

Review

# Taste and pheromone perception in mammals and flies

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## Abstract

The olfactory systems of insects and mammals have analogous anatomical features and use similar molecular logic for olfactory coding. The molecular underpinnings of the chemosensory systems that detect taste and pheromone cues have only recently been characterized. Comparison of these systems in *Drosophila* and mouse uncovers clear differences and a few surprising similarities.

Feeding is initiated in terrestrial animals with the detection of volatile (airborne) chemicals. Generally referred to as odorants, these chemicals are released from food sources towards which animals move by monitoring the concentration gradient of a particular odor. Naturally, noxious volatile substances are also detected by the same sensory epithelia, in this case leading to avoidance of the odor source. In both mammals and insects, volatile cues are detected by odorant receptor proteins, which are G-protein-coupled receptors (GPCRs) encoded by a single large gene family expressed in the cognate olfactory epithelia in the nose and antenna of mammals and insects, respectively. The odorant receptor gene family consists of about 1,000 genes in mice and 60 in *Drosophila*. Surprisingly, the odorant receptor genes in mammals and insects are not related to each other at the sequence level (beyond encoding GPCRs), even though they recognize a largely overlapping array of chemical compounds. The olfactory systems of insects and mammals have analogous anatomical features and use similar molecular logic for olfactory coding, however [1].

Once a potential food source is identified, animals taste it by means of contact between chemicals from the source and chemosensory receptors located in the gustatory (taste) organs, predominantly the tongue in mice and the labellum (proboscis) in *Drosophila* (both species also have secondary taste organs). Distinct sets of taste-receptor proteins in specific taste cells allow the organism to discriminate between

'delicious' food, generally associated with rich nutrition, and bitter-tasting substrates, typically present in contaminated, non-edible food sources.

Courtship and mating are also initiated by chemosensory signals, better known as pheromones, although other sensory systems are also important for these behaviors. Pheromones are sometimes sex-specific and are secreted by specialized glands or cells to trigger distinct behavioral and endocrine responses in members of the same and opposite sexes of the same species. Specialized sensory structures or cells recognize pheromones: the mammalian vomeronasal organ is deeply embedded in the nasal cavity [2], while a subset of gustatory and possibly olfactory neurons are thought to be responsible for the detection of pheromones in *Drosophila* [3-5]. In both mice and *Drosophila*, the major pheromones are non-volatile chemicals, so detection of pheromones requires direct contact of the sensory cells with the pheromone source [6-8]. Candidate pheromone-receptor genes have been identified in mammals, but only a few have recently been functionally characterized [9].

The main focus of this article is the recent progress in our understanding of the taste and pheromone receptors in mouse, humans and *Drosophila*. Despite the rather different anatomical structures and organs involved in the detection of tastes and pheromones, and the different structures of taste and pheromone receptors, a few intriguing parallels

and similarities have emerged from recent studies. We note that the mode and role of pheromone recognition has diverged significantly within mammal and insect species, so the findings summarized here might not be general to all genera within each group of animals.

### The mouse chemosensory system

Most mammals, including mice, have three separate chemosensory systems, each of which is dedicated to the detection of biologically distinct groups of chemicals (Figure 1a). The olfactory epithelium, a layer of densely arrayed sensory neurons in the nasal cavity, expresses about 1,000 different olfactory receptors that interact with the vast repertoire of volatile chemical compounds in the environment [10,11]. Non-volatile chemicals are detected in the taste buds, which are composed of clusters of taste cells that express distinct groups of GPCRs and channels responsible for the detection of different taste qualities, namely bitter, sweet, umami (the savory taste of glutamate), sour and salty [12]. Taste buds contain 50-120 taste cells and are located in three distinct taste papillae of the tongue, as well as in the palate and the pharynx. The third chemosensory organ, the vomeronasal organ, is dedicated to the detection of pheromones [13]. (Not all pheromones are detected by the vomeronasal organ, however). Anatomically, the vomeronasal system (also referred to as the accessory olfactory system) is more similar to the main olfactory system than to the taste system: in both the vomeronasal organ and main olfactory epithelium, the cells expressing the receptor are neurons and project directly to the brain, whereas the cells in the tongue that express taste receptors are not neurons and mediate receptor activation via the gustatory nerve to the brainstem. But, interestingly, the vomeronasal organ seems to sense non-volatile chemicals through direct contact (even though it is capable of sensing odorants under certain conditions [14,15]), and hence, in this regard, pheromone perception is more similar to gustation than olfaction. It is therefore not surprising that the recently identified taste receptors and vomeronasal receptors are structurally similar to each other, while neither has any similarity to the odorant receptors.

