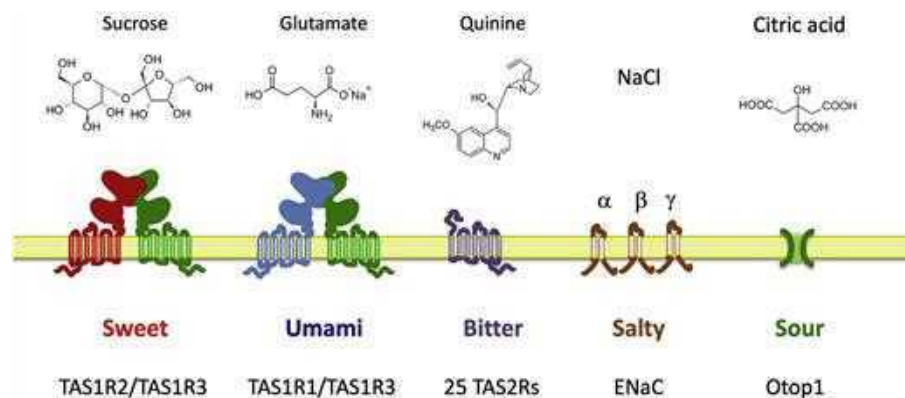


Figure 4.1 Example of natural stimuli and taste detectors involved in the recognition of the five primary taste qualities. Carbohydrates and sweeteners are perceived by the heterodimeric TAS1R2/TAS1R3 receptor. The umami stimuli, L-glutamate, is detected by the heterodimer of TAS1R1/TAS1R3 receptor. Bitter compounds such as quinine are perceived by a set of 25 bitter taste receptors, named TAS2Rs. The sodium salt is detected with the help of a cation channels made of the assembly of three subunits. Detection for sour molecules such as citric acid is achieved by a proton-selective ion channel named Otop1.

beers for which a certain level of bitterness is appreciated. The chemical structures of the molecules perceived as bitter are very diverse. Bitter molecules belong to different chemical classes and, thus, their structure can be varied, such as salts, flavonoids, acids, alkaloids, amino acids, and peptides. Differences in temporal bitterness sensory profile were reported for bitter compounds of different chemical structures; however, the causal reasons for these differences remain unknown (Higgins et al., 2021).

4.2.1.1 Salts

Several simple mineral salts are perceived as bitter. Potassium and calcium chloride, in addition to their relative contribution to the salty taste, are well known for their bitterness characteristic. Potassium chloride is used as sodium chloride substitute in reformulated low-salt foods (Barat et al., 2011; Hooge and Chambers, 2010; Toldra and Barat, 2009), but in several cases, the bitter off-flavor has to be masked with other food additives (Bastianello Campagnol et al., 2011a,b). Calcium chloride is widely used in food industry mainly as a texturing agent and can contribute also to bitterness perception. In goat cheeses, it was found to be the major component responsible for bitterness (Engel et al., 2000).

4.2.1.2 Amino acids, biogenic amines, peptides

Free amino acids are involved in the complex taste of many foods. Bitter amino acids can be found among both series D and L. In the L series, the amino acids with a hydrophobic lateral chain such as L-leucine, L-isoleucine, L-valine, L-arginine, L-methionine, L-phenylalanine, L-tyrosine, L-tryptophan, and L-histidine exhibit bitterness while

the same amino acids in the *D* series rather exhibit a sweet taste (Kato et al., 1989). These differences in the taste of enantiomeric forms can be explained by their respective affinity with TAS1R2-TAS1R3 sweet receptor and for a specific group of TAS2R bitter receptors (Bassoli et al., 2014).

Biogenic amines such as cadaverine or histamine are generally formed by the enzymes of raw animal food products or are generated by the decarboxylation of the amino acids by microorganisms. The presence of these components in foods indicates an advanced level of protein material degradation. If present in high concentration, these compounds can bring bitter taste to food (Kubickova and Grosch, 1998).

Bitter peptides generally contain an important number of hydrophobic amino acid residues and their bitterness is often empirically related to their overall hydrophobicity. However, the structure of these peptides, such as the order of the amino acids or the number of amino acids, highly influences their bitterness intensity (Roudot-Algaron, 1996). The detection of bitter peptides is not related to the activation of a single broadly tuned TAS2R receptor but to the activation of a set of TAS2R bitter taste receptors (Kohl et al., 2013). Bitter peptides can be generated during food processing by proteolysis during maturation of foods such as cheeses (Habibi-Najafi and Lee, 1996). In particular, the hydrolysis of nonbitter peptides can generate bitter peptides. Interestingly, cellular assays have revealed that some beef protein-derived can behave as bitter taste receptor blockers (Zhang et al., 2018).

4.2.1.3 Flavonoids

Flavonones and flavonols are found in many fruits and vegetables. As examples, naringin is the main bitter compound of orange juice and quercetin is the major bitter compound in immature apple. Theaflavins are responsible for bitterness in tea. Theaflavin, theaflavin-3-O-gallate, theaflavin-3'-O-gallate, and theaflavin-3,3'-O-digallate, the four major theaflavins of tea, were purified and their role in the activation of bitter receptors was proven to be rather complex. Among the 25 human TAS2Rs expressed in HEK293 T cells, hTAS2R39 and hTAS2R14 were activated by theaflavins. Both hTAS2R39 and hTAS2R14 responded to theaflavin-3'-O-gallate. In addition, hTAS2R39 was activated by theaflavin and theaflavin-3,3'-O-gallate, but not by theaflavin-3-O-gallate. In contrast, hTAS2R14 responded to theaflavin-3-O-gallate (Yamazaki et al., 2014).

4.2.1.4 Other bitter compounds

Alkaloid is a very large family of bitter compounds. These compounds are found not only in several categories of food, such as tea, coffee, **chocolate**, but also in some vegetables. Some of them can have a high toxic effect and are poisonous.

Compounds originated from the condensation of amino acids and sugars (Maillard reaction) or more generally from heating a mixture of different organic molecules can present an intensive bitterness. As example, the condensation of proline and glucose, in presence of cysteine, lead to the formation of a novel bitter compound, furo[2,3-beta]thiazine (Hofmann, 1999).

Alpha- and beta-acids from hops (*Humulus lupulus* L.), such as humulone, are the major contributors to the bitterness of beer (Verzele and Potter, 1978). Fifteen hops acids of various chemical structures were tested for bitter receptors activation. It was reported that all these compounds activated various combinations of only three bitter taste receptors: hTAS2R1, hTAS2R14, and hTAS2R40 (Intelmann et al., 2009).

Saponins are triterpene glycosides that occur in a wide variety of legume seeds such as pulses. They consist of nonpolar aglycones coupled with one or more sugar chains. A large number of different saponins may occur within and between plant species in various proportions (Heng et al., 2006). These compounds are involved in the bitterness of pulses and lower their acceptability by the consumers.

Many other bitter compounds categories, either from natural or artificial origin, are now well-known but will not be detailed in this chapter, such as lipids, sulfamates, catechines, heterosides, terpenes, glucosinolates, phenols (Canivenc-Lavier et al., 2019) or isothiocyanates.

4.2.2 Sweet molecules

Sucrose, known as table sugar or more precisely α -D-glucopyranosyl-(1 $\rightarrow$ 2)- β -D-fructofuranose is the reference compound for the sweet taste. Other natural disaccharides are also known to elicit this taste. Lactose (galactose and glucose) is the most abundant sugar found in milk with a sweetening power approximately four times lower than sucrose. Maltose (two units of glucose joined by a 1-4 alpha bond) is a disaccharide formed in breaking down starch by amylase. It is approximately 30% as sweet as sucrose. Trehalose (two glucose units joined by a 1-1 alpha bond), produced by a large panel of organisms (invertebrates, plants, fungi ...), exhibits approximately 45% of the sweetness of sucrose. In fruits and vegetables, glucose, fructose, and sucrose are the most abundant. In tomato juice, glucose and fructose represent about 60% of the dry matter (Salles et al., 2003).

Since the end of the 19th century, artificial sweet-tasting molecules have been progressively developed and commercialized (Belloir et al., 2017). These artificial sweeteners were first used to lessen the health problems related to sugar consumption. Actually, the most common sweeteners are saccharin, cyclamate, acesulfame-K, aspartame, neotame, advantame, and sucralose. Some of them are currently used by food industry in order to partially or totally substitute sugar in “healthy” drinks and foods. However, questions remain about their safety and impact on energy metabolism. This section will be limited to the short description of some of them.

Saccharin (E954), known as *o*-benzoic sulfimide, is 300 times sweeter than sucrose and generates a slightly bitter and metallic aftertaste that has been explained by its capacity to activate the human bitter taste receptor hTAS2R44 (Meyerhof et al., 2010). The presence of an allosteric inhibitory binding site for saccharin in the transmembrane domain of TAS1R3 subunit of sweet receptor has been identified, explaining the sweet “water-taste” generated by saccharin (Galindo-Cuspinera et al., 2006). Aspartame, a sweet dipeptide L-aspartyl-L-phenylalanine methyl ester (E951), is 160–220 times sweeter than sucrose, with no distinct aftertaste. It is known to synergize sweet taste with some other sweeteners, in particular acesulfame-K and saccharin.

Neotame and advantame are other sweet peptides chemically related to aspartame. Neotame (E961) is approximately 11,050 times sweeter than sucrose and aspartame, respectively. The taste of neotame resembles that of sucrose, without aftertaste at low and medium concentrations. Neotame and aspartame bind the N-terminal domain of TAS1R2 sweet receptor subunit (Xu et al., 2004). Finally, advantame is another sweetener, 20,000 times sweeter than sucrose.

Sucralose is a semisynthetic sweetener resulting from a chemical modification of sucrose by the replacement of three hydroxyl groups on sucrose by chlorine atoms (4'-, 1'-, and 6' positions), in order to increase sweetening power. Sucralose, approximately 600 times sweeter than sucrose, with a slight bitter aftertaste, binds the N-terminal domains of TAS1R2 and TAS1R3 (Maitrepierre et al., 2012). However, it is noticeable that another chlorinated sugar derivative, alpha-methyl-4,6-dichloro-4,6-dideoxy-D-galactopyranoside, has a masking effect on the sweet taste of sucrose.

Though proteins generally have no taste, a limited number of proteins elicit a strong sweet taste. Originating from different tropical plants, these sweet-tasting proteins are thaumatin, monellin, brazzein, pentadin, mabinlin, neoculin, and miraculin. These proteins differ in their sequence, structure, and surface charge.

Thaumatococcus is actually a mixture of two intensely sweet-tasting proteins, thaumatin I and thaumatin II. These two monomeric proteins are composed of 207 amino acids (22 kDa), and differ by only about 3% in their amino acid sequence. Thaumatococcus is very stable with respect to pH and heat denaturation. The alkaline residues (lysine and arginine) on the surface of thaumatococcus are crucial for its sweet-tasting properties (Ohta et al., 2011). It is approximately 1600 times sweeter than sucrose on a weight basis and 100,000 times higher on a molar basis.

Monellin, a heterodimeric protein (11.4 kDa), is composed of two chains, A and B, containing 42 and 50 amino acid residues, respectively, and is approximately 3000 times sweeter than sucrose (Kohmura et al., 1990). It is relatively unstable to high temperature and to acidic pH, due to the weak forces assembling the two chains.

Brazzein is a sweet-tasting protein (6.4 kDa) composed of a single polypeptide chain of 54 amino acid residues. A short alpha helix and three antiparallel beta-sheets stabilized by four disulfide bridges constitute its three-dimensional structure (Nagata et al., 2013). Brazzein's compact structure makes it very stable to heat and pH denaturation. Sensory analyses have revealed that brazzein is approximately 2000 times sweeter than a 2% sucrose solution on a weight basis (Poirier et al., 2012; Neiers et al., 2021). Interestingly, it has been shown that the cysteine-rich domain of TAS1R3 is a major determinant for the response of the TAS1R2/TAS1R3 sweet taste receptor toward brazzein (Jiang et al., 2004), but the mechanism of sweet taste receptor activation is not well understood yet. The study of synthetic peptides corresponding to the sweetness loop of Brazzein reported that multiple sites, including the N-terminal, and the loop L40-43 of Brazzein, were bound to the sweet taste receptor subunit TAS1R2 and that sweet proteins recognize distinct binding sites different from that recognized by lower molecular weight sweeteners (Suh et al., 2014).

Another sweet-tasting protein called pentadin (12 kDa) has been identified, as brazzein, in the seed pulp of the fruit of the West African plant *Pentadiplandra brazzeana*. It is 500 times sweeter than sucrose. To date, nothing more is known on this protein.

Miraculin transforms sour taste into a sweet taste. Miraculin is a tetramer and dimer of a 25 kDa protein composed of 191 amino acids. Both the tetramer and the dimer have taste-modifying properties. Miraculin has been estimated to be as much as 400,000 times sweeter than sucrose on a molar basis. The mechanism involved in the sweetness of miraculin is unique and differs to that of other sweet-tasting proteins. At neutral pH, miraculin interacts with the sweet taste receptor TAS1R2/TAS1R3, but it does not activate the receptor and partially suppresses the response to other sweeteners. At acidic pH, miraculin changes its conformation and activates the sweet taste receptor.

Neoculin (previously named curculin) is the first and only protein known to elicit sweet taste and also to exhibit sweet-taste modifying properties able to convert sourness to sweetness. Neoculin is a heterodimer showing two chains with molecular weights of 13 kDa and 11 kDa connected by four disulfide bonds.

4.2.3 **Umami and kokumi compounds**

Umami is the typical taste of monosodium glutamate (MSG) found naturally in different foods such as cheese, meat, vegetables, and seafood. Other important umami tastants belong to the group of **purine-5'-nucleotides: inosine-5'-monophosphate (IMP) and guanosine-5'-monophosphate (GMP)** (Yamaguchi and Ninomiya, 1998). For humans, L-glutamate and L-aspartate are only umami-tasting. Numerous peptides, generated by proteolysis of proteins originated from plant or animal products or obtained by chemical synthesis, may elicit an intense umami taste (Lioe et al., 2006; Roudot-Algaron, 1996). These peptides are rather hydrophilic and contain at least one glutamyl or aspartyl residue such as Gly-Asp, Ala-Glu, Gly-Asp-Gly, Val-Asp-Val. The octapeptide Lys-Gly-Asp-Glu-Glu-Ser-Leu-Ala, hydrolyzed from beef, was described with umami taste properties (Tamura et al., 1989). However, the taste properties of these umami peptides were controverted (Hau et al., 1997; van Wassenaar et al., 1995). Later, other umami small peptides were isolated from Japanese soy sauce (Lioe et al., 2006; Zhuang et al., 2016), and larger umami peptides from peanut hydrolysate (Su et al., 2012). Umami peptides were also identified in dry hams (Dang et al., 2015).

Synergistic effects were observed between different umami-tasting molecules. An important discovery was the potentiation of MSG umami taste by IMP and GMP (Fuke and Ueda, 1996). Although IMP or GMP does not generate a receptor response alone, they can interact with L-glutamate naturally present at low concentration in saliva to generate umami perception (Zhang et al., 2008). Moreover, if small peptides containing glutamyl or aspartyl residues isolated from different food systems did not all show umami taste by themselves, some of them, Glu-Glu, Glu-Val, Ala-Asp-Glu, Ala-Glu-Asp, Asp-Glu-Glu, and Ser-Pro-Glu were found to enhance the umami taste of IMP (Maehashi et al., 1999). Other umami tastants have been identified in various

foods. As example, pyroglutamyl di- and tripeptides were identified in an enzymatic hydrolysate of deamidated wheat gluten (Schlichterle-Cerny and Amado, 2002). Some glycoconjugates compounds prepared by Maillard type model reaction also revealed an umami taste (Blank et al., 2002; Festring and Hofmann, 2010; Suess et al., 2014).

More recently, the “Kokumi” taste meaning “mouthfulness and thickness” was described (Ueda et al., 1997). Kokumi molecules are not tasty by themselves, but enhance sweet, salty, and umami tastes. Kokumi molecules mainly impact mouthfulness, thickness, and long-lasting savory profiles (Li et al., 2020). As example, the tasteless glutathione (Glu-Cys-Gly, GSH) enhances umami taste and increases the long-lasting taste sensation in the presence of umami compounds. As other kokumi molecules, γ -L-glutamyl peptides were identified from matured Gouda cheese and from the aqueous extract of edible beans and sulfur-containing peptide derivatives in water extracts of garlic and onions. Kokumi taste has been shown to involve the calcium-sensing receptor (CaSR), a close relative of the class C GPCRs: TAS1R1, TAS1R2, and TAS1R3 taste receptors (Maruyama et al., 2012).

4.2.4 Salty compounds

Salty taste is elicited mainly by Na^+ but other cations, such as Ca^{2+} , K^+ , Li^+ , and NH_4^+ , have also a salty taste. Mineral and organic salts other than sodium chloride elicit a salty taste but in a lower extent (van der Klaauw and Smith, 1995). Na^+ is the only cation to produce a clean salt taste for humans. For instance, K^+ generates a bitter or a metallic taste, which limits its application as a salt substitute in food.

Peptides with a salty taste were reported by different authors (Seki et al., 1990; Tada et al., 1984), although these results were controverted by Huynh-Ba and Philippossian (1990). These compounds are dipeptides hydrochlorides such as Orn-LysHCl, Lys-GlyHCl, Orn-beta-AlaHCl, Lys-TauHCl, Orn-TauHCl. More recently, a decapeptide (Glu-Asp-Glu-Gly-Glu-Gln-Pro-Arg-Pro-Phe) isolated from a fermented soybean curd was found as potent saltiness-enhancing peptide (Chen et al., 2021).

4.2.5 Sour molecules

Sourness is mainly caused by the detection of protons. Numerous organic and mineral acids, such as citric acid, malic acid, tartaric acid, lactic acid, acetic acid, hydrochloride acid, are responsible for sourness. It may be thought that acidity is then correlated with proton concentration, but a low correlation was reported between them, especially for soft organic acids. Conversely, sourness has been shown to be more readily correlated with strong inorganic acids. This phenomenon could be attributed to the buffering/dilution properties of saliva at low acid concentrations.

Peptides with a sour taste generally contain acidic amino acids such as aspartic and glutamic acids. A dipeptide with a sour taste contains at least one acidic amino acid linked to another acidic, neutral, or aromatic amino acid (Kirimura et al., 1969).

4.3 Trigeminal molecules

Beside taste and aroma perceptions, the trigeminal system contributes to other perceptions arising from our chemical environment (Cayeux and Starkenmann, 2017). It is stimulated by chemical substances leading to particular perceptions such as cooling, burning, astringency. This trigeminal nerve (fifth cranial nerve) is responsible for the somatosensory innervation of the face including both the mouth and the nasal cavity. The physiology of the trigeminal system was detailed by Gingras-Lessard and Frasnelli, 2017.

4.3.1 Burning/warming/pungent sensation

The trigeminal detectors are ion channels exhibiting sensitivity to temperature variation and chemical stimuli (Bandell et al., 2004). Compounds such as capsaicin activate a detector leading to a painful burning sensation. Tolerance for capsaicin for people consuming regularly spicy food can be explained by an alteration of the neuron detector due to capsaicin exposition (Caterina et al., 1997). Capsaicin was also found to have an indirect impact on aroma compound release and aroma perception. A significant reduction in aroma release was observed in vivo, during oral melting of a model ice cube system containing (5 ppm) (Yang et al., 2020). The most hydrophilic compound (3-methylbutanal) was affected by capsaicin to a greater extent than the hydrophobic compound (linalool) in vivo while no impact of capsaicin on the gas-liquid partitioning equilibria was observed in vitro. An increase of saliva secretion by 75% leading to the dilution of aroma compounds in the mouth and impacting the aroma concentration into the nasal cavity is the most plausible explanation. However, another hypothesis involving capsaicin-aroma multi-sensory interaction as aroma perception was significantly increased by oral capsaicin stimulation while it does not significantly impact the average in-nose release in simple aqueous systems (Yang et al., 2021). In complex food products, other factors than capsaicinoid content such as pH, free amino acids, free sugar, acids, salt influence the perceived pungency. In particular, free sugar highly decreased pungency intensity in the mouth (Yoon et al., 2021). Finally, it is noteworthy that chile pepper species and pod-types can be differentiated on their “heat” sensory attributes (Guzman and Bosland, 2017). These reports reflect the complexity of such trigeminal perception. Incorporation of trigeminal stimuli, in addition to taste and aroma, such as capsaicin or hot pepper, increases flavor complexity and increases overall flavor impression, in order to boost the sensory appreciation of healthy foods and promote healthier eating (Spencer and Dalton, 2020). There is a potential for chili pepper or capsaicin as a healthy eating strategy, by increasing energy expenditure, decreasing food intake, and enhancing flavor and satisfaction. A suggested approach is to use the sensory impact of trigeminal stimulation (spiciness or heat) in foods, in order to cross-modally enhance tastes and odors, increase sensory satisfaction, and decrease salt and caloric intake (Spencer and Dalton, 2020).

Many other compounds can be responsible for burning sensations by activation of this detector when they are in contact with the mucosa, such as eugenol, allicin ... (Gingras-Lessard and Frasnelli, 2017). Other chemical substances such as thymol are able to activate another trigeminal detector associated with the sensation of warmth (Vogt-Eisele et al., 2007).

4.3.2 Cooling sensation

On the opposite, other molecules are able to produce a cooling sensation, such as menthol, by activating another detector sensitive to cold temperatures. Different cooling compounds have been reported such as 3-methyl-2-(1-pyrrolidinyl)-2-cyclopenten-1-one, 5-methyl-2-(1-pyrrolidinyl)-2-cyclopenten-1-one, and 2,5-dimethyl-4-(1-pyrrolidinyl)-3(2H)-furanone formed from glucose and L-proline reaction in dark malt (Ottinger et al., 2001a) and different alpha-keto enamines such as the 4-methyl-3-(1-pyrrolidinyl)-2(5H)-furanone exhibiting a strong cooling effect with a cooling threshold 35-fold below the value determined for (–)-menthol (Ottinger et al., 2001b). Another trigeminal receptor activated by cold temperatures can be activated by chemicals such as allyl thioisocyanate, cinnamaldehyde (Bandell et al., 2004). Carbonation elicits trigeminal sensations that impact the flavor perception of model beverages through interactions with aroma and taste perceptions (Saint-Eve et al., 2010). Many other “warming,” “cooling,” and pungent compounds, and their potential interactions with taste and aroma perception, are reported with more details in more recent publications (Cayeux and Starkenmann, 2017; Gingras-Lessard and Frasnelli, 2017).

4.3.3 Astringency

Astringency is another trigeminal sensation which comes mainly from tannins (polymers of flavan-3-ol subunits) and other polyphenolic compounds. It causes the drying, roughening and puckering of the mouth epithelia, mainly attributed to the interaction between tannins and the hydrophobic “pocket” of salivary proteins, leading to precipitation (He et al., 2015). While the exact chemosensory mechanism of astringency perception is not known, alternative hypotheses have been recently proposed (Canon et al., 2021).

Astringent substances are found in fruit and derived drinks such as wine and cider. They exhibit several healthy properties such as antibacterial, antiviral, antiinflammatory, antioxidant, anticarcinogenic, antiallergenic, hepatoprotective, vasodilating, and antithrombotic.

A higher astringency perception of tannins is related to their higher total concentration, average degree of polymerization, and their subunit composition and distribution. Tannins vary in size from dimers up to oligomers with more than 30 subunits. Differences in molecular sizes or conformation of phenolic compounds may induce different behaviors, and in particular different abilities to establish molecular associations, with potential impact on organoleptic properties such as color and taste, and on technological and health properties (Cheynier, 2012). One example of the importance of such

compounds is that the overall sensory property of red wines is related to the volatile compounds present, astringency, bitterness and color properties of wines, which are generally conferred by the nonvolatile compounds present in wines, especially the phenolic compounds (Li and Duan, 2019). Indeed, in red wine, phenolic reactions occur according to chemical reactivity of grapefruit phenolic compounds, but also between the oak constituents and grape-derived phenolic compounds that may modulate wine astringency, bitterness, and color.

A positive relationship is observed between polymer size, galloylation, and astringency intensity in grape seeds (He et al., 2015). Complex polysaccharides can reduce astringency by disrupting protein-tannin interactions through different possible mechanisms: inhibiting protein-tannin interactions, inhibiting the precipitation of the protein-tannin complexes, causing polysaccharides to limit the concentration of available proanthocyanidins.

4.4 Physiology of taste

Tasting compounds are perceived by approximately 5000 taste buds in the oral cavity, mainly on the tongue but also on the pharynx, epiglottis, larynx, and soft palate. Taste buds are onion-shaped structures containing 50–100 of different types of specialized taste receptor cells (TRCs). The plasma membrane of these TRCs contains specific taste detectors, able to perceive the wide variety of tasting molecules dissolved in saliva. Taste buds of the tongue are observed in three types of papillae: fungiform, foliate, and circumvallate papillae. TRCs make synapses with three afferent gustatory nerves: chorda tympani branch of the facial nerve, the glossopharyngeal and vagus nerves. TRCs are categorized in three major classes of TRCs, termed Types I, II, and Type III cells, based on ultrastructural features, protein markers, and distinct function. Type I cells and Type III receptor cells are involved in salt and sour taste detection, respectively. Type II receptor cells express taste detector for umami, sweet, and bitter compounds.

While salty and sour tastes directly activate ion channels, bitter, umami, and sweet tastes are elicited by G-protein-coupled receptors (GPCRs). GPCRs are membrane proteins sharing structural features and transduction mechanisms. The detection of bitter, sweet, umami compounds involve a common transduction mechanism. The binding of the tastants to their receptors leads to the dissociation of a heterotrimeric G protein including the $G\alpha$ subunit, named α -gustducin. The dissociation of the $G\beta\gamma$ interacts with a phospholipase C- β 2 (PLC- β 2) leading to an inositol 1,4,5-triphosphate (IP_3) increase that opens ion channels on the endoplasmic reticulum, thus generating a release of calcium. The elevation of intracellular calcium then activates the opening of a transient potential ion channel, TRPM5, generating sodium influx and the depolarization of TRCs (Behrens and Meyerhof, 2013).

The sweet receptor is formed by the assembly of two GPCR subunits, named TAS1R2 (taste receptor type 1, member 2) and TAS1R3 (taste receptor type 1, member 3), while TAS1R1/TAS1R3 heterodimer is involved in umami taste perception.

TAS1R1, TAS1R2, and TAS1R3 subunits are members of the small family of class C GPCRs. This family includes the metabotropic glutamate receptors (mGluR), the calcium-sensing receptor (CaSR), and the metabotropic GABA_B receptor (GABA_BR) (Pin et al., 2004). Class C GPCRs share structural features including a Venus flytrap domain (VFTD), connected to the heptahelical transmembrane domain by a short cysteine-rich domain. TAS1R2/TAS1R3 sweet taste receptor (Li et al., 2002; Nelson et al., 2001) is able to detect the wide chemical variety of sweet-tasting compounds, including carbohydrates (such as fructose, glucose, and sucrose) and artificial (such as aspartame, saccharin, and cyclamate) and natural sweeteners (stevioside). TAS1R2/TAS1R3 receptor is also activated by some rare plant sweet-tasting proteins, such as brazzein, monellin, and thaumatin. In addition, TAS1R3 has the ability to form a TAS1R3/TAS1R3 homodimer sensitive to sugars, but only at high concentrations (Nelson et al., 2001). The VFTD of TAS1R2 contains the primary binding site of sweet compounds. However, at least two other binding sites have been identified in this heterodimeric receptor. One is located in the VFTD of TAS1R3 and the other (Maîtrepierre et al., 2012) in transmembrane domain of the same subunit. The presence of multiple binding sites in the sweet taste receptor is at the origin of the allosteric mechanism responsible for the phenomenon of synergy known between some sweeteners.

The umami receptor is composed of the assembly of two subunits, the TAS1R1 (taste receptor type 1, member 1) and TAS1R3 (taste receptor type 1, member 3) that allows the detection of umami tastants such as glutamate. One feature of the umami taste is the potentiation of the umami taste of glutamate by the purinic ribonucleotides, inosine-5'-monophosphate (IMP) and guanosine-5'-monophosphate (GMP) (Li et al., 2002; Nelson et al., 2001, 2002). Site-directed mutagenesis combined to functional assays has revealed that the molecular mechanism of synergy occurs at the level of the TAS1R1/TAS1R3 receptor (Zhang et al., 2008). It is known that glutamate detection thresholds differ between individuals. Using functional assays, we showed that this variability is associated with gene polymorphism occurring in the TAS1R1 and TAS1R3 receptor units (Raliou et al., 2011).

On human tongue, the bitter tasting molecules are perceived by 25 different types of bitter taste receptors named TAS2Rs (taste receptor type 2) (Meyerhof et al., 2010). TRCs coexpress a subset of 4–11 different TAS2Rs (Behrens et al., 2007). In contrast with TAS1Rs receptors, bitter taste TAS2R receptors belong to the very large class of A GPCRs. Molecular modeling and site-directed mutagenesis of TAS2Rs have suggested the binding site is located within the transmembrane domain (Brockhoff et al., 2010). However, to date, the structural information on TAS2R receptors remains limited. Cellular assays have revealed the binding profile of 20 of the 25 human bitter taste receptors. It has been shown that some TAS2R receptors detect only few bitter molecules, whereas some TAS2Rs act as broadly tuned bitter receptors able to detect several bitter compounds (Meyerhof, 2005; Shi and Zhang, 2009). Activation of TAS2R receptors is responsible for the bitter aftertaste of some compounds such as the unwanted aftertaste of the artificial sweeteners, saccharin, and acesulfame K. Variation in

sensitivity of bitter perception is known to have a genetic basis. For instance, it has been shown that the phenylthiocarbamide (PTC) sensitivity is linked to a genetic polymorphism of the gene coding hTAS2R38. Some food contains compounds known to have a bitter masking effect. Recently, acidic dipeptides were shown to reduce the bitterness, acting as inhibitors of the human bitter hTAS2R16 taste receptor (Sakurai et al., 2009). Emerging trends are the use of high throughput screening assays to identify bitter taste blockers to reduce the bitter taste quality of beverages, foods, or drugs (Slack et al., 2010). A recent study revealed that certain flavones are antagonists for the human hTAS2R39 bitter taste receptor (Roland et al., 2014).

The molecular mechanisms of sour and salt detection are less known. In mice, pharmacologically experiments using amiloride have suggested the existence of two different mechanisms for salt detection. Epithelial Na^+ channels (ENaCs) are suspected to be the main low-sodium receptors sensitive to amiloride (Chandra-shekar et al., 2010). The molecular identity of the amiloride-insensitive salty detector remains to be identified. More recently, it has been shown that the Otop gene family encodes a family of ion channels that are unrelated structurally to previously identified ion channels and are highly selective for protons (Tu et al., 2018).

A lot of experimental data suggest that fat taste may constitute the sixth primary taste. A number of candidate detectors have been proposed for the oral detection of long-chain fatty acids. These detectors include a fatty acid transporter, CD36, and two GPCRs named GPR40 and GPR120 (Khan and Besnard, 2009).

Trigeminal compounds are detected by transient receptor potential (TRP) channels. This family of ion channels is expressed in taste buds, nerves fibers in the mouth serving as detectors of a variety of chemical compounds from plants responsible for pungency or coolness sensation. Among these TRPs, TRPV1 is able to detect the capsaicin, molecule responsible for the pungency of chili peppers whereas TRPM8 mediates the detection of cooling compounds such as menthol, camphor or ethanol. TRPA1 has been shown to be the detector of thiosulfinate and isothiocyanate compounds. These classes of molecules found in mustard oil, wasabi, horseradish, and garlic are responsible for their pungency.

Concerning astringency, it is well accepted that its perception is related to the precipitation by polyphenols of proline-rich proteins present in the saliva. This precipitation reduces the lubrication of the oral cavity leading to the sensation of mouth dryness. However, a recent study revealed that this complex chemosensory perception involves the activation of a GPCR, which remains to be identified (Schobel et al., 2014).

4.5 Integration of taste perception

Flavor is a multimodal perception including gustatory, oral-somatosensory, and retro-nasal olfactory signals arising in the mouth in presence of stimuli. It results from the integration of these sensations, mainly in the brain, and possibly audition and

orthonasal smell that occur when eating food or drinking (Small, 2012). Concerning taste, it activates an area of the anterior insula that represents the identity and intensity of tastes, and a part of the orbitofrontal and anterior cingulate cortex representing the reward value of taste. The brain processing of flavor is fully treated in the chapter written by E.T. Rolls. As such, this paragraph will be limited to the description of few examples related to taste perception.

The brain representation of sweet and salty taste intensity has been investigated using functional magnetic resonance imaging using solutions of different concentration of either sucrose or NaCl in water (Spetter et al., 2010). The study reported that middle insula activation increased with increasing the concentration for both NaCl and sucrose. Despite similar subjective intensity ratings, anterior insula activation by NaCl increased more with concentration than that by sucrose. This showed that amygdala activation increased with increasing the NaCl concentration, but not that of sucrose. Thus, sweet and salty taste intensities are represented in the middle insula, and amygdala activation is only modulated by saltiness.

Interestingly, the brain basis of gustatory semantic links of words whose meaning is primarily related to taste has been explored by functional magnetic resonance imaging by presenting taste words and control words, matched for a range of factors, to participants in a passive reading task (Barros-Loscertales et al., 2012). Barros-Loscertales et al. (2012) observed that whereas all the words activated the left inferior frontal (BA44/45) and the posterior middle and superior temporal gyri (BA21/22), taste-related words produced a significantly stronger activation in the same areas and also in the anterior insula, frontal operculum, lateral orbitofrontal gyrus, and thalamus, among others. They concluded that the meaning of taste words is grounded in distributed cortical circuits reaching into areas that process taste sensations.

It has also been shown that the attention network modulates the gustatory cortex during attention to taste and that the anterior cingulate cortex acts as an intermediary processing hub between the attention network and the gustatory cortex (Veldhuizen et al., 2012).

Another interesting study reports the effects of brand cues onto gustatory processing of the same beverage, showing the strong effects of brand cues on self-reported pleasantness as well as on neural responses signaling reward in the brain (Kuehn and Gallinat, 2013). A clear preference was observed for the same beverage when it was believed to be strong brands (Coca-Cola or Pepsi Cola) compared with weak brands (River Cola or T-Cola) in self-reported pleasantness ratings. The fMRI experiments showed stronger signal in medial orbitofrontal cortex (mOFC) parametrically modulated with pleasantness ratings during weak as compared to strong brand cues, suggesting a stronger reliance on stimulus value processing when the brand cue is less informative. Furthermore, stronger activation in the right amygdala was found for Coca-Cola cues compared with Pepsi Cola cues. During the taste phase the same soft drink elicited stronger activation in left ventral striatum when it was previously announced as a strong brand compared with a weak brand.

Finally, in the context of salt reduction in foods, the congruent odor-induced saltiness enhancement on the basis of both psychophysical and neuroanatomical

levels has been demonstrated (Seo et al., 2013). In particular, the authors showed that a saltycongruent combination of odor and taste produced significantly higher neuronal activations in brain regions associated with odor taste integration than an incongruent combination and/or odorless air with taste solution. In addition, they reported that the congruent odor-induced saltiness enhancement was more pronounced in the low-concentrated tastant than in the high-concentrated one.

4.6 Taste-taste interaction

As described above, the human gustatory system is able to identify five basic tastes: salty, sweet, sour, bitter, and umami. In mixtures, these basic tastes are known to interact through binary taste-taste interactions as reviewed by Keast and Breslin (2002). The physiological mechanisms involved in these interactions are not well understood yet, but it is supposed to rather occur at the taste receptor cell level. However, the integration of the taste signals at the central level cannot be excluded to explain these interactions. Several interactions are possible when two taste compounds are mixed in a solution: enhancement when the effect of the addition of one compound to another on a taste attribute is higher than the sum of the individual effects of the two compounds, additivity when this sum corresponds to the addition of the individual effects of the two compounds, and suppression or masking effect when this sum is lower than the individual effect of the two compounds (Keast and Breslin, 2002). In most of the cases, these taste-taste interactions were found to be dependent on the concentration of the taste stimuli as the perceptual effects may vary according to the subthreshold, suprathreshold, or higher stimuli concentration (Breslin, 1996; Keast and Breslin, 2002). As examples, salt and sour tastes enhance each other's intensity at low concentration while suppressive or absence of effect was reported at higher concentration. Bitterness is suppressed by salty taste whatever the concentration of the tastants. Saltiness has a variable effect on bitterness at low concentration but no effect is observed at higher concentration (Breslin, 1996; Keast and Breslin, 2002). Sweetness has been described as a dominant taste quality in binary, tertiary, and quaternary mixtures (Green et al., 2010). Saltiness enhances sweetness at low concentration while it may suppress it at high concentration. Umami taste can also interact with others. The enhancement of umami taste due to the presence of monosodium glutamate is enhanced by mononucleotides (Yamaguchi, 1967). Salty and umami tastes enhance each other but the enhancement of umami by salty taste is reinforced by the presence of phenylalanine at subthreshold level (Lioe et al., 2005). Moreover, umami taste perception due to peptides was found to suppress bitterness of substances such as salicin via the human bitter taste receptor hTAS2R16 in attenuating intracellular calcium flux induced by salicin (Kim et al., 2015). Several examples of interactions were also reported between sweetness and sourness.

These taste-taste interactions are functional in complex media such as real foods. The use of addition or omission tests from reconstituted food fractions allowed in many cases to highlight such interactions (Engel et al., 2002).

Dea et al. (2013) observed a synergetic effect of limonin and nomilin that decrease each other's threshold when present in a mixture and found that these thresholds are lower in orange juice, compared to water solution of sugars (sucrose, glucose and fructose) and acids (citric and malic). One explanation could be due to the sugar and acid concentration used, because increasing sugar levels was efficient in decreasing bitterness perception of limonin and nomilin in orange juices but the bitterness suppression was not effective when citric concentration was added. Another explanation could be that some chemical compounds presented in juices such as flavonoids may also contribute to bitterness in real sample. Sugar was found to have a significant masking effect in different foods. As an example, at low concentrations of bitter tastant, sucrose masked bitterness of goitrin, sinigrin, and quinine in aqueous sample and cabbage juice, but not of sinigrin in cabbage juice (Beck et al., 2014). In tomato juices, the omission of all the sugars led to an almost total disappearance of sweetness and a significant increase in sourness and saltiness which had been partly masked by sweetness (Salles et al., 2003).

In rice vinegar, both detection and recognition thresholds were decreased when adding vinegar ingredients (salt) inducing sourness (Hatae et al., 2009). This saltiness-sourness interaction was found asymmetric as no effect of sourness was observed on saltiness with the same model.

Concerning umami taste, saltiness perception was found to enhance umami perception and inversely, umami perception was able to enhance saltiness perception (Yamaguchi and Takahashi, 1984). Binary mixed solutions containing different umami substances revealed umami synergistic effects at neutral pH according to the concentration ratio (Wang et al., 2021).

Such interactions were also reported for trigeminal and more widely for intra- and inter- chemesthesis sensations (Byrne, 2016). This shows the interdependency of all the sensory stimuli to generate an integrated impression by the brain when eating a particular complex food.

4.7 Conclusion and future trends

Taste research during the past two decades showed that humans are equipped with a set of taste detectors that are essential to gain information on the quality of the food we ingest. There is a growing interest from this knowledge to identify new sweeteners or salt substitutes with beneficial effects on health. The discovery of taste receptors thus opens novel strategies based on taste receptor screening to identify new tasting compounds and taste modulators. The search of bitter blockers to reduce the bitterness of foods or beverages is another interesting area of investigation. Ongoing studies involving screening approaches will lead to the identification of new food ingredients with the aim of the reduction of sodium or sugar content in foods while preserving their organoleptic properties.

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Odorant metabolizing enzymes in the peripheral olfactory process

5

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5.1 Introduction

In cells, organs, and the whole body, chemical signaling (hormones, mediators, metabolites, and other compounds) is generated and mediates a very rapid response; therefore, it must be terminated rapidly to avoid continuous stimulation. Similarly, olfactory signaling, which is initiated by odorant stimuli, must also be stopped rapidly to allow the olfactory receptors to respond to new stimuli and to maintain the efficiency and sensitivity of the peripheral olfactory process. Indeed, in such ligand-receptor systems, termination is as important as stimulation because background noise may dramatically affect the response. Termination can be achieved by degradation or elimination of the signal, both of which are functions of odorant-metabolizing enzymes as olfactory perireceptor mechanisms. We will also see that metabolism can lead to the synthesis of compounds that can act as additional odorant signals to modulate the overall quality of the initial stimulation. Accordingly, there is a growing body of literature that highlights the significant function of odorant enzymatic metabolism in olfaction, and this subject will be addressed in this chapter.

Despite the fact that olfactory receptors have recently been found in places other than olfactory neurons (Feldmesser et al., 2006), they are preferentially expressed in olfactory tissues and are dedicated to the detection of odorants at the membranes of olfactory sensory neurons. Conversely, the enzymes involved in the metabolism of odorants show ubiquitous expression and have adapted their activity to the substrates present in different locations in the organism. The first section of this introduction will discuss the metabolism of whole xenobiotics, and the second section will focus on odorant metabolism.

5.1.1 Xenobiotic-metabolizing enzymes

Xenobiotics are defined as chemical molecules that are not naturally present in a living body. These foreign substances can enter the organism through various interfaces, including the skin, the lung, and the gastrointestinal tract, via, for example, cosmetics, air, and food. Therefore, the source of xenobiotics is diverse, and they include an almost infinite number of chemicals that exhibit a variety of structures. A common feature of many xenobiotics is their lipophilicity, which allows them to passively

traverse the plasma membranes of cells to reach the cytoplasm and nucleus. The concentration of xenobiotics, their chemical reactivity toward proteins or DNA (electrophilicity), and their ability to mimic the action of endogenous compounds (hormones, signaling molecules, and other compounds) can lead to more or less serious toxicity at the level of cells, organs, and the whole body. Most living organisms have developed a process that rapidly and efficiently limits xenobiotic toxicity. This process involves a network of xenobiotic-metabolizing enzymes (XMEs). Phase I enzymes catalyze the functionalization of xenobiotics (unmasking or introduction of reactive polar groups such as COOH and OH), while phase II enzymes catalyze the conjugation of xenobiotics or metabolites resulting from phase I activity (conjugation with hydrophilic compounds, including glucuronic acid, glutathione, and sulfate) (Fig. 5.1). The hydrophilic metabolites that result from biotransformation are easily excreted from the cells via phase III transporters (multidrug resistance—associated proteins, MRPs) and eliminated in the urine or feces. One should note that for some substrates (e.g., paracetamol and polycyclic aromatic hydrocarbons), xenobiotic metabolism can produce activated metabolites, some of which display high toxicity. According to the level and variety of XMEs on its surface, the liver is the main metabolic organ for detoxification of such metabolites, but XMEs are expressed in many organs and tissues, including the kidneys, lungs, intestine, skin, brain, and nasal tissues. Phase I and Phase II include various families of XMEs (see Table 5.1) that catalyze the metabolism of various chemical categories of substrates (aldehydes, esters, carboxylic acids, ketones, and others).

5.1.2 Odorant-metabolizing enzymes

Volatile molecules emanating from the environment are typically foreign chemicals that are inhaled through a sniff. This volatility is often associated with high apolarity, a characteristic that favors the access of these molecules to the cells to which they exert potential toxicity. This toxicity depends on the reactivity of the volatile molecule and their concentration; therefore, it is not surprising to find in the nasal tissue a large

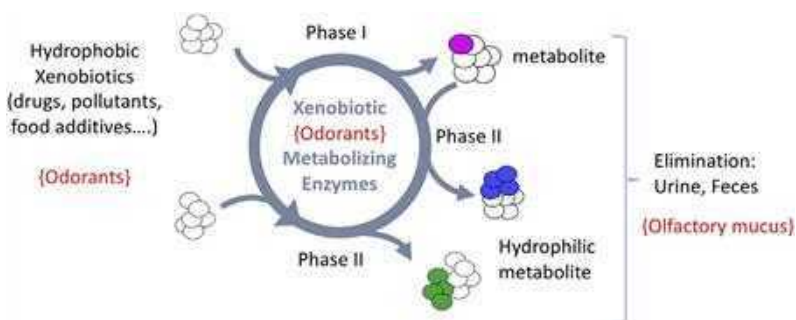


Figure 5.1 Schematic representation of the xenobiotic enzymatic metabolism mechanism. The mechanism toward odorants is shown in brackets. Depending on the odorant, the metabolism can consecutively involve phase I and phase II enzymes or only phase I or phase II enzymes.

Table 5.1 Detection of OME proteins in the olfactory epithelium

Alcohol dehydrogenase (phase I)	Sensory cilia Olfactory mucus	Mouse Human	Mass spectroscopy Mass spectroscopy	(Kuhlmann et al., 2014) (Debat et al., 2007; Yoshikawa et al., 2018)
Aldehyde dehydrogenase (phase I)	Olfactory mucus Sensory cilia Sensory cilia Olfactory mucus	Rat Rat Mouse Human	Mass spectroscopy Mass spectroscopy Mass spectroscopy Mass spectroscopy	(Heydel et al., 2019b) (Mayer et al., 2008) (Kuhlmann et al., 2014) (Debat et al., 2007; Yoshikawa et al., 2018)
Carbonyl reductase (phase I)	Olfactory mucus Sensory cilia Sensory cilia Olfactory mucus Olfactory mucus	Rat Rat Mouse Human Rat	Mass spectroscopy Mass spectroscopy Mass spectroscopy Mass spectroscopy Mass spectroscopy	(Heydel et al., 2019b) (Mayer et al., 2008) (Kuhlmann et al., 2014) (Yoshikawa et al., 2018) (Heydel et al., 2019b)
Carboxylesterase (phase I)	Sensory cilia Sensory cilia Olfactory mucus Olfactory mucus	Rat Mouse Human Rat	Mass spectroscopy Mass spectroscopy Mass spectroscopy Mass spectroscopy	(Mayer et al., 2008) (Kuhlmann et al., 2014) (Yoshikawa et al., 2018) (Heydel et al., 2019b)
Cytochrome P450 (phase I)	Sensory cilia Sensory cilia Olfactory tissues	Rat Mouse Rabbit	Mass spectroscopy Mass spectroscopy Purification, amino acid sequencing	(Mayer et al., 2008) (Kuhlmann et al., 2014) (Ding and Coon, 1991)
Dicarbonyl L-xylulose reductase (phase I)	Sensory cilia Olfactory mucus	Mouse Human	Mass spectroscopy Mass spectroscopy	(Kuhlmann et al., 2014) (Yoshikawa et al., 2018)
Epoxide hydrolase (phase I)	Sensory cilia Sensory cilia Olfactory mucus	Rat Mouse Human	Mass spectroscopy Mass spectroscopy Mass spectroscopy	(Mayer et al., 2008) (Kuhlmann et al., 2014) (Yoshikawa et al., 2018)

Continued

Table 5.1 Detection of OME proteins in the olfactory epithelium—cont’d

Paroxonase (phase I) GST (phase II)	Sensory cilia	Rat	Mass spectroscopy	(Mayer et al., 2008)
	Sensory cilia	Mouse	Mass spectroscopy	(Kuhlmann et al., 2014)
	Sensory cilia	Rat	Mass spectroscopy	(Mayer et al., 2008)
	Olfactory mucus	Human	Mass spectroscopy	(Debat et al., 2007) (Yoshikawa et al., 2018)
Sulfotransferase (phase II)	Olfactory mucus	Rabbit	Mass spectroscopy	(Robert-Hazotte et al., 2019b)
	Olfactory mucus	Rat	Mass spectroscopy	(Heydel et al., 2019b)
	Olfactory epithelium	Rat	Protein microsequencer	(Ben-Arie et al., 1993)
	Sensory cilia	Rat	Mass spectroscopy	(Mayer et al., 2008)
	Sensory cilia	Mouse	Mass spectroscopy	(Kuhlmann et al., 2014)
	Olfactory mucus	Human	Mass spectroscopy	(Yoshikawa et al., 2018)
UDP-glucuronosyltransferase (phase II)	Olfactory mucus	Rat	Mass spectroscopy	(Heydel et al., 2019b)
	Sensory cilia	Rat	Mass spectroscopy	(Mayer et al., 2008)
	Sensory cilia	Mouse	Mass spectroscopy	(Kuhlmann et al., 2014)

variety of XMEs that together are able to detoxify many volatile airborne chemicals. Protecting the nasal tissue itself and neurally connected central structures such as the olfactory bulb and the brain is one reason for the presence of high levels of XMEs, but 40 years of investigation have progressively evidenced a secondary and significant role for XMEs in the control and modulation of odorant detection and perception. Odorants are not literally xenobiotics since their presence in the nose is necessary to initiate olfactory perception. They can be considered xenobiotics that are allowed to remain for a very limited time in the peripheral olfactory apparatus of the organism and that trigger their biological effects through the activation of olfactory receptors. To avoid confusion of the role of XMEs in detoxification with their role in olfaction, it has been proposed that these enzymes be referred to as “odorant-metabolizing enzymes” (OMEs) (Heydel et al., 2019a) when their substrates are odorous molecules that find their sources in food, perfume, cosmetics, flora, or congeners rather than volatile organic compounds (VOCs) that are known for their adverse effects on health.

5.1.3 Peripheral olfactory physiology

The olfactory mucosa is a highly organized tissue that forms irregular patches in the area beneath the cribriform plate, the superior turbinate, and the corresponding septum of the mammalian nasal cavity. Its structure has been reviewed and studied for decades (Adams, 1992; Hadley et al., 2004; Morrison and Costanzo, 1992). Briefly, it is a pseudostratified columnar neuroepithelium that is covered with mucus and separated from connective tissue (*lamina propria*) by the basal lamina. The olfactory epithelium (OE) layer contains four types of cells: support cells or sustentacular cells (SCs), olfactory sensory neurons (OSNs), basal cells (BCs) and microvillar cells. The *lamina propria* is a submucosal mesenchyme that includes the lymphoid tissues, Bowman glands, blood vessels, and trigeminal and olfactory nerves (Elsaesser and Paysan, 2005). OSNs are bipolar neurons that are in direct contact with the outside environment and with the olfactory cells of the OE (Fig. 5.2). Their unique dendrites end in olfactory knobs, from which approximately 10 cilia project into the mucus to form a dense blanket at the surface of the epithelium. Olfactory and respiratory epithelium can be distinguished through electron microscopy due to the presence of these ciliated knobs that protrude at the surface. The cilia bear on their membranes olfactory receptors (ORs) that recognize odorant molecules. There are approximately 400 OR-encoding genes in the human genome and up to 1000 OR-encoding genes in the genome of the mouse. However, OR expression in neurons is monogenic and monoallelic; thus, only one type of OR is expressed in any given neuron. ORs belong to the G protein-coupled receptor (GPCR) superfamily and possess seven transmembrane segments. They are located on the cilia of OSNs and thus recognize odorants that partition with the surrounding mucus. When an odorant binds to the OR, the alpha subunit of an olfactory G protein (G_{olf}) exchanges GDP for GTP, dissociates from the beta-gamma subunits, and activates adenylyl cyclase III (ACIII). Subsequently, ACIII converts ATP to cAMP. The resulting increase in cAMP levels opens cyclic nucleotide-gated (CNG) channels, leading to an influx of Na^+ and secondary messenger Ca^{2+} ions. Ca^{2+} -activated chloride channels (CaCCs) induce a Cl^- efflux that generates waves

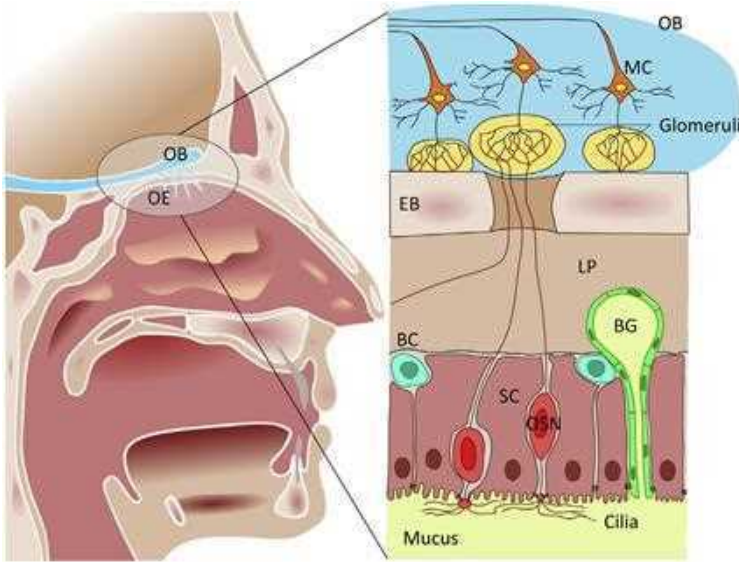


Figure 5.2 Localization and structure of the olfactory epithelium.

of depolarization, leading to an action potential in the axon. Before they are removed from the cell by Na^+ , Ca^{2+} transporters, Ca^{2+} ions play a role in the return of OSNs to the basal state by activating phosphodiesterases and calmodulin kinase II (CaMKII), which inhibit ACIII (Fig. 5.3) (Elsaesser and Paysan, 2005; Glezer and Malnic, 2019; Sharma et al., 2019). The message is conveyed through OSN axons that are grouped in nerve bundles that cross the *lamina propria* and the cribriform plate of the ethmoid bone. These axons reach the olfactory bulb (OB), where OSNs form synapses with mitral cells in globular structures called glomeruli. Neurons expressing the same OR send their axons to the same glomeruli; in other words, glomeruli concentrate messages from neurons that express a single OR type. The number of odorant molecules recognized is exponentially greater than the number of genes encoding olfactory receptors. Odorants vary greatly in their sizes, shapes, functional groups, and charges;

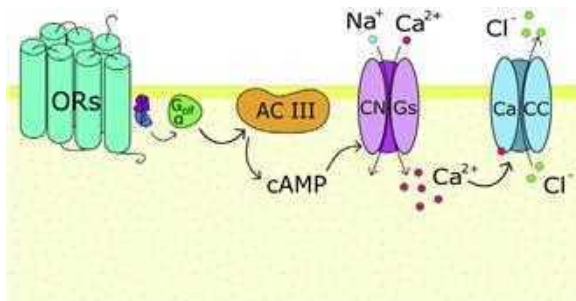


Figure 5.3 Intracellular signaling associated with odorant recognition.

however, the olfactory system is able to recognize and even discriminate stereoisomers (Krautwurst et al., 1998). This fine recognition is possible thanks to the “odor coding” model, which was first described in 1999 and has been revised since then (Kurian et al., 2021; Malnic et al., 1999). As mentioned above, OR expression in OSNs is monogenic and monoallelic; an OSN is thus specialized to recognize a single molecular pattern. However, each odorant can be considered to represent a set of molecular patterns, or odotopes, that are recognized by a specific set of ORs. The above authors described in their work that although one OR type can recognize different odorants, a specific set of ORs is activated for each molecule. The more similar the molecules are, the more overlapping OR sets are activated. Consequently, each odorant is coded by a specific set of active glomeruli. The central olfactory pathway projecting from the OB begins with mitral cell axons that project directly to the olfactory cortex, made of different interconnected nuclei. The fact that the thalamus is not the first step in this journey is a unique feature among the senses. As a consequence, the olfactory message reaches the level of consciousness later in the olfactory central pathway. From the olfactory cortex, the message is relayed to four main areas: the neocortex, the thalamus, the hypothalamus, and the hippocampus, the latter of which is involved in behavior and learning processes. This could explain why strong memories can be triggered by smell (Hadley et al., 2004). In the neuroepithelium are found sustentacular cells (SCs), columnar cells covered with microvilli at their apical poles. Their role is to seal the epithelium through tight junctions at their apical poles, thus forming a protective barrier between the mucus and the basal lamina. SCs are anchored to the basal lamina and envelop OSNs, isolating them from each other and providing them with the optimal ionic environment. Their cytoplasm is rich in secretory organelles; indeed, they participate in the secretion of the mucus layer (Hadley et al., 2004). Basal cells are the stem cells of the OE and are found near the basal lamina. Their presence at the third end of the OE near the basal poles of the SCs makes the OE a pseudostratified epithelium. Two types of BCs, globose cells and horizontal cells, have been described. Globose cells are involved in the physiological renewal of OSNs, whereas horizontal cells can differentiate into many types of cells, despite the fact that they show less mitotic activity (Hadley et al., 2004). The olfactory epithelium is pierced by the secretory ducts of the Bowman gland (BG). The main body of the BG is found in the *lamina propria*; this gland, along with the SCs, is responsible for mucus secretion. The secreted mucus proteins are diverse in nature and function and include antibacterial peptides, proteases, and heat-shock proteins, as well as OMEs and odorant-binding proteins (Debat et al., 2007).

The OE is located beneath the ethmoid bone (EB) in the superior turbinates. It is covered by mucus secreted by the Bowman glands (BG) and separates the body from the outside via tightly joined sustentacular cells (SCs). The tissue is renewed by basal cells (BCs) located near the basal lamina. Cilia (carrying olfactory receptors) of olfactory sensory neurons (OSNs) extend into the mucus, where they detect odorant molecules. The axons of the OSNs project through the *lamina propria* (LP) and ethmoid bone pores (EBs) to form synapses with mitral cells (MCs) in the olfactory bulb (OB). Synaptic zones form globular structures called glomeruli within the OB.

Odorant molecules are specifically recognized by olfactory receptors (ORs), which are expressed by olfactory sensory neurons in the olfactory epithelium. ORs are G protein-coupled receptors (GPCRs); the olfactory G protein is called G_{olf} . When an odorant molecule is recognized, the G protein exchanges a GDP (guanosine diphosphate) molecule for a GTP (guanosine triphosphate) molecule, and the α subunit dissociates. The subsequent activation of adenylyl cyclase III (ACIII) increases cyclic adenosine monophosphate (cAMP) levels, thereby activating cyclic nucleotide-gated (CNG) channels. The influx of Na^+ and Ca^{2+} ions activates Ca^{2+} -activated chloride channels (CaCCs). Cl^- efflux then generates membrane depolarization.

5.2 Olfactory expression and localization of OMEs

OMEs have been detected in the nasal mucus and in various types of cells in the respiratory and olfactory epithelia. In recent decades, various techniques, including enzyme assays, in situ hybridization, immunohistochemistry, proteomics, and electron microscopy, have been used to decipher the location of OMEs. First, enzymes were indirectly detected in the olfactory mucosa using a histochemical approach in which the tissue was stained for specific enzyme activities. Using this approach, esterase was detected in hamster OE (Taniguchi et al., 1992). During the 1980s, purification of human OE followed by isolation of enzymes from the purified tissue was a first step in demonstrating the location of OMEs (Aceto et al., 1989). More recently, mass spectrometry allowed us to identify a large number of OMEs in the nasal mucus, olfactory epithelium, and specifically in olfactory cilia, the structures that house the olfactory receptors. Techniques such as electron microscopy and immunohistochemistry allowed us to more precisely define the types of cells that express OMEs but can be limited by the availability and specificity of antibodies. In situ hybridization, which is based on RNA detection, does not present these limitations, but mRNA expression is unfortunately not always linked to expression of the corresponding protein. Techniques such as quantitative RT-PCR, which has been used to detect mRNA encoding GST in human olfactory mucosa, have the same limitation (Zhang et al., 2005). Moreover, OMEs generally belong to a large family of enzymes that have strong homology with each other, limiting the ability to determine the specific locations of the members of this family. Immunohistochemistry and electron microscopy therefore require the use of antibodies with strong affinity for one member of the family and without cross-reactivity toward the other members, and this often limits the ability to determine a given enzyme's specific localization.

Immunohistochemistry and in situ hybridization experiments have localized OMEs expression to BG, SCs, BCs (Bogdanffy et al., 1990; Getchell et al., 1993; Heydel et al., 2019b; Schwartz et al., 2020; Zupko et al., 1991), and sensory neurons (Heydel et al., 2001). Using mass spectrometry, numerous OMEs (e.g., aldehyde dehydrogenase, cytochrome P450, and glutathione transferase) were detected in the cilia of sensory neurons (Mayer et al., 2008) as well as in the nasal mucus (Debat et al., 2007; Robert-Hazotte et al., 2019a; Yoshikawa et al., 2018). In a general manner, OMEs were detected in all types of cells, including neurons in the OE as well as in the respiratory epithelium surrounding it (Neiers et al., 2021). Strikingly, a

UDP-glucuronosyltransferase has been localized to the plasma membrane of the cilia of olfactory sensory neurons using electron microscopy (Neiers et al., 2021). Additionally, the detection of these enzymes in Bowman cells, which secrete the olfactory mucus, can explain the mass spectrometry results that demonstrate the presence of OMEs in this fluid. The goblet cells that secrete the nasal mucus are located in the respiratory epithelium and can also secrete OMEs into the nasal mucus, also contributing to the presence of these enzymes in olfactory mucus.

Dicarbonyl L-xylulose reductase, glutathione transferase, and sulfotransferase were shown to be able to metabolize odorants in vitro (Heydel et al., 2019b; Robert-Hazotte et al., 2019c; Schwartz et al., 2020; Tamura et al., 1997; Zaccone et al., 2015). Moreover, as described in Section 5.3.1.3, odorant metabolites were detected in vivo and ex vivo, suggesting that these enzymes are active in vivo. However, to date, no study has shown specific activity toward odorants attached to either the mucus or to a particular cell type. Odorants are, by definition, small, volatile, hydrophobic molecules. These molecules can consequently interact with OMEs within the nasal mucus as well as with those located within epithelial cells. Their metabolism within cells will be affected by the law of mass action that governs odorant concentrations in the air contained in the nasal cavity and by their binding to olfactory receptors. OMEs located in the olfactory mucus as well as in epithelial cells and sensory neurons can also potentially participate in odorant metabolism. Numerous OME families have been detected in these locations, as indicated in Table 5.1.

5.3 Functional roles of OMEs in the olfactory process

Two main functions of OMEs make them important actors in the olfactory process.

The first function is the odorant signal termination: through their capacity to biotransform odorants into inactivated and excretable hydrophilic metabolites, OMEs clear odorants from the receptor environment and remove the stimulus. Defects in this mechanism could impair the sensitivity of odorant detection and alter the olfactory response. The second main function is the odorant signal modulation: through their capacity to synthesize metabolites that present odorant properties, they create molecules that act as additional stimuli. This allows modulation of the quality of the signal and of the corresponding olfactory response and perception.

This chapter will present the main results highlighting these two functions of OMEs. In the introduction, focus will be placed on the methodologies and techniques that have been specifically used or developed for (i) analysis of odorant metabolism and (ii) investigation of the impact of experimental disruption of enzymatic odorant metabolism on the olfactory process.

5.3.1 Methodologies and techniques

5.3.1.1 Analysis of odorant metabolism

Knowledge concerning the metabolism of odorants by olfactory tissue has led to significant advances during the last decade thanks to the development of specific

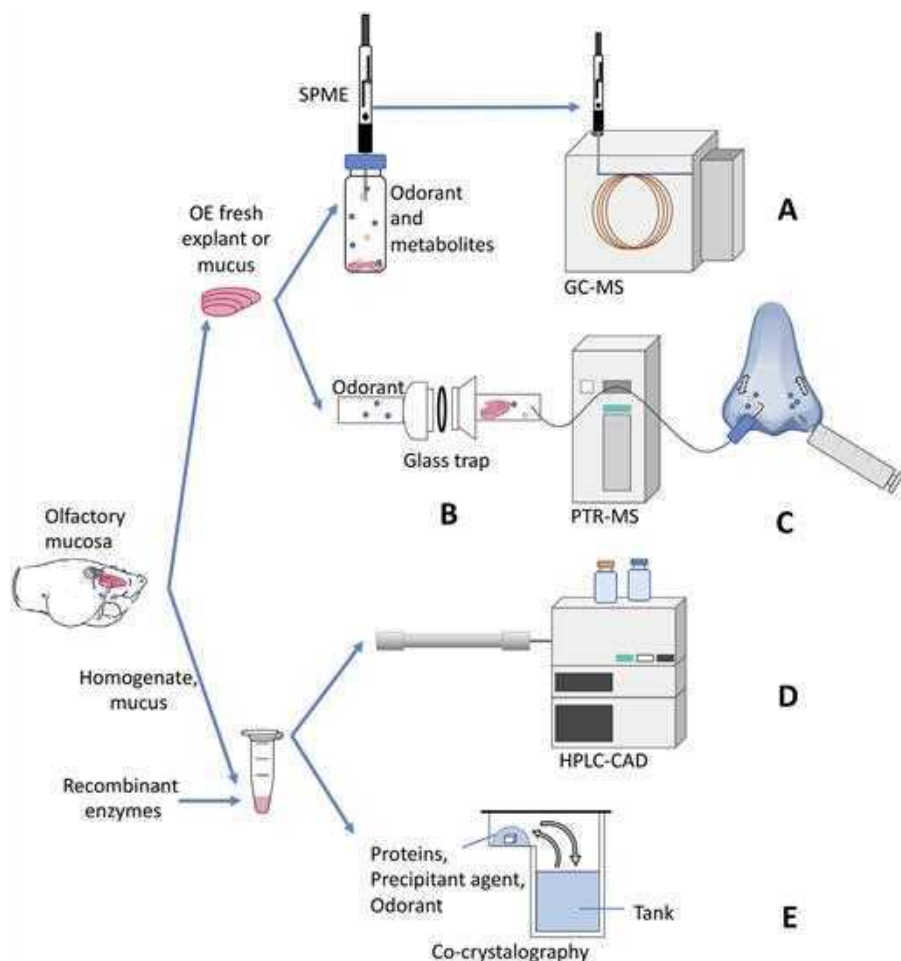


Figure 5.4 Schematic representation of the techniques and methodologies used to study odorant olfactory metabolism. A. Ex vivo SPME-GC-MS; B. Ex vivo PTR-MS; C. In vivo PTR-MS; D. In vitro HPLC-CAD; E. In vitro odorant-enzyme interaction analysis.

methodologies. Fig. 5.4 summarizes the main methodologies used to explore the metabolism of odorant molecules under in vitro, ex vivo, and in vivo experimental conditions. In all these methodologies, the strategy consists of exposing olfactory tissue (in vivo, ex vivo, or in vitro) to an odorant and then determining the fate of the odorant and/or identifying and quantifying its metabolites, both of which allow the characterization of the olfactory metabolism of the odorant of interest. Of course, controls are needed to validate the methods, especially because it is necessary to prove that odorant conversion is the result of an enzymatic process. Therefore, controls that employ heated tissue or enzyme inhibitors have been used ex vivo and in vitro.

The methodologies rely on different techniques depending on the level of exploration (in vivo, ex vivo, or in vitro) and on the type of metabolic activity involved (phase

I or phase II). As explained above (Section 5.1.1, “Xenobiotic-metabolizing enzymes”), metabolizing enzymes modify the polarity of their substrates, converting apolar hydrophobic molecules to more polar molecules (phase I metabolites) and finally to hydrophilic molecules (phase II metabolites), inactivated metabolites ready to be eliminated. Chromatography is a technique of reference for the analysis of chemical compounds such as odorants and their metabolites. Classically, odorants and their phase I metabolites, which are often apolar, are analyzed by gas chromatography (GC, Fig. 5.4A). Conversely, phase II metabolites corresponding to conjugated polar metabolites (see Section 5.1.1, “Xenobiotic-metabolizing enzymes”) were analyzed using high-performance liquid chromatography (HPLC, Fig. 5.4D). Since identification of the metabolite is necessary to characterize odorant metabolism, these techniques are often coupled with mass spectrometry (GC-MS or LC-MS). Solid-phase microextraction, in which molecules are concentrated by adsorption to a coated fiber, can be used to capture and concentrate volatile molecules present in a headspace prior to GC-MS analysis (SPME-GC-MS, Fig. 5.4A). When the above chromatographic separation techniques are used, there is unavoidably time between the exposure of the tissue to the odorant and the resulting analysis, making it impossible to accurately evaluate how quickly the enzymatic reaction occurs. Thus, real-time direct-injection proton transfer reaction-mass spectrometry has been used in several *ex vivo* (PTR-MS, Fig. 5.4B) and *in vivo* (PTR-MS, Fig. 5.4C) studies to measure both the uptake of the odorant and the release of metabolites from the tissue in the presence of olfactory tissue in real time. With the methodologies shown in Fig. 5.4A–C, the release of both odorants and their metabolites is measured in air that has been in contact with the tissue. In the methodologies shown Fig. 5.4D and E, the analysis is done under liquid conditions.

OMEs activity can be studied using either *ex vivo* models (tissue explants, mucus) or *in vitro* models (tissue homogenates, recombinant enzymes). GC-MS, PTR-MS, and HPLC-CAD are used to study OMEs activity, and cocrystallography is dedicated to the study of enzyme biochemistry (ligand affinity, 3D structure). *SPME*: Solid-phase microextraction; *GC-MS*: Gas chromatography-mass spectrometry; *PTR-MS*: Proton-transfer-reaction mass spectrometry; *HPLC-CAD*: High-performance liquid chromatography - Charged aerosol detector.

5.3.1.2 Analysis of the impact of the modulation of odorant metabolism on the olfactory process

A strategy that is often used to investigate the function of an enzyme in a biological process involves modulating the enzyme activity or expression and measuring the impact of the modulation on the progress or the finality of the process. Such a strategy has been used to explore the function of OMEs in the olfactory process. Following modulation of odorant metabolism, various parameters, including the following, can be analyzed depending on the level of exploration (*in vivo*, *ex vivo*, or *in situ*):

- **Ca²⁺ imaging**: Here, glomerular (olfactory bulb) activity following stimulation by an odorant can be estimated by *in situ* fluorescence microscopy using fluorescent indicators targeting Ca²⁺ as a marker of neuronal activity.

- **cAMP levels upon odorant-induced OR activation:** Following odorant stimulation, fluorescence is recorded in cells that express OR (in vitro) and have been transfected with a plasmid fluorescent reporter gene that is activated by cAMP.
- **In situ olfactory sensory neuron activity recording:** Ribosomal protein S6 is phosphorylated in activated neurons. Following odorant stimulation, activated neurons can be counted in situ using immunohistochemistry that targets phosphorylated ribosomal S6 protein.
- **Electroolfactogram (EOG):** Negative electrical potential evoked by odorous stimulation can be recorded at the surface of the olfactory epithelium (ex vivo animal models).
- **Olfactometry:** Using an olfactometer, diluted single or mixed odorants in the gaseous phase can be presented to subjects for psychophysical analysis (in vivo).
- **Behavioral response:** An olfactory discrimination test (in vivo) was used in rats. The perception of odorants of interest was associated with a sugar reward. In newborn rabbits, the olfactory response toward the mammary pheromone can be measured by analyzing the sucking reflex when the newborn rabbits are exposed to a glass-rod soaked in a solution containing the pheromone.
- **Sensory evaluation:** The quality of odor stimulation is evaluated using psychophysical tests (in vivo).

5.3.1.3 Studies

This section describes the different strategies used to clarify the function of OMEs in the olfactory process.

5.3.1.3.1 Odorant metabolism

The metabolism of volatile, airborne molecules that are environmentally toxic (paint, air pollutants, and similar compounds) was first investigated in vertebrates. The metabolism of a significant but more limited number of odorant molecules produced by the food or perfume industries has been investigated more recently as a way to study the function of OMEs in olfaction. Chromatographic analysis (see [Section 5.3.1.1](#)) has demonstrated the metabolic capacity of olfactory epithelium and nasal tissue toward different classes of molecules. Some examples, classified according to the animal models used, are given below.

In rodents, an animal model widely used in metabolic studies, a number of odorant substrates have been tested, including phenolic aromatic compounds (eugenol, gallicol, coumarin, quinoline, and others) ([Lazard et al., 1991](#); [Thiebaud et al., 2013](#)), terpenes (geraniol) ([Leclerc et al., 2002](#)), aldehydes (pentenal, benzaldehyde) ([Ben-Arie et al., 1993](#); [Nagashima and Touhara, 2010](#)), esters (hexyl, acetate, ethyl acetate, isoamyl acetate, acetyl isoeugenol, and others) ([Leclerc et al., 2002](#); [Robert-Hazotte et al., 2019c](#); [Thiebaud et al., 2013](#)), and ketones (pentane-2,3-dione, hexane-2,3-dione, hexane-3,4-dione) ([Robert-Hazotte et al., 2019c](#)).

The newborn rabbit model was studied to evaluate the animals' behavioral response to the mammary pheromone; in this way, alkenal metabolism was investigated (2-methylbut-2-enal = mammary pheromone, 3-methylbut-2-enal, 2-methyl-2-pentenal) ([Robert-Hazotte et al., 2019a](#); [Faure et al., 2016](#); [Legendre et al., 2014](#)).

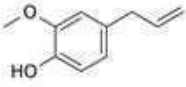
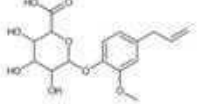
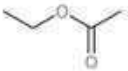
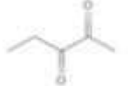
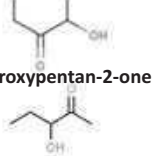
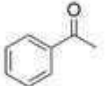
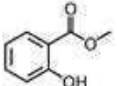
In humans, real-time mass spectrometry was used to characterize the metabolism of a phenone (2-methoxy-acetophenone) ([Schilling et al., 2010](#)), an ester (styralyl

acetate) (Schilling et al., 2010), ketones (pentane-2,3-dione, hexane-3,4-dione) (Robert-Hazotte et al., 2018), a thiol (2-furfurylthiol), an aldehyde (hexanal), and an ester (benzyl acetate) (Ijichi et al., 2019).

In these studies, measurement of the metabolism of the compounds often included characterization of their metabolites. Table 5.2 presents examples of substrates and metabolites associated with different classes of OMEs.

Using an enzymatic competitive assay in rats and humans, glutathione transferases located in the olfactory and respiratory epithelia were shown to metabolize a large panel of odorants. The odorants identified as substrates of OMEs include cinnamaldehyde, limonene, nonanal, citral, and carvone. The assay used in this work is based on measurement of the activity of the purified recombinant enzyme toward a chromophoric substrate in the presence and absence of an odorant. A reduction in activity in the presence of an odorant indicates an interaction between the enzyme and the

Table 5.2 Examples of odorant OME substrates and their corresponding metabolites

Substrate	EMO	Metabolite
Eugenol 	UDP-glucuronosyltransferase (UGT)	Eugenol glucuronide 
2-Methylbut-2-enal 	Glutathione Transferase (GST)	2-Methylbut-2-enal glutathione conjugated metabolites 
Ethyl acetate 	Carboxylesterase (CE)	Ethanol, acetic acid 
Pentane-2,3-dione 	Dicarbonyl Xylulose Reductase (DCXR)	2-Hydroxypentan-3-one, 3-Hydroxypentan-2-one 
Acetophenone 	Cytochrome P450 (CYP)	Methyl salicylate 

odorant molecule. Enzyme assays using recombinant purified enzymes can also be used to directly measure metabolite formation and thereby to assess whether odorant interactions with enzymes are enzymatically efficient (Heydel et al., 2019b; Schwartz et al., 2020). Metabolite measurements can be performed, for example, using chromatographic approaches (Fig. 5.4D).

Recently, OME activities toward odorants were additionally supported by work that solved the structure of an OME in complex with an odorant, the cinnamaldehyde link to glutathione after catalysis (glutathione-dihydrocinnamaldehyde) (Schwartz et al., 2020) (Fig. 5.4E). Knowledge of the structure of an OME in complex with an odorant opens the way to molecular modeling studies. It should allow us to predict, *in silico*, odorant substrates for the enzyme.

5.3.1.3.2 Odorant metabolism rate

The metabolism of odorant molecules was characterized by the identification of phase I and phase II metabolites. As expected, phase I metabolites showed volatility and odor descriptors close to those of the initial odorant, supporting a role of these secondary molecules in the overall odor quality through the stimulation of additional olfactory receptors. Intrinsically, the olfactory process is highly dynamic, starting with the very rapid detection of odorants by the receptors. Therefore, to ensure an adequate support for olfactory function, odorant enzymatic metabolism must exhibit a rate in the time range of odorant delivery to the OE (0.1–2 s) (Youngentob et al., 1987). The strategy used to evaluate the odorant metabolic rate in mammals was to measure the time of appearance of a metabolite following exposure of the tissue to an odorant. Such exposure can be performed *ex vivo* or *in vivo*. A recent *ex vivo* investigation in which the headspace real-time PTR-MS method was used with OE tissue explants (Fig. 5.4B) showed that the time required to metabolize different odorants was in the range of hundreds of milliseconds (Robert-Hazotte et al., 2019a,c), in agreement with the speed range of odor detection (Szyszka et al., 2014). The same method used *in vivo* in humans showed the presence of metabolites in the air exhaled from the nose approximately 300 ms after injection of an odorant into a nostril (Robert-Hazotte et al., 2018). Other studies conducted under similar conditions also concluded that the metabolism of odorants is very rapid (Fig. 5.4C), since the metabolite was detected in the first air exhaled from the nose (Ijichi et al., 2019; Schilling et al., 2010).

The olfactory function of OMEs has been investigated by disrupting their action at various levels. Complementary results have been obtained, which all support a significant role of OMEs in olfaction.

5.3.1.3.3 OMEs inhibition

As indicated above, the olfactory metabolism of esters has been characterized in rodents. Using bis(*p*-nitrophenyl) phosphate (BNPP), an inhibitor of carboxylesterase activity, it was shown by *in situ* Ca²⁺ imaging that the olfactory bulb glomerular pattern toward acetyl isoeugenol changed in comparison with the control (Nagashima and Touhara, 2010). Odor perception was also affected by BNPP since the mice had difficulty in discriminating acetyl isoeugenol in behavioral tests. Both of these results

suggest that metabolism, i.e., the synthesis of metabolites, can influence olfactory perception. In another study, BNPP inhibition applied in an EOG experiment showed that the intensity of the signal increased immediately after treatment with BNPP, indicating that odorant metabolism is necessary for signal termination (Thiebaud et al., 2013). In mice, it has been shown that the metabolism of acetophenone is cytochrome P450-dependent (Cyp1a2) (Asakawa et al., 2017). The results of experiments in which in situ olfactory sensory neuron activity was recorded (see Section 5.3.1.2), after treatment with the CYP inhibitor 1-aminobenzotriazole, confirmed the role of the methyl salicylate metabolite in the response to acetophenone (Asakawa et al., 2017).

In newborn rabbits, a mammary pheromone secreted in the mother's milk triggers the sucking reflex, which is measurable using the simple glass-rod behavioral paradigm (see Section 5.3.1.2). The dependence of this event on olfactory metabolism by glutathione transferase (GST) was characterized (Faure et al., 2016; Legendre et al., 2014). In an ex vivo experiment using an explant of EO and headspace GC-FID, the authors demonstrated for the first time the competitive metabolism of two odorants, 2-methylbut-2-enal (the mammary pheromone) and 2-methyl-2-pentenal (Hanser et al., 2017). The impact of this metabolic competition on the mammary pheromone perception was tested using the glass-rod paradigm. Strikingly, the authors observed a greater perception of the mammary pheromone when it was present in a mixture with the competitor, suggesting that the competitor inhibited the mammary pheromone metabolism and that as a result, the pheromone accumulated and activated more OR, leading to a higher perception. This was the first demonstration of a functional "odorant–odorant metabolic interaction." An inhibitory strategy was also used in vivo in humans in experiments on the metabolism of a ketone odorant ("ketone 55"). The ketone 55 nasal metabolism, which is CYP2A13 dependent, was previously characterized, yielding a metabolite that was identified (data not shown). Following the concomitant exposure of the subjects to ketone 55 and a specific inhibitor or CYP2A13, the subjects described a strong reduction in the raspberry odor corresponding to the odor descriptor of the metabolite. Here, once again, the metabolites appear to play a functional role in the perception of the overall olfactory signal. In humans, an inhibitory strategy similar to that used in newborn rabbits (see above) was conducted in vivo using another odorant as a competitive inhibitor of the olfactory metabolism of the odorant of interest (Robert-Hazotte et al., 2018). The authors first characterized the dicarbonyl-xylulose reductase (DCXR)-dependent metabolism of diketone pentane-2,3-dione and then showed metabolic competition (using the DCXR recombinant enzyme and the methodologies shown in Fig. 5.4D between the odorant butanoic acid and pentane-2,3-dione, the metabolism of which was partially inhibited. Thereafter, olfactometry experiments showed that a subthreshold mixture of the two odorants led to a significantly higher perception of pentane-2,3-dione, confirming that disruption of the metabolism of an odorant by "odorant–odorant metabolism interaction" can lead to higher nasal availability, more sensitive detection, and *fine* perception.

5.3.1.3.4 Addition or removal of OMEs

Cellular heterologous systems that express ORs have been widely used to study OR activation by odorants (cAMP levels upon odorant-induced OR activation, see [Section 5.3.1.2](#)). Coexpression of OMEs in these systems can lead to a better understanding of the function of OMEs. Using such a system, the authors showed that the presence of OMEs changes OR activity in response to odorants ([Kida et al., 2018](#)). They thus demonstrated that metabolites resulting from carboxylesterase activity (Ces1d) activated ORs distinct from the parent odorant, highlighting the stimulus properties of metabolites and the function of OMEs in the generation of new stimuli. Using the same methodological approach, a similar conclusion was obtained in cells expressing Cyp1a1, which metabolizes acetophenone by synthesizing the methyl salicylate metabolite ([Asakawa et al., 2017](#)). The authors showed that the metabolite activated a particular OR (MOR161.2). A study conducted in newborn rabbits investigated the impact of the *in vivo* removal of the enzymes responsible for the metabolism of the mammary pheromone. Glutathione transferases involved in mammary pheromone metabolism were localized to the olfactory mucus of the newborn animals. The authors washed the noses of the animals to eliminate the enzymes present in the mucus and thus achieved a significantly lower detection threshold in the glass-rod test (see [Section 5.3.1.2](#)), indicating that OMEs are indeed involved in the control of signal sensitivity.

