The physiology of taste and smell: how and why we sense flavors

J. Llorens*

* Departament de Ciències Fisiològiques II, Universitat de Barcelona, Feixa Llarga s/n, 08907 l’Hospitalet de Llobregat, Spain (E-mail: jllorens@bell.ub.es)

Abstract Taste and smell work together to identify the chemical composition of what we intend to ingest. In recent years, our understanding of the mammalian physiology of taste and smell has greatly increased. In addition to its intrinsic value, this increased understanding of the molecular and cellular basis of flavor recognition provides also a new view on our behavioral response to edible matter.

Keywords Behavior; chemical senses; flavor recognition; sensory perception; smell; taste

Sensory perception

Our response to flavors, like any other physiological or behavioral response to external or internal stimuli, depends on our sensory perception of the triggering stimulus. Sensory perception consists in the encoding of the stimulus in a pattern of activity of particular neurons in discrete areas of the brain.

The process begins in a peripheral sensory system that contains primary sensory cells (Figure 1). These cells are either neurons or specialized cells that share with neurons the ability to release neurotransmitters, substances that the nervous system uses for neuronal communication. The sensory cell acts as a transducer system that translates the properties of the stimulus into changes in neurotransmitter release. This release occurs at certain regions of the membrane of the cell where it is in close vicinity with the membrane of second order neurons. In these regions, called synapses, the membrane of the second cell contains a high density of receptor proteins that bind the neurotransmitter. This binding causes a cascade of biochemical and ionic events that finally result in increased or decreased frequency of action potentials in the axon, the thin and long extension that characterizes most neurons. Action potentials are local changes in the ion distribution between the intra- and extracellular sides of the axon membrane. These local perturbations propagate and move down the axon until they reach the axon terminals. The axon terminals make synaptic contacts with other neurons, and the arrival of action potentials stimulates the release of neurotransmitters from the presynaptic membrane.

If the primary sensory cell is already a neuron, as in the case of the olfactory system, the transduction mechanisms will originate action potentials (Figure 1). Thus, in sensory systems, there are primary sensory cells that are stimulated by the primary stimulus and then encode the information in the form of controlled neurotransmitter release, with the generation of action potentials in between as an option depending on the sensory system under consideration, and neurons that receive information in the form of neurotransmitter concentrations convert it into action potentials that travel to the other end of the neuron, and then present the information to the following neurons in the form of synaptic neurotransmitter concentrations. At each step, the information is processed. Any particular neuron receives hundreds or thousands of synaptic contacts, typically from many different presynaptic neurons, and in turn contacts many postsynaptic neurons, and this creates a complex network for powerful signal processing.
**Chemical senses and other sensory systems involved in chemical recognition**

Flavor perception is mostly carried out by the exteroreceptive chemical senses. We have also interoreceptive chemical senses, devoted to perception of internal chemical stimuli, such as the concentrations of oxygen and carbon dioxide in blood. Mammals have at least three systems for sensing external chemical stimuli, the taste system, the main olfactory system and the vomeronasal or accessory olfactory system. The vomeronasal system recognizes pheromones, substances secreted by individuals of one species that influence the sexual physiology and behavior of other individuals of the same species; this system will not be discussed here. Taste and smell work together in a highly integrated fashion to recognize flavors and take decisions on the edibility of the candidate foods and drinks; smell is also used to sense odors not related to food, but this will not be discussed in this article.

In addition to taste and smell, other sensory systems participate in the exploration of foods. For instance, the temperature and the roughness of a food are important qualities for our response to it. In some cases, chemical recognition is also achieved through sensory systems that are not primarily devoted to chemical perception. In the oral mucosa, high grade alcohols cause a warm sensation likely caused by the direct activation by ethanol of the receptors for high temperature, those that are activated by temperatures around 40°C. Refreshing compounds such as menthol directly activate the receptors for low temperature; those activated by temperatures around 28ºC (Peier et al., 2002). Perhaps the most striking example is the direct activation of the receptors for burning pain, different from the high temperature receptors mentioned above, by capsaicin, a compound present in chili peppers; this is the basis for the “hot” pungent “taste” of these peppers (Jordt and Julius, 2002). Pain receptors in the nasal cavity are also activated by irritating volatile compounds such as those in onions. In all these examples, the importance of these sensory inputs through non chemical senses to our recognition of the chemical composition of the food is fairly evident.