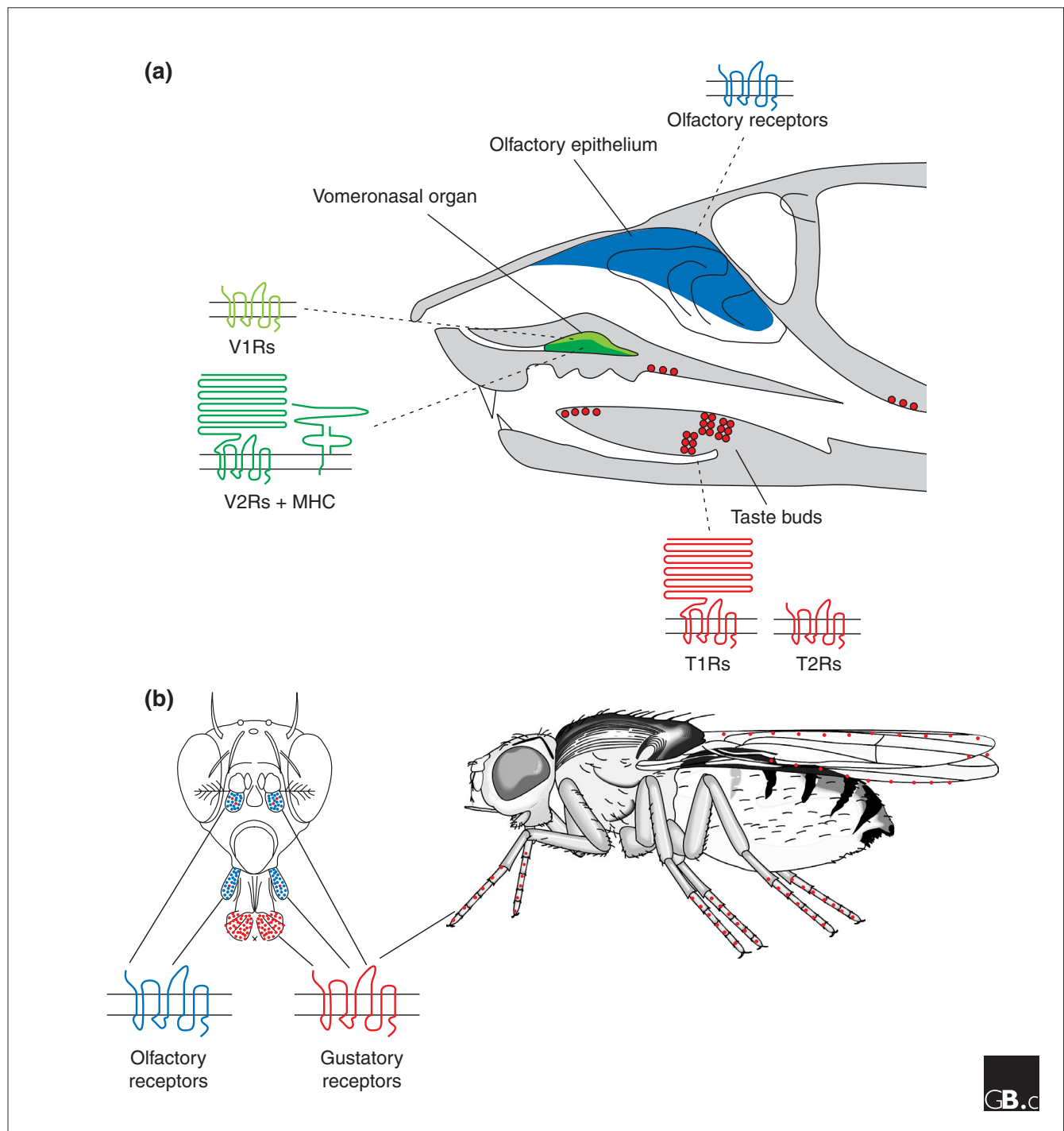
### Multiple classes of taste receptors

Among the five tastes that can be discriminated in mammals, sweet and umami sensations (of sugars and amino acids) are generally associated with nutrition and feeding, whereas bitter taste is mostly associated with repulsive behavior and many bitter-tasting compounds are toxic to mammals (and *Drosophila*). Two families of GPCRs are associated with the detection of sweet and umami compounds on the one hand and bitter-tasting substrates on the other: the T1Rs (also called Tas1Rs) and T2Rs (Tas2Rs, TRBs), respectively (see Table 1 for full details of each family) [16-18]. T1Rs are similar to other GPCRs, including the metabotropic glutamate receptors (mGluRs), metabotropic  $\gamma$ -amino butyric acid receptors (GABAbRs), and V2Rs, one of the two types of

pheromone receptors in mammals. They all have a very long amino-terminal region (approximately 550 amino acids), which is thought to bind the ligand, and seven transmembrane domains. Structural analysis revealed that mGluR-1 proteins form dimers through their amino termini, which assume a structure that looks like a venus fly trap and is thought to be crucial for binding to glutamate, their natural ligand [19]. It is quite likely that other receptors of this type form dimers. Indeed, it has been shown that GABAbR-1 and GABAbR-2 function as heterodimers. While GABAbR-1 binds to its ligand, GABAbR-2 is necessary for escorting the receptor complex to the cell surface and for coupling with G proteins [20,21].

Three members of the T1R family have been isolated from rat, mouse and human [18]. T1Rs are 30-40% identical to each other at the amino-acid level, and the genes encoding them are located in the same region on chromosome 4 in mouse (chromosome 1 in human). Like GABAb receptors, T1Rs also form heterodimers (or even more complex multimers). Expression studies have revealed that taste cells either