5.3.1.3.5 Inversion of the metabolic reaction

Recently, precise localization of UGT2A1 in the membranes of rat olfactory cilia provided the first evidence suggesting that OMEs colocalize with olfactory receptors, supporting a potential cooperation between them ([Neiers et al., 2021](#)). In this study, the odorant metabolism directed by UGT2A1 was experimentally impaired by the use of a glucuronidase enzyme that is able to invert the phase II conjugation of odorants catalyzed by UGT2A1, thereby releasing the parent odorant from the metabolites. Accordingly, in the presence of glucuronidase, EOG experiments with eugenol, a substrate of UGT2A1, showed a higher response than that obtained in the control due to the release of eugenol immediately after its conjugation. These results support the idea that UGT2A1 functions in signal termination.

5.3.1.3.6 Adaptation to the metabolite

In humans, the metabolism of 2-furfurylthiol was characterized *in vivo* using PTR-MS. Exhaled air was shown to contain the metabolite furfuryl methylsulfide at a concentration higher than the perception threshold ([Ijichi et al., 2019](#)). The authors asked whether detection of this metabolite by OR contributes to the olfactory signal. They set up a cross-adaptation study consisting of, first, reduction of the sensitivity (adaptation) toward the metabolite obtained by overstimulation with it, followed by stimulation with the parent odorant (2-furfurylthiol) and sensory evaluation tests. Under these experimental conditions, the perceived intensities of the odors of 2-furfurylthiol and its metabolite furfuryl methylsulfide were significantly decreased, suggesting that the metabolites participate in the modulation of perception.

5.4 Conclusion

For years, the sole presence of OMEs, which were detected in early research in olfactory tissues in various animal species, including insects, was considered sufficient to indicate their putative role in the clearance of odorants in excess from the receptor environment. Studies in insects were the first to explore the true function of metabolizing enzymes in olfaction (Maibeche-Coisne et al., 2004; Rogers et al., 1999). However, we have seen in this chapter that during the last decade, knowledge regarding this process in vertebrates has increased significantly, making it clear that this perireceptor mechanism is an essential part of the peripheral olfactory process. A convergence of the results that supports a functional role of OMEs in olfaction can be observed, although the experiments were conducted in different animal models and using different strategies and methodologies. Signal termination is the number one function with regard to the preservation of the sensitivity of the process, but we have seen that in the course of its action, the metabolism can modify the quality of the signal by producing metabolites that act as additional stimuli. Therefore, depending on the odorant, odorant metabolism can increase the complexity of the signal, which then becomes a mixture of the parent odorant and its metabolites. It has also been shown that “odorant—odorant interaction” occurs at the level of metabolizing enzymes. This suggests that the odorants in a mixture may act as competitors with respect to their metabolism and that this competition could result in a modified perception when one odorant is metabolized at the expense of the other, as observed in rabbits and humans. This particular point may partially explain the inconsistent results observed in the perception of mixtures. In addition to the increasing accumulation of data regarding the expression and localization of OMEs, it is also interesting to note that one enzyme (UGT2A1) has been found to be expressed in the close vicinity of ORs in the plasma membrane of olfactory cilia. This localization, which occurs in addition to the presence of OMEs in the olfactory mucus, supports the efficient and rapid metabolism of odorants that has recently been demonstrated; however, other investigations, such as the determination of the kinetic parameters of recombinant OMEs, will be interesting and may make it possible to better characterize the odorant metabolic rate. Other interesting perspectives appear in light of the modulation of the expression of these enzymes in the olfactory mucus and mucosa during human aging (Yoshikawa et al., 2018). Moreover, the level of expression of these enzymes in rat olfactory mucosa also appears to be linked to the presence of microbiota. Indeed, a lower level of expression of some of these enzymes (e.g., UGT2A1) is observed in the absence of nasal microbiota (Francois et al., 2016).

On the whole, ORs and OMEs appear to interact closely in the olfactory process since their expression appears to be modulated (development, polymorphism, etc.); they are the locus of competitive mechanisms, and one (OME) can clear or synthesize stimuli for the other (OR). For those interested in olfactory physiology or in aroma or fragrance manufacture, odorant reception and metabolism may be seen as a collaborative mechanism that enables organisms to better evaluate odors and manage their perception.

Acknowledgments

We thank Manon Biehlmann for her help in the writing and figures conception of the manuscript. This work was supported by grants from FEDER (fonds Européen de développement régional), the Regional Council of Burgundy, the Agence Nationale de la Recherche: number ANR-18-CE92-0018–01; ANR-16-CE21- 0004-01 <https://anr.fr>.

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Olfactory integration and odor perception

6

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List of abbreviations

AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
cAMP	Cyclic adenylyl cyclase
cGMP	Cyclic guanylyl cyclase
CIT	Citral
EISO	Ethyl isobutyrate
EM	Ethyl maltol
GABA	Gamma aminobutyric acid
GR	Glucocorticoid receptor
IP3	Inositol-1,4,5-trisphosphate
ISO	Isoamyl acetate
LiSS	Ligand-induced selective signaling
MTC	Mitral-tufted cell
OB	Olfactory bulb
OCT	Octanal/octanol
OM	Olfactory epithelium
OR	Olfactory receptor
OSN	Olfactory sensory neurons
PC	Piriform cortex
WL	Whiskey lactone
XME	Xenobiotic metabolism enzymes

6.1 Introduction

Odors are very complex stimuli, which are mainly raised by mixtures of odorant chemical compounds displaying different degrees of volatility. The volatility is directly related to a substance's vapor pressure¹ at a given temperature; substances with higher

¹ Vapor pressure: In a closed container, molecules from a volatile liquid escape the liquid phase and become vapor. These gaseous molecules strike the wall of the container, exerting what's known as vapor pressure. Vapor pressure is directly proportional to temperature. Increasing temperature will increase the ratio of gas: liquid molecules, thereby increasing vapor pressure.

vapor pressure vaporize more readily than a substance with a lower vapor pressure. Thus, for a given combination of odorant molecules, the compounds compete with each other for constituting the gaseous phase; this competition depends on both individual volatility properties and ratios in which the compounds are present. Altogether, this will result in a unique and precise fragrance of an odor item. The quasi infinite variety of odorant compounds and their combinations, combined with the wide range of their volatility properties, imply that the olfactory system must be thus highly sensitive and highly adaptable to new items.

In addition to having to face limitless and constantly moving stimuli, the peripheral olfactory system needs to regenerate. Indeed, in the nose, the sensory neurons are directly in contact with the exterior and can be damaged by thermal or chemical aggressions. Such an exposition is compensated by the fact that these neurons are continuously and cyclically renewed throughout the life ([Graziadei, 1973](#)). Lastly, the olfactory system must be operating from very early in the organism's life, since it intervenes in numerous survival behaviors like predator avoidance, the bounding of the young to the mother, and foraging behavior, which starts at birth by the nipple search.

The olfactory system per se comprises three main levels, which are the olfactory epithelium (OM, peripheral level), the olfactory bulb (OB, first central relay), and the piriform cortex (PC, primary cortical level). As a phylogenetically very ancient system, the olfactory system developed various adaptive strategies to face the world of odors, and it can analyze and encode them as either juxtapositions of odorant elements (elemental coding) or as constructions (olfactory gestalts = synthetic coding), or both, and this as a function of the physiological needs or motivational events.

In this chapter, the peripheral odor processing steps will not be described according to their chronological order. Indeed, the normal time frame for the operational steps, for odorant molecules reaching the OM, is binding, signaling, and coding (building of the output neural message). However, to our mind, it will be easier for the reader to understand the peripheral process in the following order: binding, coding, and signaling, the latter event shedding light on the coding mechanisms.

6.2 Peripheral odorant processing: everything begins in the nose

6.2.1 Odorants binding

The nasal cavities comprise several turbinates (three in human, four in rat or mouse), which are lined with the respiratory and OM. However, in humans, OM is limited to the upper end of the nasal cavity, which is just below the cribriform plate, through which the primary olfactory axons connect OB. This results in a surface of OM of about 2 cm² in humans against 10 cm² in rats, for example. However, despite such a huge anatomic restriction, the human olfactory system presents remarkable performances, which placed it far ahead of visual and auditory systems ([Bushdid et al., 2014](#)).

In terrestrial animals, the nose samples odorant molecules in the inhaled air. The crucial initial step which governs the odor perception is that of the interaction between

odorant molecules with specialized receptors, expressed by the olfactory sensory neurons (OSNs) lying in the OM. Through our natural rhythm of breath, the odorant molecules are captured by the mucus covering the OM and then, reach the cilia of OSNs and bind with odor receptors (ORs). In terrestrial animals ORs are devoted to airborne odorants. Over the animal kingdom, the number of genes encoding ORs varies between species and tends to decrease with the emergence of the visual perception of colors (Rouquier and Giorgi, 2007). For example, there are 906 genes in humans (from which only 322 would be functional (Glusman et al., 2001)), 1094 in dog and 1493 in rat (Quignon et al., 2005).

It was at the beginning of the 1990s that ORs were identified (Buck and Axel, 1991). ORs are G protein-coupled receptors (GPCRs), which have a common architecture consisting of seven transmembrane domains, connected by extracellular and intracellular loops and belong to the rhodopsin subfamily which comprises 672 family members, including 388 ORs (in humans). Because GPCRs present the general feature of being highly “druggable,” since then one-third of all current therapeutics are directed at them; an emerging point of view is that among these 388 ORs, most of them could be soon identified as being not only odorant targets but also drug targets (Millar and Newton, 2010).

Soon after OR identification, a core of data provided evidence that only one OR subtype (Buck and Axel, 1991; Ngai et al., 1993; Kishimoto et al., 1994) was expressed in each mature OSN in such a way that each OSN and its OR can be considered as a single unit (Chess et al., 1994; Serizawa et al., 2000, 2003), although each OSN may transiently express multiple OR at immature stage (Tan et al., 2015). OSNs expressing the same OR gene are distributed over spatially restricted zones in the OM (Ressler et al., 1993; Vassar et al., 1993); however, although the exact number of zones and their physiological function remain in debate (Bashkistrova et al., 2020; Coppola et al., 2019; Horowitz et al., 2014; Miyamichi et al., 2005; Zapiec and Mombaerts, 2020), it can be asserted that the “one OR-one OSN rules” would have one fundamental anatomo-functional role—that of ensuring the precise wiring between the olfactory epithelium zones and bulb glomeruli during the development and then over the OSNs’ cyclic renewing.

From a functional point of view, single OSN-OR units have been demonstrated as being mainly able to interact, with more or less affinity, with a large ensemble of odorant molecules leading to build a combinatorial code for odorant perception (Duchamp-Viret et al., 1999; Malnic et al., 1999; Kepchiaet al., 2017; Kida et al., 2018)(Lee et al., 2017)

Because most olfactory stimuli are blends of odorant molecules, at each breath, several molecules constituting the olfactory stimulus have the opportunity to simultaneously interact with each OSN. Thus, odorant—odorant interactions occur at OR level and OSN-OR units are signal integrators.

Odorant binary mixtures appear as inducing two kinds of OR binding interactions: competitive and noncompetitive (Rospars et al., 2008; Pfister et al., 2020; Singh et al., 2019a), which likely account for most interactions observed between two odorants—competitive ones for most suppressions (Rospars et al., 2008) and rather allosteric ones for synergistic interactions (Munch et al., 2013; Pfister et al., 2020).

In competitive interactions, the most affine and/or concentrated molecule would bind ORs at the expense of the least one. From [Singh et al. \(2019a\)](#), a minimal biophysical model of odorant–receptor interaction incorporating just the simplest possible nonlinearity, namely competition between molecules for the binding site, can successfully predict the responses of many mammalian odor receptors to complex molecular mixtures.

In non-competitive mechanisms linked to allosteric phenomena, one odorant could change the affinity and/or efficacy of OR for another odorant. [Rosparis et al. \(2008\)](#) concluded that probability of allosteric changes would increase logarithmically with the number of interacting molecules in mixture and would be quite common with natural complex odors.

6.2.2 Odorant coding

Odor coding at the periphery is central to solve the olfactory perception secret. Combinatorial coding and receptor modulation mechanisms reveal that odorant-binding at the periphery is not a passive interface that translates chemical data into electrical signals. Given that OSNs can function as signal integrators, they actively structure the chemical data that reaches the brain. It is imperative to understand and model odor coding principles based on the OSN/OR activity ([Ache, 2020](#), [Kurian et al., 2021](#)).

From the perceptual point of view in humans, the mixtures of volatile odorant molecules found in the environment are perceived in a nonlinear way. Indeed, synergy, overshadowing, masking, synthetic ([Livermore and Laing, 1998](#); [Kay et al., 2003](#)) and elemental (or analytic) processing appear to be involved ([Berglund and Engen, 1993](#)). These processes are simultaneously and complementarily exerted. Like other things, they allow the olfactory system to recognize a complex fragrance made of different odorants as an homogeneous ([Berglund et al., 1976](#)) or a synthetic object, (the rose) and they allow to distinguish two close fragrances (Damask or Bourbon rose) by detecting some molecule(s), sometimes present at only minute concentration(s).

The observed perceptual olfactory rules led us to think that suppressive and synergistic interactions among odorant could have a peripheral origin. The demonstration needed to identify peripheral “mixture interactions” by comparing the magnitude of the observed OSN’s responses when odorants are presented in mixture compared to when they are presented individually. In mammals, the first study giving a connection between the perceptive interactions of compounds in mixtures and individual neuronal responses was an *in vivo* electrophysiological approach ([Duchamp-Viret et al., 2003](#)). By analyzing single OSN’s responses to binary mixtures, we observed several types of odorant–odorant interactions which we defined according to the terminology used in psychophysics when the perceived intensities of single odors and mixtures were compared ([Laing et al., 1984, 1989](#); [Laska and Hudson, 1993](#); [Cometto-Muniz et al., 1999](#)). To do so, the perceived intensity was replaced by the discharge spike frequency of single OSN responses.

According to this correspondence, the OSN responses to mixture could reflect “hypoaddition” mechanisms, i.e., the neuronal response frequency to the mixture was equivalent to the response frequency induced by the most effective component

at the same concentration, the least effective compound in no way affecting its action. The OSN responses reflected also what was termed “suppression” (in psychophysics) in which, the mixture response frequency was lower than the frequency induced by the most effective component at the same concentration, or less than the response to either component, as initially defined by Cain and Drexler (1974) and Bell et al. (1987).

By contrast to suppression, the response frequency to the binary mixture could be higher than the one induced by the most effective component at the same concentration. Such odorant–odorant interaction was termed “synergy” (comprising partial and complete additivity mechanisms termed by Cometto-Muniz et al., 1999). Synergy implies, at least, that the two odor molecules do not counteract each other in binding processes and, at best, that they act in positive cooperation. Synergy is illustrated in Fig. 6.1. As exemplified, synergy mainly occurs on the lowest concentration range

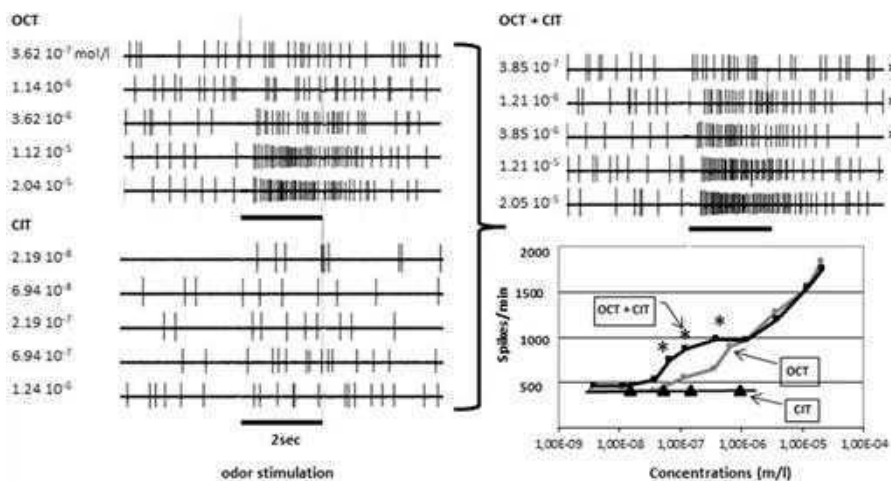


Figure 6.1 Unitary electrophysiological responses of one OSN, recorded in vivo in rat, illustrating the synergic action of CITral and OCTanal (raw spike recordings). On the left, are shown the five stimulation sequences recorded in response to OCT or CIT at increasing concentration from top to bottom. OCT induced excitatory responses which spike frequency increased with concentrations. CIT did not induce any response. Top right: OCT + CIT mixture induced, as OCT alone, excitatory response which spike frequency increased with concentrations. However, even by eye it can be seen that the three lowest concentrations (stars) of mixtures elicited higher frequency firing bursts than OCT alone. This increased efficiency is ascribed to the presence of OCT, which acts in synergy with OCT although, it was not stimulating alone. The response-curve graph plots OSN response frequencies against the total concentration for CIT, OCT, and mixture. The curves evidenced that CIT and OCT act in synergy for the three lowest mixture concentrations (stars) but at higher ones, the compounds rather act according to hypoaddition mechanisms: the presence of CIT did not alter the concentration/response curve, which perfectly overlapped the curve obtained with OCT alone. Thus, because CIT alone did not induce activation, in perceptual terms, we propose that OCT may be the dominating compound for which the perceptive intensity is increased by the presence of CIT, in the lower range of concentrations. The black horizontal bars under the single recordings indicate the 2-s stimulation delivery.

Table 6.1 Synthesis of the odorant–odorant interactions observed throughout single OSN recorded in vivo in rats. Odorant molecules: camphor (CAM), cineole (CIN), citralva (CITV), menthone (MENT), isoamyl acetate (ISO), anisole (ANI), acetophenone (ACE), *l*- and *d*-carvone (*l*, *d*-CAR); methyl-amyl-ketone (MAK); LIM), ethylvanillin (EVAN), lilial (LIL), lylal (LYR), whiskey lactone (WL), citral (CIT), octanal (OCT), ethyl isobutyrate (EISO), ethyl maltol (EM). See the extended description in the text

	Odorant molecules (by couple)			SUPPRESSION	SYNERGY	HYPO-ADDITION
Duchamp-Viret et al., 2003	Low SVP odorants CIN, CITV, MENT, ISO, ANI, ACE, CAR, MAK, LIM.	High SVP odorants CAM, LIL, LYR EVAN	Experimental High SVP + low SVP	21%	20%	59%
Chaput et al., 2012	ISO	WL	Real wine aroma	45%	25%	30%
Duchamp-Viret, 2015	CIT	OCT	Agonist/antagonist	62%	25%	13%
Petryzyn, Ferry, Duchamp-Viret, (Unpublished data)	EISO	EM	Aromatic accord	28%	43%	28%

of odorants thus boosting the detection power of single OSNs, for either the mixture regarding the single compounds, or one of compounds, depending on if the coding mode is elemental or synthetic for the mixture in question.

Throughout these electrophysiological in vivo experiments, the OSN responses have been analyzed for several couples of odorants (Table 6.1). In doing so, our major and common and unexpected outcome was that the type of odorant–odorant interaction, and the ratio in which they are expressed, relied more on the odorant identities than on the OSN/OR types (see the “odor signaling” paragraph). In our pioneer study (Duchamp-Viret et al., 2003), we designed experimental binary mixtures by associating one low volatile compound (low SVP compounds the concentration of which is comprised between 10^{-10} and $<10^{-6}$ mol/L: see odorant at left in Table 6.1) with one high volatile one (high SVP compound the concentration of which is $>10^{-6}$ mol/L: CAM, EVAN, LIL, LYR). The major outcome of this first study was that the low SVP molecules mainly exert suppressive action on high SVP activating molecules.

Then we focused on the couple isoamyl acetate (ISO) and whiskey lactone (WL), known as bearing the fruity and woody notes of Burgundy red wine (Chaput et al., 2012). This couple is described by human subjects as evolving toward the dominance of one compound or another, according the ratio and concentration of each of the compounds. From OSN responses, WL appeared as mainly reducing the ISO induced activation while, to a lesser extent, being able to synergize them. In suppressive interactions, fruity note responses are reduced in dose-dependent manner by low concentrations of woody odorants. The recent studies of De March et al. (2020), fully confirmed our observations with the same odorant couple ISO/WL. Such influence of the woody compound on the fruity one on OSN responses supports the observed

perceptual interactions between the fruity and woody notes in wines (Atanasova et al., 2005) and could match the subtle aromatic balance between these two notes observed for red wines (Thomas-Danguin et al., 2009).

Next, we studied the couple octanal-citral (OCT-CIT, Duchamp-Viret, 2016), described as acting as agonist and antagonist for common ORs (Ukhanov et al., 2010). Interestingly, their major odorant–odorant interaction was suppression which can be explained by the signaling pathways they elicited (Ukhanov et al., 2010, 2011; see next section).

More recently Duchamp-Viret et al. (2021) studied the couple ethyl isobutyrate (EISO) and ethyl maltol (EM), deemed to constitute an aromatic accord (pineapple accord) at a certain ratio, or elemental mixture at another ratio (in animal: Coureaud et al., 2011, and human: Thomas-Danguin et al., 2014). The remarkable result was that the electrophysiological responses to the binary EISO/EM mixture at the elemental ratio mainly reflected suppressive interactions between the two compounds whereas at the aromatic tuning ratio they rather reflected hypoaddition, indicating that the synthetic and elemental coding was partially and initially based on the OSNs' responses.

From the whole of our electrophysiological studies, suppressive interactions appeared to be the most common form of interaction between odorants at OSNs/ORs level. Consistently, Zak et al. (2020) found widespread antagonistic interactions in binary odor mixtures by imaging OSN axon terminals in olfactory bulb glomeruli as well as OSN bodies within the olfactory epithelium in freely breathing mice. They further noticed that in complex mixtures of up to 12 odorants, antagonistic interactions are stronger and more prevalent with increasing mixture complexity. In parallel, a recent and converging set of data (De March et al., 2020; Inagaki et al., 2020; Kurian et al., 2021; McClintock et al., 2020; Pfister et al., 2020; Xu et al., 2020; Zak et al., 2020) described how the building of the peripheral OSN combinatorial code was complexified by odorant–odorant interactions leading to widespread inhibitions. Specifically, the results show that peripheral odor coding involves odorants acting on ORs as agonists, antagonists, inverse agonists, partial agonists, and even have a synergistic effect. As an example, a two-photon imaging of OSN in vivo reports that inhibitory responses already exist at the level of OSN somata and are widespread phenomena in the mammalian OSNs (Inagaki et al., 2020). Contemporarily, the extensive study of Xu et al. (2020) confirms the quantitative importance of inhibitory mechanisms at OSN level. Altogether, antagonism leading to inhibitory mechanisms being a common feature of odor mixture encoding in OSNs, it would expand the spectrum of odor coding—allowing the combinatorial codes of mixtures to differ from the simple summation of the OR response patterns of the component odorants (De March et al., 2020) and help in normalizing activity to reduce saturation and increase information transfer (Zak et al., 2020).

The analysis of OSN responses led us to conclude that, at the OM stage, odorant mixtures would be processed by large ensembles of OSNs/ORs throughout odorant–odorant interaction widespread mechanisms, the latter mainly depending on the compound identity and, to a lesser extent, on the OSN/OR entity. The extensive inhibition, antagonism, and synergy at the peripheral level contributes to the robust odor coding in the mammalian olfactory system.

6.2.3 Odorant signaling

As extensively described in the synthesis of [Ronnett and Moon \(2002\)](#), the binding between one odorant and compatible ORs initiates intracellular signal transduction mechanisms, which result in converting olfactory stimuli into electrical signals. This binding induced ORs' conformational changes which led to the olfactory-specific G-protein (*Golf*) activation, this resulting in stimulating adenyl cyclase (cAMP). Then, the cAMP concentration increases, causing the opening of a cyclic nucleotide-gated channel, and the entrance of Na^{++} and calcium ions (see [Boccaccio et al., 2021](#) for a review) ([Nakamura and Gold, 1987](#); [Firestein and Werblin, 1989](#)).

Beside the major cAMP signaling, odorant binding can also increase phosphoinositide hydrolysis and the production of inositol-1, 4, 5-trisphosphate (IP3) ([Ronnett et al., 1993](#); [Breer and Boekhoff, 1991](#); [Miyamoto et al., 1992](#); [Schandar et al., 1998](#)) as well as cyclic guanylyl cyclase (GMP) production. The cAMP pathway has been demonstrated to be the indispensable requirement for the olfactory response genesis ([Wong et al., 2000](#)), while the IP3 one merely appears as secondary, which would mainly intervene in complement to the first one. Lastly, the GMP pathway would not be involved in the early phase of the olfactory peripheral responses, but would rather intervene in modulation or desensitization of OSN's response ([Zufall and Leinders-Zufall, 2000](#)).

How do the intracellular signaling pathways connect the odorant coding observations? [Ukhanov et al. \(2010, 2011\)](#) deciphered some of the intracellular signaling mechanisms, underlying odorant–odorant interactions by recording single OSN calcium responses in vitro. Indeed, they demonstrated that, in a simple binary mixture, the two components could alone and simultaneously engage two distinct signaling pathways, namely cAMP and IP3 ones, acting in opposite directions on CNGC channels, thus on the OSN polarization. Finally, in agreement with previous work and hypotheses [Spehr et al. \(2002\)](#), [Zhainazarov et al. \(2004\)](#), [Brady et al. \(2006\)](#), [Ukhanov et al. \(2011\)](#) showed that the IP3 pathway solicitation exerts an inhibitory influence and can be proposed as the intracellular signaling supporting odorant–odorant suppressive interactions. This suppressive mechanism would be a widespread property of odorants regardless the OR type ([Ukhanov et al., 2011, 2013](#)). This observation is in agreement with our in vivo observations ([Duchamp-Viret et al., 2003](#); [Chaput et al., 2012](#) and personal unpublished data). Having more than one mechanism underlying peripheral inhibition likely reflects the importance of this functionality to olfactory integration.

However, one true question which remains is: How does the selection of PI3K (over cAMP) pathway occur regardless of the OR type? ORs could be therefore viewed as a signaling pathway gate ([Ukhanov et al., 2011](#)) wherein cAMP, the prominent signaling pathway may be engaged or disengaged in favor of PI3K pathway, according to “the nature of the ligand and the dynamically changing intracellular environment.” The two pathways, IP3 and cAMP, are thus differentially triggered according to the ligand-induced selective signaling (LiSS, [Millar and Newton, 2010](#)). The concept of LiSS was demonstrated for many G-protein-coupled receptors (GPCRs) to which ORs belong and states that the nature of the ligand and the dynamically changing intracellular environment can alter the manner of signaling for many different GPCRs ([Rosenbaum et al., 2009](#); [Millar and Newton, 2010](#)). This implies that the receptor

would be not simply activated or inactivated but would adopt many conformations; each of them leading to a highly specific ligand–receptor interaction and each conformation acting in turn with a specific intracellular signaling complex. [Millar and Newton \(2010\)](#) wrote: “The LiSS concept is creating a new level of sophistication, which challenges the dogma that ligand engagement of a GPCR consistently elicits a specific intracellular signal.” However, the preponderance of a signaling pathway in an OSN may stabilize one conformation among others, leading the OR to increase its specificity for certain ligands.

Noteworthy is that odorant binding and signaling mechanisms, linked to the GPCR functioning comprising the LiSS concept, enlighten extremely promising explanations for supporting the odorant processing sophistication observed at OSN-OR level. Indeed, depending on the OR, each putative ligand could be the weakest or the strongest one(s). Thus, from these complex and multiplexed interactions either dominating or interacting odorants will arise. For interacting odorants, molecular interactions at binding/transduction levels could be mutually suppressive or synergistic. Suppressive and synergic interactions between components directly affect the perception of odor mixtures and could make surge synthetic information about olfactory objects since the peripheral stage.

6.2.4 Perireceptor events

The term “perireceptor events” gathers all events, which could facilitate, limit, delay, or block odor signaling, i.e., interactions between chemical molecules and ORs. The nasal mucus, which is secreted by Bowman glands, protects the OM and ensures ionic environment favorable to the transport of odorant molecules and to electrogenesis in the OSN’s cilia. The mucus contains some of the main elements involved in perireceptor events: the olfactory binding proteins and xenobiotic metabolism enzymes (XME; [Heydel et al., 2013, 2019](#)). The lipophilic characteristic of odorant molecules involves the existence of transport mechanisms to facilitate their access to ORs; this role is filled by OBPs, secreted by nasal gland, which interact with odorant molecules ([Nagnan-Le Meillour, 2018](#)). XMEs are degradation enzymes and catalyze numerous biotransformations of the exogenous compounds which will make them excretable via biologic fluids, especially throughout the large blood vascularization of OM. XMEs are very largely present in the organism, especially in the liver, for example, and comprise several enzyme families which are classified according to their three-phase action: functionalization, conjugation, and excretion. In OM, several types of toxic agents can be present and XMEs are expressed very early in the organism life; some of them appearing as directly regulated as a function of the olfactory system development. Because OSNs, and more largely the OM, can offer a privileged gateway to the brain ([Minn et al., 2002](#)), it is especially crucial for the peripheral system to set up a line of defense via XMEs, and maybe also via OBPs ([Pernollet and Briand, 2004](#)). In addition to XMEs and OBPs, small protecting proteins (heat shock proteins) could also intervene when OM is exposed to some chemicals, odorant or nonodorant molecules ([Carr et al., 2001](#)). Lastly, antioxidative enzymes are also highly expressed in OM ([Reed et al., 2003](#)).

Because they are highly expressed in OM, XMEs could also ensure the biotransformation of odorant molecules, thereby preventing OSNs' saturation and (or) eventual toxic effects at high concentrations. The results that, in rats, OM global responses to quinoline, coumarin, or isoamyl acetate (electro-olfactograms) were shown to be increased by blocking XMEs highly support for such a role (Thiebaud et al., 2013). XMEs could thus both change odorant stimulating properties and (or) favor the clearance of odorant molecules (Asakawa et al., 2017; Hanser et al., 2017; Ijichi et al., 2019; Robert-Hazotte et al., 2019). Moreover, because XMEs are expressed very early in the OM, they could also be involved in perceptive modulation of some specific odor signal as, for example, of mammary pheromone by the newborn rabbits (Legendre et al., 2014; Hanser et al., 2017). As a temporary conclusion, it can be proposed that, in addition to their role of toxicological barrier, XMEs would play a role in the odor peripheral processing, which is, at the moment, undoubtedly undervalued (Heydel et al., 2019; Neiers et al., 2021) and would widen the olfactory perception mechanisms; for example, the expression of one XME has been shown to increase in fasting rats (Longo et al., 2000). This part is more detailed in Chapter 6.

6.2.5 Conclusion

Odor processing at the periphery is central to unravel the secret of odor final perception. Along the binding, signaling, and coding events, the interactions of odorants with OR-OSN entities include several successive steps in which the complexity originates first, in the ability of OR-OSN to interact with large sets of molecules; second, in duality of binding interaction modes; third, in the plurality of intracellular signaling; and fourth, in the LiSS concept. These successive peripheral steps probably interrelate, involving not only the various odorant qualities but their concentrations and ratios; as the interdependence increases and becomes more complex, so do the odorant mixtures. The result is that the mixture components can simultaneously act as agonist, antagonist, or inverse agonist and so build the unique and precise OSNs' combination which will define simple as well as highly complex mixtures. Such combined possibilities should almost infinitely widen the peripheral coding possibilities, which appear as being in perfect agreement with the quasi infinite number of stimuli.

6.3 OB odorant processing

6.3.1 Peripheral signal amplification: convergence

Once primarily integrated by OSNs, the olfactory signal is relayed in the OB, as the first central relay. Overall, electrophysiological data indicate that the OB filters and transforms the incoming peripheral message, so that, for example, signal-to-noise enhancement, normalization (Zak et al., 2020), and contrast enhancement operations (Haney et al., 2018; Adams et al., 2019) occur before the processed olfactory information diverges to the olfactory cortices (Persaud, 2013).

In OB, OSN-axons make synapse at level of discrete, dense, subspherical neuropil structures, called glomeruli (Fig. 6.2). The “one OR-one OSN rule” designs the projection map; OSNs expressing a given OR converge on the same glomeruli and

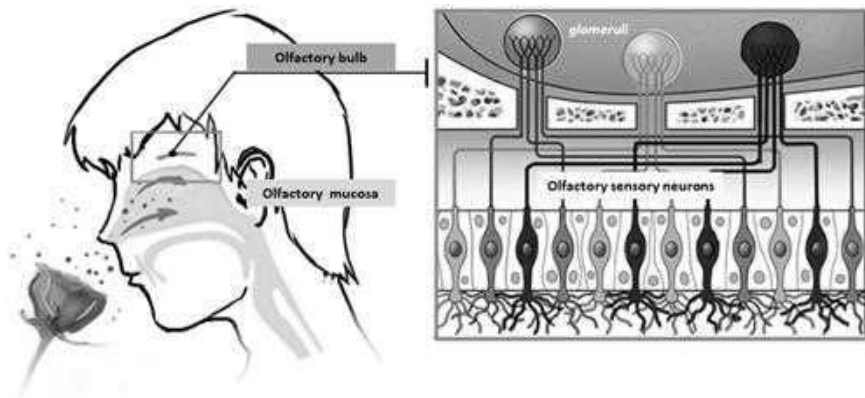


Figure 6.2 Anatomical scheme of first two stages of the olfactory system detailing the projection of OSNs' axons on OB: OSNs expressing the same OR type (light gray, dark gray, or black), converge to the same glomerulus. This stereotyped projection originates a spatial map in glomeruli.

each glomerulus receives only one type of OR projection (Treloar et al., 2002; Vassar et al., 1994). Accordingly, volume of each glomerulus linearly correlates with the number of connected OSNs, making glomerulus's size a highly reliable indicator of OSN number in the OM (Bressel et al., 2016). This immutable rule allows the olfactory system to be operating very early in the organism's life and then, throughout life, a stable rewiring for the new OSNs originating from the cyclic and constant neurogenesis (Cheung et al., 2013).

The OSN-axons convergence ratio depends on the ratio between the total number of expressed OR genes and glomeruli (Maresh et al., 2008; Zapiec and Mombaerts, 2015). For example, in mice, each OSN express only 1 of possible 1100 ORs, thus the 3600 glomeruli yield a convergence ratio that approximates 1 OR for 3 glomeruli. In humans, only 350 intact genes are expressed, thus the 5500 glomeruli yield a convergence ratio of 1 OR for 16 glomeruli. The glomerular structuring is intrinsically induced by OSNs' endings (Takeuchi and Sakano, 2014) and is so robust that if OB is experimentally removed, they form ectopic glomeruli on the first brain targets they encounter (Nakatani et al., 2003; Graziadei et al., 1978; Graziadei and Samanen, 1980).

Whatever the species, one glomerulus and the main output neurons, namely mitral-tufted cells (MTCs), connected to it, receive the peripheral information from thousands of OSNs expressing the same OR (Hellman and Chess, 2002). This quantitative convergence results in amplification of weak signals (van Drongelen et al., 1978). In computational terms, this averages out uncorrelated noise and leads to an increase in the signal-to-noise ratio (Persaud, 2013). Consequently, MTCs can statistically detect odorants at lower concentrations than individual OSNs can do (Duchamp-Viret et al., 1989).

In the OB, not only MTCs receive the OSN input but also periglomerular interneurons (PG), mainly GABAergic, which form simple inhibitory and reciprocal synapses with MTCs. We have demonstrated that GABAergic PG cells exerted a gain control

mechanism: they maintain MTCs under a tonic inhibition in order to limit the effect of quantitative convergent inputs; such control results in widening the MTC coding concentration range over several log units of concentration (Duchamp-Viret and Duchamp, 1993). Indeed, if the PG inhibitory network is pharmacologically blocked, MTCs shift their response threshold toward lower concentrations and the slope of their concentration/firing frequency response-curve became steeper. In addition, PG tonic inhibition was also shown as modulating MCT spontaneous activity and thus the signal-to-noise ratio (Duchamp-Viret et al., 2000; Rospars et al., 1994). The second main inhibitory control of MTC excitability is exerted by GABAergic neurons located deeper in OB; granular interneurons which also influence MTC spontaneous and evoked activity, and finalize the output rhythm of the OB information (Duchamp-Viret et al., 1993) thus contributing to the synchronization of co-active MTC columns (Egger and Kuner, 2021). However, some basal forebrain GABAergic neurons target OB granular interneurons leading to a functional disinhibition of MCs (Duchamp-Viret et al., 1993); this central modulation of intrabulbar GABAergic circuit likely reduces spike precision of MC cells and lowers the intensity of oscillatory activity in the OB, thus influencing the MCs' temporal and spatial dynamics (Villar et al., 2021).

6.3.2 *Peripheral input mapping: sorting*

As seen above, the sorting out and convergence of OSNs' axons, is strictly built from the genetically preestablished "one OR-one OSN rule." As such, the stereotyped projection on OB creates a spatial map of activated glomeruli targeted by OSN responses. The pervasiveness of the glomerular map explains why many studies attempted to establish the extent to which it relates a chemotropic stimulus representation on which quality coding and discrimination would be based (Tabor et al., 2004; Lin Da et al., 2006; Carlsson et al., 2007; Johnson and Leon, 2007; Silbering and Galizia, 2007; Grossman et al., 2008; Krofczik et al., 2008; Frederick et al., 2009; Johnson et al., 2009; Kuebler et al., 2012; Meyer and Galizia, 2012; Schubert et al., 2014). More especially, by analyzing glomerular patterns for odor mixtures, the question was to know if OB processing rather prioritizes the elemental odorant components or engenders a global code, or the reverse, or ensures both. The preservation of elemental component information implies a linear summation of single compound patterns, although giving birth to a completely novel quality from mixture would imply nonlinear summation of single compound patterns (Fig. 6.3). The issue being raised, the analysis of the bibliography led us to report that regardless the animal model, from insect to the mammal, data and conclusions failed to reach consensus. Indeed, according to the author, the comparison of the glomerular patterning, induced by single components or their mixtures, reflects either a linear summation or a non-linear combination of single compound patterns. However, from recent works, the linear summation hypothesis seems more and more implausible and really too much simplistic. Indeed, [Economo et al. \(2019\)](#) report that as well as OSNs, glomerular responses quantitatively amplify and integrate the activity of OSNs endowed with the same OR and mainly show suppressive interactions between odorants. Thus, inhibitory OB circuits nonlinearly transform odor representations and support a model of selective and

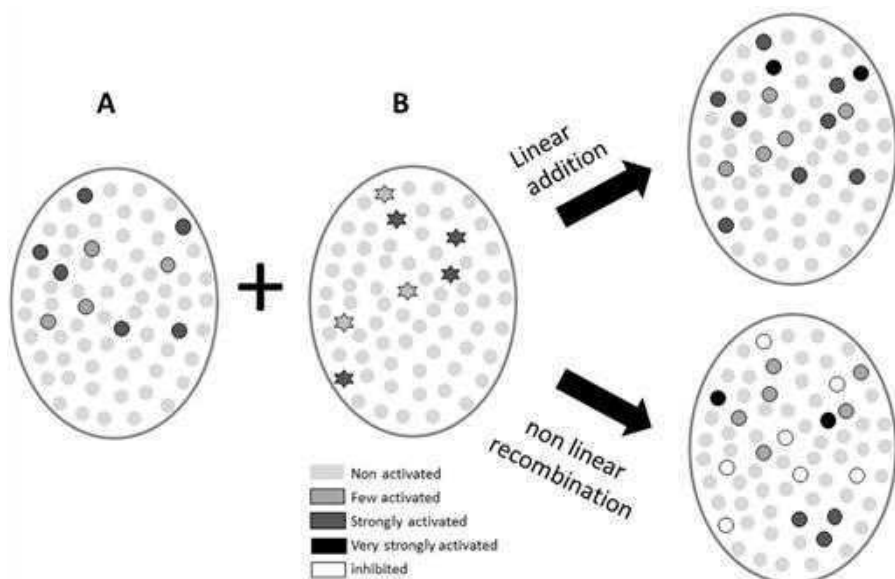


Figure 6.3 Schematic and theoretical representation of an odor-induced glomerular map (view of OB dorsal part). Glomeruli are represented by *dots*. No activated glomeruli remain in light gray, activated glomeruli are the black-countered *dots* or stars; darker the *dot*/stars, more activated the glomerulus. By activating glomeruli, the odorant A gives birth to the left map, and B to right one. The binary mixture A + B gives birth to a glomerular map which is either the linear addition of A and B maps (top right corner) or a recombination (lower right corner). The proposed recombination includes inhibited glomeruli (white-filled black-countered *dots*) as recently described by [Zavitz et al. \(2020\)](#) but is totally hypothetical and various other types may have been imagined.

nonrandom inhibition among glomerular ensembles ([Economo et al., 2016](#); [Zavitz et al., 2020](#)). It remains that, as shown by Bhattacharjee and colleagues, the similarity of two glomerular patterns and their activation strength can carry a part of the resemblance between two stimuli ([Bhattacharjee et al., 2019](#)), the time needed by mice to discriminate these stimuli being inversely correlated.

The apparent topographical shape of the OB information may be the tree that hides the forest since, in any case, neuronal information is not fixed in a given time and therefore in a fixed spatial configuration. Indeed, the spatial dimension must not make us forget the fine temporal dimension of the OB network activation, the electrical events which are playing at the millisecond scale, the scale of MTCs' spiking activities. Meaningful information from the OB is indeed provided by the temporal and dynamic activities of the MTC elicited by sensory inputs; the activation time of the glomeruli itself can be exploited to extract odor-related information ([Perl et al., 2020](#)). Throughout their firing response patterns, single MTC responses could encode both elementary information about mixtures' chemical composition, or synthetic olfactory objects. Indeed, some MCT responses to mixtures were very similar to responses to one of the component and appeared as mainly devoted to the elemental mixture coding ([Giraudet et al., 2002](#); [Wilson and Stevenson, 2003](#); [Tabor et al., 2004](#)). By contrast, in

other MTCs, temporal response patterns to mixtures were clearly distinct from those to single components. Such emergence of a specific response temporal patterns for mixture would rather favor synthetic mixture coding (Wilson and Stevenson, 2003), the latter remaining also based, at less partly, on spatial pattern of activated glomeruli (Chong et al., 2020).

Initially, Wehr and Laurent (1996) proposed that the MTC odor code would be based on fine temporal tuning of spiking activity within cell assemblies (Fig. 6.4). The authors presented such a coding mode in OB as an alternative to the spatial one; the two codes can of course coexist and complement each other (Economo et al., 2016). These synchronized assemblies would transfer sensory information throughout burst sequences using the gamma oscillation as a clock (Cenier et al., 2009; David et al., 2009; Gschwend et al., 2012). Thus, the brain would assign “meaning” to the temporal pattern in which MTC assemblies would succeed.

The perceptual responses not only depended on which groups of MTCs were activated, but also on their activation latencies, i.e., “temporal sequences akin to timed notes in a melody” (as written by Chong et al., 2020). The latter authors using single-spot optogenetic stimulation of the OB, mimicking synthetic odors showed that temporal perturbations (<10 ms) in the sequence of activation of OB spots led to graded changes in perception in mice. They proposed that the most perceptually relevant activation latencies were defined relative to other cells; earlier-activated cells

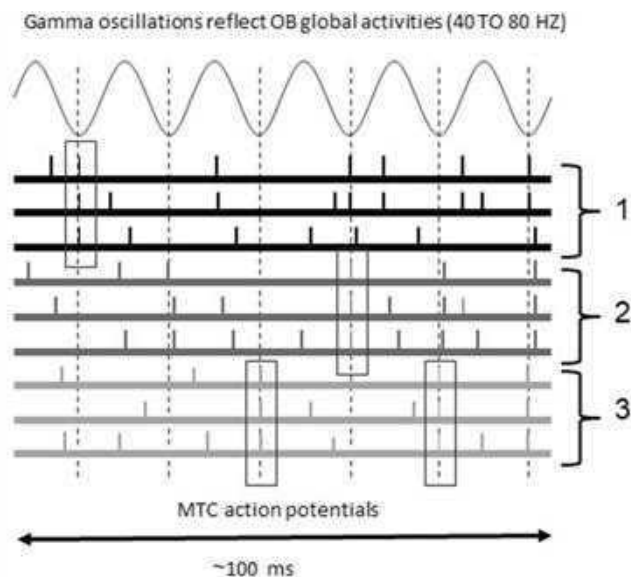


Figure 6.4 Illustration of the coding theory based on synchronized neural assemblies. In response to olfactory stimulus, some MTC are activated and some synchrony occurs in small fractions of spikes (black surrounded rectangle) thus defining three neural assemblies. Here, the code is not only defined by the activated MTCs, but also by the precise temporal sequence (black, light gray, dark gray, and light gray again) in which the three assemblies intervene. The MTC synchronization is furthermore clocked on gamma OB oscillations. Such a code offers a reliable, robust, very precise and flexible code and supports the complex mixture combinatorial codes.

in the sequence had a larger effect on behavioral responses. In mice also, using a 2P photostimulation of individual neurons, [Gill et al. \(2020\)](#) described how inhalation of different odors leads to changes in the set of neurons activated, as well as when neurons are activated relative to each other (synchrony) and the onset of inhalation (latency). The authors underlined that stimulus detection depends strongly on the synchrony of activation across neurons; mice being able to detect single action potentials evoked synchronously across less than 20 MTCs.

OB coding has been shown as being largely impacted and morphed by wakefulness, experience, and memory, and further, by stimulus physiological relevance ([Bhalla and Bower, 1997](#); [Linster and Hasselmo, 1997](#); [Buonviso et al., 1998](#); [Carey et al., 2009](#); [Buonviso and Chaput, 2000](#); [Gschwend et al., 2012](#); [Kato et al., 2012](#); [Patterson et al., 2013](#)); (non-exhaustive citations). Among others, because mammals dynamically sample odorants and can discriminate them in one breath, OB mixture coding is de facto impacted by breathing rhythm and wakefulness. Indeed, the OB circuit is characterized by beta and gamma oscillations nested in a slower theta carrier wave ascribed to respiration ([Buonviso et al., 2003](#); [Rojas-Libano et al., 2014](#)).

In awake rodents, MTC responses constitute more discriminative odor representations than in anesthetized animals, throughout a diversification of their temporal dynamics ([Kato et al., 2012](#)). As a matter of fact, in addition to the basic respiratory rhythm (2–4 Hz), the arrival of volatile stimuli in the nose triggers active sampling behavior (sniffing-rhythm) whose ranges can vary from 2 to 12 Hz. Furthermore, even in the absence of odor the rhythmic movement of air is thought to cause activity locked to this rhythm in OSNs ([Rospars et al., 2008](#); [Iwata et al., 2017](#)) and MTCs ([Bathellier et al., 2008](#); [Moran et al., 2021](#); [Ackels et al., 2020](#)), forming the fundamental rhythm that shapes much activity within the early olfactory states.

MTC temporal synchronization (evaluated through local field potential recordings) have been shown modulated by the animal experience ([Martin et al., 2004](#); [Martin et al., 2006](#); [Courtiol et al., 2011](#); [Vinograd et al., 2017](#); [Ramirez-Gordillo et al., 2018](#); [Liu et al., 2020](#); [Kudryavitskaya et al., 2021](#), etc.). Additionally, changes in the balance between sensory and corticofugal inputs to OB interneurons can alter timing of beta and gamma oscillatory states, suggesting that information transfer from the OB is influenced by top-down signaling ([David et al., 2015](#)). Very recently, [Losacco et al. \(2020\)](#) asked whether the high gamma and beta oscillations carry different information when they are observed within particular phase windows of the theta carrier wave during associative learning. The authors concluded that the encoding of stimulus identity from high gamma oscillation changed.

Indeed, by coupling experience and precise submillisecond synchrony, MTCs' assemblies can convey both odor identity and its reward meaning. Such a synchrony relates a small fraction of spikes in MTC pairs and was observed between MTCs which may be at any distance apart in OB. ([Doucette et al., 2011](#)) proposed that the precise OB synchrony would be mainly established and reinforced by coincident excitatory centrifugal inputs ([Restrepo et al., 2009](#); [Matsutani, 2010](#)).

Thus, by operating concurrently and simultaneously, synchrony, rate- and sniff-locked coding would specify various stimulus features giving birth to a multiplexed code ([Gire et al., 2013](#)). Such a multiplexed code at different timescales appears all

the more relevant in the olfactory system, since the latter has to face multidimensional stimuli the inputs of which can be fragmented across OB (Cleland and Sethupathy, 2006) and to link to them associational significance to arbitrary combinations of these inputs; sniff-phase MTC discharges may constitute dense identity coding and, sparse synchrony may convey behavioral relevant information.

What about discrimination for binary mixtures? MTC response temporal patterns to a binary mixture have been shown as smoothly morphing from the first component pattern to the second component one, reflecting more or less their respective concentration ratio (Shen et al., 2013). Moreover during odor morphing, some MTC responses to mixtures temporally shifted regarding the respiratory phase; such phase-position should provide supplemental neuron-level parameter for synthetic odor mixtures (Khan et al., 2012). By observing both simple additivity and novel time-locked representations of odor mixture, the latter authors concluded that MTC temporal responses to mixtures could morph from elemental to synthetic representations. To our point of view, given odorant-odorant interactions occurring at OSNs' level, the notion of "simple additivity" would not stand up facing a mixture more complex than a binary one. Indeed, Barnes et al. (2008) by using 10 component mixtures reported that MTC responses were not simply predictable from the change in stimulus (one component being removed or exchanged).

Mixture sensory coding implies both discrimination and stable representation of stimuli. Indeed, the olfactory system needs to discriminate but also to recognize, even some missing information, and to categorize stimuli according to experience or familiarity; the latter process being an appropriate "generalization." What about the olfactory perceptual stability throughout the MTC response morphing? From Shen et al. (2013), OB temporal response patterns reflect some completion or generalization mechanisms; this of course, to a much lesser degree than piriform cortex cells (PC) do.

As a conclusion, it should be retained that MTC fine temporal activities result in morphing assemblies the activities of which are thus shaped by the OB intrinsic network, synchronized on respiratory, gamma, or beta oscillations' rhythm and highly under centrifugal control. Throughout their activation patterns, MTC responses could encode both elementary information about mixtures' chemical composition or synthetic olfactory objects. However, a multiplexed code based simultaneously on MTC time-locked firing and synchrony appears capable of ensuring simultaneously the odor quality coding and behavioral relevance. Lastly, if MTCs in response to odor mixture appear as being especially gifted to perform discrimination among close stimuli (Khan et al., 2012; Shen et al., 2013), they are also able to make some completion or generalization, as PCs are (Shen et al., 2013).

6.4 The piriform cortex: birth of the odorant percept

6.4.1 *Spatial disorganization and odor identity coding through neuron ensembles: elemental or synthetic coding mode?*

The OB directly and mainly projects on the piriform cortex (PC), the largest subregion of the olfactory cortex, which is probably the locus for the formation of the odor

percept. This projection does not follow any apparent topographic rule (Ghosh et al., 2011; Miyamichi et al., 2011; Sosulski et al., 2011), in such a manner that single odors activate a distributed subpopulation of neurons across the cortex without spatial preference (Rennaker et al., 2007; Poo and Isaacson, 2009; Stettler and Axel, 2009; Zhan and Luo, 2010). The projection mode of MTCs on PC neurons is both spatially divergent (Ojima et al., 1984) and quantitatively convergent (Franks and Isaacson, 2006). Such a loss of the spatiality between OB and PC (Sosulski et al., 2011) means that in the two structures the coding mechanisms should be based on different odor representations (Carey and Wachowiak, 2011; Shusterman et al., 2011; Miura et al., 2012). Stettler and Axel (2009) literally wrote: “PC discards OB spatial segregation as well as chemotropy and returns to a highly dispersed organization in which different odorants activate unique ensembles of cortical neurons” (Stettler and Axel, 2009).

Indeed, in PC, two different odorant molecules elicit two distinct, sparse, not clustered in space, and partially overlapping activity patterns of PC neurons (Roland et al., 2017). PC neurons are impinged from multiple MTCs and are activated only if these MTCs are synchronously stimulated. This mechanism increases the discrimination of odorants that are structurally similar. In fact, although two similar odorants generate very close spatial patterns in OB glomeruli, they will activate different and multiplexed PC neurons, generating two clearcut ensembles in PC without topographic organization. The earliest coactive cells in OB have an outsized role in shaping odor representations in PC (Wilson et al., 2017; Stern et al., 2018). Blazing and Franks (2020) have just revealed that simply knowing which PC neurons fired action potentials within the first 100 msec. after inhalation is sufficient to accurately classify odors. In addition, electrophysiological recordings from large populations of PC neurons revealed that odor identity can be decoded using simple binary response vectors of activated PC neurons, while odor intensity is best decoded using the spike timing of the population. These results suggest that PC may use a multiplexed, ensemble-membership identity code and an ensemble synchrony code for odor intensity (Bolding and Franks, 2017, p. 2018).

Regarding odorant mixtures, the questions are: How are mixtures represented in the piriform cortex? Can the identity of components be read out from mixture representations in the piriform cortex? These two questions are tackled by Penker et al. (2020). In PC, interactions between components illustrate the same type of interactions previously reported from OSN and MTC responses; PC neurons thus integrate non-linear representations from OB and OM responses. They showed mainly hypoaddition and suppression, according to data reported in OSNs, and rarely synergy; however, “mixture-specific” PC neurons described by Stettler and Axel (2009) likely involved synergy.

From the start, Wilson et al. replaced the cortical mixture coding issue in the context of experience, memory, and learning (Wilson, 2003; Wilson et al., 2006). From the author, 10 or 50 s of odorant stimulation seem to be enough to establish a synthetic representation of mixture in PC neurons, and to discriminate it from individual components. For the authors, PC appears as characterized by a rapid neural plasticity, experienced PC neurons gaining in competence. Such, implicit memory and learning would highly contribute to PC processing in a way that odors are analyzed regarding where,

when, and in what context their perception occurred. [Wilson and Stevenson \(2003\)](#) propose that this functioning rather promotes a synthetic rather than an analytic coding, and that analytical feature discrimination is only an initial step. As a matter of fact, most common tasks that mammals should achieve are mixture identifications and involve a synthetic treatment of olfactory information (gestalt recognition) rather than an elementary analysis of distinct odorants.

However, such a most common functioning does not alter the fact that mixture elemental information is kept in PC. Indeed, by comparing electrophysiological PC neuron responses to a configural mixture to those evoked by an elemental mixture, [Wilson et al. \(2020\)](#) reported that the elemental mixture was coded as similar to the components while the configural mixture was coded as distinct from its components. Moreover, mixture components can be identified from PC activity by pooling responses of a small population of neurons ([Penker et al., 2020](#)).

Altogether, elemental and synthetic olfactory coding modes appear as being simultaneously performed all along the olfactory pathways. Thanks to the olfactory system performances, we are not obliged to choose between one or the other since the two information types are available, even being more or less easily accessible. Intuitively, the synthetic mode should mainly depend on learning and memory and would likely occur at both OB and PC levels. However, at OSNs' level, some synthetic attributes of odorants emerge early from mixture interactions ([Duchamp-Viret et al., 2021](#)).

6.4.2 Discrimination against generalization: pattern separation or pattern completion?

The important features of PC neurons should be linked to experience, learning, and memory thanks to which PC neuron ensembles appear as capable to ensure the perception stability throughout “completion” processing, while it remains acute for discriminating the perception variability throughout “separation.”

The olfactory system discrimination abilities are high and could be exerted on very similar stimuli and PC representations are well suited to perform signal to background discrimination without the need for learning ([Penker et al., 2020](#)). Recent models even propose that target single odorant can be detected against background mixture thanks to some single PC neurons ([Mathis et al., 2016](#); [Singh et al., 2019b](#)). However, if some tasks or behaviors require discriminating between very close odors, others require assimilating these similar odors as being the same general percept. The olfactory system's abilities should thus balance the two main perceptual necessities, which are stability (for recognition despite missing element) and discrimination (for relevant choice). [Barnes et al. \(2008\)](#) reported that, despite the fact that some single PCs respond differentially to close, overlapping mixtures, the cortical ensemble could disregard some missing and consistent functions with pattern completion. Such a completion allows minor variation in the stimulus to be disregarded, a function that is critical for stability of olfactory percept of complex stimuli ([Wilson, 2009](#)).

Interestingly, changes in PC neuronal responses are more important when one constituent was substituted in the mixture than when one was simply removed

(Barnes et al., 2008). Thus these authors showed that PC neuron ensemble responses progressively decorrelated when the initial mixture was progressively depleted in components. However, some individual PC neurons easily “refilled” one missing element, by processing some “pattern completion.” By contrast, if one mixture element is replaced by a new one, the PC perceptual balance became clearly in favor of discrimination; PC neurons clearly detected the novel element by processing some “pattern separation” (Barnes et al., 2008). Thus this suggests that one compound replacement in an odor mixture should be easily detected. Some available data on behavioral discrimination abilities in rats (Barnes et al., 2008; Lovitz et al., 2012) and humans (Ferreira et al., 2002) confirm this suggestion.

In addition to operant learning, recent evidence suggests that PC can also support unsupervised learning, in which repeated presentation of an odor selectively strengthens synapses between coactive neurons to form odor neuron assemblies that can then help stabilize odor-evoked cortical activity patterns, and therefore presumably odor percept (Bolding et al., 2020; Pashkovski et al., 2020).

6.4.3 Piriform cortex: a pure associative cortex?

PC neuronal circuits transform OB input to implement different computations that support features of odor perception such as concentration invariance and odor learning. Thus PC is not a static sensory feature detector, but is instead a dynamic circuit that continuously shapes odor representations to extract statistical regularities in the odor environment to facilitate adaptable, odor-driven behaviors (Endo et al., 2020).

PC appears as an archeocortex within which the pure associative processing (Wilson and Rennaker, 2010) may be based on random both convergent and divergent excitatory inputs from MTCs (Stettler and Axel, 2009; Blazing and Franks, 2020). The associative processing rather promotes synthetic rather than analytical coding modes (Wilson and Rennaker, 2010). The processing of complex stimulus patterns and defining objects by associative circuits, both allow the robust stimulus recognition despite missing inputs and discrimination of overlapping patterns.

Because the odorant world contains a limitless number of items, OSNs are not selective in order to face this reality, and both OB and PC structures may match a pure associative processing. Let us admit for a while that the olfactory function would be based on absolutely not preformatted neuron networks (on a functional point of view) and let us follow the related line of reasoning. Since the organism birth, the olfactory hardwiring, managed by OR-dependent immutable rules, ensures the anatomical stability of OB inputs. On this basis, the representation of the stimulus at the OB level would mainly depend on, and evolve with, the animal experience. In naïve animals, the hardwiring would ensure an olfactory perception since the first odorant molecule docks OSNs. No recognition, no discrimination, only perception. Then, molecule by molecule, scent by scent, the olfactory experience would enrich by matching sensory information with encountered olfactory items and segregating odorous signals; relevant from irrelevant, nociceptive from innocuous, palatable from nonpalatable, etc. Here qualitative and quantitative parameters of the olfactory signals are connected with the story of individuals, throughout individual and

collective memory and learning. Progressively the olfactory software will develop, establishing in the OB and cortex highly adapted and adaptable working networks, which would process the information according to the organism holistic point of view. Of course, such a hypothesis although proposing OB and PC processes entirely based on experience networks does not exclude some invariants which are imposed by wiring rules; reproducible glomerular maps can be observed in several animals. Altogether, the ancient sense of olfaction is robust, suitably efficient, and especially highly adaptable to the changing extrinsic or intrinsic environment of living organisms.

6.5 Plasticity mechanisms at the peripheral and OB levels

Throughout the phylogenetic evolution, given the crucial involvement of olfaction in vital behaviors, the olfactory system has given priority to the functioning sustainability and robustness. In addition, given the limitless and constantly changing number of potential stimuli, the olfactory system also gave priority to plasticity. Such priorities may account for some of the exceptional features which are expressed all along the olfactory pathways, from the periphery to cortices.

6.5.1 *Peripheral olfactory-experienced induction or imprinting*

In olfaction, a major process that implements and modulates perception and contributes to the immediate and long-term adaptation of organisms to their environment is plasticity, which occurs from the peripheral captors. Olfactory perceptual changes (plasticity) induced by sensory experiences have been originally described in humans by Wysocki et al. (1989); these changes have been termed “experienced incidental induction” or imprinting (Nevitt et al., 1994). The mechanisms underlying such plasticity have been then mostly studied in animals, insects, and rodents. Here we will focus on findings regarding plasticity of olfactory perception and on the recent reports, linking this plasticity to molecular, cellular, and functional changes, in the first two stages of the olfactory system.

OSNs are continuously renewed along the lifetimes of individuals (Graziadei, 1973) (turnover: every 6–8 weeks) and the renewal can be paired with OR expression plasticity. During their maturation, neo-OSNs would be “educated” by the surrounding adult OSNs. Indeed, odor-induced activities of the latter might direct their OR expression choice (Mombaerts, 2004; Yu et al., 2004), an established mechanism which would ensure both continuation and plasticity. However, OR expression could also be modulated independently from the OSN cyclic renewal, by the olfactory environment, experience, and internal parameters.

Is perceptual plasticity a general phenomenon? Since the 1980s, Wysocki et al. (1989) reported that the ability to perceive an olfactory stimulus could be acquired by anosmic people. Indeed, several weeks of discrete exposures to androstenone increased the subject sensitivity to this molecule. More recently, olfactory training

(Pekala et al., 2016; Hummel et al., 2018; Jiang et al., 2019) and aversive learning in humans (Cavazzana et al., 2018) have been shown to increase OSNs' responses and olfactory performances for the conditioned stimulus (CS), in normosmic, hyposmic, or anosmic subjects. In animals, odorant exposition or learning has been shown to increase the electrophysiological responses of OSNs (Wang et al., 1993; Nevitt et al., 1994; Youngentob and Kent, 1995). The latter result fits with our recent study in rabbit neonates (Duchamp-Viret et al., 2021). We showed that a single and brief MP-induced odor learning episode was sufficient to alter OSNs' responses to CS and mixtures including it. Moreover, using behavioral tests, we evidenced that CS detection threshold was shifted toward lower concentrations, supporting that MP-induced odor learning relies on induction phenomenon.

Other experiments did not experimentally manipulate the olfactory environment of animals but only reported observations made at different seasons, feeding states, or in coincidence with breeding. European starlings show seasonal differences in their ability to respond to odor cue (De Groof et al., 2010). In *Drosophila*, the expression of chemoreceptor genes such as OBPs proteins was shown to change with age, reproductive state, and social interaction (Zhou et al., 2009). In the mosquito, blood meals were shown to induce a general reduction in antennal transcript levels of chemosensory genes, although a subset of ORs was modestly enhanced after feeding (Rinker et al., 2013). In honeybees, some results suggested that scent environment may regulate floral scent perception (Reinhard et al., 2010). Although no study investigated odor learning and olfactory receptor expression per se, it suggests that experience-induced olfactory receptor plasticity may be a phenomenon occurring in all animals that have to manage changing odor environments.

Is plasticity in OR expression a general phenomenon? Recent experiments done in invertebrates and vertebrates established a clear relationship between changes in perception and OR expression. In insects submitted to an olfactory learning paradigm consisting in pairing the queen pheromone with glucose reward, the expression of the specific OR was downregulated while the peripheral OSN global electrophysiological response was reduced (Claudianos et al., 2014). Although downregulation of some ORs following odor chronicle passive exposition intuitively makes sense, it may seem counterintuitive during memory formation resulting from an olfactory learning. However, a reduced number of ORs can be sufficient for the detection of familiar odorant. Correspondingly, it would be advantageous to have other ORs comparatively upregulated, for example, to ensure that new floral scents are detected, allowing honeybees to adapt to their ever-changing scent environment (Menzel and Muller, 1996; Eisenhardt, 2014).

In mice, effects of odorant exposure on OR number and olfactory sensitivity are contradictory depending on the context (either passive or active, via a positive or negative associative learning, through a continuous or discontinuous exposure). Passive odorant exposure has contrasted effects (Barbour et al., 2008; Cadiou et al., 2014). By contrast, aversive or fear learning using odorant as CS induces huge changes in early sensory processing at OM and OB levels. This increases CS-dedicated OR number and transmitter release probability from activated OSNs, enlarges glomerular size, reduces OB presynaptic inhibition mediated by GABA_b receptors (Jones et al., 2008;

Bhattarai et al., 2020), and the incidence of lateral inhibition in OB interneurons. This latter effect can even lead to a lesser discrimination resulting in a generalization of the fear reaction to several nearby stimuli (Kass and McGann, 2017). Such effects can persist over time and can even be transmitted to the next generation through still unknown mechanisms (Dias and Ressler, 2014). When performed in the perinatal period, which could be assumed to be a positive associative learning due to motherly presence, odor exposure also influences glomerular refinement and functioning with contrasted effects on OSNs/ORs (Kerr and Belluscio, 2006; Todrank et al., 2011; Valle-Leija et al., 2012; Geramita and Urban, 2016; Monjaraz-Fuentes, 2017; Dewaele et al., 2018).

Two recent reports reconcile most of the studies by showing that changes in OSN repertoire abundance (Ibarra-Soria et al., 2017) as well as birth rates of neurons expressing given ORs would be highly dependent on the environment, and therefore on olfactory stimulation (Van der Linden et al., 2020). Along this line, in rabbit neonates conditioned using mammary pheromone odorant (Duchamp-Viret et al., 2021), the increase of OSNs' response to CS supports an increase of either the density of ORs dedicated to CS processing or of the number of OSNs expressing such ORs (mainly through an activity-dependent orientation in OR selection in newly mature OSNs) or both.

Thus, the analysis of the literature currently leads to consider induction as a generic phenomenon, with a "positive side" (enhancement of olfactory abilities) that would mainly occur after discontinuous exposure and/or conditioning, whereas passive and continuous exposure to odor cues would rather reveal a "negative side" (loss in olfactory reactivity or habituation). It can be proposed that such plasticity while leading to a stronger processing of experienced reinforced stimuli would drive the expression of the most adapted peripheral captors (Kass et al., 2016); this selection could potentially lead to quantitatively reduce their number. In conjunction, the system would favor the detection of new odors (new experiences) at captor level. Such a hypothesis would be perfectly adapted to the olfactory system, a sensory system approached by a quasi-infinite number of stimuli. Moreover, olfactory training appears as a potent tool to increase as well as to restore specific olfactory abilities since the periphery (Kim et al., 2019).

6.5.2 Plasticity in OB: tight interdependency between neurogenesis and centrifugal neuromodulator systems

OB integrates the primary sensory information throughout a complex neural network, which is largely under centrifugal controls. Indeed, several neuromodulator systems massively project to OB and are known as crucially involved in plasticity and learning (Matsutani and Yamamoto, 2008) as in food-intake control (Schneider et al., 2020). The main modulator systems are the cholinergic, which centrifugal fibers pass throughout the horizontal part of the Broca band, the serotonergic, originating of raphe nucleus (McLean and Shipley, 1987), and the noradrenergic systems, originating of Locus Coeruleus (Shipley et al., 1985). These modulator systems mainly target the OB periglomerular and granular interneurons, with an emphasis on the latter.

Yet, OB benefits lifelong from the arrival of precursor GABAergic interneurons: up to 1000 daily, migrating from the rostral flow from the subventricular zone (Imayoshi et al., 2008). The integration and survival of these newborn interneurons have been shown as depending on sensory inputs, perceptive or operating learning experiences (Li et al., 2018; Livneh et al., 2009), and centrifugal inputs (Moreno et al., 2012; Hanson et al., 2017, 2020). Indeed, sensory deprivation has been shown as decreasing survival of newborn neurons (Livneh et al., 2009).

From a global point of view, in OB, perceptive plasticity, learning mechanisms, neurogenesis, and centrifugal neuromodulation are strongly interconnected and highly interdependent. Indeed, for example, a blocking of the neurogenesis in the rostral sub-ventricular flow, as well as a manipulation of noradrenergic transmission by OB centrifugal inputs, prevent improvement in odorant discrimination which is normally induced by perceptual learning (Moreno et al., 2009) or by operant learning (Lepousez et al., 2013). In addition, the OB newborn interneurons display a higher level of survival and integration into active OB network, i.e., in animals submitted to odorant exposures (Rocheffort and Lledo, 2005) or operant learning (Mandairon et al., 2011). For the latter, neurogenesis seems essential whereas it does not for some simple discrimination tasks (Imayoshi et al., 2008; Sakamoto et al., 2011). Similarly, a recent study demonstrated the necessity of OB newborn interneurons in complex perceptual learning (Forest et al., 2020) and thus their essential role for olfactory adaptation.

The continuously renewed interneurons are GABAergic, mainly exerting inhibition on MTCs and the centrifugal modulator system highly targets these interneurons. On the whole, these interneurons would especially come to reinforce the OB function of pattern separator (Shani-Narkiss et al., 2020) linked to discriminatory processes. By the way, improvement in discrimination performance is widely observed after training or conditioning. As, for example, after fear learning, which has been shown to enhance perceptual discrimination abilities of very close odor cues (Li et al., 2008) and alter odorant-evoked neural activity in the piriform cortex and olfactory bulb (Li et al., 2008; Fletcher and Bendahmane, 2014). In agreement, in mice, Kass et al. (2013) showed that the pairing of a neutral olfactory stimulus with a shock enhances the OSN responses to this neutral stimulus, and thus their input to OB glomeruli. In addition, such pairing also increased the numbers of OSNs expressing M71 (paired odor specific ORs) and increases the size of target glomeruli in OB (Jones et al., 2008). However, the emotional salience strength of fear learning would be not only especially potent to induce plasticity in conditioned mice, the effects of which could be evidenced throughout all the olfactory pathways, but could influence olfactory behavior and OR expression in subsequent generations (Dias and Ressler, 2014). The prospects opened by the latter results are that experienced induction of genotypic alterations could be transgenerationally inherited.

Altogether, in rodents, the olfactory system appears as especially tuned toward plasticity since within it, the local intrinsic neurogenesis of OSNs and induction mechanisms of ORs are coupled with OB interneuron continuous replacement by newborn neurons coming from the brain sub-ventricular zone. Shani-Narkiss et al. (2020) propose a theoretical model explaining how a small proportion of young and excitable

neurons contribute to efficient coding in the OB mature circuit and hypothesize that such a model would hold in the hippocampus. Moreover, in both the OB and hippocampus, continuous adult neurogenesis has recently been proposed to be involved in the constitution of the neural trace of social memory (Lunardi et al., 2021). However, as expressed by Brennan and Keverne (2015), this raises the question as to how the system balances the necessity of keeping some “old” memories and faces, or prioritizes new information. Of course, the olfactory system could quickly adapt to new environmental chemical cues; however, even in humans, it appears also trustworthy to make surge very ancient remembrances and place the brain under emotional influences. Brennan and Keverne (2015) write that the olfactory system’s adaptability is extravagantly supported by the vast deployment of ORs’ gene and neurogenesis phenomena, and would be especially adapted to the lifestyle of small brain mammals. Indeed, in primates, the gene pool and OB neurogenesis would tend to decrease. Nevertheless, even if, with phylogenetic evolution, neocortex, auditory, and visual information had apparently taken the place of the primary sensory systems for decision, the human olfactory function displays remarkable performances which placed it far ahead of visual and auditory systems (Bushdid et al., 2014).

6.6 Genetic, gender, and aging variations in the olfactory system performances

6.6.1 Genetic variations

In humans, the olfactory sensory perception varies, not only between populations, but also between individuals within a population. Genetic factors largely contribute to these inter-individual differences. Indeed, if the genes encoding olfactory signal transduction cascade are roughly conserved between humans, OR gene loci are one of the most genetically diverse regions in their genome, not only in the coding regions, but also in promoters (Ignatieva et al., 2014). Thus, variations in human smelling abilities could partly result from different functional OR repertoires, variable expressional levels, and polymorphisms in the copy number or sequences of the OR genes (Gilad and Lancet, 2003; Hasin et al., 2008; Trimmer et al., 2019). As a consequence, each individual has a unique set of OR gene repertoire. Such uniqueness should contribute to the diversity of odorant-specific sensitivity phenotypes and appears as supporting a variety of changes in olfactory perception, from subtle odorant-specific to general anosmia (Hasin-Brumshtein et al., 2009; Karstensen and Tommerup, 2012).

Anosmia for specific odorants has been described for dozens of odorant molecules. For the specific anosmia to androstenone described by Wysocki and Beauchamp (1984), the link between an olfactory sensitivity genetic polymorphism originated from gene single mutation of a narrow-tuned receptor, the *OR7D4*, and the specific and complete anosmia has been recently demonstrated (Keller et al., 2007). Elevated detection threshold for the sweaty odorant isovaleric acid, methanethiol, *cis*-3-hexen-1-ol, or β -ionone was also described for allelic variants of *OR11H7P*, *OR2M7*, *OR2J3*

or OR5A1, respectively (Menashe et al., 2007; Eriksson et al., 2010; McRae et al., 2012; Jaeger et al., 2013). At the OB level, a single-nucleotide polymorphism in the voltage-gated potassium Kv1.3 channel was associated with a decreased performance in healthy humans tested with odorant sticks (Guthoff et al., 2009).

In addition to odorant-specific anosmia, more complex disorders, such as general anosmia and severe hyposmia are described in human populations. Congenital general anosmia, an inherited loss of smell, associated or not with other anomalies, is described in a few familial cases. Despite evidence for a strong degree of heritability, no causative mutation has been yet found in the olfactory signaling pathways of these cases (Feldmesser et al., 2007), except a stop mutation in the cyclic nucleotide-gated gene CNGA2 recently identified in two brothers (Karstensen et al., 2015). Anosmia is also part of the clinical picture in various syndromic diseases, for which molecules expressed in the olfactory mucosa are mutated (Karstensen and Tommerup, 2012): in ciliopathies and congenital insensitivity to pain, anosmia results from loss of function mutations in intraciliary transport proteins or in the voltage-gated sodium channel SCN9A, which affects OSN functioning (Kulaga et al., 2004; McEwen et al., 2007; Weiss et al., 2011). In the Kallmann syndrome, a heterogeneous genetic disorder characterized by gonadotrophic deficiency and anosmia, the neuronal migration process during embryogenesis is impaired. Mutations in the KAL1 locus in the X-linked recessive form and other genes in the autosomal dominant form, such as fibroblast growth factor receptor 1 (FGFR1/KAL2), fibroblast growth factor 8 (FGF8/KAL6), PROKR2, and PROK2 are observed (Falardeau et al., 2008; Kim et al., 2008; Dode and Hardelin, 2009; Sarfati et al., 2013). Loss of function of these genes disrupts embryonic migration of the gonadotropin-releasing hormone (GnRH)-synthesizing neurons from the OM to the hypothalamic region of the brain results in OB structural abnormalities that prevent its functioning from the birth. Even if they are rare, these genetic diseases usually result in serious problems in the everyday life of impacted people. Together with problems in the detection of noxious environments, the enjoyment of fragrances and food are diminished, resulting in nutritional imbalances.

Considering the high number of genes involved in the regulation of odorant sensitivity (and among them, the olfactory receptors family), these data reveal a relative low occurrence of dramatic phenotypic effect associated to polymorphism. However, it remains difficult to correlate odor perception and genotype at the peripheral level; genetic OR allele polymorphisms only partly explain the observed variations in perceived intensity or valence (Mainland et al., 2014). In addition, the combinatorial receptor coding rules as well as the peripheral plasticity and induction mechanisms, which impact the olfactory system sensitivity, spread confusion and reduce our chances to identify genetic variations in odorant perception (Wysocki et al., 1989; Wang et al., 2004). However, the exploration of the genetic diversity using highthroughput based tools such as GWAS (genome wide association studies) or next-generation transcriptome sequencing will probably illuminate hundreds of new candidate auxiliary olfactory genes putatively impacting the perception (Keydar et al., 2013). Their identification will be the first step to the development of gene-based therapy.

6.6.2 Gender variations

In chemosensory perception in humans, gender differences are known since the 19th century in terms of detection, discrimination, and identification of odorous substances, particularly regarding the physiological and psychological effects of odorous sex-specific steroids. Women typically outperform men, whatever their age, mostly thanks to sex-specific hormonal, neural, and cognitive advantages. This is particularly true when considering the olfactory sensitization, which is observed in women upon repetitive exposure to previously unscented odors (Dalton et al., 2002; Diamond et al., 2005). Most studies describe a higher sensitivity in women, while some of them fail to show any discernible sexual dimorphism in normal (reviewed in Brand and Millot, 2001; Doty and Cameron, 2009) or symptomatic situations (Malaspina et al., 2012). A gender effect was observed on the ability to detect food odors, women displaying better perception than men (Michon et al., 2009). A recent metaanalysis confirms a weak superiority of female in terms of threshold, discrimination, and identification (Sorowski et al., 2019). However, none of these studies gives any convincing proof of the functional difference at the OM or OB level.

Up to now, there are very few insights into gender differences at the cellular and molecular levels that support published sensibility differences. At the perireception level, sparse data suggest that mucus composition differs between male and female. The alpha-glutathione S transferase, a biotransformation enzyme putatively involved in the termination of odorant signals, and two cyclic nucleotides cAMP and cGMP, are expressed in higher levels in female mucus as compared to male (Krishna et al., 1995; Henkin and Velicu, 2008). Regarding OSNs, no morphologic difference in the number or density of neurons in the mucosa was found between male and female, whatever the age of subjects (Jafari et al., 2008). There is no major sex-related difference in olfactory gene receptor expression too (Verbeurg et al., 2014). In the human OB, the data related to gender indicate an overall smaller volume of the OB, a larger number of neurons and glial cells, but a lower number of tyrosine hydroxylase- and aromatic L-amino acid decarboxylase-positive dopaminergic neurons in women in various regions of the bulb (Buschüter et al., 2008; Oliveira-Pinto et al., 2014; Alizadeh et al., 2015). The results suggest that the olfactory information might be differentially integrated in women and men OB. On the contrary, other authors noticed that there is no gender-related difference in MTCs number and size, which rather supports that the olfactory information processing is similar in men and women (Sama-ul-Haq et al., 2008). Therefore, although minor sexual dimorphisms in the chemosensory performances are evidenced in humans, peripheral olfactory system structural differences should be further documented to support these observations.

In animal models, despite numerous works dealing with this issue, the question is not fully resolved. Most of the reports claiming that the olfactory system of adult rodents is sexually dimorphic have been done in the accessory olfactory system, which responds to sex-differentiated pheromones. This was particularly investigated in flies, where sexually dimorphic neural circuits are described. In rodents, the analysis of the transcriptome of the main and accessory olfactory tissues in mice reveals that some olfactory receptors and OBPs are up- and downregulated in males as compared to

females, these variations being minor (Shiao et al., 2012). In contrast, no difference in the total number of OSN after stereological analyses (Kawagishi et al., 2015) or in the catalog of expressed genes after deep sequencing were found between males and females OM (Kanageswaran et al., 2015). This observation should be weighted according to recent data showing that at least a small population of OSN, devoted to sex-specific semiochemicals and generated by individual experience through a mechanism involving the proapoptotic gene Bax is differentially represented between the sexes (Vihani et al., 2020). At OB level, biochemical analyses revealed minor sex differences: a higher concentration of dopamine and its metabolites, a less restricted clustering of the cell adhesion protocadherin-20 labeling in adults, and a higher number of neurocalcin-immunoreactive interneurons were observed in male (Gomez et al., 2007; Lee et al., 2008). A more conclusive study using in vivo optical neurophysiology has shown that various odorants elicit a more rapid odor-induced signaling response and the activation of more glomeruli in females than in males (Kass et al., 2017). Therefore, sex differences in olfactory abilities likely originate in the variability and functioning of primary sensory neurons and associated glomeruli, but do not exclude other molecular changes supporting the behavioral differences at higher levels as recently shown for the treatment of sexual odors in the amygdala (Kikusui et al., 2018).

6.6.3 Aging variations

Age-related physiological decline in olfactory function has been largely documented in a rich and detailed literature in psychophysiology in humans (Pinto et al., 2015; Godoy et al., 2015). Indeed, such a decline reaches around 2% of the population at 65 years of age, and then rises till 80 years; over 80 years, olfactory deficits are described in 75% of the elderly (Doty, 2009). With aging, all the authors conclude to a decreased detection threshold as well as impaired odor identification and detection, due to cognitive processing deficits as well as peripheral changes in the olfactory system (Rawson, 2012; Mobley et al., 2014; Attems et al., 2015; Kondo et al., 2020) and references herein. Although age-related general olfactory loss (presbyosmia) is a prevalent impairment, aging can differentially affect the olfactory performances. The phenomenon is gradual and multifactorial, since associations with neurodegenerative diseases are found in aged populations. The decline in odor identification performance and cognitive measures with age seems to be sex-dependent, making gender a good predictor of episodic memory (Wehling et al., 2016a,b). Some old subjects seem to display subtle differences in odor sensitivity depending on odorant type; they would become less sensitive to heavy molecules and thus would differentially impair their detection and identification (Sinding et al., 2014).

At the peripheral level, anatomical modifications of the olfactory network due to aging occurs quite early and are visible since 65 years; it consists in a disparate decrease of the OSNs' population and a patchy replacement of the olfactory epithelium by the respiratory one (Paik et al., 1992). These structural modifications may be attributed to a local diminution in nutritive supply to OSN turnover, a diminution in local immunologic or enzymatic defense mechanisms (critical for maintaining the integrity

of the epithelium) as well as to possible defaults in the metabolites' clearance attributable to a decrease of adrenergic innervation of OM blood vessels (Chen et al., 1993; Krishna et al., 1995; Getchell et al., 1995). This could result in changes in mucus composition and de facto affect proteins involved in inflammation, metabolism, and detection of odorants. The abundance of some of these proteins being correlated to age-dependent sensory impairments (Yoshikawa et al., 2018), they could provide early markers of neurodegenerative conditions, such as for schizophrenia, Alzheimer disease, multiple sclerosis, and Parkinson disease (Escada et al., 2009; Kondo et al., 2020). In Alzheimer disease, the olfactory problems would precede classical symptoms, making the latter a crucial indicator for an early detection of this disease (Doty, 2009).