To serve their exteroreceptive role, the primary sensory cells of the chemical senses are

---

**Figure 1** The first steps in taste and smell perception resulting in the transduction of the chemical stimuli into a precise pattern of neuronal activity in discrete brain areas. In the taste system, specialized cells of epithelial origin act as transducer devices. In the olfactory system, the first sensory cell is already a neuron.
in contact with the external world through a diffusing media that carries the substances to be perceived, the saliva in the oral cavity or the mucus layer covering the olfactory mucosa. Thus, solubility in these media is a required property of tastants and odorants. The part of the membrane of the cells that is in contact with the saliva or the mucus contains the specific molecular machinery responsible for sensory transduction. The understanding of the molecular characteristics of this machinery and of the relationship between the stimulus and the response of the cell has greatly increased in recent years. In the case of smell, the acquired knowledge has also been useful to decipher the relationship between the sensory cell and the second order neurons. These advances in understanding the basic physiology of taste and smell also enlighten our understanding of our integrated responses to flavors.

**Smell**

The primary cells of the olfactory system are neurons located in the olfactory mucosa of the nasal cavity. This is the only place in the mammalian body where there are neurons in direct contact with the external world. In one end, the olfactory neurons have an apical dendrite, a short prolongation that has many cilia, filiform prolongations that are imbedded in the mucus. The odor molecules (odorants) carried by the air dissolve in the mucus and reach the membrane of the olfactory neurons at the cilia. This ciliary membrane contains the odorant receptors and the associated transduction machinery. The other end of the olfactory neuron is the origin of the axon that extends (“projects”) up to a region of the central nervous system, the olfactory bulb, first area of the brain involved in odor perception. The olfactory bulb is thus the place of the first olfactory synapse, formed between the primary sensory neuron and the second order neuron, the latter belonging to one of two different types, the mitral and the tufted cells. This first relay of the olfactory information shows a characteristic organization that results in a morphological pattern recognizable at the light microscopy level. Thousands of primary neurons contact tens or hundreds of mitral and tufted cells in a quite defined area called glomerulus, a globular mass of pre-synaptic axon terminals and postsynaptic dendrites. The olfactory bulbs, one on each side, contain several hundreds of glomeruli bidimensionally arranged in the most external layer of the bulb (Buck, 1996).

When an odorant reaches the olfactory mucosa, it binds to particular odorant receptors, and this generates action potentials in the axons of the olfactory neurons that contain these receptors. In the glomeruli of the olfactory bulbs, the action potentials in the primary neuron will cause the release of neurotransmitters and this will activate the mitral and tufted neurons.

**Odorant receptors and olfactory transduction mechanisms**

Much evidence led to the conclusion that the odorant receptors were members of a family of membrane receptors know as the G-protein-coupled membrane receptors (Torre *et al.*, 1995; Buck, 1996). These receptors have seven transmembrane domains, that is, are proteins that cross seven times the membrane of the cell. The extracellular side of these receptors will recognize the odorant molecules. In the intracellular side, the receptors are coupled to a multimeric G-protein that catalyzes the formation of cyclic-AMP, a second messenger molecule. The binding of the odorant causes conformational changes in the receptor protein, this results in activation of the G-protein, and hence the increase in the intracellular concentration of c-AMP. The increased c-AMP concentrations will then be responsible for a cascade of biochemical changes, most notably changes in the properties of several membrane ion channels, finally generating the action potentials.

The identification of the genes encoding for the odorant receptors disclosed that we have around 1,000 of them (Buck and Axel, 1991). All of them were expressed, that is, they were true genes really translated into proteins, not pseudo-genes having lost their function after
multiplication during evolution. In our genome, apparently containing only some
30–40,000 genes, this is by far the largest gene family, a fact revealing the great importance
of olfactory function for mammalian life. The characterization of the expression patterns of
these receptors revealed that each primary olfactory neuron express one, and only one, of
these genes (Chess et al., 1994). Thus we have about 1,000 different types of olfactory neu-
rons that differ in the odorant receptor they express and hence in their sensitivity to odor-
ants (Figure 2). The interaction of the odorants with the receptors is based on chemical
affinity. Each odorant receptor is able to bind many different odorants that share some
chemical features, and its affinity for these odorants may vary as a function of variations in
these chemical features. The receptors have a high specificity for certain molecular features
but high tolerance for others. For instance, the rat 17 odorant receptor binds aliphatic alde-
hydes with a maximal affinity for octanal. Substitution of the aldehyde group by other func-
tional groups caused a complete loss of affinity, while other changes in the molecule, as
increases or decreases in chain length from the optimal size of 8, or unsaturation of the
chain, resulted in more graded variations in affinity (Araneda et al., 2000). Conversely, an
odorant will be recognized by several different receptors that may bind the molecule based
in either similar or different chemical features. Complex molecules showing several func-
tional groups will be typically recognized by many receptors, some of which will be quite
selective for a particular group, such as an alcohol, a nitrile or an aldehyde group. The pri-
mary olfactory neurons are thus able to read the chemical features of the odorant (or the
odorant mixture) reaching the olfactory mucosa.