coexpress T1R1 and T1R3 or T1R2 and T1R3, but not T1R1 and T1R2 [22,23], and it has recently been shown that these distinct combinations of T1Rs bind to different sets of compounds, corresponding to sweet and umami substances [23-25]: in mouse, T1R2-T1R3 hetero(di)mers respond to sugars and sweeteners, whereas T1R1-T1R3 hetero(di)mers are activated by many L-amino acids, including L-glutamate and L-arginine, both of which are umami-tasting to humans. It is not known, however, whether these other L-amino acids are perceived as umami taste by mice. In humans, T1R1 and T1R3 receptors appear to be less broadly tuned and are sensitive mainly to L-glutamate and L-arginine [25]. It has been suggested that T1R1 and T1R2 may determine the ligand specificity of each heterodimer. T1R3 may also have distinct roles in sweet and umami sensation, however, because some polymorphisms in the mouse *T1R3* gene affect only sweet sensation but not L-amino-acid perception [24].

The T2Rs, responsible for the detection of bitter-tasting compounds, have no detectable sequence similarity to T1Rs and form a larger family of GPCRs than the T1Rs [18]. T2R proteins are from 25% to more than 80% identical to each other, and their genes are located in gene clusters on chromosomes 6 in mouse (chromosomes 7 and 12 in humans). In contrast to T1Rs, T2Rs lack a long amino-terminal extracellular domain. There are 28 potentially functional T2R genes in human and at least 33 in mouse [26-28]. Mouse T2R5 is a receptor for cycloheximide [29] and human T2R16 responds to several bitter compounds, all of which have a similar chemical signature: a hydrophobic residue attached to glucose via a  $\beta$ -glycosidic bond [30] (see Table 1). It has long been known that some people taste the bitter compound phenylthiocarbamide (PTC) at much lower concentrations than others. This recessive trait has been mapped to a region on chromosome 7 and is referred to as the PTC locus.