When *in vitro* OSN calcium responses were compared between young and aged human donors, the unexpected result was that OSNs are more responsive in older than in younger subjects (Rawson et al., 2012). The authors interpreted such a result as an age-dependent modification in OSN selectivity; the latter decreased in aged subjects and may be responsible, at least partly, for their difficulties in odorant detection and recognition. Changes in OSN response rate and selectivity could affect glomerular structure and OB processing, even if contradictory data are reported. Indeed, in some cohorts, OB and olfactory tract volumes, number of glomeruli, as well as number of MTCs decline after 50 years of age (Bhatnagar et al., 1987; Yousem et al., 1998; Meisami et al., 1998). Other studies found an unaffected number of glomeruli, but a higher incidence of atypical glomerular patterning (Maresh et al., 2008).

In rodents, age-related changes in the olfactory system appear similar to those in humans while deeper investigations can be done, especially thanks to the use of transgenic mice. Most studies, usually conducted in animals older than 2 years, described a decline in OSN density (Hinds and McNelly, 1981; Lee et al., 2009), paired with a reduction in OSN proliferation associated to a decrease in growth factors signaling (e.g., EGF and IGF-1), and an increase in inflammatory cytokines (Ohta and Ichimura, 2000; Ueha et al., 2018). Surprisingly, despite such age-dependent structural and molecular changes, OR gene expression is relatively stable (Khan et al., 2012) and the overall sensitivity for a variety of odorants is roughly preserved (Loo et al., 1996; Schoenbaum et al., 2002; Lee et al., 2009). However, the detection threshold for simple odorants such as ethyl acetate is better for young rodents than for old ones (Patel and Larson, 2009; Kraemer and Apfelbach, 2004) for which moreover, the fine discrimination of binary odorant mixtures is impaired (Enwere et al., 2004). Consistent with the decrease in OSN densities and impairment in glomerular patterning observed in humans, glomerular axon targeting is increasingly diffuse with age: glomeruli being only partially innervating by OSNs' axons in elderly mice (Costanzo and Kobayashi, 2010). In OB alterations in neuronal long-term survival and differentiation, as well as a diminution in neurons' responsiveness to environmental enrichment would also participate to the impairment in elderly (Rey et al., 2012; Moreno et al., 2014). Yet, *in vivo* optical neurophysiology observations in old mice recently showed that normal aging does not alter OSN response dynamics at OM level, or neurotransmission release and intensity of glomeruli responses, at OB level (Kass et al., 2018). This suggests that a

local circuitry plasticity could preserve odor sensitivity in aging nose, and that changes in higher-order neural circuits that mediate olfactory-driven behaviors may counteract this adaptation.

Thus, in animals and humans, as for other sensory functions, olfaction declines with aging, maybe rather early, while some anatomical and physiological indices are found, since the peripheral stages, and may support such a decline. However, when “olfactory professional brains” are imaged, the story is obviously reversed. Indeed in “old” experienced perfumers, the olfactory expertise does not only counteract this decline but, on the contrary, induces a higher anatomic development of olfactory brain area, as compared with young beginners (Royet et al., 2013).

6.7 Olfactory function under neurohormonal controls (other than those involved in metabolic status)

6.7.1 Stress

Anxiety- and stress-inducing stimuli largely affect the brain structures by activating the hypothalamic-pituitary-adrenal (HPA) axis. If such environmental adversity may temporarily rewire neural circuitry to modulate the cortical processing of odors, data obtained in animals support the idea that HPA activity can impact the peripheral olfactory system level. First, in rodents, the presence of functional glucocorticoids receptors (GR) in the olfactory epithelium strongly suggests that the OM, and especially the OSNs, are sensitive to natural or induced variations of the HPA axis functioning: GR are expressed in the OM apical region, including the sustentacular cells' cytoplasm and dendrites of OSN, but also within the *lamina propria*, in Bowman glands, and in olfactory nerve bundles (Robinson et al., 1998; Nishimura et al., 2002; Vaz et al., 2018). Second, acute in vitro or in vivo chronic treatment with the synthetic glucocorticoid, dexamethasone, alters the OSNs' responses to odorants (Kamakazu et al., 2003; Wei et al., 2009; Meunier et al., 2020), induces changes in OM gene expression (Nishimura et al., 2002; Tian et al., 2015), and could inhibit the OM cell proliferation (Ohta et al., 2002) but not its neurogenesis (Siopi et al., 2016). Lastly, a chronic variable stress exposure in rodents induces a reduction in electrophysiological responses to odorants and increases the OM apoptosis level, suggesting that stress events encountered could result in structural and functional long-lasting effects (Raynaud et al., 2015; Vaz et al., 2018).

In addition, GR are also expressed in the OB, since the embryonic stages in rodents (Kitraki et al., 1996) being localized in OB granular interneurons, and MTCs in adults (Sousa et al., 1989). However, the consequences of stress events on the OB plasticity are not yet clear, probably due to species and susceptibility's window differences. Whereas a stressful event rapidly induces granule cell death in adults (Komano-Inoue et al., 2015), a prenatal stress has no impact on adult bulbar neurogenesis and plasticity in mice (Belnoue et al., 2013).

In human, the deleterious consequences of major chronic stressing conditions encountered during early life, such as childhood maltreatment, have been reported as being both anatomical and functional: both the OB volume and olfactory sensitivity for various odorants are decreased in women (Croy et al., 2013). Among possible mechanisms, these authors proposed that the stress would mainly impact the OB neurogenesis, thus impairing olfactory plasticity and learning mechanisms as confirmed by Siopi et al. (2016) who showed that corticosterone treatment induces a pronounced deficit in olfactory acuity, i.e., fine discrimination of odorants, and olfactory memory associated to a twofold decrease in the number of new interneurons in all OB layers. Conversely, some recent studies have shown that a short acute stress increases the detection threshold for a malodor, thus overraising the sensory vigilance (Pacharra et al., 2016) and, furthermore that increased cortisol levels are associated with a higher odor identification performance and intensity ratings (Hoenen et al., 2017).

Therefore, if stress obviously impacts olfactory sensitivity in various situations, the direction of modulations might depend on differences in protocols (window of exposure, type of stressing agent, odorant nature) and models. Among others, confounding effects could be involved. For example, long-term effects of dexamethasone treatment on OM could be indirectly attributed to its antiinflammatory properties rather than its effect on HPA axis (Crisafulli et al., 2018).

6.7.2 *Circadian rhythms*

In addition to the master clock located in the hypothalamic suprachiasmatic nucleus, an increasing number of brain areas are revealed as functioning according to endogenous regulators responsible of circadian rhythms, and among them, the OB (Granados-Fuentes et al., 2004; Guilding and Piggins, 2007). OB can oscillate independently and does not require signals from the SNC for sustained rhythmicity; thus, olfactory sensitivity fluctuations over the 24 h have long been described in humans (Lotsch et al., 1997; Nordin et al., 2003; Herz et al., 2017). Accordingly, levels of olfactory sensitivity in rodents are also far higher during the early nighttime than the daytime (Granados-Fuentes et al., 2006, 2011).

A subset of genes of the core molecular “clock” is expressed in the OB, such as *Per* or *Cry* family genes, and exhibit a circadian rhythm *in vivo*, the latter one being under the control of vasoactive intestinal peptide in interneurons of the external plexiform and periglomerular layers of the OB (Miller et al., 2014). Melatonin receptor mRNAs are also functional and fluctuate over 24 h in the OB (Corthell et al., 2014). The final enzyme in melatonin biosynthesis is locally present, also suggesting a possible paracrine effect. Connexins, AMPA receptors, and monoamines also display diurnal variations (Corthell et al., 2012, 2013). Thus, rhythmic fluctuation of these molecules and neurotransmitters could influence OB dynamic responses to odorants at various levels. For example, fluctuations of core clock genes and of *Bmal1* are observed upon scheduled feeding and could participate in food anticipatory rhythms in the OB (Natsubori et al., 2013; Patton et al., 2014). Very recently, an autonomous circadian rhythm of these genes was also demonstrated in the OM, suggesting that these genes also could promote circadian function of OSNs, by controlling the expression of several

OSN-specific genes involved in odor processing (Saleh et al., 2015). Accordingly, OM sensitivity varies during the day in part due to modulation of the very first step of odorant detection (François et al., 2017).

6.7.3 Reproductive neuroendocrine status

6.7.3.1 Influence of menstrual phase cycle

The relationship between olfactory sensitivity and menstrual ovarian cycle-related changes has been largely investigated by several groups who have published various, and contradictory conclusions, making complex the relationship between reproductive hormones and olfaction (Doty and Cameron, 2009). Indeed, if cyclic alterations in the olfactory sensitivity are doubtless in humans for a number of odorants, none of the studies performed provided firm evidence of a systematic and large shift, probably due to differences in frequency of sample collection, method of categorization of the cycle phases, cohort sizes, and tested odorants. The olfactory sensitivity has usually been determined by calculating the threshold for various odorants, such as for the pheromone candidate, the synthetic musklike odorant, exaltolide, while others have used more general odorants with no obvious biological relevance. Increased sensitivity has been reported for some substances a few days before mid-cycle or at ovulation (Le Magnen, 1952; Doty et al., 1981; Mair et al., 1978), whereas other authors have reported an increase of sensitivity during the follicular phase or menstruation (Henkin, 1974; Vierling and Rock, 1967). One study has reported a decrease of sensitivity at menstruation (Schneider and Wolf, 1955), some results suggesting that the modulation may depend on odorant volatility (Mair et al., 1978). Others claimed that olfactory sensitivity was not significantly influenced by the menstrual cycle in humans whatever the odorant challenged (Herberhold et al., 1982; Amoore, 1982; Hummel et al., 1991; Pause et al., 1996; McNeil et al., 2013). Finally, by scoring the olfactory contrast that measures the ability to recognize a change in the odorant intensity, a better olfactory performance at menstruation has been confirmed (Watanabe et al., 2002), as for the ovulation phase (Navarrete-Palacios et al., 2003b). Thus, despite conflicting results, it could be concluded from human studies that olfactory sensitivity varies moderately across the menstrual cycle and is partly linked to the gonadal hormonal changes occurring across cycle, since ovariectomy (Pietras and Moulton, 1974), but not oral contraceptive use (Doty, 1986), eliminates the cyclicity. However, the use of contraceptives lowers the perception of social chemosignals (Renfro and Hoffman, 2013; Endevelt-Shapira et al., 2020). Although naturally ovulating females display a decline in body odor discrimination when entering the luteal phase, women under oral contraceptives display such decline later, at the premenstruation time, during the withdrawal period of oral contraception (Endevelt-Shapira et al., 2020). Such ovarian cyclical changes in odor detection have also been published in female rodents, which show a peak in detection ability during either estrus or proestrus, in the same period as for humans (Schmidt et al., 1982; Kumar and Archunan, 1999).

Concerning male, no alteration in detection threshold for relevant odors, such as female urine, or for ethyl acetate was observed upon castration (Carr et al., 1962; Doty, 1986).

If the molecular bases for such modulations reported in chemosensory function during menstrual cycle are poorly understood, and very few mechanisms have been yet investigated, some data indicate that ovarian hormones obviously act on olfactory structure and function at both short- and long-term. Evidence of steroids receptors expression in the nasal epithelium and OB (Leimola-Virtanen et al., 2000; Mitra et al., 2003) together with cytological modifications of the mucosa along the ovarian cycle (Navarrete-Palacios et al., 2003a) are in favor of a direct role for ovarian hormones, even if the attempt to find receptors for female sex hormones in the nasal epithelium of cycling women failed (Paulsson et al., 1997).

Once again, animal models helped to increase our knowledge of the mechanisms throughout which female sex steroids modulate olfactory signaling. Data support both genomic and nongenomic actions. Indeed, long-term estradiol treatment increases basal cell proliferation in the OM that could potentially lead to an increase in tissue thickness, preserves the OB by increasing synaptogenesis following ovariectomy (Nathan et al., 2012), and influences adult neurogenesis (Veyrac and Bakker, 2011). Moreover, estradiol has acute effects by decreasing odor-induced responses in the mice vomeronasal organ (Cherian et al., 2014). Recently, using electrophysiological approaches such as EOG and whole cell patch-clamp recordings in mice, Kanageswaran et al. (2016) showed that a direct application of progesterone or estradiol rapidly decreases odorant-evoked signals in OSNs. As for metabolic hormones (see Chapter 15), a local synthesis of sex steroids-metabolizing enzymes in rat OM questions the physiological relevance of a pathway for sex steroids genesis in this tissue (Horie et al., 2017).

The biological significance of the olfactory cyclicity remains to be determined, but it could participate in mate finding or choice, since the larger variations were observed with musklike odors (Mair et al., 1978; Vierling and Rock, 1967). Some data suggest that it might help in food selection upon physiological needs (McNeil et al., 2013) or to orientate food preferences (Bignetti et al., 2009).

6.7.3.2 Influence of pregnancy

Even if pregnancy hyperosmia is a commonplace observation due to abundant anecdotal experience (Gilbert and Wysocki, 1991), the direction and timing of changes are less clear in the literature given the variety in experimental designs and cohorts, questionnaire formulation, and type of olfactory measurements. However, it can be ad minima reported that the gonadal hormones, but also some placental ones (steroids, gonadotropins, metabolic hormones), dramatically fluctuate during this period and thus, inescapably impact the olfactory perception.

The first full longitudinal study that tested olfactory sensitivity toward 12 odorants of pregnant and age-matched controls has revealed a significant higher detection threshold in the last trimester (Cameron, 2007), a critical period where olfactory alteration was confirmed using TDI scores (Ochsenbein-Kölble et al., 2007), or threshold

tests, but not for all odorants (Laska et al., 1996). Accordingly, absence of changes in olfactory threshold or odor discrimination between pregnant and nonpregnant height and weight-matched women has been registered when taking into account the first trimester (Kölble et al., 2001). Only two studies noticed an increase in olfactory sensitivity in this period, after a self-rating study (Cameron, 2007) or when considering specific odors (Nordin et al., 2005), in a way that might participate to odor intolerance development. However, no correlation between olfactory sensitivity at early pregnancy and scores to a nausea tests was found (Hummel et al., 2002), nor evidence of an adaptive mechanism (Swallow et al., 2005). Finally, olfactory sensitivity was not significantly different between nulliparae and women who had given birth to at least one child, indicating that the number of pregnancies has no effect (Wohlgemuth et al., 2008).

Altogether, these data consistently indicate that fluctuations in olfactory sensitivity during pregnancy are not large enough to be significant using validated methods for measuring thresholds, and support that anecdotic hyperosmia comes primarily from changes in the valence of odors, thus heightening the attention to odors, as shown by Cameron (2014). Therefore, few efforts have been taken to identify physiological bases for such changes at the olfactory bulb and mucosa levels. Some works mention that hormonal changes linked to pregnancy affect nasal airflow (Demir et al., 2015), olfactory structure, and vascularization (Güven and Örtug, 2006), that estrogen could mediate enhanced proliferation of neurons as shown in vomeronasal organ (Oboti et al., 2015) but that progesterone reduces sensitivity to odorants in the OM (Kanageswaran et al., 2016).

In rodents, prolactin, whose concentration is high during the first half of pregnancy and decreases until term, can increase the number of interneurons in the OB, whereas such an effect is not observed with estradiol or progesterone (Shingo et al., 2003). Such a neurogenic activity in the OB, as well as in the other regions of the brain, participates to the expression of maternal behaviors in several species (Larsen and Grattan, 2010; Levy et al., 2011). Pregnancy-derived hormones could support neural bases for a differential stimulus discrimination as shown for the activation of early genes in sensory processing: late-pregnant female display a reduced neural activity as compared to virgin ones for socially neutral stimuli, but display an increase of early genes for pups' odors (Navarro-Moreno et al., 2020).

Besides, in women, cognitive higher level of integration involving attentional mechanisms has been also recently reviewed to explain changes in olfactory perception during pregnancy (Cameron, 2014). Such plasticity that increases awareness of potentially harmful chemicals, odorous and toxic environments to extend maternal protection, probably originates from central cognitive processes.

6.8 Conclusion

In order to encode olfactory stimuli and give the most relevant representation of the environment, the olfactory system needs to process the olfactory cues per se, but also to evaluate them, according to individual's history and physiological current

status. Thus, any changes in the internal physiological reproductive, emotional, circadian status will result in chemical signal releases which directly or indirectly will dynamically impact the olfactory processing at several levels: all regulations being intended to facilitate the individual's adaptive behaviors. However, on the current state of knowledge, the mechanisms, by which these multiple internal cues are orchestrated and prioritized, regarding the nature and valence of the external stimuli, still need to be deciphered.

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Multimodal sensory interactions

7

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7.1 Introduction

A central sensory characteristic of food is its flavor, which, most of the time, confers to a given food product its identity and typicality, and thus contributes to its liking (Prescott, 2015). Flavor has been defined as a sensory percept induced by food or beverage tasting. This holistic perception is constructed through the functional integration of information transmitted by the chemical senses: olfaction, gustation, and oral and nasal somatosensory inputs (Thomas-Danguin, 2009). The flavor may be influenced by other nonchemical sensory inputs such as texture, sound, and color (Spence, 2013).

The functional integration of information transmitted by anatomically distinct senses relies on multimodal processing, which is fundamental for our interaction with and behavioral adaptation to our environment. In the case of food flavor, the multimodal integration of chemosensory cues induces cross-modal perceptual interactions in which the perception of a tastant may affect the perceived intensity of an odorant, and vice versa (Delwiche, 2004). Nevertheless, although cross-modal interactions can result from perceptual processes, other factors may also contribute to the overall construction of the food flavor percept.

In this chapter, we propose a review of multimodal interactions in the context of food flavor construction and modulation. In the first part, we focus on interactions within the chemical senses. We report shreds of evidence for the integration of olfactory and gustatory information at sub- and suprathreshold levels, and then review the mechanisms underpinning aroma–taste interactions, as well as the neurophysiological bases of perceptual flavor integration. Afterward, we provide more details on the impact of olfactory, gustatory, and trigeminal interactions on food flavor perception. In the second part, we present interactions between aroma, taste, and texture perceptions while summarizing the possible mechanisms, and we consider the influence of texture on aroma and taste and the reverse.

Along with this chapter, several terms are used with a specific meaning that is not necessarily consensual, depending on the scientific area. The terms *taste*, *odor*, and *aroma* refer to the **perceptions** induced by chemicals which are, respectively, *tastants* or *odorants* (resp. nonvolatile and volatile molecules); *odors* correspond to *odorants* perceived through the orthonasal route, whereas *aroma* corresponds to *odorants* perceived through the retronasal route. We also use the term *aroma compounds* for a mixture of odorants formulated to produce a specific aroma perception. Finally,

we use the term *texture* to define the perception of surface texture by means of touch (e.g., hardness, thickness, etc.), and the term *textural properties* to define the physical properties of the object that activate somatosensory receptors. The term *structure* refers to the physical organization of the food matrix. Finally, the term *flavor* defines the unified mental representation of food elaborated from the aroma/odor, taste, and texture perceptions.

7.2 Multimodal interactions within the chemical senses

7.2.1 Integration of aroma and taste at subthreshold level

The major evidence of cross-modal integration between taste and odor was provided by Dalton et al. (2000), who applied a psychophysical method to show the summation of subthreshold concentrations of gustatory and olfactory stimuli. This psychophysical method, based on a forced-choice detection task, was designed to limit attentional bias that could account for the observed perceptual integration (see Section 7.2.3). A group of 10 subjects was tested to assess whether an odor and a taste stimulus, each individually below their respective detection thresholds, could be detected when presented simultaneously. To do so, subjects were asked to sniff a bottle with the odorant while holding the tastants solution in the mouth. Benzaldehyde (almond/cherry-like odor) was the odorant, while the taste stimulus was either water (neutral), monosodium glutamate (MSG, umami taste), or saccharin (sweet taste). The results showed that the benzaldehyde detection threshold was significantly diminished when the odorant was associated with saccharin, but not with water or MSG. The authors concluded that the specificity of the saccharin/benzaldehyde integration can be explained by the stimulus congruency of sweet taste and fruity odor, previously encountered in combination during food tasting, at least for US inhabitants.

These fundamental results have been further extended by Pfeiffer et al. (2005), who demonstrated that spatial and temporal coincidence of odor and taste stimuli are important factors for odor–taste integration. Whereas Dalton et al. (2000) presented the taste and odor stimuli simultaneously, but from different locations (mouth and nose, respectively), Pfeiffer et al. (2005) explored, using the same stimuli, the effect of asynchronous taste and ortho- or retronasal odor stimulation on perceptual integration. Indeed, in an ecological food intake situation, taste comes first when food is placed into the mouth, and aroma comes later after swallowing, that is through the retronasal route (Buettner et al., 2001). The results showed that the benzaldehyde detection threshold decreased when associated with saccharin, but only when taste and orthonasal odor stimuli were delivered simultaneously (equivalent to the experiment by Dalton et al. (2000)), or when retronasal aroma stimulus was delivered just after taste stimulus swallowing (i.e., ecological food tasting situation). Additional pieces of evidence of the importance of ortho- or retronasal odor stimulation on odor–taste integration have been obtained in brain imaging studies (Small et al., 1997, 2004).

Overall, these studies have demonstrated the concept of taste-induced changes in odor perception, since the focus was on odor threshold. Another study showed that

subthreshold concentrations of an odorant, whose odor is associated with sweet taste, can increase the sweetness of a sucrose solution (Labbe et al., 2007). Such an odor-induced change in taste seems to be odorant specific because it was observed for ethyl butyrate but not for maltol; both odorants, however, are related to a sweet dimension (fruity and caramellike odor, respectively). Moreover, at subthreshold levels, the odor-induced taste enhancement did not depend on the odorant's concentration (Labbe et al., 2007).

7.2.2 Interaction of aroma and taste at suprathreshold level

At the suprathreshold level, one of the first reports on odor–taste interactions indicated that the fruity odor of ethyl butyrate and the sweet taste of saccharin combine additively. Indeed, the perceived intensity of the odor–taste mixture was almost the sum of the intensity of the stimuli rated separately (Murphy et al., 1977). Moreover, the results of this pioneering study revealed that while the pure saccharin solution had a strong sweet taste, but little odor dimension, the solution of pure ethyl butyrate had a strong fruity odor but also a considerable taste magnitude. This result thus supports the idea that odors may have taste dimensions, a hypothesis that has been definitely demonstrated 20 years later by Stevenson et al. (1995).

A series of studies demonstrated that certain odors can modulate the intensity of particular tastes and that these odor-induced changes in taste perception are both odor and taste specific (Frank, 2003; Clark and Lawless, 1994; Schifferstein and Verlegh, 1996; Stevenson et al., 1999; Sakai et al., 2001). For instance, Frank and Byram (1988) used ecological food tasting conditions in which participants had to perform a time-intensity task to rate either sweetness or saltiness of whipped cream samples containing either sucrose or sodium chloride, and flavored with either strawberry or peanut butter aroma. The results showed that the strawberry aroma enhanced the sweetness of the sweet whipped cream, whereas the peanut butter aroma did not, which demonstrates that an odor's ability to enhance sweetness is odor-dependent. Moreover, it was found that strawberry aroma did not enhance the saltiness of the salty whipped cream, thus indicating that an odor's ability to enhance taste is tastant-dependent.

A limitation to the Frank and Byram (1988) study is that the time-intensity method they used relies on intensity ratings using linear scales. Nevertheless, such a method is prone to measurement artifacts called halo and dumping effects, which may happen when restricted or inappropriate rating scales are provided to panelists (Clark and Lawless, 1994). To overcome this issue, Djordjevic et al. (2004a) designed an experiment in which they did not use intensity ratings, but the accuracy of detecting a weak sweet taste when associated with a strawberry or a ham odor. They observed that the detection of sucrose in water was significantly better when subjects smelled a strawberry odor, than when they smelled a ham odor. This result definitively confirmed that perceptual integration between odor/aroma and taste is an authentic phenomenon that is odor-specific for a given taste.

7.2.3 Mechanisms underpinning aroma–taste interactions—perceptual integration versus physicochemical interactions

Interactions between odor and taste may result from different mechanisms taking place at the physical or the perceptual/cognitive levels (Noble, 1996; Delwiche, 2004). Physicochemical effects can influence the amount of odorants or tastants released from a food matrix, and reaching the sensory neurons (Saint-Eve et al., 2009). For instance, the increase in the amount of nonvolatile solutes (e.g., sucrose, NaCl) in a more or less complex food matrix could increase the release of volatiles into the headspace. This physicochemical phenomenon, known as the “salting-out” effect, can therefore contribute to a higher odorants’ release and by consequences of a higher perceived aroma intensity (Salles, 2006).

Nevertheless, in several studies, odor–taste interactions were observed even though the composition of the headspace volatiles was not altered by the addition of nonvolatile solutes. For instance, increasing the sugar concentration of blueberry and cranberry fruit juices increased their fruitiness, although no difference in aroma was perceived by sniffing alone (Von Sydow et al., 1974). The monitoring of volatiles release in vivo during food consumption allowed ruling out any physicochemical mechanisms in the observed odor–taste interactions (Pfeiffer et al., 2006). Moreover, it has been reported that perceived and mentally imagined odor–taste mixtures showed the same patterns of interaction (Djordjevic et al., 2004b; Algom et al., 1993). Therefore, it is obvious that taste and odor perception could interact at a cognitive level.

According to Valentin et al. (2006), two different cognitive mechanisms could contribute to odor–taste interactions. The first one relies on a general tendency to integrate all information into a total intensity impression and corresponds to the aforementioned dumping effect (Clark and Lawless, 1994). This effect is often considered a response bias in cross-modal interaction studies (Pointot et al., 2013). Indeed, this mechanism, which is sensitive to the number of rating scales, can lead subjects to transfer their perception of, for example, a strawberry aroma onto the only provided sweetness scale; the consequence being an apparent overestimation of the sweetness of a sweet strawberry-flavored solution. Nevertheless, this response bias cannot solely account for odor–taste interactions, since several pieces of evidence have been reported in studies using paradigms free of dumping response biases (Dalton et al., 2000; Djordjevic et al., 2004a; Lawrence et al., 2011).

The second cognitive mechanism that could account for perceptual odor–taste interactions results from the coencoding of an odor and a taste, and thus would be mixture- and culture-dependent (Valentin et al., 2006). Indeed, cross-modal interactions are thought to occur through learned association among tastes and aromas (Stevenson et al., 1995; Prescott, 1999), which subsequently become congruent with each other (Schifferstein and Verlegh, 1996). In that sense, odor–taste interactions appeared to share several characteristics with learned synesthesia, in which a stimulus in one sensory modality reliably elicits a consistent corresponding stimulus in another modality (Stevenson and Tomiczek, 2007). Therefore, odor–taste interactions could result from odor–taste learning, which occurs via simultaneous repeated exposure

to both odor and taste. This learning appears to be implicit and highly resistant to extinction and interference. Astonishingly, it seems that only a single taste–odor association is required for the learned synesthesia to be established (Prescott et al., 2004). However, trials to replicate this finding were not compelling and few data were published. In a recent study, authors partly replicated this study with a new method. Participants were repeatedly exposed (three times a day, over 5 days) to an aroma (either basil or orange flower) and sucrose combined in a chewing-gum base (Fondberg et al., 2021). However, the authors did not find evidence of associative learning, and advanced analyses showed that the effects were either absent or insignificant in magnitude. Therefore, more studies are needed to answer the intriguing question of whether odor–taste interactions depend on associative learning versus natural or even innate associations (cf. review Spence, 2022).

We should acknowledge that odor–taste learning designs are difficult to implement because the critical parameters of the exposure phase (time of exposure, repetitions, consolidation phase) are not well known for odor–taste integration. Furthermore, the design is time-consuming and necessitates for the participants to come several times to the laboratory. Another approach to address this question consists in performing cross-cultural studies. With this approach, we consider that the exposure phase is the individual diet experience of each participant. The assumption is that if countries have different and still pregnant traditional culinary cultures, the food exposure will differ between countries and would allow seeing associative learning effects. In this case, the culinary traditions redraw the odor–taste congruencies among different countries and constitute a relevant testing paradigm of the associative learning hypothesis without intervention. However, to date, odor–taste associative learning has been only few tested in cross-cultural studies. Two studies investigated the effect of vanilla on sweet taste enhancement in water-based solutions (Nguyen, 2000; Bertelsen et al., 2021). Nguyen (2000) during his Ph.D. thesis (data unpublished) showed that while vanilla was an effective sweetness enhancer in Vietnam and France, the enhancement was higher in France, while lemon enhanced sweetness only in Vietnam. Bertelsen et al. (2021) were the first to publish a cross-cultural study on odor-induced taste enhancement (OITE). They compared vanilla-induced sweetness enhancement in Chinese and Danish populations. They found OITE in both countries but with a higher enhancement in Denmark. All these results converge to the point where OITE is more effective in countries where the aroma is traditionally used in food preparation. However, it has to be noticed that, in the two studies, the vanilla-induced sweetness enhancement, even if not traditionally used in Asia, was effective although to a lower degree compared to Europe. This finding might be explained by the global market expansion and the availability of cross-cultural products (e.g., coffee-based drinks, soft drinks ...) in most parts of the world, which has likely favored nontraditional odor–taste associations.

A final point that argues in favor of associative learning consists in considering the association between aroma and taste in natural food products (Guichard et al., 2020). The gas chromatography/olfactometry-associated taste (GC/O-AT) technique allowed identifying the taste-associated dimension of aromas by separating and delivering each odorant of a food extract (GC/O) to participants who have to describe their perception

using taste descriptors (sweet, salty, sour, bitter). To confirm the potential taste enhancer effect, the identified odorants can be tested for OITE in water solutions or congruent food or beverages. Application of such an analytical strategy has led to the demonstration of significant OITE with three sweet-associated odorants from a multifruit juice (the best enhancer being 2-methylbutanoate (Barba et al., 2018)), eight sweet-associated odorants from banana (e.g., 3-methylbutyl butanoate (Xiao et al., 2021)), five saltiness-associated odorants, and two umami-associated odorants from soy-sauce (e.g., 3-(methylthio)propanal to enhance both salty and umami tastes (Zhou et al., 2021)). These studies showed that, even if not all aromas are associated with sweetness or saltiness, the OITE phenomenon is shared across foods/beverages and types of tastes, and is the result of cognitive constructs most probably learned, even if we cannot rule out some innate associations.

7.2.4 Neurophysiological bases of flavor integration

Integration of information is a general property of the mammalian nervous system in all senses. It enhances identification or detectability and facilitates decision when a single sensory modality provides ambiguous, incomplete, or low perceptibility information. To understand the neurophysiological bases of flavor multimodal integration, we may explore the different possible mechanisms of integration, as reviewed by, for example, Small (2008), Small and Prescott (2005), and Verhagen and Engelen (2006).

The most basic mechanism of multimodal integration linked to food perception is based on the previously exposed evidence that an odor may evoke a taste (Stevenson et al., 1995). A neurobiological hypothesis that could support this phenomenon relies on the construction of direct connections between a unimodal taste-responsive neuron and a unimodal odor-responsive neuron. The connection may be strengthened by the repeated experience of taste and odor together, during food tasting. However, such a simple organization is unlikely because it does not take into account the existence of bimodal neurons that clearly play a role in flavor perception (Kadohisa et al., 2004; Rolls and Baylis, 1994). These multisensory neurons have been discovered thanks to in vivo electrophysiological recordings in the macaque brain, which offered a reliable neural model for human gustation (Scott and Plata-Salamán, 1999).

Therefore, an alternative hypothesis should include multisensory neurons. Multisensory taste–smell neurons have been found in the posterior part of the orbitofrontal cortex (OFC) in primates (Rolls and Baylis, 1994). In the same region were found multisensory neurons that can respond to single olfactory, gustatory, or trigeminal stimulus, but better respond to combinations of two sensory modalities (Kadohisa et al., 2004) maybe even three. Multisensory neurons that integrate gustatory and trigeminal stimuli have also been shown in the amygdala of primates (Kadohisa et al., 2005). Furthermore, taste–somatosensory bimodal neurons have been found in rat insula (Hanamori et al., 1997). Although several studies identified responses of the same neurons to individual gustatory or trigeminal inputs from the tongue in the nucleus tractus solitarius (NTS) (Travers et al., 1986, 1987; Travers and Norgren, 1995) and in the parabrachial nucleus of the pons (PBN) of rats (Halsell and Travers, 1997), the possibility of a better response to mixtures of trigeminal-gustatory stimuli

in contrast to purely trigeminal and gustatory ones has not been investigated, so far. In humans, no direct proof of chemosensory multimodal neurons has been reported. One issue with this theoretical model is that it does not explain why bimodal neurons fire when a single odorant is presented, and do not fire for a single tastant. Indeed, a vanilla odor may evoke a sweet taste; however, a sweet taste could not evoke a vanilla odor on its own. The only way to overcome this issue is to add a layer of integrative neurons. Indeed, if one considers the example of taste–odor integration, the pattern of primary inputs dispatched among gustatory, olfactory, and somatosensory areas would be associated as follows: taste and odor would be associated in bimodal taste–odor neurons, and taste and touch would be associated in bimodal taste–somatosensory neurons. It is important to mention that odors mostly rely on mixtures of odorants, which would also be configurally associated as odor-objects (Thomas-Danguin et al., 2014) in memory areas (Barnes et al., 2008; Stevenson and Boakes, 2003; Wilson and Stevenson, 2003, 2006). Actually, a single odorant may evoke lemon or strawberry; however, a tastant does not evoke any taste-object, but sweetness, saltiness, etc. Odor-object would then be associated in memory areas with both bimodal projections, including other sensory dimensions, which would allow to create a flavor-object. This third level of association could appear through “autocorrelation memory network,” and may be localized in the superior temporal sulcus (Calvert and Thesen, 2004; Verhagen and Engelen, 2006; Calvert, 2001). In this latter conceptual model, although bimodal odor–taste neurons can be activated by separated odor or taste, without an odor-object activated in memory, activation of a flavor-object is impossible. Interestingly, bimodal taste–odor cells have been found in OFC and amygdala and these two areas have been shown to encode pleasantness and disgust (de Araujo, 2005; McCabe and Rolls, 2007; Rolls et al., 2003; Wicker et al., 2003). Bimodal neurons could then act as reinforcers of associations between odor-object, somatosensation, and taste, but would not be sufficient to activate the whole flavor-object engram on their own.

fMRI techniques have allowed identifying brain areas that integrate odor and taste perceptions to form the flavor perception. This integration process is captured with fMRI when brain areas produce a higher response to “flavor” vs. “odor and taste” presented separately (i.e., superadditive response). In the following section, we listed the brain areas that showed superadditive response in six fMRI studies and we organized them according to the number of occurrences in these studies: OFC, anterior cingulum, superior temporal cortex, central insula, amygdala (de Araujo et al., 2003; Small et al., 2004; McCabe and Rolls, 2007; Eldeghaidy et al., 2011; Seo et al., 2013; Seubert et al., 2015). These brain areas are all high-order areas able to transform, integrate, and even produce endogenous perceptions. However, in part of these studies, the primary gustatory cortex (i.e., anterior insula/frontal operculum) also presented this superadditive response to flavor (Small et al., 2004; Eldeghaidy et al., 2011; Seo et al., 2013; Seubert et al., 2015). Although in humans the primary olfactory cortex was never shown to be activated in response to taste stimulations, it was shown in rodent with electrophysiological techniques (Maier, 2017). These results question the mechanisms of flavor construction in the brain. Is the flavor formed early or late during the odor-taste processing; involving either a lower or a higher level of organization? These results challenge the view that olfactory and gustatory cortices are only communicating in

high-order brain areas. However, recent results in humans recorded with electroencephalography (EEG) bring the first hint of the response. To highlight the brain chronometry of OITE, participants were stimulated with three different solutions: a salty OITE solution, a salty solution, and the aroma solution while being recorded with EEG. The results did not show early odor–taste integration (corresponding to primary sensory areas) but only late brain integration (corresponding to high-order integratory areas) (Sinding et al., 2021). Recent EEG techniques are relevant to highlight fine time resolution brain mechanisms (in the order of ms). In comparison, other techniques employed in the studies above mentioned either did not have a sufficient time resolution to show early brain processing or did not show early activations of primary sensory areas. Therefore, these former results could not ensure that olfactory and gustatory cortices communicate at the very early steps of the processing, but they might reflect a top-down process from the high integratory areas (flavor construction areas) to the primary gustatory and olfactory areas. This explanation complies with the idea that, to have increased sweetness or aroma perceptions, these primary gustatory and olfactory areas should be reactivated at the end of the flavor processing.

7.2.5 Influence of odor on taste perception

Most of the studies published so far evidenced that specific odors like strawberry, vanilla, lemon, caramel, or lychee can enhance sweet taste either in water solutions or in food systems (Frank and Byram, 1988; Sakai et al., 2001; Schifferstein and Verlegh, 1996; Stevenson et al., 1999; Barba et al., 2018; Wang et al., 2019a). But still, changes in taste perception induced by odors are not limited to sweet taste. For instance, lemon and strawberry odors were found to enhance the sourness of citric acid (Frank, 2003), soy-sauce odor enhanced salty or umami taste (Djordjevic et al., 2004b; Zhou et al., 2021), while other odors can increase sourness or bitterness (Salles, 2006; Thomas-Danguin et al., 2019).

In a series of studies focused on salty taste enhancement, it has been demonstrated that well-selected odors can increase the perceived saltiness of both model solutions and real food systems (Lawrence et al., 2009, 2011; Nasri et al., 2011, 2013; Syarifuddin et al., 2016). First, it has been shown possible to select the most promising odors for saltiness enhancement through a high throughput screening process based on the expectation tastes profile of food products being evoked by their names (Lawrence et al., 2009). Indeed, food odors can evoke the salty taste through mental imagery (Djordjevic et al., 2004b), primed by food names. Moreover, the “smelled taste” of the odorants might be a good predictor of odor-induced taste enhancement (Stevenson et al., 1999). In a 1-h test session, a group of consumers estimated taste intensity (bitterness, sourness, saltiness, and sweetness) of 86 written food names. The results revealed a great consensus between subjects for expected tastes. Moreover, significant differences in saltiness between food names were obtained: anchovy, bacon, smoked salmon, dry sausage, peanuts, and sardine were evaluated as the saltiest, whereas vanilla, orange, fig, strawberry, milk chocolate, cinnamon, and lemon were evaluated as the least salty. Interestingly, the expected saltiness of the food names was correlated with the actual sodium content of the corresponding food products

(Lawrence et al., 2009). In another experiment, a group of consumers rated the perceived intensity for the four tastes, as well as the odor of water solutions containing a selection of aroma compounds identified in the previously described screening experiment. The results clearly showed that some odors had a salty dimension (sardine, bacon) while others had a sweet (carrot) or sour (tomato) dimension, at least for French consumers. Moreover, the saltiness perception of solutions containing a small amount of salt was significantly enhanced by the addition of odorants perceived to have a salty dimension (e.g., sardine or bacon odor). This perceptual phenomenon has been called Odor-Induced Saltiness Enhancement (OISE, Lawrence et al., 2009).

Beyond taste and odor specificity, OISE is also affected by the intensity of both odor and taste (Frank and Byram, 1988; Murphy et al., 1977; Labbe et al., 2007). For example, odor intensity was found to influence saltiness enhancement according to the odor quality (Lawrence et al., 2009). When an odor is associated with a taste, the level of OISE depends on the odor intensity. In contrast, when an odor is not associated with a taste, no OISE can be observed, whatever the odor intensity. OISE also varies according to salt concentration (Nasri et al., 2011): it is more pronounced at low-salt concentrations. When salt concentration increases, thus eliciting a higher salty taste intensity, the OISE effect size decreases. It has been suggested that this effect may result from the negatively accelerating form of the psychophysical functions, or to attentional processes (Nasri et al., 2011).

OITE seems also to depend on the physiological states of individuals, weight status, sex, age. Three studies showed that OITE was different in people with normal-weight and obesity. For example, in a custard dessert, the sweetness enhancement induced by a butter aroma was found only in the group with obesity compared with a normal-weight group (Proserpio et al., 2016, 2017). This result was also found with vanillin in apple juice (Aveline et al., 2021). Aveline et al. (2021) also showed a similar effect with saltiness enhancement. A smoky bacon aroma used in salty water increased saltiness in normal-weight and obese groups, but the strength of the enhancement was higher in the group with obesity. Gender seems to have an effect on OITE. Although a first study showed no difference between males and females (Proserpio et al., 2016), a second study highlighted that Italian women were more prone to butter aroma-induced sweetness enhancement (Proserpio et al., 2017). Similarly, in a Danish population, females were more susceptible to perceiving a vanilla-induced sweetness enhancement in water solutions (Bertelsen et al., 2020a). Finally, age appears to have little effect since odorants are usually used at high concentrations, and therefore reduced olfactory function due to age has little effect on the flavor perception (Philipsen et al., 1995). However, Bertelsen et al. (2020a) showed in a large sample of young adults that the 19–21-year-olds did not perceive vanilla-induced sweetness enhancement, while OITE occurred in the 22–25 years old. This difference might be explained by a change of diet for the participants who were young adults starting university.

In the context of worldwide nutritional recommendations to lower sugar, fat, and salt consumption, it is obvious that OITE can be one of the strategies to develop healthier food while maintaining salty taste and consumer acceptability (Thomas-Danguin et al., 2015, 2019; Ghawi et al., 2014; Prescott, 2015; Busch et al., 2013). Indeed, it has been reported that odors can acquire other qualities than taste, such as fatlike

ones (Sundqvist et al., 2006). Therefore, well-selected odors can be used to enhance fat perception in real food systems, depending on the structure–texture properties of the food (Syarifuddin et al., 2016). Moreover, recent methodological developments have led to the identification of the most potent natural odorants that can be enhancers of taste. For instance, in a fruit juice, the application of gas chromatography/olfactometry-associated taste (GC/O-AT; Barba et al., 2018) allowed the identification of odorant compounds associated with taste attributes (sweet, salty, bitter, and sour; Guichard et al., 2020). Nine odorants were selected for their odor-induced sweetness and were further tested for the odor-induced sweet taste enhancement in 32% sugar-reduced fruit juice. The sweetness of the fruit juice odor was significantly enhanced by ethyl 2-methylbutanoate. Consequently, multimodal interactions involving olfactory perception could likely be used to formulate food with lower amounts of salt and/or sugar and/or fat, as recommended by health organizations while compensating for taste loss. Because odors can also suppress taste (Stevenson et al., 1999), it is also possible to imagine using odors to limit undesirable sour or bitter tastes (Isogai and Wise, 2016) in food or medicines.

7.2.6 Influence of taste on aroma perception

Several studies reported modulation of retronasal olfactory information (i.e., aroma) by taste. For instance, sodium chloride or monosodium glutamate is often considered a flavor enhancer because of its ability to increase the perceived intensity of beef broth, or other flavors (Noble, 1996). Nevertheless, most of the published reports describe the influence of sweet and/or sour tastants on aroma perception (Davidson et al., 1999; Pfeiffer et al., 2006; Hewson et al., 2008; King et al., 2007; Wiseman and McDaniel, 1991; Green et al., 2012; Fujimaru and Lim, 2013; Lethuaut et al., 2004; Tournier et al., 2009). It is usually found that the addition of a sweet tastant increases the perceived intensity of sweet-related aromas. The perceptual origin of this phenomenon has been demonstrated by *in vivo* flavor release measurements, which showed no variation of odorants' concentration in the nose as a function of the tastant level. Besides the bias potentially induced by dumping effects in time-intensity experiments, a limitation in some of the aforementioned studies is that the concept of “flavor” could have been sometimes misused, since it does not precisely refer to the olfactory information (Noble, 1996), and its rating might have led to halo effects (Clark and Lawless, 1994).

In a series of studies on cheddar cheese flavor, the influence of various tastants on aroma and overall flavor was assessed systematically, using either model solutions or combined gustatory and olfactory stimulation devices. It has been found that removing tastants from a model flavor solution significantly reduced overall cheese flavor intensity (Niimi et al., 2014b), as well as the intensity of specific aroma attributes (Niimi et al., 2015). Moreover, sweet and salty tastes (sucrose or NaCl) increased overall cheese flavor intensity (Niimi et al., 2014a,b). Sour taste alone (lactic acid) decreased overall cheese flavor intensity (Niimi et al., 2014a). Umami taste (MSG) could increase flavor intensity, depending on aroma intensity, whereas bitter taste (caffeine) did not affect flavor intensity (Niimi et al., 2014a). Interestingly, these studies also

revealed that a mixture of the five tastes had a greater flavor-enhancing effect, compared to any single taste (Niimi et al., 2014a,b).

One of the most remarkable observations concerning the influence of taste on the aroma is that taste, especially sweet taste, could be a driver of overall flavor intensity. Indeed, several studies used dedicated multichannel flavor delivery systems to provide subjects with aqueous solutions containing tastants and/or odorants at well-known concentrations, in a well-controlled timing. Their results showed that the temporal perception of flavor is closely linked to the temporal perception of taste in the oral cavity, but not aroma (Hort and Hollowood, 2004; Pfeiffer et al., 2006; Hewson et al., 2008). One hypothesis that may contribute to explaining this observation would be that while the olfactory information is known to carry most of the perceptual identity of food (Hornung and Enns, 1989), retronasal odor perception is often considered to be perceived in the oral cavity. This mislocalization, known as the referral of retronasal odors to the mouth (Lim and Johnson, 2011, 2012), is likely an important feature of the holistic perception of food flavor (Rozin, 1982; Murphy and Cain, 1980; Small and Prescott, 2005). Therefore, the long-lasting perception of a taste sensation into the mouth may be sufficient to consider that the overall food flavor is still there, namely in the mouth, even if the concentration of odorants reaching the olfactory cleft is much reduced.

7.2.7 Interactions between aroma, taste, and trigeminal sensations

Trigeminal sensations and, more particularly, their interactions with other sensory modalities are difficult to study for three reasons. The first reason concerns the identification of trigeminal sensations per se, because they do not correspond to a unique category of sensations, and are not activated by a unique category of stimulation as in olfaction (odorant) and taste (tastants) (Thomas-Danguin et al., 2012). Indeed, trigeminal nerves are composed of different somatosensory and pain fibers that can react to mechanical, thermal, or chemical stimuli. Their description can be as variable as burning, fizzy, soft, warm, cold, tingling, prickling, pungent, creamy, irritating, etc. Therefore, psychophysical evaluation of trigeminal sensations is laborious. In this part, we will review only chemical stimuli. The second reason concerns the duality of stimuli. Most odorants and tastants also carry a trigeminal component. In other words, one odorant can activate olfactory as well as trigeminal fibers. For example, most odorants become pungent at high concentrations. Similarly, most tastants induce a trigeminal sensation at high concentration, and bitter molecules are specially tuned to activate the trigeminal system (nicotine, caffeine, quinine, strychnine, capsaicin; see Liu and Simon, 1998). The third reason concerns the anatomy of trigeminal efferences, which are widespread in the whole face, and innervate most of the sensory modalities such as vision, olfaction, and gustation. Moreover, their small fibers are located very closely to gustatory and olfactory neurons. Likely, this may result in peripheral interactions, as desensitization or inhibition of gustatory neurons by trigeminal neurons at the tongue level (Faurion, 2006; Boucher et al., 2003). These peripheral effects may

then impact central multisensory integration, as detailed previously in this chapter. In the following sections, only studies presenting a comparison of mixtures and single components are presented.

Interactions between taste and trigeminal sensations, revealing multisensory integration, have been observed in a few studies. [Cometto-Muñiz et al. \(1987\)](#) and [Yau and McDaniel \(1992\)](#) have shown that the trigeminal stimulus carbon dioxide (CO₂) enhanced the sourness and saltiness of various tastants, but did not show enhancement of sweetness. [Coward \(1998\)](#) has shown that CO₂ decreased sweet and salty tastes. Capsaicin has been widely studied, as it is one of the most powerful pure trigeminal molecules, found in natural foods such as chili peppers. It reduces sweet, salt, and bitter tastes when mixed in solutions ([Lawless and Stevens, 1984](#); [Lawless et al., 1985](#)). Lawless and collaborators suggested that the reduced taste intensity would result from a shift of attention toward burning sensation, at the expense of taste. However, as [Prescott et al. \(1993\)](#) suggested, this cognitive effect could not fully account for the suppression of taste by irritants. Indeed, infrequent chili eaters, more sensitive to capsaicin, do not show stronger taste suppression, compared with frequent eaters ([Lawless et al., 1985](#)). Therefore, this effect is likely the result of desensitization of gustatory neurons by trigeminal small fibers within taste buds, which would result in a reduced perception of taste, as suggested by [Gilmore and Green \(1993\)](#). [Prescott et al. \(1993\)](#) showed that the capsaicin burning sensation was enhanced by sodium chloride. However, here again, central multisensory integration has not been shown, and this effect would likely be the consequence of the irritant component of salt. At threshold level, it has been found that the addition of capsaicin in the peri-threshold range produced lower taste thresholds for sweet, sour, salty, and bitter but not for umami ([Han et al., 2021](#)).

As far as interactions between olfactory and trigeminal sensations are concerned, [Kobal and Hummel \(1988\)](#) have been the first to use a mixture of pure olfactory and trigeminal stimuli, vanillin, and CO₂. Interestingly, both psychophysical evaluation of intensity and cerebral recording with EEG were reported and could be compared. Although they showed a reduction of the perceived intensity between the mixture of CO₂ and vanillin, compared with vanillin alone, they identified a higher evoked potential amplitude, as recorded with EEG. However, they did not find a difference in evoked potential amplitude between the mixture and CO₂ presented alone. Therefore, CO₂ appeared to contribute the most to the evoked potential. The authors suggested that it may be the result of insufficiently fast excitation of olfactory receptor cells due to vanillin, which would be needed to activate synchronously the number of cortical neurons necessary to produce a recordable evoked potential. As a second result, they found shorter latencies of the evoked potential for the mixture, as compared to both single components. It may highlight interaction mechanisms at the peripheral level since central integration would likely appear later. However, this result may also be induced by changes in cognitive or emotional processing ([Livermore et al., 1992](#)) because the mixture of vanillin and CO₂ may, in all probability, be perceived as unpleasant. Nevertheless, interactions at the peripheral level were proven by [Tremblay and Frasnelli \(2018\)](#), who evaluated the interaction between olfactory and trigeminal systems by measuring the effect of an olfactory costimulation on the ability to localize

a trigeminal stimulus. They found that only the ipsilateral (same nostril) stimulation with a pure odorant and a trigeminal compound increased the capacity to localize the trigeminal stimulus, which can only be explained by interactions between the olfactory and trigeminal systems at the mucosal level.

Very few studies deal with the interactions between the three chemical modalities (olfactory-gustatory-trigeminal), due to the difficulty to identify the impact of each modality, especially the trigeminal one, as previously explained. Four studies reported interactions in beverages (Saint-Eve et al., 2010; Clark et al., 2011; Hewson et al., 2009) and semisolid food (Labbe et al., 2008). In aqueous model systems including sugar, CO₂, and a mint aroma compound, Saint-Eve et al. (2010) showed that CO₂ induced a decrease in sweetness perception, an increase in sourness, and an enhancement of the mint odor. Sweetness decreased the freshness perception, but not the tingling sensation. These effects may be the result of peripheral interactions and/or central integration. Furthermore, the mint odor was found to enhance tingling and freshness perceptions, a fact that may highlight the trigeminal activation induced by the mint aroma compound. Labbe et al. (2008) used a complex viscous model food system in which they systematically varied concentrations of aroma compounds (peach or mint), tastants (citric acid), and a trigeminal compound (cooling agent). Based on sensory profiling of the various samples, they observed overlapping olfactory/trigeminal/taste interactions such as between mint odor, cooling sensations, and sweetness. However, the results are highly intricate and difficult to interpret. As suggested by the authors, further investigations are required to better understand the interactions between the three modalities and their origin.

7.3 Interactions between aroma, taste and texture

7.3.1 *Mechanisms underpinning aroma–taste–texture interactions—perceptual integration versus physicochemical interactions*

Although the quality and quantity of odorants and tastants are major determinants of food products perceptions (Overbosch et al., 1991), food matrix structure plays a critical role in the control of the availability and accessibility of these compounds to gustatory and olfactory receptors. The release of odorants and tastants in naso-oro-pharyngeal cavities is indeed controlled by food oral processing during drinking or eating. Food oral processing depends both on individual physiological parameters, and on the structure and composition of food products (Chen, 2015; Doyennette et al., 2014; Salles et al., 2011). In addition to these physicochemical and physiological phenomena, perception can also be modulated by cognitive interactions between aroma, taste, and texture perceptions (Baek et al., 1999; Cook et al., 2003a; Delwiche, 2004; Hollowood et al., 2002a; Weel et al., 2002). To highlight these physicochemical and cognitive interactions, and to dissociate their respective role in food perception, the coupling of sensory methodologies and instrumental measurements is necessary.

Such a multidisciplinary approach allows identifying and quantifying: (1) the role of physicochemical interactions of odorants and tastants with the components of food matrix on perception, (2) the role of food oral processing on stimuli release, as well as further perception, and (3) the contribution of cognitive interactions to food perception.

An overview of the literature reveals that many different tagging methodologies have been associated with the study of aroma—taste—texture interactions. For sensory methods (Poinot et al., 2013), some conventional sensory descriptive analyses or rapid methodologies, such as free sorting or free choice profiling, have been applied. Temporal methodologies, for example, Temporal Dominance of Sensations, are increasingly being used, and provide results that help to understand the respective roles of physicochemical and perceptual interactions in food perception. For instrumental measurements, the contribution of food texture on tastants and odorants release can be taken into consideration through (1) the study of thermodynamic properties of tastants and odorants such as partition or mass transfer coefficients in food matrix (Paçi Kora et al., 2004; Boisard et al., 2013), and (2) in-mouth and in-nose measurements during food consumption (Pionnier et al., 2004a,b). To monitor real-time changes in the concentration of odorants in the air phase within the nasal cavity, two techniques have been used: APCI-MS (Atmospheric Pressure Chemical Ionization—Mass Spectrometry) (Taylor, 2000), and PTR-MS (Proton Transfer Reaction—Mass Spectrometry) (Lindinger et al., 1998). These in-nose measurements have highlighted the influence of food oral processing on stimuli release, depending on individual oral physiological characteristics (salivation, temperature, mucosa, chewing force, or swallowing) (Gierczynski et al., 2007; Labouré et al., 2014; Feron et al., 2014; Muñoz-González et al., 2021). Moreover, during food consumption, the oral processing behavior is continuously adapting thanks to the incoming sensory information, which depends on the food matrix structure and texture, and has major consequences on flavor perception (Buettner and Beauchamp, 2010; Noble, 1996; Salles et al., 2011).

7.3.2 Influence of texture on aroma and taste perception

The literature on texture—taste and texture—aroma interactions is mostly based on semisolid food products and reports contradictory results. The main explanation of this inconsistency is likely that these interactions highly depend on product structure and composition.

Concerning taste perception, a decrease in perceived intensity for different types of tastants was generally observed for an increase in product viscosity, usually resulting from the addition of a thickening agent (Cook et al., 2003a; Izutsu and Wani, 1985; Lethuaut et al., 2003). In order to explain the observed interactions, physicochemical mechanisms have been proposed, since the release of tastants in the mouth cavity can be largely driven by products' structure and composition, and food oral processing (Boisard et al., 2014; Lawrence et al., 2012a,b). Thus, texture—taste interactions could be explained by the access of tastants to the receptors, which can be modulated by the product texture (Proserpio et al., 2021). Nevertheless, cognitive interactions involving thickness perception in combination with taste perception could not be ruled out.

Regarding olfactory perception, some studies showed no effect of texture on aroma, when the products' texture modification did not rely on a major change in composition (Lethuaut et al., 2003; Tournier et al., 2009). Besides, numerous studies highlighted a decrease in perceived odor and aroma intensity induced by different odorants when thickeners are added in model or real food products (Baines and Morris, 1987; Guinard and Marty, 1995; Kälviäinen et al., 2000; Pangborn et al., 1978; Wendin et al., 1997). Pangborn and Szczesniak (1974) were the first to show that hydrocolloids depressed the odor and aroma of different volatile compounds. They also showed that the type of thickener, rather than its concentration, generally determines the observed perception decrease. Consequently, in these studies, the impact of texture on aroma is mainly explained by thermodynamic changes in the properties of the matrices, and also by chemical binding between the thickener and the odorants (Cook et al., 2003a; Guichard et al., 1991). In addition, oral processing can be at the origin of differences in the evolution of *in vivo* retronasal odorants release induced by different textures, which, in turn, may drive aroma perception (Arancibia et al., 2011; Boland et al., 2006; Gierczynski et al., 2008). However, when sensory and instrumental data are not reconcilable, a cognitive mechanism is usually advocated to explain the observed interactions (Baek et al., 1999; Cook et al., 2003a; Gierczynski et al., 2008; Hollowood et al., 2002a; Tournier et al., 2009; Weel et al., 2002).

Cognitive interactions, induced by the integration of texture and aroma perceptions, have been evidenced in a series of studies on yogurt. In a first study, it has been shown that the addition of a thickening agent decreased the perception of green apple aroma, whereas no effect of thickener on the release of hexanal—the odorant responsible for the green apple aroma—was observed in instrumental measurements (Paçi Kora et al., 2004). These findings strongly supported a perceptual mechanism behind the interactions between texture and aroma. In another study, it was found that yogurts with fatty odor notes (coconut and butter) were judged to be thicker than those presenting green notes (green apple and almond) that were considered to be smoother (Saint-Eve et al., 2004). The hypothesis of a cognitive mechanism has been strengthened by the results of studies in which the texture of the food product was modified only through mechanical treatment. Such an approach avoided the products' composition changes and thus limited chemical interactions between thickeners and odorants. Moreover, perceptual interactions between odor and texture perceptions were clearly highlighted in a study performed by delivering odorants into the subject's nasal cavity via a continuous airflow, while holding into the mouth a solution varying in viscosity (thickener addition). A decrease in odor/aroma intensity with increasing oral stimulus viscosity was reported when odorants were presented ortho- or retronasally (Bult et al., 2007).

Few studies looked at the multimodal interactions in beverages. The texture perception investigated in these studies is generally the mouthfeel and it relies on texture—taste interactions at the physicochemical but also perceptual levels (see below). Mouthfeel has a very large definition; it is defined as a mixed experience derived from sensations in the mouth that relate to physical or chemical properties of a stimulus (AFNOR NF EN ISO 5492, 2009). To clarify the terminology, we will define the mouthfeel as the experience of the viscosity in the mouth. Sucrose is a solid compound that strongly interacts with water and results in a thickening of the beverage (Goff and

Guo, 2019). Therefore, the reduction of sugar often impacts the texture and especially the mouthfeel of beverages (Miele et al., 2017). For example, the reduction of sugar content in an orange nectar decreased the viscosity of the beverage, and the participants perceived a reduced mouthfeel (Pineli et al., 2016). This reduced mouthfeel was accompanied by a reduced acceptance in 54% of the panel tested. This effect can likely be extended to other beverages and highlights the difficulties to reduce sugar in food and the necessity to better understand cross-modal interactions to maintain food acceptance. Considering texture perception and the importance to maintain acceptable mouthfeel when reducing sugar content, viscosity in beverages can be increased using high-ester pectin (Miele et al., 2017). However, increasing viscosity with high-ester pectin decreases sweetness perception in particular, and more generally increasing viscosity reduces taste intensity (Moskowitz and Arabie, 1970; Arabie and Moskowitz, 1971; Pangborn et al., 1973; Christensen, 1980; Tournier et al., 2009) and aroma intensity (Hollowood et al., 2002b; Weel et al., 2002; Cook et al., 2003b; Lethuaut et al., 2005; Bult et al., 2007), even when aroma release was not affected (Weel et al., 2002; Lethuaut et al., 2005). These results show again that texture effect on aroma and taste perception relies also on central mechanisms. Following on the idea to maintain mouthfeel while reducing sugar content, encouraging results have been shown in a study testing the perceptual interactions between perceived viscosity (using high-ester pectin), sugar, and vanillin aroma in water and apple nectar bases (Bertelsen et al., 2020b). The authors found no effect of perceived viscosity on taste or aroma perceptions in none of the tested beverages, but they found a vanilla-induced sweetness in the apple nectar compared with the water solution. This result seems to be in contradiction with former studies, however, the authors used a low amount of pectin compared with previous studies, and even if the increase of viscosity was perceived, the pectin concentration was sufficiently low to not produce cross-modal effects that would have reduced sweetness. Therefore, a fine dosage of high-ester pectin or other polysaccharides, combined with OITE, may represent a relevant mixed strategy to reduce sucrose in beverages, while maintaining texture and mouthfeel, and in turn liking.

7.3.3 Influence of aroma and taste on texture perception

Among the studies dealing with texture—flavor interactions, only a few focused on the impact of odor/aroma and taste on texture perception (Cayot et al., 1998; Lethuaut et al., 2003; Tournier et al., 2009; Pangborn et al., 1973; Saint-Eve et al., 2004). As far as taste and texture are concerned, it has been reported that increasing the levels of sucrose, citric acid, and sodium chloride could alter the perceived oral viscosity and the astringency of model solutions (Burns and Noble, 1985; Christensen, 1980; Ishikawa and Noble, 1995; Peleg et al., 1998). Regarding the influence of odor on texture perception, the few available reports focused on the influence of the chemical type and concentration of the aroma compounds on texture perception; the results are quite contrasted (Jaime et al., 1993; Kälviäinen et al., 2000; Pangborn and Szczesniak, 1974). To study this type of interaction, different approaches have been used: (1) wearing or not wearing a nose-clip to turn off or on the sense of smell, (2) comparing

flavored and unflavored matrices, (3) adding an aroma compound varying in quality and complexity in food products (Labbe et al., 2008; Paçi Kora et al., 2003; Saint-Eve et al., 2004; Symoneaux et al., 2015).

For instance, in yogurts, the addition of an odorant eliciting a green apple odor enhanced astringency, while the increase in the odorant's concentration tended to decrease perceived thickness (Paçi Kora et al., 2003). In the same way, Saint-Eve et al. (2004) studied the impact of the quality and complexity of aroma compounds on the perceived texture of yogurts. They found that the addition of coconut and butter aroma induced higher perceived thickness than the addition of green apple aroma. In line with this result, Bult et al. (2007), who used a very well-controlled stimulation device, highlighted that the presence of a cream odor increased the perceived thickness and creaminess of milk-like food products. In the case of solid food (e.g., model cheeses), the addition of aroma compounds seemed to increase perceived hardness, whereas no instrumental texture properties of the products were modified (Saint-Eve et al., 2009). In these latter studies, the cognitive origin of the aroma–texture interaction is very likely, which is also the case in a study on ciders, showing that these beverages were perceived more astringent when tasted without a nose clip, namely when the beverage aroma was perceived (Symoneaux et al., 2015).

7.4 Conclusion: multimodal interactions and food innovation

Multimodal interactions are at the core of food flavor construction and modulation by food texture. Two main types of mechanisms underpin these interactions. Physico-chemical mechanisms drive the chemical stimuli release from the food matrix as a function of food oral processing, while perceptual mechanisms result from sensory information interplay along the integration pathway from the receptors to the brain, with a major input of cognition. Deciphering the contribution of each mechanism is still a major scientific and technological challenge, which relies on the study of relationships between sensory and instrumental data on both model and real food products. Moreover, it is likely that brain exploration approaches would also largely contribute to fulfilling this challenge while providing better insights into our understanding of the brain processes implied in multimodal interactions, and the holistic perception of flavor (see Chapter 10: Holistic Perception and Memorization of Flavor).

Beyond the interactions reviewed in this chapter, and focused on odor/aroma, taste, trigeminal, and texture perceptions, multimodal interactions related to food perception also include visual and auditory cues as extrinsic and intrinsic properties of the food (Wang et al., 2019b; Spence, 2022). For instance, potato chips could be made to taste crunchier by manipulating the crunching sounds that a person heard when biting into such a dry foodstuff (Zampini and Spence, 2004), or fruit-flavored beverages would be more accurately identified when colored appropriately (Zampini et al., 2008). Overall, it is clear that, through multimodal interactions, it is possible to modulate the perception of a sensory dimension by acting on the stimulus of another dimension (e.g.,

modulating taste by changing odorants), a fact that opens new opportunities in terms of cross-modal compensations.

Cross-modal compensation appears, therefore, as a strategy that can contribute to formulating or reformulating food products. This phenomenon allows considering nutritional, economical, or ecological constraints, while keeping acceptable food sensory properties, which, in turn, could help maintain consumer liking. For instance, it seems possible to design aroma compounds that could help maintaining saltiness or textural properties of low-salt or low-fat foods (Thomas-Danguin et al., 2015, 2019; Ghawi et al., 2014; Prescott, 2015; Busch et al., 2013; Sundqvist et al., 2006; Syarifuddin et al., 2016). Moreover, such a strategy could be advantageously combined with other strategies to improve cross-modal enhancement effects and, thus, compensate for high-level reductions while maintaining good acceptability (Emorine et al., 2012). These strategies would thus contribute to designing and proposing innovative food products that aim to improve consumers' well-being and health.

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Flavor: brain processing

8

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8.1 Introduction

A schematic diagram of the taste and related olfactory, somatosensory, and visual pathways in the **primate** brain is shown in Fig. 8.1, with a view of their locations in the brain in Fig. 8.2. Neurophysiological studies in **primates** provide a foundation for understanding taste, olfactory, and flavor processing and neuroimaging in humans, for investigation of the tuning of individual neurons provide the fundamental information about how these stimuli are encoded in different brain areas using a sparsely distributed representation in which each neuron is tuned differently to other neurons (Kadohisa et al., 2005; Rolls, 2008a, 2015a, 2016a, 2021a; Rolls et al., 2010a; Rolls and Treves, 2011). Studies in nonhuman **primates** are especially relevant (Rolls, 2014a, 2015b, 2016b, 2021a), as the taste pathways in **primates** proceed via the thalamus to the taste cortex whereas in rodents there is a pontine taste area which has direct subcortical connections (Small and Scott, 2009; Rolls, 2016b, 2021a); effects of satiety are found peripherally in the nucleus of the solitary tract in rodents (Rolls and Scott, 2003; Scott and Small, 2009; Rolls, 2016b); and rodents do not have the major part of the **primate** including human orbitofrontal cortex, the granular part (Wise, 2008; Rolls, 2014a, 2019b, 2021a) (see Fig. 8.3). This makes the rodent a poor model of taste, olfactory, and flavor processing in the brains of humans and other **primates** (Rolls, 2016c, 2021a).

8.2 Flavor processing in the **primate** brain

8.2.1 Taste processing

8.2.1.1 Pathways

A schematic diagram of the taste and related olfactory, somatosensory, and visual pathways in **primates** is shown in Figs. 8.1 and 8.2 shows where these pathways are on a **primate** brain. The multimodal convergence that enables single neurons to respond to different combinations of taste, olfactory, texture, temperature, and visual inputs to represent different flavors produced often by new combinations of sensory input is a theme of the research that will be described.

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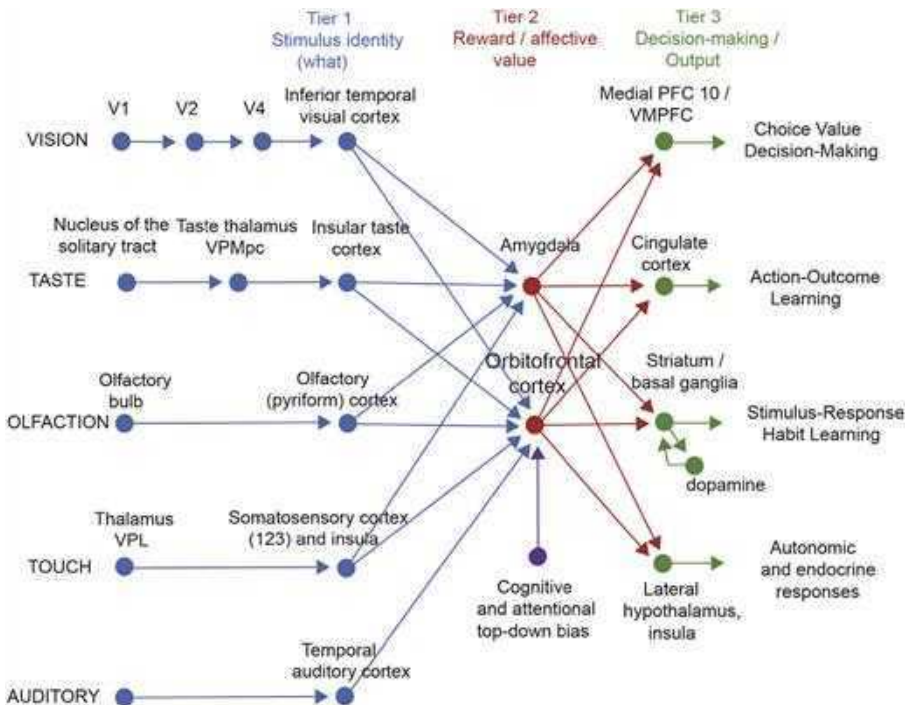


Figure 8.1 Schematic diagram showing some of the gustatory, olfactory, visual, and somatosensory pathways to the orbitofrontal cortex, and some of the outputs of the orbitofrontal cortex, in [primates](#). The secondary taste cortex and the secondary olfactory cortex are within the orbitofrontal cortex. V1 - primary visual cortex. V4 - visual cortical area V4. PreGen Cing – pregenual cingulate cortex. Tier 1: the column of brain regions including and below the inferior temporal visual cortex represents brain regions in which “what” stimulus is present is made explicit in the neuronal representation, but not its reward or affective value which are represented in the next tier of brain regions (Tier 2), the orbitofrontal cortex and amygdala, and in the anterior cingulate cortex. In Tier 3 areas beyond these such as medial prefrontal cortex area 10, choices or decisions about reward value are taken, with the mechanisms described elsewhere ([Rolls and Deco, 2010](#); [Rolls, 2014a, 2021a](#)). Top-down control of affective response systems by cognition and by selective attention from the dorsolateral prefrontal cortex is also indicated. Medial PFC area 10 – medial prefrontal cortex area 10; VPMpc – ventralposteromedial thalamic nucleus.

8.2.1.2 The primary taste cortex

[Rolls \(2016b\)](#) has shown that the primary taste cortex in the [primate](#) anterior insula and adjoining frontal operculum contains not only taste neurons tuned to sweet, salt, bitter, sour ([Scott et al., 1986](#); [Yaxley et al., 1990](#); [Rolls and Scott, 2003](#)), and umami as exemplified by monosodium glutamate ([Baylis and Rolls, 1991](#); [Rolls et al., 1996a](#)), but also other neurons that encode oral somatosensory stimuli including viscosity, fat texture, temperature, and capsaicin ([Verhagen et al., 2004](#)). Some neurons in the

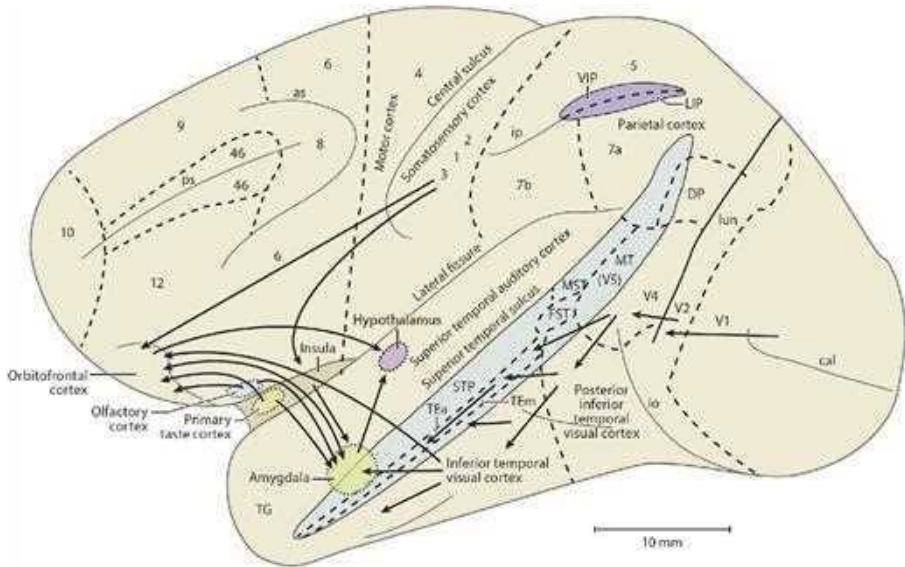


Figure 8.2 Some of the pathways involved in processing food-related stimuli are shown in this lateral view of the **primate brain** (macaque). Connections from the primary taste and olfactory cortices to the orbitofrontal cortex and amygdala are shown. Connections are also shown in the “ventral visual system” from V1 to V2, V4, the inferior temporal visual cortex, etc., with some connections reaching the amygdala and orbitofrontal cortex. In addition, connections from the somatosensory cortical areas 1, 2, and 3 that reach the orbitofrontal cortex directly and via the insular cortex, and that reach the amygdala via the insular cortex, are shown. *AIT*, anterior inferior temporal cortex; *as*, arcuate sulcus; *cal*, calcarine sulcus; *cs*, central sulcus; *FST*, visual motion processing area; *io*, inferior occipital sulcus; *ip*, intraparietal sulcus (which has been opened to reveal some of the areas it contains); *lf*, lateral (or Sylvian) fissure; *LIP*, lateral intraparietal area; *lun*, lunate sulcus; *MST*, visual motion processing area; *MT*, visual motion processing area (also called V5); *PIT*, posterior inferior temporal cortex; *ps*, principal sulcus; *STP*, superior temporal plane; *sts*, superior temporal sulcus (which has been opened to reveal some of the areas it contains); *TA*, architectonic area including auditory association cortex; *TE*, architectonic area including high order visual association cortex, and some of its subareas TEa and TEm; *TEO*, architectonic area including posterior visual association cortex; *TG*, architectonic area in the temporal pole; *V1–V4*, visual areas V1–V4; *VIP*, ventral intraparietal area. The numerals refer to architectonic areas, and have the following approximate functional equivalence: 1, 2, 3, somatosensory cortex (posterior to the central sulcus); 4, motor cortex; 5, superior parietal lobule; 7a, inferior parietal lobule, visual part; 7b, inferior parietal lobule, somatosensory part; 6, lateral premotor cortex; 8, frontal eye field; 12, part of orbitofrontal cortex; 46, dorsolateral prefrontal cortex.

primary taste cortex respond to particular combinations of taste and oral texture stimuli, but do not respond to olfactory stimuli or visual stimuli such as the sight of food (Verhagen et al., 2004). Neurons in the primary taste cortex do not represent the reward value of taste, that is the appetite for a food, in that their firing is not decreased to zero by feeding the taste to satiety (Rolls et al., 1988; Yaxley et al., 1988; Rolls, 2016b).

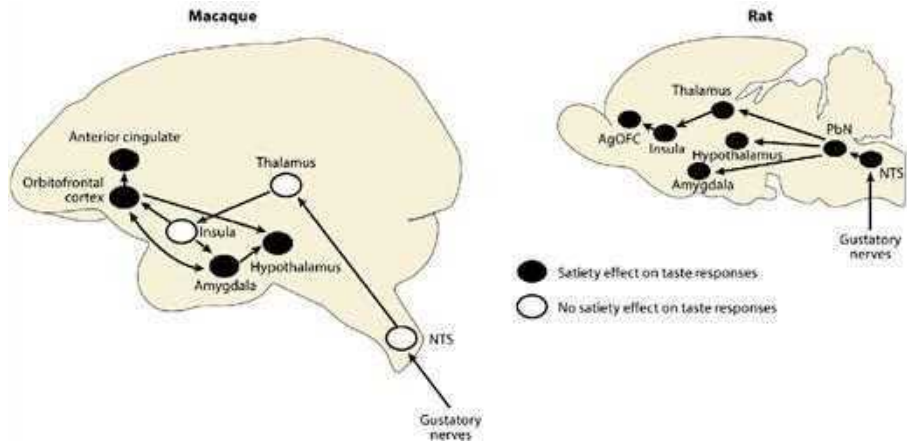


Figure 8.3 Taste pathways in the macaque and rat. In the *macaque*, gustatory information reaches the nucleus of the solitary tract (NTS), which projects directly to the taste thalamus (ventral posteromedial nucleus, pars parvocellularis, VPMpc) which then projects to the taste cortex in the orbitofrontal cortex (Insula). The insular taste cortex then projects to the orbitofrontal cortex and amygdala. The orbitofrontal cortex projects taste information to the anterior cingulate cortex. Both the orbitofrontal cortex and the amygdala project to the hypothalamus (and to the ventral striatum). In macaques, feeding to normal self-induced satiety does not decrease the responses of taste neurons in the NTS or taste insula (and by inference not VPMpc) (see text). In the *rat*, in contrast, the NTS projects to a pontine taste area, the parabrachial nucleus (PbN). The PbN then has projections directly to a number of subcortical structures, including the hypothalamus, amygdala, and ventral striatum, thus bypassing thalamo-cortical processing. The PbN in the rat also projects to the taste thalamus (VPMpc), which projects to the rat taste insula. The taste insula in the rat then projects to an agranular orbitofrontal cortex (AgOFC), which probably corresponds to the most posterior part of the [primate](#) OFC, which is agranular. (In [primates](#), most of the orbitofrontal cortex is granular cortex, and the rat may have no equivalent to this (Wise, 2008; Small and Scott, 2009; Passingham and Wise, 2012; Rolls, 2019b, 2021a). In the rat, satiety signals such as gastric distension and satiety-related hormones decrease neuronal responses in the NTS (see text), and by inference therefore in the other brain areas with taste-related responses, as indicated in the figure.

8.2.1.3 The secondary taste cortex

A secondary cortical taste area in [primates](#) was discovered by [Rolls et al. \(1990\)](#) in the orbitofrontal cortex, extending several millimeters in front of the primary taste cortex, which projects anatomically to the orbitofrontal cortex ([Baylis et al., 1995](#)). Different neurons in the orbitofrontal cortex respond not only to each of the four classical prototypical tastes sweet, salt, bitter, and sour ([Rolls, 1997](#); [Rolls and Scott, 2003](#)), but also to umami tastants such as glutamate (which is present in many natural foods such as tomatoes, mushrooms, and milk) ([Baylis and Rolls, 1991](#)) and [inosine monophosphate](#) (which is present in meat and some fish such as tuna) ([Rolls et al., 1996a](#)). This evidence, taken together with the identification of glutamate taste receptors

(Zhao et al., 2003; Maruyama et al., 2006; Roper and Chaudhari, 2017), leads to the view that there are five prototypical types of taste information channels, with umami contributing, often in combination with corresponding olfactory inputs (Rolls and Baylis, 1994; Rolls et al., 1998; McCabe and Rolls, 2007; Rolls, 2009), to the flavor of protein. In addition, other neurons respond to water, and others to somatosensory stimuli including astringency as exemplified by tannic acid (Critchley and Rolls, 1996c), and capsaicin (Rolls et al., 2003b; Kadohisa et al., 2004). Taste responses are found in a large mediolateral extent of the orbitofrontal cortex (Critchley and Rolls, 1996c; Pritchard et al., 2005; Rolls, 2008a, 2015b; Rolls and Grabenhorst, 2008).

8.2.1.4 *The pleasantness of the taste of food, sensory-specific satiety, and the effects of variety on food intake*

The modulation of the reward value of a sensory stimulus such as the taste of food by motivational state, for example, hunger, is one of the important ways by which motivational behavior is controlled (Rolls, 2014b, 2016c). The subjective correlate of this modulation is that food tastes pleasant when hungry, and tastes hedonically neutral when it has been eaten to satiety. Following Edmund Rolls' discovery of sensory-specific satiety revealed by the selective reduction in the responses of lateral hypothalamic neurons to a food eaten to satiety (Rolls, 1981; Rolls et al., 1986), it has been shown that this is implemented in a region that projects to the hypothalamus, the orbitofrontal (secondary taste) cortex, for the taste, odor, and sight of food (Rolls et al., 1989; Critchley and Rolls, 1996a; Rolls, 2015b).

This evidence shows that the reduced acceptance of food that occurs when food is eaten to satiety, the reduction in the pleasantness of its taste and flavor, and the effects of variety to increase food intake (Cabanac, 1971; Rolls and Rolls, 1977, 1982, 1997; Rolls et al., 1981a, 1981b, 1982, 1983a, 1983b, 1984; Rolls and Hetherington, 1989; Hetherington, 2007) are produced in the orbitofrontal cortex, but not at earlier stages of processing where the responses reflect factors such as the intensity of the taste, which is little affected by satiety (Rolls et al., 1983c; Rolls and Grabenhorst, 2008; Rolls, 2015b, 2019b). In addition to provide an implementation of sensory-specific satiety (probably by habituation of the synaptic afferents to orbitofrontal neurons with a time course of the order of the length of a course of a meal), it is likely that visceral and other satiety-related signals reach the orbitofrontal cortex (as indicated in Fig. 8.1) (from the nucleus of the solitary tract, via thalamic and possibly hypothalamic nuclei) and there modulate the representation of food, resulting in an output that reflects the reward (or appetitive) value of each food (Rolls, 2014a, 2019b).