Encoding of olfactory information in the brain
The finding that each olfactory neuron expresses only one odorant receptor gene made pos-
sible to obtain a result pursued for a long time: to know how the projections of the primary
sensory neurons are organized in the olfactory bulb and what is the physiological meaning
of this organization. The answer was highly rewarding: all the neurons expressing the same
odorant receptor send their axon to the same glomerulus (to be more precise, two, one on
each side) (Figure 2) (Vassar et al., 1994; Ressler et al., 1994). By expressing the same
receptor, these neurons are exactly activated by the same odorants, so the amount of neuro-
transmitter released at the synapses of this glomerulus, and hence the activity of the post-
synaptic neurons, mitral and tufted cells, is a direct function of the receptor’s affinity for the
odorant. In other words, the chemical features of the odorants are encoded by neuronal
activity in a bidimensional map of glomeruli in the olfactory bulbs. This conclusion, natu-
rally derived from previous data, has been fully supported by recent experimental data
(Uchida et al., 2000).

What conclusions can be derived from the recent advances in olfactory physiology? The
existence of 1,000 different receptors and the combination of high specificity for certain
molecular features but high tolerance for others constitute an excellent system to encode
thousands of odorants in a highly discriminative manner. It seems that most of the mole-
cules reaching the olfactory receptors will be able to stimulate one or a few of them. The
organization of the olfactory projection indicates the efficient encoding of the chemical
features of the odorants in the olfactory bulb, and suggests that each odorant will produce
there a unique pattern of neuronal activity. So the system seems adapted to encode an end-
less list of odorants, and to discriminate among them according to chemical features. It’s a
very powerful system for chemical analysis. In addition, the recognition of chemical fea-
tures seems also adapted to assign a unique odor perception to any molecule or mixture
interacting with the olfactory receptors, even if completely new to the system. Because
similar substances will more likely activate similar groups of receptors than more different
substances, a new odor will easily be recognized as similar to the previously known and
similar substances. It may be worth noting that the different affinity of the diverse receptors for one particular odorant implies that increasing concentrations of the odorant will not only more strongly activate the neurons expressing the receptors that have greater affinity for it, but also will progressively cause the activation of neurons expressing other receptors with progressively less affinity for the odorant. This is probably why there are many substances that seem to change their odor when their concentrations increase.

**Taste**

The primary cells for taste are not neurons but modified epithelial cells instead. The taste cells cluster in onion-shaped taste buds. Taste buds can be found isolated in the mucous epithelium of the oral cavity but are more typically found grouped in the taste papillae of the tongue. Each taste bud opens to an apical taste pore. The apical ends of the taste cells have cilia that are bathed by saliva in the taste pore. In these cilia, the cellular membranes contain the taste receptors and channels responsible for taste transduction. In response to the tastants, the taste cell releases neurotransmitters at the synapses formed between the basolateral membrane of the cell, and nerve terminals of the first taste neuron. Note that this first taste synapse occurs in the oral epithelium. The second taste synapse is formed in the central nervous system by the other end of the first taste neuron.

After the studies of Henning in 1922 it was accepted that there were four basic taste modalities: sweet, salty, sour and bitter. The existence of a fifth taste modality has been object of much controversy until very recently, but this “umami” taste seems now firmly established. The name umami is Japanese and is difficult to translate, may be meaty

---

**Figure 2** Encoding of the chemical properties of the odorants in the form of neuronal activity in the second order neurons in the olfactory bulb. Each olfactory neuron expresses only one type of about 1,000 different available types of odorant receptors. All the olfactory neurons expressing the same type of receptor then send their endings to the same glomerulus in the olfactory bulb. Thus, the activity of the second order neurons in that particular glomerulus will be a function of the activation elicited by the odorant in the odorant receptor, that is, of the concentration and the affinity of the odorant for the receptor.
or substantial, but is also sometimes translated into delicious. It is now accepted that a few other taste modalities may exist, but little is known about the candidate modalities such as astringent and fatty tastes. In any case, there are a small number of basic taste modalities corresponding to different transduction mechanisms in taste cells.