**Figure 1**

The location of chemosensory organs in the mouse and *Drosophila*. **(a)** A sensory neuron in the olfactory epithelium of mice expresses one of about 1,000 olfactory receptors. Neurons in the apical and basal layers of the vomeronasal organ express distinct, unrelated classes of G-protein-coupled pheromone receptors (V1Rs in the apical and V2Rs in the basal layer). In addition, a small family of MHC class I-like molecules is coexpressed with V2Rs in neurons of the basal layer. The taste cells in the tongue, palate and pharynx express other classes of GPCRs, one encoding sweet-taste receptors (T1Rs) and one encoding receptors for bitter compounds (T2Rs). Note that V1Rs and T2Rs are related to each other, as are V2Rs and T1Rs, respectively. **(b)** The olfactory neurons of *Drosophila* are located in two pairs of appendages in the head, the third antennal segment and the maxillary palps, and each neuron expresses very few, possibly just one, of the 61 olfactory receptor genes identified so far. The gustatory or taste sensory neurons are located in numerous organs, including the two labial palps on the head, internal sensory clusters in the pharynx (not shown), all the legs and the anterior wing margin. Each neuron expresses a few, possibly just one, gustatory receptor gene. A few gustatory receptor genes are also expressed in olfactory neurons of the antenna and maxillary palps.

**Table 1****Taste and pheromone receptor gene (sub-)families in mice and *Drosophila***

	Receptor	Number of intact genes	Conservation* within each family	Sites of expression	Known ligands (examples)	Structural notes
Mouse/ human	T1R	3 (human) 3 (mouse)	30-40%	Taste cells in the tongue; T1R1 plus T1R3 or T1R2 plus T1R3 are preferentially coexpressed, with few cells expressing all three genes	Sweet chemicals (T1R2 plus T1R3) L-amino acids, umami chemicals (T1R1 plus T1R3)	Similar to V2R (20-30% identical)
	T2R	28 (human); approximately 40 (mouse)	25% to more than 80%	Taste cells in the tongue; most cells express many, if not all, T2R genes	Bitter compounds, such as cycloheximide (mouse T2R5), salicin (human T2R16), and PTC (human T2R38)	Similar to V1R (15-20% identical)
	V1R	5 (human) 137 (mouse)	25% to nearly 100%	Basal layer in the vomeronasal organ; probably one V1R gene expressed per cell	2-heptanone (V1Rb1), 6-hydroxy-6-methyl-3-heptanone, n-pentylacetate, and isobutylamine	Similar to T2R (15-20% identical); important for maternal aggression
	V2R	None in human; approximately 140 in mouse	25% to nearly 100%	Apical layer in the vomeronasal organ; probably one V2R gene expressed per cell	None identified	Similar to T1R (20-30% identical); forms a complex with MHC class Ib and $\beta$ 2-microglobulin; may be required for aggression between males
	MHC Ib	None in human; 9 expressed in the mouse	40% to more than 80%	Apical layer in the vomeronasal organ; one or a few MHC Ib genes expressed per cell; coexpressed with a V2R gene	None (in the VNO)	Forms a complex with $\beta$ 2-microglobulin and V2Rs; may be required for aggression between males
Fly	GR	69	Approximately 15-75%	Spatially defined in one or several taste organs (labellum, labral and cibarial sense organs, legs, wings, and female genitalia)	Sugars and presumably other classes of compounds, including pheromones	Distantly related to olfactory receptor genes (Or83b); gustatory receptor probably recognize the whole spectrum of small soluble ligands; up to 20 subfamilies (with 1-8 genes each)
	GR <sub>S</sub> <sup>†</sup>	8	44-75%	Foreleg and labellum (Gr5a), possibly other taste sensory organs	Trehalose (Gr5a)	The knockout fly has lower sensitivity to trehalose; member of a subfamily of 7 genes

\*The numbers in this column refer to amino-acid sequence identity in mice and amino-acid sequence similarity in *Drosophila*, respectively. <sup>†</sup>Indicates proposed rather than functionally established subfamilies of gustatory receptor genes that might function as sweet (S) receptors. This information is based on the functional characterization of a single receptor in this subfamily.