8.2.2 *The representation of flavor: convergence of olfactory, taste, and visual inputs in the orbitofrontal cortex*

Taste and olfactory pathways are brought together in the orbitofrontal cortex where flavor is formed by learned associations at the neuronal level between these inputs (see Fig. 8.1) (Rolls and Baylis, 1994; Critchley and Rolls, 1996b; Rolls et al., 1996b, 1996c; Verhagen et al., 2004; Rolls, 2011a, 2014a). Visual inputs also become

associated by learning in the orbitofrontal cortex with the taste of food to represent the sight of food and contribute to flavor (Thorpe et al., 1983; Rolls, 1996; Rolls et al., 1996b). The visual and olfactory as well as the taste inputs represent the reward value of the food, as shown by sensory-specific satiety effects (Critchley and Rolls, 1996a).

8.2.3 The texture of food, including fat texture

Some orbitofrontal cortex neurons have oral texture—related responses that encode parametrically the viscosity of food in the mouth (shown using a methyl cellulose series in the range 1–10,000 centiPoise) (see example in Fig. 8.4), and others independently encode the particulate quality of food in the mouth, produced quantitatively, for example, by adding 20–100 μm microspheres to methyl cellulose (Rolls et al., 2003b). Very interestingly, some neurons encode the oral texture of fat (Rolls et al., 1999; Verhagen et al., 2003; Rolls, 2011c, 2015b), and for a population of oral fat-sensitive neurons this is independent of texture, as illustrated in Fig. 8.5 (Rolls et al., 2018). The oral fat-sensitive neurons encode fat by the coefficient of sliding friction (Rolls et al., 2018; Rolls, 2020b). This discovery is very likely to be important in the design of foods in future, which can be designed to produce the pleasant mouth feel of fat with designed nutritional content (Rolls, 2020b). These oral fat-encoding neurons are separated from a small population that responds to free fatty acids, and which may be important instead in encoding “off” flavors of food (Rolls et al., 1999; Verhagen et al., 2003; Rolls, 2011c, 2015b, 2020b). Somatosensory signals that transmit information about capsaicin (chilli) and astringency are also reflected in neuronal activity in these cortical areas (Critchley and Rolls, 1996c; Kadohisa et al., 2004, 2005). Different neurons respond to different combinations of these food texture inputs and taste, with examples shown in Fig. 8.4.

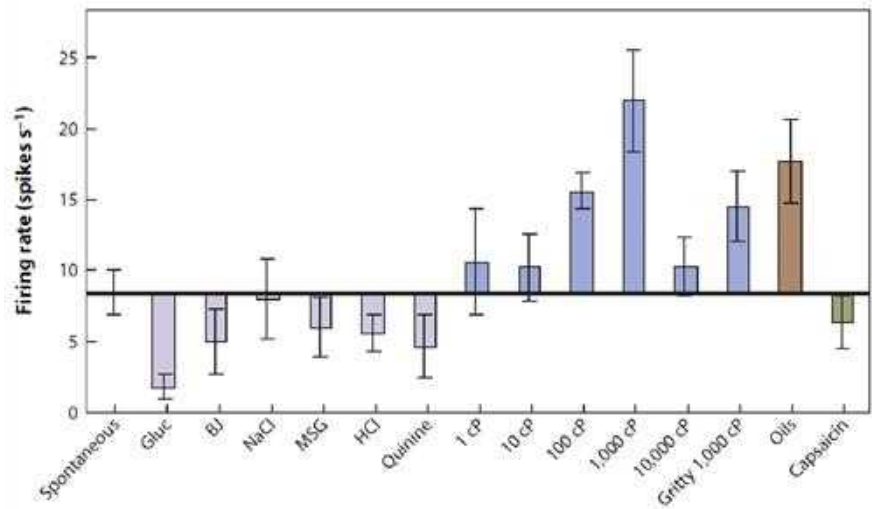
In addition, we have shown that some neurons in the orbitofrontal cortex reflect the temperature of substances in the mouth, and that this temperature information is represented independently of other sensory inputs by some neurons, and in combination with taste or texture by other neurons (Kadohisa et al., 2004, 2005).

8.3 Flavor processing in the human brain: functional neuroimaging

8.3.1 Taste

In humans it has been shown (Rolls, 2012b, 2014a, 2015a, 2015b) in neuroimaging studies using functional Magnetic Resonance Imaging (fMRI) that taste activates an area of the anterior insula/frontal operculum, which is probably the primary taste cortex (O’Doherty et al., 2001; de Araujo et al., 2003b; Small, 2010; Rolls, 2016b), and part of the orbitofrontal cortex, which is probably the secondary taste cortex (Francis et al., 1999; O’Doherty et al., 2001; de Araujo et al., 2003b; Rolls, 2005b; Rolls, 2008a). We pioneered the use of a tasteless control with the same ionic constituents as saliva

a Cell bk244



b Cell bo34

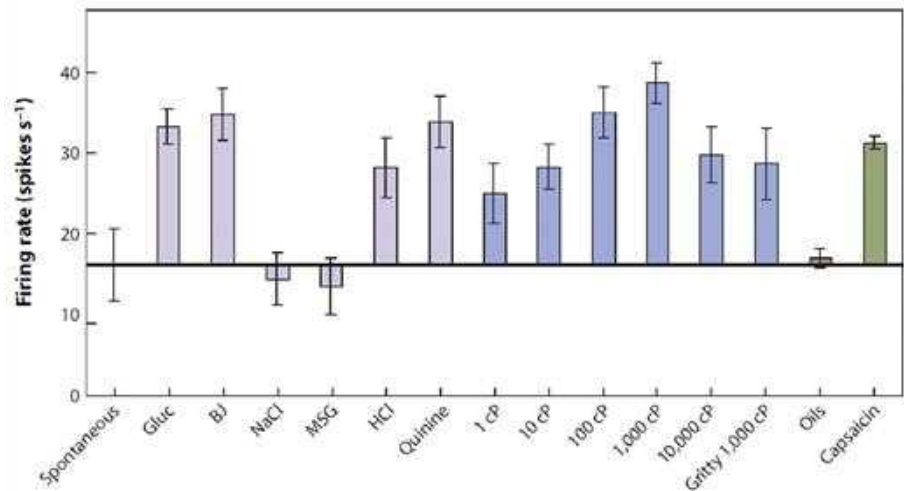


Figure 8.4 Above. Firing rates (mean $\pm$ s.e.m.) of macaque orbitofrontal cortex viscosity-sensitive neuron bk244 which did not have taste responses. The firing rates are shown to the viscosity series (carboxymethylcellulose in the range 1–10,000 centiPoise), to the gritty stimulus (carboxymethylcellulose with Fillite microspheres), to the taste stimuli 1M glucose (Gluc), 0.1M NaCl, 0.1M MSG, 0.01M HCl and 0.001M QuinineHCl, and to fruit juice (BJ). Spont = spontaneous firing rate. Below. Firing rates (mean $\pm$ s.e.m.) of viscosity-sensitive neuron bo34 which had no response to the oils (mineral oil, vegetable oil, safflower oil, and coconut oil, which have viscosities which are all close to 50 cP). The neuron did not respond to the gritty stimulus in a way that was

(O'Doherty et al., 2001; de Araujo et al., 2003b), as water can activate some neurons in cortical taste areas (Rolls et al., 1990) and can activate the taste cortex (de Araujo et al., 2003b). Within individual subjects separate areas of the orbitofrontal cortex are activated by sweet (pleasant) and salt (unpleasant) tastes (O'Doherty et al., 2001).

The primary taste cortex in the anterior insula of humans represents the identity and intensity of taste in that activations there correlate with the subjective intensity of the taste, and the orbitofrontal and anterior cingulate cortex represents the reward value of taste, in that activations there correlate with the subjective pleasantness of taste (Grabenhorst and Rolls, 2008; Grabenhorst et al., 2008a; Rolls, 2015b, 2016b) (Fig. 8.6).

We also found activation of the human amygdala by the taste of glucose (Francis et al., 1999). Extending this study, O'Doherty et al. (2001) showed that the human amygdala was as much activated by the affectively pleasant taste of glucose as by the affectively negative taste of NaCl, and thus provided evidence that the human amygdala is not especially involved in processing aversive as compared to rewarding stimuli. Zald et al. (1998, 2002) also showed that the amygdala, as well as the orbitofrontal cortex, responds to aversive (e.g., quinine) and sucrose taste stimuli.

Umami taste stimuli, of which an exemplar is monosodium glutamate (MSG) and which capture what is described as the taste of protein, activate the insular (primary), orbitofrontal (secondary), and anterior cingulate (tertiary; Rolls, 2008a) taste cortical areas (de Araujo et al., 2003a). When the nucleotide 0.005M inosine 5'-monophosphate (IMP) was added to MSG (0.05M), the blood oxygenation-level dependent (BOLD) signal in an anterior part of the orbitofrontal cortex showed supralinear additivity, and this may reflect the subjective enhancement of umami taste that has been described when IMP is added to MSG (Rolls, 2009). The supralinear additivity refers to a greater activation to the combined stimulus MSG + IMP than to the sum of the activations to MSG and IMP presented separately. This evidence that the effect of the combination is greater than the sum of its parts indicates an interaction between the parts to form in this case an especially potent taste of umami, which is part of what can make a food taste delicious (Rolls, 2009). Overall, these results illustrate that the responses of the brain can reflect inputs produced by particular combinations of sensory stimuli with supralinear activations, and that the combination of sensory stimuli may be especially represented in particular brain regions, and may help to make the food pleasant.

8.3.2 Odor

In humans, in addition to activation of the pyriform (olfactory) cortex (Zald and Pardo, 1997; Sobel et al., 2000; Poellinger et al., 2001), there is strong and consistent activation

unexpected given the viscosity of the stimulus, was taste tuned, and did respond to capsaicin. Other neurons respond to fats and other oils independently of viscosity (see text Rolls et al., 1999; Verhagen et al., 2003; Rolls et al., 2018; Rolls, 2020b).

After Rolls, E.T., Verhagen, J.V. & Kadohisa, M., 2003b. Representations of the texture of food in the primate orbitofrontal cortex: neurons responding to viscosity, grittiness and capsaicin. *J. Neurophysiol.* 90, 3711–3724.

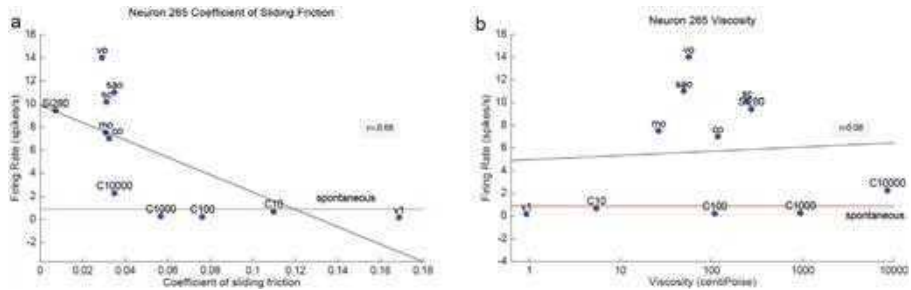


Figure 8.5 An orbitofrontal cortex neuron with responses nonlinearly correlated with decreases in the coefficient of sliding friction (A). The neuron responds almost not at all until the coefficient of sliding friction falls below 0.04. The neuron is thus very selective for fat texture, because of its nonlinear response in relation to the coefficient of sliding friction. The linear regression line has a correlation of $r = -0.68$ ($P = .02$). (B): There is a much weaker relation to viscosity ($r = 0.08$, $P = .82$), with the oils producing a larger response than predicted linearly. Further, a regression line through the nonoil stimuli would have a lower slope. C10–C10000: carboxymethyl cellulose with the nominal viscosity of 10, 100, 1000, and 10,000 cP v1: water (1 cP). co: coconut oil; mo: mineral oil; sa: safflower oil; vo: vegetable oil; sc: single cream. Si280: silicone oil with a nominal viscosity of 280 cP. Li: linoleic acid; La: lauric acid. The horizontal red line indicates the spontaneous firing rate. The Pearson correlation between the firing rate of each neuron and (A) the coefficient of sliding friction, and (B) the viscosity, was calculated to show to what extent the firing of a neuron reflected one or other of these measures. Linear regression lines are shown in the figure for how the firing rates were related to the coefficient of sliding friction, or to the log of the viscosity. After Rolls, E.T., Mills, T., Norton, A., et al. 2018. Neuronal encoding of fat using the coefficient of sliding friction in the cerebral cortex and amygdala. *Cereb Cortex* 28, 4080–4089.

of the orbitofrontal cortex by olfactory stimuli (Zatorre et al., 1992; Francis et al., 1999; Rolls et al., 2003a). This region appears to represent the pleasantness of odor, as shown by a sensory-specific satiety experiment with banana versus vanilla odor (O'Doherty et al., 2000), and this has been confirmed by Gottfried et al. (personal communication, see Gottfried (2015)), who also showed that activations in the pyriform (primary olfactory) cortex were not decreased by odor devaluation by satiety. Further, pleasant odors tend to activate the medial, and unpleasant odors the more lateral, orbitofrontal cortex (Rolls et al., 2003a), adding to the evidence that it is a principle that there is a hedonic map in the orbitofrontal cortex, and also in the anterior cingulate cortex, which receives inputs from the orbitofrontal cortex (Rolls and Grabenhorst, 2008; Grabenhorst and Rolls, 2011). The primary olfactory (pyriform) cortex represents the identity and intensity of odor in that activations there correlate with the subjective intensity of the odor, and the orbitofrontal and anterior cingulate cortex represent the reward value of odor, in that activations there correlate with the subjective pleasantness (medially) or unpleasantness (laterally) of odor (Rolls et al., 2003a, 2008, 2009; Grabenhorst et al., 2007; Rolls and Grabenhorst, 2008; Grabenhorst and Rolls, 2011; Rolls, 2019b, 2021a). Indeed, the reward-related medial orbitofrontal cortex/ventromedial prefrontal cortex connects preferentially with the reward-related pregenual anterior cingulate cortex;

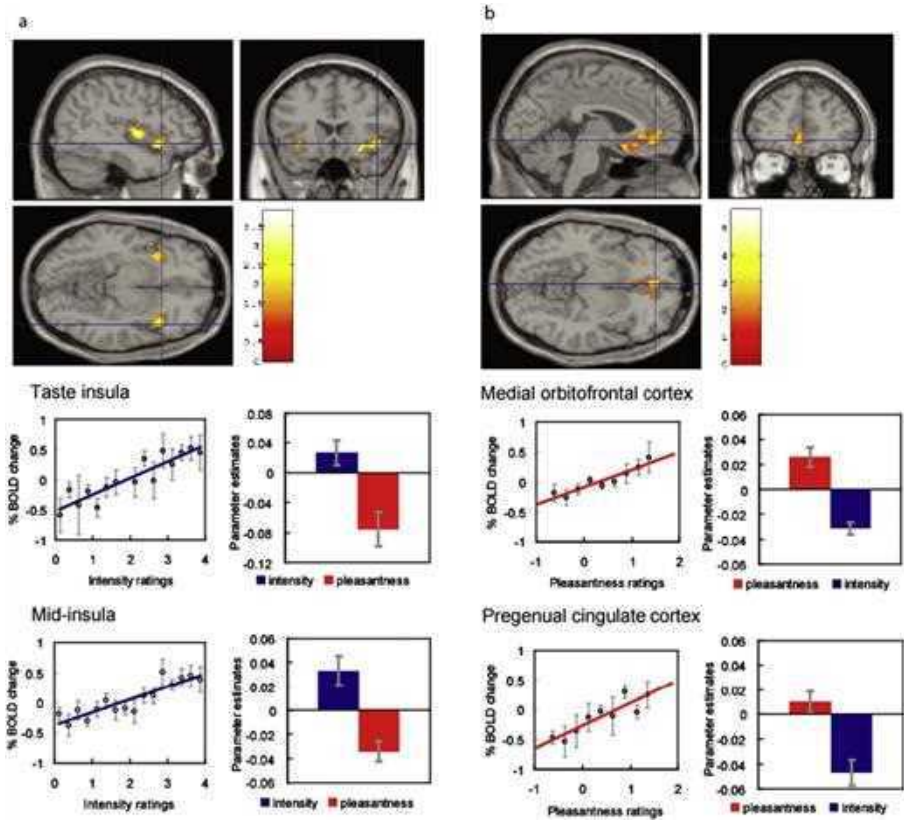


Figure 8.6 Effect of paying attention to the pleasantness versus the intensity of a taste stimulus. (A) Top: A significant difference related to the taste period was found in the taste insula at [42 18 -14] $z = 2.42$ $P < .05$ (indicated by the cursor) and in the mid-insula at [40 -2 4] $z = 3.03$ $P < .025$. Middle: Taste Insula. Right: The parameter estimates (mean $\pm$ sem across subjects) for the activation at the specified coordinate for the conditions of paying attention to pleasantness or to intensity. The parameter estimates were significantly different for the taste insula $t = 4.5$, $df = 10$, $P = .001$. Left: The correlation between the intensity ratings and the activation (% BOLD change) at the specified coordinate ($r = 0.91$, $df = 14$, $P < .001$). Bottom: Mid-Insula. Right: The parameter estimates (mean $\pm$ sem across subjects) for the activation at the specified coordinate for the conditions of paying attention to pleasantness or to intensity. The parameter estimates were significantly different for the mid-insula $t = 5.02$, $df = 10$, $P = .001$. Left: The correlation between the intensity ratings and the activation (% BOLD change) at the specified coordinate ($r = 0.89$, $df = 15$, $P < .001$). The taste stimulus, monosodium glutamate, was identical on all trials. (B) Top: A significant difference related to the taste period was found in the medial orbitofrontal cortex at [-6 14 -20] $z = 3.81$ $P < .003$ (toward the back of the area of activation shown) and in the pregenual cingulate cortex at [-4 46 -8] $z = 2.90$ $P < .04$ (at the cursor). Middle: Medial orbitofrontal cortex. Right: The parameter estimates (mean $\pm$ sem across subjects) for the activation at the specified coordinate for the conditions of paying attention to pleasantness or to intensity. The parameter estimates were significantly different for the orbitofrontal cortex $t = 7.27$, $df = 11$, $P < 10^{-4}$. Left: The

and the punishment/nonreward-related lateral orbitofrontal cortex connects preferentially with the punishment/nonreward-related supracallosal anterior cingulate cortex (Du et al., 2020; Hsu et al., 2020; Rolls et al., 2020; Rolls et al., 2022). The concept is that the orbitofrontal cortex encodes the reward value of the stimuli, and the anterior cingulate cortex uses these inputs to reinforce actions that are being made and signaled to the posterior cingulate cortex from the parietal cortex (Rolls, 2019a).

8.3.3 *Olfactory-taste convergence to represent flavor, and the influence of satiety on flavor representations*

Taste and olfactory conjunction analyses, and the measurement of supraadditive effects indicating convergence and interactions, showed convergence for taste (sucrose) and odor (strawberry) in the orbitofrontal and anterior cingulate cortex, and activations in these regions were correlated with the pleasantness ratings given by the participants (de Araujo et al., 2003c; Small et al., 2004; Small and Prescott, 2005). These results provide evidence on the neural substrate for the convergence of taste and olfactory stimuli to produce flavor in humans, and on where the pleasantness of flavor is represented in the human brain. The first region where the effects of this convergence are found is in an agranular part of what cytoarchitecturally is the insula (Ia) that is topologically found in the posterior orbitofrontal cortex, though it is anterior to the insular taste cortex, and posterior to the granular orbitofrontal cortex (see Fig. 8.6) (de Araujo et al., 2003c).

McCabe and Rolls (2007) have shown that the convergence of taste and olfactory information appears to be important for the delicious flavor of umami. They showed that when glutamate is given in combination with a consonant, savory, odor (vegetable), the resulting flavor can be much more pleasant than the glutamate taste or vegetable odor alone, and that this reflected activations in the pregenual cingulate cortex and medial orbitofrontal cortex. The principle is that certain sensory combinations can produce very pleasant food stimuli, which may of course be important in driving food intake; and that these combinations are formed in the brain far beyond the taste or olfactory receptors (Rolls, 2009).

To assess how satiety influences the brain activations to a whole food which produces taste, olfactory, and texture stimulation, we measured brain activation by whole foods before and after the food is eaten to satiety. The foods eaten to satiety were either chocolate milk or tomato juice. A decrease in activation by the food eaten to satiety

correlation between the pleasantness ratings and the activation (% BOLD change) at the specified coordinate ($r = 0.94$, $df = 8$, $P < 0.001$). Bottom: Pregenual cingulate cortex. Conventions as above. Right: The parameter estimates were significantly different for the pregenual cingulate cortex $t = 8.70$, $df = 11$, $P < 10^{-5}$. Left: The correlation between the pleasantness ratings and the activation (% BOLD change) at the specified coordinate ($r = 0.89$, $df = 8$, $P = .001$). The taste stimulus, 0.1M monosodium glutamate, was identical on all trials. After Grabenhorst, F. & Rolls, E.T. 2008. Selective attention to affective value alters how the brain processes taste stimuli. Eur. J. Neurosci. 27, 723–729.

relative to the other food was found in the orbitofrontal cortex (Kringelbach et al., 2003) but not in the primary taste cortex. This study provided evidence that the pleasantness of the flavor of food, and sensory-specific satiety which is an important component of appetite and the control of food intake (Rolls, 2014a, 2016c) are represented in the orbitofrontal cortex.

8.3.4 Oral viscosity and fat texture

The viscosity of food in the mouth is represented in the human primary taste cortex (in the anterior insula), and also in a mid-insular area that is not taste cortex, but which represents oral somatosensory stimuli (de Araujo and Rolls, 2004). Oral viscosity is also represented in the human orbitofrontal and perigenual cingulate cortices, and it is notable that the perigenual cingulate cortex, an area in which many pleasant stimuli are represented, is strongly activated by the texture of fat in the mouth and also by oral sucrose (de Araujo and Rolls, 2004). We have shown that the pleasantness and reward value of fat texture is represented in the mid-orbitofrontal and anterior cingulate cortex, where activations are correlated with the subjective pleasantness of oral fat texture (Rolls, 2009, 2010b; Grabenhorst et al., 2010) (Fig. 8.7). This provides a foundation for studies of whether activations in the fat reward system are heightened in people who tend to become obese (Rolls, 2012b). Interestingly, high fat stimuli with a pleasant flavor increase the coupling of activations between the orbitofrontal cortex and somatosensory cortex, suggesting a role for the somatosensory cortex in processing the sensory properties of food in the mouth (Grabenhorst and Rolls, 2014).

8.3.5 The sight of food

O'Doherty et al. (2002) showed that visual stimuli associated with the taste of glucose activated the orbitofrontal cortex and some connected areas, consistent with the primate neurophysiology. Simmons et al. (2005) found that showing pictures of foods, compared to pictures of places, can also activate the orbitofrontal cortex. Similarly, the orbitofrontal cortex and connected areas were also found to be activated after presentation of food stimuli to food-deprived subjects (Wang et al., 2004).

8.3.6 Top-down cognitive effects on taste, olfactory, and flavor processing

To what extent does cognition influence the hedonics of food-related stimuli, and how far down into the sensory system does the cognitive influence reach? To address this, we performed an fMRI investigation in which the delivery of a standard test odor (iso-valeric acid combined with cheddar cheese odor, presented orthonasally using an olfactometer) was paired with a descriptor word on a screen, which on different trials was “Cheddar cheese” or “Body odor.” Participants rated the affective value of the test odor as significantly more pleasant when labeled “Cheddar Cheese” than when labeled “Body odor,” and these effects reflected activations in the medial orbitofrontal cortex

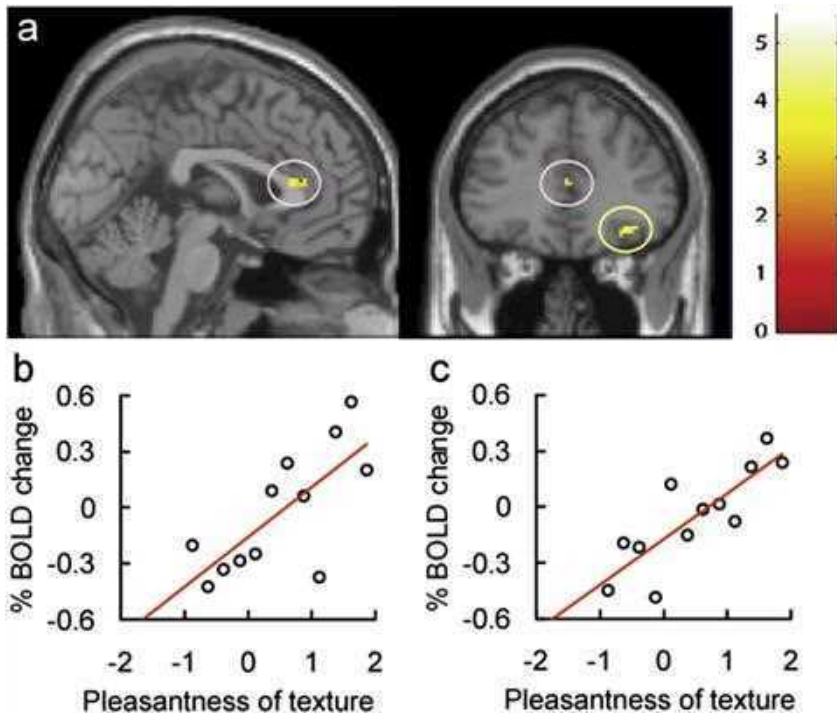


Figure 8.7 Brain regions in which the activations were correlated with the subjective pleasantness of fat texture: Mid-orbitofrontal cortex ($[32\ 34\ -14]$ $z = 3.38$ $P = .013$) (A) yellow circle, (C) showing the relation between the % change in the BOLD signal and the rating of the pleasantness of the texture) and anterior cingulate cortex ($[2\ 30\ 14]$ $z = 3.22$ $P = .016$) (A, pink circles, and B).

After Grabenhorst, F. & Rolls, E.T. 2010. Attentional modulation of affective vs sensory processing: functional connectivity and a top-down biased activation theory of selective attention. *J. Neurophysiol.* 104, 1649–1660; Grabenhorst, F., Rolls, E.T., Parris, B.A., et al. 2010. How the brain represents the reward value of fat in the mouth. *Cereb Cortex* 20, 1082–1091.

(OFC)/rostral anterior cingulate cortex (ACC) that had correlations with the pleasantness ratings (de Araujo et al., 2005). The implication is that cognitive factors can have profound effects on our responses to the hedonic and sensory properties of food, in that these effects are manifest quite far down into sensory and hedonic processing (in the orbitofrontal cortex, see Fig. 8.1), so that hedonic representations of odors are affected (de Araujo et al., 2005).

Similar cognitive effects and mechanisms have now been found for the taste and flavor of food, where the cognitive word-level descriptor was, for example, “rich delicious flavor” and activations to flavor were increased in the orbitofrontal cortex and regions to which it projects including the pregenual cingulate cortex and ventral striatum, but were not influenced in the insular primary taste cortex where activations reflected the intensity (concentration) of the stimuli (Grabenhorst et al., 2008a) (see Fig. 8.8).

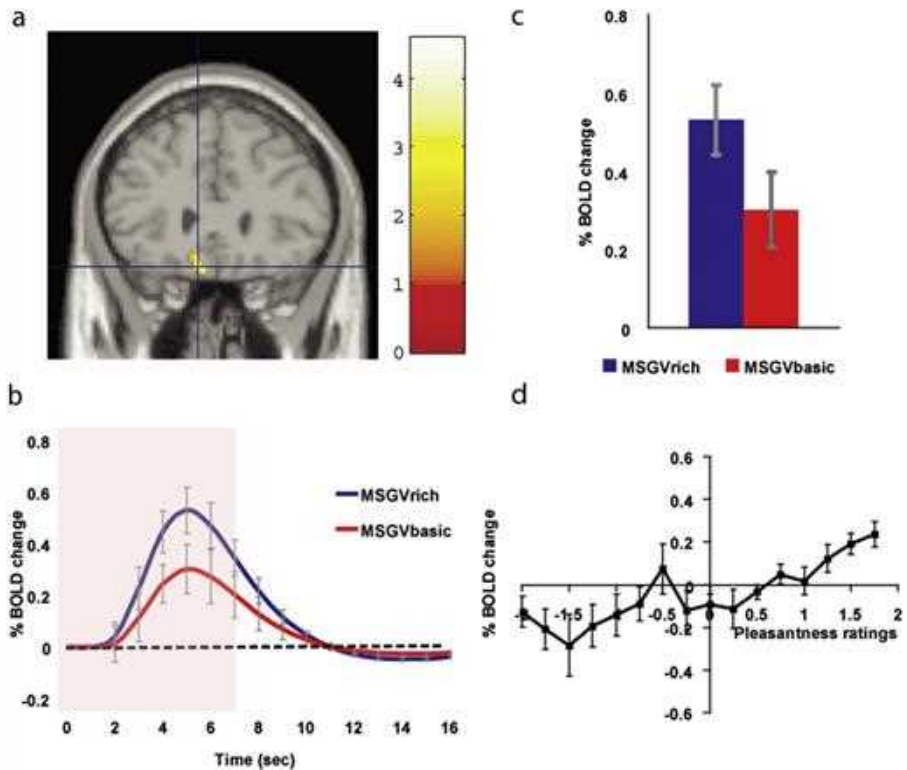


Figure 8.8 Cognitive modulation of flavor reward processing in the brain. (A) The medial orbitofrontal cortex was more strongly activated when a flavor stimulus was labeled “rich and delicious flavor” (MSGVrich) than when it was labeled “boiled vegetable water” (MSGVbasic) ([-8 28 -20]). (The flavor stimulus, MSGV, was the taste 0.1M MSG + 0.005M inosine 5’ monophosphate combined with a consonant 0.4% vegetable odor). (B) The timecourse of the BOLD signals for the two conditions. (C) The peak values of the BOLD signal (mean across subjects $\pm$ sem) were significantly different ($t = 3.06$, $df = 11$, $P = .01$). (D) The BOLD signal in the medial orbitofrontal cortex was correlated with the subjective pleasantness ratings of taste and flavor, as shown by the SPM analysis, and as illustrated (mean across subjects $\pm$ sem, $r = 0.86$, $P < .001$). After Grabenhorst, F., Rolls, E.T. & Bilderbeck, A. 2008a. How cognition modulates affective responses to taste and flavor: top down influences on the orbitofrontal and pregenual cingulate cortices. *Cereb Cortex* 18, 1549–1559.

8.3.7 Effects of selective attention to affective value versus intensity on representations of taste, olfactory, and flavor processing

We have found that with taste, flavor, and olfactory food-related stimuli, selective attention to pleasantness modulates representations in the orbitofrontal cortex (see Fig. 8.6), whereas selective attention to intensity modulates activations in areas such

as the primary taste cortex (Grabenhorst and Rolls, 2008; Rolls et al., 2008). Thus, depending on the context in which tastes and odors are presented and whether affect is relevant, the brain responds to a taste, odor or flavor differently. These findings show that when attention is paid to affective value, the brain systems engaged to represent the stimulus are different from those engaged when attention is directed to the physical properties of a stimulus such as its intensity.

The source of the top-down modulation by attention of the orbitofrontal cortex appears to be the lateral prefrontal cortex, as shown by PPI (psychophysiological interaction) analyses (Grabenhorst and Rolls, 2010) and Granger causality analyses (Ge et al., 2012; Luo et al., 2013). The mechanism probably involves a weak top-down biased competition effect on the taste and olfactory processing (Desimone and Duncan, 1995; Deco and Rolls, 2005; Rolls, 2008b). Because whole streams of cortical processing are influenced (orbitofrontal and cingulate cortex, and even their coupling to the primary taste cortex, by pleasantness-related processing; and insular taste cortex and the mid-insula by intensity-related processing (Grabenhorst and Rolls, 2010; Luo et al., 2013)), the process has been described as a biased activation model of attention (Grabenhorst and Rolls, 2010; Rolls, 2013).

This differential biasing by prefrontal cortex attentional mechanisms (Grabenhorst and Rolls, 2010; Ge et al., 2012) of brain regions engaged in processing a sensory stimulus depending on whether the cognitive demand is for affect-related versus more sensory-related processing may be an important aspect of cognition and attention, which have implications for how strongly the reward system is driven by food, and thus for eating and the control of appetite (Grabenhorst and Rolls, 2008, 2011; Rolls et al., 2008; Rolls, 2012b). The top-down modulations of processing have many implications for investigations of taste, olfactory, and other sensory processing, and for the development of new food and perfumery products.

8.3.8 Individual differences in flavor processing in the brain

There are some fascinating differences in the brain systems that respond to food flavor in different individual humans.

There are age-related differences in the acceptability of foods and beverages (Birch, 1999; Hetherington et al., 2011). To examine the neural foundations underlying these age-related differences in the acceptability of different flavors and foods, an fMRI study was performed to investigate brain and hedonic responses to orange juice, orange soda, and vegetable juice in three different age groups: Young (22), Middle (40), and Elderly (60 years) (Rolls et al., 2015). Orange juice and orange soda were found to be liked by all age groups, while vegetable juice was disliked by the Young, but liked by the Elderly. In the insular primary taste cortex, the activations to these stimuli were similar in the three age groups, indicating that the differences in liking for these stimuli between the three groups were not represented in this first stage of cortical taste processing. In the agranular insula (anterior to the insular primary taste cortex) where flavor is represented, the activations to the stimuli were similar in the Elderly, but in the Young the activations were larger to the vegetable juice than to the orange drinks; and the activations here were correlated with the unpleasantness

of the stimuli. In the anterior mid-cingulate cortex, investigated as a site where the activations were correlated with the unpleasantness of the stimuli, there was again a greater activation to the vegetable than to the orange stimuli in the Young but not in the Elderly. In the amygdala (and orbitofrontal cortex), investigated as sites where the activations were correlated with the pleasantness of the stimuli, there was a smaller activation to the vegetable than to the orange stimuli in the Young but not in the Elderly. The Middle group was intermediate with respect to the separation of their activations to the stimuli in the brain areas that represent the pleasantness or unpleasantness of flavors. Thus age differences in the activations to different flavors can in some brain areas be related to, and probably cause, the differences in pleasantness of foods as they differ for people of different ages (Rolls et al., 2015).

In another example, it has been shown that there are larger responses in regions such as the orbitofrontal cortex and anterior cingulate cortex to the sight or taste of chocolate in chocolate cravers (Rolls and McCabe, 2007).

In another investigation, resting state functional connectivity was measured to investigate whether even when food is not being presented, there are individual, different, regions in the brain that relate to the liking for food and then perhaps as a consequence of that to obesity (Rolls et al., 2021). In 37,286 humans from the UK Biobank, resting state functional connectivities of the orbitofrontal cortex, especially with the anterior cingulate cortex were positively correlated with the liking for sweet foods (FDR $p < .05$). They were also positively correlated with the body mass index (BMI) (FDR $p < .05$). Moreover, in a sample of 502,492 people, the “liking for sweet foods” was correlated with their BMI ($r = 0.06$, $p < 10^{-125}$). In a cross-validation with 545 participants from the Human Connectome Project, higher functional connectivity involving the orbitofrontal cortex relative to other brain areas was associated with high BMI (≥ 30) compared to a mid-BMI group (22–25; $p = 6 \times 10^{-5}$); and low orbitofrontal cortex functional connectivity was associated with low BMI (≤ 20.5 ; $p < .024$). It is proposed that high BMI relates to increased efficacy of orbitofrontal cortex food reward systems, and low BMI to decreased efficacy (Rolls et al., 2021). This was found with no stimulation by food, so there is an underlying individual difference in brain connectivity that is related to food reward and BMI (Rolls, 2021b; Rolls et al., 2021).

Individual differences in the reward value of different types of stimuli may be a key way in which evolution by natural selection based on individual variation operates (Rolls, 2014a).

8.4 Beyond the reward value of flavor to decision-making

Representations of the reward value of food, and their subjective correlate, the pleasantness of food, are fundamental in determining appetite and processes such as economic decision-making (Rolls, 2005a, 2014a, 2021a; Padoa-Schioppa, 2011; Padoa-Schioppa and Cai, 2011). But after the reward evaluation, a decision has to be made about whether to seek for and consume the reward. We are now starting to understand how the brain

takes decisions as described in *The Noisy Brain* (Rolls and Deco, 2010), *Emotion and Decision-Making Explained* (Rolls, 2014a), and *Brain Computations: What and How* (Rolls, 2021a), and this has implications for whether a reward of a particular value will be selected (Rolls, 2008b, 2011b, 2014a, 2021a; Rolls and Grabenhorst, 2008; Rolls and Deco, 2010; Grabenhorst and Rolls, 2011; Deco et al., 2013).

A tier of processing beyond the orbitofrontal cortex, in the medial prefrontal cortex area 10, becomes engaged when choices are made between odor stimuli based on their pleasantness (Grabenhorst et al., 2008b; Rolls et al., 2010b, 2010c, 2010d) (tier 3 in Fig. 8.1). The choices are made by a local attractor network in which the winning attractor represents the decision, with each possible attractor representing a different choice, and each attractor receiving inputs that reflect the evidence for that choice. (The attractor network is formed in a part of the cerebral cortex by strengthening of the recurrent collateral excitatory synapses between nearby pyramidal cells. One group of neurons with strengthened synapses between its members can form a stable attractor with high firing rates, which competes through inhibitory interneurons with other possible attractors formed by other groups of excitatory neurons (Rolls, 2010a, 2021a). The word *attractor* refers to the fact that inexact inputs are attracted to one of the states of high firing that are specified by the synaptic connections between the different groups of neurons. The result in this nonlinear system is that one attractor wins, and this implements a mechanism for decision-making with one winner (Rolls, 2008b, 2014a, 2016a, 2021a; Wang, 2008; Rolls and Deco, 2010; Deco et al., 2013). The decisions are probabilistic as they reflect the noise in the competitive nonlinear decision-making process that is introduced by the random spiking times of neurons for a given mean rate that reflects a Poisson process (Rolls and Deco, 2010; Rolls et al., 2010c; Rolls, 2021a). The costs of each reward need to be subtracted from the value of each reward to produce a net reward value for each available reward before the decision is taken (Rolls, 2008b, 2014a, 2021a; Rolls and Grabenhorst, 2008; Grabenhorst and Rolls, 2011). The reasoning or rational system with its long-term goals (introducing evidence such as “scientific studies have shown that fish oils rich in omega 3 may reduce the probability of Alzheimer’s disease”) then competes with the rewards such as the pleasant flavor of food (which are partly gene-specified (Rolls, 2005a, 2014a), though subject to conditioned effects (Booth, 1985; Rolls, 2014a, 2021b)) in a further decision process which may itself be subject to noise (Rolls, 2008b, 2014a, 2021a; Rolls and Deco, 2010). This can be described as a choice between the selfish phene (standing for phenotype) and the selfish gene (Rolls, 2011b, 2012a, 2014a, 2020a, 2021a). In this context, the findings described here that the cognitive system can have a top-down influence on the reward system including the flavor reward system are important advances in our understanding of how these decisions are reached.

8.5 Synthesis

These investigations show that a principle of brain function is that representations of the reward/hedonic value and pleasantness of sensory including food-related stimuli

are formed separately from representations of what the stimuli are. The pleasantness/reward value is represented in areas such as the orbitofrontal cortex and pregenual cingulate cortex, and it is here that hunger/satiety signals modulate the representations of food to make them implement reward. The satiety signals that help in this modulation may reach the orbitofrontal cortex from the hypothalamus, and in turn, the orbitofrontal cortex projects to the hypothalamus where neurons are found that respond to the sight, smell, and taste of food if hunger is present (Rolls and Grabenhorst, 2008; Rolls, 2014a). We have seen above some of the principles that help to make the food pleasant, including particular combinations of taste, olfactory, texture, visual, and cognitive inputs.

A hypothesis is developed elsewhere that obesity is associated in part with overstimulation of these reward systems by very rewarding combinations of taste, odor, texture, visual, and cognitive inputs that together produce the flavor of food (Rolls, 2005a, 2011d, 2012b, 2014a, 2015b, 2016c, 2021b).

Acknowledgments

This research was supported by the UK Medical Research Council. The participation of many colleagues in the studies cited is sincerely acknowledged. They include Ivan de Araujo, Gordon Baylis, Leslie Baylis, Wei Cheng, Hugo Critchley, Ruiqing Feng, Paul Gabbott, Fabian Grabenhorst, Chu-Chung Huang, Mikiko Kadohisa, Michel Kellerhals, Morten Kringelbach, Christian Margot, Francis McGlone, Ciara McCabe, Thomas Mills, Ian Norton, John O'Doherty, Barbara Rolls, Juliet Rolls, Thomas Scott, Zenon Sienkiewicz, Simon Thorpe, Maria Ines Velazco, Justus Verhagen, and Simon Yaxley.

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Holistic perception and memorization of flavor

9

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9.1 Introduction

During ingestion the sense of taste, retronasal olfaction (smelling via the posterior nares), and oral somatosensation combine to form flavor (Mozell et al., 1969). Flavor is also impacted by perceptual events that occur prior to ingestion. These include the visual examination of food, its smell (sniffing via the anterior nares), its sound (e.g., as it fizzes, cooks or cools), and its feel via touching by hand, knife, fork, or spoon (Spence et al., 2010; Wang et al., 2019). In this chapter two related issues are examined. The first concerns the general consensus view that flavor in the mouth is something more than the sum of its parts—namely it is perceived in a holistic manner (Auvray and Spence, 2008; Lawless, 1995; McBurney, 1986; Prescott, 2004; Rozin, 1982; Small, 2012). The second issue concerns how flavor experiences are memorized and how this affects subsequent flavor perception—both prior to and during ingestion. These issues are fundamentally linked because it is the contention here that they all serve to support future food choice (Stevenson et al., 2014).

To address these various issues the chapter is split into two sections. The first addresses the nature of the flavor percept. While there may be a consensus that flavor perception is holistic, the evidence for this claim has generally not been well examined. Here, the aim will be to identify the characteristics of flavor perception that suggest holistic processing, examine the form that this holistic percept takes (e.g., full or only partial integration of the different senses), and to consider briefly how this unitization might occur. The second part of the chapter considers flavor memorization. Here, it is argued that when people encounter a food, they can access information about its probable effects (e.g., its taste, affective properties, energy content, safety), both implicitly through flavor-related learning processes—the main focus here—and via various explicit processes too (e.g., via packaging, advertisements, conversation, etc.).

9.2 Holistic flavor perception

Most researchers who have worked on flavor perception favor the idea that what is perceived represents some form of central integration of the senses that are activated during ingestion—namely taste, retronasal olfaction, and oral somatosensation (Auvray and Spence, 2008; Lawless, 1995; McBurney, 1986; Prescott, 2004;

Rozin, 1982; Spence, 2016; Small, 2012). In other domains where multisensory integration has been studied, the characteristics that lead researchers to claim that integration has occurred have been well documented (e.g., for ventriloquism, see Bertelson and Aschersleben, 1998), but this has not generally been the case for flavor. Thus, while it has been suggested that flavor is perceived holistically, the psychological features on which this suggestion rests have not been well defined or investigated. The aim of this part of the chapter is to document what these psychological features are, what they imply about the nature of this percept (e.g., are all the senses merged?), and how full or partial unitization might occur.

9.2.1 *The putative features of holistic processing*

9.2.1.1 *The modality content dissociation for retronasal olfaction*

For over a century various students of flavor have remarked that most people do not seem to know that smell is involved in flavor perception (e.g., Brillat-Savarin, 1825; Titchener, 1909). This is surprising for two reasons. The first is that we generally know which sensory system is being stimulated—even in classic multisensory illusions like ventriloquism (Spence, 2016). Most people are well aware that visual experience depends upon the eyes, hearing on the ears, and touch upon skin-related sensors. Similarly, nobody would have a problem in identifying the senses required to detect a gas leak, the temperature of bath water, or a car alarm, yet people do not seem to know that they need a nose for flavor. The second reason is that people have many opportunities to observe the relationship between events in the mouth and the sense of smell, yet they still fail to make the connection. People are often taught to pinch their nose when consuming an unpleasant medicine. Moreover, there is a strong correlation between the way foods smell prior to ingestion and what they “taste” like when they are consumed. Strawberries, cheese, and meat smell appreciably like they taste, and while this correlation is imperfect, it is sufficiently robust for most people to be able to recognize food odors *both* when they are placed into their mouth and when they are sniffed via the nose (e.g., Sun and Halpern, 2005).

Given these opportunities to learn, and that other sensory experiences are generally accompanied by modality awareness, one might expect that people would come to know that smell is involved in flavor perception—but this does not seem to be the case. Two lines of evidence suggest this. The first is language related. Science has identified two routes of olfactory perception and each has its own discrete name—orthonasal and retronasal. There is no lay equivalent of this distinction in any major language (Rozin, 1982). In addition, when participants are asked to complete sentences about consuming various foods and drinks using either the term “taste” or “flavor,” many foods that have a major olfactory component are as likely to be completed by the use of the word taste as flavor (Rozin, 1982). This would suggest that these terms are generally used interchangeably and that flavor does not uniquely capture the olfactory component of ingestive sensory experience.

The second line of evidence that suggests little awareness of the role of smell in flavor perception comes from patients attending specialist clinics for taste and smell disorders. Many patients who develop anosmia report both that they cannot smell *and* that they can no longer *taste* food (e.g., [Fujii et al., 2004](#); [Gent et al., 1987](#)). Subsequent testing typically reveals that the sense of taste is largely intact and that the deficit is mainly olfactory ([Deems et al., 1991](#)). As with the lack of a specific term to describe the role of retronasal smell in flavor perception, this too would imply that people are not generally aware that the sensory modality of smell is involved in flavor perception.

While there may be a lack of modality awareness, people do seem to experience olfactory-related perceptual content during eating and drinking. This is suggested by the noticeable decrement in food enjoyment that occurs with anosmia (e.g., [Hummel and Nordin, 2005](#)), and a similar impairment in flavor perception and recognition when retronasal olfaction is artificially disrupted (e.g., [Mozell et al., 1969](#)). The food industry, which relies extensively on sensory evaluation of its products, often depends upon judgments that concern olfactory-related sensations (e.g., [Stone and Sidel, 1993](#)).

It could of course be that the other modalities involved in flavor perception are also accompanied by a dissociation between perceptual content and modality awareness, but in the main this does not seem to be the case. Taste sensations seem to be readily recognized such as when tastants are applied to the tongue, and major damage to the tongue (usually bilateral) can also be self-identified as a gustatory loss (e.g., [Porter et al., 2010](#)). Similarly for proprioception, participants can recognize oral touch, warmth/cold, and irritants, and while they may not know that these are all mediated by the somatosensory system, they can correctly attribute them to the appropriate sub-modality (e.g., [Munoz and Civile, 1987](#)). The only exception here may be for fat perception, which is multimodal, involving taste receptors, smell and oral proprioception ([Chale-Rush et al., 2007](#)). It *may* be the case here that the relative contribution of each of these senses cannot be properly identified.

9.2.1.2 *Psychological interactions between the flavor senses*

Several authors have documented the many types of interaction that occur between the flavor senses (e.g., see [Delwiche, 2004](#); [Stevenson, 2009](#); [Wang et al., 2019](#)). The majority of these result from local causes—chemical reactions, changes in food structure during chewing, and from receptor-related effects. However, certain interaction involving olfaction and taste, and olfaction and oral somatosensation, seem to be central in origin, indicating that the component flavor senses are not perceived independently.

There are two forms of interaction between taste and smell in the mouth, and while they seem to be related, and may even have a common cause, there is no compelling evidence as yet to suggest they represent the same phenomenon. One type of odor—taste interaction is termed odor-induced taste enhancement. This is odorant and tastant specific (e.g., [Frank and Byram, 1988](#)), and occurs when a previously experienced combination (e.g., cherry and sucrose) is sampled by mouth, and the participant is asked to judge the intensity of the taste component. Under these conditions, participants generally report that the taste is more intense when contrasted to ratings of the

same tastant made alone (e.g., [Schifferstein and Verlegh, 1996](#); [Stevenson et al., 1999](#)). The central nature of this type of interaction is suggested by two findings. The first is the experience dependent nature of the effect, which has been confirmed in several studies (e.g., [Isogai and Wise, 2016](#); [Veldhuizen et al., 2018](#)). The second is that the effect occurs even if the odorant is delivered to the nose orthonasally, so that it has no direct contact with the tastant in the mouth—ruling out physiochemical interactions (e.g., [Sakai et al., 2001](#)). It has been suggested that the odor-induced taste enhancement is a consequence of not including odor-relevant intensity judgments when the participant is asked to evaluate taste intensity ([Clark and Lawless, 1994](#)). However, this is to miss the point. As noted above, it is the experience-dependent nature of this effect that is important ([Wang et al., 2019](#)). This seems to lead to participants conflating sensory experiences related to taste with *particular* sensory experiences related to olfaction (e.g., strawberriness).

A second type of effect is taste-induced odor enhancement (e.g., [Green et al., 2012](#); [Sydow et al., 1974](#)). Unfortunately this effect has been less well studied. It would appear again that prior experience with a particular tastant and odorant results in the odor being experienced as more intense in the presence of its associated taste, than when sampled alone. While this would point to a commonality between odor-induced taste enhancement and taste-induced odor enhancement, it is unclear how symmetrical these effects are and more importantly, whether experience is a necessary condition for the effect to occur. Indeed, there are theoretical grounds to suspect that a taste may boost the perceived intensity of any odorant, especially if the concentrations are low (but above threshold), and this could be independent of other effects based upon experience (e.g., sucrose might boost the perceived intensity of any odorant at low concentrations, but only of odors it had been experienced with at higher concentrations; [Stevenson, 2014](#)). However, this is not the only perspective, as [Linscott and Lim \(2016\)](#) have suggested that enhancement may only occur for nutritive-related taste cues. More work will be needed to test this assertion.

In addition to centrally based interactions between tastes and odors, there are also interactions between oral somatosensation and odor. Oral somatosensation encompasses a large range of submodalities including temperature, irritation, proprioception, and active and passive touch. Most work has focused on viscosity. When a viscous fluid is in the mouth, odors are perceived as less intense both when they are delivered as part of the oral stimulus and when presented orthonasally at the same time as the test fluid (e.g., [Bult et al., 2007](#)). This suggests that the effect is central in origin, but it does not appear to be experience dependent, noting that this has not been well explored. It is also unclear why viscous fluids result in a reduction in perceived odor intensity in the mouth.

A second form of interaction has also been documented, which is far more complementary to the effects described for odors and tastes. Certain odors appear able to alter participants' judgments of viscosity in an experience-dependent manner, such that adding them to a viscous fluid (e.g., creamy odor to custard) leads to greater viscosity ratings—odor-induced viscosity enhancement (e.g., [Han et al., 2019](#); [Weenen et al., 2005](#); [Yackinous and Guinard, 2000](#)). This effect is seemingly asymmetric in that viscosity only reduces perceived intensity of odors in a nonexperience dependent manner (contrast with odor-taste effects).

9.2.1.3 Access to parts

While it is possible to evaluate many components of flavor reliably, there are limits imposed on accessing the olfactory component. A series of studies by [Laing et al. \(2002\)](#), [Marshall et al. \(2006\)](#) examined participants' ability to identify tastants and odorants in mixtures presented to the mouth. Participants were above chance at identification when additional tastants were added to a mixture, and while able to identify one odorant in a mixture above chance, the addition of extra tastants or odorants rapidly reduced this ability to chance level. That is, the capacity to perceive individual odorants in a flavor mixture is far more constrained than the capacity to experience individual tastes in a flavor mixture.

A further aspect of this relates to the perception of odor-taste mixtures, which as noted above may often interact if they have been experienced together before. This would suggest that participants may find it hard to selectively attend to taste independent of smell (and vice versa) in the mouth ([Ashkenazi and Marks, 2004](#)). It is certainly possible to selectively attend to tastes in the mouth ([Marks and Wheeler, 1998](#)), but it is not possible to do so for odors presented in the mouth ([Ashkenazi and Marks, 2004](#)). Moreover, it also appears difficult to selectively attend to a taste in the mouth when an odor is present and vice versa ([Ashkenazi and Marks, 2004](#)). Of course it may be that this just reflects a general lack of practise in telling apart tastes and smells in the mouth, something that people are not generally asked to do. However, setting aside the fact that the people in [Laing et al. \(2002\)](#), [Marshall et al. \(2006\)](#) and Mark's ([Ashkenazi and Marks, 2004](#); [Marks and Wheeler, 1998](#)) studies were specifically trained to do so, it is still possible that more extensive expertise might lead to an ability to separate taste from smell in the mouth. The literature suggests otherwise (but see [Spence \(2019\)](#), for a more qualified conclusion). Although one study did find evidence of better segregation of taste and smell in experts (trained sensory panelists) relative to novices, different tests were used on each group, so a direct comparison is problematic ([Bingham et al., 1990](#)). The other two studies reported that participants with flavor expertise (chefs and trained sensory panelists) were as likely to conflate taste with smell in the mouth as novices ([Boakes and Hemberger, 2012](#); [Davidson et al., 1999](#)). It would seem then that there may be fundamental limits to the information that can be accessed in a flavor percept, and that the limits may be stricter for smell than for taste.

9.2.1.4 Perceived location of taste and smell

During flavor perception the experience is perceived as being located in the mouth ([Spence, 2016](#)). For oral somatosensation this is no surprise because one of its functions is to locate stimulation on the surface of the body. However, for taste and smell respectively, localization becomes a progressively more complex feat. Taste receptors are primarily on the tongue, and the localization of taste sensation to the mouth appears to be the result of hard-wired interactions between taste and oral somatosensation ([Green, 2003](#)). This is suggested both by physiology, with interactions between these senses occurring at all levels from the receptor to cortex (e.g., [Oakley, 1985](#); [Plata-Salaman et al., 1993](#)), and by psychological studies.

The close interaction between oral somatosensation and gustation can be seen in a study by [Todrank and Bartoshuk \(1991\)](#). They dragged a tastant saturated Q-tip from the anterior side of the tongue, round over the tip, finishing on the opposite anterior side. During this transit, participants were asked to evaluate taste intensity at various points. Taste intensity was lower initially on the anterior side of the tongue, as there are fewer taste receptors there, but as the Q-tip contacted the anterior tip of the tongue ratings increased as receptor density increased. The key finding is that ratings then stayed high as the Q-tip continued its transit to the opposite anterior side. So even though fewer receptors were now being stimulated, it would seem that immediately prior somatosensory activation of the tongue tip acts to “smear” taste sensation around this area.

While the localization of taste to the tongue (and mouth) is understood, how olfaction is localized to the mouth during flavor perception is a far more complex question. This is because the olfactory receptors are located at a distance from the mouth in the nasal vault, and also because these same receptors serve both orthonasal *and* retronasal smelling. During orthonasal smelling (e.g., sniffing), volatile chemicals are perceived as odors arising in the environment with the sense modality being readily apparent (e.g., [Mainland and Sobel, 2006](#)). During eating and drinking the receptors are stimulated via the posterior nares and the nasopharynx, and this is accompanied by only limited (at best) awareness of this sensory system ([Rozin, 1982](#)).

Clearly a number of possible mechanisms suggest themselves, all of which may contribute to the localization of olfactory experience to either the mouth or nose. One possibility is that the direction of nasal airflow in the anterior and posterior parts of the nose dictates localization (e.g., [Small et al., 2005](#)). Another is that concurrent somatosensory activity (with or without taste) captures olfactory experience and locates it to the origin of the touch and taste ([Lim and Johnson, 2011](#); [Stevenson et al., 2011](#)). It would appear that all of these accounts have some support, except those based on oral somatosensation alone ([Spence, 2016](#)).

A combination of a taste and oral somatosensation seems to be needed to localize an olfactory experience to the mouth ([Lim and Johnson, 2011](#); [Stevenson et al., 2011](#)). Moreover, it has been suggested that this to may be experience-dependent ([Lim and Johnson, 2012](#)). [Fondberg et al. \(2018\)](#) examined this question using mixtures of odors and tastes (sip and spit) that systematically varied in congruence. Participants were asked to evaluate the perceived location of the experience, finding greater localization to the mouth with more congruent mixtures. However, greater incongruence was not associated with greater referral to the nose, so congruence may just augment existing localization to the mouth rather than being the causal agent. If congruency was the decisive factor, then presumably greater incongruence would have led to greater referral to the nose.

9.2.1.5 Perceived time course of the flavor senses

The occurrence of oral somatosensation and taste sensation are generally yoked in the mouth, with the availability of tastants to the receptors following the same broad time course as active and passive movement of food in the mouth. However, this is not

necessarily the case for retronasal olfaction. Volatile chemicals can reach the olfactory epithelium via posterior nares and the nasopharynx under two conditions. First, during rhythmic chewing, pulses of volatile laden air may be ejected into the nose (Hodgson et al., 2003). Second, after swallowing, and during exhalation, volatile laden air may again pass into the nose (Trelea et al., 2008). What is important here is that this form of stimulation is seemingly discontinuous, in contrast to taste and oral somatosensation, which is largely concurrent and continuous. Thus, there may be periods where there is no olfactory stimulation during eating, yet these absences do not seem to be readily noticeable. This *may* suggest that a further aspect of flavor perception is a smoothing out of the discontinuous nature of retronasal olfaction, so that periods of presence and absence are less noticeable.

There have only been a few studies examining the deliberate manipulation of the timing of the gustatory and olfactory component. Kobayakawa and Gotow (2016) had participants make judgments of whether two stimuli drawn from three different modalities (tastants, odorants, lights) occurred simultaneously or successively. They reported that congruency affected participants judgments for tastants and odorants, with congruent odor-taste pairs being judged as unitary at longer intervals between the onset of each member of the stimulus pair. In a more detailed report (the latter being an abstract) by Gotow and Kobayakawa (2021), it is apparent that for an incongruent odor-taste mixture (no congruent pair was used in this study), judgments tended to favor simultaneous experience more than for odor—visual and taste—visual pairs. This would seem to favor the idea of a general bias toward holistic processing with odor-taste pairs, even when they are incongruent.

Finally, Isogai and Wise (2016) examined the impact on odor-induced taste enhancement, of varying the timing of the odorant delivery. Enhancement of taste intensity was maximal under conditions of simultaneous delivery (and see Han et al., 2019, for similar effects extending into texture perception). This suggests that flavor perception may be quite sensitive to time differences between taste and odor delivery, which is seemingly hard to reconcile with what is known about the intermittent and pulsatile nature of retronasal olfactory delivery during “natural” flavor perception (Hodgson et al., 2003; Trelea et al., 2008). It also contrasts with the findings of Gotow and Kobayakawa (2021), but they used an incongruent odor—taste pair while Isogai and Wise (2016) used only congruent odor—taste pairs. It could be that congruent pairs are somehow more sensitive to the effects of timing, but really what we need here is more data.

9.2.1.6 Discussion

If the senses do combine in some way there should be evidence for this. Based upon the above, there appear to be five suggestive features of this occurring: (1) a dissociation between the capacity to experience olfactory content in the mouth and capacity to identify the modality involved in generating it; (2) a difficulty in identifying modality boundaries between taste and smell sensation, and smell and oral somatosensation, resulting in rating scale conflation; (3) limitations on the ability to perceive parts in a flavor, especially relating to olfactory components; (4) the localization of taste and

smell experience to the mouth; and (5) the possible smoothing out of the pulsatile nature of retronasal olfaction and some indication of decreased sensitivity to delayed onset between taste and smell stimuli. There are two notable conclusions to draw about these five features. The first is that they all involve olfaction. The second is that to the extent that holistic implies the complete loss of modality boundaries, this is not the case. Rather the modality boundary losses (i.e., integration between the senses) are seemingly complete only perhaps for olfaction, which may merge to become part of taste and to a more limited extent with certain facets of oral somatosensation (related to fat [viscosity] perception).

9.2.2 How does holistic perception arise?

Two basic classes of explanation have been advanced to account for the holistic aspects of flavor perception. The first concerns hard-wired processes, which result from the way in which the nervous system is genetically determined to function. The most well-established example of this has already been considered, namely the localization of taste sensation to the mouth by oral somatosensation, which relies upon the close entwining of sensory processing of taste and oral somatosensation from the receptor to high-level cortical processing (Green, 2003). The second class of explanation concerns more central cognition-related processes, notably attention and learning (and hence later—memory). These two classes of explanation are not mutually exclusive, and both are examined below.

9.2.2.1 Innate factors

Setting aside taste and oral somatosensation, which were considered earlier, it is possible to derive a model of many of the phenomena described above in Section 9.2.1, based upon a hard-wired system. According to this account, taste and smell in the mouth form a discrete sensory modality and attentional channel (Stevenson, 2014). The model assumes that this joint channel is an in-built feature of the nervous system that serves some functional need of the organism (see Auvray and Spence, 2008; Gibson, 1966; and more later on function). The model has a number of specific features. First, it requires the presence of a taste to activate the joint channel, which is suggested by the finding that odors in the mouth appear to increase in perceived intensity only when taste (but not oral somatosensation alone) is present. Second, more channel bandwidth is available to taste than to smell. This, so it is argued, arises from the greater need to identify individual taste signals—such as bitter for poison and sweet for energy—that may be simultaneously present. A smaller bandwidth for olfaction is consistent with the generally unitary nature of olfactory perception, in which only one odor entity (e.g., coffee) is perceived at a time (Stevenson and Wilson, 2007). Third, it includes a capacity to learn flavor experiences.

The key prediction of this account is that unfamiliar tastes and smells should be experienced as flavors in the mouth, demonstrating many of the features identified above. Thus if one sampled a novel fruit that had a bitter/sweet taste and a unique smell, the experience would be localized to the mouth, there would be smoothing of

any retronasal discontinuities, and the content/modality dissociation for olfaction would still occur. Features that might be absent would be odor-induced taste enhancement and taste-induced odor enhancement, which may be experience-dependent. Nonetheless, the presence of a taste should still result in the odorous component being experienced as more intense. The key question then is whether there is evidence that novel taste/odor combinations show these predicted features.

Unfortunately, the body of research on this question is small. One group has found that localization of odors to the mouth may depend upon whether the person has prior experience of that particular combination (Lim and Johnson, 2012; Lim et al., 2014). Another group has found that localization of odors to the mouth can occur even with odor/taste combinations that have not been experienced before (Stevenson et al., 2011). It is perhaps difficult to determine which of these latter two findings are more informative due to their methodological differences, as the first-mentioned used odors and tastes delivered to the mouth, while the second used odors delivered to the nose and tastes to the mouth. However, it should be noted that the technique of delivering an odor to the nose and a taste to the mouth does not affect demonstration of key effects (e.g., odor-induced taste enhancement) that are suggested to reflect holistic odor-taste processing (Dalton et al., 2000; Sakai et al., 2001). So perhaps these methodological differences are less important than has been suggested (Spence, 2016).

Evidence for binding of unfamiliar odors and tastes has come from three other sources. First, Ashkenazi and Marks (2004) found that limited selective attention for tastes and smells in the mouth occurs independently of whether the combination has been experienced before, suggesting a hard-wired process. Second, when an odor is paired in the mouth with a pleasant (e.g., sweet) or unpleasant (e.g., bitter) taste, the outcome is that liking for the odor changes in the direction of the associated taste, a phenomenon termed *evaluative conditioning* (Baeyens et al., 1990). Recent work has suggested that the capacity to form odor-taste pairings may be prepared, suggesting an innate predisposition to associate stimuli from these modalities (Ruszel and Gast, 2020), relative to these stimuli with those from other modalities (e.g., sounds, labels). Again, this would favor the idea of a hard-wired common attentional channel.

A third finding comes from a study by Stevenson and Mahmut (2015). They examined the reliability of participants' odor descriptions, using these to index how clearly people could perceive the odor (i.e., if an odor is hard to perceive, people's judgments of what it smells like will not be very reliable). Using an odor with no history of association with sweet tastes, which was presented at the nose, participants' odor descriptions were more reliable when there was a sweet taste in the mouth than when water was in the mouth. Reliability improved further if the sweet taste was more concentrated. These findings suggest that participants' capacity to reliably describe an odor benefits from having a taste in the mouth, even if that taste has not previously been associated with that odor (i.e., no congruence). However, if the odor being used is congruent with a sweet taste, the outcome is rather different. In this case, the reliability benefit of moving from water to sucrose is much reduced, perhaps because the congruent odor-sucrose mixture makes it harder to perceive the odor independent of the taste. Finally, no one has as yet examined whether the modality/content dissociation is affected by prior experience with odor/taste combinations.

9.2.2.2 *Cognitive factors*

Just as it is possible to build a model based upon innate predispositions to process taste and smell in a common attentional channel, it is equally possible to assume that the same effects derive solely from learning. That is the cooccurrence of particular tastes and smells leads to them being processed as a single entity, such that it is not possible to attend to just one of these components without automatically attending to the other. It is readily apparent that learning plays some role in flavor perception, the key question is how much. A basic role is most strongly suggested by the odor–taste interaction literature, with the finding that odor-induced taste enhancement and (probably) taste-induced odor enhancement both likely rely on having experienced the two components together before. While this seems to make sense, more direct tests of this idea have not provided overwhelming support. That is, if an unfamiliar odor and taste are paired together by mouth repeatedly, this does not automatically result in greater odor-induced taste enhancement. In some studies such an effect has been observed (e.g., [Prescott, 1999](#)) and in other studies it has not (e.g., [Stevenson et al., 1995](#)).

If learning is necessary to establish a common attentional channel, then flavor perception of novel foods should be rather different to flavor perception of familiar foods. While it is likely that more attentional resources will be devoted to a novel food, anecdotally at least, flavor does not seem to “fall apart” into its elemental constituents when eating something unusual. Indeed, perhaps the strongest piece of evidence against this idea is that if unfamiliar foods did evoke more elemental processing, this would likely draw more attention to the individual flavor parts, thereby enhancing awareness of the role of olfaction in flavor perception. As we encounter many novel foods during development, and during adulthood, this would seem unlikely—but as there has been rather little study of the development of flavor perception, it is not possible to know whether flavor perception in children is more elemental as a learning-based account might suggest.

9.2.3 *Discussion*

Clearly flavor perception is more than just experiencing a set of individual parts. There is a combinatorial process at work, which results in a partially holistic percept. Partially, because it is still possible to identify some features of the flavor percept, with other features being more difficult to discern. Participants seem largely unaware that smell is involved in flavor perception, and may have difficulty in distinguishing certain gustatory from olfactory components of flavor. All of these experiences are localized to the mouth, and there may be smoothing of discontinuities in retronasal olfactory perception. All of this may come about through an innate and/or learned disposition to coprocess taste and smell in the mouth via a common sensory/attentional channel. An obvious question—indeed perhaps the most important one to ask of all—is why should flavor information be processed in this manner? The second section of the chapter addresses this issue.

9.3 Memorization of flavor

As Rozin (1976) originally identified, omnivores face a challenging task in obtaining energy from a myriad of different potential food sources. The first problem is that new foods may lead to illness, even death. There is then a need to detect likely signals of dangerous foods, notably bitter tastes, and to *learn* the identity of foods that result in illness so they can be avoided in the future. The second problem is securing foods that are nutritious. This also involves the same interplay between innate sensory processes—namely the detection of sweet, fatty, and proteinaceous tastes—and a capacity to *learn* about the immediate (tastes good) and delayed consequences (is filling) of the food. The third problem is that apparently familiar foods may be adulterated, rotten, or simply different (e.g., seasonal variation)—and so a capacity for detecting deviations is required. This too must draw upon an ability to retain memories of previous flavor experiences associated with each food.

A solution to the first and second problems requires the formation of associations between the immediate and delayed consequences of eating, and the food's flavor. The functional impact of this can be seen when later appraising a potential food for consumption. Sniffing the food's odor can provide both affective (e.g., Baeyens et al., 1990) and sensory (e.g., Stevenson et al., 1995) information about the immediate and delayed consequences of eating that food. Both of these sorts of information are valuable because while affective signals may be modulated by physiological state (hungry vs. full), sensory information is less subject to such variability (Cabanac, 1971). Thus the smell of a food can appear pleasant when hungry and less so when full, while always *smelling* sweet and fatty. More generally, the key contention here is that holistic flavor perception evolved in part as a way to represent the prior perceptual and affective experience relating to a *particular* food (i.e., *one unitary flavor experience* for *one food object*), with one part of this memory (the smell) able to consciously recover much of the whole (affective and sensory [gustatory and somatosensory] experience).

As mentioned in the Introduction, not only do we smell food prior to eating it, we also look at it. This form of appraisal represents a powerful complementary system drawing upon both explicit knowledge about food and implicit knowledge about the *expected* flavor. People may know much about the nutritional value of a food from packaging, appearance, and other sources of information, and such explicit knowledge is likely to be a powerful determinant of what we eat. People also know implicitly what a particular food should taste like, even though they may not be able to voluntarily *experience* a flavor “image” of that food. Rather humans may form flavor expectancies based upon appearance. When the food is then eaten and its flavor becomes apparent, this may be automatically compared against the flavor memory of that food. If a deviation is detected, this may result in rejection.

In the following sections, the themes identified here are explored in more detail, starting with the role of flavor learning in altering the sensory and affective properties of smell, followed by the role of flavor learning in forming visually or verbally cued expectancies.

9.3.1 *Orthonasal smell and flavor—sensory aspects*

When an unfamiliar taste and a smell are sampled by mouth, this experience seems to affect later experience of the smell, when it is sniffed orthonasally at the nose (Stevenson and Boakes, 2004). The first studies of this effect paired an unfamiliar odorant (such as water chestnut or lychee) with either sucrose or citric acid (Stevenson et al., 1995, 1998). Participants were asked to sample small portions of these mixtures (e.g., lychee and sucrose; water chestnut and citric acid) alongside other stimuli (e.g., water alone, saline solution). Both before this learning phase, and after it, participants were asked to sniff each odor and judge the degree to which it smelled “sweet” or “sour.” While these are taste properties, participants have little difficulty in applying these descriptors to odors. Indeed, such taste descriptors are often used spontaneously by naïve participants to describe particular smells (e.g., Harper et al., 1968), and in many cases the taste identified would likely have been one previously experienced with that odor (e.g., describing strawberry odor as sweet, lemon as sour, and coffee as bitter). Following pairings of the tastes and smells, several laboratories have now reported that odors paired with sweet tastes get to smell sweeter, odors paired with sour tastes get to smell sourer, and odors paired with bitter tastes get to smell more bitter (e.g., Privitera et al., 2012; Yeomans and Mobini, 2006). It would appear that the taste and smell components of flavor are stored in memory, and that this flavor memory is reintegrated when the smell component is later sniffed alone (Stevenson and Boakes, 2004). This then provides an immediate impression of what the odor object would “taste” like if it was placed in the mouth.

This type of odor-taste learning has a number of properties that seem to set it apart from other examples of human associative learning. The most notable is the claim that it occurs with a minimal level of conscious awareness (Brunstrom, 2004). Most human learning requires that the participants attend to both elements for an association to form between them (Shanks, 2010). Attempts to test whether participants have knowledge of the experimental contingencies during flavor learning have suggested that they do not; however, this form of evidence is weak for two reasons (e.g., Stevenson et al., 1998). First, it is built upon a null result and second, it may be that participants are aware during learning, but this information is no longer available after learning is complete. One reason to suspect that odor—taste learning may occur implicitly is because of the problem people have in naming even common odors (e.g., Cain, 1979). This may make it difficult to track the contingent relationship between the taste and the odorant during an odor—taste learning experiment. Moreover, as the material reviewed in Section 9.2 suggests, participants may also find it difficult to selectively attend to the odor independent of the taste, making it hard to even *know* that there are two things to associate (and this probably goes hand-in-hand with the suggestion of preparedness between gustatory and olfactory stimuli in the mouth; Ruzsipel and Gast, 2020). Although, these reasons would seem to provide good grounds for thinking that explicit processes do not underpin odor—taste learning, the issue remains unresolved.

A second unusual aspect of odor-taste learning concerns its resistance to interference (Stevenson et al., 2000). Once an odor—taste memory is acquired, pairing the odor with another taste does not eliminate the existing taste pairing (e.g., if an odor

were paired first with sucrose, then with citric acid, it would continue to smell sweet). This resistance to interference seems to result in particularly long-lived flavor memories, something that is already recognized with smell. In addition to resistance to interference, a further unusual aspect of this form of learning is that it involves the experience of a different sensory modality (taste) when another sensory modality is stimulated (smell). This is usually termed *synaesthesia*, and there has been a marked reluctance to use this label principally because the experience seems to be nearly universal and because it is learned (Stevenson and Tomiczek, 2007). Perhaps a more productive way to think about it is to see it in relation to the earlier idea of a *joint* taste–smell attentional channel in the mouth. In the mouth, taste activates a putative joint taste/smell attentional channel. At the nose, smell activates memories of that joint sensory channel. From this perspective, taste and smell are not independent modalities.

While most research attention has focused on odor–taste learning, there is also a capacity to learn relationships between odors and particular somatosensory properties. An early study examined whether fatty-related characteristics of different milks could become associated with particular smells (Sundqvist et al., 2006). While the odorant that had been paired with more viscous milks was judged to smell fattier after conditioning, it was hard to tell the extent to which this was driven by fat-related *odors* in the milk. This concern arises as odor–odor learning and is a well-established phenomenon (Wilson and Stevenson, 2007). A more recent study paired odors either with an odorless and tasteless viscous fluid, a sweetened viscous fluid, or water (Stevenson and Mahmut, 2011). The only odorant that was judged to smell “thicker” post-conditioning was the odor paired with the sweetened viscous fluid, suggesting that a taste may be necessary to support odor–somatosensory learning.

One feature of these odor–somatosensory learning experiments was that they involved an enhancement test, in which the conditioned odor was presented with a weakly creamy or viscous fluid, and the participant had to make a judgment of viscosity among other things. Under these conditions it was evident that the conditioned odor acted to enhance, respectively, the creaminess of milk and the thickness of a mildly viscous fluid (Stevenson and Mahmut, 2011; Sundqvist et al., 2006). This provides a link back to the odor–somatosensory interactions discussed in Section 9.2.1.2, suggesting that they may well result from prior learning. However, as noted in Section 9.2.1.2, the problem here is that for odor–taste learning a strong link back to odor-induced taste enhancement has not been well substantiated.

9.3.2 *Orthonasal smell and flavor—affective aspects*

When a food odor is appraised, it will as with most odors induce an affective response. This affective response can be significantly impacted by familiarity (Tuorila et al., 1994), the immediate sensory properties of the flavor (e.g., Baeyens et al., 1990) and also by its delayed consequences—namely whether it makes a person vomit or feel nauseous (e.g., Cannon et al., 1983) or whether the associated food delivers a significant caloric load (e.g., Mobini et al., 2007). There are also a number of other forms of learning that can probably also affect the perception of food odors. These include the psychoactive consequences of the food (e.g., caffeine, alcohol) and the impact

of observing others consuming that food. As these have less direct relevance to flavor, they are not further examined here.

Familiarity is a powerful predictor of liking for both odors and for food. Unfamiliar foods tend to be disliked, at least the thought of eating them, and tasting an unfamiliar food may also be associated with reduced liking, although findings here are more variable (Pliner et al., 1993; Raudenbush et al., 1998). Mere exposure to foods (and in some cases simply information about a food) can significantly increase liking in infants, young children, and adults (e.g., Birch and Marlin, 1982; Pliner, 1982). Presumably, this also translates into increased liking for the food's smell. While this has not been explicitly tested, this would seem likely given the well-established link between familiarity and odor liking (e.g., Rabin and Cain, 1984). As the effects of exposure suggest that a memory of the flavor is retained following mere exposure, it would seem highly likely that this same memory is also used to identify foods that significantly depart from what the visual and olfactory cues prior to eating suggest it should taste like. This is explored in greater depth in [Section 9.3.3](#).

When a food is placed in the mouth it may taste pleasant to some participants if it is sweet (just as it might with mildly salty, fat-related and meaty tastes although these have been less well explored) and unpleasant if it is bitter or excessively sour. This has been termed flavor–flavor learning. The hedonic sensation generated by the taste (and possibly by somatosensory stimuli as well) can become associated with the olfactory component of the flavor. In an early demonstration of this phenomenon, Zellner et al. (1983) had participants consume novel teas either with or without sucrose. Later, teas were sampled with no added tastant, and teas that had previously been paired with sucrose were more preferred. This basic effect has now been observed using a variety of different paradigms (e.g., Baeyens et al., 1990; Capaldi and Privitera, 2007; Mobini et al., 2007; Ruzsipel and Gast, 2020), most have examined liking changes in the same context as conditioning occurred (e.g., like Zellner et al., 1983, testing the flavor in the absence of the taste). That is they have used retronasal olfaction, as it appears to be the olfactory stimulus that demonstrates the change in liking. Two important points can be made here. First, the effects can also be detected when the taste-paired odor is sniffed via the nose, namely the effects transfer across from retronasal to orthonasal olfaction (e.g., Stevenson et al., 2000). Second, and as with odor–taste sensory learning, the affective change may be dependent upon the odor alone reintegrating the whole flavor memory (e.g., strawberry-liked-sweet).

These two forms of odor–taste learning (sensory and affective) share many properties, including resistance to interference (Baeyens et al., 1995) and the apparent ability for learning to occur with minimal conscious awareness of the contingencies (e.g., Dickinson and Brown, 2007; noting that not all agree—see Wardle et al., 2007; and there are circumstances where this probably does depend upon explicit memory, Ruzsipel and Gast, 2020). Nonetheless these two forms of flavor learning are dissociable. Some people do not like the sweetness of a given concentration of sucrose, while others may be indifferent, and yet others still may like it. These varying affective responses dictate the type of hedonic change observed during a flavor–flavor learning paradigm (e.g., Yeomans et al., 2006). However, participants' initial hedonic response to sucrose (and its impact on affective learning) is independent of the

occurrence of sensory odor-taste learning. Participants still come to learn that a sucrose paired odor smells sweet irrespective of their affective response to this taste (Yeomans et al., 2006). What this seems to suggest is that when participants experience an odor that has previously occurred in a food, the odor may recover a memory of the flavor that encompasses both its sensory and affective features, both of which can vary independently.

While flavor—flavor learning likely depends upon retaining a memory of the flavor experience, flavor-nutrient learning involves associating some as yet to be identified component of the postingestive experience with the flavor, with nutrient sensing seemingly a likely candidate (Small and DiFeliceantonio, 2019). In particular, it would seem again that it is probably the olfactory component of the flavor that is associated with the delayed consequence and while this has not been tested, this would presumably have to be the case as odor is a major differentiating feature between foods. Flavor nutrient learning is also independent of flavor—flavor learning (Capaldi and Privitera, 2007), and has been demonstrated in both children (e.g., Birch et al., 1990; Kern et al., 1993) and in adults (Brunstrom and Mitchell, 2007; Mobini et al., 2007).

Flavor—nutrient learning appears to be a more difficult phenomenon to demonstrate in the laboratory than flavor—flavor learning, with several documented failures to observe an effect (e.g., Appleton et al., 2006; Yeomans et al., 2005). There may be several reasons for why it is difficult to demonstrate: (1) acquisition and performance may be state-dependent (Mobini et al., 2007); (2) capacity to attend to internal sensory signals may affect learning, assuming these are important (Brunstrom and Mitchell, 2007); and (3) in “real-life” eating situations where a person is exposed to multiple flavor components in a meal, it is difficult to envisage how each of these different sensory experiences—or which one—become linked to a common postingestive outcome.

While flavor-nutrient learning generally involves a positive affective shift, flavor-aversion learning as the name suggests involves negative change. While there is much debate about the role of conscious processing in the form of learning considered so far (Brunstrom, 2004), flavor aversion would genuinely seem not to involve any explicit form of learning. The main reason for making this bold claim is that flavor-aversion learning can occur even when the participant *knows* that the resulting aversion to a particular food had nothing to do with that food. That is, the aversion may have resulted from other forms of illness (e.g., gastric flu), intoxication (e.g., excessive intake of alcohol), or chemo/radiotherapy (e.g., Bernstein, 1991). All of these—and including food poisoning—can result in a marked and lasting aversion to foods that are associated with nausea and vomiting (Logue et al., 1981).

9.3.3 Flavor expectancies

When people visually appraise a food or drink, and sniff its smell, they form sensory and affective expectations, which if violated on ingestion may reduce their liking for the food or even lead to rejection (e.g., Zellner et al., 1988). There appear to be three important issues to consider when thinking about flavor expectancies. The first is that the expectancies that surround particular foods and drinks are probably built up *both* implicitly and explicitly over multiple exposures. Some expectancies are clearly

explicit and can be readily verbalized—coffee should be hot and orange juice cold (e.g., Zellner et al., 1988), one's personal food likes and dislikes are easy to list, and gross aspects of flavor can be described (e.g., salted crisps should be crisp and salty). Other expectancies are not so readily described and instead rely upon the same system described earlier for familiarity judgments, whereby a library of flavor memories is acquired incidentally via exposure. It is these flavor memories—not directly accessible except perhaps through orthonasal olfaction—that are compared to current flavor experience.

This raises a second issue. Does seeing a food partially activate a particular flavor template (e.g., of vanilla ice cream) or does no activation occur until a food is placed in the mouth? Although in both cases the resulting flavor in the mouth must be compared to existing flavor memories, visual identification of the food prior to ingestion may be instrumental in generating both an explicit (e.g., vanilla ice cream is cold, sweet and creamy) and an implicit (e.g., vanilla ice cream flavor memory) template. Identification would *not* seem at all relevant here—as others have noted before (e.g., Morin-Audebrand et al., 2012)—because the functional benefit of this process is to detect deviations from expectation, deviations that might flag ingestive risk—novelty and contamination by chemicals, bacteria, or indigestible objects. Indeed, several studies have now indicated that people are generally quite good at detecting deviations in taste, somatosensation, and odor, when asked to do so relative to an earlier incidental flavor experience (e.g., Koster et al., 2004; Mojet and Koster, 2005; Moller et al., 2007).