**Ionic channel taste modalities**

Sour and salty tastes are associated with high concentrations of H\(^+\) and Na\(^+\) ions, respectively. Current knowledge indicates that transduction of these taste modalities depends on membrane ion channels (Figure 3).

**Sour.** For sour taste, membrane channels selective for hydrogen ions make the entrance of these ions into the cell. Inside the cell, the hydrogen ions block a type of channels selective for potassium, thus inhibiting the outward displacement of potassium driven by the electrochemical potential for this ion. In addition, the hydrogen ions open another type of cation channels that will then allow further inward cationic currents. The result of all these actions is a depolarization of the cell, i.e. a change from highly negative towards zero of the charge in the intracellular side of the cellular membrane. This drives the release of neurotransmitters at the synapses between the taste cell and the taste neuron. The identification of the molecular actors involved in sour perception is in progress (Ugawa *et al*., 1998). The direct dependency of this taste modality on hydrogen ion concentrations implies that this modality is basically a pH-meter.

**Salty.** The taste cells are activated by sodium ions because of the direct entrance of these ions into the cell through selective Na\(^+\) channels (Figure 3). At similarity to the sour transduction, the entrance of the sodium ions into the cell is a depolarizing event that causes the release of synaptic neurotransmitters. The salty taste modality is basically a Na\(^+\)-meter.

**G-protein-coupled receptor taste modalities**

In contrast to sour and salty, sweet, bitter and umami taste modalities depend on membrane receptors of the seven transmembrane domain/G-protein-coupled receptor family (Figure 3) (Magolskee, 2002). These taste modalities will thus be associated with chemical recognition. However, as we will discuss here, this chemical recognition greatly differs from the highly discriminating analysis performed by smell. The key differences are the number of receptor genes and their expression patterns. One recent important finding is that bitter and sweet taste receptors are expressed in different subsets of cells, although bitter and taste cells are found in the same taste buds; this means that bitter and sweet are truly different taste modalities.

**Bitter.** The T2R receptors constitute a family of about 30–40 genes expressed in taste cells that respond to bitter stimuli (Adler *et al*., 2000; Chandrashekar *et al*., 2000). Many of these receptors, probably all of them, are expressed in the same subset of taste cells, and ligand binding to any of these receptors will trigger the same response in the taste cell. The bitter taste is thus able to respond to a wide diversity of noxious tastants, but is unable to discriminate among them. This is why many different compounds have an identical bitter taste. The bitter taste thus seems adapted to signal the presence of potentially dangerous compounds, while giving no information on the precise nature of these compounds.

**Sweet.** The sweet taste is associated with energy-rich carbohydrates. The recent identification of the sweet receptor genes indicates that very few of them may exist: so far, only three candidate genes have been identified, and it seems unlikely that many more will be discov-
Interestingly, these receptors are expressed differentially among the taste cells, some expressing both T1R1 and T1R3 receptors, others expressing T1R2 and TR3, and others expressing T1R3. This opens the possibility that different sweet taste sensations may exist. The T1R2 and T1R3 combination has been clearly demonstrated to form a sweet receptor (Nelson et al., 2001).

Umami. The umami taste is elicited by glutamate and other aminoacids. Glutamate is also one of the main neurotransmitter substances used by the nervous system. A variety of receptors bind glutamate at synapses to elicit the postsynaptic response to it. A truncated form of a particular glutamate neurotransmitter receptor was first proposed as the receptor for umami (Chaudhari et al., 2000). However, the T1R1+T1R3 combination of the candidate sweet receptors has now been shown to function as a broadly tuned L-amino-acid sensor (Nelson et al., 2002), suggesting that there may be a complex relationship between the sweet and the umami tastes. This would not contradict evolutionary wisdom, because sweet and umami seem to be adapted to recognition of nutritive foods, rich in carbohydrates (sweet) or proteins (umami).

Taste encoding
The relatively small number of taste receptors and ion channels, and their expression patterns in the taste cells, indicate that the taste system is incapable of detailed chemical analysis and only provides danger signals (too bitter, too salty or too sour) as well as signals for content in nutritive compounds (sweet and umami tastes) and for balanced ionic content (slightly salty, moderate pH values).