Interestingly, a T2R-encoding gene, *T2R38*, is closely linked to the PTC locus. Recently, Kim *et al.* [31] have shown that PTC sensitivity correlates with polymorphisms in the *T2R38* gene that are located to positions 49 (intracellular domain 2) and 262 (transmembrane domain 6). Expression of T2Rs has been extensively analyzed, and it has been shown that individual taste cells express a large number of, if not all, different T2R genes [32]. This might explain the poorly developed

ability of mice and humans to discriminate between different bitter-tasting compounds.

Unlike sweet and bitter tastes, sour and salt tastes are thought to be mediated by ion channels. The mDEG-1 and HCN1/4 ion channels have been proposed to act as sour receptors, whereas salty taste appears to be mediated by the amiloride-sensitive sodium channels [12,33,34]. There are as

yet no functional data *in vivo*, however, that link these channels directly to the sour and salty tastes.

### Pheromone receptors

The vomeronasal organ is the major pheromone-detecting organ in rodents and probably most other mammals (except humans), although some pheromones are detected by the olfactory epithelium. The sensory epithelium of the vomeronasal organ is arranged in a basal and apical layer, each of which expresses one type of pheromone receptor belonging to either the V1R or the V2R family of GPCRs (Figure 1a and Table 1) [11,35]. Like olfactory neurons, but unlike taste cells, each neuron in the vomeronasal organ expresses only one (or, at most, a few [36]) receptor. The apically expressed V1R family has 135 members in the mouse, which have from 25% to nearly 100% amino-acid sequence identity to each other, and their genes are organized in several gene clusters [37]. These receptors are related to the T2R receptor family (with 15-20% amino-acid sequence identity), suggesting that the genes encoding these two receptor families derived from a common ancestral gene. Boschat *et al.* [38] identified a putative pheromone, 2-heptanone, as a ligand for one member of the V1R family (V1Rb2). They used knockin mice in which all V1Rb2-expressing cells also express the green fluorescent protein (GFP) as a cell marker. Using calcium-imaging experiments to monitor neuronal responses in terms of the release of Ca<sup>2+</sup> from intracellular stores, they showed that GFP-positive neurons in the vomeronasal organ respond specifically to 2-heptanone. Moreover, they showed that GFP-expressing cells of mice in which the *V1Rb2* gene was replaced by the *GFP* gene no longer responded to 2-heptanone. In another study that addressed the function of V1R genes, Del Punta *et al.* [9] deleted about 600 kilobases (kb) of a gene cluster containing 16 different V1R genes and created transgenic mice with this deletion. The most obvious phenotype in these mice is a reduction of maternal aggressive behavior. Furthermore, the vomeronasal organs of these knockout mice do not respond to three out of eight putative pheromones tested. Curiously, even though the deleted gene cluster includes *V1Rb2*, the vomeronasal organs of the knockout mice nevertheless respond to 2-heptanone, suggesting that multiple receptors might recognize and respond to this compound.

A handful of putative V1R genes have been reported in the human genome, but humans appear to lack a functional vomeronasal organ, as well as a functional TRPC2 ion channel [39], which is required for the function of the vomeronasal organ in the mouse [40,41]. It is therefore not clear whether the few human V1R sequences that have been identified are expressed as functional receptors, in tissues, such as the main olfactory epithelium.

Members of the second pheromone receptor gene family, the V2Rs, are expressed in the basal layer of the vomeronasal

organ. Like the V1Rs, V2R proteins are between 25% and nearly 100% identical to each other and the genes encoding them are also organized in several gene clusters. Interestingly, the V2Rs are also related to taste receptors, in this case to the T1Rs, with which they have 20-30% amino-acid sequence identity. In the mouse the number of genes encoding members of the V2R family is estimated to be between 100 and 200, and no functional V2R genes have yet been reported in humans.