A third issue concerns the consequences of generating a food that is likely to be at odds with a participant's expectation. An important consideration here is whether or not the participant will notice the deviation. If they do, and especially if the circumstances support especial attention to the food (e.g., novelty, being provided unusual information about it [monkey meat], in an unusual restaurant, etc.), then participants are likely to demonstrate a phenomenon termed *contrast*, in which their prior expectations about the food contrast with their affective reactions to it. This has been demonstrated in a number of studies, with two important phenomena being identified. The first, as noted above, is that cues that facilitate attention to the food are likely to promote sensitivity to even relatively small departures from expectation (Zellner et al., 2004). The second, is that when significant departures occur, such as participants *thinking* that smoked salmon ice cream is in fact raspberry ice cream, a far more negative reaction to the food is displayed, than if they are told what is it or not provided any information prior to tasting (Yeomans et al., 2008). Finally, if the difference between expectation and actuality is not particularly large, assimilation may occur, where affective judgments relating to expectation (e.g., this brand of cola will taste good) and reality (e.g., the least preferred brand of cola is served in the can of the most preferred brand) will converge (e.g., Cardello and Sawyer, 1992).

9.4 Conclusion

Flavor memory probably functions to support the identification of foods that are safe and nutritious. It does so by two primary means, passive learning of flavor experiences,

and the formation of associations between a food's flavor and its postingestive consequences. These allow a food's odor to yield sensory and affective information about the food without risk of ingestion, as well as support the construction of explicit and implicit expectations about what the food should taste like when placed in the mouth.

9.5 General discussion

The characteristic features of flavor perception suggest that what is experienced is neither just a set of parts nor a completely integrated sensation. Rather, flavor is partially holistic, with taste and smell as a common sense, and with some aspects of oral somatosensation also joined to smell. This has a distinct functional benefit. It allows orthonasal smell to recover the key sensory (taste and fat) and affective properties of the flavor, without having to risk ingestion. Moreover, encoding this partially holistic flavor memory also allows future flavor experiences to be compared to it, allowing for the detection of departures from expectation, expectations that are probably cued by the visual appearance of the food and by its smell. Thus the two parts of this chapter, the first on holistic perception, and the second on memorization, are essentially linked by the common functional goal of identifying safe and nutritious food.

The capacity to perceive and encode flavor as a partially holistic entity may well have evolved to support dietary habits that are very different from those of today. While it is not possible to reconstruct the dietary patterns of our ancestors, some indication can be gleaned from anthropological studies of hunter-gatherers (see [Woodburn, 1968](#)). One feature to emerge from such studies is that food combinations were generally simpler than now. Often single foods would be eaten to repletion. The benefit of this is that it allows the flavor system to accurately assign the postingestive consequences of that food to its flavor. Experimenters construct their studies of flavor learning around the hunter-gatherer model, using single foods that are discretely flavored. Yet the modern meal often provides multiple flavors within the same bout, and often multiple courses within that. Of course it could be that key components of flavor learning occur during childhood when diets tend to be less complex, but there is no clear indication that this is so. The implications of this for healthy eating have not been widely considered.

While some aspects of modern eating habits might defeat the flavor system, the developing scientific understanding of how perception arises might allow more ingenious solutions to the current problem with overconsumption. There has already been some work on exploiting odor-induced taste enhancement to, for example, reduce the amount of salt that needs to be added to food (e.g., [Onuma et al., 2018](#); [Nasri et al., 2011](#)). A similar approach could be adopted for sweet tastes, and also for fat—although far more needs to be learnt about how the somatosensory and olfactory systems interact. Indeed, the possibilities for commercially exploiting aspects of flavor perception do not seem to have been fully realized. The degree to which more healthful ingredients can be substituted for less healthy ingredients represents both a major

challenge for food technologists and for those studying the perception of flavor. If science can determine what gets noticed and what does not during flavor perception, and how holistic processing may limit perception of parts, all of these things can be used to engineer tasty but more healthy foods.

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Acquired tastes: on the learning of human food preferences

10

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10.1 Introduction

All animals—including humans—need to eat. Eating is a necessity of life, but it can also be a rewarding experience and food is thus an important source of pleasure. What specific foods comprise a rewarding, comforting, or enjoyable experience tends to differ between individuals. *De gustibus non est disputandum*—there is no accounting for taste. Although food preferences are fairly idiosyncratic, they are not totally stochastic. Indeed, there is overlap in types of foods widely considered to be pleasurable and preferred. For example, most people prefer chocolate to cauliflower. But why is that?

People are born with few specific food preferences. Neonates like sweet foods and dislike bitter foods (Ganchrow et al., 1983). Although it is frequently argued that these are basically the only flavor preferences any person starts life with, there is some evidence that more particular preferences for flavors of given foods or dishes are heritable and that specific taste genes are associated with specific food likes and dislikes. A twin study by Breen et al. (2006) showed that monozygotic twins have a larger overlap in food preferences than dizygotic twins have, suggesting that food preferences are at least partly inherited. However, an important limitation of this study was that the researchers asked the parents of the twins to indicate commonalities in food preferences. It is not hard to imagine that the parents of a monozygotic twin are biased to observe any commonality in their children, be it appearance, behavior, or indeed food preferences. A similar design was used by Fildes et al. (2014a) when examining the contribution of genes versus shared environment to specific food preferences in twins. This study included data from well over 2000 children (i.e., monozygotic vs. dizygotic twins). Observed food preferences appeared to be determined by both shared environment and genes. Genetic influence was consistent but seemingly small, especially regarding snack foods, starchy foods, and dairy products. But genetic influence appeared more prominent regarding children's dislike for vegetables. Although one might argue that parents of the monozygotic twins in this study too would exaggerate any overlap in liking (or dislike) for certain foods, this obviously cannot account for the differences in genetic contribution to liking for different food groups (e.g., snacks vs. vegetables).

Another line of research has focused on determining the precise genetic contribution to food preferences, trying to identify the specific genes that might be associated with specific food preferences. [Gasparini \(2012\)](#) tested different ethnic populations along the Silk Road—a single designation for a number of ancient trade routes connecting Mediterranean Europe with China through Central Asia—for possible links between variations of known taste genes and food preferences. The modern people living in Silk Road countries are genetically diverse, but they share a lot of culinary traditions (i.e., dishes and cooking techniques). By testing the people of different Silk Road communities, Pirastu et al. found that taste gene TAS1R2 is associated with a preference for vodka and wine. Variations of a different gene (ITPR3) were associated with distaste for mutton.

In more recent genome-wide association studies (GWAS), genes other than taste-related genes were identified to contribute to specific food preferences. Genes thus contribute to the expression of certain food preferences, but this genetic influence seems to partly hinge on indirectly affecting the acquisition of novel food preferences by modulating reward sensitivity and reward processing (see [Robino et al., 2019](#)). There is still little evidence that many specific food preferences are genetically determined by birth, though. [Rozin and Millman \(1987\)](#) argue that this makes perfect functional sense. We humans are omnivorous and should not be constrained in our eating behavior by a narrow range of genetically fixed food preferences. We need to be able to adapt to sudden changes in the food environment, to quickly learn to recognize what is edible and what foods are nutritious. Much of that learning seems mediated by hedonics ([Young, 1966](#)). For example, disliked foods are often described as inedible and similarly people tend to feel disgusted by foods they do not recognize as being edible (e.g., insects; [Koch et al., 2021](#)). In sum, a food preference, or the hedonic evaluation of a given food, can be learned. It is acquired through experience. Different ways in which such a food or flavor preference can be acquired are described. Further, we discuss how these techniques may be applied to promote healthier food choices and dietary habits, particularly in children.

10.2 Tasting to preference

Mere exposure refers to an increase in liking for a particular stimulus to which one is repeatedly exposed. This can be any type of stimulus. For example, in one experiment [Zajonc \(1968\)](#) exposed students to Chinese characters, told the students that these characters were adjectives, and that after being exposed to these characters they would be asked to indicate each character's "goodness" on a scale. Students were exposed to these characters with either a low or high frequency. The students regarded the high frequency characters more positively than the low frequency characters. Mere exposure to a stimulus such as a Chinese character can lead to a positive shift in attitude toward that stimulus. It is a basic phenomenon that does not require much conscious awareness and applies to a wide variety of sensory input (see [Zajonc, 2001](#)). It also applies to food.

Pliner (1982) had participants taste and rate four different tropical fruit juices. The participants were exposed 20, 10, 5 times, or never to these fruit juices. Pliner found that the liking for the fruit juices depended on the number of exposures with more exposure leading to better liking. Similarly, Birch and Marlin (1982) demonstrated in two-year-old children that repeated exposure to either novel cheeses (Experiment 1) or fruits (Experiment 2) fostered familiarity and preference for these foods.

Most children go through a phase termed neophobia—a fear for novel stimulation. It starts around 2 years of age and peaks when approximately 6 years old (Dovey et al., 2008). In case of food, neophobia primarily concerns a reluctance to try new vegetables (Cooke et al., 2004). The results by Pliner (1982) and Birch and Marlin (1982) suggested that mere repeated exposure is an efficient way of overcoming this apparent fear of the flavor of vegetables. But how much and what kind of exposure would be necessary to achieve this?

Birch et al. (1987) conducted a study in which they exposed two–five-year-old children to different novel sweet foods (e.g., figs or sugar palm). The exposure comprised either repeatedly looking at or tasting the food. Although looking increased the visual appeal of the exposed food (see also Heath et al., 2011), only the actual tasting of the food induced a positive shift in flavor preference. The results suggested that the mere exposure effect is modality specific and thus hinges upon actual ingestion of the food. Furthermore, the study suggested that a relevant positive preference shift requires as many as 15 taste exposures (see also Sullivan and Birch, 1990). In other words, the mere exposure effect requires ingesting the food on a substantial number of occasions. More recent research, however, has shown that the mere exposure effect does not always require actual food ingestion.

In a recent study by Rioux et al. (2018), a total of 70 3 to 6-year-old children were randomly assigned (per cluster) to a simple exposure group, a diverse exposure group, and a control group (i.e., no exposure group). In the first two groups, the children were exposed to pictures of vegetables printed on placemats placed on the tables in the children's school cafeteria. In the diverse exposure group, the depicted vegetables were presented in atypical colors in four different ways. Before and after a 2-week period of exposure, all children received a taste test in which they were offered a variety of vegetables to try, including vegetables depicted on the placemats in the exposure groups but also new unfamiliar vegetables. The children in the simple exposure group, but not the diverse exposure group, showed an overall increase in their willingness to try vegetables. So simple repeated visual exposure to vegetables already can have a positive effect on vegetable acceptance that extends beyond the presented vegetables (see also Nekitsing et al., 2018).

The above mentioned exposure effect does not limit itself to the visual sensory modality. Nederkoorn et al. (2018) examined whether haptic exposure to a specific texture may increase acceptance of a food with the same texture. In this study, children (3–10 years old) were randomly assigned to one of two conditions: exposure or control. In the exposure group, the children were asked to play with a colourless and odorless jelly for 10 min. They were encouraged to use their hands to touch, scoop, and shape the jelly. In the control group, the children played a simple game for 10 min. At the test, all children were offered strawberry desserts including a strawberry jelly

pudding. The children in the exposure group were significantly more willing to try the jelly pudding, relative to the control group (see also [Nederkoorn et al., 2019](#)).

Repeated exposure to a food's appearance or texture can already induce a meaningful increase in food acceptance. Furthermore, such a mere exposure effect does not always seem to require a substantial number of exposures. In some cases just a single exposure to a food can be enough to markedly increase its acceptance (see e.g., [Birch et al., 1998](#)). By adding foods and dishes to one's diet, this increases the probability for sensory overlap between a newly tasted and already familiar food thus promoting generalization of food acceptance—the “tastes-like-chicken-effect” ([Havermans, 2009](#)). Indeed, [Williams et al. \(2008\)](#) found that the number of exposures required for trying new food is reduced with an expanding dietary variety.

As for vegetable intake, [Lakkakula et al. \(2010\)](#) found that school children demonstrate an increase in liking for initially disliked peas, tomatoes, and carrots with 10 weekly taste exposures (see also [Mustonen and Tuorila, 2010](#)). Similarly, [Wardle et al. \(2003\)](#) instructed parents to serve their children a certain vegetable daily for 14 days. Children who tasted the vegetable at least 10 times showed increased liking and intake for this and other vegetables at a subsequent taste test.

In sum, mere exposure is a simple technique for increasing preference and acceptance of novel foods that can be readily applied to, for example, promote healthier eating behaviors in children. Recent research suggests that such an effect does not require repeated food tasting and ingestion. However, [Nekitsing et al. \(2018\)](#) found that actual tasting of vegetables (rather than just being exposed to the visual appearance of vegetables) does seem to be more effective at increasing its acceptance. The difficulty with this method then lies in convincing children to try healthy but unfamiliar or perhaps disliked foods. In this respect, some scholars have argued for classical (or Pavlovian) conditioning methods to facilitate the acquisition of healthy food preferences, especially in children ([Havermans, 2009](#)).

10.3 The Pavlovian love of food

[Pavlov \(1927\)](#) discovered that his laboratory dogs would ‘psychically’ salivate in the presence of cues predicting food. When further investigating this psychological reflex, he systematically paired conditioned stimuli (e.g., an electronic buzzer, a ticking metronome, or a ringing bell) with a biologically relevant unconditioned stimulus, namely food. Food elicited the unconditioned salivary reflex in his laboratory dogs. Conditioned stimuli would also come to elicit this reflex on the condition that these stimuli reliably predicted food administration. In other words, Pavlov's dogs learned to associate the conditioned stimuli with food.

Pavlov studied conditioning hoping to learn more about the workings of the brain and the role of the central nervous system in orchestrating digestion, but psychologists readily adopted and adapted his conditioning paradigm to demonstrate the role of associative learning in a wide range of psychological phenomena, including the acquisition of flavor preferences ([Rozin and Zellner, 1985](#)).

10.3.1 Flavor–nutrient learning

Mehiel and Bolles (1984) examined associative learning of flavor preferences in rats, hypothesizing that a positive nutritional outcome (e.g., energy repletion) would reinforce a preference for a flavor associated with that outcome. The animals were food deprived and then received one of two distinctly flavored solutions daily in an alternating sequence for 8 days. For half of the rats, the two flavors were isocaloric. For the other half, one flavor had a higher caloric density than the other. Only the rats in this latter group developed a preference for one of the two flavors, namely the flavor that had been relatively rich in energy. The rats had learned to associate that flavor with the functionally positive nutritional outcome of energy repletion.

Flavor–nutrient learning has also been demonstrated in humans. Kern et al. (1993) established a preference for a specifically flavored yoghurt drink in children (approximately 5 years old) by pairing the yoghurt with a relatively high fat content. Fat is the most calorically dense macronutrient (9 kcal/g) and so adding even small amounts of fat markedly increases the energy density of any food or drink. Apparently, the post-ingestive consequence of added energy promotes the acquisition of a flavor preference in children too (see also Johnson et al., 1991). In line with this flavor–nutrient learning, when examining children’s fruits and vegetable intake, children tend to prefer those fruits and vegetables with the highest caloric density (Gibson and Wardle, 2003).

Once established, flavor preferences are remarkably robust. They do not extinguish easily (Havermans and Jansen, 2007b). In theory, it should be possible to condition a preference for a vegetable by pairing its flavor with a positive nutritional outcome after which one could remove the previously added macronutrients leaving the preference intact. This is exactly what Zeinstra et al. (2009) attempted to achieve in 7–8-years-old children. These children were offered two different vegetable drinks. One of these drinks had a much higher energy density (a difference of 150 kcal) by adding maltodextrin to it. The experimental manipulation failed. The children did not acquire a preference for the maltodextrin-enriched vegetable drink because they were extremely hesitant to taste the drinks in the first place. Flavor–nutrient learning requires a post-ingestive effect and in the absence of ingestion clearly no such effect can arise.

More recently, Attuquayefio et al. (2020) examined if adults develop better liking for a high-calorie novel flavored beverage relative to a noncaloric beverage over a 2-week period of daily consumption at home. No evidence for flavor–nutrient learning was found. That does not mean that flavor–nutrient learning does not take place in humans, but the authors rightfully point out that their null finding suggests that flavor–nutrient learning in humans is not as strong or rapid as prior animal studies implied. Flavor–nutrient learning nicely explains why we tend to prefer high-energy dense foods such as snacks, confectionery, and chocolate, but the flavor-nutrient conditioning paradigm does not so easily lend itself to establishing novel (healthier) food preferences.

10.3.2 Flavor–flavor learning

There are other options than flavor–nutrient learning for promoting food preferences. One alternative is positive flavor–flavor learning. This paradigm refers to a form of

evaluative conditioning in which the positive valence of the so-called unconditioned stimulus due to its contiguous presentation with a neutral (or even disliked) stimulus transfers to this latter conditioned stimulus, effectively increasing one's liking for that stimulus (De Houwer et al., 2001; Havermans, 2009; Havermans and Jansen, 2007a).

Holman (1975) studied flavor–flavor learning in rats. Rats, like humans, are born with a strong preference for sweet taste. Holman hypothesized that, in rats, sweetness functions as a reward and hence acts as an unconditioned stimulus reinforcing a preference for flavors consistently paired with it. Holman's rats indeed came to prefer flavored solutions paired with the sweet taste of noncaloric saccharin.

Zellner et al. (1983) conducted an experiment on flavor–flavor learning in humans and found that their participants, much like Holman's rats, developed a preference for flavors of tea that had consistently been sweetened during the conditioning phase. Even when at test the tea was left unsweetened, the participants still preferred its flavor.

Unlike flavor–nutrient learning, flavour–flavour learning does not hinge upon any postingestive effect. Effective flavour–flavour learning relies mainly on the sensation of an already preferred taste, such as sweet taste. Havermans and Jansen (2007b) set out to examine whether flavor–flavor learning may be applied to increase children's liking for vegetables. Children alternately had to take a sip from a sweetened and another unsweetened vegetable drink. With just a few sips, these children showed a positive shift in preference for the sweetened vegetable flavor, again even when at test this flavor was left unsweetened. Capaldi and Privitera (2008), using a similar flavor–flavor learning paradigm effectively conditioned a preference (or rather less of an aversion) for grapefruit in children. Further, in a randomized controlled trial, Johnston et al. (2011) examined children receiving regular vegetable tasting sessions at school. One group of these children received the vegetables together with a food they already preferred: peanut butter. After 4 months, the peanut butter group was found to eat more and a larger variety of vegetables than did the mere exposure (i.e., vegetables, but no peanut butter) comparison group.

Havermans and Jansen (2007b) found no change in liking with mere repeated tastings of the unsweetened vegetable drink, and thus they concluded that flavor–flavor learning is superior to mere exposure in promoting a positive shift in food liking (see also Johnston et al., 2011). However, later studies have called this supposed superiority into question. Anzman-Frasca et al. (2012) tested toddlers comparing a group regularly receiving vegetables paired with a favorite dip and a group of toddlers just being exposed regularly to these vegetables. Both groups demonstrated an increase in vegetable liking. There was no difference between the two groups and hence the increase in liking could be attributed to mere exposure alone.

Hausner et al. (2012) examined toddlers' acceptance of a novel pureed vegetable. Toddlers were repeatedly exposed to unadulterated puree (mere exposure condition), or sweetened puree (flavor–flavor learning condition), or energy dense puree (flavor–nutrient learning condition). Intake and acceptance of the vegetable puree increased over time, but both flavor–flavor learning and flavor–nutrient learning did not appear to promote vegetable liking above and beyond mere exposure. These latter two studies suggest that flavor–flavor learning provides little benefit over mere exposure.

10.3.3 Flavor—consequence learning

A final form of Pavlovian conditioned food preferences concerns flavor—consequence learning. Caffeine is a methylxanthine that has been shown to reinforce flavor preferences. [Richardson et al. \(1996\)](#) demonstrated that participants who regularly consumed caffeine (e.g., as tea, coffee, or cola) developed, over the course of 10 workdays, a positive change in liking for a fruit juice when it was paired with the intake of a capsule containing 100 mg of caffeine relative to a group of participants who received a placebo with their fruit juice.

Employing a within-subject design, [Yeomans et al. \(2005\)](#) also found that caffeine could reinforce a preference for a novel flavor, concluding that this effect is the likely “consequence of conditioned associations between the flavour and the effects of caffeine” (p. 55). This leaves the question what exactly the reinforcing consequences of caffeine ingestion are. One obvious candidate is caffeine’s psychoactive properties. Caffeine consumption makes you feel alert and energized. It increases vigilance and attention, and quickens your reaction time (see [Rogers and Richardson, 1993](#)). In regular users, caffeine also alleviates possible withdrawal symptoms. These consequences of caffeine might be considered to constitute the reward that both positively and negatively reinforces a flavor preference ([Rogers et al., 1995](#)). However, theobromine, another methylxanthine, has only limited psychostimulant properties ([Smit et al., 2004](#)) and still has been found to reinforce flavor preference in much the same way as caffeine does ([Smit and Blackburn, 2005](#)).

In sum, nonnutritive substances such as methylxanthines can effectively condition a preference for paired flavors. The main reinforcing property of methylxanthines like caffeine and theobromine appears to be the alleviation of any withdrawal effects. In case of caffeine, such withdrawal comprises dysphoric mood, deteriorated cognitive performance, fatigue, and headaches. It is not quite clear what that withdrawal comprises in case of theobromine though. [Fig. 10.1](#) summarizes the role of Pavlovian learning in the acquisition of flavor preferences by providing an example of how Pavlovian conditioning can explain the acquired preference for chocolate.

10.4 Acquired food cravings

Food craving, an intense desire for a specific food item, is very common. Most people report they have experienced such craving, and [Weingarten and Elston \(1990\)](#) thus argued that understanding human feeding requires the consideration of food cravings (see also [Styn et al., 2013](#)). Importantly, cravings are elicited by cues; that is, cues that predict food intake, cues that function as Pavlovian conditioned stimuli.

Pavlovian food preference learning does not just increase liking for a particular food, but also leads to the transfer of incentive value to the sensory cues (appearance, smell, and taste) associated with such food, or any cue that reliably predicts intake of that food. For example, the sight and smell of **chocolate** can be a cue that elicits strong craving for **chocolate**. Similarly, if you are used to eating a piece of **chocolate** in the evening while watching an episode of your favorite television show, then eventually

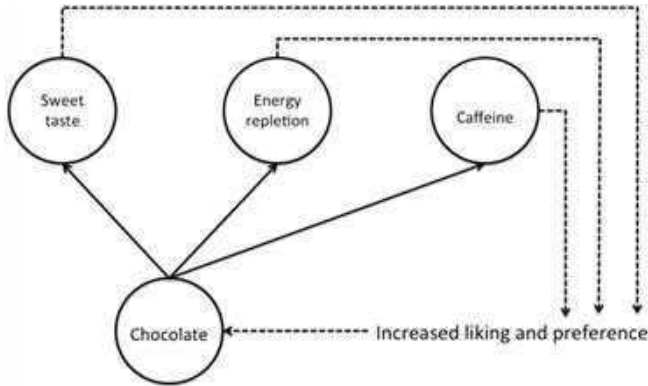


Figure 10.1 A preference for **chocolate** is acquired. The **chocolate** flavor functions as a conditioned stimulus (or CS) that with **chocolate** consumption is paired (1) with the already preferred sweet taste of sugar, (2) with energy repletion due to **chocolate**'s high caloric density, and with (3) the rewarding pharmacological consequences of **chocolate**'s methylxanthines like theobromine and caffeine. The combination of these various rewards will induce a conditioned preference for **chocolate**.

watching television in the evening becomes a cue that will evoke **chocolate** cravings (Jansen, 1998). Cue-elicited food craving is sometimes referred to as food “wanting,” resulting from transfer of incentive value from a highly rewarding food to cues associated with that food, a process which Berridge (2009) has termed “incentive sensitization.” It is what makes food-related cues desirable in their own right (Havermans, 2013).

Pavlovian food cues, by acquiring an incentive value, can come to motivate food-seeking behavior. A prominent example of such motivating power is a phenomenon called Pavlovian-instrumental-transfer (or PIT), which was first demonstrated in animal research. Estes (1943) taught a group of rats to press a lever for food (instrumental learning phase). Next, he exposed the same rats to repeated tone-food pairings; a tone was always followed by food (Pavlovian learning phase). At test, when these rats were given the opportunity to press a lever again, they would show invigorated lever pressing with presentations of the tone, even though the tone had never been directly paired with lever pressing. The Pavlovian learning phase had endowed the tone stimulus with an incentive value that, at test, clearly motivated instrumental food seeking in the rats.

PIT is not limited to rats. It has been shown in numerous animal species, including humans. For example, Lehner et al. (2017) first subjected participants (i.e., healthy volunteers) to a computer controlled manual grip force task, where performance was reinforced with a small amount of money, or compliments (a picture of a person smiling approvingly and giving a “thumbs up”), or Malteser **chocolates**. After that, participants were shown different fractals on a screen. These fractal pictures were either paired with a monetary, social, or food reward (as specified above) in a Pavlovian conditioning session. Finally, participants again had to perform the grip force task.

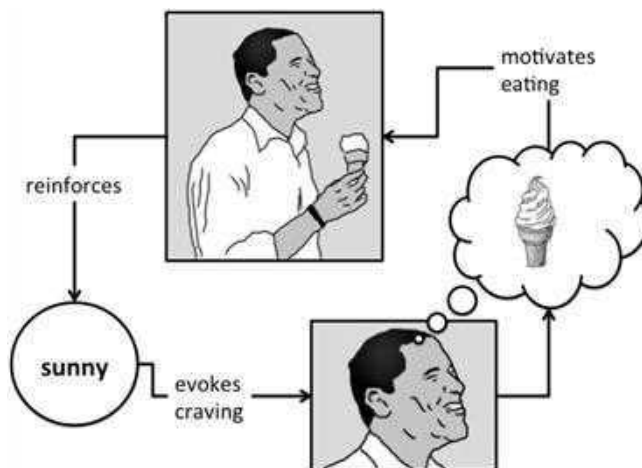


Figure 10.2 According to a Pavlovian learning perspective, any environmental cue that is reliably paired with the intake of a highly palatable food becomes associated with that food. For example, if you frequently consume ice cream in sunny weather, then sunny weather may come to function as a conditioned stimulus (or CS) that predicts ice cream. Due to this acquired association with enjoying ice cream it will come to elicit craving for ice cream. Craving motivates ice cream seeking behavior and subsequent consumption that further reinforces the predictive value of sunny weather.

However, different fractals were now shown on screen during the task. Much like Estes' rats, the participants showed invigorated performance on the task when the Pavlovian stimuli (i.e., the fractals associated with a reward) were presented.

In sum, Pavlovian learning is thought to play a very important role in the etiology of human food preferences. Fig. 10.2 displays a simple scheme of how various cues are thought to come to function as Pavlovian conditioned stimuli predicting the intake of specific foods and how, as a result of Pavlovian conditioning, these cues then come to elicit intense craving for that food.

10.5 Instrumental food preferences

Pavlovian learning mediates perceived palatability and desirability of food. Preferred foods are often not the healthiest products. Although parents and health professionals could certainly use different Pavlovian learning techniques to promote healthier flavor preferences, there is also the often-overlooked possibility of employing instrumental learning techniques. Instrumental (or operant) learning refers to the learning of an association between an act and its outcome. Such conditioned behavior is purposeful. The organism responds or acts in a certain way knowing that it will have a certain consequence. For example, Skinner (1953) would teach his pigeons to peck at a certain response key through a small hole in the wall of an operant chamber in exchange for

access to food. Food serves as a reward that reinforces the behavior (key pecking in this example) that led to this reward. Is it possible to use rewards to promote the etiology of healthy food preferences? Could you positively reinforce the consumption of vegetables and if so, would this adventitiously provoke increased vegetable preference?

The use of extrinsic rewards in trying to get people to act in a certain way has sometimes been viewed as a manipulative disregard for an individual's autonomy. In some ways it is, but self-interest sometimes conflicts with longer term or wider communal interests. We are occasionally asked (or indeed ordered) to do things that we may not particularly enjoy doing. Remuneration for those things can motivate us to do whatever (we or someone else feels) needs to be done. In case of a working job, such remuneration is called a salary. There does not appear to be anything inherently nefarious about earning a living, but according to self-determination theory, tangible rewards for certain behavior effectively undermine intrinsic motivation for that behavior (Deci, 1971; Gagné and Deci, 2005; Ryan and Deci, 2000). Therefore, self-determination theory (or cognitive evaluation theory) posits that there are limits to motivating performance with rewards, and hence there are limits to the range of behaviors one can condition by means of instrumental learning. However, this view has not gone unchallenged. In fact, a series of metaanalyses showed that there are in fact very few instances in which extrinsic rewards appear to undermine intrinsic motivation. Overall, only tangible rewards for already enjoyed acts undermine intrinsic motivation for such an act, and then only when the reward is unrelated to level of performance (Cameron et al., 2001).

There are not too many studies that have examined the effects of reward on increasing preference and intake of vegetables, but these studies do suggest that it is possible to promote healthy food preferences using instrumental conditioning. Horne et al. (2011) examined the efficacy of a modeling and rewards intervention designed to increase preschool children's vegetable and fruit consumption. The children received tasting sessions at a daycare facility. They obtained individual rewards (stickers) and earned group rewards (pieces of a toy) if they tasted a served fruit or vegetable. These reward tokens effectively reinforced consumption. And this effect generalized to other fruits and vegetables (though not completely). More importantly, the increase in fruit and vegetable intake in these preschoolers persisted for at least 6 months after the program had ended and intake was no longer rewarded. This latter result is unexpected, unless one presumes that rewards not only reinforce intake, but also promote a positive shift in flavor preference. There is evidence that it does.

Wardle et al. (2003) compared repeated exposure and a reward-based exposure intervention to increase children's vegetable preference and intake and found that both interventions increased children's liking and consumption over time, though the effect appeared larger with just mere exposure. More recently, Fildes et al. (2014b) examined whether a low-cost parent-administered exposure and rewards intervention would increase children's liking and intake of an initially disliked vegetable. The exposure comprised 14 daily tastes of the target vegetable. Trying the vegetable was rewarded with a sticker. Liking for the target vegetable (as reported by the parents) increased relative to a control group. Similarly, intake of the target vegetable increased

significantly in the experimental group, thus showing that an exposure and reward program can effectively increase a child's acceptance of a disliked vegetable. But is a tangible reward such as a sticker really the best possible reward to increase a child's preference for an initially disliked vegetable?

Cooke et al. (2011) compared different reward-exposure programs to increase children's liking for a vegetable, namely: tangible reward and exposure; social reward and exposure; exposure without a reward. Exposure comprised 12 daily tastes of a disliked vegetable and the three different exposure programs were compared to a no treatment control group. Relative to control, all exposure treatments increased liking for the target vegetable and that increase was retained 3 months after treatment. There were no differences between the programs. Children consumed more of the vegetables if they had received an exposure treatment, with or without rewards. However, increased consumption was only retained for a longer period of time in the two reward groups.

In sum, rewards (e.g., stickers or compliments) reinforce the consumption of initially disliked foods such as vegetables. It also leads to increase in liking for these foods. This latter effect may be an epiphenomenon due to repeated exposure to the food rather than the direct result of the reward being associated with the flavor of the food. This would explain why rewarding vegetable intake does not seem to be more effective than mere exposure at increasing a child's acceptance of vegetables. But more research is needed here.

10.6 Social learning—"I'll have whatever she has"

Another way to learn food preferences is through social learning. For adults, eating behavior is influenced by their social environment, such as eating more and/or different types of food with other people present (de Castro, 1990; Vartanian et al., 2007). There are some indications that social influences, like modeling the eating behavior of others, can also improve food acceptance and food preference.

Learning behaviors through modeling is explained by Social Learning Theory (Bandura and McClelland, 1977). Modeling the eating behavior of familiar adults or peers can be an effective method to encourage the acceptance of novel or previously disliked foods in children. What this means is that children are more likely to try an unfamiliar or disliked food when they see a parent, teacher or friend eating it. Many food preference learning techniques rely on actual consumption, as described above, but the taste of a food can be a barrier—especially when it is a novel or disliked food. Social learning may offer a solution for increasing the willingness to try those foods.

Children are likely to eat most of their meals with a familiar adult present, such as parents or teachers. Addessi et al. (2005) showed that children ate more of a novel food when they see a familiar adult eating the same food (or what they believe is the same food). However, children's intake was not affected when the familiar adult was eating a different food or when they were not eating food. This suggests it is not simply the presence of others that is influencing food intake. It is a modeling effect. Children

consider what the model is eating and behave accordingly. Self-reported parental modeling has been related to diet quality in children (Draxten et al., 2014; Palfreyman et al., 2014), but there are some inconsistent results in experimental research about parental modeling (Blisset et al., 2016; Holley et al., 2015). This may be explained by the fact that modeling of familiar adults is more effective when the adults are showing enthusiasm for the foods (Hendy and Raudenbush, 2000), or when modeling is combined with nonfood rewards (e.g., stickers and praise) (Holley et al., 2015). Moreover, the presence of other children may also have an effect. Modeling eating behavior of familiar adults has been shown to be less effective than peer modeling (Hendy and Raudenbush). Eating with peers can influence the acceptance of novel foods (Hendy, 2002) and even change food choices (Birch, 1980).

In a study by Birch (1980), the researcher gave children the choice of two foods and measured which food the children preferred. Then she made sure the target children shared the table with other children who selected and ate the other food. Birch showed that the target children started to prefer the previously nonpreferred food. While this type of positive peer modeling can influence the acceptance of novel foods, negative peer modeling can influence the rejection of novel foods. Unfortunately, negative peer modeling may have a stronger effect on intake than positive peer modeling, and appears difficult to reverse (Greenhalgh et al., 2009).

In real-life situations, positive peer modeling of disliked foods may be difficult to achieve. However, several studies have shown that watching a cartoon (Farrow et al., 2019; Horne et al., 2011) or peer model (Staiano et al., 2016) consuming a vegetable in a video or a computer game can increase children's intake of vegetables. To summarize, social learning can be used to improve the acceptance of novel or disliked foods. Modeling by familiar adults may be particularly effective when adults show enthusiasm for the food, and when modeling is combined with nonfood rewards. Modeling can also be combined with other forms of food preference learning. For example, Jansen and Tenney (2001) tested the relative efficacy of flavor–nutrient learning and social learning in promoting primary school children's preference for yoghurt. Social learning comprised consumption of yoghurt in the context of two teachers eating their yoghurt while repeatedly praising it for its taste. Jansen and Tenney found that teacher modeling significantly added to the effect of flavor–nutrient learning alone.

10.7 Conclusion and future trends

There are various ways of acquiring a preference for any type of food, but all these techniques share a common factor: repeated exposure. Repeatedly trying a certain food will reduce one's fear of the food, increase its acceptability, and promote a positive shift in preference. Adding nutrients or any other substance that provokes a positive postingestive effect will condition a positive shift in food liking as well. Coaxing a person to try a certain food by means of tangible rewards may also increase acceptance of the food. Importantly, rewards are not the only factor that can motivate

food acceptance. Modeling, vicariously observing important others enjoying certain foods, can increase one's willingness to try these foods and hence grow a liking for it.

The implication here is that there are definite techniques that clearly promote preference, liking, and intake of certain food. Obviously, the food industry already applies these techniques to sell as much of their product as possible. These products are not necessarily healthy foods. It is important to realize that this should not prevent anyone from applying these very same techniques to increase, for example, children's liking for healthier alternatives. As research clearly demonstrates, parents and health professionals can use mere exposure, associative learning techniques, and social modeling to successfully promote acceptance and even a preference for healthy foods. Much of that research was conducted or at the very least inspired by Leann Birch, who passed away in 2019. As Anzman-Frasca et al. (2020, p. 1343) wrote: "Leann Birch was a pioneer in bringing a developmental psychology perspective to the study of children's nutrition as a means to respond to real-world questions raised by parents." Unmistakably, the current chapter attests to that pioneering work. We are fortunate to build on the work of Leann Birch and to extend it for the benefit of future research and—of course—children's health and well-being.

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Relationships between early flavor/texture exposure, and food acceptability and neophobia

11

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11.1 Introduction

Eating behavior is a complex activity which is critical for development and survival. It is essentially learned, in particular during early years (Nicklaus, 2015; Nicklaus and Remy, 2013; Schwartz et al., 2011b). It can be broken down into several components: when, how, what, and how much to eat (Butte et al., 2004; Schwartz et al., 2011b). We will mainly focus here on the influence of early flavor and texture exposure on the development of “what” to eat, or in other words, food preferences and choices, including food neophobia. It is relevant to focus on *early* flavor exposure, because food habits are formed early during childhood under the effect of experience and are likely to track over childhood until the beginning of adulthood (Nicklaus et al., 2004, 2005a).

The present chapter is organized into three main sections. In the first section, an overview of what is known about early flavor exposure and distinguishing between taste and flavor (aromatic) exposure is provided. In the second section, we will describe what has been researched regarding the influence of early flavor and texture exposure on the development of food preference, looking at prenatal exposure, exposure received in the context of milk feeding, and exposure received in the context of complementary feeding. The third section is a description of what has been shown regarding the relationships between early exposure and food neophobia. For further information regarding the mechanisms underlying the learning process described here, the reader may refer to Chapter 10 R. Havermans and E. van den Heuvel.

11.2 Early flavor exposure

Here we briefly describe the types of flavor exposure received by fetuses, infants, and toddlers. Further information about flavor exposure in biological fluids may be found in Chapter 3 by B. Schaal in this book. Whereas it is now more and more widely acknowledged that early exposure to environmental stimulus may alter metabolic functions in the short and in the long run (Bateson et al., 2004), exposure to flavor

has only been recently looked and compared to, for instance, nutritional (Gillman and Ludwig, 2013; Singhal et al., 2001) or other environmental exposure (Prescott, 2010).

Food preferences are learned from experience and experiences likely to shape food preference start very early, in utero. Hence, we will describe here the early flavor exposure starting in utero. Whenever possible, we describe separately exposure to taste compounds from exposure to aromatic compounds, because their sensing pathways are different.

11.2.1 *Flavor exposure in utero*

During fetal life, the fetus is exposed to a fluid the composition of which is evolving according to the metabolic and nutritional status of the mother. In particular, the amniotic fluid flavor properties are likely to be modified by the flavors of the foods consumed by the mother during pregnancy (Schaal, 1988): for instance, the flavor of garlic (Hepper, 1995), of cumin seeds (Spahn et al., 2019), anise (Schaal et al., 2000), and carrot (Mennella et al., 2001) are likely to be transferred to the amniotic fluid. The flavors of undesirable compounds such as alcohol and nicotine are also likely to be present in the amniotic fluid, although in this area, the evidence is indirect in humans or based on animal studies (Bell et al., 2021b).

The amniotic fluid also contains compounds that are likely to impart a taste: mineral salts including sodium which contribute to the salty taste, urea which has a bitter taste, glucose which is sweet, etc. (Schwartz et al., 2009). It is certainly possible that the intensity of these exposures may vary according to the maternal serum concentration and to maternal condition, but very few studies have systematically looked at characterizing the taste and flavor properties of amniotic fluid. Notably, glucose concentration in amniotic fluid appears to be higher in infants carried by mothers with gestational diabetes mellitus than in those carried by healthy mothers (Bell et al., 2021a).

Chemosensory exposure during fetal life becomes especially important when the fetus starts swallowing, i.e., after the sixth month of gestation (Schaal, 1988). The circulation of the amniotic fluid in relation with swallowing makes the renewing of the molecules in contact with the olfactory epithelium and taste buds possible, which enables the emergence of a stimulation.

11.2.2 *Flavor exposure in lacto*

After birth, infants are exposed during several months to a single food, milk, which may come from the breast or be commercially prepared (formula). The breast may be flavored by conspecific odorants (Schaal et al., 2008). Breast milk contains a variety of flavor compounds: acids, alcohols, aldehydes, alkenes, aromatic compounds, esters, heterocyclic compounds, ketones, lactones, terpenes, sulfides (Shimoda et al., 2000; Buettner, 2007; Bingham et al., 2003b; Hausner, 2009). Moreover, in much the same way as amniotic fluid is flavored by the foods consumed by the mother during pregnancy, breast milk may be flavored by the foods consumed by the mother during lactation. Thus, the flavors of breast milk are likely to vary from one feeding episode to another (Mennella, 1995). Moreover, the flavors of breast milk are also likely to vary

within one feeding episode, as fat content of milk is increasing during feeding (Jensen, 1995; Emmett and Rogers, 1997), which may modify the saturation point of the flavor compounds. Several mother's dietary compounds have been identified in breast milk: vanilla (Mennella and Beauchamp, 1996b), carrot (Mennella et al., 2001), garlic (Mennella and Beauchamp, 1991a, 1993), alcohol (Mennella and Beauchamp, 1991b; Mennella, 2001), *D*-carvone (Hausner et al., 2010), nicotine, and caffeine (Geraghty et al., 2015). However, some studies showed that some compounds from herbal tea are not transferred in breast milk (Bakke et al., 2020). Analysis of retrieval of different flavors (3-methylacetate, *l*-menthol, *D*-carvone, *trans*-anethole) in breast milk revealed several facts (Hausner et al., 2009): one compound was not retrieved (3-methylacetate) probably as it was metabolized; for the other compounds, the time of maximal concentration in breast milk peaked at 2 h post-ingestion (*D*-carvone, *trans*-anethole) or plateaued from two to 8 h post ingestion; the concentration in milk was highly variable from one woman to the other, revealing different aptitudes to metabolize these compounds, and suggesting a high variability in exposure from one infant to the other.

The flavors of formula milks may be viewed as more constant; however, they are also likely to differ according to the formula types (Schwartz et al., 2010). Concerning odorants, a comparison of the chromatograms of mother's milk and infant formula revealed that on average, mother's milk contained twice as many volatile compounds than formula (Hausner et al., 2008). Moreover, from a qualitative point of view, both types of milk were rich in lipid-derived volatile compounds; but formulas contained more volatiles related to thermal treatment; and breast milk a higher variety of terpenes. Concerning tastes, different formulas may present different sensory profiles (Mennella et al., 2009; Schwartz et al., 2010): antiallergic formula are prepared with hydrolyzed protein, which have a bitter and sour taste; antidiarrheic formula may contain more salt and thus be saltier than regular formula; **fermented** formula may be sourer than regular ones.

11.2.3 Dietary exposure in complementary foods

11.2.3.1 Flavor exposure in complementary foods

After the initiation of complementary feeding, infants become exposed to a wider variety of foods from different groups (cereals, vegetables, fruits, meat, fish, cheese, cakes, convenience foods, etc.), which increase the diversity of flavor, taste, and texture exposure they receive (Nicklaus, 2011; Nicklaus et al., 2015). Describing the complexity of the flavor exposure infants receive through complementary foods is a challenge because each individual food is composed of several odorant compounds; thus it appears easier to describe the perceived odor of the foods (Wagner et al., 2014). Describing the tastes of the foods infants receive is a first step that some teams initiated, based on sensory profiles of foods undertaken by adult panels (Schwartz et al., 2010; Martin et al., 2014; Viskaal-van Dongen et al., 2012; Bakke et al., 2020). It should be more systematically conducted, in order to enable a better understanding of taste exposure over the first year (Schwartz et al., 2010, 2011a). A case study from the OPALINE cohort in France showed that during the first year,

the exposure to tastes of French infants was dominated by exposure to sweet taste (in relation with the sweet taste of milk, and of a number of foods introduced after the initiation of complementary feeding, such as fruits, sweetened dairy products, or desserts) (Schwartz et al., 2010). Moreover the dietary exposures to sweet taste and to fattiness over the first year were compared (Yuan et al., 2016b). Both sweetness and fattiness exposures increased during the first year, in relation to the introduction of complementary foods into the child's diet, but exposure to sweetness increases more rapidly than exposure to fattiness (Nicklaus et al., 2019). Given the complexity of the flavor world, it seems unrealistic to conduct a systematic analysis of children's dietary flavor exposure; however the focus on some specific flavor components can convey useful insights (Wagner et al., 2019).

11.2.3.2 *Texture exposure in complementary foods*

From birth the infant was only fed with liquid (milk) and the onset of complementary feeding corresponds to the beginning of exposure to (semi-)solid foods. The textures of complementary foods offered by the parents evolve over months, and as function of the child's oral capacities development, supporting the child in the transition toward family foods along the complementary feeding period. As for flavor and taste, characterizing texture exposure during the complementary feedings is a challenging task taking into account the texture diversity of foods (raw fruit and vegetables among others) as well as the different cooking strategies used by the parents to prepare the foods for their infant. In an attempt to evaluate how infants are exposed to food textures, Demonteil et al. (2018) proposed a survey composed of a list of 64 food products commonly fed to infants and for each food different textures, leading to a total of 188 food—texture combinations. A sample of ca. 3000 mothers of children aged between 4 and 36 months and living in France completed the survey to report which combination they already fed their child with. The food—texture combinations were grouped in three texture levels: purees, soft small pieces, and hard/large pieces and double textures. In this sample, children were mainly exposed to purees over the first year. Soft and small pieces were slowly introduced between 6 and 22 months, whereas hard/large pieces were mainly introduced from 13 months onwards. Moreover, in this study, individual factors associated with texture exposure were studied. This showed that parental practices with regard to texture introduction appeared adapted to their child's characteristics: among children of a given age, parents offered a larger texture variety to children who had a more developed dentition and were able to eat alone with their finger or a fork (Demonteil et al., 2018). Parental texture feeding practices were also associated with their other feeding practices: texture exposure was higher in children introduced to complementary feeding earlier, or in those who were offered only homemade/nonspecific (i.e., adults commercial) foods during the second year, but lower in children who were offered only commercial infant foods (Demonteil et al., 2018).

Introducing food texture via spoon-feeding (i.e., starting with purees) is however not necessarily chosen by all parents. Baby-led weaning (BLW) is an alternative method for introducing solids during the complementary feeding period, which has

gained in popularity since ca. 10 years (Wright et al., 2011). BLW infants are directly offered pieces of whole foods from the beginning of complementary feeding on. Solids are offered in a format that infants can pick up alone with their hands. It usually takes place not before 6 months of age given the too limited child hand-mouth coordination before this age, and limited food oral processing capacities. The first offered foods are often fruit and vegetables (Brown and Lee, 2011; Cameron et al., 2012). This method obviously should have an effect on texture exposure during the first months of complementary feeding. However following a baby-led approach is often associated with a later introduction to solid foods (Brown et al., 2017). To the best of our knowledge, the effect of spoon-feeding versus BLW method on infant's exposure to food textures along the complementary feeding period has not been specifically assessed yet.

11.3 Influence of early flavor and texture exposure on the development of food preferences

11.3.1 Influence of in utero flavor exposure on the development of food preferences

The possibility that uterine flavor exposure may impact the future development of food preference and by extension eating behavior implies that the fetus is able to detect the flavors and to memorize them. Several bodies of evidence confirm that the olfactory and taste sensing systems are functional before birth, around the end of the second trimester of gestation for the taste system (Ganchrow and Mennella, 2003) and by the seventh month for the olfactory system (Schaal, 1988; Marlier et al., 2001; Marlier, 2009). For instance, preterm born infants are able to differentiate the odor of vanilla from that of butyric acid and exhibit more negative facial expressions when smelling the odor of butyric acid (Marlier et al., 2001). Moreover, it was shown in preterm newborns that the presentation of a vanilla odor in the incubator is likely to modify premature newborn's physiological state, as attested by the reduction of sleep apnea in presence of vanilla (Marlier et al., 2005).

The fine olfactory capacities of newborns are also attested by studies showing their preference for the odor of amniotic fluid compared to the odor associated with post-natal foods (Marlier et al., 1998). This reveals that even in the young organism, familiarity with a flavor is an important component of the preference/acceptance of this flavor.

The effect of uterine exposure to the flavors of dietary compounds ingested by the mothers during pregnancy was studied at different developmental stages and through different approaches. During the first hours or days after birth, it was shown that newborns exhibit a higher preference for an odor experienced in utero, after the consumption by their mother of foods flavored with this odor, than newborns whose mother had not consumed such an odor during pregnancy: this was observed after the consumption of garlic (Hepper, 1995) and of anise-flavored foods (Schaal et al., 2000). When

infants are presented with some of their first complementary foods, around the age of 6 months, it was shown that those whose mother had consumed carrot juice for 3 weeks at the end of pregnancy exhibited less negative facial reactions when tasting a carrot-juice flavored cereal than a plain cereal compared to those whose mother had not consumed carrot juice (Mennella et al., 2001). When looking at associations between flavor exposure in utero and liking of odor of the food with the same odors at 8 and 12 months, an observational cohort study showed that at the age of 8 months only, positive correlations were found between liking of some unpleasant odors and early exposure to these odors through mother's diet (Wagner et al., 2019). However the same result was not observed regarding pleasant food odors. On a longer run, it was shown that school-aged children (8–9 years) prenatally exposed to garlic ate more garlic-flavored potato gratin than plain potato gratin compared to their peers who had not been prenatally exposed to garlic (Hepper et al., 2013). These studies show that the exposure to a specific flavor compound in utero is associated to behavioral modifications in postnatal life, which has been assessed for compounds/foods bearing a similar flavor. More generally, one may wonder whether “generalized” dietary exposure during this period is likely to affect food acceptance later in life. An analysis in an Australian cohort compared the effect of maternal dietary exposure to fruit and vegetable during pregnancy and in early childhood on children's acceptance of fruit and vegetables revealed that the effect of maternal diet during early childhood was prominent (Ashman et al., 2016). The analysis of data from a French cohort, focusing on maternal vegetable dietary variety during pregnancy also concluded to an absence of effect of maternal variety of vegetable during pregnancy on children's acceptance of vegetables at 2 years (Nicklaus et al., 2014).

Evaluation of the effect of uterine exposure to tastants is generally indirect. It was reported that if mothers had more frequent/stronger vomiting episodes during pregnancy, which is likely to be associated with mineral and sodium loss, the progeny is more likely to have a different behavior toward sodium. For instance, 16-week-old infants exhibit less negative facial expressions when tasting salty water and consumer more of it (Crystal and Berstein, 1998), and adolescents have a higher salt use and consume more salty foods (Crystal and Berstein, 1995). In a similar fashion, early event leading to sodium loss, such as vomiting episodes or diarrhea may lead to an increased preference for the salty taste (Leshem, 1998). As noted above, such effects are relatively persistent over childhood, as they were observed when children are aged from 8 to 15 years (Shirazki et al., 2007); and in teenagers aged 16–20 years (Crystal and Berstein, 1995; Málaga et al., 2005). Animal studies show further that maternal consumption of acesulfame-K (a nonnutritive sweetener) during pregnancy is associated with an increased preference for the sweet taste in the progeny (Zhang et al., 2011).

Animal studies also bring interesting evidence regarding the effect of alcohol and nicotine consumption during pregnancy, which is difficult to assay in humans for ethical reasons. In humans, prenatal alcohol exposure is associated to a decreased ability to identify odors in school-aged children (Bower et al., 2013). Experimental evidence suggests that exposure to alcohol during late uterine life is associated with the development of a preference for alcohol (Abate et al., 2008), in complement of

other unwanted consequences of prenatal alcohol exposure. In a similar way, fetal nicotine exposure may increase preference for nicotine odor in the offspring, but only at early stages of adolescence, not in adults (Bell et al., 2021b).

The mechanisms underlying these changes can only be explored in animals. Prenatal flavor exposure may affect a variety of feeding behaviors and physiological processes (Oostindjer et al., 2009, 2010, 2011), and affect the development of the olfactory bulb (Todrank et al., 2011). As suggested by studies of perinatal odor exposure, it may also affect the development of the olfactory epithelium (Cadiou et al., 2014).

That prenatal exposure to a flavor is associated with postnatal development of a preference for this flavor may be seen as an adaptive mechanism that prepares the developing organism to the postnatal life, in an environment where the flavor cues with biological significance are likely to resemble those present during the developmental course in utero. When the flavor cues are associated with unhealthy substance, the effects of this learning are not adaptive.

Recent reviews expanded knowledge in this area. The first one concluded that, despite cumulating proof of flavor transfer from the maternal diet to amniotic fluid, a systematic conclusion could not be drawn to describe the relationship between mothers' diet during pregnancy and children's overall dietary intake (Spahn et al., 2019). The second review which focused on analyzing the proof of early flavor learning in the case of vegetables concluded that there was emerging evidence regarding learning related to flavor exposure at perinatal stage (Bell et al., 2021b).

11.3.2 Influence of flavor exposure during the milk-feeding period on the development of food preferences

Dietary flavor exposure during the milk-feeding period may originate from breast, breast milk, formula, or other beverages.

The human breast emits odorants (Schaal et al., 2006, 2008) that help guiding the infant toward the nipple and facilitates the transition toward oral feeding after birth (Doucet et al., 2009, 2012; Porter and Winberg, 1999). Even in preterm infants, breast milk odor triggers nonnutritive sucking (Bingham et al., 2003a, 2007), and it attracts infants as demonstrated by cephalic orientation in term born infants (Marlier et al., 1997; Marlier and Schaal, 2005). The breast may also carry flavors from pomades, perfumes, and other cosmetic products. The nursing situation represents a highly positively reinforcing event. It was observed that an odor experienced at the breast becomes more liked by infants than a nonexperienced odor, and equally liked as milk (Delaunay-El Allam et al., 2006). This increased preference for the breast-associated odor was stable when infants were aged between 7 and 21 months (Delaunay-El Allam et al., 2010).

Learning for specific flavor compounds occurs during breastfeeding. Maternal consumption of specifically flavored foods during nursing is associated to higher acceptance of foods bearing similar flavors after the onset of complementary feeding compared to the absence of consumption: this was observed when carrot was

consumed (Mennella et al., 2001), or a caraway-flavored food (Hausner et al., 2010). However, a study with exposure to carrot during nursing showed a lower acceptance of carrot-prepared cereals than of plain cereals just after breastmilk consumption (Mennella and Beauchamp, 1999). More generally, experiences in the breastfeeding context are likely to influence the infant's eating behavior. Compared to formula-fed infants, breastfed infants display a higher acceptance of a new food when acceptance is evaluated during the first days of the complementary feeding period (Jagnow et al., 2000; Maier et al., 2008; Sullivan and Birch, 1994), or within 1 month after the onset of complementary feeding (Hausner et al., 2010). However, this difference is not observed anymore when acceptance of new foods is averaged over a 2-month period (Lange et al., 2013). Moreover, after 10 days of exposure to a flavored food, breastfed and bottle-fed infants do not differ in their acceptance of this food compared to an unflavored version (Hausner et al., 2010). A recent study confirmed that infant exposure to unpleasant food odors, through the maternal consumption during lactation, was associated to a higher liking of odor of the foods with the same odor at 8 but not at 12 months (Wagner et al., 2019). However, as during pregnancy, this phenomenon was not observed regarding pleasant food odors, which may be easier to learn by children.

Beyond exposure to specific flavor compounds, the positive impact of breastfeeding on further food acceptance may be mediated by the *variety* of flavor exposure in the milk context (Mennella et al., 2001; Hausner et al., 2010). This impact may be limited to the very beginning of complementary feeding (Hausner et al., 2010). Flavor learning is also likely to happen in the context of formula feeding. A study evaluated the impact of experience with formula, which was flavored with vanilla during a certain period of time, or with breast milk (Haller et al., 1999). Adults had to express their preference for a plain ketchup or a ketchup flavored with vanilla at a "barely detectable" level. Two-thirds of the formula-fed participants preferred the vanilla-flavored ketchup while two-thirds of the breast-fed participants preferred the plain ketchup. This confirms the flavor learning effect in the milk feeding context and also reveals that such an effect is likely to have long lasting consequence, in this specific case. More generally, as noted in the previous paragraph in the case of uterine flavor transfer, recent reviews suggest that no firm conclusion can be drawn regarding flavor transfer related to mothers' diet during lactation and children's overall dietary intake (Spahn et al., 2019), but, in the case of vegetables the cumulating studies regarding learning related to flavor exposure at lactational stage suggest "emerging evidence" for an effect on vegetable liking (Bell et al., 2021b).

The taste experience in the milk feeding context may also modify further food preferences. The longer the breastfeeding duration, the higher the acceptance of an umami-tasting solution at the age of 6 months (Schwartz et al., 2013), which may be interpreted in relation with the high glutamate content of breast milk compared to formula (Agostoni et al., 2000). Exclusive breastfeeding was also shown to be associated with a lower acceptance of salty cereals compared to plain cereals in 4- to 6-month-old infants, which may be related to the lower sodium content of breast milk compared to formula (Harris et al., 1990). Exposure to hydrolyzed-protein formula, which has stronger bitter, sour, and umami tastes than regular formula is associated

to a higher preference for sour, bitter, or umami cereal at the beginning of complementary feeding (Mennella et al., 2009) and to different taste preference patterns for fruit juices with modified tastes up to the age of 5 years (Mennella and Beauchamp, 2002; Liem and Mennella, 2002). Does exposure to hydrolyzed protein formula impact acceptance of bitter foods? Infants aged 5–11 months previously exposed to hydrolyzed protein formula reject more a broccoli/cauliflower puree than infants fed with a regular formula (Mennella et al., 2006), but at 4–5 years mothers report that exposed children liked it better than those who consumed regular formula (Mennella and Beauchamp, 2002). Furthermore, it was demonstrated that hydrolyzed protein formula may be preferentially accepted only during a certain time window. It is easily accepted at the age of 2 months but not at the age of 7 months (Mennella and Beauchamp, 1996a), except if at this age the infant had received previous exposure to such a formula type (Mennella et al., 2004). Moreover, the earlier the exposure to hydrolyzed protein formula and longer the exposure, the higher its acceptance (Mennella et al., 2011). In other respect, it was observed that infants exposed to sugar water during the milk feeding period had a higher preference for the sweet taste in water at 6 months and at 24 months (Beauchamp and Moran, 1982, 1984), but this effect was not generalized to other sweet beverages.

Epidemiological studies complement the above-reported experimental observations related to the effect of the type of milk feeding by revealing the association between breastfeeding practices and dietary habits at a later age. Breastfeeding duration is positively associated to food variety later: it is associated to a variety of free food choices by 2- to 3-year-old children (Nicklaus et al., 2005b), to healthy eating habits at 2 years (Abraham et al., 2012), to food variety at 2 years (Scott et al., 2012), to fruit consumption at 6–8 years (Skinner et al., 2002a), and to a healthy eating pattern (consumption of meat, fruits, and vegetables) at 2–8 years (Grieger et al., 2011). A longer breastfeeding duration was consistently related to higher fruit and vegetable intake in 2–4-year-old children when taking into account data from four different European cohorts (de Lauzon-Guillain et al., 2013). Exclusive breastfeeding for at least 3 months is associated with a higher consumption of vegetables at 4 years (Burnier et al., 2011). These effects may be partly mediated by the exposure to a more varied flavor profile in the context of breastfeeding compared to formula feeding; however, it does not preclude the possibility for other factors to be involved in this phenomenon. For instance, breastfeeding could be associated to a better development of oral abilities that may help the transition to solid foods (Nicklaus et al., 2015), and it may be associated to different maternal attitudes regarding child feeding (Taveras et al., 2004, 2006).

11.3.3 Influence of dietary exposure at the onset of complementary feeding on the development of food preferences

11.3.3.1 Flavor exposure at the onset of complementary feeding

Introduction to complementary foods is a process which corresponds to the transition between a single food such as milk, toward a diversity of family foods. At the age

when complementary feeding is recommended to be conducted, around 6 months (WHO, 2003), the infant displays limited physiological capacities (i.e., intestinal maturity, renal functions and oral function development), and therefore family foods need to be adapted. They are adapted in terms of nutritional content (The Commission of the European Communities, 2006). They are also often adapted in terms of texture and are initially offered in the form of purées or soup, because of the limited oral skills of the infant (Nicklaus et al., 2015).

The sensory properties of complementary foods may partly determine their acceptance, as will be described here. Moreover, several factors related to flavor exposure are now known to be involved in the acceptance of foods at complementary feeding, in particular factors likely to determine the flavor exposure infants receive, such as repeated exposure, and variety of foods offered.

11.3.3.1.1 Flavor acceptance at the onset of complementary feeding

The analysis of the acceptance of all new foods offered to a sample of French infants at the beginning of complementary feeding showed that most foods (90%) were accepted, with a slightly lower acceptance of vegetables and fruits (Lange et al., 2013). A more detailed analysis of the tastes of complementary foods offered between 5 and 7 months showed that reactions to new vegetables were more positive if the vegetable was salted or contained a salty ingredient (Schwartz et al., 2011a). That salt may trigger a higher food intake was also observed in toddlers (Bouhlal et al., 2011). Dietary exposure to sodium in complementary foods was shown to be associated with a higher acceptance of salty taste in preschoolers (Stein et al., 2012).

The contribution of flavor as a whole to the initial acceptance of vegetables can be interpreted by comparing the effect of exposure to a variety of vegetables on the acceptance of carrot (Gerrish and Mennella, 2001) or of green beans (Mennella et al., 2008). Acceptance of green bean appears more difficult to promote than that of carrot, no doubt in part due to the difference in tastes of the two vegetables with one being sweeter than the other. Moreover, a study showed that the acceptance of green beans is easier to enhance than the acceptance of artichoke (Barends et al., 2013).

Individual differences in reactivity to tastes may explain differential acceptance of new foods at the beginning of complementary feeding (Schwartz et al., 2011a): at the age of 6 months, infants who accepted more easily the sour, umami, and sweet tastes in water solutions also displayed more positive reactions toward sour-, umami- and sweet-tasting complementary foods, respectively. In a similar fashion, individual differences in reactivity to food odors were shown to explain differences in reactions toward new foods (Wagner et al., 2013, 2014): at the age of 12 months, the more toddlers liked the odor of trimethylamine (fish odor), the more their parents reported they liked fish; and the more they liked the odor of dimethyl disulfide (sulfurous odor of some cheeses and of some vegetables), the more their parents reported they liked cheese with a sulfurous flavor note (e.g., camembert, Munster, Epoisses) and the more they tend to like vegetables with a sulfurous flavor note (e.g., broccoli, cabbage, cauliflower, Brussels sprouts, leek).

11.3.3.1.2 Role of repeated exposures

The repetition of exposures to a food is one of the primary determinants of its acceptance beyond the initial reaction the food may trigger. Several studies have shown that a food is consumed more and is judged by an adult (generally the mother) as more liked by the infant after several offers. The first study related to the effect of exposures in infants at the beginning of complementary feeding clearly demonstrated an increase in acceptance of a new green vegetable after 10 exposures (Sullivan and Birch, 1994). A further study also showed a similar exposure effect: after eight exposures to a new fruit or vegetable, intake increased (Birch et al., 1998). The effect of repeated exposures was potent enough to increase the acceptance of foods which had been previously identified by the mother as being refused by her infant at the beginning of the complementary feeding process, which were most often green vegetables, but also pumpkin (Maier et al., 2007).

Repeated exposure to foods with an added flavor may help increasing their acceptance even in a plain version, if the flavor is liked: this is described as flavor–flavor learning. In infants, at the start of the complementary feeding period, repeated exposures were shown to be as effective as associating a new vegetable with a liked flavor (the sweet taste) to increase its intake (Forestell and Mennella, 2007; Remy et al., 2013); whereas associating it with a higher energy content (by adding oil) did not increase its intake, probably through learned satiation (Remy et al., 2013). In older children (1–3 years), the same effects were observed; but the effect of learning was attenuated compared to that in infants (Caton et al., 2014). In toddlers aged 2–3 years, repeated exposure to a new vegetable, salsify, with a pinch of salt (0.2% w/w NaCl) led to a higher increase in salsify intake than flavor–flavor learning with a higher salt content (0.5% w/w NaCl) or with nutmeg flavor (Bouhlal et al., 2014). In toddlers aged from 1.5 to 4 years, a significant increase in intake was observed after seven exposures to vegetable crisps offered with a liked dip (flavor–flavor learning) or with a neutral dip (simple repeated strategy) (de Wild et al., 2015). Description of the effects of repeated exposure and of flavor–flavor learning beyond the complementary feeding period can be found elsewhere (Issanchou and Nicklaus, 2015). In a recent umbrella review about factors influencing vegetable liking in children up to the age of 5 years, repeated exposure to vegetables at complementary feeding was one of the two feeding strategies for which the cumulating evidence was considered “promising” (Bell et al., 2021b).

11.3.3.1.3 Role of the variety of foods offered

As described previously, repeated offerings of a given food may enhance its acceptance. Moreover, repeated offerings of a variety of foods may also promote the acceptance of an unknown food. Infants aged ~6 months were shown to better accept carrot, a new food, either if they had been repeatedly exposed to carrot (repeated exposure effect) or to a variety of foods differing from 1 day to the next, but not if they had been repeatedly exposed to potato (Gerrish and Mennella, 2001). Moreover, infants in the variety group better accepted chicken than children in the two other groups. Further studies showed that this “exposure to food variety” effect might enhance the

acceptance of a less liked food than carrot, such as green bean, only if the exposure to variety is higher than the variety necessary to increase acceptance of carrot (Mennella et al., 2008). Green bean acceptance increased only if, in the variety condition, pairs of different foods were presented over several days, not if different foods were presented over several days (Mennella et al., 2008). This suggests that exposure to variety might be interpreted at the day level or at the meal level. A practical consequence of this observation is that introducing more than one food per eating occasion (i.e., more flavor variety) might be a way to enhance exposure to flavor variety, and therefore acceptance of new foods.

The role of timing of exposure to flavor variety was explored. A study revealed that offering three different foods three times by alternating foods from 1 day to the next resulted in a higher acceptance of new foods than offering each of the three different foods for a period of 3 days (Maier et al., 2008). This effect was observed for several new foods (zucchini-tomato, peas, meat, and fish). Furthermore, it was suggested that the efficiency of the exposure to variety effect may depend on the infant age at the beginning of complementary feeding (Coulthard et al., 2014). This study showed that among children introduced to complementary foods after 5.5 months, the acceptance of a new food, pea, was higher in infants previously exposed to a variety of foods (and thus of flavors) than in infants previously exposed to a single food (but there was no difference between exposure groups when infants were weaned before 5.5 months). Altogether, these findings suggest that exposure to “flavor” variety is a robust mechanism favoring the acceptance of new foods.

A randomized controlled trial conducted in UK, Greece, and Portugal specifically investigated whether exposure to a variety of vegetables early in the complementary feeding process would prevent the observed decline in liking and intake of vegetables at a later age (Fildes et al., 2015). Parents of 4–6-month-old infants were randomized to receive shortly before the start of complementary feeding either (i) guidance on introducing a variety of culturally appropriate vegetables as first complementary foods or (ii) usual care. Infants in the intervention groups showed increased consumption and liking of an unfamiliar vegetable in the short term, but only in countries where single vegetables are not already amongst the common first foods offered to infants (UK and Greece). Beneficial effects of the intervention were not maintained at the 6- or 9-month follow-up, although results from the Greek sample suggest that there may be a positive effect of the intervention on vegetable variety and general vegetable acceptance.

In a recent umbrella review about factors influencing vegetable liking in children up to the age of 5 years, exposure to a variety of vegetables at the onset of complementary feeding was the second feeding strategy for which the cumulating evidence was considered “promising” (Bell et al., 2021b).

11.3.3.2 Influence of texture exposure on development of food preference

11.3.3.2.1 The role of feeding skills development on food acceptance

Infancy is a period of rapid growth and of important physiological developments. Among those, children feeding skills undergo important developments relying on

the anatomical, physiological, and functional development of the masticatory function (for an in-depth description on the development of the masticatory function in early childhood, refer to [Le Reverend et al. \(2014\)](#) and [Nicklaus et al. \(2015\)](#)). At a given age, infant's feeding skills determine their ability to cope with textured foods and thus their acceptance of these foods. Children prefer textures that are easily eaten (infants and toddlers prefer pureed foods to food with more complex texture ([Blossfeld et al., 2007](#); [Lundy et al., 1998](#)) and food textures are particularly rejected when they are difficult to process in the mouth. But eating skills develop with age after the introduction of foods other than (breast) milk into the diet, during the complementary feeding period: as they grow up children become more and more efficient in eating textured foods and the time necessary to chew a standardized piece of food decreases with age ([Gisel, 1991](#)). Chewing efficiency was also demonstrated by the measurement of infant's ability to break down a model gel via oral processing ([Tournier et al., 2019](#)). One study tracked infant texture acceptance alongside oral development between 6 and 18 months ([Demonteil et al., 2019](#)). Acceptance was defined as the child being able to swallow the food. This study demonstrated a transition between sucking and chewing behaviors during the first months of complementary feeding, chewing behaviors emerging at approximately 8 months and being well established by 10 months, coinciding with the acceptance (ability to eat and swallow) of harder and more complex textures. Texture acceptance continued to develop up to 18 months. Raw vegetable pieces and pasta were accepted by more than 50% of the children at the age of 18 months ([Demonteil et al., 2019](#)).

11.3.3.2.2 Role of texture exposure on food acceptance

As for flavor, exposure to food texture during complementary feeding plays a key role in the development of oral feeding skills and thus food acceptance by infants. Providing textured food to children is necessary for them to learn the movement patterns necessary to process (solid) foods, such as lateral tongue moving motions in the oral cavity, crushing movements between the jaws, as well as providing the muscular loading necessary for the development of masticatory apparatus (bones and muscles) and the supportive neural circuitry ([Harris and Mason, 2017](#); [Nicklaus et al., 2015](#)). As a consequence, the higher children are exposed to a variety of food textures, the higher their ability to eat them and the higher their acceptance of complex textures ([Blossfeld et al., 2007](#); [Lundy et al., 1998](#); [Tournier et al., 2021a, 2021b](#)). Another benefit for exposure to more complex textures should be underlined. Processing of solids in the oral cavity plays a role in the desensitization of children's inner sides of the cheeks and the back of the tongue. Conversely, lack of texture exposure could result in inadequate oral lateral movements when eating foods, potentially inducing eating difficulties and tactile hypersensitivity which may both drive to aversions in children ([Harris and Mason, 2017](#)).

Two aspects of texture exposure are likely to be important for optimal acceptance of foods: the timing of texture introduction ("when") and the type/the variety of food textures offered to the child ("what").

Concerning the "when" a longitudinal study conducted in the UK reported that children who received lumpy foods after the age of 9 months had more feeding difficulties,

were fussier, and ate less family foods than children who were introduced to lumpy foods earlier than the age of 9 months (Northstone et al., 2001). At the age of 7 years, they consumed less of key food groups from a nutritional perspective such as fruits and vegetables (Coulthard et al., 2009). These long-term feeding problems associated with late introduction to lumpy foods are a matter of concern. Based on this scientific evidence, the current recommendations of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition is to discourage the prolonged use of pureed foods and to offer lumpy foods by 8–10 months at the latest (Fewtrell et al., 2017).

To study the “what,” the predictors of food texture acceptance in children aged between 4 and 36 months old were researched in a French survey (Tournier et al., 2021b). Acceptance was evaluated by mothers as their child’s ability to eat a food they had already offered to their child (among the list of 188 food–texture combinations possible). Food texture introduction was the main factor associated with food acceptance. Among children of a given age range, those having the higher acceptance score were those who had been provided with the opportunity to experience a large variety of foods as pieces or double texture. In another study familiarity with different textures predicted interindividual variability observed among 12-month-old infants regarding the willingness to eat chopped carrots (Blossfeld et al., 2007). Altogether, even if the role of exposure to texture has been less studied than the role of exposure to flavors, the facilitating effect of a repeated and varied exposure to flavor at the beginning of complementary feeding to promote food acceptance also seems to apply to food texture (Bell et al., 2021b). Thus, a timely and frequent introduction of complementary foods differing both in flavors and in textures is a necessary step to develop food acceptance.

11.3.3.2.3 Effect of introduction of food texture during complementary feeding on food acceptance: learnings from intervention studies

Contrary to studies focused on flavor and taste exposure, intervention studies to understand the effect of texture exposure has been poorly addressed except until very recently. Da Costa et al. evaluated the effect of the textural properties of commercially available baby foods on the development of chewing ability in a pilot intervention (da Costa et al., 2017). Two groups of 8-month-old infants were exposed (4-week exposure, in-home setting) to commercially available savory meals and fruits. One group (group 1) received products with few, small and soft pieces, the other group (group 2) received products with more, larger and harder pieces. After the exposure intervention period, infants were given test foods: cooked carrot, cooked potato, and banana in pieces and in a freshly mashed format. Infants from group 2 had higher chewing capability scores for the carrot and potato pieces but neither for banana piece nor for mashed foods than infants from group 1.

Another study was run in France where texture introduction was not a topic very much highlighted in national guidelines on complementary feeding so far. It aimed at testing the effect of providing detailed advice, compared to usual care, promoting the introduction of textured foods between 8 and 15 months on parental practices of

use of textured foods and the effect of such practices on children's acceptance for a variety of textured foods (Tournier et al., 2021a). The intervention consisted of advice and tips on the why and how to introduce textured food, provided in the form of a 32-page booklet, monthly counseling via phone calls by a dietician, and two baskets containing food preparation utensils and commercial textured foods; it was delivered in the intervention group ($n = 30$). The control group ($n = 30$) received general current information on healthy eating provided by the food guides of the relevant health authority (Program National Nutrition Santé), phone calls collecting general information, and two baskets containing baby gifts. Providing information was effective in promoting the introduction of small and soft food pieces, but not hard pieces and double texture, which certainly are the most challenging textures. Food acceptance assessed in the laboratory was relatively equal in both groups. However, children who better accepted textured foods were those whose parents reported a most varied food texture introduction, confirming the positive effect of exposure to a variety of food textures on acceptance (Tournier et al., 2021a). Another randomized control trial examined children eating behavior at the age of 12 months for infants weaned using traditional spoon-feeding or Baby-Led Introduction to Solids (BLISS). Authors reported that infants who followed a baby-led approach were described by their mothers as less likely to be fussy eaters and more likely to enjoy food (Taylor et al., 2017). To the best of our knowledge, the role of baby-led weaning on the development of food texture acceptance by children has not been specifically studied.

11.4 Relationships between flavor exposure, texture exposure, food preferences and neophobia

As children grow older, they may develop a neophobic phase when they start to refuse foods even if they previously enjoyed them (Dovey et al., 2008b; Nicklaus, 2009). The food neophobia and pickiness phase is associated with consequences on children's food choice. The variety of free food choices decreases between 2 and 3 years old (Nicklaus et al., 2005b). The diversity of intake lowers between 2 and 5 years old (Cox et al., 1997) and picky children have a less varied diet (Carruth et al., 1998; Falciglia et al., 2000). Between the ages of 2 and 9 years, neophobic children eat less fruit and especially less vegetables (Jacobi et al., 2003; Cooke et al., 2003; Galloway et al., 2003, 2005). Follow-ups in birth cohorts show that children with eating difficulties (poor eating, food refusal, unable to get into a routine), as described by their parents at 2 years, were likely to have lower fruit and vegetable intake, as well as a lower variety score at 3–5 years than those with no difficulty. This suggests that the presence of eating difficulties could be an early indicator of a worse dietary profile later in life (de Lauzon-Guillain et al., 2014). Moreover, picky eaters were twice more likely to be underweight at 4.5 years than children who had never been picky (Dubois et al., 2007). However, there is not systematic link between food neophobia and weight status, as stated in different literature syntheses (Brown et al., 2016; Nicklaus and Monnery-Paris, 2018).

Could food neophobia be prevented by early flavor exposure? First, one has to consider whether food neophobia is associated with sensitivity to flavors. In a study where taste and olfactory sensitivities were reported by the parents thanks to a questionnaire, a higher “taste/smell sensitivity” was associated with lower fruit and vegetable consumption, lower variety of liked fruits and vegetables, and higher food neophobia in 2–5-year-old children (Coulthard and Blissett, 2009). The relationship between food neophobia and intake of plant-based foods may be partly mediated by sensitivity to the bitterness of PROP, at least in boys (Tsuji et al., 2012). Assessing smell and taste differential reactivity in toddlers (i.e., reactivity toward several stimuli) using experimental behavioral measurements as well as food neophobia with a questionnaire enabled to show that food neophobia scores were modestly but significantly positively correlated with smell differential reactivity but not with taste differential reactivity (Monnery-Patris et al., 2015). This suggests that foods that do not “smell right” to food neophobic children may be initially rejected based on olfactory cues alone. This confirms that the olfactory system warns children about potentially dangerous foods that may be toxic or are unknown.

Evaluating the effect of “overall” flavor exposure on food preferences and food neophobia is relatively challenging, since characterizing overall exposure in terms of odors or tastes is not easy to systematize, as noted earlier. On the one hand, some studies have shown the stability of food preferences from the early years on until later in childhood (Nicklaus et al., 2004, 2005a; Skinner et al., 2002a, 2002b; Nicklaus and Remy, 2013). On the other hand, some studies have tried to evaluate the impact of feeding experience after the introduction of complementary foods on later preferences (Hetherington et al., 2015; Yuan et al., 2016a). The first study evaluated the effect of a progressive introduction of flavor variety in the infant diet, first in milk, then in cereals (Hetherington et al., 2015). Infants who received a variety of flavors in milk then in rice cereal liked and ate the target vegetable purees more than infants with regular care immediately after the intervention; but the effect was not sustained at the 6-month and 18-month follow-ups, providing evidence of a short-term effect of flavor exposure. In the second study, liking of 5-year-old children for several food categories (“fruit and vegetables,” “meat, fish and eggs,” desserts, and cheese) was evaluated by direct interview of the children (Yuan et al., 2016a). Structural modeling showed that food neophobia at 4 years predicted liking for all food groups; but infant feeding experience during the first year was not systematically associated with children’s liking: it was only observed for the meat/fish/eggs group. Further research is clearly needed to clarify and systematize the analysis of early flavor exposure on the establishment of sustainable healthy eating habits.

As for flavor, texture plays a role in food refusal and pickiness. In 32- to 48-month-old children, this is still true: intake of a strawberry-raspberry yogurt containing raspberry pieces was significantly lower than of a yogurt without pieces (Werthmann et al., 2015). Texture refusal along with food neophobia and eating only selected favorite foods underpin food refusal in picky eaters (van der Horst et al., 2016). Children’s sensitivity to tactile sensation might play a role in the rejection of food (Nederkoorn et al., 2015; Harris and Mason, 2017). Infant’s early reactions to a vegetable were found to be associated with tactile overresponsivity (Coulthard et al., 2016). In this

line, tactile defensiveness is playing a role in food rejection (Dovey et al., 2008a). Using questionnaires on eating habits, differences between tactile, defensive and nontactile defensive in 3–10 years children were reported (Smith et al., 2005): tactile, defensive children had fair to poor appetite, hesitated to eat unfamiliar foods, and had a problem eating vegetables, among others. How to introduce food texture in these children requires further investigation.

To conclude, providing children with the opportunity to experience a large variety of food textures during the first months of complementary feeding (especially after the age of 8 months) is the only way to help them correctly develop their chewing skills and accept textured foods before the onset of food neophobia by the end of the second year. Therefore, some authors considered that this period is a “critical period” for the introduction of textures and for the development of oral motor function (Harris and Mason, 2017). However, food neophobia goes beyond the refusal of food textures and more largely relates to the degree of familiarity of the child with the food, and can be managed by other means than texture adaptations (Nicklaus and Monnery-Patris, 2018).

11.5 Conclusions

As described, children are exposed to a variety of flavors during their uterine and post-natal life, and as their chemosensory senses become functional, these exposures are likely to further modify their flavor and food preferences. Altogether, the familiarity with a flavor appears as critical for the acceptance of foods bearing this flavor, and most likely, the earlier the flavor exposure, the higher the acceptance of this flavor. However, several of the studies showing an effect of early flavor exposure also suggest that this learning phenomenon is relatively specific to each flavor/taste. In some instances, it appears conceivable that the effect of flavor exposure may generalize to new flavor/food even in the absence of a specific exposure, as in the case of flavor exposure through breastfeeding, but there are still a lot of aspects to understand more deeply in this area. How sustainable are flavor learning effects related to exposure at different early stages? Are there specific periods when flavor exposure is more likely to produce sustainable effects on food preference? May early flavor exposure (in the absence of exposure to the food) be sufficient to reduce food neophobia, and if yes, what would it take (is it necessary to expose to food flavors? How early and varied should flavor exposure be)? Are taste exposures more impactful on food preferences than flavor exposures? How to convince parents to modify their feeding practices in order to promote a variety of flavor exposures? The future of research in this area is likely to bring interesting insight to these questions.

Contrary to flavor acceptance for which the sensory systems (taste and olfaction) are functional at birth, texture acceptance is based on the progressive development of feeding skills. The effect of exposure to food textures acts both on the physiological and functional development of the chewing skills as well as on the desensitization of the mouth. Most children are refusing foods that are (too) difficult to eat, especially at

the first occurrence. The first year (and more specifically the period before the age of 10 months) is a critical period for exposing children to food textures and enlarging their food repertoire. Parental feeding practices should support this development by repeatedly exposing children to foods with more and more complex textures. There are large variations in the progression of child's chewing skills, and texture introduction may require a more responsive approach to feeding from parents to adapt their practices to their child evolving skills.

Having a conjoint look to the development of food flavor and texture acceptance may also help to gain insight into what is the ideal feeding scheme at the time of complementary feeding to promote the acceptance of healthy foods such as fruit and vegetables, the consumption of which is harder to promote at later stages of development.

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Sensory influences on food choice and energy intake: recent developments and future directions

12

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12.1 Introduction: the role of sensory cues in food choice and intake

People select and consume more of their energy from the foods they like, and tend to avoid foods they dislike. Food liking is largely determined by the physical and chemical properties that are sensed by a number of independent and integrated sensory systems. Vision and olfaction are distal senses that are primarily involved in the location of food sources, guiding choice in the anticipation of food intake, and stimulating sensory-specific appetites. The proximal senses of audition, taste, retronasal olfaction, touch (texture), and trigeminal stimulation are activated during food consumption, and form an important connection between what is experienced during the meal (satiation) and the postingestive feeling of satisfaction derived in response to the integrated sensory experience (satiety) (Forde, 2018b). The brain integrates these sensory signals into a single but dynamic sensory perceptual impression that determines liking, and guides food and beverage choice and intake behavior (Forde, 2016).