In the taste buds, several taste cells make synaptic contact with branching terminals of the same neuron. Much evidence indicates that cells responding to different taste modalities are contacted by the same neuron. When the response of the neurons to different tastants is recorded, many of them show a response to different taste modalities. There is thus a convergence of taste information, and the taste perception must be dependent on activity patterns in the neuronal population rather than on specific information carried on by single neurons. While this organization complicates our understanding of its operating mechanisms, we can speculate that this may be the reason why we add sugar to our coffee.

---

**Figure 3** Transduction mechanisms in salty and bitter taste modalities, as examples of an ionic channel taste modality, and a G-protein-coupled receptor taste modality.
increase in sweet content turns unpleasant bitter matter into acceptable edible matter. It seems that taste is mainly devoted to performing a rough analysis of the overall content in nutritious or dangerous components to indicate whether it is worth intaking the candidate food or drink, and the potential danger associated to it. We have powerful methods for toxin inactivation, but they are costly in terms of metabolic energy: maybe we can accept the moderate bitterness signaling the presence of toxic compounds if associated with a high enough amount of energy or necessary nutrients.

**Flavor perception and behavior**

Smell, taste and the other sensory modalities of the oral and nasal cavities produce a highly integrated compound flavor perception. The study of the behavioral responses to this integrated perception has a long history, but many data are enlightened by the current advances in the basic physiology of these systems.

**Innate flavor preferences**

Studies in humans and experimental animals clearly indicated that there are innate preferences for flavors. The simplest example is probably the acceptance or rejection responses shown by human neonates to sweet and bitter tastes, respectively. The obvious innateness of these responses, and the now known properties of the sweet and bitter receptors allow us to conclude that these receptors were likely selected during evolution as a function of the consequences of the intake of the tastants involved (whether they facilitated or hampered survival) rather than as a function of their chemical features.

**Flavor neophobia**

Neophobia is the avoidance of the new. The intake of flavors perceived as new is largely avoided until they are no longer new. The typical behavior is the intake of small quantities of the candidate food or drink until the new flavor is made acceptable by repeated experience. A few strong motors drive this learning: hunger, innate taste preferences, innate curiosity and teaching by other individuals (particularly mothers).

**Conditioned (learned) flavor aversion**

The full sense of flavor neophobia is given by the robustness of the conditioned flavor aversion (Bernstein, 1991). When the intake of a new flavor is followed by unpleasant feelings like discomfort or illness, this new flavor will be subsequently rejected. The response may be quite strong, and flavors associated by experience with overt illness may elicit unequivocal rejection reactions, such as nausea and vomiting. When the subject feels dangerously intoxicated, not only new, but also old known flavors may suffer conditioned avoidance. The phenomenon is well known to cancer therapists, who administer highly toxic compounds to combat cancer, and see how the patients develop strong aversions to the foods they had last before the treatment. Note that the association of the flavor with the illness does not mean that both are caused by the same molecules. In experimental analysis of behavior, a widely used paradigm in rats uses intraperitoneal injections of lithium chloride to elicit an aversion to a saccharin solution offered as drinking water.

**Learning flavor preferences**

In addition to innate flavor preferences, flavor neophobia and learned flavor aversion, we have a strong capacity to learn about acceptable flavors. For instance, we learn to like bitter foods or drinks if associated with a positive balance of consequences, and they contain odorants that allow us to recognize that food as edible. Coffee is bitter, and an overdose of caffeine will certainly kill us. However, a moderate concentration of caffeine, in a rich...
solution of odorants, will be associated with a pleasant stimulating effect, so most of us have learned to like coffee, after having either added or not energy value to the solution.

**Conclusion**

The integrated system for flavor perception seems to operate at three levels. At one level, mostly relying on taste, genetic information selected during evolution is used to perform a fast estimation of the potential of the candidate edibles as foods worth intaking or matter better to avoid. At the second level, mostly based on the olfactory system, a detailed analysis of the chemical composition of the candidate edible stuff is performed. At the third level, the sensory information is integrated and compared with the data available in the databank of previous experiences, to determine our behavioral responses by means of a more pleasant or unpleasant feeling.

What are then the unpleasant flavors that will be rejected?: those associated with harmful effects during evolution, those associated with harmful effects by personal experience and those that are new and not perceived similar enough to known and pleasant flavors. It is thus not surprising that we reject unpleasant flavors, because this behavior is a biologically sound response with a protective value. If you don’t like it, don’t drink or eat much of it: it’s likely to be dangerous to your health.

**References**