Recently, two groups [42,43] have reported an unusual class of major histocompatibility complex (MHC) class I genes that are expressed in a subset of neurons in the vomeronasal organ. MHC class I proteins form a complex with  $\beta_2$ -microglobulin and are better known for their critical role in antigen presentation in the immune system. These new studies [42,43] showed that nine MHC class I genes of the M10 and M1 subclass are exclusively expressed by the vomeronasal organ. Moreover, each of these MHC genes is differentially expressed in a subset of neurons in the vomeronasal organ that also express one of the V2R genes. Importantly, a given V2R gene seems to be coexpressed with a particular MHC gene, and, in the vomeronasal organ, the MHC proteins and  $\beta_2$ -microglobulin appear to form a complex with V2R proteins as shown by immunoprecipitation studies [43]. Furthermore, protein localization experiments have shown that the MHC- $\beta_2$ -microglobulin complex is essential for V2R protein expression on the dendritic surface of neurons in the vomeronasal organ. The importance of the MHC- $\beta_2$ -microglobulin complex for cell-surface expression of V2R proteins was further confirmed in tissue-culture experiments. When V2R genes are expressed in a testis cell line, V2R receptor proteins remain inside the cell, but when the cells are cotransfected with MHC and  $\beta_2$ -microglobulin genes, V2R receptor proteins can be detected on the cell surface. Even though  $\beta_2$ -microglobulin is essential for normal aggressive behavior between males, as shown in  $\beta_2$ -microglobulin knockout mice, no specific function has yet been assigned to any of the V2R or MHC class I receptors expressed in the vomeronasal organ.

### The *Drosophila* chemosensory system

The chemosensory system of the *Drosophila* adult can be functionally separated into the olfactory as well as the gustatory and pheromone systems (Figure 1b) [5]. Volatile olfactory cues are detected by about 60 olfactory receptor proteins expressed in two pairs of appendages located on the fly's head - the third antennal segment and the maxillary palps [44-46]. Conversely, the gustatory system is widely dispersed throughout the fly's body [5]. In the adult, the two labial palps (proboscis), considered to be the 'insect tongue', are the major taste organs. Each palp harbors three rows of about 10 to 13 taste sensory bristles, containing four (type A) or two (type B) gustatory neurons and a single mechanosensory neuron. Electrophysiological studies on type A bristles

have revealed that these neurons respond to distinct stimuli (sugar, water, and high and low salt concentrations) [47-49]. In addition, there are about 30 neurons arranged individually at the base of taste pegs between pseudotracheae on the surface of each labial palp. Finally, there are three sensilla clusters in the pharynx (the labral sense organ and the distal and proximal cibarial sense organs) that are composed of a total of 40 additional neurons. An adult fly has therefore about 260 outer and 40 internal taste sensory neurons in the labellum [5]. Taste bristles contain a pore that provides access for substrates to the dendrite of the neurons. In principle, the *Drosophila* taste bristles are analogous to the mammalian taste buds: both mammals and *Drosophila* have distinct functional taste units that are mainly classified on the basis of structure and location. Interestingly, mammals also have clusters of taste cells in the pharynx, which might correspond functionally to the small group of taste neurons in the fly pharynx and be involved in the sucking reflex.

In addition to the neurons in the labellum, at least twice as many gustatory receptor neurons can be found in taste sensilla on the tarsi of all legs and the anterior wing margins. Interestingly, males have a significantly larger number of gustatory bristles on their forelegs than females (50 versus 37), and a few taste bristles have also been described in the female genitalia [5,50,51]. The large number of gustatory receptor neurons in the legs and wings indicates that they contribute significantly to the fly's sensory intake.

### The gustatory receptor gene family

The gustatory receptors in *Drosophila* are encoded by a family of about 70 genes [52-54]; most of the predicted gustatory receptor proteins are 15-30% similar to each other, but the most highly conserved receptors have up to 75% sequence similarity. The gustatory receptors can be grouped into several subfamilies on the basis of sequence similarity, with members within each subfamily having 33% or more identity. Genes within a subfamily are often clustered in the genome; in fact, about half of the 70 genes are found in arrays containing up to six genes each. Surprisingly, genes within a cluster appear not to be expressed in an orchestrated fashion: they are regulated independently and can be expressed in distinct taste organs [53]. Gustatory receptor genes arrayed head-to-tail (in the same 5' to 3' orientation) in two loci appear to be alternatively spliced: alternative exons at the 5' end of the genes, encoding the amino terminus, are spliced to common 3' exon(s) that encode the carboxyl termini, including the seventh transmembrane domain and the short cytoplasmic tail of the receptor; these 3' exons are present in all transcripts [52-54].