Food consumption does not occur in a vacuum, and previous research has highlighted that in addition to sensory perception, consumers anticipate the consequences of ingestion in the wider context of their goals, motivations and attitudes toward the role of food in good nutrition and health (Rozin and Vollmecke, 1986). Beyond perception and motivation, consumption norms, meal context, and the perceived appropriateness of the food in the specific consumption context are also considered, such as eating turkey at Thanksgiving/Christmas (Al-Swidi et al., 2014). Although these cognitive top-down effects may impact choice and intake, sensory signals form the biological basis for ingestive behavior and are the focus of the current chapter.

The sensory signals from foods and beverage are operational before, during, and just after eating and drinking (Blundell et al., 2010). Sensory cues occur early before and during consumption before endocrine and visceral changes, and exert most influence on intake to fullness (satiation), with less influence on postingestive experiences of fullness (satiety) (De Graaf et al., 1999). We learn to associate the postingestive

feelings of fullness and satisfaction with the sensory cues experienced during food intake (Yeomans, 2006). This process of flavor consequence learning means we develop the ability to estimate the postingestive consequences that come from consuming specific foods and drinks and this informs our expectations of fullness and the amount of calories (portion) we choose to consume (i.e., portion size) (Forde et al., 2015). These perceptions guide our daily food choices and appropriate portion size selections, ultimately resulting in habitual meal and dietary patterns that form the basis for healthy or unhealthy eating patterns (Brunstrom, 2007).

A higher palatability (liking) of a certain food leads to an increased likelihood of selection of that food among alternatives within the same category (De Graaf et al., 2005). Food producers optimize their products' sensory appeal to enhance liking to win greater share of the market. Liking has been shown to increase acute intake (Yeomans et al., 2001; Yeomans, 1998), and although this relationship is initially linear, it plateaus and becomes attenuated such that food intake does not continue to increase linearly at high levels of liking (De Graaf et al., 2005). This highlights that in a world dominated by highly palatable foods, the usefulness of palatability in explaining large variations in dietary energy intake in the real world may be somewhat limited, and other aspects of a food's sensory properties are likely to contribute to observed variations in intake.

The current chapter provides an update on what is known about the role of sensory cues in driving choice and intake behavior. We begin by discussing the role of each sense modality in food choice and intake, focusing on odor, taste, and texture. Recent years have seen progress in our understanding of the role of the senses in ingestive behavior and nutrition, beyond their impact on palatability (McCrickerd and Forde, 2016), and extended this to understand dietary patterns of intake within a food environment and population. A perspective on progress has been made in understanding how sensory cues influence our dietary patterns, and offers directions for future application of sensory science in supporting healthy and sustainable diets.

12.2 Impact of food odor on food choice and intake

Odor detection is important for food choice and intake, and plays an important role in the detection of danger, irritation (e.g., smoke, household gas, industrial and/or agricultural pollution), and social interactions (Boesveldt and de Graaf, 2017). There are a wide diversity among odor qualities and combinations, and we integrate this complexity into a single holistic impression such that our primary response to odors is emotional (valence; like vs. dislike). Odor associations are flexible, and may depend on culture and experience, through which odors acquire their meaning and their association with certain foods/objects (Marty et al., 2017). Odors can often acquire their meanings through how they are labeled, and previous research has shown that the hedonic valence of an odor mixture can change from liked to disliked when labeled as either "vomit" or "parmesan cheese" (Herz and von Clef, 2001). This is also seen in brain responses to the same or similar odors that are labeled differently (De Araujo et al., 2005).

Olfaction is a distal sense, and volatile compounds detected remotely can exert an influence on appetite, food choice, and intake through orthonasal *odor* detection (“sniffing” odor) and during consumption via retronasal (*aroma*) perception. Orthonasal *odor* perception provides remote access to information from the food environment through peripheral odor receptors and is mainly involved in the anticipation of consumption, stimulating a desire for specific food choice and intake. Retronasal odor perception is when volatile compounds are released during mastication and after swallowing and combine with a foods’ taste and texture information to produce the overall perceived flavor. Orthonasal and retronasal odors are perceived differently and have different responses in the central nervous system, and therefore they also have a different role in eating behavior.

12.2.1 Ambient odors perceived orthonasally; effect on appetite, choice, and intake

Most people recognize that when they are hungry and smell a particular food, it tends to prime you to the pleasure of consuming that food. Early studies that demonstrate the appetizing effect of ambient odors conducted by [Fedoroff et al. \(1997, 2003\)](#) and later studies ([Ferriday and Brunstrom, 2008](#); [Ramaekers et al., 2014a](#)) confirmed that specific odors (e.g., pizza or cookies) enhance appetites for odor-cued food. Further studies of sensory-specific appetites showed that specific appetites generalize to some extent to similar foods within the same or similar sensory and nutritional properties. For example, banana odor induces a higher appetite for bananas but also the appetite for sweet tasting foods, whereas it suppresses the appetite for savory tasting foods. By contrast, the savory odor of meat enhances the appetite for meat, increases the appetite for other savory foods, but suppresses the appetite for something sweet ([Ramaekers et al., 2014a,b](#)). Sensory-specific appetites also generalize across categories of foods with either a low or high energy density ([Proserpio et al., 2017](#)). This aligns with the evidence showing that humans have better spatial memory for odors that signal the presence of higher energy foods, compared to low energy-density foods ([de Vries et al., 2020](#)).

The role of ambient odors on actual food choice and intake is somewhat less clear compared to the effect on sensory-specific appetites. Studies that investigate the effect of food odor on food choice have exposed subjects to low intensities of unattended odors of different sources to compare the impact on subsequent food choice. In one such study, a lemon odor was presented in a waiting room and participants were later asked to choose foods from a menu ([Gaillet et al., 2013](#)). Exposure to lemon odor was associated with subjects choosing a starter with vegetables; however, there were not more choices for fruits and vegetables at the main menu and/or dessert. In a follow-up study, subjects were exposed to a pear odor which was associated with a higher frequency of selecting a dessert with fruits, but not with vegetables and/or fruits with starters or main menu ([Gaillet-Torrent et al., 2014](#)). This was confirmed in a larger study where over 100 participants were again presented with an unattended pear odor which was associated with a higher frequency of selecting a dessert containing

fruit from a buffet style lunch, whereas control subjects were more likely to choose a brownie (Gaillet-Torrent et al., 2014). A subsequent study exposed a group of 45 non-obese children and 29 children with obesity to no-odor, a fruity odor, or a fatty-sweet odor and observed the impact on food choice among children (Marty et al., 2017). Priming children with obesity with a fruit odor led to an increase in subsequent choices for fruit; however, among the normal weight group, odor exposure led to a decrease in choice for specific foods. Extensive follow-up studies on the effect of consciously attended and unattended odors on food choice and intake failed to find an effect of exposure on actual choice (Morquecho-Campos et al., 2020), suggesting these effects are inconsistent and often rely on the specificity of the food odor quality, its perceptual intensity, and the nature of the food choice task.

Taken together these results suggest that the impact of ambient odor exposure on actual food choice and intake is mixed and are likely contingent on many factors. Whereas effects on sensory-specific appetites and food choice are somewhat consistent, there is less evidence to support an effect of odor exposure on food intake. Early studies showed that food cue odor exposure had a larger effect on food choice among restrained eaters rather than unrestrained eaters following (specific) food odor exposure (Fedoroff et al., 1997, 2003). Similarly, subsequent studies have shown small increase in “chocolate rice” intake after being exposed to a chocolate odor, but not after exposure to other odors (Proserpio et al., 2017). A later study observed that women with obesity tended to eat more soup after being exposed to bread odor, than in an “unscented” condition (Proserpio et al., 2019). The potential application is to apply odors to guide choice and stimulate specific appetites, and this could be a cost-effective approach to stimulate and encourage food intake among populations that are vulnerable or at risk of malnutrition. When patients with Alzheimer disease were exposed to ambient meat odors before a lunchtime meal on two occasions, there was a positive effect of the ambient odor exposure on meal consumption in the first, but not the second meal (Sulmont-Rossé et al., 2018). Studies have also tried to stimulate macronutrient specific appetites and link to intake by exposing participants to odors representing various macronutrient sources (carbohydrates, protein, fat) and tastes (sweet, savory), but this has failed to influence subsequent intake (Morquecho-Campos et al., 2019, 2020).

Retronasal aroma release and perception during consumption has a significant impact on flavor perception and consumers appreciation for a food’s sensory appeal. When suffering from a cold the retronasal aroma is blocked and people often complain that food has “no taste,” highlighting the important role of aroma in flavor perception and hedonic appeal. Similarly, people suffering from anosmia often express lower food enjoyment during consumption than those with normal smell function (Boesveldt and de Graaf, 2017). In this way retronasal aroma perception can play an important role in food liking and can have a positive impact on intake. However, studies have also explored the potential of retronasal aroma perception to influence eating behavior during a meal and stimulate an earlier onset of satiation, thus reducing energy intake (Ruijschop et al., 2008a). Studies have carefully manipulated the delivery of retronasal aromas to independently influence perceived intensity from that released from the consumed food itself. Initial results from these studies suggested that the duration

and intensity of retronasal aroma stimulation could influence the onset of satiation, with small effects of retronasal aroma on subjective ratings of appetite or ad libitum food intake (Ruijschop et al., 2008a,b, 2009a,b,c, 2010). The potential application of adding low energy volatile odors to a food to help moderate intake is an attractive proposition, yet the overall effect-size and reproducibility of their impact on intake is disappointing. Later attempts to replicate the effect of odor stimulation on food intake confirm that this is unlikely to be an effective approach to reducing energy consumed in a realistic meal, and that odor stimulation is more likely to influence the initiation of food intake, than its termination at the end of a meal (Boesveldt and de Graaf, 2017).

Whereas ambient odors seem to have a reproducible effect of stimulating sensory-specific appetites, the effects on food choice and intake have been more difficult to replicate, and may depend on a range of individual and food-related conditions. For example, the efficacy of this approach is likely to be influenced by the properties of the person such as age, gender, weight status, degree of restrained eating, acute hunger status, whereas the perceptual conditions, such as the odor duration, intensity, and quality and whether or not it is consciously perceived are all likely to influence choice behavior. The public health nutrition potential of odor stimulation has yet to be fully realized, and it remains unclear whether priming appetites and choice for healthier food items using unattended ambient odor may be used to positively impact eating behavior in a real-life eating situation.

12.2.2 Odor perception and body weight

There has been increased interest in the relationship between odor sensitivity and weight status, with the suggestion that deficits in perceptual acuity may be linked with higher food intake and body weight. A recent systematic review of studies on odor sensitivity and body weight concluded that there is a relationship between impaired olfactory perception and obesity (Peng et al., 2019). For example, studies report olfactory decline among patients with higher BMI, but studies with bariatric patients who received both *Roux-en-Y* gastric bypass and particularly sleeve gastrectomy showed a recovery in olfactory function post-surgery (Peng et al., 2019). Others have shown a negative correlation between olfactory discrimination and BMI in 74 subjectively olfactory healthy subjects (Besser et al., 2020). This may be linked with brain anatomical changes and research has shown a lower mean olfactory bulb volume among 28 subjects with obesity, compared to 28 control normal-weight subjects (Poessel et al., 2020a). However, there was no relationship between weight status and olfactory function as measured by the TDI olfactory performance test, and a subsequent study from the same group showed no relationship between odor-induced brain responses and BMI (Poessel et al., 2022). Research from the same group found no relationship between BMI and odor sensitivity, but observed a negative relationship between odor sensitivity and insulin sensitivity across normal weight, overweight, and obese subjects (Poessel et al., 2020b).

The mechanisms through which olfactory deficits may lead to overeating are not clear though some suggest that people with diminished odor sensitivity enjoy food less and therefore consume more to derive a similar sensation and food reward.

However, many studies have shown that olfactory loss often leads to a decline in appetite and desire to eat (Arikawa et al., 2020). Current evidence for a systematic relationship between reduced olfactory function, food intake, and diet-related chronic disease remains inconsistent across studies. In addition, it is worth noting that people with anosmia have similar weight trajectories as people with a normal olfactory functioning (Aschenbrenner et al., 2008), and there are no marked differences in food preferences between people with noncongenital anosmia and people with a normal sense of smell (Postma et al., 2020).

12.3 Impact of taste on food choice and intake

12.3.1 Taste-nutrient relationships in diets across the world

The sense of taste plays an important role in both food choice and food intake, and has been described as a “gatekeeper” for ingestion, since all foods and beverages must pass over the tongue before being swallowed (Mattes, 2021). Taste functions as a “nutrient-sensor” that provides a signal to the brain and body about the arrival of specific food macronutrients to the brain and metabolic system (De Graaf and Kok, 2010). The role of taste has a biological origin that has evolved since the dawn of mankind, and the functional impact of taste is associated with nutrient and metabolic consequences. From this perspective, it is important to understand how dietary taste patterns differ by weight status and in different diets and food environments across the world. Recent developments in sensory methods have made it possible to objectively quantify the predominant taste qualities of individual foods, and when linked to quantitative dietary intake data, provide novel insights into the taste patterns across a range of healthy and unhealthy dietary diets and geographical regions around the world (Teo et al., 2018).

Table 12.1 shows the average taste intensities of a representative set of foods from countries across the world (Teo et al., 2021; Martin et al., 2014; Lease et al., 2016;

Table 12.1 Average intensities of sweet, sour, bitter, umami, salt, and fat sensation on a 100 mm line scale across representative food supplies across the world. Taste intensities were rated with the help of the spectrum method (Meilgaard, Civille & Carr, 2007), where subjects were provided with anchored points on the line scale with the help of specific concentrations of sucrose for sweet, citric acid for sour, caffeine for bitter, monosodium glutamate for umami, NaCl for salt (Lease et al., 2016; Martin et al., 2014; Teo et al., 2018, 2021; van Langeveld et al., 2017)

	Sweetness	Sourness	Bitterness	Umami	Saltiness	Fat sensation
Australia	27	10	4	8	17	22
Netherlands	22	11	4	8	17	31
Malaysia	20	7	3	15	19	24
France	17	13	8	8	19	21
Singapore	18	6	7	11	14	22

van Langeveld et al., 2017, 2018). Average taste intensities are highest for sweet, salt, and fat sensation, and lowest for bitter. Sour taste mainly comes together with sweet taste in fruit products and drinks (Teo et al., 2021; van Langeveld et al., 2018). Table 12.1 suggests that the average umami intensity may be somewhat higher in the two Asian countries, Malaysia and Singapore, compared to the three countries with a Western diet, i.e., France, Australia, and the Netherlands. Overall, the rated taste intensities are not dissimilar across these geographically diverse food supplies (Table 12.1), suggesting there is a relatively narrow range of acceptable taste intensities across cultures, despite wide dynamic ranges of taste intensities available. For example, for salt intensity it is clear that people will tend not to accept diets that are very low in salty taste, but they also refuse diets that are too high in salt taste intensity. Table 12.2 pools data from a number of published studies on taste patterns in diets around the world, and shows the associations between the taste intensities of sweet, umami, salt, and fat sensation, and energy content, carbohydrate, protein, salt, and fat content. These data combine measures from over 2000 different individual foods rated for their predominant taste properties, and highlight associations between rated taste intensity and the presence of a macronutrient substrate that reflects this taste. The strength of the associations suggests that taste quality and intensity signal the presence of corresponding macronutrient substrates across representative samples of foods from diverse food environments across the world. It is often suggested that sweet taste intensity can act as a proxy indicator of a foods energy content. The data summarized in Table 12.2 show that sweetness intensity is a poor predictor of food energy content and that “fat” sensation and “fat-salty” combinations are more highly correlated with the kcal content of foods.

Comparison of taste intensity data from these studies in Europe, America, and Asia suggests that despite the enormous variety of food products and cuisines around the world, dietary taste patterns tend to have similar patterns and taste-nutrient relationships tend to be similar across different food supplies. In various critiques on modern diets it is often argued that taste-nutrient relationships are corrupted by food processing (Teo et al., 2021). These results demonstrate that the nutrient-signaling function of taste remains intact across a wide range of modern food environments and levels of food processing around the world.

Whereas taste in general has a clear role to play in nutrient selection and intake, it is also clear that this varies considerably with taste quality, since sweet, fatty, salty, and savory are often associated with higher sensory appeal and energy intake, whereas bitter and sour tastes are more often associated with organic acids and bitter glycoside compounds found in vegetables. The following sections profile the role of specific taste qualities in food choice and intake.

12.3.2 Bitterness

We are born with an innate aversion to strong bitter tastes, and the average contribution of bitter taste to energy intakes across diets globally tends to be quite low, either due to bitter foods being infrequently consumed or bitter products often being low in energy. The contribution of bitter tasting food to the total energy intake is below 10% in the

Table 12.2 Correlation coefficients ($\times 100$) between basic taste intensities of sweet, umami, salt, and fat sensation, and sugar, carbohydrate, protein, salt, fat, and kcal content of food supplies across the world. Taste intensities were assessed with the spectrum method as referred to in [Table 12.1](#), and nutrient concentration were derived from food composition tables.

	Number of foods	Sweet Sugar	Sweet Carbohydrates	Umami protein	Salt Sodium	Fat sensation Fat	Sweet Kcal	Umami Kcal	Salt Kcal	Fat sensation Kcal
Australia	377	70	41	27	64	65	−08	09	33	53
USA	237	71	42	n.a.	72	n.a.	11	n.a.	43	n.a.
Netherlands	489	82	54	54	69	75	11	00	22	58
Malaysia	423	62	33	51	52	42	04	04	16	26
France	350	84	57	62	77	72	−11	29	44	64
Singapore	189	73	38	48	62	61	29	−05	22	44

Adapted from Lease, H., Hendrie, G.A., Poelman, A.A.M., Delahunty, C. & Cox, D.N., 2016. A Sensory-Diet database: a tool to characterise the sensory qualities of diets. *Food Qual. Prefer.* 49, 20–32; Martin, C., Visalli, M., Lange, C., Schlich, P. & Issanchou, S., 2014. Creation of a food taste database using an in-home “taste” profile method. *Food Qual. Prefer.* 36, 70–80; Teo, P.S., Van Langeveld, A.W., Pol, K., Siebelink, E., De Graaf, C., Martin, C., Issanchou, S., Yan, S.W. & Mars, M., 2018. Training of a Dutch and Malaysian sensory panel to assess intensities of basic tastes and fat sensation of commonly consumed foods. *Food Qual. Prefer.* 65, 49–59; Teo, P.S., Tso, R., Van Dam, R.M. & Forde, C.G., 2021. Taste of modern diets: the impact of food processing on nutrient sensing and dietary energy intake. *J. Nutr.* In press; Van Langeveld, A.W., Gibbons, S., Koelliker, Y., Cville, G.V., De Vries, J.H., De Graaf, C. & Mars, M., 2017. The relationship between taste and nutrient content in commercially available foods from the United States. *Food Qual. Prefer.*, 57, 1–7.

diets of the Netherlands, Malaysia, and Singapore (Table 12.1). Across the global diets profiled bitter taste most often comes from drinks like black coffee, tea, and/or alcoholic beverages. These foods often tend to be lower in energy but often have another postingestive reinforcing element that conditions a preference for the bitter taste, and associates bitterness consumption and “reward” (Yeomans et al., 2000). For example, coffee bitterness can be reinforced by the presence of the bitter tasting cardiovascular stimulant caffeine, whereas bitter alcoholic beverages provide postingestive reinforcement through the positive effects associated with alcohol intake (Al Mansouri et al., 2014).

The bimodal trait genetic sensitivity to the taste of bitter compounds has been termed “PROP” status, where numerous studies have tried to link sensitivity to bitterness with resultant dietary patterns and health status. This has led to ambiguous results with several early reports suggesting a link between PROP and BMI (Tepper and Nurse, 1998), while others have linked PROP taster status to vegetables (Drewnowski et al., 2000), alcohol (Duffy et al., 2004), and fat perception and intake (Yackinous and Guinard, 2001, 2002). However, results have been inconsistent and attempts to replicate these findings and predict dietary intake patterns as a function of PROP status have not been successful. Although PROP sensitivity is likely to influence perceptual responses, our food preferences evolve and are learned through repeated exposures, and PROP taster status does not seem to consistently affect food preferences, dietary patterns, or weight status (Stoner et al., 2019; De Toffoli et al., 2019). For example, an initial disdain for bitter vegetables among PROP tasters can be overcome through repeated exposure to produce a higher acceptance (Nor et al., 2021).

Bitter taste receptors (T2R’s) are expressed throughout the alimentary canal, starting at the tongue, and running throughout the stomach and gastrointestinal tract (Harmon et al., 2021). Beyond a simplified role in food choice and liking, bitter taste receptors are now thought to play a key role as “chemosensory sentinels” that help to regulate our endocrine, behavioral, and immunological responses to bitter compounds. Several groups have leveraged the discovery of bitter taste receptors in the gut to study the potential impact of intragastric delivery of bitter substances on gastric emptying, satiety, and biological markers related to satiation and satiety (see (Rezaie et al., 2021; Feinle-Bisset and Horowitz, 2021)). These results are promising and merit further consideration to better understand how T2R’s can influence metabolic responses and understand whether intragastric infusion can reproducibly impact energy intake and metabolism and gastric emptying.

12.3.3 Sourness

Sour taste is primarily associated with the presence of organic acids in foods and beverages and is associated with unripe fruits or foods spoiled by microorganisms (Salles, 2021). Alongside an innate dislike for bitterness is an inborn aversion toward foods with a strong sour taste. However, the contribution of “sourness” to dietary energy intakes is higher than that of bitterness and mainly originates from sweet-sour tasting foods such as fruits/fruit juices, soft drinks, and sweetened yoghurt drinks. There are virtually no foods/drinks that only have a sour taste, and most sourness is

consumed as a combination of sweetness and sourness in foods and beverages. The diets in the Netherlands, France, Malaysia, and Singapore each contain a cluster of foods/drinks that are characterized by a combination of a high sweetness/high sourness and low intensity of the other tastes and fat sensation. These sweet-sour tasting foods contribute to the total energy content of the diet with between 10%–15% in the Dutch diet, and 6%–9% in the Malaysian and Singaporean diet (Teo et al., 2018, 2021; van Langeveld et al., 2017).

Children tend to have higher sourness preferences than adults, and are more tolerant of higher sour tastes (Forestell and Mennella, 2015). Liem et al. (2004) observed that there was a substantial group of children who liked foods and drinks with a strong sourness (Liem et al., 2004). Children that had a higher liking for sourness also score higher on sensation seeking, suggesting that sourness has an arousing, energizing effect. An increased preference for sour foods was related to higher fruit consumption (Liem and Russell, 2019).

As with bitterness, the importance of sour taste may not simply be in its role in guiding food preferences, as sour taste induces a much stronger cephalic phase saliva response compared to the other taste primaries (Neyraud et al., 2009). The rationale is that saliva buffers the low pH of sour organic acids, and therefore protects the oral mucosa from damage. Even the thought of a sour taste is sufficient to produce a salivary response (Neyraud et al., 2009). Recent research suggests sour taste may be instrumental in inducing a swallowing responses among patients with dysphagia (Dietsch et al., 2019), suggesting an important application of sour taste intensity for clinical populations in the future.

12.3.4 Saltiness

Salt taste and umami taste are distinct qualities, with independent receptor systems and molecular transduction mechanisms; however, in practice across the food supply salt and umami taste qualities are highly correlated (Teo et al., 2018, 2021; van Langeveld et al., 2017). Correlations between salt and umami intensity across the food supplies were 0.66 ($n = 590$) in France (Martin et al., 2014) and 0.72 ($n = 377$) in Australia (Lease et al., 2016) with similar correlations found in the Netherlands and Malaysia (Teo et al., 2018). These correlations persist, despite the fact that these ratings were obtained using sensory panels that had been trained to distinguish between umami and salt taste qualities. Electrolytes such as NaCl are essential nutrients, playing a critical role in regulating osmotic pressure in cells and maintaining muscle function and nerve cell signaling. Urinary electrolyte levels are a marker of hydration status and secretion provides the body with an opportunity to rebalance electrolyte levels that are too high (Polycarpe et al., 2004). Conversely, sodium-deficient animals develop a craving for salt (Leshem, 2009), and salt perception and intake are related to fluid intake and mineral balance (Leshem, 2020).

Salty tasting foods play an important role in moderating energy intake within the modern food environment, and in the Netherlands “salty/umami/fatty” cluster contributes to approximately 20%–25% of all calories consumed in the diet (van Langeveld et al., 2018). These figures rise even higher in Malaysia and Singapore where salty/

umami/fatty foods comprise approximately 50% of calorie intake (Teo et al., 2021). A high liking and intake for salty-fatty foods is also associated with higher prevalence of obesity (Teo et al., 2021; van Langeveld et al., 2018). One possible reason for this association between salt intensity and higher energy intakes may be due to our reduced ability to discriminate between fat-contents at higher salt taste intensity (Bolhuis et al., 2016, 2018). Research has shown that we can accurately discriminate between fat contents at lower taste intensity (Drewnowski and Schwartz, 1990), but this ability is significantly attenuated when fat is combined with higher taste intensity. Higher salt taste intensity has been shown to promote an increase in energy intake and psycho-hedonic functions of salt-fat mixtures show a 30% increase in energy intake when fat is consumed at an optimal salt intensity (Bolhuis et al., 2016). As such, salt (NaCl) contains no calories but is highly taste active whereas fat is highly energetic (9 kcal/g) but has low taste activity. Evidence to date suggests that the taste-nutrient combination of “salt-fat” contributes disproportionately more to higher energy intakes (Teo et al., 2021; van Langeveld et al., 2018).

Dietary nutrition and health recommendations and reformulation efforts in many countries across the world put on a societal pressure to reduce salt intake. Early studies from the 1980s do suggest that an exposure to a low-salt diet decreases preferences for optimal salt levels in foods (Bertino et al., 1982). Today salt intakes are much higher than recommended and the decline in average salt intake in various countries remains very slow (Hyseni et al., 2017). High salt concentrations can promote palatability to an optimum level, but could salt taste intensity also play a role in the onset of satiation? Previous research has explored the impact of salt intensity on satiation and energy intake within a meal of tomato soups that were equally palatable but different in the salt intensity (Bolhuis et al., 2012). Preferred salt concentration was measured using the psycho-hedonic function for each individual subject, and salt intensity was raised and lowered per participant to ensure perceptible intensity changes in equally palatable versions of the tomato soups. A first study demonstrated that salt intensity had no impact on ad libitum intake when soup was the only food served to a group of hungry participants. However a follow-up study using the same stimuli showed that when high-salt soup was served with an ad libitum sandwich lunch, energy intake was 8% lower in the higher salt condition compared to the low salt condition suggesting that higher intensity increased the onset of satiation during consumption (Bolhuis et al., 2010). These small effects merit consideration, as they suggest the potential application of taste *intensity* to help moderate or reduce intake within a meal, without the need for additional calories of a reduction in meal satisfaction. Further research is needed to clarify the potential of such an approach across different taste qualities and product formats.

12.3.5 Umami

Umami or savory taste has been associated with the detection and intake of dietary protein, whereas salt taste perception seems more related to the maintenance of fluid and mineral balance. As shown in Table 12.2, umami taste intensity in food is moderately correlated with the protein content across food supplies in Malaysia, Singapore, the

Netherlands, Australia, and France. The issue of protein intake is one of the most crucial and important issues in the field of nutrition, health, and sustainability, where recent years have seen an increasing trend to move away from animal protein toward plant-based proteins in the food supply (Tso et al., 2021). A sufficient intake of high-quality proteins is an essential prerequisite of good nutrition across the world (Tso and Forde, 2021).

Umami was first isolated and discovered by Ueda in 1908 (Fuke and Shimizu, 1993) and its characteristic “delicious” taste has been recognized as a basic taste primary for more than 30 years (Beauchamp and Pearson, 1991). The rated umami intensity of the Malaysian and Singaporean diets is higher than that of diets in Australia, France, and the Netherlands (Table 12.1) and is also reflected in the contribution of umami/salty/fatty foods to energy intakes in Singapore and Malaysia. Umami-fatty taste clusters contribute more than 50% to energy intakes in these countries, whereas in the Netherlands this contribution is about 20%–25% (Martin et al., 2014; Teo et al., 2021; van Langeveld et al., 2018). The central role of protein in guiding dietary choice and intake has been promoted through the protein leverage theory of Simpson and Raubenheimer (2005), who argue that protein intake is tightly regulated as a proportion of dietary energy intake in humans and other species. The idea of a constant relative contribution of protein to dietary energy intake is reinforced by various data sources and in the Netherlands protein intake has been constant since the early 1980s, with an average level of around 80 g per person per day (Van Rossum et al., 2020). A recent paper highlights that protein intakes are more stable than carbohydrate and fat intakes, such that pooled data from 15 countries encompassing men and women from different ethnic and socioeconomic, weight status groups, at different stages of their lifespan and varying in physical activity, the protein intake only varied between 15.3% and 18.5% energy (Lieberman et al., 2020). Our protein intakes and turnover are tightly regulated, and given umami taste intensity is associated with a food’s protein content, the implication is that taste can act as an environmental protein cue to stimulate intake and offset the risk of dietary imbalances.

Whereas the protein leverage has been widely demonstrated in animals and insects, much fewer studies have been conducted to study human food choice and intake for protein. In a 14-day fully controlled diet intervention, 37 subjects were exposed to diets that were high or low in protein and subsequent food choice and intake were studied (Griffioen-Roose et al., 2012b). After a protein deficit, food preferences and food intake pivot toward more umami tasting foods showing adaptive changes in dietary intakes to compensate for deviations in protein intake and restore adequate protein status. Similarly, it was observed that a 4-day protein-deficit diet led to increases in appetite for something savory and a higher intake of savory tasting foods, suggesting that protein intake is regulated and is operational through temporal changes in umami preferences (Gosby et al., 2011). These trials demonstrate the adoption of behavioral strategies to counteract protein imbalance, which becomes operational through an increased preference for savory-high protein umami tasting foods. Further acute studies have also shown the impact of savory taste on subsequent food choice and intake (Masic and Yeomans, 2017). The taste exposure of participants was controlled for a 24-h period to provide predominantly sweet or savory foods, followed by an ad

libitum buffet of mixed tastes (Griffioen-Roose et al., 2012a). Taste exposure influenced food choice at the buffet, such that following the sweet diet preference for savory went up, whereas following the savory diet preference for sweetness increased. Importantly, despite these sensory-specific effects of taste on dietary choice, the predominant taste of previous 24-h diet had no effect on overall macronutrient intakes.

Previous research has compared the satiating potential of different taste qualities, based on anecdotal reports that sweet foods are less satiating on kcal per kcal level than savory foods. Early research studies demonstrate that postmeal feelings of fullness are equivalent from savory (umami) and sweet versions of a test meal (De Graaf et al., 1993), and this was later confirmed in terms of energy consumed to fullness (satiation) (Griffioen-Roose et al., 2009). Further research has shown that we compensate in the same way when energy is added to our diets as either a sweet or a savory food (Tey et al., 2018), suggesting that sensory cues are likely to only be influential during consumption, rather than during the intermeal interval. Savory stimulation is thought to have a biphasic role in appetite control (Masic and Yeomans, 2014), stimulating intake through enhanced preference in some contexts (Hollis and Henry, 2007), but also contributing to earlier satiation or enhanced satiety and reduced energy intake in others (Masic and Yeomans, 2014). For example, umami enhancement trials have successfully demonstrated increased palatability and intake for meals enhanced with monosodium glutamate (MSG) among vulnerable older populations (Mathey et al., 2001; Abbott et al., 2013; Methven et al., 2012), whereas others have failed to replicate this effect (Essed et al., 2007). Research has also successfully demonstrated that when meals are enhanced with umami, it can produce a small but significant change in energy intake or reduce later food intake (Miyaki et al., 2016; Imada et al., 2014), whereas others have shown effects only on rated appetite but not later energy intake (Anderson et al., 2018; Carter et al., 2011). Overall, the effect of savory taste enhancement has provided equivocal results in terms of energy intake, suggesting that if there is likely a small impact on intake and satiety, and that this is highly dependent on food, consumption context, and intensity of the tastant. In addition to its functional role in food intake, the primary savory/umami compound MSG has also been shown to support salt reduction and food reformulation (Katsuyuki, 2020) by ameliorating the reduction in palatability often associated with low salt versions of foods, where added MSG has been shown to facilitate a salt reduction from 0.9% to 0.3% without reducing liking (Hayabuchi et al., 2020).

A related sensation is the *Koku* perception of “mouth fullness” which is not in itself a taste, but an oral sensation that has been observed to contribute to savory intensity, complexity, and duration. This sensation is stimulated by *kokumi* tripeptides that are low-calorie taste and mouthfeel enhancers that enhance sensations of mouthfulness, continuity, and complexity, often mimicking the sensory impact of fat. Whereas much research to date has focused on their sensory perception, preliminary recent findings demonstrate that addition of *kokumi* compounds can enhance sensory dimensions linked to calorie expectations, and promote higher estimated calories and expected fullness across a series of equicaloric broths (Tang et al., 2020). Future research should further aim to explore the potential of *Kokumi* compounds to support calorie reduction while maintaining a products sensory appeal.

12.3.6 Sweetness

In contrast to bitter and sour tastes, humans and other mammals are born with an innate liking for sweetness (Coward, 1981). Exposure to sweetness is pleasant, calming, and soothing and has an analgesic effect among children, such that sweet stimuli are often used to distract from the pain of vaccination in young babies (see Harrison et al. (2010), for a review). The dictionary definition of “sweet” is something pleasant, satisfying, agreeable, and delightful.

The psychohedonic optimal sweetness is significantly higher in infants than in adults, and slowly declines from early infancy throughout childhood and into early adolescence (Liem and Mennella, 2002; De Graaf and Zandstra, 1999). This figure aligns with the observation that the contribution of mono- and disaccharides to energy intake is about 33% in toddlers and declines to about 20% in adulthood, and these figures have been stable in the Netherlands since the 1980s (Van Rossum et al., 2020). Recent data on the predominant taste of calories consumed in the Dutch diet show that sweet-sour and sweet-fatty tasting foods comprise approximately 25%–30% of the energy intake (van Langeveld et al., 2018). However, much of the societal narrative around sweetness centers on the “sweet tooth,” and the excessive energy consumed from sugary soft drinks and foods considered as discretionary calories that promote energy consumption and eventually lead to obesity (Anderson, 1995). The rationale of this reasoning is that sweetness is pleasant and that people with obesity tend to consume a greater proportion of their energy from sweet foods than people in the normal weight range. However, this reasoning is not supported by available data. As is clear from Table 12.2, sweetness intensity is poorly correlated with the energy content of food, and this has been observed across the global diet from the USA, to Europe and Asia. A further proposition is that people with obesity must have a higher liking for sweetness compared to those in the normal weight range, but again this hypothesis is not backed by data. Multiple studies since the early 1980s fail to demonstrate a clear relationship between weight status and the psychohedonic function for sweetness (Cox et al., 2016). Experimental and observational data have failed to show a difference in sweetness preference by weight status in children (Bobowski and Mennella, 2017) or adults (Cox et al., 1998). Consumption of sweet foods also does not stratify by weight status (Teo et al., 2021; van Langeveld et al., 2018).

In the modern food environment there is pressure to reduce sugar from foods and beverage to reduce their energy content. However, what remains less clear is whether sugar content or the associated sweetness perception is the driver of consumption. Few trials to date have explored whether exposure is driving preferences and intake for sweet foods, and today it remains unclear whether high exposure to sweetness leads to increased liking for high “sweetness” level or conversely a low sweetness exposure leads to lower preference for “sweetness.” A recent systematic review showed no consistent data in this direction, and observed that whereas short-term effects of sweetness exposure lead to a decline in sweetness liking, there are limited available data to conclude on the longer-term implications of sweetness exposure (Appleton et al., 2018). One RCT to date has controlled for dietary exposure to sweetness and only found transitory changes in rated sweetness intensity, though no sustained changes

in sweet liking (Wise et al., 2015). Further research is needed to better understand whether sweetness preferences are hard-conditioned from early life, or are malleable in response to tastant exposure within our food environment.

Earlier in the chapter we highlighted that umami preferences adapt in response to deviations in protein status, and sweetness perception also plays an important role in our metabolic response to sugar (mono- and disaccharide) consumption. Consumption of simple carbohydrates stimulates early cephalic release of enzymes and hormones, such that over time, sweetness becomes predictive of sugar and carbohydrate ingestion, and stimulates insulin release (Härtel et al., 1993; Teff et al., 1995). However, others have failed to show a clear and reproducible relationship between sweet stimulation and subsequent cephalic phase responses; therefore, the role of sweetness stimulation on carbohydrate-insulin metabolism remains an important debate among researchers in the sensory nutrition field. Relationships between sweet taste and the subsequent delivery of energy are learned, so any disruption in the link between the sensory cue (sweet taste) and subsequent nutrient deliver (carbohydrates/energy) content could potentially disrupt these learned associations and impact later food intake behavior. It has been suggested by some researchers that decoupling of sweetness from energy delivery may enhance appetite stimulating excessive energy intakes, or disruption of the normal glycemic response to carbohydrate ingestion (Swithers and Davidson, 2008; Swithers et al., 2010; Pepino, 2015). However early findings in animal studies have not been replicated in humans, and several recent meta-analyses of studies have shown use of nonnutritive sweeteners in place of sugar support reductions in energy intake, body weight, and BMI (Toews et al., 2019; Rogers et al., 2016). The balance of evidence supports the role of low and no-calorie sweeteners in reducing sugar content while still maintaining the sensory appeal.

12.3.7 *Fat sensation*

Recent studies have shown that free fatty acids (FFAs) can elicit a “taste” response (Keast and Costanzo, 2015), and this taste of fatty acids is believed to influence fatty metabolism during digestion (Mattes, 2009). This sensation has been described as a distinct sensory quality and christened “oleogustus,” to delineate the taste of free fatty acids on the tongue (Running et al., 2015), from other mouthfeel sensations associated with fat consumption. Whereas results have reproducibly shown free fatty acids such as linoleic or oleic acid to elicit a taste response, it is also acknowledged that this taste quality is difficult to describe and recognize, and people tend to articulate this sensation quite differently. The qualitative description of FFAs and separation of the taste of fatty acids from the attendant mouthfeel properties of triglycerides have made it challenging to characterize the impact of these compounds in everyday food choice and intake, where fat is typically consumed in the form of oils, and free fatty acids are typically a marker of rancidity or spoilage (Mattes, 2021). Nevertheless, sensitivity to the oral sensations arising from FFA consumption are likely to vary within the population and previous research has suggested that people with a lower sensitivity to FFAs are at

an increased obesity risk (Stewart et al., 2010, 2011). Further research has shown that participants in the overweight to obese weight range had a lower sensitivity for the taste of free fatty acids compared to normal weight subjects (Liu et al., 2016). People have been shown to adapt to high and/or low-fat levels in food, and this has an impact on their subsequent ad libitum energy intake and body weight, suggesting that fatty acid taste sensitivity is influenced by the taste environment rather than purely by genetics (Costanzo et al., 2018). Further research is needed to establish a clear role for fatty acid taste in food perception and preference and the development of dietary patterns.

Fat makes a significant contribution to daily energy intakes, and is by far the most energy dense macronutrient (9 kcal/g), compared to protein and carbohydrates (4 kcal/g). Fat is omnipresent in diets across the world and the sensory appeal of fat/sugar and fat/salt mixtures in driving food preference has been widely studied (Drewnowski, 1997). In several recent comparisons of the relative contribution of different taste clusters to daily energy intakes, it was observed that in Malaysia and Singapore “savory-fatty” tasting foods contribute more than 50% to total energy intakes, compared to 20%–25% in the Netherlands (Teo et al., 2018, 2021; van Langeveld et al., 2018). Conversely, for “sweet-fatty” foods the contribution is higher in the Netherlands (20%–25%) than in Asia (5%–10%). There are several possible reasons why fat sensation is universally regarded as pleasant. Fat liking may be conditioned through flavor-nutrient conditioning where we learn to associate the sensory sensation of fat with the positive postingestive experience of fullness and satisfaction, which can reinforce the initial hedonic appeal (Kern et al., 1993). The addition of fat to food also makes it easier to eat, providing a built-in source of lubrication that makes food softer, easier to chew, and contributes to oral comfort and an increased eating rate (Bolhuis and Forde, 2020). Adding a fat-rich topping to bread or crackers enhances bolus formation through improved lubrication and ensures a food that requires less chewing and can be eaten at a faster rate (Van Eck et al., 2019). Fat also acts as a reservoir for many nonpolar flavor compounds, and a food’s fat content strongly influences the temporal release of volatile aroma compounds during consumption (Brauss et al., 1999; Relkin et al., 2004; Paravisini and Guichard, 2016). By extension, one of the challenges associated with fat reduction is that low-fat foods often shift the temporal release profile of aroma compounds due to differences in partitioning and temporal release of lipophilic aroma compounds relative to hydrophilic compounds (Plug and Haring, 1993). As such, fat, unlike the other primary taste qualities, has a multimodal effect on perception and exerts a strong dynamic influence on flavor release and oral processing, and a disproportionately large contribution to energy intakes.

Fat contributes to mouthfeel and texture perception, but in reciprocal manner, texture and the related oral processing behaviors contribute to flavor release and perception. In addition to its role in flavor perception, food texture informs our oral processing behaviors and plays a central role in moderating the flow of calories through our diets. This is discussed in the following section.

12.4 Impact of texture on eating rate and food intake

12.4.1 Texture oral processing and the food intake

Food texture is often an overlooked food sensory property, and in some cases only merits consideration when it deviates from expectations (Szczesniak, 2002). However, texture is central to our appraisal of food quality (Kilcast and Lewis, 1990), freshness, and acceptance and as described earlier, can significantly influence the rate and extent of food taste and odor substances from the food matrix during consumption (Gierczynski et al., 2011). For example, harder foods of plant origin need to be masticated and broken down before their taste and smell compounds can be released from within the cell walls to be perceived (Bonneau et al., 2018). Mastication is necessary for dynamic temporal changes in flavor release and perception, but also to prepare solid foods for safe swallow, where the initial structure is deformed to a fragmented bolus, lubricated agglomerated safely swallowed (Witt and Stokes, 2015). A foods trajectory from initial structure to bolus swallow has been described by the “mouth-process model,” which describes the specific changes in structure, size, and lubrication needed for a bolus to reach the swallow phase (Hutchings and Lillford, 1988). This model was originally developed to describe the changes required in bolus form and texture to achieve safe swallow, but when we overlay additional information on oral processing behaviors (i.e., bite size, chews per bite, orosensory exposure time) and eating speed (fast/slow), it is also a useful model within which to conceive the impact of food texture on habitual eating behaviors (Fig. 12.1). This figure illustrates the

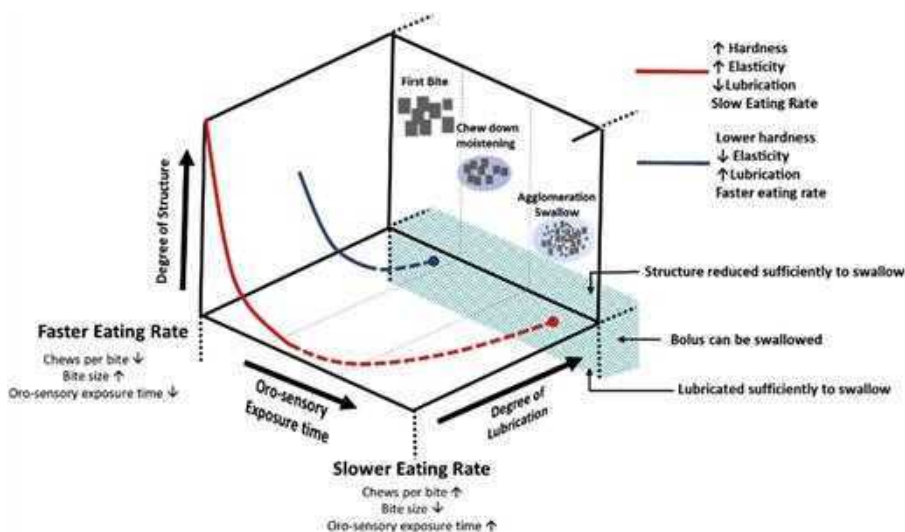


Figure 12.1 Mouth process model of food oral breakdown which illustrates the impact of food texture and lubrication on oral processing behaviors and eating speed.

Image adapted by M. Stieger from Hutchings, J.B. & Lillford, P.J., 1988. The perception of food texture - the philosophy of the breakdown path. *J. Text. Stud.* 19, 103–115.

importance of foods' mechanical properties and lubrication state in moderating the time required to prepare a bolus for swallow (orosensory exposure time) and the rate at which we consume calories during a meal.

Extensive research has highlighted the important role of “food form” on energy intake to satiation and postmeal satiety and shown that we tend to consume more from liquid foods and these foods tend to deliver less fullness post-meal (satiety) on a kcal for kcal basis (Dhillon et al., 2016). Further studies in recent years have illustrated that within food form (liquid, semisolid solid) texture differences can influence both eating rate and energy intake (for a review see Bolhuis and Forde (2020)). Initial findings from semisolid and semiliquid foods highlight the importance of viscosity on eating rate and intake (Zijlstra et al., 2008), and dietary learning (Mars et al., 2009).

Studies reveal that people tend to consume approximately 30% more energy from liquids than semisolids, and these differences in intake were attenuated (12%) but maintained even after controlling for subject eating effort (Zijlstra et al., 2008). Further research with solid foods revealed that we tend to adapt our eating rate in response to the food texture consumed within a meal and increasing the texture challenge can both slow and decrease intake within a meal. Across a trio of controlled feeding studies, harder food texture reduced eating rate and was associated with a 10%–15% reduction in ad-libitum energy intake (Bolhuis et al., 2014; Forde et al., 2013a,c; McCrickerd et al., 2017b). Importantly, these reductions in energy intake did not produce lower sensory appeal (Forde et al., 2013c) or a weaker post-meal satiety response (McCrickerd et al., 2017b) or later compensatory eating (Bolhuis et al., 2014). The implication is that food texture could be used to guide the rate of calorie intake and mitigate potential risks associated with consuming high energy foods at a faster rate (Bolhuis and Forde, 2020). Faster eating rate is now recognized as a risk factor for obesity and diet-related chronic diseases such as type-2 diabetes (Teo and Forde, 2020). The rate at which an individual consumes a meal has been shown to be very consistent over time (McCrickerd and Forde, 2017) and it can be influenced by underlying differences between individuals in their drive to eat (Fogel et al., 2020) and by the texture and properties of the food environment they choose to consume (Bolhuis and Forde, 2020). As such, eating rate is a consistent property of both the individual and the food—a faster eater will eat bread faster than a slow eater, but will also consistently eat yoghurt faster than a slower eater, and in both cases the average eating rate of bread will be slower than that of yoghurt (see van den Boer et al., 2017a) for a comprehensive list of Dutch food eating rates). As eating rate is such an important variable for intake, we first summarize available evidence on why there are differences in eating rate between individuals, and then describe the impact of different food textures on eating rate and intake.

12.4.2 The origins of differences in eating rate and association with energy intake and obesity

Large-scale epidemiological studies show that people who self-report to eat faster have a higher risk for obesity than those reporting to eat slower. A systematic review and

metaanalysis of 23 studies mainly from Asia showed that eating quickly is positively associated with excess body weight (Ohkuma et al., 2015). These observations have been confirmed both in Western populations (van den Boer et al., 2017b) as well as in Korean (Kang et al., 2021), Japanese (Zhu et al., 2015), and Singaporean populations (Teo et al., 2020a,b). This literature is reviewed in more detail in Teo and Forde (2020).

Habitual eating behaviors, including eating rate, emerge early and remain stable throughout childhood. Research has shown that both genetic and early life food environment can influence the development of eating behavior (Llewellyn et al., 2014), with data from the GEMINI twin cohort showing that among 9–10-year-old British children faster eating rate is a heritable trait that associates with higher BMI (Llewellyn et al., 2008). Subsequent studies have shown that among 4-year-old children faster eating rate is a biobehavioral marker for the development of childhood obesity (Berkowitz et al., 2010). Across a series of studies within the Growing up in Singapore to healthier outcomes (GUSTO) birth cohort, it was observed that 4.5-year-old children who ate faster during an ad libitum test meal consumed significantly more, and tended to have both higher BMI_z scores and adiposity than children eating at a slower rate (Fogel et al., 2017a,b). This eating behavior was described as “obesogenic” as normal weight children eating faster at 4.5 years continued to do so at a later time point (6 years), and this was associated with increases in BMI_z score and adiposity at the later timepoints (Forde et al., 2019; McCrickerd et al., 2017a; Quah et al., 2019). Importantly, the transition from early life risk to overweight or obesity in later childhood was only observed among children exhibiting eating behaviors such as faster eating among children in the GUSTO cohort, suggesting eating rate may be an important early life modifiable risk factor for childhood obesity (Fogel et al., 2020).

Few studies exist on adolescent eating rates, but studies in young adults reveal that eating rate is consistent at the individual level, and a strong predictor of ad libitum energy consumption (Martin et al., 2005). Across four separate study groups, when participants were invited to consume the same meal for lunch once a week over four consecutive weeks, individual eating rates on the first week were a strong significant predictor of both later eating rate and energy intake during the subsequent ad libitum meals (McCrickerd and Forde, 2017). This level of consistency suggests that although eating rate can be moderated by the texture properties of the meal consumed, it is also likely strongly influenced by an underlying drive to eat and habitual preferred rate of eating. This has led to speculation that differences in individual eating rates may be driven by an underlying difference in energy requirements which strongly associates with basal metabolic rates and lean muscle mass (Henry et al., 2018; Blundell et al., 2020; Wells et al., 2021). In a preschool population of children, faster eating rates have also been found to associate with higher trait impulsivity, child appetitive traits (Fogel et al., 2018a,b, 2019b), and parental feeding practices (Fogel et al., 2019a), suggesting a wide range of inherited and environmental factors are likely to combine to influence rates of eating. Identifying the eating behaviors that consistently predict greater energy intakes is important to connect genetic predisposition to obesity risk to the biobehavioral eating behaviors that later result in obesity and metabolic dysfunction. This creates new opportunities to intervene and targets specific eating behaviors

in early childhood diets (Forde, 2018a; Forde et al., 2019; Fogel et al., 2020). Limited studies to date have targeted eating rate in behavioral interventions to tackle obesity, though evidence suggests this could be an effective approach to changing behavior and body weight. In one trial with children at risk of overweight and obesity, participants were supported to reduce their eating speed through the use of computer-based verbal prompts within a meal which led to reduced eating speed and a clinically significant reduction in BMI. Although further studies are needed to test the long-term impact of these behavioral interventions, initial findings suggest this may be a viable approach (Ford et al., 2010). Whereas digital devices offer control in an experimental setting, the sustained effect and long-term adherence to such regimes remains unknown (Jasper et al., 2016; Zhang and Amft, 2017, 2020). In this regard, a potentially more ecologically meaningful approach would be to manipulate oral processing behavior and eating speed through the application of meal textures. In the next section we describe how food texture been shown to effectively moderate eating speed and intake.

12.4.3 Food texture, eating rate, and energy intake

There is wide natural variation in eating rate (g/min) of foods and meals, and this has been observed across studies that sampled food in different parts of the world. The eating rates of commonly consumed solid foods tend to vary from 10 g/min for foods like puffed rice crackers, tortilla chips, or baked tofu puffs to up to 120 g/min for softer foods like tinned tomato or rice porridge (Congee) (Forde et al., 2017; Forde et al., 2013b; van den Boer et al., 2017a; Viskaal-van Dongen et al., 2011; Ferriday et al., 2016). For liquids and semisolids eating rate is much higher, and can rise to 500–600 g/min for beverages like apple juices, soft drinks, or chocolate milk (van den Boer et al., 2017a; Viskaal-van Dongen et al., 2011). Foods that are eaten slower tend to be consumed with smaller bites, more chews per bite, and a longer orosensory exposure (seconds) than foods that are consumed quickly (Ferriday et al., 2016; Forde et al., 2013a; McCrickerd et al., 2017b).

A systematic review and metaanalysis of studies that have measured eating rate and intake confirmed that energy intake is higher when we eat faster, and this effect persists whether the eating rate is manipulated by instructions (i.e., chew slowly), is prompted by a device (i.e., digital feedback to slow down during a meal), or by changes in food texture (Robinson et al., 2014). Instructing participants to chew more during a meal has been shown to reduce eating rate and meal size, though this approach does not always yield consistent findings (Zhu and Hollis, 2014a,b; Martin et al., 2007; Andrade et al., 2008). A recent systematic review and metaanalysis investigated the effects of sensory and physical characteristics of food on intake and found that textural parameters have a strong consistent effect on satiation such that foods that were harder, chunkier, or more viscous, voluminous led to earlier satiation (Appleton et al., 2021). However despite the consistency of texture-based reductions in eating rate and energy intake, research to date has produced equivocal findings on the impact of texture and meal eating rate on postmeal satiety (Hollis, 2018). Extending the number of chews from 15 to 40 led to an increase in postmeal satiety and associated neuroendocrine satiety hormones following the consumption of a fixed meal (Zhu et al., 2013), whereas participants

that naturally ate a fixed portion fried rice meal also reported higher subjective feelings of postmeal satiety (Goh et al., 2020). However, others have failed to show differences in postmeal satiety as a result of eating rate (Choy et al., 2021; Tan et al., 2016) suggesting that the food textures are more influential on the energy intake consumed within a meal to fullness (satiation), and less likely to enhance post-meal fullness in a consistent way that reduces subsequent food intake (satiety).

Beyond the impact of food texture on energy intake, texture-based changes to oral processing have also been shown to influence bolus formation and oral phase of digestion and metabolic responses to food (Forde and Stieger, 2022). A longer chewing time is associated with greater bolus surface area, saliva uptake, a longer time for enzymatic action in the oral cavity, and has been shown to stimulate early glucose release and stimulate a stronger postprandial insulin response (Goh et al., 2020, 2021). Whereas this area has potential to apply texture and behavioral support to a healthy postprandial glucose responses, current findings suggest food texture is likely to influence temporal changes rather than total glucose (Choy et al., 2021) and differences in eating rate account for individual variability in glycemic responses, rather than having a significant metabolic impact on postprandial glucose responses. Further research is needed to evaluate the potential of texture-based differences in food taken orally to support euglycemia in the future.

12.5 Future directions: application of sensory approaches to public health

The current chapter summarizes available evidence on the impact of smell, taste, and texture on food choice, intake, and nutritional behavior. Whereas nutrition primarily focuses on food composition, and food science on structure and food formulation, the link to consumer choice and intake behavior is sometimes overlooked. The evidence presented in the current chapter highlights that sensory science can be viewed as a “bridge” that connects food and health through an understanding of consumer choice and eating behavior (Forde, 2018a). Optimizing diets through an understanding of how sensory cues influence food choice and eating behaviors represents a largely untapped opportunity for public health nutrition, where sensory approaches can be applied to support future initiatives to design nutritious foods and promote healthy dietary patterns.

Many of the studies presented in the current overview are based on acute, 24-h laboratory-based trials, and further research is now needed to evaluate whether these sensory effects are observed over the longer term and in the real food environment. The growing availability of new noninvasive techniques to track intake behaviors and metabolic responses away from the laboratory (Lasschuijt et al., 2021) make it possible to better understand whether acute variability in eating behaviors observed in a laboratory will have a meaningful long-term impact on metabolic markers of health and disease in consumers’ everyday lives. A challenge for future sensory and

nutrition researchers is to transform the acquired insights on the impact of texture on eating rate (g/min) and energy intake rate (kcal/min) into actionable food design principles to promote healthier diets that maintain their sensory appeal.

Across the global food industry significant efforts are underway to reformulate foods to reduce the salt, sugar, fat, and energy content in many categories. Beyond palatability, the studies summarized in the current chapter highlight an important functional role of sensory properties in guiding eating behaviors and moderating food intake. A recent randomized controlled trial (RCT) highlights this further, where consuming a diet comprising highly processed foods has been shown to promote sustained higher energy intakes and weight gain (Hall et al., 2019). Importantly, findings from this RCT also demonstrate that higher energy intake was mediated by the softer texture and higher energy density of foods in the processed diet, highlighting the interplay between sensory (texture) and nutrient properties (energy density) in promoting observed higher energy intakes (Forde et al., 2020). Whereas higher energy intake rates (kcal/min) have been implicated in excess energy intakes within the modern food environment, research presented in Section 12.4.2 of the current chapter offers potential solutions, through the application of food texture to slow and reduce the rate and extent of ad libitum energy intakes. Further, long-term controlled nutrition intervention studies should consider the effects of food sensory properties in addition to composition when developing diet and behavioral approaches to reduce the risk of excess energy intakes.

The recent development of approaches to quantify the sensory intensity of foods and through this link perception to dietary intake patterns was described in Section 12.3.1 (and Tables 12.1–12.2). We have described this approach as “sensory epidemiology,” and it is a powerful approach to explore dietary patterns through the perceptual properties of the foods habitually chosen and consumed. When sensory epidemiology is applied to longer-term cohorts, it will become possible to understand the development of dietary taste and texture patterns that associate with poor cardio-metabolic health and all-cause mortality. Future research is needed to understand the long-term impact of dietary interventions, and clarify whether diets lower in sugar or salt result in a shift in sweet and salt taste preferences, and whether these diets can be modified through dietary taste exposure. Salt reformulation has progressed slowly, and overall salt intakes are higher than recommended. Central efforts to reformulate the salt content of foods and diets will be a better understanding of how malleable salt-preferences are, and whether reduced exposure can sustain preferences for reduced salt foods. Recent years have seen the emergence of many low-calorie ingredients that can impart high sweet and savory taste intensity, and future research is needed to understand how these stimuli can be applied to reduce the burden of public health-sensitive nutrients (i.e., salt, sugar, fat) while still maintaining a products sensory appeal and eating pleasure.

Diet-related chronic diseases such as obesity and type-2 diabetes are largely avoidable and are the result of the foods we choose and the quantity and frequency with which we consume them. Acute food choice and energy intake decisions are more strongly influenced by the sensory and cognitive aspects of eating, than the underlying nutritive properties of the food consumed, yet chronic disease and ill-health are

influenced by the prolonged exposure to a diet with poor nutritive properties and high energy. The research summarized in the current chapter highlights that a food's sensory properties guide the foods we choose, and the quantity and frequency with which we consume them. A deeper understanding of the relationship between sensory perception, choice, and intake behavior will therefore be central to efforts to moderate habitual dietary patterns and sustain a move to healthier eating patterns.

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Familiarity, monotony or variety: the role of flavor complexity in food intake

13

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13.1 Introduction

In the human omnivore, food intake and food choice are determined by a large number of factors, varying from physiological factors such as hunger, thirst, and satiation, to the memories of sensory pleasures and of postingestional feelings based on intestinal perception and to psychological, social, and cultural factors and feelings of well-being and situational appropriateness (Köster, 2009). One aspect of food choice is often forgotten, however: the delicate balance between feelings of familiarity that act as an appeasing force against the natural food neophobia that all omnivores share (Rozin, 1976) and the equally natural dislike of monotony and boredom as a result of lack of arousal raised by well-known and/or too simple dishes (Zuckerman, 1979; Köster and Mojet, 2007b). The arousing capacity of perceived complexity plays an important role in the hedonic appreciation of art and music (Berlyne, 1967, 1974; Heyduk, 1975). It is a truly “collative” property, i.e., it depends both on the nature of the stimulus by the amount of its perceptible sensory properties and on the optimal level of stimulus complexity the perceiving subject is used to. Thus, complexity is not a fixed property, but it changes with the subjects’ experience with the stimulus or with similar stimuli. Stimuli that seem very complex at first sight to a person usually lose their complexity upon repeated exposure (Berlyne, 1960; Walker, 1980), and this has different consequences for the development of their appreciation by the subject, depending on the original relationship between the stimulus complexity and the level of complexity the perceiver likes most. If the stimulus originally seems too complex to the perceiver and is therefore not liked, repeated exposure will lead to an increase in appreciation as supposed in the “mere exposure” theory formulated by Zajonc (1968). If on the other hand, the stimulus complexity is equal or below the level of complexity the perceiver is used to, repeated exposure to it will lead to boredom. Furthermore Dember and Earl (1957) and Dember (1965) have shown that exposure to stimuli that are somewhat more complex than the complexity level the perceiver is used to, and considered optimal, may cause a shift in his/her liking in the direction of a higher optimal complexity level. They also showed that repeated exposure to less than optimally complex stimuli has no effect on the optimal complexity level of the perceiver, but just

leads to boredom and loss of interest in the stimulus (see also Walker, 1980). This means that during life the optimal level of perceived complexity of perceivers will probably continue to rise, a phenomenon well known to classical music lovers, visual art lovers, and wine drinkers. The double dependence of perceived complexity on both the complexity of the product properties and on the optimal complexity level of the perceiver has severe consequences for the way in which this interaction must be studied. It means at least that one has to segment the population under study on the basis of their optimal complexity level instead of just averaging overall subjects. In the areas of the visual arts or of classical music, this has been done to some degree by using groups of people who differed in the frequency with which they visited museums or symphonic concerts. In one of the first really thorough tests of the theory in the field of food and/or drink consumption (Levy et al., 2006), the original optimal level of complexity of the perceivers was established on the basis of their liking for a range of stimuli differing in complexity. They were divided into five groups depending on their highest preference for one of the complexity levels (see below for a detailed description). Subsequent exposure to either more or less than optimal complex stimuli in these groups led indeed to different shifts in the liking of the products that were in accordance with the theories of Berlyne (1974), Dember and Earl (1957), and Walker (1980). Other authors, who did not segment their subjects (Porcherot and Issanchou, 1998) or did not establish the perceived complexity of the products by independent measurements (Zandstra et al., 2004) were unable to find such effects. This indicates how important it is to clarify and define the notion of perceived complexity. Similar clarifications might be needed for the frequently used, but often quite loosely defined and seemingly common notions of familiarity, novelty, boredom, and their relation to food liking, choice, and food intake.

13.2 Perceived complexity: definition and measurement

In their original paper on perceived odor complexity, Jellinek and Köster (1979) described four types of fragrance complexity: (1) chemical complexity depending on the number of independent chemicals in a stimulus, (2) physiological complexity, depending on the number of receptor cell types involved in the perception of the stimulus, (3) perceived complexity, depending on the number of odor impressions the observer experiences when smelling the stimulus, and (4) perfumers' complexity, depending on the number of definable odor notes the perfumer detects in the stimulus.

The authors devoted most of their attention to the relationship between the chemical and the perceived complexity and to the relation of the latter with familiarity of and preference for the stimuli. They found that perceived complexity was not related to chemical complexity. Thus, the odor of a single molecule like iso-eugenol was shown to be perceived as much more complex than a musk perfume composition containing 30 different molecular components. This independence was later confirmed in a second study (Jellinek and Köster, 1983) with different substances and an even more precise perceived complexity assessment method. Furthermore, they were able to show

that men had a preference for fragrances with lower complexity, whereas women liked complex odors better and also preferred more familiar ones. In their study, they did not yet segment the subjects on the basis of the differences in the levels of complexity they preferred. This was also not yet the case in a study by [Levy and Köster \(1999\)](#) in which three alcoholic beverages, differing in complexity and familiarity (the traditional market product and two new versions: one less and one more complex than the traditional product) were compared over three normal at home aperitif time sessions. They showed that the traditional product that in the first session was clearly preferred over the other two products was already equaled by the new complex product in the third session, while the liking for the less complex product had dropped to a much lower preference than during the first session. They also demonstrated that these effects were much clearer when the preferences were measured by a choice method (choosing a free bottle of one of the drinks) than by a method in which the liking had to be scaled with liking scales that are commonly used. This might indicate that hedonic evaluation is more influenced by familiarity and tradition than actual choice behavior and that scaling might obscure new choice tendencies evoked by the appeal of stimulus complexity. Nevertheless, scaling was extensively used in a study by [Levy et al. \(2006\)](#) on the influence of complexity and repeated exposure on the appreciation of seven orange drinks differing in perceived complexity, which was the first and thus far only example in which the participants were segmented on the basis of their optimal complexity appreciation level and the truly collative property of perceived complexity was measured. Thus, it could be shown that the results were in perfect accordance with the theory of [Dember and Earl \(1957\)](#) ([Fig. 13.1](#)).

As can be seen in [Fig. 13.1A–D](#), exposure to a drink with lower than optimal complexity did neither change the perceived complexity ([Fig. 13.1A](#)) nor the liking ([Fig. 13.1B](#)) of the seven drinks, but exposure to a drink with a higher than optimal complexity did reduce the perceived complexity ([Fig. 13.1C](#)) for all seven drinks and had different effects on the liking ([Fig. 13.1D](#)) leading to a reduction in liking for the drinks below the optimal complexity level and to an increase of liking for the drinks above the optimal complexity level. This latter result can be explained by the shifts in optimal complexity ([Fig. 13.1E](#)) caused by exposure to the different levels of complexity in the five groups (group 1 being exposed to much lower optimal complexity level and group 5 to much higher than optimal complexity).

At about the same time as the experiments mentioned here ([Leon et al., 1999](#)) carried out extensive experiments on the stability of measurements of food liking in children from 4 to 10 years using three nonverbal methods: paired comparison, ranking by elimination, and hedonic categorization. Her results showed that children from 5 years started to make repeatable food choices and that the hedonic categorization did less well than the other two methods in predicting their final choice. These findings indicate again, like in the results of adult drinkers of alcoholic beverages mentioned above, that hedonic categorization may not be the best indicator of food choice. The results of Leon were later analyzed in more detail and in view of different ideas about possible influences of factors such as complexity on the stability of the choices made in successive measurements by the children ([Köster et al., 2002](#)). In a complete paired comparisons design in which all possible pairs were tested in each of three sessions, it could be

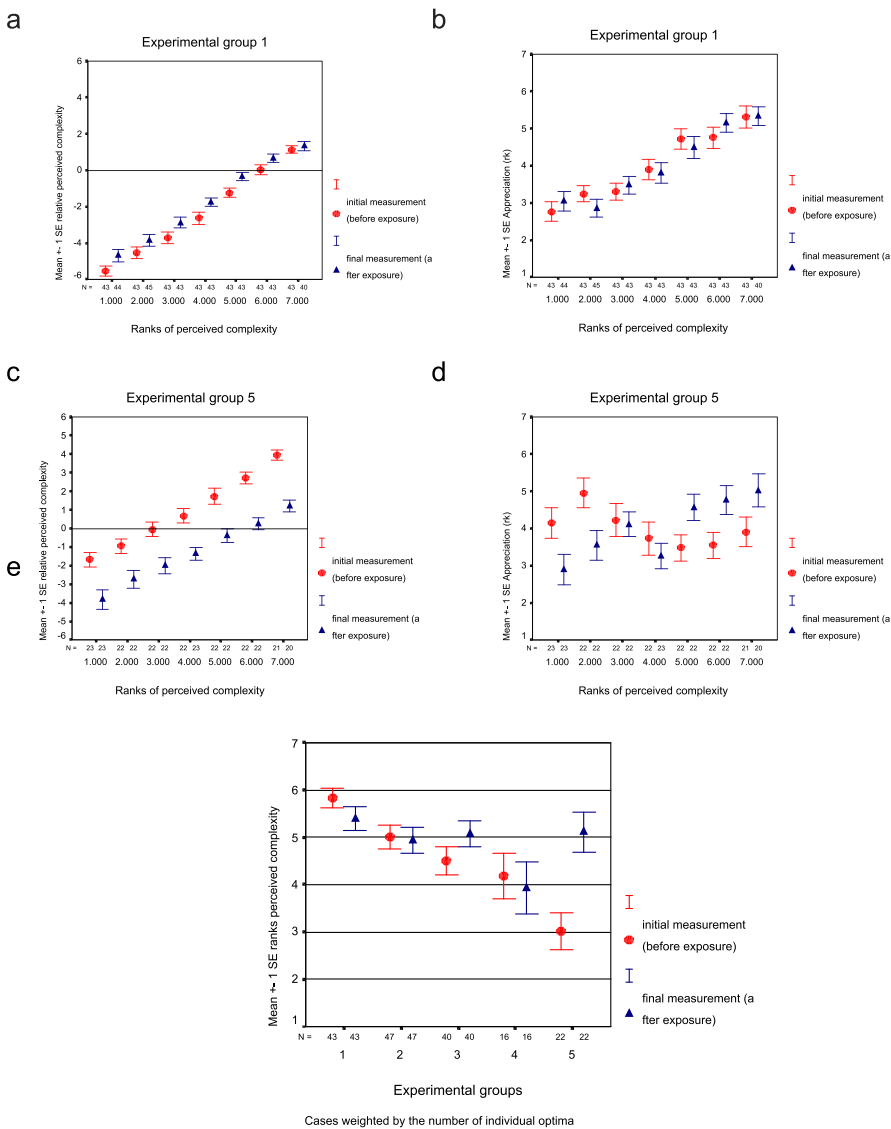


Figure 13.1 Effects on the perceived complexity (A) of and on liking (B) for the seven (1.000–7.000) drinks after repeated exposure to stimuli that are below the optimal complexity of the participants and after stimuli that are above the optimal complexity (respectively, (C) and (D) for perceived complexity and liking of the seven drinks. Also shown (E) are the changes of the level of optimal complexity in the five groups that were exposed to stimuli of lower complexity (groups 1 and 2), equal complexity (group 3), and of higher complexity (groups 4 and 5) than their optimal complexity.

shown that children, who during the first session had a preference for rather familiar but rather simple fruit flavors in jam-topped cookies (cherry, raspberry, and strawberry), switched already after three exposures predominantly in their choice to the much more complex taste of wild strawberries (Fig. 13.2). This indicates that the common belief that children like simple tastes may be misleading. In fact children learn to like more complex tastes very quickly (perhaps even in one-trial learning) as was demonstrated also more recently by [Reverdy et al. \(2010\)](#).

As can be seen, the original preference for the simple flavors (cherry, raspberry, and strawberry) changed pre-dominantly into a preference for the more complex wild strawberry (respectively, 49%, 57%, and 68%). In the other pairs the percentages change toward the finally most liked products where all are well below 50% with the exception of the change of 52% toward raspberry in the children who originally most liked cherry flavor in the first pairwise comparison.

On average the original preference of the complex wild strawberry flavor changed less (41%) into that for the other flavor in the different pairs, than the original liking for the three simpler flavors (respectively 49%, 48%, and 49% for cherry, raspberry, and strawberry). This indicates that the optimal complexity of the children has shifted toward the higher complexity.

All of these results are in accordance with the theories of Berlyne, of Dember, and Earl and of Walker. They indicate that the children rather quickly get bored with the originally most liked simple products. Furthermore, when confronted with a complex flavor they quickly overcome the uncertainty created by stimuli of more than optimal complexity during a phase of specific exploration and then in the following phase of diversive exploration learn to appreciate more arousing stimuli and shift their optimal level of complexity toward them ([Berlyne, 1960](#); [Dember and Earl, 1957](#)).

As pointed out elsewhere ([Köster and Mojet, 2007b, 2012a,b](#)) this has clear consequences for the long-term acceptability of products in the market and the neglect of

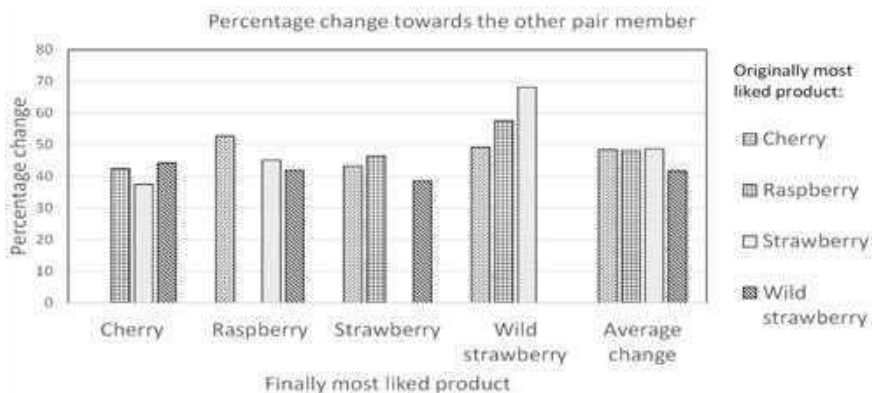


Figure 13.2 The percentages of children that change their original preference for the most liked product during the first session in each pair toward a preference for the other pair member (finally most liked product) during the third session.

these considerations in the marketing of new products that are launched after just consumer tests based on first impression, has probably strongly contributed to the high flop rate and shorter life cycles of new food products.

Up to this point the perceived complexity described in this paper was based on the impression of the number of different flavor notes that the perceiver has at a given moment. This is called simultaneous perceived complexity and should be distinguished from temporal perceived complexity, which indicates the number, the order, and the speed with which impressions succeed each other while consuming a product. The flavor impressions of some products hardly change over time while eating them, but in other products different impressions succeed each other as the dominant feature in the perception during the eating. In a way, these successive impressions and their momentary accords form the melody of the product. In recent years, the study of succession of dominant sensations (TDS) (Pineau et al., 2009) has been combined with measurements of liking (TDSL) and still more recently with emotion measurements (TDE) (Jager et al., 2014). Although it can be shown that understanding the “melody” of the product may be extremely important, it is doubtful whether the task of the subjects in such pluridimensional approaches does not become too strenuous. Furthermore, there is a need for more systematic research to establish general rules that can be used to successfully predict highly appreciated “product melodies.” In the beginning of this research the present authors executed a number of confidential experiments in which they were able to understand and predict the relative market success and downfall of respective snack products like the Mars bar and the Nuts bar. In general, more research is needed on sequential liking effects both within products and between components of a dish or even a meal. Some of the methods that could be used have been described (Köster, 1990) in a French manual of sensory methods, together with methods that were successfully applied in confidential research on the composition of assortments of hard candy or of chocolates and of cookies, where successive liking may be crucial for market success. Thus, it was found in the case of an assortment of hard candy the majority of people start with one or two red ones (either a strawberry or a raspberry flavor) and then after a while usually move to a yellow or green (lemon or lime) candy. But this raises the difficulty that after the lemon or lime flavor, one has difficulties to go back to strawberry or raspberry (a low sequential preference). This problem can be overcome by taking a taste like a blackberry in the assortment that can serve as an intermediary to come back to the strawberry or raspberry (good sequential preferences). The unpublished results of this procedure were shown in a large positive shift in the market success of the extended assortment some 20 years ago.

Sequential preferences are almost always implicated in perceived complexity (even in what is considered to be simultaneous complexity), and it is surprising that they have not been studied more. In fact, they are important product-related properties that in themselves are relatively stable and contribute much to the perceived complexity impression of the total product.

13.3 Familiarity and variety as concepts

Measuring familiarity is a common procedure in much of sensory product research, but very few people seem to realize that familiarity is a rather unclear notion that can mean either of two things: (1) the frequency of having perceived the actual stimulus at earlier occasions or (2) the strength of the resemblance to another more well-known stimulus. These two notions are fundamentally different and may not even be related to each other at all. They also give rise to a completely different memory search by the subject. In a recent experiment (Mojet et al., 2015) they were both measured in three sets of two yoghurts and the nonsignificant correlations between them were below $r = 0.24$ in two sets and below $r = 0.40$ in the third set. It could also be shown that the two types of familiarity differed strongly in their relationship with respectively the expected liking of the yoghurts before tasting and with the liking after tasting. Nevertheless, many authors rate familiarity as if it was a unitary concept. In the future this should be avoided, because it does not tell us anything about the form of flavor memory that was involved in the familiarity measurement.

Variety as a concept is clearer, and it is in a way closely related to temporal complexity albeit on a wider time scale. In general, people dislike monotony and opt for variety as a source of arousal and pleasure (Van Trijp, 1994). Nevertheless this tendency differs from activity to activity and in food consumption from meal to meal. In many countries people eat for instance the same breakfast every day and in some countries the same behavior may even be seen for lunch, but there are very few places where people eat the same dinner every day, unless they are forced to do so for lack of variable food sources (other than cassava, for instance). To our knowledge the only country where people always eat the same meals out of free will is Nepal, where they eat twice a day Dal Bhat, and often refuse to eat anything else in their main courses than this very delicately spiced and therefore probably sufficiently complex dish.

For the rest of the world variety in different successive meals as well as between bites within the meal seems to be an essential factor in avoiding boredom (otherwise known as sensory specific satiety), which has been studied extensively in the laboratory by many authors (Rolls et al., 1981). In normal everyday life we do all we can to avoid it by taking differently composed successive bites if we can. Even when eating stewed dishes we try to obtain bite to bite variety by selecting successively meat-containing and non-meat-containing bites even without conscious awareness of selecting. Variety seeking is a common element in all omnivores, and it provides us the arousal we need to live pleasurably (Hebb, 1949; Berlyne, 1960). Variety seeking has been measured by van Trijp and Steenkamp (1992) who developed a scale to measure it and applied it (Van Trijp et al., 1992) to sandwich choices, but with rather moderate success, finding no significant relationship between variety seeking-tendency and variation in the experimentally varied sandwich choices. This may have been due to the strong habit formation of the subjects and the fact that eating simple bread sandwiches might not have involved the high variety seekers strongly enough. Also the internal variation within the individual sandwiches may not have sufficed to satisfy them.

Recently, the delicate balance between habit and variety seeking that may take place has been described in a “conceptual and empirical model of habitual choice, and the factors that result in transitions to two strategies other than habitual selection: utility-maximizing choice and a variety-seeking strategy model” (Adamowicz and Swait, 2012). This model was tested on two types of products (ketchups and yoghurts) and the heterogeneity across types of products in the decision strategies and routine choice patterns was shown, thus stressing our earlier made point about the truly “collative” nature of the factors involved in food choice.

Both the inclinations of the subjects and the differences in product throw their weight in the balance and both consumer segmentation (on habitual behavior or on variety seeking) and product characterization (using liking and/or complexity) should be employed to obtain meaningful results. Adamowicz and Swait stress the importance of using behavioral choices rather than scalar methods to form segments. They also stress the fact that habitual behavior is often subconscious, belonging to the class of intuitive thinking (Kahneman, 2003) and should not be measured with clearly explicit methods, whereas variety seeking is often much more conscious and reasoned. Nevertheless, people may not be aware of their variety-seeking tendencies themselves. The conceptual model Adamowicz and Swait developed is based on the notion of intertemporal switching between strategies or decision-making styles and provides a good illustration of the complex interactions between product-related and person-related factors that are neglected in much sensory and consumer research.

13.4 Theories predicting the development of product appreciation over time

The complex interactions between habits and variety seeking that are sketched in the theory of Adamowicz and Swait resound the extensive and basic theoretical discussions about the roles of passive or active and unconscious or conscious factors in the development of preferences that characterized motivational theories in the second half of the 20th century (see overview in Köster and Mojet, 2007a).

Modern motivation theory was founded by Hebb(1949) who broke away from the traditional view that need—and drive—reduction were the only motivational action forces of an otherwise passive organism and who proposed that each individual strives actively toward an optimal level of stimulation and activation. This implicated already the existence of an individual optimal level of activation or arousal.

Berlyne in 1960 extended these ideas by describing four sources of arousal in a stimulus encounter: novelty, uncertainty, conflict, and complexity. He also describes two forms of exploratory behavior that is evoked by these forms of arousal: (1) *specific exploration* which is directed at resolving the uncertainty implicated in each of the four sources and precedes a second stage called (2) *diversive exploration* in which the person seeks entertainment and relief from boredom. In this latter aspect stimulus complexity plays a major role. Unfortunately, this is often poorly understood in present day market research, which often tries to avoid the necessary specific exploration by

making products very simple and free from uncertainty, but which, in doing so, forgets that such products will very soon become too boring to provide pleasure in the diversive exploration phase. Thus, such products are doomed to be short-lived in the market after their initial success.

As explained and demonstrated above, such problems can only be overcome by presenting stimuli that are originally more than optimally complex and then, after the uncertainty reduction during specific exploration, remain sufficiently complex and stimulating to meet the optimal complexity level necessary for true diversive exploration. Furthermore, under the influence of repeated stimulation with such stimuli the optimal complexity of the consumers will shift a bit in the direction of the higher complexity of the new stimulus (Dember and Earl, 1957, see Fig. 13.1). These are the stimuli with continuing growth potential in the market. When properly introduced (see below) they also have the advantage that under the influence of the rising optimal complexity level, they make the competitor's products in the market look less complex and more boring.

Mere exposure theory, claiming that mere repetition of the stimulation sufficed to change liking for it positively, was launched by Zajonc (1968) and applied in the development of liking in different arts. Zajonc ascribed the effects mainly to the dissipation of neophobia, or when translated in Berlyne's terms to the uncertainty reduction in the specific exploration phase. When mere exposure was applied to the area of human food appreciation, the results were variable. Zajonc applying his testing exposure to vegetables in groups of students found strong positive correlations between the degree of exposure and positive liking, but Stang (1975) using different well-known spices found a steady decrease in liking, a phenomenon he described as *satiation* and which seemed very similar to Cabanac's *Aliesthesia* (1971) and to Sensory Specific Satiety (Rolls et al., 1981). Pliner (1982) on the other hand, using tropical fruit juices and a clever within-subjects design that "made it possible to distinguish the effects of mere exposure from those of other factors such as boredom and fatigue," found again strong and positive mere exposure effects. Much seemed to depend again on the collative relationship between the foods used and the experience with them of the people taking part in the experiment. In view of this dependence and the role that the subjects' optimal complexity level seemed to play in it, Köster and Mojet (2007b) proposed to consider Zajonc's mere exposure theory as a special case in a model integrating the theories of Berlyne, of Dember and Earl, and of Walker. According to them mere exposure only takes place for stimuli that are more complex than the optimal complexity of the observer. This may be due to causes such as the novelty of the stimulus or its more than optimal complexity. In cases of familiar or suboptimally complex stimuli there will be no positive mere exposure effect (as predicted by Dember and Earl) and boredom will set in (as explained by Walker's theory).

The relationships in this model are shown and further explained in Fig. 13.3.

According to Walker, experience with the stimulus reduces its perceived complexity (curved lines at the right side of the graph. If one presents the most liked stimulus A, experience will lead to loss of complexity and to loss of liking (boredom)). If, according to Dember and Earl, one presents repeatedly the originally less liked but more than optimally complex stimulus B, the optimal complexity will not only shift in

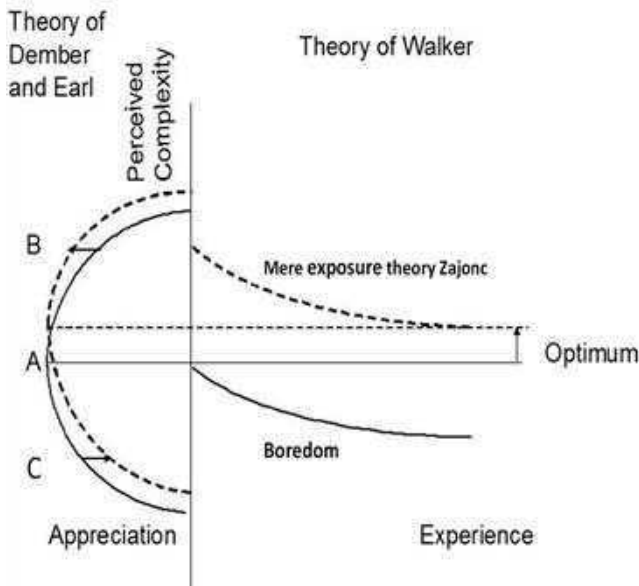


Figure 13.3 Addition of Walker's theory to the theory of Berlyne, which is shown on the left side of the vertical perceived complexity axis and indicates the relationship between the appreciation of the stimuli and their complexity.

its direction (a shift of the curved line to the dotted curved one on the left of the graph and as a consequence a shift of the straight line to the dotted straight horizontal line on the right side of the graph) but under the influence of experience this stimulus B will become less complex and will approach (dotted curved line) the new optimum (dotted straight line on the right side). This latter case describes the mere exposure theory of Zajonc and the figure makes clear that mere exposure only works with more than optimally complex stimuli, while a lower than optimal stimulus (C) just becomes more boring and loses even more liking under exposure to B (after [Köster and Mojet, 2007b](#)). Together these theories seem to explain all of the effects caused by repeated exposure to stimuli of a given perceived complexity to people who by their previous exposures to stimuli have acquired a given optimal perceived complexity level at a certain moment in life.

13.5 Learning experience, culture, and the formation and development of optimal complexity of the consumer with experience and age

As pointed out above and shown in the experiments of [Léon et al. \(1999\)](#) and of [Reverdy et al. \(2010\)](#), implicit learning by exposure to more than optimally complex stimuli has

already an effect on the development of food preferences from a very early age and may even be effected by one-trial learning. Depending on the importance of the role of food as a source of pleasure in different cultures (Rozin et al., 1999), it may contribute more or less to the general wellbeing of people. In a country like Italy where eating is very traditional, the food is seemingly simple, but based on a very fine feeling for sequential liking and an internal product melody with a high level of complexity. Italian people have difficulty with other kitchens that miss such refinement and so do the French with their many regional cuisines and great diversity of local dishes and cheeses, which make them perhaps the most conscious and gastronomically interested people of Europe. On the other hand there are a number of countries where food is treated as a necessity and where quantity and satiation seem more important than quality and complexity of taste. Nevertheless even in these countries there are great differences between segments of the population with regard to optimal complexity, and this means that just averaging over people may obscure the role of complexity in the market opportunities of products and thus may reduce their success. Other examples of the role of complexity in the development of preferences are countries where new eating or drinking habits are coming up. Thus, in Britain where traditionally beer was drunk (except in a small upper-class portion of the population that traditionally drank rather complex Bordeaux wines and often even owned the vineyards where they were produced), the new and quickly growing acceptance of wine drinking by the population shows a steadily growing demand for more and more complex wines as might be expected according to Dember and Earl's theory. The simple wines that had much appeal in the beginning become boring and the populations' optimum shifts toward more complexity.

Similar developments are characteristic also for the development of optimal complexity with age in the personal life of people up to the point where the sensory capacities start going down. For olfaction, which is the most important one in the area of food appreciation, this decay starts already after the 50th year in some people, whereas others retain a remarkable sensitivity up till a very high age. Before the breaking down of olfaction, most people develop more and more optimal complex levels for the foods they like. After the loss of the sense of smell usually texture experienced by the sense of touch takes over the leading role in relating the actual experience to memories of earlier occasions, but much of the complexity experience conveyed by smell is lost and some elderly people start losing their interest in complex food and wines and in many cases adopt eating habits in which the pleasure of eating comes mainly from remembrances evoked by traditional foods via texture memory or they adopt rather boring dutiful routines to keep their health up. For these people old age anorexia is a real threat. A number of authors have tried to counter these tendencies by flavor enhancement, but often with little or no success (Schiffman, 1988; Bellisle et al., 1991; Schiffman and Warwick, 1993; Mathey et al., 2001; Mojet et al., 2005; Kremer et al., 2007). Mattes (2002) discussed the issue critically. Mojet et al. (2005) supposed that even a diminished flavor and texture perception had the power to awaken the situations in which foods were eaten at earlier occasions. According to them, such remembrances played an important role in the fact that loss of taste sensitivity did not lead to loss of eating pleasure in their experiments.

Only a few happy elderly who still have their full sense of smell continue to take pleasure in discovering new and more complex food.

13.6 Practical implications for product development and marketing

What can we learn from all this if we want to improve our marketing strategy and the introduction of new products? We must be aware that people change in more than one way when repeatedly consuming the product. In the first place they overcome their hesitation and uncertainty under the influence of specific exploration and in the second place they change their optimal complexity level, provided the product is more complex than their original optimal level. This has the following methodological consequences for the research needed to base product launching decisions on:

1. The first impressions that people have from a product are almost never a good indicator of their long-time acceptance, unless the first impression of a product is extremely negative and it is really rejected on the basis of this. But the new product that is most liked at first sight is at high risk to become quickly boring, because it is not complex enough. Repeated exposure, helping people to overcome their first uncertainty in specific exploration and to select products that are sufficiently complex to be above the optimal complexity level of the consumers, should therefore be considered a must in consumer research. Knowing the development of product appreciation over a number of encounters is essential in order to avoid untimely market flops.
2. The repeated exposure should be carried out with product variants of different, but always more than optimal complexity during a number of central location tests (3–5) separated by home use of one of the different products carried out under normal everyday circumstances as possible. This means that people receive one product variant for home consumption in sufficient quantities to taste them with their families several (1–3) times as normal meal components, in normal quantities and at normal intervals, depending on the customary consumption pattern for the type of product involved. Over the whole period the liking for all products are measured in the intervening central location tests and the time course for the liking of products that rise in appreciation is noted and taken into account in the composition of a special market introduction deal. This deal is a packet of the new product at a very low prize that will serve the household for a number of uses and long enough to let specific exploration help to overcome the original hesitation and uncertainty evoked by the complex product and to let the growing product appreciation set in.
3. The success of this approach could be tested in a small-scale market test of a few weeks with groups of users of different brands segmented on the basis of their optimal complexity level and should show rises in appreciation of the new product and losses of appreciation for competitor products, which, because of the changed optimal complexity level of the subjects, start becoming too simple and boring for them.

This approach has successfully been tried in confidential research with rather different products varying from detergent odors to pasta sauces and chocolate cookies and has led to more long-term and growing acceptance. Long-term acceptance can also be extended even more by gradually raising the complexity of the product after a few months by the gradual addition of minimal quantities of new flavors or odors, which are indeed small enough not to be noticed as product changes by the consumer.

13.7 Conclusion

Since the earlier edition of this chapter, the role of stimulus complexity in the long-term acceptance of food and fragrance products is still underestimated, and this has had serious consequences for the development of the market. Also, there has been very little attention devoted to the study of implicit odor memory. Almost all publications in the field are set up along the same lines as visual and acoustic experiments, and the clear evidence that olfaction is a different sense is neglected. We have shown (Degel et al., 2001; Møller et al., 2012; Köster et al., 2014) that olfactory memory is based on novelty and change detection in normal everyday human life and is closely linked to the first situation in which the odor was encountered. This means that memory experiments in laboratory settings and with explicit odor memory instructions are misleading and irrelevant for understanding the true function of olfaction as a warning sense and not an orienting sense like vision and hearing. We immediately notice changes in the odors of well-known situations, and they put us on the alert, but we do not try to identify them by name and we do not notice the odors that we know to belong to the situation. Also the sense of smell, like the sense of touch, another warning sense, adapts completely, showing that continuous stimulation is of no interest whereas change remains important.

Still, the introduction of the rather shallow first impression consumer tests by the marketing departments of many industries as an important element in the launching decision has led to a considerable shortening of the life cycle of products in the market and to a higher rate of new product flops than in the time when expert product developers with their more complex taste preferences made the launching decisions (Köster and Mojet, 2012a,b). In view of the psychological theories about the function of complexity in the development of preferences, this is a logical consequence of the fact that products that are liked at first sight will soon start to lose the interest of the consumer and that products that in the beginning are a bit confusing because of their higher complexity may grow in preference over time provided they are well designed, balanced, and tested. Both the industry and the consumer might therefore benefit from attention to product complexity and adequate testing procedures to take it into account before launching new products in the market.

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The metabolic status and olfactory function

14

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In humans and animals, eating behavior, comprising food seeking, onset, and end consumption, is mainly triggered by internal metabolic needs, signaled by fluctuating levels of metabolic-related hormones and peptides (leptin, insulin, ghrelin, orexin), and of nutriment, such as glucose. However, the food consumption is also regulated by hedonic and sensory signals, including olfaction (Rolls, 2012), this making food-related odors as essentially involved in the food intake control (Le Magnen, 1959).

An intuitive perception from everyone's experience is that the olfactory function can be modulated by the metabolic state. Indeed, both the olfactory mucosa and bulb are influenced by metabolic hormones, peptides, and nutrients, which modulate odor processing according to the internal energetic status at short- and long-term. This chapter aims to shed light on how endogenous signals linked with the feeding or metabolic state regulate olfactory sensitivity and olfactory-driven behaviors in humans and animals, with a special emphasis on the impacts of metabolic disorders, such as obesity, diabetes, and eating disorders. It also gives insights into the programming effect of the maternal metabolic context as a way to support long-term effects on offspring's olfactory capacities.

14.1 How is the olfactory function influenced metabolic-related hormones and peptides and of nutriment: neuroanatomical evidence

In the past 50 years, numerous efforts have been undertaken to localize hormones/peptides and their receptors by immunohistochemistry, radioimmunoassay (radioactive or not), hormone binding assays, and more recently molecular biology. The demonstration that most metabolic anorexigenic and orexigenic hormones and peptide receptors traditionally considered to be feeding-related are expressed in the olfactory system in many species strongly came to support the findings that odor processing can be modulated by the nutritional status; especially in the first two levels of the olfactory system, the olfactory mucosa (OM), and the olfactory bulb (OB), well before the involvement of cortical integration (Lucero, 2013; AlKoborssy et al., 2014; Nogi et al., 2020).

14.1.1 Anatomical distribution of receptors to metabolic-related hormones and peptides along the olfactory pathways

14.1.1.1 The olfactory mucosa

In mammalian OM,¹ mature olfactory sensory neurons (OSNs), key cells interacting with odorant molecules and transducing the odorant signal, express a large array of receptors dedicated to major anorexigenic or orexigenic metabolic hormones: orexin receptors (OXR) have been localized in the apical ends of the sensory neurons (Caillol et al., 2003; Gorojankina et al., 2007), leptin receptor (Ob-R) (Baly et al., 2007), and insulin receptor (IR) (Lacroix et al., 2008) in dendritic knobs, ghrelin receptor (Ghslra) (Loch et al., 2015), and endocannabinoid receptor CB1 in mature OSN (Hutch et al., 2015). To a lesser extent, neuropeptide Y receptor (NPY–Y1R) is expressed in a subset of OSNs dispersed within the OM (Negroni et al., 2012). Moreover, the adiponectin receptor (AdipoR1), through which adiponectin regulates glucose levels and fatty acid catabolism, is also present in mature OSNs (Hass et al., 2008). Immature neurons, for their part, only express Ob-R and IR. Moreover, the nonneuronal sustaining cells, ensheathing OSNs, express most of the so-far mentioned receptors, except NPY-Y1Rs. Finally, the basal cells that ensure the OSN's renewing express IR, Ob-R, NPY-Y1R, and CB1. In the *lamina propria*, Ob-R has been reported in the Bowman glands and IR in the endothelium of microvessels (Getchell et al., 2006; Baly et al., 2007; Lacroix et al., 2008).

14.1.1.2 The olfactory bulb

The olfactory bulb (OB) being the first olfactory structure of the central nervous system, a great effort has been done in localizing metabolic-related receptors expression since decades in this tissue. The mitral-tufted cells (MTC) that receive direct sensory inputs from OSNs and transfer it to next brain olfactory area, express a large number of metabolic-related receptors, including some of those reported in the OM such as IR (Fadool et al., 2000; Lacroix et al., 2008; Marks et al., 1990), Ob-R (Baly et al., 2007; Prud'homme et al., 2009), OXR (Caillol et al., 2003; Hardy et al., 2005; Shibata et al., 2008), CB1 (Tsou et al., 1998; Wang et al., 2012), and additional ones such as Growth Hormone Secretagogue Receptor for ghrelin (GHSR) or Cholecystokinin 2 receptor (CCK2R). More precisely, Ob-R, OXR, GHSR, CCK2R are expressed in the periglomerular area (OB peripheral layer where OSNs' axons synapse with MTCs' dendrites) while IR, Ob-R, ORX, GHSR, and, to a less extent NPYR2, are present in the granular cells layer (Mercer et al., 2000; Tong et al., 2011; Aimé et al., 2012; Okuhara et al., 2018).

¹ The olfactory mucosa is located in the upper region of the nasal cavity and comprises the olfactory epithelium and the underlying lamina propria, connective tissue containing fibroblasts, blood vessels, Bowman's glands, and bundles of fine axons from the olfactory neurons.

14.1.2 Local synthesis of metabolic-related hormones/peptides in olfactory tissues

Metabolic hormones/peptides related to the receptors mentioned above mostly originate from peripheral organs (pancreas, adipocytes, gastrointestinal tract), and reach OM and OB by the general circulation thanks to the rich vascularization of the *lamina propria*. Some others are synthesized and secreted in brain areas and released at the OB level via centrifugal fiber connections. Besides these sources for metabolic factors, local synthesis in the olfactory tissues has also been reported for orexin, leptin, insulin, NPY, endocannabinoids. In OM, some of them are synthesized by OSNs themselves (Caillol et al., 2003; Getchell et al., 2006; Baly et al., 2007; Lacroix et al., 2008) or by supporting cells (Montani et al., 2006; Jia et al., 2013; Hutch et al., 2015). Insulin has also been detected in the mucus that bathes the ORNs' cilia and sustaining cells' microvilli, suggesting a local production by nasal glands (Henkin, 2010). Similarly, in OB, several hypothalamic peptides and hormones are locally synthesized as putative key neuromodulators in regulating olfactory processing (Palouzier-Paulignan et al., 2012; Russo et al., 2018; Thiebaud et al., 2019). The reasons for the local synthesis are not yet understood, but the fact is that its level varies upon feeding conditions modifications (see Section 14.2) suggesting that a sustained paracrine synthesis would benefit the tissue homeostasis.

14.1.3 The olfactory system, a target for circulating nutriment

In addition to being sensitive to metabolic hormones and peptides involved in food intake regulation, a large body of evidence indicates that the olfactory system would be also directly targeted by blood circulating nutrients, such as glucose, amino acids, and lipids as recently reviewed (Julliard et al., 2017; Wu, 2020).

Glucose is the main energy source for cells, and glucose/lactate is essential in metabolic exchanges in the brain, between astrocytes and neurons (Benarroch, 2014). Glucose and lactate transporters or sodium glucose cotransporters (GLUTs, MCTs, SGLT1) have been described in various cell types of the OM and OB (Choeiri et al., 2002; Nunez-Parra et al., 2011; Aimé et al., 2014; Al Koborssy et al., 2014; Lacroix et al., 2015). GLUTs (1, 3, and 4) have been reported in the OB (mainly in the MTC and granular cell layers) and OM (GLUT1 in OSNs, Bowman glands, and endothelial cells; GLUT1 and 3 in sustentacular cells). Moreover, GLUT4, a transporter of particular interest since being an insulin-responsive glucose transporter, likely involved in obesity and insulin resistance pathology (Lumeng et al., 2007), is also expressed in the OM (Lacroix et al., 2015). Thanks to these transporters and to glucose metabolizing enzymes, sustentacular and Bowman's gland cells could participate in the transport of glucose from the blood vessels to the mucus to sustain OSN chemotransduction (Acevedo et al., 2019).

Fatty acid receptors, such as CD36 or GPR40, are expressed in neurons of olfactory structures, which raises the question of their role(s) in lipid olfactory sensing (Lee et al., 2015; Nakamoto et al., 2012). CD36, which is involved in oleic aldehyde

perception, is prominently present in OSN cilia during the suckling period where it could fix oleic acid, a major milk component (Oberland et al., 2015; Lee et al., 2017).

In OB, the recent localization of GLUT5, GLUT9, and elements of the primary metabolic pathway for fructose, a major sweetener in processed foods has also opened the possibility for its active metabolization in this structure (Oppelt et al., 2017).

Regarding more particularly the interactions between the metabolic signals and olfactory function, the expression of a myriad of metabolic receptors in various cell types of the OM obviously makes the olfactory tissue a privileged target of chemical nutritional cues from the systemic circulation (this point will be largely discussed in the next sections). However, in OM, the presence of metabolic receptors means that these receptors can be also targeted by inhaled molecules, not a priori devoted to the transmission of metabolic information. Indeed, it has been reported that odorants could bind some metabolic receptors as CB1 cannabinoid receptor (Audouze et al., 2014). Here, we are on the edge of the pure olfactory function and the next question is: Would such odorant-metabolic receptor interactions extend the role of odorant molecules from the role of olfactory stimuli to other functions?

In any case, putative roles for feeding-related hormones and peptides probably differ between species. For example, in amphibians, OM endocannabinoid receptors (CB1 and CB2) modulate OSN sensitivity, thus contributing to the food intake control (Czesnik et al., 2007; Breunig et al., 2010). However, in mice unlike amphibians, OM endocannabinoids would not directly modulate the peripheral odorant detection, but would rather influence the cell homeostasis (Hutch et al., 2015).

The potential cross-over effects between the purely olfactory and/or modulatory function of odorants on hormone receptors and the species-differential effects of hormones on neuronal receptor function give us insight into the multiplexing between pure odorant and metabolic drug signaling, making the peripheral olfactory stage a strategic site for metabolic influences.

14.2 Prandial state and olfactory function

From all the neuroanatomical observations, it becomes evident that a myriad of internal physiological hormonal fluctuations due to the modification of the metabolic status linked to food intake rhythms putatively modulate the odorant signaling. Such a metabolic modulation of the olfactory processing could be induced, either directly through the modification of local synthesis of metabolic related-factors, or indirectly through endocrine signals released in the general circulation. Accordingly, the effect of fasting has been largely investigated in the past years.

14.2.1 In humans

Since the 1950s, many studies have been designed to investigate the influence of the nutritional state on the olfactory perception processing at the peripheral level, a question that is still a matter of debate. Most studies used experimental devices or protocols

allowing a broad evaluation of the olfactory performances by scoring several dimensions, such as threshold, discrimination, identification, and pleasantness of various odors. Earliest studies concluded, as intuitively expected, that fasting increased olfactory sensitivity (Goetzel et al., 1950; Schneider and Wolf, 1955), and were confirmed by later ones (Furchtgott and Friedman, 1960). Besides, other studies were less conclusive. Indeed, some data described a trend for lowered odor threshold under hunger state, but failed to achieve statistical significance due to individual variations (Furchtgott and Friedman, 1960), while others reported no link between the modulation of the olfactory perception and the feeding state (Koelega, 1994). These discrepancies can be mostly attributable to the fact that results have been gathered from very different conditions and paradigm methodologies: practice trial or not before the experimental investigation, size and age of the cohorts, within or between subject design, preevaluation or not, of the hunger and mood state of the subject, nature and administration mode of the stimulus, duration of the fasting, time of the day at which the tests were performed, type of meal.

More recent studies, in which experimental paradigms have been roughly standardized, further emphasized the need to make a distinction between the sensitivity toward food versus nonfood odors. Here lies the general common question of the classification of odors as strictly food-related or not. Indeed, by using the n-butanol generally considered as a nonfood odor, the olfactory sensitivity is mostly found to be increased by fasting (Stafford and Welbeck, 2011; Cameron et al., 2012; Hanci and Altun, 2016), except in Albrecht's study (Albrecht et al., 2009) where it was unchanged. For food related-odors (2-heptanone/blue cheese odor, isoamyl acetate/banana odor, herb odor), different studies reported that the olfactory sensitivity was increased, but, unexpectedly, only in satiated conditions (Berg et al., 1963; Albrecht et al., 2009; Stafford and Welbeck, 2011). The last study suggested that such an increased sensitivity following the meal might help the subject to detect and reject spot foods that are no longer required, since they have been consumed at satiety. However, this observation was only concerned with high body mass index (BMI) subjects, suggesting that maintained sensitivity for food odors after meal rather reflects a decrease in the sensory-specific satiety (Cabanac, 1971) and would sustain food intake at the expense of the physiological needs.

Other studies reported the general chemosensory performances for nonfood odors—here lies the general common question of the classification of odors as strictly food related or not—are improved in hunger state (Cameron et al., 2012) and decreased in satiety state (Hanci and Altun, 2016). In agreement with these results, the administration of insulin, mimicking a postfeeding episode in normosmic human, led to a decrease in sensitivity for nonfood odors (Ketterer et al., 2011; Brunner et al., 2013) while it could also otherwise improve odor-cue spatial memorization (Brunner et al., 2013, 2015). In the same line, in patients with postinfectious loss of smell, the intranasal insulin application could immediately improve their olfactory performances: both detection and cognitive recognition (Schopf et al., 2015). Similarly, increase in odor detection was observed at high insulin doses, for neutral odors in normal and overweighted subjects (Thanarajah et al., 2019). Thus, according to the task, the type/concentration of odors and the status of the subjects, healthy or with pathology,

insulin could induce effects on the olfactory-driven performances that seem paradoxical. For completeness, the demonstration of a differential effect of insulin on olfactory sensitivity according to the sex, a parameter which has been neglected in most studies, complicates the investigations (Rodriguez-Raecke et al., 2018). Moreover, it must be stressed here that the physiological satiation state cannot be limited to the only insulin secretion.

With regard to the hunger state, Tong et al. (2011) reported that fasted subjects, systemically injected with ghrelin (aiming at reinforcing the physiological increase of this appetite-stimulating peptide before a meal), displayed increased sniffing rates for both food and nonfood odorants (Tong et al., 2011). Indeed, sniffing behavior is a crucial element of the olfactory function, which mirrors the olfactory exploration, high nostril flow rate being associated with enhanced odorant detection (Laing, 1983; Sobel et al., 2000).

In conclusion, in healthy and normal BMI humans, a specific decrease in food odor sensitivity is mainly observed after a meal and is associated with a hedonic value decrease for a food consumed to satiety, as described earlier (Rolls and Rolls, 1997). It could participate in the food intake regulation by reducing the olfactory pleasantness in humans, but this effect depends on various parameters.

14.2.2 *In animals*

Important data were obtained by exploring global odor-driven behavioral responses in relation to hormonal regulation in animals, mainly in rats and mice (Pager et al., 1972; Gervais and Pager, 1982; Mulligan et al., 2002; Apfelbaum and Chaput, 2003). These experiments, by ensuring a better standardization in experimental conditions, broadly led to the same conclusion, namely that olfactory sensitivity is strongly modulated by the satiety state, and further, allowed to unravel some of the neuronal underlying mechanisms. The introduction of a food odor in the environment of satiated rats increased their basal activity (moving around, grooming) and sniffing activity. Such behaviors are amplified in fasted animals and might be mimicked by intracerebroventricular administration of orexigenic chemicals as orexin (Prud'homme et al., 2009) or insulin (Lacroix et al., 2015) in satiated animals. Conversely, the administration of anorexigenic chemicals, such as leptin or orexin antagonist, decreases food odor exploration times of fasted rats (Prud'homme et al., 2009). Olfactory behavioral tests in rat, based on conditioned olfactory aversions, also clearly showed that nutritional status and metabolic-related hormones/peptides modulate odor sensitivity. Furthermore, the odor sensitivity increase, observed upon physiological fasting (Aimé et al., 2007; Ferry and Duchamp-Viret, 2014), was mimicked in satiated rats by injection of orexigenic factors, such as ghrelin (Tong et al., 2011) or orexin (Julliard et al., 2007; Ferry and Duchamp-Viret, 2014). Conversely, the decrease in odor sensitivity observed in satiated animals could be mimicked by administration of anorexigenic factors, such as leptin (Julliard et al., 2007) or insulin (Marks et al., 2009). However, the effects of fasting on enhancement of olfactory behaviors also depend on the metabolic context of animals, since rodent models displaying low energetic backgrounds, such as the lean

Lou/C rats, boost their olfactory sensitivity upon fasting, whereas obese Zucker rats do not (Badonnel et al., 2014).

The introduction of a familiar food odor in the environment of a fasted animal increases the OSNs electrical activity leading to enhanced c-fos labeling (immediate-early gene) in OB. The same effect on c-fos labeling was obtained in satiated rats by intracerebroventricular injection of orexin (Prud'homme et al., 2009). Inversely, leptin and orexin antagonist administrations decreased c-fos response to a food odor (Prud'homme et al., 2009). Therefore, the opposite effects obtained with the appetite-stimulating and appetite-suppressing peptides on the olfactory system are in line with their expected impacts on behaviors linked to food consumption.

The direct demonstration of the action of metabolic hormones and the ways by which they modulate food odor processing have been brought by electrophysiological studies that allowed unambiguous identification of the targeted neurons and mechanisms in the past few years. At the olfactory system peripheral level, as intuitively expected, a local application of anorexigenic or orexigenic factors has been shown to impact the amplitude of electroolfactogram (EOGs: odorant-induced electrical response of a population of OSNs). The two potent anorectic peptides, insulin and leptin, decreased the amplitude of EOGs (Lacroix et al., 2008; Savigner et al., 2009) whereas, conversely, the orexigenic neuropeptide Y increased it, but only in fasted animals in which Y1 receptors are overexpressed (Negroni et al., 2012). Another starvation signal, adiponectin, increased EOG responses (Loch et al., 2013) and then OB responses (Loch et al., 2015), independently from the feeding state. In addition, the endocannabinoid system (CB1) was found as being involved in the regulation of food intake and odorant detection in fasted mice. Indeed, CB1 receptors endow centrifugal cortical fibers that project on OB inhibitory granule cells, their activation would inhibit these interneurons resulting in turn in a disinhibition of the MTCs (Soria-Gomez et al., 2014). Thus, such a CB1 system control, involving cortical feedback on OB, could couple metabolic states and perception abilities (see Terral et al., 2020 for a review).

In OB, patch-clamp recordings showed that the circulating hormones exert directly their effects on MTCs (Fadool et al., 2000; Apfelbaum et al., 2005; Hardy et al., 2005; Kuczewski et al., 2014). More precisely, Kuczewski et al. showed that insulin can act on mitral cells both directly and indirectly, throughout the GABAergic interneuron network. By doing so, insulin could alter both rest and evoked activities of mitral cells. The use of these data to construct a mathematical model demonstrated that such an insulin action could differentially either increase or decrease the olfactory discrimination abilities of the OB network. This led Kuczewski et al. to propose that insulin, as one of the major hormones involved in feeding behaviors, would put the olfactory function under feeding signal control, according to the alimentary/ethological valence of the olfactory stimulus. However, if intranasal insulin administration impacts short-term olfactory processing, by modulating MTC firing in the OB in animals (Fadool et al., 2000; Tucker et al., 2013; Kuczewski et al., 2014), it displays negligible long-term effects, suggesting adaptive processes (Bell and Fadool, 2017). As for the anorectic hormone leptin, it reduces odor discrimination by decreasing the spontaneous firing of single

MTCs and the odor-evoked beta and high gamma local field potential response (Sun et al., 2019). Moreover, application of prokineticin 2, a hypothalamic anorexigenic neuropeptide, significantly decreases food intake by lowering olfactory sensitivity (Cheng et al., 2006; Mortreux et al., 2019). Data on awake, head-fixed mice confirm that fasting enhances spontaneous firing rate of MTCs and the number of cells showing an excitatory response following food and nonfood odors administration while it slightly decreases the neural discrimination (Wu et al., 2020).

The strong consensus that the olfactory performances rely on feeding conditions, through the feeding-state-dependent metabolic-related factors, is in full agreement with the fact that the expression of these factors and their receptors are modulated in the olfactory system, according to the nutritional state. Indeed, after 48 h of fasting, Ob-R and IR expressions in the OM are increased in rat (Baly et al., 2007; Lacroix et al., 2008). However, such an increase is not observed in the OB, suggesting that the modulation is tissue-specific and might answer to specific needs (Baly et al., 2007; Lacroix et al., 2008; Aimé et al., 2012). Moreover, the nutritional status impacts the local synthesis of these metabolic-related factors. Fasting increases leptin and insulin concentrations in the OM (Baly et al., 2007; Lacroix et al., 2011) or insulin in the mucus (Henkin, 2010) whereas decreases orexin (OXB) and prokineticin levels in the OB (Shibata et al., 2008; Mortreux et al., 2019). Even if these variations are small regarding the circulating concentrations, such paracrine control within the local environment of neurons may have functional repercussions. Moreover, due to the pleiotropic roles of these hormones and peptides in other tissues, they probably also more broadly target and impact some cellular processes, such as neuronal proliferation, apoptosis, and neuronal plasticity, as it has been shown for NPY and insulin in OM (Hansel et al., 2001; Doyle et al., 2008; Jia and Hegg, 2010; Lacroix et al., 2011), or for ghrelin in the OB, that could participate in interneurons' differentiation (Li et al., 2014) or to synaptic reinforcement between OSN and mitral cells (Russo et al., 2020). In the same way, in OM, NPY secreted by microvillar cells is not only essential for their own differentiation but also to send neuroproliferative signals to basal precursor cells, thus participating in neurogenesis, in basal conditions and after injury (Jia et al., 2013; Doyle et al., 2018; Huang et al., 2019). In addition, in mice, endocannabinoids are involved in the homeostatic regulation of cell proliferation of the basal cell population in the OM (Hutch et al., 2015; Hutch and Hegg, 2016). At last, leptin, by regulating OM mucus secretion, may modulate odorant–receptor interactions (Badonnel et al., 2009).

In comparison with the acute endocrine variations linked to fasting, the experimental modification of food-intake pattern of rats, i.e., a chronic food restriction, leading to long-term slight modifications of metabolic hormone circulating levels, also altered food-odor-driven behaviors and metabolic genes expression in the olfactory system (Badonnel et al., 2012). This result reflects the adaptation of both food searching behavior and olfactory signal processing to the metabolic state. Such long-term effects which also could result from ground hormones imbalances could be involved in some olfactory deficits (see the section on metabolic disorders). Such an adaptation of feeding-related neuromodulators expression was also reported when mice are trained with odor–food association (Nogi et al., 2020).

Finally, the olfactory system functioning is not only impacted by metabolic hormones but also upstream by some circulating nutriment associated to food intake and digestion. Among these, glucose is a reliable indicator of the nutritional status, since its concentration rapidly fluctuates around meal, its fluctuations being critical for glucose sensing neurons. In rat OB, a patch-clamp study showed that changes in glucose concentration could rapidly alter MTCs' firing frequency (Tucker et al., 2013). In agreement with this result, the expression and regionalization of GLUT4 in OB is described as being feeding-state-dependent (Aimé et al., 2014; Al Koborssy et al., 2014), suggesting that GLUT4, in addition to peptides involved in food intake regulation, could account, at least partly, for the olfactory sensitivity variations observed between satiated and fasted rats (Aimé et al., 2007; Al Koborssy et al., 2014). At last, OB glomerular astrocytes also participate in the regulation of metabolic sensing upon fasting thanks to an astroglial morphological plasticity controlled by anorexigenic and orexigenic peptides (Daumas-Meyer et al., 2018).

14.3 Metabolic disorders linked, or not, to eating disorders and olfactory function

In absence of metabolic diseases, the previous section showed that metabolic-related hormones/peptides and nutriment individually participate in the regulation of the olfactory signaling. However, it is still unclear if, and how, they interact in a complex metabolic environment in order to modify the olfactory function, particularly in case of severe pathologies characterized by chronic energy imbalance and food intake deregulation. A metaanalysis review in humans highlights the difficulties to definitely conclude on the association between the olfactory performances and abnormal eating behaviors, but underlines that data support an alteration of olfactory performances in obesity and anorexia nervosa disorders (Islam et al., 2015). Furthermore, the bidirectionality of such a relation is supported by a study reporting that, in mice, experience-induced loss of smell seems to prevent diet-induced obesity or block weight gain (Riera et al., 2017).

14.3.1 Obesity

Worldwide, obesity is becoming a major challenge for public health in Westernized societies over the past decades, causing a well-defined risk of cardiometabolic disease, osteoarthritis, and different types of cancer. Obese individuals display increased weight gain, metabolic disorders, and deregulated food intake (Paquot et al., 2012). It can be hypothesized that, facing highly palatable foods, the homeostatic mechanisms that regulate the energy balance are overwhelmed and changes in brain reward-circuitry probably occur. The last decade researches were undertaken to evaluate the olfactory function in obese subject, its modifications, and impacts in food intake deregulation.

14.3.1.1 *In humans*

In humans, data are difficult to synthesize due to large heterogeneity in social origins, food habits, lifestyle, and moods of people, as well as, biological differences, heredity, level of adiposity, experimental conditions (olfactory stimuli and metabolic state), age, gender, and severity of obesity. Moreover, the studies exploring the effects of obesity on olfaction often consider a combination of parameters involving simultaneously the olfactory sensitivity, odorant identification and discrimination, reward evaluation, and lastly, food intake quantification and preferences. The higher cortical processing, which is largely and directly affected by obesity too, also influences most of the resulting behaviors, but is not discussed here.

In cases of the extreme morbid obesity in adults, decreased odor detection abilities are clearly reported as compared to lean, age-matched, control subjects (Richardson et al., 2004, 2012). Observational and clinical cases confirm that olfactory function is negatively correlated with body weight (Fernandez-Aranda et al., 2016; Peng, 2019). Obesity is associated to a smaller OB volume, but whether it is a cause or a consequence for obesity is unsolved (Poessel et al., 2020). When using BMI value as a risk factor of olfactory loss, predicting food intake disorders going with obesity development, data on olfactory performances are conflicting. Considering a large panel of ages (19–75 years, the latter for which obesity and aging effects might be confused), olfactory dysfunction seems to be more encountered in high BMI than in low ones (Richardson et al., 2004; Patel et al., 2015; Skrandies and Zschieschang, 2015). Simchen et al. (2006) made the same observation but, only in subjects younger than 65 years; older ones despite a normal BMI displayed a decreased ability to detect and identify odors (Simchen et al., 2006). In earlier ages, high BMI adolescents show a greater olfactory sensitivity than normal BMI adolescents (Herz et al., 2020), which is not true in children (Obrebowski et al., 2000; Navarrete-Munoz et al., 2020). Among possible explanations to these inconclusive findings are the characteristics of the odorant used in the threshold assays, which could differentially affect the trigeminal nerve (Obrebowski et al., 2000; Herz et al., 2020) or involvement of reward areas, which are sensitive to BMI (Jacobson et al., 2019). Accordingly, women with high BMI display an increased sensitivity and preference for an energy-dense food odor only, suggesting that the nature of the stimulus is determinant (Stafford and Whittle, 2015). Moreover, it seems that, rather than the BMI itself, the endocrine profile of subjects (which is rarely considered) influences odor sensitivity. For example, insulin resistance strongly disserves the relationship between BMI/waist-hip ratio and olfactory sensitivity for food odor in young people (Poessel et al., 2020). In women, the level of fasting plasma circulating 2-arachidonoylglycerol, acting on endocannabinoid receptors, and obesity, interact to decrease olfactory threshold, discrimination, and identification score (Pastor et al., 2016). It also seems that the nutritional state modulates olfactory scores since high BMI people display a higher sensitivity to food odors in the satiated versus nonsatiated state and a better discrimination ability for food odors, than low BMI ones, whatever their age (Stafford and Welbeck, 2011). In men, consistent with the latter data, the subcutaneous adiposity is correlated with increased odor sensitivity and, high odor identification scores are associated with

high serum leptin levels (Hubert et al., 1980; Karlsson et al., 2002). Thus, the subcutaneous adiposity might participate in the modulation of olfactory performances, probably through the modification of circulating levels of leptin. Altogether, even if individual data are sometimes difficult to conciliate, they almost all indicate that odor detection and discrimination could be altered in obese patients. Recently, a retrospective case-control chart review has confirmed that high BMI is associated with subjective olfactory dysfunction that might by itself contribute to a spiral of increasing food intake and increasing obesity (Patel et al., 2015).

The question remains to know whether these sensory changes originate and/or participate in the development of the pathology. This is why, in the past few years, the causal relationship between obesity and olfactory sensitivity has been especially focused after reversion of the metabolic syndrome. When obesity was reversed by surgery procedures, the observed effects on a possible restoration of olfactory performances, after successful weight loss therapy, are contradictory. Indeed, Richardson et al. showed that the negative consequences of morbid obesity on smell identification are not reversed by a gastric bypass surgery and thus, suggested that the olfactory dysfunction may have contributed to the obesity pathology development (Richardson et al., 2012). However, contradictory data showed that threshold detection index scores could be restored following laparoscopic gastric bypass and sleeve gastrectomy surgery in obese subjects (Holinski et al., 2015; Zerrweck et al., 2016; Makaronidis et al., 2016). In the same line, Roux-en-Y gastric bypass patients frequently report olfactory changes and yet more pronounced and immediate shifts have been observed among sleeve gastrectomy recipients (Peng et al., 2019). Sensory restoration could be moreover lower on smell than on appetite or taste, and is often associated with the development of aversion to specific food (Graham et al., 2014; Makaronidis et al., 2016). Besides high level of heterogeneity in the cohort size, obesity status, and olfactory tests, discrepancies as regards the improvement in the olfactory performances might also be related to the fact that these bariatric procedures differently influence nutrient-sensing regulatory mechanisms and hormonal patterns over time (Peterli et al., 2012). However, it seems clear that, postoperatively, patients regularly report some taste/smell changes and signs of food aversions. Unfortunately, to our knowledge, no study has measured the effects of long-term calorie-restricted diets on olfactory performances of former obese people, what has been recently investigated in obese mice models (Thiebaud et al., 2014). In order to solve “the egg and chicken” question linking obesity and olfactory sensitivity, it would be interesting to follow step by step the effect of hypo- or hypercaloric diets, or surgery, on the olfactory performances in order to clarify the relationship between metabolic imbalance and peripheral sensitivity. Almost all studies compared subjects having evolved in a stable metabolic status for many years, but no one has fully explored the critical time window around the transition from the healthy to the altered physiological status.

14.3.2 In animals

In animal models, most data focusing on the link between obesity and olfaction have been obtained using genetically modified rodent strains displaying gene-targeted

deletion for metabolic-related hormones or their receptors, leading to obese status independently of the diet. Such a situation is rarely encountered in human populations, but results on mutants largely allowed pointing out interesting mechanisms involving metabolic hormones and their receptors.

One of the first conclusive studies exploring the link between olfaction and obesity at the peripheral level using transgenic mice has been done in 2006. Using a general olfactory sensitivity test, the authors showed that obese mice lacking leptin signaling (ob/ob and db/db) performed faster to localize a hidden fatty cookie than their wild-type counterparts (Getchell et al., 2006). Interestingly, in ob/ob mice, the experimental leptin supplementation reversed this performance behavior and induced changes in oscillatory dynamics in their OB indicating a central role for this anorexigenic hormone in their food odor sensitivity (Chelminski et al., 2017). In agreement, olfactory responses to food cues were also found to be increased in leptin receptor-deficient obese Zucker rats compared to their lean counterparts (Aimé et al., 2014; Badonnel et al., 2014). Thanos et al. (2013) especially showed that fed obese rats showed enhanced nose-poke activities, indifferently for novel or familiar food odor. The same result was observed using a tea-ball test in obese satiated Zucker rats which responded to food odor in the same way as in the fasted state (Badonnel et al., 2014). Moreover, Zucker rats display a better olfactory sensitivity than lean rats in conditioned aversion tests using nonfood odors associated to an alteration of OB glucosensing pathways (Aimé et al., 2014). Altogether, these results reinforce the idea that obesity induces modifications in the olfactory system functioning that participate in the observed hyperphagia. However, Tucker et al. (2012) using a gene-targeted-deletion-model of obese/diabetic mouse (the melanocortin receptor null mouse), reported that animals were less efficient in olfactory tests, taking longer time to localize a fatty scented cracker than lean animals; the deficits being mainly attributed to elevated serum leptin and insulin. However, all the experimental models resulting from targeted deletions have several limitations, since important metabolic hormones signaling pathways, mainly leptin, are not functional. Moreover, some perturbations of other metabolic ways associated to the targeted deletion are often observed. Therefore, recent studies have been conducted on diet-induced obesity (DIO) models in order to better fit with the complex surroundings encountered in humans, i.e., overconsumption of palatable food associated or not to a genetic susceptibility (Thiebaud et al., 2014; Lacroix et al., 2015; Lietzau et al., 2020).

In obesogenic environment, Thiebaud et al. (2014) observed learning impairment and decreased discrimination between nonfood odors in obesity-prone mice fed with high-fat/high-sugar diet during several months. These olfactory impairments were paired with a marked loss of OSNs and their axonal projections, and a reduction in EOG amplitude responses to nonfood odors. In agreement with this study, obese-prone rats made obese by DIO consumption for several months, exhibiting insulin and leptin-resistance and increased food intake during their rest phase, were less efficient than lean ones (fed with normal chow) in food-odor driven olfactory behaviors and task memory (Lacroix et al., 2015). Obese animals were also less sensitive to insulin in an odor-driven test, suggesting that the insulin resistance classically reported in obese subject for functions related to other peripheral tissues could be extended to

olfactory processing pathways. Moreover, severe modifications of cell homeostasis at both OM and OB levels were observed in the obese DIO fed rats (Lacroix et al., 2015).

Therefore, the latter studies clearly conclude to a dramatic effect of long-term over-nutrition on olfactory neuronal function that could be related to the known pleiotropic roles of hormones on tissue homeostasis. Consequently, it seems that obesity, depending on the diet, endocrine and phenotypic profiles, might lead to severe modifications of olfactory behaviors, associated to long-lasting structural and functional changes in the first two stages of the olfactory system (Thiebaud et al., 2014; Lacroix et al., 2015; Fardone et al., 2019). As also shown by Thiebaud et al. (2014), despite the renewal of the OM and bulb neurons, such impairments are not reversed upon diet changes, even after several months of low energy diet, suggesting that central cortical impairment might also be involved. It would be interesting to assess whether such dramatic structural and functional effects are also observed in OM of obese patients and whether the anatomical loss of OSNs could be reversed by bariatric surgery.

14.3.3 Diabetes

Type 1 diabetes (insulin-dependent), often associated to a chronic autoimmune disorder, results in the destruction of the β -cells in the pancreatic islets of Langerhans and affects people at any age (see for a review van Belle et al., 2011). Type 2 diabetes (insulin independent), is often associated with obesity and is acquired at older age, which complicates the identification of causal elements. Regardless of cause, diabetes mellitus (DM: group of metabolic diseases commonly referred to as diabetes) results in high levels of circulating glucose, caused by insufficient insulin functionality. From the aforementioned results highlighting the importance of insulin in the olfactory signal processing (Lacroix et al., 2008; Marks et al., 2009; Fadool et al., 2011; Aimé et al., 2012) and from data supporting that insulin resistance could result in some olfactory dysfunction (Lacroix et al., 2015), it is likely that DM would have deleterious effects on olfactory sensitivity. Indeed, several studies have reported an association between DM and impaired olfactory function: decrease in odor identification (Weinstock et al., 1993; Le Floch et al., 1993; Bramerson et al., 2004) and detection (Patterson et al., 1966; Hubert et al., 1980). However, these data were collected on mixed cohorts of type 1 and 2 DM. The first study discriminating between the DM types reported a decreased olfactory function only in 2 DM patients, compared to 1 DM ones (Naka et al., 2010). This was recently confirmed that noncomplicated-type 1 DM patients exhibit normal olfactory function (Altundag et al., 2017).

Also, some of the observed differences seem linked to patient profiles, type 2 DM displaying higher BMI and oldest ages. Moreover, associations of olfactory impairments with other anthropometric and clinical outcomes, such as waist circumference, cholesterol level, hypertension, or fasting glycemic level also recently emerged in type 2 DM patients (Gallo et al., 2020; Catamo et al., 2021). Accordingly, the olfactory deficits only concern patients displaying diabetes-associated pathologies as type 2 DM patients without major complications exhibited normal olfactory function (Naka et al., 2010; Brady et al., 2013). Therefore, olfactory impairments associated to type 2 DM have been proposed as resulting from neuropathy and macrovascular diseases

(coronary artery and peripheral vascular diseases), as previously mentioned (Weinstock et al., 1993; Le Floch et al., 1993), even if this observation is not totally corroborated by more recent studies (Gouveri et al., 2014; Sanke et al., 2014). Besides, the decreased performances in odor identification and discrimination suggest an impaired global cognitive processing (including working memory, attention, judgment language function, and decision making) as well as a decreased odor threshold score with peripheral neuropathy (Brady et al., 2013; Gouveri et al., 2014; Sanke et al., 2014).

The analysis of literature highlights the difficulties to conclude whether the reduction in olfactory functions in DM patients is due to diabetes pathology and/or to further complications, such as neuropathology, with or without pain, drug intake, duration, and severity of the disease or combination of different factors. In any case, obesity seems to worsen DM-induced olfactory disorders (Zhang et al., 2019).

In animals, the nature of the diabetes-induced diet, either rich in lipids, carbohydrates, or both, and the feeding protocols could participate in specific behavioral outcomes. Using two type 2 DM-inducing obesogenic diets, one containing a high proportion of fat (HFD) and one with moderate fat, but high sugar referred as Western diet (WD), Lietzau et al. (2020) showed an earlier impact of WD on odor-related learning and olfactory memory. They suggested that a high sugar content diet could exacerbate glucose intolerance and insulin resistance. Similarly, moderate- or high-fat diet has a differential impact on olfactory-driven behaviors, which suggests a role for adiposity level too (Thiebaud et al., 2014). It is possible that these diets differentially affect the lipid composition of OSN membranes, as shown for omega-3 imbalanced diets (Khoury et al., 2020), with variable electrophysiological consequences on olfactory signaling. More studies, considering all these combined parameters, are necessary to definitely demonstrate that the olfactory dysfunction is modulated from the periphery in DM patients and, if it can be used as a biomarker for neurodegeneration in these patients.

14.3.4 Anorexia

Patients suffering from anorexia nervosa (AN) display an obsessive fear of gaining weight, avoidance of high-energy food, and eating disorders associated with decreased pleasure to eat. In response to this severe energy restriction, alterations occur in many endocrine axes including those related to food intake and olfactory function control (Misra and Klibanski, 2014). In a search for clinically AN markers, a number of metabolic, endocrine, and neural biomarkers associated to malnutrition (leptin, NPY, ghrelin ...) have been found as being abnormal. Regarding the implication of these biomarkers in olfaction and food intake relationship, it is largely reasonable to speculate that AN patients could have altered olfactory functions. But as for other studies on pathologies related to food-intake deregulations in humans, discrepancies in results on AN effects have been noticed. These are likely attributable to variations of the following criteria: size of the cohorts (often quite low), gender of patients, age (timing of the development of the pathology), feeding state (fasting or not, duration of the starvation) and depressive state (medication). Moreover, the studies mostly lack matched control samples.

First report examining this question resulted in divergent observations, despite the use of the same olfactory score test. [Kopala et al. \(1995\)](#) reported a normal olfactory function, whereas [Fedoroff et al. \(1995\)](#) concluded in an impaired ability to identify and detect odors in very low-weight AN-patients ([Kopala et al., 1995](#); [Fedoroff et al., 1995](#)). More recent studies built a relative consensus on the following observations: AN patients express (i) a lower pleasantness of odors, particularly of food ones in a hungry state ([Lombion-Pouthier et al., 2006](#); [Schreder et al., 2008](#); [Soussignan et al., 2011](#)), (ii) a decrease of their general olfactory abilities evaluated by computing scores of odor threshold, discrimination, and identification ([Schreder et al., 2008](#); [Aschenbrenner et al., 2008](#); [Dazzi et al., 2013](#)). However, when examined separately, each of these three scores are difficult to conciliate. Indeed, if odor discrimination seemed reduced in most patients ([Schreder et al., 2008](#); [Aschenbrenner et al., 2008](#); [Roessner et al., 2005](#); [Dazzi et al., 2013](#)), some authors did not observe any difference with control subjects ([Kopala et al., 1995](#); [Rapps et al., 2010](#)).

Odor identification scores were mostly reported as being reduced ([Fedoroff et al., 1995](#); [Schreder et al., 2008](#); [Rapps et al., 2010](#)), except in one study where they were unchanged ([Aschenbrenner et al., 2008](#)). The odor sensitivity was reported to be either unchanged ([Aschenbrenner et al., 2008](#); [Rapps et al., 2010](#); [Dazzi et al., 2013](#)) or decreased ([Roessner et al., 2005](#)) for food odor, but only in hungry conditions ([Schreder et al., 2008](#)) or exclusively in low-weight anorexic patients ([Fedoroff et al., 1995](#)). Only two studies reported increased odor sensitivity ([Lombion-Pouthier et al., 2006](#); [Bentz et al., 2017](#)). Authors suggested that it could account for the over-evaluation of odorant intensities and lower score of hedonic valence, which were frequently observed in anorexia patients. In the same lines, some enhanced olfactory identification performances were reported in AN adolescent, compared to normal matched groups ([Schecklmann et al., 2012](#)) or in young women with recent-onset AN and who have just recovered ([Bentz et al., 2017](#)). Recent metaanalyses support the idea that AN patients have intact olfactory function compared to health controls in terms of threshold, identification, and discrimination, but that the severity of AN could alter olfactory threshold score ([Islam et al., 2015](#); [Mai et al., 2020](#)).

Besides the restricting AN, a few studies have evaluated the olfactory function in patients diagnosed for bulimia nervosa and, interestingly, most of them did not find any difference between bulimic and control patients ([Kopala et al., 1995](#); [Fedoroff et al., 1995](#); [Aschenbrenner et al., 2008](#)). Only one study has reported an overall decrease of the olfactory function, mainly due to a decreased odor sensitivity and discrimination ([Dazzi et al., 2013](#)). Development of appropriate animal models of anorexia/bulimia is difficult, as the etiology of these multifaceted eating disorders likely involves complex interaction between genetic, environmental, social, and cultural factors, thus making it impossible to precisely pinpoint the respective roles of anorexia and malnutrition on olfactory function ([Mequinion et al., 2015](#)). This is likely why, to date, few models have been developed to investigate olfactory function related to anorexia.

14.3.5 Maternal metabolic status

According to the concept of Developmental Origins of Health and Disease (DoHaD), the metabolic environment during fetal life would influence offspring's health in the long-term, with behavioral consequences (Barker, 2007). Among them, alterations of feeding behavior are reported (Sullivan et al., 2015). As the olfactory system (i) develops during embryonic life, (ii) is sensitive to the metabolic environment and (iii) participates in food intake, the possible impact of the maternal metabolic status on olfactory sensitivity in offspring has been tested. Maternal obesity induced by high fat or high fat/high sugar diet during pregnancy and lactation has been reported to alter the OM sensitivity, measured by EOG, at weaning and later (Merle et al., 2019; Panchenko et al., 2019). However, offspring born after a high fat/high sugar in utero diet exhibits reduced olfactory abilities at weaning despite no alteration of OM functioning, rather suggesting a more central processing alteration (Merle et al., 2019). Whether these effects are linked to events restricted to the in utero period or to later modifications of the metabolic profile of the offspring remains to be studied by decoupling the pre- and the postnatal phase in cross-fostering experiments. Indeed, post-partum environment, resulting from nutritional, but also from associated features (maternal-infant bond perturbation, food transition-induced stress) could participate in functional modifications of the olfactory system sensitivity, irrespectively of nutritional considerations. The mother's preconceptional status should also be considered, as it has been shown that maternal weight loss could normalize the offspring metabolic phenotypes, while it nevertheless induced an unexpectedly deleterious effect on olfactory performance: reduction in olfactory sensitivity. Furthermore, in fasted male offspring, such reduction was accompanied by an inability to induce olfactory motivation (Panchenko et al., 2019). Noteworthy is that such a programming effect of the maternal metabolic context could participate to the vicious circle of food intake deregulation, with putative intergenerational consequences.

14.4 Conclusion

From this chapter, it is clear that olfaction and food intake are intimately linked at several levels of the olfactory system and that olfactory circuits are sensitive to changes in the organism energy balance. Aberrant metabolism-related hormones production in chronic pathologies or acute variations linked to normal food intake cycles highlights that some olfactory processes are involved to adapt the olfactory sensitivity to the physiological needs. The understanding of the links between olfaction and food intake may serve as a potential strategy to fight, at least partly, against metabolic disorders, and thus may offer therapeutic pathways leading to new preventive diagnostics and curative strategies. The development of auxiliary therapeutic treatments based on intranasal metabolic-related molecules delivery, as performed in rodents models (Marks et al., 2009; Jia and Hegg, 2010; Schulz et al., 2012) and in healthy normosmic humans (Brunner et al., 2013) or in patients suffering from various CNS pathologies (Chapman et al., 2013) could then be considered as promising for upscaling therapeutic

treatments of diseases with CNS involvement, such as Alzheimer disease, Parkinson disease, Huntington disease, depression, anxiety, autism spectrum disorders, seizures, drug addiction, or eating disorders.

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15.1 Introduction

Often overlooked and underdiagnosed, taste disorders are frequent and serious conditions: they are implicated in loss of appetite, unintended weight loss, and malnutrition, and lead to reduced quality of life. The lack of consideration given to taste impairment compared with other disabilities is striking: it is obvious that a person with hearing loss may no longer be interested in opera, or a person with visual impairment may no longer enjoy films, but the consequences of taste impairment for those affected are still taken too lightly. Yet taste provides a vital tool for screening soluble chemicals for food evaluation and selection, and thus avoiding potentially toxic substances. The loss of taste is a genuine disability. Do not we say “to lose the taste for life”!¹ In current medical practice, the importance and therapeutic management of taste disorders is receiving renewed interest as evidenced by recent reviews (e.g., Maheswaran et al., 2014; Malaty and Malaty, 2013; Fark et al., 2013; Feng et al., 2014; Risso et al., 2020). Methods to explore, and identify qualitative or quantitative taste alterations are described elsewhere (Bromley, 2000; Venail et al., 2008; Ruo Redda and Allis, 2006; Galindo-Cuspinera et al., 2009; Hong et al., 2009; Wismer, 2008; Doty, 2018; Spotten et al., 2017).

15.2 Taste disorders

15.2.1 Abnormal taste sensation or taste perception?

Sensory receptors give sensations, which are conscious psychophysical phenomena to identify external or internal stimuli. It is conventional to recognize three components in sensation (Cabanac, 2014): the nature of the stimulus, its intensity, and the pleasure it provides. Therefore, once the information is sent and processed by the brain, it is possible to describe the taste sensation in terms of its quality (sweet, salty, bitter,

¹ The French said, « perdre le gout de vivre » (lose the taste/the flavor of life).

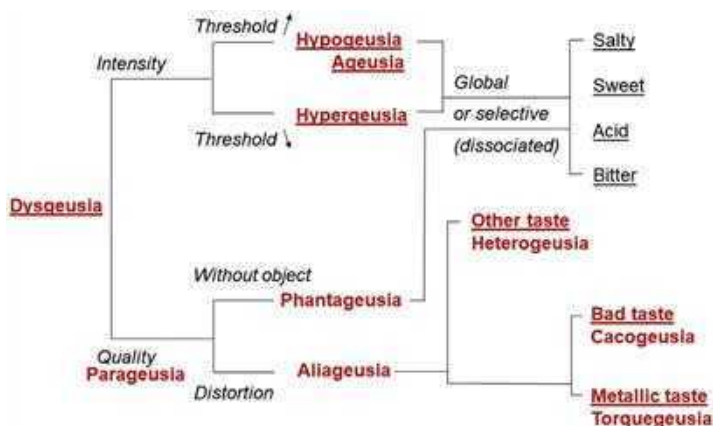


Figure 15.1 Semiology of the taste disorders.

Adapted from Kettaneh, A., Fain, O., Stirnemann, J. & Thomas, M., 2002. Taste disorders. *La Revue de medecine interne*.

sour), intensity (very or slightly salty) and hedonics (pleasant or not). Therefore, the semiology of taste disorders (dysgeusia) distinguishes between gustatory alterations depending on the abnormalities of each component (Fig. 15.1): a disorder may involve the identification of the taste [one taste appears instead of another (heterogeusia) or appears for no reason (phantageusia)], its intensity (ageusia, hypogeusia, or hypergeusia), or the hedonic sensation it induces [bad taste (cacogeusia) or metallic taste (torquegeusia)] (Kettaneh et al., 2002; Hummel et al., 2011).

Taste consciousness is not limited to sensations; it incorporates the sensory information coming from other sensory modalities and these messages are continually compared with memory stock to give rise to perception (Cabanac, 2014). Thus, perception is the function by which the mind represents objects that surround one's body according to the internal state and experience. We therefore acknowledge the importance of cognitive factors, habits, experiences, learning, environment, and culture in taste perception and its construction, as well as the importance of internal factors (hunger, nutritional status, pain ...), attention, and mood. Finally, the taste of a food can be disagreeable due to the environment or the experience. As an example, what is the taste of a given food (and the pleasure it could induce) for a patient in bed in hospital, eating alone, feeling pain, plunged in anxiety, when the mediocre meal is served in bed on a plastic tray placed on the patient's knees, while the dying patient lying in a nearby bed is groaning, with the overpowering smell of the hospital, and the staff bustling around? This far from exceptional² situation has to be taken into account (Porben, 2006; Sullivan et al., 1989), because, added to the organic taste disorder is an environment that may worsen the perception of taste sensation.

² Unfortunately, this is a description of modern hospital life and is not based on a paragraph from "Les Misérables" by Victor Hugo.

Furthermore, smell and taste disorders are frequently associated, which may worsen the handicap linked to the gustatory dysfunction and the subject's quality of life [e.g., in cancer (Brisbois et al., 2011a)].

15.2.2 Many diseases induce taste abnormalities

As indicated in Table 15.1, taste disorders have numerous etiologies. There are of course local causes (glossitis, dentures, root canal treatments), nutritional deficiencies

Table 15.1 Etiologies of taste disorders.

Common causes	Less common causes	Uncommon causes
Oral and perioral infections (e.g., candidiasis, gingivitis, herpes simplex, glossitis, periodontitis, sialadenitis) Idiopathic facial paralysis Oral appliances (e.g., dentures, filling materials, tooth prosthetics) Dental procedures (e.g., tooth extraction, root canal) Age, menopause	Nutritional factors (e.g., vitamin deficiency [B ₃ , B ₁₂], trace metal deficiency [zinc, copper], malnutrition, chronic renal failure, liver disease [including cirrhosis]) Cancer Acquired immunodeficiency Syndrome (SIDA) Tumor or lesions associated with taste pathways (e.g., oral cavity cancer, neoplasm of skull base, tonsillectomy) Head trauma (Fracture, head injury) Toxic chemical exposure (e.g., benzene, benzol, butyl acetate, carbon disulfide, chlorine, ethyl acetate, formaldehyde, hydrogen selenide, paint solvents, sulfuric acid, thichloroethylene) Industrial agent exposure (e.g., chromium, plumb, copper) Radiation treatment of head and neck	Psychiatric conditions (e.g., depression, anorexia nervosa, bulimia) Epilepsy (gustatory aura) Migraine, headache (gustatory aura) Sjögren syndrome Multiple sclerosis, stroke, tumor, bleeding, peripheral neuropathy Central neurology degeneration (e.g., Alzheimer, Parkinson disease) Endocrine disorders (e.g., adrenocortical insufficiency, Cushing syndrome, diabetes mellitus, hypothyroidism, panhypopituitarism, pseudohypoparathyroidism, Kallmann syndrome, Turner's syndrome) Burning mouth syndrome

(deficiencies in B vitamins or zinc), chronic liver or kidney failure, poisoning, which can be associated with radiation therapy of the head and neck, trauma of the face, cancers, and chronic inflammatory syndromes, as well as neurodegenerative (Alzheimer disease), psychiatric (depression syndrome), or endocrine (adrenal insufficiency, diabetes) causes (Desport et al., 2011; Bromley, 2000; Venail et al., 2008; Fark et al., 2013).

Aside from those, burning mouth syndrome (BMS) is generally a chronic idiopathic disorder characterized by a continuous burning sensation of the oral mucosa, in particular affecting the tongue (Mock and Chugh, 2010; Aravindhan et al., 2014; Fark et al., 2013). Classically, BMS is accompanied by quantitative or qualitative taste disturbances, such as impaired perception of bitterness, a metallic taste, or both (Ship et al., 1995) and subjective xerostomia. By definition, no macroscopic change of the oral mucosa is observed (Jaaskelainen, 2012; Scala et al., 2003). BMS is frequently associated with diabetes and vitamin deficiencies and occurs most often but not exclusively in peri- and postmenopausal women in context of anxiety and depression.

15.2.3 Many drugs can lead to taste disorders

As mentioned in Table 15.2, the drugs that induce taste disturbances belong to numerous pharmacological classes (antibiotics, antidepressants, antihistamines and decongestants, antineoplastic agents, antipsychotics) (Doty et al., 2008; Bromley, 2000; Desport et al., 2011; Fukasawa et al., 2008; Naik et al., 2010). Some disorders are related to the taste of the drug, others to modifications in saliva (anticholinergics, chemotherapy), to alterations of the receptors (antiseptics, diuretics, calcium channel blockers), or to the neurotransmission (antiparkinsonian agents, benzodiazepines). Generally, the alterations are reversible on discontinuation of the treatment. In contrast, zinc, which is often prescribed in hypogeusia, improves taste function as it is a key component of gustin (Shatzman and Henkin, 1981), a salivary metalloprotein that facilitates the contact between ligands and taste cells and neurotransmission between taste cells and cortical areas.

15.2.4 Many mechanisms lead to taste disorders

The mechanisms leading to taste disorders are numerous, sometimes interdependent, not always well known and play a role at various levels (Venail et al., 2008; McLaughlin and Mahon, 2012; Desport et al., 2011; Hovan et al., 2010). For local causes, taste disorders may be due to:

- Poor presentation of the sapid substance to the taste receptors because of impaired saliva either in terms of volume (dry mouth by Sjögren syndrome or treatment with atropine) or composition (ionic composition, pH, richness in protein or in mucus, thick saliva due to candidiasis or bacterial infection), dental disorders, mucositis with xerostomia or glossitis.
- Alterations of taste cells or in transducing mechanisms: inflammatory or infectious glossitis, radiation and antimicrobial drugs leading to a decrease in the number of receptors, reduction of G-proteins in Albright syndrome, impaired epithelial sodium channels by amiloride, decreased intracellular calcium release by calcium channel blockers.

Table 15.2 Principal drugs responsible of taste disorders.

Antibiotics Ampicillin Azithromycin (Zithromax) Ciprofloxacin (Ciflox) Clarithromycin (Biaxin) Griseofulvin (Grisactin) Metronidazole (Flagyl) Ofloxacin (Floxin) Tetracycline Antidepressants Amitriptyline (Elavil) Clomipramine (Anafranil) Desipramine (Norpramin) Doxepin (Sinequan) Imipramine (Tofranil) Nortriptyline (Pamelor) Antihistamines and decongestants Chlorpheniramine Loratadine (Claritin) Pseudoephedrine	Anticonvulsants Carbamazepine (Tegretol) Phenytoin (Dilantin) Lamotrigine (Lamictal) or Topiramate (Epitomax) Antihypertensives, diuretic and cardiac medications Acetazolamide (Diamox) Amiloride (Midamor) Betaxolol (Betoptic) Captopril (Capoten) Diltiazem (Cardizem) Enalapril (Vasotec) Hydrochlorothiazide (Esidix) and combinations Nifedipine (Procardia) Nitroglycerin Propranolol (Inderal) Spironolactone (Aldactone) Losartan (Cozaar)	Antiinflammatory agents Auranofin (Ridaura) Colchicine Dexamethasone (Decadron) Gold (Myochrysine) Hydrocortisone Penicillamin (Cuprimine) Antimanic drug Lithium Antineoplastics Fluorouracil (5-FU) Cisplatin (Platinol) Doxorubicin (Adriamycin) Methotrexate (Rheumatrex) Vincristine (Oncovin) Paclitaxel (Taxol) Antiparkinsonian agents Levodopa (Larodopa; with carbidopa: Sinemet)	Antipsychotics Clozapine (Clozaril) Trifluoperazine (Stelazine) Antithyroid agents Methimazole (Tapazole) Propylthiouracil Anxiolytics Diazepam Zopiclone Antihyperlipidemic Fluvastatin (Lescol) Lovastatin (Mevacor) Pravastatin (Pravachol) Muscle relaxants Baclofen (Lioresal) Dantrolene (Dantrium)

Adapted and completed from Bromley SM. 2000, McLaughlin L. & Mahon S.M. 2012.

- Impaired transmission: impaired encoding due to antiparkinsonian, antiserotonergic, or benzodiazepines drugs; impairment of afferent neural pathways following surgical intervention for oropharyngeal carcinoma, dental surgery, trauma of the face, or medical disorder, such as postinfluenza neuropathy, Bell's palsy, herpes, porphyria, systemic lupus erythematosus.
- Central lesion: tumor, stroke, or hematoma; multiple sclerosis; Parkinson or Alzheimer disease.

Numerous systemic causes, whose mechanisms are more or less understood, may also induce taste alterations. This is the case of endocrine diseases, hepatocellular and renal deficiencies, nutritional disorders, and inflammatory syndromes (with increased α -TNF, interleukins, oxidants, antiinflammatory drugs) or cortical activation linked to pain or to anorexia.

15.3 Taste disorders in metabolic pathologies

About 600 million adults in the world suffer from obesity, defined by a body mass index (BMI) of 30 kg/m² or more. Furthermore, 42 million children less than 5 years old are overweight or obese (WHO, 2015). Diabetes is a chronic metabolic disease with a global prevalence of around 9% among adults. Around 1.5 million deaths are directly caused by this condition (WHO, 2015).

Both obesity and diabetes are strongly linked to feeding behavior. Taste sensitivity plays an important role in food preferences and choices, and thus consumption. Data about the role of taste thresholds and disorders in the pathophysiology of obesity and diabetes are somewhat contradictory.

15.3.1 Taste disorders in obesity

15.3.1.1 Taste sensitivity in obese patients

Different studies have shown no difference between lean and obese humans for sensitivity to basic flavors (sweet, salty, sour, and bitter) (Anderson, 1995). However, there are conflicting results.

Thus, while some studies reported that obese and normal-weight individuals have the same sensitivity for sweetness (Grinker, 1978; Grinker et al., 1972), others showed that sensitivity for sweetness was lower in obese persons than in normal-weight controls (Bartoshuk et al., 2006). Simchen et al. (2006) focused on the relationship between BMI, and sensory capabilities, particularly odor and taste sensitivities. In this study, overweight adults under 65 years old demonstrated lower taste perception and capability for odor identification and detection. In contrast, among elderly subjects (>65 years), higher relative body weight was associated with stronger abilities in odor identification, odor detection, and taste perception.

Sartor et al. (2011) studied the implicit attitude of overweight/obese individuals toward sweet food/drinks. Young overweight/obese individuals perceived sweetness and salty as being less intense than did normal-weight persons, and they showed a trend toward higher pleasantness scores for the sweet taste, but the latter finding is probably due to the higher proportion of males in this group. Indeed, pleasantness scores for a sweet drink were higher in males than in females (Laeng et al., 1993). Young overweight/obese individuals have a stronger implicit attitude toward sweet food than their normal-weight counterparts. Moreover, in this study, healthy normal-weight subjects underwent 1 month of supplementation with soft drinks. This intervention altered taste perceptions of both the intensity and pleasantness of sweetness. Furthermore strong

trends have been found toward a significant positive correlation between leptin levels and dietary sugar intakes, and leptin levels and preference scores for sweetness. It is thus suggested that individuals with chronically higher leptin levels are less able to perceive the sweet taste reward. Consequently, they have to increase sugar intake to experience the same reward as persons with chronically lower leptin levels and high sweet taste reward. Concerning the reward system, it is known that obese individuals have fewer dopamine D2 receptors than normal-weight controls as shown by Positron Emission Tomography (PET) (Wang et al., 2001) and may seek more palatable foods to compensate for the decreased dopamine-induced reward (Davis et al., 2004).

More recently, studies showed that weight gain was negatively correlated with the density of fungiform papillae, in children and young adults, highlighting changes in taste during this period (Kaufman et al., 2020; Maméli et al., 2019). Moreover differences in the ecological indexes of microbial alpha-diversity have been found between these obese children compared to normal-weight ones (Maméli et al., 2019).

15.3.1.2 *Taste sensitivity after bariatric surgery*

There have been numerous reports about changes in food choice after bariatric surgery (Munzberg et al., 2015). The most commonly observed effect in humans is a shift from overly sweet and fatty energy-dense foods to less energy-dense foods (Laurenus et al., 2013; Miras and le Roux, 2013).

In general, studies show that bariatric surgery is associated with taste change, which results in less preference for high-calorie food and possibly reduced calorie intake (Shoar et al., 2019). However, results in literature are severely discrepant, according to direct or indirect means used to assess taste function and ingestive behavior following bariatric surgery (Nance et al., 2020). Reported changes in taste and food preferences are rather related to changes in the rewarding value of food. It seems that these surgeries alter central processes of reward, which could then lead to altered hedonic responses to food (Nance et al., 2020). A number of functional neuroimaging studies in the context of obesity, eating behavior, and bariatric surgery in humans have been published in the last 10 years (Behary and Miras, 2014). Hypothalamic, brain-stem, limbic and cortical brain areas form part of a wellcoordinated brain system that responds to central and peripheral neuronal, hormonal, and nutrient signals. Gautier et al. (2000) showed that decreases in activation of the hypothalamus in response to glucose or a meal, which lead to satiation, were attenuated in obese but not in normal weight subjects. Responses to visual and gustatory appetitive stimuli in the mesolimbic dopamine system are exaggerated in obese subjects and decreased after bariatric surgery (Sweet et al., 2012). Rothmund et al. (2007) showed higher activation of the reward system in response to pictures of foods and/or high-calorie foods in obese patients than in normal-weight subjects. Functional magnetic resonance imaging (fMRI) studies after bariatric surgery showed that RYGB surgery decreases the activation of brain regions involved in hedonic control, in response to high-calorie but not to low-calorie food cues (Ochner et al., 2012). However, there are differences between the effects of RYGB and gastric banding surgery on the brain reward system with lower activation in response to high-calorie food pictures after RYGB

than after gastric banding (Scholtz et al., 2014). Researchers have demonstrated higher opioid receptor availability and altered dopamine D2R receptor availability after RYGB and/or SG (Karlsson et al., 2016).

15.3.2 Taste disorders in diabetes

Prediabetic patients do not show decreased sweet taste sensitivity when compared with normoglycemic subjects (Wasalathanthri et al., 2014). However, in this study, prediabetic patients and normoglycemic subjects were identified according to their HbA1c level even though the specificity of HbA1C for identifying prediabetes is very low when compared with the oral glucose tolerance test (OGTT) (for the OGTT, normoglycemic status is defined by blood glycemia 2 h post OGTT of less than 7.8 mmol/L and prediabetic status is defined by blood glycemia 2 hours post OGTT between 7.8 and 11.0 mmol/L).

An interesting electrogustometry study based on electromyograms in diabetes patients versus healthy patients showed significantly reduced gustatory function in the former. In the same study, exploration of morphology of the tip of the tongue by contact endoscopy showed impairment of the gustatory anatomical structures in diabetics (Pavlidis et al., 2014).

Impaired taste sensation has been described in patients with diabetes mellitus (DM) (Chochinov et al., 1972; Lawson et al., 1979). These impairments are found mostly for sweet sensation than for other taste modalities (Gondivkar et al., 2009). Several factors which have significant correlations with taste thresholds must be considered, such as blood glucose concentrations and HbA1C levels, duration of diabetes, and peripheral neuropathy (Le Floch et al., 1990). Even though there is no conclusive evidence to indicate whether the decrease in sweet taste sensitivity in DM patients occurs as a result of an alteration of glucose homeostasis or vice versa, the blunted taste response can facilitate a vicious cycle which leads to a deterioration in glycemic control. However, in uncomplicated T2DM, taste recognition thresholds were yet higher, and central obesity was significantly associated with this impairment (De Carli et al., 2018).

Overweight patients with type 2 diabetes mellitus exhibit a decreased ability to detect sweet taste and a reduced appetitive response to sugar-rich and fatty foods compared with healthy normal-weight, age- and gender-matched controls. Sweet taste detection was improved and appetitive and consummatory responses to fatty foods were decreased after 3 months of treatment with the GLP-1 analog, liraglutide. Liraglutide also led to improvements in body weight, glycemic control, and in the android to gynoid fat ratio, which is a surrogate marker for cardiovascular risk. However, the changes in these parameters did not correlate with changes in food hedonics, suggesting a GLP-1-specific effect (Brindisi et al., 2019).

15.3.3 Taste disorders in metabolic syndrome

Several different dietary patterns, including Mediterranean-style diets (Jones et al., 2012), low-fat diets (Neuhouser et al., 2012), and vegetarian and vegan diets (Rizzo et al., 2011) have been shown to be protective against metabolic syndrome. However,

different tasting profiles may moderate a person's ability to adhere to a healthy diet. The tasting profile, such as sweet likers (SLs) or supertasters (STs), may be influenced by genetics and may influence dietary intake. STs are thought to have heightened taste perceptions and are able to discriminate small changes in the nutrient composition of foods more so than non-STs (Hayes and Keast, 2011).

Results concerning supertasters and BMI are contradictory; some of them show that non-ST have a higher BMI (Tepper et al., 2008), others show no differences in BMI between ST and non-ST (Drewnowski et al., 2007; Yackinous and Guinard, 2002) and no effect of the ST genotype on BMI or dietary intake (Hayes, 2010). Concerning SL, a preference for sweet solutions has been associated with increased preference for sugar-sweetened desserts (Drewnowski et al., 1999), but other studies have reported contradictory results. Turner-McGrievy et al. (2013) tested around 200 patients and investigated the relationships and interactions between both SL and ST status and metabolic syndrome. This study found that the pattern of dietary intake was consistent with the pattern of metabolic syndrome occurrence, and revealed lower intakes of fiber and higher intakes of caloric beverages among individuals with a combined SL (high consumption of added sugars) + ST (avoidance of vegetables) status followed by those with a non-SL + non-ST status as compared to ST or SL only. Despite several limitations in this study, the authors concluded that counseling individuals who are both SL and ST or are non-SL and non-ST on ways to increase fiber and decrease caloric beverage intake may be needed to modify metabolic syndrome risk.

15.3.3.1 *Future direction*

Assessing genetic differences in taster profiles may be useful in the development of specific dietary interventions to prevent and treat metabolic diseases. Better understanding of the role of taste thresholds in overweight and obesity might help us to manage these diseases. Better understanding of the physiology of modified eating behavior after RYGB is a current objective.

15.4 Taste disorders in neurological diseases

Many neurological diseases have been associated with impaired gustatory functions (Heckmann and Lang, 2006; Brondel et al., 2013). However, taste impairment is often underdiagnosed because it is eclipsed by sensory and motor symptoms caused by neurological diseases. Several different pathophysiological mechanisms can lead to taste disorders in neurological diseases: taste receptor dysfunction caused by an autoimmune mechanism, or peripheral afferent gustative nerve lesions and central lesions with damage to the cortical taste areas. Certain authors argued that central lesions cause disorders of perception (hema ageusia or hypogeusia) whereas peripheral nerve lesions result in altered taste interpretation with preservation of taste perception (Landis et al., 2006). Finally, these taste disorders described in neurological diseases

can be potentiated by drug consumption. In fact, many drugs used in neurological illnesses can lead to taste dysfunction (Table 15.2). Taste disorders can also occur after deep brain stimulation (Gilard et al., 2014).

15.4.1 *Peripheral disorders*

The main illness causing taste receptor disorders is myasthenia gravis (MG) (Nakazato et al., 2008; Chabwine et al., 2014). MG is an autoimmune disorder characterized by fluctuating muscle weakness and ocular or bulbar signs. Taste disorders concern 5% of cases, especially in severe MG with thymoma, and it can be the first symptom of MG. Dysgeusia can occur for all the primary tastes, but sweet dysgeusia is the most frequent. Dysgeusia evolves in parallel with antiacetylcholine receptor antibody (AChRAb). AChRAb is a plausible etiology of sweet taste loss, possibly due to an autoimmune mechanism targeting G-protein-coupled receptor (GPCR) taste cells. The taste disorders improve with MG therapy.

Many neurological diseases can cause peripheral afferent gustative nerve lesions. The most frequent is facial palsy regardless of the etiology: Bell's palsy, facial palsy due to herpes virus or head trauma (Walker, 1990). Taste stimuli from the anterior two-thirds of the tongue are in fact carried by chorda tympani, a division of cranial nerve VII. Chorda tympani involvement during facial palsy is very common. Altered taste is one of the most frequent symptoms in Bell's palsy. A previous study observed taste disorders in 35% of patients with Bell's palsy, and it was the first symptom in 8% of cases (De Seta et al., 2014). Indeed, when examined objectively, 83% of patients had ageusia or dysgeusia in the ipsilateral half tongue (Peitersen, 2002). The difference can be explained by the fact that patients can use the normal half tongue to detect taste and were therefore unaware of the taste dysfunction. Altered salivary secretion, which is also controlled by cranial nerve VII, can worsen the taste disorders (De Seta et al., 2014). Guillain-Barré syndrome, an acute polyradiculoneuropathy, can also cause dysgeusia for all the primary tastes, without facial palsy. It is probably due to an autoimmune mechanism (Higuchi et al., 2015; Odaka et al., 2002). Familial dysautonomia is another cause of altered taste, leading to partial dysgeusia (Gadoth et al., 1997).

Finally, taste disorders such as dysgeusia for sweet, salty, and sour tastes can be associated with neuropathic trigeminal pain regardless of the etiology: idiopathic trigeminal neuralgia, trigeminal postherpetic neuralgia, and burning mouth syndrome (Siviero et al., 2010). It can be explained by an altered interaction between the trigeminal and chorda tympani afferences. The bitter taste remains normal because for most fibers it is mediated by the glossopharyngeal nerve.

15.4.2 *Central disorders*

Central lesions of the gustatory cortices induce several types of taste disorders and can be due to ischemic or hemorrhagic strokes, temporal epileptic seizures, head trauma, intracranial tumors, multiple sclerosis, and neurodegenerative diseases such as Parkinson and Alzheimer diseases. Temporal epileptic seizures can provoke transient episodes of a metallic taste. Multiple sclerosis is a rare cause of taste disorders

(ageusia, hypogeusia, dysgeusia, or parageusia). A quantitative alteration of the sense of taste has been found at rates varying from 0.25% to 7.7% of patients with a demyelinating illness (Nocentini et al., 2004; Rollin, 1976). Hema ageusia in multiple sclerosis can be induced by a demyelinating lesion in the tractus solitarius nucleus (Pascual-Leone et al., 1991).

Patients who suffer from ischemic or hemorrhagic strokes often have taste disorders. A previous study reported a gustatory loss in 30% of stroke patients and a lateralized impairment of taste function in 6% of cases (Heckmann et al., 2005). The most frequent disorders are hypogeusia and dysgeusia, such as difficulties to distinguish between the sweet and sour taste. Predictors of impaired taste function were male gender, high National Institutes of Health Stroke Scale (NIHSS) score at admission, coexisting swallowing dysfunction, and a stroke of the anterior circulation. In fact, patients with taste disorders more frequently have stroke lesions in the frontal lobes, which correspond to the location of the cortical taste areas (Heckmann et al., 2005; Dutta et al., 2013). Elderly people are more likely to experience these taste disorders after stroke (Aliani et al., 2013). Altered taste induced by stroke of the posterior circulation is also possible (Aliani et al., 2013; Onoda and Ikeda, 1999; Green et al., 2008; Janssen et al., 2015), in particular in the brainstem, where the tractus solitarius nucleus is located (Aliani et al., 2013; Heckmann and Lang, 2006). It is currently believed that stroke per se produces a general, nonspecific effect on taste function that resolves during recovery from the stroke (Heckmann et al., 2005).