Expression of some gustatory receptor genes has been analyzed using a transgenic approach that takes advantage of the UAS-Gal4 system [52,53]. The putative promoter of a gustatory receptor gene (the 5' region upstream of the corresponding coding sequence) is fused to the coding sequence

of the yeast transcriptional activator *gal4*, which tightly controls the expression of an appropriate reporter gene (the *gfp* or *lacZ* gene linked to the Gal4 target sequence UAS [55]. Even though expression of only about ten gustatory receptor genes has been reported, some general rules have emerged from these investigations. First, and foremost, for all but one gustatory receptors, expression is restricted to a very small fraction (1-2%) of the gustatory receptor neurons, and the neurons that express each gene are mostly located in one or two taste organs; the exception to this rule is *Gr22e*, which is expressed in about 5 to 10% of gustatory receptor neurons across all taste organs [53]. Second, most receptors appear to be expressed in a single neuron within a taste bristle. Third, gustatory receptor genes are not coexpressed in large numbers in the same cells. Finally, as mentioned earlier, even closely related and clustered gustatory receptor genes appear not to be expressed in a coordinated fashion - they are expressed in different gustatory receptor neurons within a given taste organ, such as the labellum, or in entirely different taste organs. For example, members of the *Gr22* gene family, which consists of six tightly clustered genes (*Gr22a - Gr22f*), are only expressed in the labellum (*Gr22a* and *Gr22f*), in the labellum and legs (*Gr22c*), in the labellum, legs and cibarial sense organ (*Gr22b*) or in the entire taste system, including the wings (*Gr22e*). This is in contrast to the situation for mammalian taste receptors, especially the T2Rs, many of which are expressed in single taste cells. The establishment of discrete sets of sensory neurons in the *Drosophila* taste system that express one or a small number of distinct receptors provides a basis for the discrimination of potentially many different substrates.

### Detection of sugars

Direct evidence that the gustatory receptor gene family encode taste receptors was obtained from genetic studies, in which a gene conferring sensitivity to the sugar trehalose was mapped to a single locus on the X chromosome that was later identified as the *Gr5a* gene [56-58]. Trehalose is an abundant carbohydrate generated as a metabolic by-product in yeast, which is a major food source of *Drosophila melanogaster*. Sequence analysis of the *Gr5a* genes of numerous strains with reduced sensitivity to trehalose (*tre*<sup>-</sup> strains) identified single point mutations in the *Gr5a* coding sequence [57,58]. Moreover, deletions of the *Gr5a* gene were recently recovered and shown to produce the same reduction in sensitivity as observed in the initially isolated *tre*<sup>-</sup> strains, suggesting that their mutations were in fact null mutations. Final proof that *Gr5a* is indeed a functional trehalose receptor was provided with a *Gr5a* transgene derived from a highly sensitive strain, which rescued the phenotype of a *tre*<sup>-</sup> strain [57]. The cellular expression of *Gr5a* has not been assessed yet, however, and it remains to be seen whether this receptor is expressed in a pattern analogous to other gustatory receptor genes.

Even though no other specific ligands for gustatory receptors have been identified, it is safe to say that they belong to

distinct chemical classes, because the perhaps a dozen biologically relevant sugars are not numerous enough to require a repertoire of 70 proteins for detection. *Gr5a* is one of eight members of a subfamily, consisting of *Gr5a*, *Gr61a* and six additional genes clustered in region 64 of the left arm of the third chromosome (*Gr64a* - *Gr64f*). The proteins encoded by these eight genes share up to 75% sequence similarity to each other and it is likely that they represent a group of receptors involved in the detection of structurally related compounds, such as various sugars. Future expression and functional studies will be necessary to define the taste sensilla and gustatory receptor neurons in which all these receptors are expressed and to identify the specific sugar ligands they recognize. It will be interesting to see whether individual receptors in this subfamily are coexpressed; if so, distinct sweet receptors in *Drosophila* might function as dimers or multimers, like the mammalian T1Rs. In any case, it is likely that other subfamilies recognize a variety of different non-sweet substrates, including pheromones.