In Parkinson disease (PD), data concerning taste disorders are less widespread than results about olfactory functions, and they are often controversial. According to different studies, altered taste is less frequent than olfaction disorders, and affects between 9% and 27% of Parkinson patients (Kashihara et al., 2011; Kim et al., 2011; Shah et al., 2009). Different types of taste disorders are described: diminished taste perception, altered sense of taste, or burning mouth (Kashihara et al., 2011). Taste functions appear to be worse in patients with Parkinsonism and dementia than in patients with dementia and without Parkinsonism (Lang et al., 2006). The alteration of the perception threshold of taste in PD is controversial (Shah et al., 2009; Sienkiewicz-Jarosz et al., 2005). Taste disorders do not differ according to gender, age, disease severity, the presence of cognitive or olfactory impairment, and the dopa-therapy, but they seem to increase with disease duration (Kashihara et al., 2011; Shah et al., 2009). A recent study reported a differential taste disorder in PD: damage to cranial nerve IX could release central inhibition on cranial nerve VII at the level of the brainstem, resulting in enhanced taste intensity on the anterior tongue at the expense of the posterior tongue (Doty et al., 2015). The pathophysiological mechanism underlying taste dysfunction in PD is currently unknown. Several hypotheses are proposed: Does Lewy body storage exist in the gustatory cortex like in the olfactory tubercle or limbic structures? Are there lesions of the gustatory afferent nerves as well as the demonstrated loss of the epidermal nerve fibers (Nolano et al., 2008)? Are taste disorders worsened by depression or drugs against PD?

In Alzheimer disease (AD), taste disorders are poorly described. Most of the authors showed an impairment of taste memory (Schiffman et al., 2002). Gustatory deficit in AD could be described as an associative agnosia. Taste disorders seem to be due to

central lesions with deterioration of the cortical taste area, whereas the gustatory thresholds are preserved in mild AD (Broggio et al., 2001). According to a subjective taste test (“taste trips”), a recent and interesting study (Steinbach et al., 2010) observed that patients with mild cognitive impairment (MCI—an early stage of cognitive disorder which can lead to AD) or with AD had gustatory dysfunction for sweet, salty, sour, and bitter tastes. These taste disorders were as severe in MCI as in AD patients, suggesting that they could be an early marker for AD. In MCI patients, a significant correlation existed between the total taste score and the Mini-Mental State Examination (a global neuropsychological assay which gives a global indication of the patient’s cognitive functions). Another recent study observed that gustatory dysfunction could be an independent predictor of cognitive impairment (Churnn et al., 2019). The underlying physiological mechanisms are not fully understood.

15.5 Taste disorders in cancer

Taste disorders are common in oncology. These refer to changes in the sense of taste and in the perceived flavor of foods (Murtaza et al., 2017; Boltong et al., 2011; Hong et al., 2009; van Oort et al., 2018) or in food hedonics (Bartoshuk, 1990; Boltong et al., 2012). Screening for taste disorders reported by oncology patients should be done at the slightest doubt by questionnaires even if no standard tool or approach can be proposed (Enrique Fernandez et al., 2020; Epstein et al., 2019). According to different authors, these disorders affect 15%–100% of patients (Wisner, 2008; Ravasco, 2005; Hutton et al., 2007; Hovan et al., 2010; Zabernigg et al., 2010; Bernhardson et al., 2008; Gamper et al., 2012). A review based on the analysis of 26 studies reporting dysgeusia after cancer therapies (Hovan et al., 2010) reported a weighted prevalence of dysgeusia ranging from 56% to 76% depending on the type of treatment, with half of the patients with taste disorders after chemotherapy, two-thirds after radiation therapy, and three-quarters after the combination of the two types of treatment.

Children are not spared after chemotherapy, even if in a heterogeneous way (Loves et al., 2019; Van den Brink et al., 2021). Taste alterations are especially common in advanced cancer (even without active treatment), but may occur early on and even precede treatments (Brisbois et al., 2006; Mattes et al., 1987; Belqaid et al., 2014). All types of cancers can produce alterations in taste, but cancers of the head and neck, gastrointestinal tract, breast, and lung are at the forefront (Brisbois et al., 2011a; Gamper et al., 2012). Anthracyclines, paclitaxel, carboplatin, and docetaxel are the chemotherapeutic agents producing the highest taste disturbance rates; cisplatin and 5-fluorouracil induce the lowest complaints (Amézaga et al., 2018). Taste dysfunction is more common when the oral cavity, and specifically the anterior two-thirds of the tongue, are irradiated (proton beam therapy and customized bite blocks reduce dose to the gustatory field and subsequent loss of taste (Gunn et al., 2021). Obviously, taste disorders vary over time. Taste impairment often appears 4–6 days after chemotherapy, which usually induces a temporary effect but is repeated with each chemotherapy cycle and diminishes after the drug is discontinued in general within

2 months (Wickham et al., 1999; Boltong et al., 2014; Bernhardson et al., 2008) but sometimes in 1–3 years (Macquart-Moulin et al., 2000; Boer et al., 2010; Jensen et al., 2008). Taste disorders may even last more than 12 years in childhood cancer survivors (Cohen et al., 2014). After radiotherapy to the head and neck area, taste impairment often starts during the first weeks and are maximal at 3–5 weeks after the beginning of irradiation. Taste thresholds can increase at 15–30 Gy and almost all patients experience loss of taste acuity at a dose of 60 Gy with impairment of all basic tastes (Ruo Redda and Allis, 2006; Ripamonti and Fulfaro, 1998). Generally, gradual improvement occurs between the 20th and the 60th day after the end of radiotherapy (Hovan, 2010) and taste thresholds recover within 8 weeks to 1 year (Yamada et al., 2006; Yamashita et al., 2006b, 2009; Sandow et al., 2006), although taste alterations may persist for 7 years (Ripamonti and Fulfaro, 1998; Ruo Redda and Allis, 2006).

15.5.1 Main mechanisms

The causes for taste disorders, which are not entirely known, are multifactorial and related to micronutrient deficiency (zinc, vitamin A, vitamin D, vitamin PP), infections and poor oral hygiene (infection, tobacco, alcohol), dry mouth, sticky saliva, mucositis, nerve damage, and because of the treatment, the alteration of receptor cells (decrease in their number, modification of their structure, deficient coding) (Hong et al., 2009; Komaki et al., 2004). Some mechanisms are quite specific to neoplastic diseases especially after chemotherapy, such as the destruction of the pores of the taste buds, the decrease in the gene expression of T1R3 and T2R5 receptors or impaired mitosis in replicating receptor cells, the poor connection of synapses (pre- to postsynaptic cells), the sensitization of the neurons of the chorda tympani (without alteration of the detection threshold of the receptor cells), the peroxidation of the epithelial cells (due to decreases in vitamins C and E), the bitter taste of some drugs and the mood disorders related to the severity of the disease (Hong et al., 2009; Halyard et al., 2007; Henkin et al., 2011; Yamashita et al., 2006b; Tsutsumi et al., 2016).

15.5.2 Savor-specific alterations

It is the bitter taste that is affected most often and earlier by cancers or their treatments (Comeau et al., 2001; Johnson, 2001; Gamper et al., 2012; Sanchez-Lara et al., 2010; Sarhill et al., 2003): the bitter taste detection/recognition threshold is often reduced, thus resulting in an intensification of the bitter sensation (Hutton et al., 2007; Davidson et al., 1998; Ovesen et al., 1991; Coa et al., 2015), but it may also be increased (Sandow et al., 2006; Yamashita et al., 2006a,b; Sanchez-Lara et al., 2010; Skolin et al., 2006), in which case it is combined with a more or less selective hypogeusia. It has also been reported that patients with phantogeusia show increased expression of T2R taste receptor genes (bitter taste) in their tongues (Hirai et al., 2012).

For other tastes, alterations are various, not stereotypical, and show increased or decreased sensations (Boltong and Keast, 2012). In one study, the salt threshold showed the earliest and the greatest impairment (Steinbach et al., 2009), while the sweet threshold showed the least. The preservation of the sweet taste may be related

to the observation that most taste buds in the oral cavity are devoted to the perception of the sweet taste (Mossman and Henkin, 1978). However, contradictory observations are reported: sweet and bitter tastes (Sanchez-Lara et al., 2010) or sweet and salty tastes (Boer et al., 2010) are the most and least accurately identified after chemotherapy. For some authors, an increase in the detection/identification threshold of glutamate (umami taste) is observed after chemotherapy (Boltong et al., 2014) or radiotherapy (Yamashita et al., 2009; Ruo Redda and Allis, 2006; Shi et al., 2004), while it was not changed for others (Sanchez-Lara et al., 2010).

Besides, cancer patients treated with chemotherapy commonly report the presence of a metallic taste in the mouth, which is frequently observed when they eat red meat in particular (Mattes et al., 1987; Johnson, 2001). The prevalence of a metallic taste ranged from 9.7% to 78% among patients with various cancers, chemotherapy and radiotherapy treatments, and treatment phases (Ijima et al., 2015; Ravasco, 2005; Comeau et al., 2001; Sarhill et al., 2003; Newell et al., 1998; Bernhardson et al., 2008; Coa et al., 2015).

15.5.3 *Changes in hedonic sensations and aversion*

Abnormalities of gustation during cancers not only concern modifications of the nature or the intensity of the sensation. Hedonic sensations can also be affected (Bartoshuk, 1990; Boltong et al., 2012; Ganzer et al., 2015; Johnson, 2001). For several authors, changes in food hedonic sensations are more important than changes in taste function per se (Boltong et al., 2014; Aravindhan et al., 2014). A decreased liking for sweet food and an increased liking for salty foods is often noted (Bossola et al., 2007; Boltong et al., 2014), but the decrease in food liking can be either global, for foods previously liked, or for novel foods (Boltong et al., 2012). Disgust for protein-rich foods (Boakes et al., 1993; Mahmoud et al., 2011) or monotonous food selection can also be found, and these contribute to reduced intakes (Mattes and Cowart, 1994; Hutton et al., 2007; Mahmoud et al., 2011). A return to the initial food liking can be observed 2 or 3 months after treatments (Mattes et al., 1987).

Some complaints, such as food aversions in patients with cancer, are not related to altered sensory physiology per se but to learned aversions that arise during the noxious effects of radiotherapy and chemotherapy (Schiffman, 2007). Aversions are observed in 30%–50% of patients on radiochemotherapy (Capra et al., 2001; Kokal, 1985; Mattes et al., 1987). Food aversions may consist of intense disgust with the refusal to eat after chemotherapy a food eaten immediately before the radiochemotherapy (Andresen et al., 1990; Bernstein and Bernstein, 1981; Andrykowski and Otis, 1990). This phenomenon has been observed for ice-cream (Bernstein and Webster, 1980), grape, or lemon-lime flavored beverages (Mattes et al., 1987), distinctive beverages (Schwartz et al., 1996). Aversions can also be noted for caffeinated foods and drinks: tea, cola, and chocolate (bitter taste), red meat (umami taste), and citrus fruits or juices (sour taste) (Boltong et al., 2012; Boakes et al., 1993). Nausea has been associated with food aversion during chemotherapy treatment (Schwartz et al., 1996).

15.5.4 Consequences on quality of life

Alterations in taste (changes in the intensity or nature of taste, appearance of metallic taste, changes in taste hedonics, or the development of food aversion) are frequently associated with alterations in smell (due to malignancy or therapeutic interventions) (for a review see [Gamper et al., 2012](#)), and both greatly affect the quality of life of cancer patients (for reviews see [Hovan et al., 2010](#); [Rathod et al., 2015](#)). In fact, studies have reported that taste alterations with other complaints, such as a dry mouth, sticky saliva, difficulty swallowing, oral pain and modifications in social eating diminish quality of life ([Hutton et al., 2007](#); [Comeau et al., 2001](#); [Macquart-Moulin et al., 2000](#); [Boltong et al., 2012](#); [Zabernigg et al., 2010](#); [Brisbois et al., 2011a](#); [Wickham et al., 1999](#); [Irupe et al., 2014](#); [Bernhardson et al., 2007](#); [Ruo Redda and Allis, 2006](#); [Epstein et al., 2002](#)). Chemosensory alterations are almost always associated with anorexia (for a review see [Boltong et al., 2012](#)). Chemosensory alterations may also be associated with early satiety ([McGreevy et al., 2014](#); [Davis et al., 2006](#)), a reduced desire to procure food, changed or impaired patterns of food intake, nausea, and vomiting ([DeWys, 1974](#); [Davis et al., 2006](#); [Ravasco, 2005](#); [Mcgreevy et al., 2014](#); [Bernhardson et al., 2008](#); [Kokal, 1985](#); [Capra et al., 2001](#)). All in all, taste and smell alterations may lead to malnutrition ([Schiffman, 2007](#); [Grant and Kravits, 2000](#)) and weight loss ([Belqaid et al., 2014](#); [Mahmoud et al., 2011](#); [Boltong et al., 2014](#); [Comeau et al., 2001](#); [Peregrin, 2006](#)). Changes in the sweet detection threshold and bitter recognition threshold in cancer patients under chemotherapy are often associated with lower energy and lower nutrient ingestion ([Sanchez-Lara et al., 2010](#)). Taste and smell alterations can also reduce compliance with treatments ([Doty et al., 2008](#)), modify rituals and social activities ([Bernhardson et al., 2008](#)), and cause emotional distress ([Brisbois et al., 2006](#); [Bernhardson et al., 2007](#)).

15.5.5 Care

Therefore, it is imperative to consider the subject's chemosensory phenotypes in order to adjust the sensory properties of the food to the taste alterations in order to meet the subject's dietary needs and recommendations ([Ravasco, 2005](#); [Brisbois et al., 2011a](#)). In all cases good dental and oral hygiene is necessary. Treatment of oral candidiasis can be proposed if necessary (chlorhexidine) and analysis of treatments altering taste sensitivity must be carried out ([Doty, 2019](#); [Schiffman, 2018](#)). Several strategies can be recommended when patients complain about a metallic taste ([Ijpma et al., 2015](#)): use plastic utensils, avoid red meat, decrease the consumption of foods with a metallic or bitter taste (coffee, tea), increase the consumption of low-flavor protein-rich foods (chicken, fish, eggs, dairy products), eat cold or frozen foods, add strong herbs, spices, sweeteners, or acidifiers to foods, eat sweet and sour foods, use "miracle fruit" supplements ([Wilken and Satiroff, 2012](#)) and rinsing with chelating agents. Treatment of a martial deficiency if it exists can be useful but the removal of amalgams and metal crowns is not very effective ([Doty, 2019](#)).

With regard to the other chemosensory alterations, limited suggestions have been proposed and recommendations have been published (Hong et al., 2009). Suggestions include eating blander foods, drinking more water with foods, oral care before eating, and eating smaller portions with more frequent meals (Rehwaltdt et al., 2009), or avoiding strong-smelling or strong-tasting foods as well as cooling the food in order to decrease a distasteful flavor (Peregrin, 2006; Wickham et al., 1999; Grant and Kravits, 2000) or, in contrast, enhancing flavor (Wickham et al., 1999; Bartoshuk, 1990; Steinbach et al., 2009; Schiffman et al., 2007). Oral nutritional supplements have to be adapted to subjects' preferences but fresh milk-based supplements seem to be well accepted (Cohen et al., 2011; Trinidad et al., 2012) and supplements have to offer a wide variety of flavors to prevent taste fatigue (Ravasco, 2005). Patients have to be encouraged to try new foods or supplements on days when they are not receiving chemotherapy (Capra et al., 2001). In all cases, nutritional interventions and education are of great interest (Lindman et al., 2013; Grant and Kravits, 2000; Ravasco, 2005; Schiffman et al., 2007) since some foods seem to be frequently preferred (e.g., fruits and vegetables, soup, poultry, pasta, fish) and others avoided (e.g., greasy/fried foods, spicy foods, acidic citrus foods, Indian and Mexican foods) (Coa et al., 2015).

The prophylactic use of zinc sulfate or amifostine (a scavenger of free radical compounds produced by chemo- or radiotherapy) is of limited benefit (Hovan et al., 2010; Halyard et al., 2007; Komaki et al., 2004; Thorne et al., 2015) even though an early administration of a formulation containing polaprezinc improved taste alterations in 70% of the patients. Tetrahydrocannabinol and ghrelin have been proposed in the palliation of chemosensory alterations to improve food enjoyment (Brisbois et al., 2011b; Neary et al., 2004), but these drugs need further investigation before being used in routine practice. A broad variety of treatment options were also described including radio-protectors, vitamins and supplements, marinol, megestrol acetate and synsepalum dulcificum, antixerostomia agents, and active swallowing exercises (Sevryugin et al., 2021; Thorne et al., 2015). A study reported that repetitive transcranial magnetic stimulation procedures correct taste distortions (phantageusia) (Henkin et al., 2011) and that photobiomodulation could improve taste alterations (El Mobaddere et al., 2019). For head and neck cancers, the radiation therapy protocol should preserve taste sensation by using Intensity-Modulated Proton Therapy to reduce the radiation dose to the taste buds (Deshpande et al., 2018). In all cases, nutritional counseling can help patients in minimizing the symptoms of dysgeusia (Hovan et al., 2010; Nolden et al., 2019; Drareni et al., 2019).

15.6 Taste disorders in COVID-19 infection

Frequently, patients with SARS-COV-2 infection experience smell and taste disorders (for review see Ibekwe et al., 2020; Mastrangelo et al., 2021; Meunier et al., 2021). These mainly consist of a decrease or loss of smell (hyposmia and anosmia) and taste (hypogeusia and ageusia); alterations in the chemesthesis and/or variations in the

quality of chemosensory perception (phantosmia and parosmia). While reports were at first anecdotal and generally without quantitative measurements, a recent study on around 4000 participants from more than 40 countries confirms that COVID-19 broadly impacts chemosensory function across multiple sensory modalities (Parma et al., 2020).

There are different postulated mechanisms by which viruses affect smell (Meunier et al., 2021). ACE2 (angiotensin-converting enzyme 2) was characterized as the main entrance receptor for SARS-CoV-2 (Letko et al., 2020) interacting with its spike proteins, which allows the entrance into the host cell via a fusion domain (Delmas and Laude, 1990; Matsuyama et al., 2010). They are mainly expressed in the upper part of the respiratory tract (Hou et al., 2020) and the highest density of these proteins is found in the olfactory epithelium. The currently available evidence suggests that the most likely cause of anosmia during COVID-19 is an altered function of olfactory sensory neurons, associated with the infection and death of microvillar cells, and vascular pericytes. the virus, being neurotropic, could penetrate through the cribriform plate to infect the olfactory bulb and follow the olfactory pathway to attack the olfactory cortex of the temporal lobe of the brain responsible for smell. However, other inflammation-mediated mechanisms, involving focal mucosal swelling and airflow obstruction could also possibly occur, and the hypothesis of a direct infection of olfactory sensory neurons deserves additional investigations (Lee et al., 2020).

Only limited data are available on the mechanisms involved in the pathogenesis of taste disorders in COVID-19 (Cooper et al., 2020). ACE2 was suspected to be expressed mainly outside the taste buds (Cooper et al., 2020). This was confirmed by a comprehensive study of the ACE2 expression profile in mice tongue showing that ACE2 is mainly expressed in epithelial cells outside of taste papillae which contain the taste buds (Wang et al., 2020). Thus it could be hypothesized that, similarly to what is suggested for olfactory disorders, the pathogenesis of taste disorders in COVID-19 may involve indirect damage of taste receptors through infection.

The evolution and prognosis of smell and taste disorders in COVID-19 while appearing favorable, can vary greatly in time (Mastrangelo et al., 2021; Boscolo-Rizzo et al., 2020). Some observational studies have shown that a very prolonged course could be possible even for months (Chiesa-Estomba et al., 2020). These disorders could influence severely the quality of life of affected subjects (Meunier et al., 2021; Croy et al., 2014).

15.7 Conclusion

Improving knowledge about gustatory alterations in different pathological conditions should encourage physicians not to neglect them. Taste sensitivity is decreased in most cases but it can also increase. These abnormalities in taste quality or in the hedonic component of the sensation, associated with alterations in smell may perturb the subjects' nutritional state. Therefore, it is imperative to establish the personal taste complaints of every individual according to their physiological condition, disease, and

treatment. In obesity and in metabolic diseases, orosensory detection of carbohydrate or fat may be impaired, thus leading to the overconsumption of foods too rich in these nutrients. It is therefore important to understand if and how taste sensations contribute to the construction of feeding behavior by directing consumer choices. In neurological diseases, taste disorders are often underdiagnosed because they are eclipsed by sensory and motor symptoms. In neurodegenerative diseases such as Parkinson or Alzheimer diseases, taste impairment could be an early marker of neurodegeneration. In cancer, increased taste sensitivity, in particular for the bitter taste, is more common than decreased sensitivity and patients often experience a metallic taste. They also report a wide range of modifications in food preferences and aversions. Finally, the recent COVID-19 pandemic underlines the fact that viruses can have an impact on the chemosensory system and thus affect the way patients can change their feeding behavior. The ultimate goal in all pathological situations is, after identifying the taste alterations specific to each individual, to adapt the food choices in order to avoid malnutrition and a deterioration in their general state, which would weaken their ability to fight against the disease. Personalized nutritional guidance is therefore imperative.

Acknowledgments

We thank Philip Bastable of the “Pole de Recherche” of Dijon University Hospital for revising the English.

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Olfactory disorders and consequences*

16

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16.1 Introduction

Generally, three functions are assigned to the sense of smell, namely warning us of potential danger, social communication, and importance for eating and drinking (Stevenson, 2010; Croy et al., 2014a; Schäfer et al., 2021). These functions are also reflected in some of the complaints of patients with smell disorders: occurrence of household accidents, inability to smell family members, loss of flavor perception (Miwa et al., 2001; Santos et al., 2004; Temmel et al., 2002; Keller and Malaspina, 2013).

Despite these important functions, many people live without a sense of smell. This is especially true for older people. Approximately 5% of the general population is anosmic (Brämerson et al., 2004; Vennemann et al., 2008; Kern et al., 2015; Doty, 2019a). Every fourth person aged 53 or older has an impaired sense of smell (Murphy et al., 2002; Pinto et al., 2015). Here it is interesting to note that a decreased sense of smell seems to predict mortality (Liu et al., 2019), even independently of cognitive functioning (Choi et al., 2021), and that healthier people seem to have a better sense of smell than people who are not so healthy (Mackay-Sim et al., 2006; Landis et al., 2003).

16.2 Classification of olfactory loss

Quantitative smelling disorders: anosmia describes the lack of ability to smell, and specific anosmia describes the inability to perceive a specific odor, whereas the vast majority of odors are normally perceived. Such specific anosmias have been described for a series of different odors (Amoore, 1991); they are considered to be due to the lack of

* Citation: Hummel T, Croy I, Georgiopoulos C, Haehner A (2022) Olfactory disorders and consequences. In: Voilley A, Salles C, Guichard E, Etievant P, Sykes R (eds.) Flavor: From food to behaviors, wellbeing and health - Woodhead Publishing.

certain receptors (Keller et al., 2007; Verbeurgt et al., 2014) and to serve functions in terms of filtering olfactory input (Croy et al., 2015). The term *functional anosmia* refers to a significantly reduced ability to smell, although some smell sensations can still be present (Hummel et al., 2017a). Hyposmia refers to a reduced ability to smell, and hyperosmia to an enhanced ability to smell. While hyposmia is frequent, hyperosmias are rare (e.g. Henkin, 1990).

Qualitative smell disorders: A distinction is made between parosmia and phantosmia. The latter describes the perception of odors in the absence of a relevant odor source, and the former describes the qualitative “wrong” perception of odors. Patients, for example, perceive something after being presented with an odor of coffee, which is not the expected odor of coffee, but rather a distorted and typically unpleasant odor. This phenomenon can expand to a number of odors and foods, making life very difficult (Frasnelli et al., 2003; Zou et al., 2021).

A simple classification of qualitative smell disorders can be made based on three criteria: daily/not daily (1 or 0 points, respectively); intense/not intense (1 or 0 points, respectively); social or other notable consequences (e.g., weight increase/loss/social or other consequences, or no consequences 1 or 0 points, respectively): The sum of the points gives the degree of parosmia or phantosmia (0 to 3rd degree) (Hummel and Welge-Luessen, 2009). Other approaches to parosmias and phantosmias have been described (Landis et al., 2010). More recently, tests for the quantification of parosmia have been proposed based on the patients’ ratings of odors (Liu et al., 2020b).

16.3 Causes of olfactory disorders

Apart from aging (Hummel and Oleszkiewicz, 2020), the four main causes of smell disorders are (1) trauma, (2) infections of the upper respiratory tract, (3) sinonasal disease such as chronic rhinosinusitis with or without nasal polyposis (please see Table 16.1), and importantly, (4) smell disorders associated with aging or without aging or unknown causes, some of which will later develop into neurodegenerative diseases such as Parkinson disease or Alzheimer disease (Hummel et al., 2017a).

Smell disorders after head trauma are possibly due to rupture of the olfactory nerves when crossing the cribriform plate (Delank and Fechner, 1996), and also the contusion of the olfactory bulb and secondary olfactory-related areas of the brain such as the orbitofrontal cortex or the temporal lobe (Rombaux et al., 2006b; Lotsch et al., 2015, 2016). Viral infections are assumed to cause damage to the olfactory mucosa (Yamagishi et al., 1994; Brann et al., 2020) or may change their receptor expression patterns (Xu et al., 2020). Olfactory dysfunction can be induced by a range of agents including Sars-CoV2 (Konstantinidis et al., 2006; Suzuki et al., 2007; Wang et al., 2007; Meinhardt et al., 2020). Sinonasal disease involves inflammation-related functional impairment (Klimek and Eggers, 1997; Chen et al., 2019; Jung and Lane, 2016) or changes in terms of the mechanical access to the olfactory epithelium (Seiden, 1997). Olfactory loss is among the first symptoms of Alzheimer disease (Kesslak et al., 1988; Murphy et al., 1990; Murphy, 2019) or Parkinson disease (Ponsen et al., 2004;

Table 16.1 Characteristics of major causes of olfactory loss

	Skull-brain trauma	Infection of the upper respiratory tract	Rhinosinusitis w/o polyps
Probable cause	Lesion of olfactory fibers in the region of the lamina cribrosa; contusion of important “olfactory areas” of the brain	Viral damage to the olfactory epithelium, possibly also to olfactory bulb	Mechanical shifting, edema/functional impairment as a result of inflammation processes in the mucous membrane/ olfactory bulb (?)
Occasional smell sensations	Seldom	Frequently	Frequently
Epithelium	Degeneration	Metaplasia, abnormal development of the ORN	Usually normal
Estimate of the rate of occurrence of lasting smell dysfunction	About 5%	<1% (in COVID-19 5%–20%)	About 2/3 of all patients with chronic sinusitis
Typical age	20–50 years	Older than 50 years	30–60 years
Onset of smell disorders	Acute	Acute	Slow
Loss of smell	Severe	Moderate	Moderate
Rate of occurrence of parosmia	Frequent	Very frequent	Seldom
Probability of improvement of the smell disorder	Less often, improvement mostly in hyposmic patients	Often, improvement also over several years	Very often, improvement due to surgery or treatment with systemic or topical corticosteroids, however often only short-term

Doty and Hawkes, 2019; Haehner et al., 2009; Webster Ross et al., 2008). In Parkinson disease these symptoms precede the onset of the motoric symptoms by 4–10 years or more (Braak et al., 2003; Haehner et al., 2019; Pont-Sunyer et al., 2015).

In addition to these four main causes of olfactory loss, there are many other causes, including congenital anosmia, exposure to toxic substances, psychiatric illnesses such as schizophrenia and depression, epilepsy or systemic diseases such as sarcoidosis, lupus erythematosus, as well as endocrine disorders like hypothyroidism, or isolated organ deficiencies like kidney failure, liver failure, or tumors (e.g., esthesioneuroblastoma and other intranasal carcinomas and benign or malignant brain tumors) (Hummel et al., 2017a). Iatrogenic causes of smell disorders are neurosurgical operations, radiotherapy, or otorhinolaryngology-related procedures. Often the cause of the smell disorder cannot be determined; some of these causes are due to inflammation (Heilmann et al., 2004; Hald et al., 2020).

With regard to side-effects of medications (Henkin, 1986; Ackerman and Kasbekar, 1997; Lötsch et al., 2015b) the sense of smell is relatively robust (Doty and Bromley, 2004)—different from the sense of taste (see Naik et al., 2010; Doty et al., 2008; Wang et al., 2017). However, as olfactory drug effects are not part of drug development requirements, they have to be mainly gathered using available information, which is largely based on anecdotal reports (Lötsch et al., 2015a). In addition, when using these reports unfortunately it is often unclear whether the side-effects relate to a loss of retro-nasal function or to a taste distortion; it is hoped that new approaches like characterization of drug target expression pattern in human olfactory tissue combined with developments in bioinformatics will provide new insights into this area (Lötsch et al., 2015a).

16.4 Patient examination

The first step is a detailed patient history (for a detailed form see Welge-Luessen et al. (2013)). This may also cover eating, drinking, and smoking habits; accidents; operations; and medicines taken, as well as upper respiratory tract infections (URTI) preceding the olfactory disorders and the presence of nasal complaints (nasal obstruction, rhinorrhea, facial pain). Questions might also be asked about thyroid function, depression, lupus erythematosus, and allergies.

The questionnaire should be followed by a physical examination including nasal endoscopy, in particular, checking for pus or polyps (Soler et al., 2016; Poletti et al., 2018). One specific condition described as “olfactory cleft disease” (Biacabe et al., 2004; Jiang and Liang, 2020) consists of an isolated obstruction of the olfactory cleft (Lima et al., 2006) that possibly also involves hamartomas (Nguyen et al., 2014, 2020). An additional neurological or psychosomatic consultation may be useful. Magnetic resonance imaging (MRI) examination is often necessary, for example, for idiopathic smell disorders (Rudmik et al., 2014; Hoekman et al., 2014), for cerebral causes of smell disorders such as brain tumors, and of course for the evaluation of congenital anosmia with hypoplasia/aplasia of the olfactory bulb and a flattening of the olfactory sulcus (Huart et al., 2011).

Psychophysical testing of olfaction is most useful to assess the patient’s olfactory status. Numerous tests have been developed for that—most of them are either only

odor identification tests, or the test battery contains an odor identification test in addition to other tests (Doty et al., 1984, Hendriks, 1992, Kobal et al., 1992, Hummel et al., 1997, Cain, 1989, Thomas-Danguin et al., 2003, Besser et al., 2019, Sorokowska et al., 2019). Various tests are available for the screening (Mueller et al., 2005) or exhaustive psychophysical testing of olfactory dysfunction (Oleszkiewicz et al., 2019); for review see Doty (2019b). The reason for diverse tests of olfactory function is the assumption that different tests concern portions of the processing of olfactory information (Royet et al., 2001; Lotsch et al., 2008; Hedner et al., 2010), but also see Doty et al. (1994, 1995) (Fig. 16.1). For example, thresholds are thought to be determined to some degree by low-level perceptual functions whereas higher olfactory functions, such as discrimination and identification, pose more cognitive demands. It is of interest to note that there are a number of examples of performance dissociations in different olfactory functions (Whitcroft et al., 2017). For example, olfactory thresholds have been found to increase (decreased sensitivity) in sinunasal disease (Stuck et al., 2003) septal deviation (Pfaar et al., 2004), and other conditions (e.g. Wang et al., 2004), although odor identification or odor discrimination are more or less unchanged.

Extensive smell tests allow differentiation between normosmia, hyposmia, and anosmia, whereas screening tests only differentiate between healthy and not healthy. The commercial availability of these tests and their standardized use in various centers means that different clinical tests can be compared. Other tests are based, for example, on measurement of the sniffing behavior (e.g., CompuSniff Test (Frank et al., 2006)).

Electrophysiological procedures to study clinical olfaction are available (Gudziol and Guntinas-Lichius, 2019). They include the olfactory event-related potentials (OERPs) (Kobal, 1981; Hummel and Kobal, 2001; Lascano et al., 2010) or the analysis of electroencephalogram (EEG)-related olfactory activation (Huart et al., 2012; Schriever et al., 2017; Guducu et al., 2015). The olfactometers used must allow the



Figure 16.1 Photographs of some of the tests used for routine clinical investigations (“Sniffin’ Sticks” for orthonasal testing, taste powders for retronasal testing, air-dilution olfactometry for the recording of olfactory event-related potentials (OERP), taste sprays for whole-mouth taste testing, taste strips for lateralized taste testing, mostly for CN VII [chorda tympani]).

presentation of chemical stimuli of defined duration, concentration, and stimulus rise time (for details see [Kobal \(1981\)](#) or [Hummel and Kobal \(2001\)](#)). If there is activation, one can assume that there is an ability to smell ([Lotsch and Hummel, 2006](#); [Rombaux et al., 2007](#); [Gudziol et al., 2020](#)).

In addition to the assessment of orthonasal olfactory function, it is also possible to investigate retronasal olfactory function, “flavor.” For clinical use several tests have been developed, for example, the “Schmeckpulver” (taste powders) ([Heilmann et al., 2002](#); [Leon et al., 2007](#); [Yoshino et al., 2021](#)) and the “candy test” ([Renner et al., 2009](#)). In case of the taste powders 20 different powder-form foods and spices are placed in the mouth (e.g., cinnamon), and patients are asked to identify the “taste” from a list of descriptors. In addition, screening tests have been developed ([Besser et al., 2020](#)), and the assessment of retronasal odor thresholds also appears possible ([Yoshino et al., 2021](#)).

Neuroimaging plays an important role in the clinical assessment of patients with impaired olfaction. Computed tomography (CT), with its exquisite demonstration of bony details, is typically the modality of choice for an initial assessment of the nasal cavity. CT allows the evaluation of bone remodeling and mucosal thickening, which is associated with inflammatory processes in the sinonasal compartment, as well as the presence of hemorrhage or fracture along the cribriform plate after head injury ([Hall et al., 2015](#)). In benign inflammatory diseases, such as chronic sinusitis and polypsis, CT is essential in assessing the pattern of sinonasal drainage impairment and in presurgical planning ([Maroldi et al., 2008](#)). However, for the evaluation of malignant sinonasal disease, CT needs to be used in conjunction with MRI.

MRI is superior in delineating soft-tissue pathology compared to CT, with the additional advantage of not being associated with irradiation. Conventional MRI is, therefore, an important component of evaluating both the peripheral and the central olfactory pathways ([Lie et al., 2021](#)), and an essential part of the diagnostic work-up for patients with suspected neurodegenerative disorders ([Lie et al., 2021](#); [Reimão et al., 2020](#)). Moreover, this imaging method enables volumetric measurements of the olfactory bulbs (OB), which can be considered a volumetric indicator of olfactory function ([Huart et al., 2013](#)). It has been shown that the OB decreases in volume when people lose their sense of smell ([Yousem et al., 1996](#); [Rombaux et al., 2006a](#); [Mueller et al., 2005](#)). However, it also increases again when people regain olfactory function ([Haehner et al., 2008](#); [Gudziol et al., 2009a](#); [Gürbüz et al., 2021](#)). In addition, volume changes of brain regions intimately related to olfactory functioning have been reported in patients with olfactory loss ([Bitter et al., 2010a, 2010b](#); [Han et al., 2017, 2018a](#)).

Advanced MRI techniques, such as functional MRI (fMRI) and Diffusion Tensor Imaging (DTI), are widely used in an effort to better understand and delineate central olfactory pathways ([Chen et al., 2020](#)). The most common fMRI technique employs the Blood Oxygen Level Dependent (BOLD) contrast in order to make inferences about neuronal activity ([Han et al., 2018b](#)). However, the clinical use of olfactory fMRI for diagnosis and individual patients remains problematic ([Yunpeng et al., 2020](#); [Morrot et al., 2013](#); [Gottfried, 2006](#)). DTI allows noninvasive characterization of white matter tracts and is highly sensitive to microstructural tissue changes

(Skorpil et al., 2011). However, these methods have not been routinely used in clinical practise, due to the high variability of the results and the nonstandardized test protocols (Yunpeng et al., 2020; Morrot et al., 2013).

The sum of the various procedures and tests allows not only to come up with a proper diagnosis but also detailed knowledge about olfactory function. This is important in order to provide the patient with information on the prognosis of the disease and to come up with suggestions for treatment (London et al., 2008; Hummel and Lutsch, 2010; Rombaux et al., 2010; Liu et al., 2020a). For example, the prognosis is worse in patients with posttraumatic olfactory loss compared to patients with olfactory loss following an URTI (Reden et al., 2006; Hummel et al., 2017a). Prognosis also depends on remaining olfactory function—the more the better. And finally it is important to establish current olfactory function in order to be able to judge future changes in relation to therapy (Gudziol et al., 2006). All in all, in terms of the diagnostic work-up of the patient it seems to be most important in the first place to obtain a detailed history and to perform structured psychophysical olfactory testing (Welge-Luessen et al., 2013).

16.5 Treatment of smell disorders

There are only limited treatments available for olfactory dysfunction (Mainland et al., 2020; Hummel et al., 2017a; Boesveldt et al., 2017; Damm et al., 2019; Scangas and Bleier, 2017). It seems to be best in patients with olfactory loss due to sinonasal disease where surgical and conservative techniques are available (e.g., corticosteroids [topical and systemic], antibiotics [topical and systemic], nasal douche, antibodies against inflammatory mediators (Seiden and Duncan, 2001; Damm et al., 2014a; Fokkens et al., 2020) or sodium-citrate (Panagiotopoulos et al., 2005; Whitcroft and Hummel, 2019). A special case here is olfactory cleft disease (Trotier et al., 2007; Biacabe et al., 2004; Nguyen et al., 2020). Here inflammatory obstruction is usually bilateral, confined to the clefts, with no sign of obstruction or any inflammatory disease in the rest of the nasal cavities and sinuses. The particular work by Trotier et al. (2007) seemed to indicate that the human olfactory clefts function differently from other regions of the nasal cavity; local inflammatory events do not respond very well to corticoid and antibiotic treatments (see also Nguyen et al. (2014); Nguyen et al. (2020)).

Regarding posttraumatic and postviral olfactory loss, prognostic factors have been identified which help to predict the development of the disorder, with most important positive factors being younger age and better current olfactory status (Hummel and Lutsch, 2010; Rombaux et al., 2010, 2012; London et al., 2008; Portier et al., 2000; Doty, 2019c); regarding sinonasal olfactory loss see Minovi et al. (2008); Schriever et al. (2013); Fokkens et al. (2020). As to therapy, more recent studies show the effectiveness of smell training (Hummel et al., 2009; Damm et al., 2014b; Konstantinidis et al., 2013; Sorokowska et al., 2017; Addison et al., 2021). The simple instruction

to patients is to smell four different odors each morning and each evening for a period of 6 months and longer. This results in improvements in up to ~60% of patients during 6–12 months of treatment.

With regard to drugs in the treatment of olfactory loss, a number of unblinded studies have been done, providing interesting results on drugs like alpha-lipoic acid, theophylline, caroverine, sodium-citrate buffer, local vitamin A, omega3, zinc, and pentoxifylline (Quint et al., 2002; Hummel et al., 2002, 2017b; Henkin et al., 2009; Panagiotopoulos et al., 2005; Gudziol and Hummel, 2009; Hirsch et al., 1996; Yan et al., 2020; Jiang et al., 2015). However, blinded studies in large groups of patients are needed (Doty, 2019c; Whitcroft and Hummel, 2019).

To summarize, although limited, there is treatment of olfactory dysfunction. In this context, again, it seems to be very important to inform patients about the likelihood of spontaneous recovery within the context of their individual conditions.

16.6 Quality of life in patients with olfactory loss

Several questionnaires have been developed to detect changes related to quality of life in olfactory loss (e.g. Miwa et al., 2001; Hufnagl et al., 2003; Takebayashi et al., 2011; Nordin et al., 2011; Shu et al., 2011). For example, the frequently used Questionnaire of Olfactory Disorders (QOD) assesses daily life problems associated with olfactory loss (Frasnelli and Hummel, 2005; Neuland et al., 2011; Mattos et al., 2018). It consists of “negative” statements indicating patients suffering from olfactory impairment, “positive” statements related to coping with the disorder, and statements of social desirability indicating whether the patients are answering truthfully or not. Another questionnaire asks about the importance of olfaction in daily life (Croy et al., 2010; Oleszkiewicz and Hummel, 2019). This questionnaire does not focus on impairments, but on the question how much people rely on their sense of smell. However, here it should always be kept in mind that olfactory loss is often confounded with comorbidity, e.g., difficult nasal breathing. So it is challenging to determine whether Quality of Life (QoL) reduction is due to the olfactory or the comorbid disorder (e.g., Litvack et al., 2009).

Patients with olfactory disorders have been reported to be impaired in terms of food intake, safety, personal hygiene, and in their sexual life (Tennen et al., 1991; Keller and Malaspina, 2013; Gudziol et al., 2009b; Zou et al., 2021; Schäfer et al., 2021; Merkonidis et al., 2015). For example, patients with olfactory disorders enjoy their food less (Ferris and Duffy, 1989; Pellegrino et al., 2020) and lose appetite (Blomqvist et al., 2004; Boesveldt and de Graaf, 2017) although this does not necessarily mean that patients lose weight (Ferris and Duffy, 1989; Aschenbrenner et al., 2008; Boesveldt et al., 2017). Many patients also have trouble with food-poisoning because the olfactory system no longer provides appropriate warnings (Santos et al., 2004; Hummel et al., 2017a).

Another frequently reported problem is uncertainty about environmental hazards, e.g., the detection of smoke or gas (Nordin et al., 2011), and of course it is problematic that, for example, the own body odor cannot be perceived, which again produces uncertainty (Nordin et al., 2011; Miwa et al., 2001; Croy et al., 2012).

Importantly, social relations seem to be affected by olfactory loss (Bramerson et al., 2007; Varga et al., 2000; Schäfer et al., 2021). Much of this is probably related to loss of social competence related to loss of the sense of smell—much of which is owed to food-related incompetence.

Perception problems in working life are generally reported less frequently (e.g., Nordin et al., 2011). However, when more specific questions are asked about work-related problems, up to 60% of the patients report special adjustments on their job and 5% of the patients report not being able to work anymore in their former profession, e.g., chefs and other professions related to food (Haxel et al., 2011).

Many patients with olfactory dysfunction exhibit signs of depression (Rottstadt et al., 2018; Croy et al., 2014b). For example, Deems et al. found that about 25% of their 750 patients reported Beck Depression Inventory (BDI) scores in the range of mild to severe depression (Deems et al., 1991) (compare Smeets et al., 2009; Temmel et al., 2002; Chen et al., 2021). These percentages were even higher in patients with parosmia or phantosmia. A relatively high degree of depressive symptoms has also been reported in people with congenital anosmia (Croy et al., 2012). Importantly, those enhanced depression symptoms are only observed in individuals who present themselves to specialized diagnosis and treatment. An investigation in individuals who were not aware of their olfactory deficit did not reveal enhanced depression (Oleszkiewicz et al., 2020).

Importantly, the majority of patients develop strategies to adjust to the olfactory disorder. Problem- and emotion-focused coping strategies are applied by about 80% of the patients (Nordin et al., 2011; Blomqvist et al., 2004). Croy et al. (2011) reported that, compared to hyposmic patients, anosmic patients stated that they try to use the sense of smell less often in daily life, and both groups rated their sense of smell as less important than a group of normosmic people. Interestingly, 13% of the patients expressed enhanced scores on an aggravation scale (e.g., “without the sense of smell my life would be worthless”), indicating that they exhibited major problems adjusting to the deficit. These patients also exhibited significantly higher depression scores. However, there seems to be only a small number of patients with major problems in coping with the impairment.

16.7 Summary

Smell and taste disorders can markedly affect the quality of life. Validated and reliable methods have been developed for the assessment of the ability to smell and to address questions related to quality of life. In addition, today we know more about the

spontaneous recovery of olfactory dysfunction and the predictors of such recovery. Based on the diagnostic tools in combination with thorough counseling of the patient, more and more therapeutic options become available in the therapy of olfactory loss.

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17.1.1 Overview of oral microbiota

Flavor. <https://doi.org/10.1016/B978-0-323-89903-1.00009-8>
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17.1.2 Geographical differences in the oral microbiota

The oral cavity is the first segment of the digestive tract. The inside of this cavity is heterogeneous due to the presence of soft and hard tissues. Soft tissues represent 80% of oral surfaces such as the protective mucosa inside the cheeks, lips, palate, gingival sulcus, and the tongue. These tissues are characterized by a constant renewal of epithelial cells, which are subsequently found in saliva (Fiorillo, 2020). Hence, microorganisms adhering to soft tissues are regularly released with epithelial cells. This explains the formation of only a thin layer of microorganisms on the epithelial surface, except for the tongue. Indeed, the tongue is the only soft tissue for which the turnover phenomenon is low. This allows the formation of a complex, multilayer biofilm with microorganisms embedded in an extracellular matrix, adhering to each other and to the lingual cells' surface. Beside soft tissues, teeth are the only hard tissue found in the oral cavity. They are covered with enamel, which makes cellular renewal impossible and favors biofilm formation. Those phenomena allow tongue and teeth to host the largest number of microorganisms of the oral cavity (Kilian et al., 2016; Arweiler and Netuschil, 2016). For example, the tongue biofilm is capable of hosting up to 30% of oral microorganisms and the most predominant are shown in Table 17.1. Oral cavity facilitates the development of microorganisms due to its moist, warm, and nutrient-rich environment derived from the host (salivary proteins, glycoproteins ...). As a result, different specific ecological niches are formed in hard and soft tissues. All of them are unique in terms of nutrients and physicochemical microenvironment (pH, temperature, available adhesion surface) (Mark Welch et al., 2019). These factors determine which microorganisms can colonize and grow in these specific sites becoming the major or minor members of those. Each habitat contains specific microorganisms, and all these communities represent the oral microbiota (Lyng Pedersen and Belstrøm, 2019; Fiorillo, 2020).

The location of fungi, viruses, protozoa, and *Archaea* in the oral cavity has been less described than for bacteria. For this reason, only bacterial niches of healthy individuals will be described here. Each niche has its own predominant bacteria and core. Precisely, predominant bacteria can be part of the core, but not all bacteria present in the core are predominant bacteria.

Besides the variability occurring into the oral cavity of a same individual, a strong variability in bacterial composition also exists between individuals. Several studies have shown that microorganisms found in different niches can vary between subjects (interindividual variability) (Zaura et al., 2017; Mark Welch et al., 2019). These differences are boosted between subjects from different countries and cultures (Nasidze et al., 2009). However, those differences of microbiota are specially remarkable at the strain level. In other words, at higher taxonomic levels the difference between individuals is less important. Each microbiota has a different microbial composition resulting from a specific colonization process for each individual, as well as, a persistent evolution shaped by external and internal factors that occur throughout the life of the individual (Mark Welch et al., 2019).

Table 17.1 Predominant and core bacterial taxa found in oral niches. This table compiles several studies that use different depths of sequencing levels, which explains the differences in taxonomic resolutions

Ecological niches	Predominant bacteria	Bacterial core	References
Sub and supragingival plaques	<i>Actinomyces, Capnocytophaga, Corynebacterium, Denticola, Fusobacterium, Granulicatella, Leptotrichia, Neisseria, Porphyromonas, Prevotella, Rothia, Streptococcus, Tannerella, Veillonella.</i>	Subgingival plaque: <i>Capnocytophaga, Corynebacterium, Fusobacterium, Pasteurellaceae unclassified, Prevotella.</i> Supragingival plaque: <i>Actinomyces, Capnocytophaga, Cardiobacterium, Corynebacterium, Fusobacterium, Lautropia, Leptotrichia, Neisseria, Parascardovia, Pasteurellaceae unclassified, Prevotella Rothia, Veillonella.</i>	(Deo and Deshmukh, 2019; Bik et al., 2010; Verma et al., 2018; Zaura et al., 2009; Mark Welch et al., 2016, 2019)
Gingival sulcus	<i>Gemella (Gemella morbillorum), Granulicatella, Moraxella, Neisseria, Streptococcus (S. mitis, S. oralis), Treponema.</i>	<i>Acinetobacter, Haemophilus.</i>	(Sharma et al., 2018; Jiang et al., 2015; Li et al., 2013; Mark Welch et al., 2019)
Hard palate	<i>Catonella, Gemella morbillorum, Mogibacterium, Streptococcus (S. mitis, S. oralis).</i>	<i>Gemella, Lactobacillales, Pasteurellaceae unclassified, Prevotella, Staphylococcaceae, Veillonella.</i>	(Cruz Quintana et al., 2017; Mark Welch et al., 2019)
Soft palate	<i>Corynebacterium, Haemophilus, Neisseria.</i>	<i>Gemella, Pasteurellaceae unclassified, Staphylococcaceae.</i>	(Sharma et al., 2018; Li et al., 2013)
Cheeks	<i>Acidobacteriaceae, Atopobium, Bacilli, Catonella, Gemella (G. haemolysans, G. morbillorum), Phocoenobacter, Prevotellaceae, Streptococcus (S. mitis, S. oralis) Xylanibacter.</i>	<i>Gemella, Pasteurellaceae unclassified, Staphylococcaceae.</i>	(Cruz Quintana et al., 2017; Li et al., 2013; Mark Welch et al., 2019)

Continued

Table 17.1 Continued

Ecological niches	Predominant bacteria	Bacterial core	References
Throat	<i>Haemophilus</i> , <i>Neisseria</i> , <i>Staphylococcus</i> , <i>Streptococcus</i> .	<i>Actinomyces</i> , <i>Fusobacterium</i> , <i>Lachnospiraceae</i> , <i>Pasteurellaceae</i> unclassified, <i>Prevotella</i> , <i>Veillonella</i> .	(Cruz Quintana et al., 2017; Li et al., 2013)
Tongue	<i>Actinomycetes</i> (<i>A. odontolytus</i>), <i>Bacille</i> , <i>Clostridiales</i> <i>Fusobacterium</i> , <i>Granulicatella adiacens</i> , <i>Lactobacillales</i> unclassified, <i>Pasteurellaceae</i> , <i>Peptostreptococcus</i> , <i>Prevotella melanogenica</i> , <i>Oribacterium</i> , <i>Rothia mucilaginosa</i> , <i>Streptococcus</i> (<i>S. mitis</i> , <i>S. salivarius</i> , <i>S. parasanguinis</i>), <i>Treponema</i> , <i>Veillonella parvula</i> .	<i>Actinomyces</i> , <i>Fusobacterium</i> , <i>Lactobacillales</i> unclassified, <i>Neisseria</i> , <i>Pasteurellaceae</i> unclassified, <i>Prevotella</i> , <i>Veillonella</i> .	(Sharma et al., 2018; Li et al., 2013; Mark Welch et al., 2019)
Saliva	<i>Actinomycetales</i> , <i>Fusobacterium</i> , <i>Haemophilus</i> , <i>Neisseria</i> , <i>Streptococcus</i> , <i>Pasteurellaceae</i> , <i>Porphyromonas</i> <i>Prevotella melanogenica</i> , <i>Tannerella</i> , <i>Veillonella parvula</i> .	<i>Capnocytophaga</i> , <i>Fusobacterium</i> , <i>Neisseria</i> , <i>Pasteurellaceae</i> unclassified, <i>Porphyromonas</i> , <i>Prevotella</i> , <i>Rothia</i> , <i>Veillonella</i> .	(Sharma et al., 2018; Li et al., 2013; Mark Welch et al., 2019)
Teeth	<i>Actinomyces</i> (<i>A. naeslundii</i>), <i>Campylobacter</i> , <i>Corynebacterium</i> (<i>C. matruchotii</i>), <i>Granulicatella</i> , <i>Kingella</i> , <i>Lautropia mirabilis</i> , <i>Leptotrichia</i> , <i>Rothia</i> (<i>R. aeria</i> , <i>R. dentocariosa</i>), <i>Streptococcus</i> (<i>S. mitis</i> , <i>S. sanguinis</i>)	<i>Capnocytophaga</i> , <i>Eikenella</i> , <i>Fusobacterium</i> , <i>Granulicatella</i> , <i>Neisseria</i> , <i>Prevotella</i> .	(Sharma et al., 2018; Li et al., 2013; Mason et al., 2018; Mark Welch et al., 2019)

17.1.3 Oral microbiota changes along life

Tracking the geographical evolution of microbial communities over time (from birth to old age) in humans is something difficult to achieve. The purpose is to characterize and define the composition of “normal” oral microbiota from healthy individuals, in order to identify the composition and variations occurring in a “sick” oral microbiota. One of the biggest studies ever conducted in oral microbiota is the one of [Huttenhower et al. \(2012\)](#) where the majority of the oral niches were characterized for a certain time. However, carrying out longitudinal monitoring, from birth to old age, of microorganisms from different niches is a work that has never been done due to its complexity. Only few studies have followed bacterial growth in teeth, gingiva, and a few more soft tissues during a defined period. [Crielaard et al. \(2011\)](#) and [Holgerson et al. \(2015\)](#) showed the variation of oral microbiota in the dentition during periods of major physiological changes such as the first year of newborn life and the puberty. On the other hand, the impact of adulthood or old age on the evolution of the oral microbiota within different niches has been less studied. However, it is known that oral microbiota composition changes along life. From prenatal to old age, each individual experience may affect the oral microbiota. During gestation, a healthy fetus is supposed to be sterile. However, some studies support that amniotic fluid can be contaminated by the mother’s oral microbiota in 70% of pregnancy cases when the mother has oral microbiota pathologies ([Bearfield et al., 2002](#); [Sampaio-Maia and Monteiro-Silva, 2014](#)). Transient bacteremia is one of the main hypotheses explaining the migration of oral bacteria into the amniotic fluid ([Sampaio-Maia and Monteiro-Silva, 2014](#); [Deo and Deshmukh, 2019](#)). This particular condition may increase the risk of colonization of the fetal oral cavity by *Streptococcus species* and *Fusobacterium nucleatum*, which are some of the bacteria present in pathogenic oral cavity ([Bearfield et al., 2002](#); [Gauthier et al., 2011](#)). At birth, “first” colonizations of the oral cavity take place. The mode of delivery is decisive for the implantation of some microorganisms. During natural childbirth, the newborn oral cavity comes into contact with various microbiota from the mother; the vaginal and intestinal tract microbiota (feces), and the skin microbiota ([Langella, 2017](#); [Socransky and Manganiello, 1971](#)). Consequently, the dominant microorganism present in the vagina, feces, and the skin of the mother will be the most abundant taxa present in the newborn oral cavity. However, during cesarean delivery, the oral cavity of the newborn is mainly colonized by the microbiota of the mother’s skin and of the medical staff present. Later on, the newborn oral cavity will be colonized by microorganisms from the family and will be influenced by lifestyle like the environment and diet (i.e., breastfeeding) ([Dominguez-Bello et al., 2010](#)). The first colonizations remain relatively unstable within 24 h after birth. The pioneer microorganisms are bacteria of the genera *Streptococcus* and *Staphylococcus* but also yeasts such as *Candida*. These will be able to produce changes in oral environment by metabolizing new products that facilitate the growth and implantation of other species. For example, *Streptococcus salivarius* can adhere easily to epithelial cells due to the high number of adhesins expressed on their surface, which allow further implantation of other microorganisms. In addition, these species can produce extracellular polymers from sucrose to which other bacteria such as *Actinomyces* species can adhere

(Sampaio-Maia and Monteiro-Silva, 2014; Cruz Quintana et al., 2017). On the contrary, all the microorganisms that have not been able to adhere to the oral surfaces or to the growing biofilm will be eliminated in the next few days. This phenomenon is called *transient colonization*. Transient microorganisms will be constantly replaced in response to changes in the successive ecosystems, until a complex and stable microbial community is formed (Feres et al., 2016; Hall et al., 2017). When children are 3 years old, the oral microbiota is rich and stable. However, this stability will be threatened throughout life by multiple factors:

- **Oral environmental factors:** temperature, pH, anaerobic conditions, availability of nutrients, variations in salivary flow ...
- **Physiological and genetic factors:** host defense mechanisms, age, hormones, stress, physiological changes (tooth eruption, puberty, tooth loss ...) (Mason et al., 2018).
- **Bacterial factors:** bacterial adhesion as well as interactions between bacteria.
- **External factors:** diet (high consumption of carbohydrates and other sugars, snacking ...), oral hygiene, drugs (antibiotics), smoking (Fiorillo, 2020).

Some of these factors act daily on the oral microbiota without causing imbalance; this is explained by the phenomenon of resilience. Resilience is the ability of an ecosystem to cope with disturbances without causing lasting changes (Kilian et al., 2016; Zaura et al., 2009). However, the resilience decreases with age, explaining why in adulthood or during old age, oral microbiota imbalances are more frequent and can lead to pathologies.

17.1.4 Establishment of dysbiosis, pathologies, and probiotic treatments

In a healthy oral ecosystem, commensal and opportunistic bacteria live together in symbiosis with the host. This balance (eubiosis) is ensured by commensal bacteria who are responsible for maintaining a good oral health. However, when the factors mentioned above exceed the resistance of the resident microbiota, this equilibrium is broken, leading to what is called *dysbiosis*. The oral environment is modified and the commensal bacterial species decrease, which is associated with a reduction of diversity. In addition, opportunistic bacterial pathogens, which are found in small proportions in a healthy mouth, will proliferate and modify the environment. Those new environmental conditions will favor a pathogenic bacterial development. Dysbiosis maintained over time can lead to a pathological state (Kilian et al., 2016) and bacterial oral pathologies are usually due to an imbalance of oral microbiota in general and not only to the overgrowth of a specific microorganisms varying from one individual to another (Fig. 17.1).

Oral pathologies like dental caries or periodontal diseases are some of the most frequent oral diseases in humans (Vos et al., 2012). These diseases are due to an imbalance of the oral microbiota created by a modification of the pH, which can lead to an acidification (dental caries) or basification (periodontal disease) of the mouth environment (Lamont et al., 2018; Rosier et al., 2018).

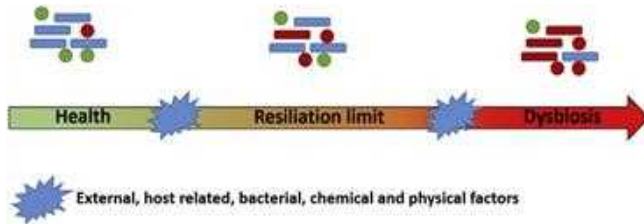


Figure 17.1 Most of the surfaces of the mouth are colonized by commensal bacteria (green). Few places remain for the adhesion of pathogenic or opportunistic agents. Bacteria live in equilibrium with the host and provide it a good state of health. However, this equilibrium is threatened by a set of external, bacterial, chemical, physical factors or due to the host (represented by a blue star). Those factors modify oral microbiota little by little until this equilibrium is broken (dysbiosis). Dysbiosis leads to the proliferation of opportunistic bacteria (in red) likely to cause pathologies.

Regarding current treatments, none of them is able to restore bacterial balance. The polymicrobial origin of these pathologies, as well as the strong interindividual variation between subjects, makes nontargeted treatments ineffective. However, the use of specific probiotics and prebiotics to each pathology may contribute to an improvement in the bacterial balance (Langella, 2017). Probiotics are defined by World Health Organization as “living microorganisms which, consumed in adequate amounts, have a beneficial effect on health of the host, beyond traditional nutritional effects.” The administration of probiotics is often combined with prebiotics, which are nondigestible dietary fibers that selectively stimulate probiotic bacteria as their source of nutrients (Schrezenmeir and de Vrese, 2001). Most of the probiotics like *Lactobacillus*, *Bifidobacterium*, *Propionibacterium*, and *Streptococcus* promote oral health. Among these bacterial genera, some species have been shown to be good probiotics aiding in the restoration of oral homeostasis. For example, the bacterial species *Lactobacillus rhamnosus*, *Lactococcus lactis*, or *Streptococcus thermophilus* is capable of adhering to dental surfaces and to integrate the biofilm community (Shetty and Shetty, 2015). Indeed, each probiotic can act differently, by competing with other microorganisms for nutrients and surface adhesion of the oral cavity, by preventing the growth of species that promotes oral alterations. Some probiotics are even capable of forming their own biofilm to prevent pathogens to access mouth tissues or to modify oral environment by modulating pH and redox potential. Despite the different strategies used by probiotic bacteria, those are not enough to maintain a long-lasting microbial balance but a transitory one, only during the period of probiotic intake (Shetty and Shetty, 2015).

Diet, along with all the products consumed daily, contributes to oral microbial diversity. In particular, fermented foods such as fermented milks (Rungsri et al., 2017), drinkable yogurts (Lodi et al., 2015), cheeses (Ahola et al., 2002; Gomes da Cruz et al., 2009) have a beneficial effect for intestinal and oral health. These products constitute an important daily intake of living microorganisms. For example, in the study of Ahola et al. (2002), subjects consume 15 g of cheese 5 times a day containing at least

10^7 cfu/g. The total bacteria consumed per day for one fermented product reaches 10^9 cfu, which is substantial, comparing to the 10^{10} bacterial resident. The frequent consumption of fermented foods could lead to a “probiotic effect” but also favors the transient or long-term bacterial implantation in the oral cavity, which could shape oral microbiota (Kort et al., 2014).

17.2 Fermented foods

Fermented foods come from the transformation of raw material by microorganisms (bacteria, yeasts, or fungi). Microbial enzymes metabolize organic substrates of raw material, releasing new products. These products give a better shelf life as well as more interesting health, organoleptic and nutritional qualities to new finished products (Marco et al., 2017; Tamang et al., 2016).

17.2.1 Different types of fermentation

In biochemistry, fermentation refers to the production of energy from anaerobic metabolism. Current food fermentation includes not only typical anaerobic reactions, such as acidic and alcoholic fermentations, but also aerobic processes like alkaline fermentation (Nout, 2014; Chojnacka, 2010). Regardless of the type of reaction, microorganisms are the base of fermentation. They must be present in sufficient amount and be metabolically active in order to modify organoleptic characteristics of food (flavor, texture, appearance) and other nutritional, stabilization, and storage properties. There are two approaches ensuring the presence of active microorganisms in food: spontaneous (or natural) and controlled fermentation. Spontaneous fermentation begins from endogenous food flora when the environment allows it (Goy, 2015; Nout, 2014). This spontaneous flora is complex and difficult to reproduce because composition and initial quantity of microorganisms remain unknown. An alternative is back-slopping fermentation which consists of using a small amount of previously fermented batch to inoculate a new batch. This results in the domination of the best-adapted strains, but the fermented products are still unrepeatable and uncontrollable. For these reasons, as well as for reasons of hygiene and health, controlled fermentations, induced by microbial starters, are widely used by food industries. Starters are additives containing a high number of living microorganisms (single or mixed cultures) used to initiate fermentation. The use of starters allows controlling and accelerating fermentation process, in order to create interesting food properties while having highly reproducible products (Kårlund et al., 2020; Terefe, 2016; Anal, 2019).

Regardless of the fermentation method chosen, natural or starter, foods and drinks can be classified in many ways depending on the microorganisms used, the products formed, the substrates used by the microorganisms, etc. Among these classifications, Steinkraus classifies fermentations according to the type of products (Steinkraus, 1997). The most common types of fermentation are acid, alcohol, and alkaline fermentations and will be detailed here (Table 17.2).

Table 17.2 Summary of the main fermentations used in food industry, the main food products resulting from these fermentations, the microorganisms used, and the end products present in food.

Types of fermentation	Fermented food	Microorganism	End products
Homolactic fermentation	Fermented vegetables: sauerkraut, pickled cucumbers, radishes, carrots, olives ... Dairy products: yogurts, cheese ... Sourdough breads Fermented meats: sausage cured meat silage (Alain, 2004)	<i>Lactobacillus</i> , <i>Streptococcus</i> , <i>Lactococcus</i> , <i>Enterococcus</i> , <i>Pediococcus</i>	Principal product: >95% lactic acid
Heterolactic fermentation	Semihard cheese, kefir ... (Alain, 2004)	<i>Leuconostoc</i> , <i>Weissella</i> , <i>Lactobacillus</i> (facultative heterolactic)	Lactic acid, acetic acid, ethanol, CO ₂ , and H ₂
Propionic fermentation	Semicooked cheese such as Comté, Gruyère, and Emmental (Tamang et al., 2016; Alain, 2004)	<i>Propionibacterium</i> (genus) <i>Clostridium</i> (<i>Clostridium</i> is not used in food industry).	Propionic acid, acetic acid, succinic acid, H ₂ , and CO ₂
Butyric fermentation	Swelling of cooked cheeses such as Emmental	<i>Clostridium saccharolyticum</i> : <i>C. tyrobutyricum</i> , <i>C. butyricum</i> . <i>Pasteurianum</i>	Butyric acid, acetic acid, CO ₂ , and H ₂
Acetic fermentation	Vinegar cider (Nout, 2014; Steinkraus, 1997)	<i>Acetobacter aceti</i> . (more used species) <i>Acetobacter</i> , <i>Gluconobacter</i> and some species of <i>Lactobacillus</i> yeast: <i>Brettanomyces</i> et <i>Schizosaccharomyces rouxii</i>	Acetic acid
Malolactic fermentation	Deacidification of wine and cider	<i>Œnococcus</i> (genus) <i>Leuconostoc</i> , <i>Pediococcus</i> et <i>Lactobacillus</i> <i>Leuconostoc oenos</i> (more used species)	Transformation of malolactic acid into lactic acid

Continued

Table 17.2 Continued

Types of fermentation	Fermented food	Microorganism	End products
Alcoholic fermentation	Drinks: wine, beer, kefir Solid foods: bread, pastries (Tamang et al., 2016; Chojnacka, 2010; Steinkraus, 1997)	Yeast: <i>Saccharomyces cerevisiae</i> (more used), <i>Candida</i> , <i>torulopsis hansenula</i> Molds: <i>Aspergillus oryzae</i> , <i>Hansenula</i> , <i>Rhizopus</i> spp., <i>Endomycopsis fibuligera</i> Heterolactic bacteria: <i>Leuconostoc mesenteroides</i> , <i>Lactobacillum</i> <i>plantarum</i>	Ethanol, CO ₂ and aromas
Alkaline fermentation	Asian products: natto, soy sauce, tempeh, kinema ... African products: dawadawa, soubbala, tayohounta, iru (Nout, 2014; Okpara, 2019; Steinkraus, 1997)	<i>Bacillus</i> spp. (<i>bacillus subtilis</i> , <i>bacillus</i> <i>licheniformis</i> .) <i>Phycomycetes</i> , <i>Aspergillus</i> spp, <i>Actinomucor</i> spp	Proteolysis by deaminases, peptidases, and transaminases and release of amino acids and ammonia

(1) **Acid fermentation** is the most used fermentation in food industry. This fermentation involves the acidification of food by formation of organic acids such as lactic, propionic, butyric, acetic, and malolactic acids. Depending on microorganisms and the type of acid produced, acid fermentation is divided into different subcategories:

- Lactic acid fermentation is mainly provided by lactic acid bacteria but also by certain yeasts (Terefe, 2016). These microorganisms are able to do at least one of the two types of lactic fermentation, homo- and heterolactic. Microorganisms used in these fermentations use complex and simple sugars as substrates, which are degraded into pyruvate during glycolysis. The differences between these fermentations are based on the fermentation products synthesized. In homolactic fermentation, lactic acid represents more than 95% of the final products (Alain, 2004). This fermentation is possible for bacterial genera like *Lactobacillus*, *Streptococcus*, *Lactococcus*, *Enterococcus*, and *Pediococcus* (Goy, 2015).

In heterolactic fermentation, several products such as lactic acid, CO₂, H₂, ethanol, and acetic acid, are formed. The proportions of different products vary depending on the microorganisms used, the amount of substrate, the medium (pH, oxidation-reduction potential, etc.). The main heterolactic bacterial genera are *Leuconostoc* and *Weissella*. Likewise, some species of *Lactobacillus* are able to alternate the two types of lactic fermentation. These bacteria are qualified as facultative heterolactic (Goy, 2015).

- In propionic acid fermentation, bacteria use lactose, glucose, or lactic acid as the main substrates, which are transformed into propionic acid, acetic acid, succinic acid, H₂, and CO₂. The proportions of these products can change depending on the substrate used and the environment. Bacterial genera capable of carrying out this fermentation are *Propionibacterium* and *Clostridium* (Nout, 2014). Only the genus *Propionibacterium* is used in food industry, in particular for ripening of cooked pressed cheese. Propionic acid and acetic acid are then responsible for cheese flavor, and carbon dioxide is responsible for hole formation in some cheeses such as Gruyère and Emmental (Alain, 2004).
- Butyric acid fermentation is called “secondary fermentation” because it follows lactic acid fermentation. During this fermentation, *Clostridium* metabolizes lactic acid as the main substrate into butyric acid, acetic acid, CO₂, and H₂. The release of CO₂ and H₂ is responsible for the late swelling of cooked pressed cheeses. For this reason, it is essential to properly control this fermentation in order to avoid breaking crust of cheeses. In addition, butyric acid gives these foods a rancid and sometimes pungent taste (Alain, 2004).
- Acetic acid fermentation follows alcoholic fermentation (described below). This reaction is characterized by the oxidation of ethanol into acetic acid by strict aerobic bacteria such as *Acetobacter aceti*, which is the most used bacteria in this fermentation. However, acetic acid can also be produced by other bacterial genera such as *Gluconobacter*, *Lactobacillus* (heterolactic fermentation) and by some yeasts such as *Brettanomyces* or *Schizosaccharomyces rouxii*, the latter is used in the fermentation of Italian balsamic vinegar (Nout, 2014; Alain, 2004).
- Malolactic fermentation precedes alcoholic fermentation, especially of wine and cider. During this fermentation, *Oenococcus oeni* (main specie involved) metabolizes malic acid into lactic acid and CO₂. This reaction reduces the acidity of the product and makes it more easily consumable (Alain, 2004).

(2) During **alcoholic fermentation**, glucose, fructose, and sucrose are metabolized into ethanol, CO₂, and aromas like linalool, nerol, geraniol... which can be found in wine. This reaction

can be ensured by molds (*Aspergillus oryzae*), yeasts (*Saccharomyces cerevisiae*, *Saccharomyces pombe*, *Pichia anomala* ...) as well as by some heterofermentative lactic acid bacteria (in lower proportions) such as *Leuconostoc mesenteroides* or *Lactobacillus plantarum*. This fermentation is used in particular during the production of alcoholic beverages (beer, grape and palm wine, etc.) but also during the production of bread and certain pastries (Nout, 2014; Tamang et al., 2016).

- (3) **Alkaline fermentation** is mainly made in African and Asian countries with matrices containing a high protein percentage such as seeds (soybeans, African beans, etc.) or fish. During this reaction, microorganisms secrete proteolytic enzymes like deaminases, peptidases and transaminases, capable of breaking proteins down into amino acids and ammonia leading to an increase of the pH (around 7–8). The responsible microorganisms are some filamentous fungi (*A. oryzae*, *Rhizopus*, *Mucor*, *Actinomucor* spp.) and some bacteria of the genera *Bacillus* (*Bacillus subtilis*, *Bacillus pumilus*, etc.) (Nout, 2014).

Different types of fermentation are summarized in Table 17.2.

17.2.2 Role of fermentation in the production of taste compounds

All of these fermentations modify and impact nutritional and organoleptic properties of food. Depending on the type of fermentation, the microorganisms involved differ as well as their secreted enzymes. These enzymes will modify texture, taste, aroma ... We illustrated here the different metabolic ways occurring during fermentation and impacting taste. To further simplify, we focused on lactic acid fermentation. The metabolization of carbohydrates into organic acids by glycolytic enzymes is one of the main reactions modifying the taste of the finished product (Hu et al., 2020). This reaction is the most obvious and characteristic of lactic acid fermentation. For legumes like seeds, beans, lactic acid fermentation is necessary for the degradation of antinutritional elements. Fermentation microorganisms secrete enzymes such as tannases, phytases, and alpha-galactosidases capable of degrading and metabolizing polyphenols (tannins), phytic acid, as well as some toxins (Licandro et al., 2020). In addition, to make the food digestible, the metabolism of these antinutritional factors can soften the bitter taste of the food (Sharma et al., 2020). Degradation of highly protein concentrated raw materials (meat, fish, seeds, etc.) plays an important role in modifying the sour taste of fermented products. Indeed, some microorganisms secrete enzymes with strong proteolytic activity, capable of cleaving proteins into peptides and amino acids and thus modifying the organoleptic characteristics of the food. The contribution of amino acids to taste perception of food was shown a century ago. Since then, numerous teams have determined the taste associated with each amino acid (Table 17.3) (Roudot-Algaron, 1996; Zhao et al., 2016).

Because of the action of proteolytic enzymes, peptides and their derivatives are also formed during fermentation, giving to these products bitter, salty, sweet, sour, or umami notes. The composition, the location, and the number of amino acids forming the peptide play a role in taste and perceived intensity. For example, bitter peptides contain hydrophobic amino acids (proline, glycine, alanine). Peptides of more than three amino acids will have an enhanced bitter taste if a hydrophobic amino acid is

Table 17.3 Classification of the different amino acids according to their taste and representative foods. The amino acids between brackets were perceived differently depending on the studies and may be associated with two different tastes. Cysteine is not shown in the table (Roudot-Algaron, 1996).

Amino acids	Associated typical foods
Bitter (hydrophobic amino acids often have a bitter taste)	
Tryptophan	Soybean
Phenylalanine, leucine, and valine	Chocolate
Histidine	Tuna
Arginine	Nuts
Isoleucine (most bitter)	Eggs
Tyrosine	Cheese
Methionine	Sea urchin
Asparagine	Asparagus
Sweet	
Glycine	Crustacean
Alanine	Meat and fish
Serine	Milk
Lysine	Spirulina
Proline	Nuts cashew
Threonine	Seaweed
Salty	
Lysine HCL and proline	Bread crust
Sour	
Aspartic acid and glutamic acid	Soy sauce and grapefruit
Glutamine	Cottage cheese
Umami	
Aspartic acid and glutamic acid	Miso, soy sauce, parmesan, and ripe tomatoes

at the N-terminus of the peptide (Roudot-Algaron, 1996). Despite the numerous studies reporting the taste of different peptides, current knowledge on the responsible microorganisms and their metabolization pathways remains incomplete (Roudot-Algaron, 1996; Zhao et al., 2016). Despite this lack of knowledge, food technology makes it possible to optimize fermentation strategies. For example, nowadays it is possible to reduce formation of biogenic amines (which give a bitter taste to the product) by using bacteria such as *Staphylococcus xylosus* or *Lactobacillus sakei* capable of degrading histamine and tyramine, thus improving the final taste of the product (Zhao et al., 2016). Those bacteria, as well as fermentative bacteria, can be found in the oral cavity after consumption of fermented products. The presence of these bacteria in the mouth allows us to hypothesize that the local production of new metabolites, as during fermentation, can influence taste perception.

17.3 Influence of oral microbiota on taste perception

Taste perception is elicited by the stimulation of taste receptors mainly located in the taste papillae. These papillae can be differentiated into four types according to their morphology: the circumvallate, the fungiform, the foliate, and the filiform papillae. The latter do not contain taste buds but they have a mechanical role by contributing to friction and mechanosensation (Sarkar et al., 2019). These papillae are mainly located on the tongue dorsum with the exception of foliate papillae, which are also present in the mucosa of soft palate, the back of the mouth, the mucous membrane of epiglottis and pharynx (Laurent Brondel, 2013). Taste papillae harbor numerous taste buds made up of 50–150 cells including the taste cells, which contain the taste receptors. Perception of taste can be modulated by many factors occurring before the interaction between the taste molecule and the receptor. Among them, saliva plays a determinant role, since it is the fluid that interacts with food, bathes and protects taste buds as a film form. This salivary film directly influences taste perception since taste molecules have to diffuse through it before attending the taste buds (Neyraud and Morzel, 2019). Another factor has been recently suspected of influencing taste perception: the oral microbiota. Indeed, the structure of papillae forms ecological sites that allow the accumulation not only of saliva but also of microorganisms and various debris. The presence of these constituents creates a favorable environment for the development of microorganisms, since cellular debris together with salivary glycoproteins constitute the main endogenous food supply for bacteria (Takahashi, 2015). In addition, taste papillae and in particular circumvallate papillae have a dome-shaped structure that favors the development of bacterial communities (Besnard et al., 2020; Batisse et al., 2017).

The first data concerning the relationships between oral microbiota and taste perception have emerged recently. In 2012, Solemdal et al. carried out an experiment on elderly people with poor dental hygiene. The aim of the study was to determine if oral health may influence taste perception. One of the main results was that a poor oral hygiene was associated with a reduced sensitivity to taste; the hypothesis being that taste sensitivity is strongly impacted by the thickness of the lingual bacterial biofilm. A possible explanation was that this biofilm may constitute a physical barrier limiting the access of tastants to taste receptors leading to a reduced taste perception (Neyraud and Morzel, 2019). With the development of sequencing techniques allowing the identification of bacterial species, recent studies have shown associations between taste perception and the oral microbiota composition in humans. Besnard et al. (2018) studied fat taste perception and the bacterial composition near the circumvallate papillae in obese and normal-weight adults. This study could not show any difference between obese and normal-weight groups for fatty taste perception and their oral microbiota composition, but a specific bacterial composition has been found in individuals less sensitive to fat taste, regardless of their body mass index status (normal-weight or obese). Another study carried out by Cattaneo et al. (2019a) found differences in the proportions of certain bacterial taxa between two experimental groups characterized by their sensitivity to PROP (propylthiouracil). PROP is a bitter substance that

is perceived differently between individuals according to their genetic status. Depending on the sensitivity to this substance, two experimental groups; “sensitive” and “not very sensitive” were created. These groups were characterized by different microbial compositions on the tongue dorsum. To go more into detail, subjects characterized by greater reactivity to PROP exhibit a higher relative abundance of certain taxa (*Actinomyces*, *Oribacterium*, *Solobacterium*, *Catonella*, and *Campylobacter*) compared to less reactive subjects. In a following study, the same group (Cattaneo et al., 2019b) went further by identifying specific bacterial taxa attributed to the orders Clostridiales and Bacteroidales. Those can be linked to a great sensitivity to salty and sour tastes. Feng et al. (2018) also observed an association between bacterial phyla and taste perception. In this study, the authors observed two significant correlations; a positive one between *Bacteroidetes* in tongue film and sensitivity to bitter taste and a negative one between *Actinobacteria* in whole resting saliva and saltiness. Today it is still difficult to propose an explanation of such statistical links, as complementary studies are needed. Nevertheless, some hypotheses have been proposed to explain the mechanisms involved in the modulation of taste perception by bacteria. Cattaneo et al. (2019b) suggested that some oral bacteria can hydrolyze carbohydrates from food into simple sugars (disaccharides, monosaccharides ...). These simple sugars are going to be used as “building materials” for bacterial biofilms directly impacting the thickness of the lingual bacterial biofilm. Leung and Covasa (2021) present some hypotheses concerning the influence of the immune system in taste perception. They suggest that the presence of microbial elements like lipopolysaccharides (LPS) or flagellin may induce inflammatory process. When near the taste cells, this local inflammation can protect taste buds from pathogens, but it also can modulate taste perception by disrupting normal taste transduction or cell renewal in taste buds (Wang et al., 2009). Neyraud and Morzel (2019) come up with others hypotheses concerning the impact of bacterial products (organic acids, simple sugars, amino acids, etc.) metabolized near taste buds on taste perception. They suggest that these products could participate in the sensory adaptation phenomenon. Sensory adaptation occurs when taste receptors are exposed to stimuli for an extended period of time. Then, taste receptors tend to adapt to the stimulus concentration by decreasing their ability to respond and then become less sensitive. The perception of a taste compound occurs when the exogenous concentration of this compound is higher than its endogenous salivary concentration. The authors illustrated their point through the example of the metabolization of sugars into organic acids by oral bacteria and the potential consequences in terms of perception of sweetness and sourness. This metabolization could have two different consequences in terms of adaptation depending on the bacterial charge and/or metabolism at the vicinity of the taste receptors: (i) with a low bacterial metabolism, sugars are less metabolized leading to a higher concentration of sugar at the receptors vicinity and a high adaptation of these receptors to sugars, then higher concentrations of exogenous sugars will be required in order to trigger perception; (ii) with a high bacterial metabolism, sugars are more metabolized into organic acids; this leads to a higher concentration of acids at the receptor level leading to an adaptation to acids and then higher concentration of exogenous acids will be required to trigger sour perception. This model agrees with the observations of Solemdal et al. (2012) where perception of sour taste was particularly

reduced in elderly subjects with strong lactobacilli growth in oral cavity. This appears logical since lactobacilli metabolism consumes simple sugars and produces organic acids. The presence of these bacteria close to taste receptors could therefore explain the increase in acid concentration at the local level and sensory adaptation of the receptors to sour taste. The associations between taste perception, bacterial composition, bacterial products, and substrates have been studied further by [Feng et al. \(2018\)](#). In this work, beside some relationships observed between phyla and sensitivity to various tastes detailed above, they found relationships between organic acids and sugar and taste sensitivity but different in whole saliva and tongue film. Saliva was characterized mainly by positive relationships between organic acids concentration and taste sensitivity whereas tongue film, mainly by negative relationships between sugars concentration and taste sensitivity. This shows that, in order to study the impact of bacterial products or substrates on perception, it is important to consider the location. The concentration of metabolites at the vicinity of the receptor is probably more relevant since the dilution of metabolites in whole saliva due to secretions of the various salivary glands will make the interpretation of these observations complex. All the studies previously presented allowed the scientific community to create new links between oral microbiota and taste perception. However, further studies are needed to corroborate all those hypotheses as well as to formulate new ones.

17.4 Conclusion

The oral microbiota presents a considerable complexity linked to the multiple ecological niches of the oral cavity and its variation between individuals and along life. Most of its functions remain unknown or at the state of hypotheses. This is the case of its implication in taste perception. Even if the researches in this field have increased in the past years, the results present mostly associations between some microorganism and sensitivity to various tastes, but the mechanisms involved remain unexplained. Besides the potential role of resident oral microbiota, the impact of the massive arrival of exogenous microorganisms provided by the consumption of fermented food is still unknown. However, their potential impact on the oral microbiota and the consequences on taste perception could be real. This opens large perspectives of research in order to give to oral microbiota a similar place as the intestinal microbiota.

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