#### Detection of bitter substrates, salts, acids and pheromones

Electrophysiological as well as behavioral studies have revealed that alkaloids and other compounds that taste bitter to humans, salts and acids are also recognized by neurons of the taste bristles located in the various taste organs of the fly [47-49]. The observation that different gustatory receptor genes are expressed in apparently distinct subsets of taste neurons in *Drosophila* suggests that some of the gustatory receptor proteins recognize non-sugar compounds; this is further supported by the fact that the number of gustatory receptors (70) by far exceeds the number of biologically relevant sugars encountered in the wild. Thus, one likely scenario is that distinct gustatory receptor subfamilies recognize distinct groups of chemical compounds present in the food or the environment in general.

An intriguing, albeit still hypothetical, function for some gustatory receptor genes (or a gustatory receptor subfamily) might include a role in the detection of pheromones. This hypothesis is mainly supported by the fly's anatomy as pheromone perception in *Drosophila* is not mediated by a specialized organ (such as the vomeronasal organ of mice) but appears to be directly mediated by a subpopulation of taste neurons located in the labial palps as well as the forelegs, both of which are extensively employed by the male during the elaborate male courtship ritual [3,4]. Moreover, specialized taste bristles in the male forelegs are further implicated by the observation that they are more abundant in males (approximately 50) than females (about 37) [5,50,51]. It is therefore likely that neurons of these bristles express pheromone receptors that may be sex-specific and that are crucially involved in the detection of female pheromones. But systematic expression analyses of all gustatory receptor genes will be necessary to identify among them potential candidates for pheromone receptors, and

future studies involving live markers of neuronal activation, such as G-CaMP (a calcium-sensitive calmodulin-GFP fusion protein) [59-61], might aid in the identification the ligands for these receptors; it is possible that these ligands are among the known *Drosophila* pheromones, which are long-chain hydrocarbons [6,7,62,63].

In conclusion, although many genetic pathways and genes are conserved between insects and mammals, including the sensory receptor proteins involved in the detection of light (rhodopsins) and of touch and pain (specific ion channels), the chemosensory receptors of the olfactory, taste and pheromone systems of insects and mammals have no sequence similarity. This is rather surprising, given that many mammals and insects exhibit similar and overlapping profiles of odor and taste preference. But despite the lack of sequence similarity between the cognate receptor proteins, striking similarities in the logic of olfactory sensory coding have been established [64,65].

There are significant differences in taste and pheromone perception between mammals and *Drosophila*, however. For example, the largely overlapping receptor expression profile of mammalian taste receptors is in striking contrast to the defined expression map of the gustatory receptor genes in the fly. Even though little is known about the organization of the taste-processing centers in the brains of mammals and flies, the distinct expression profile of gustatory receptor genes in the taste sensory system of *Drosophila* might be translated into a complex map in the subesophageal ganglion in the fly's brain and hence afford at least the possibility of rather sophisticated taste discrimination, a feature not associated with the mammalian taste system.

Should the *Drosophila* pheromone receptors emerge as a subfamily of the gustatory receptors, then at least one, and rather striking, similarity between the contact chemosensory receptors of mice and *Drosophila* would become apparent, namely the evolutionary conservation of taste and pheromone receptors in both species.

One common goal in the near future for both the mammalian and *Drosophila* taste- and pheromone-receptor fields is the 'de-orphanization' of these receptors, as we still lack broad knowledge of their cognate ligands. A second important task will be to elucidate how taste information is encoded in the brain. Of particular interest will be to investigate the taste discrimination of *Drosophila*, which, on the basis of expression data of gustatory receptor genes, might quite possibly accommodate more than just the five taste modalities known to humans. Finally, how taste receptors signal their activation is only partly understood in mammals and completely unknown in *Drosophila*; identifying the signaling components associated with these receptors will therefore be another field of intense study on the way to demystifying taste and pheromone perception.

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