Published as: *Cell*. 2009 October 16; 139(2): 234–244.

Common Sense about Taste: From Mammals to Insects

David A. Yarmolinsky[1], **Charles S. Zuker**[1,*], and **Nicholas J.P. Ryba**[2]

[1]Department of Biochemistry and Molecular Biophysics and Department of Neuroscience, Howard Hughes Medical Institute, Columbia College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA

[2]National Institute of Dental and Craniofacial Research (NIDCR), Bethesda, MD 20892, USA

Abstract

The sense of taste is a specialized chemosensory system dedicated to the evaluation of food and drink. Despite the fact that vertebrates and insects have independently evolved distinct anatomic and molecular pathways for taste sensation, there are clear parallels in the organization and coding logic between the two systems. There is now persuasive evidence that tastant quality is mediated by labeled lines, whereby distinct and strictly segregated populations of taste receptor cells encode each of the taste qualities.

Unlike touch, vision, audition, or olfaction, which function in diverse behavioral contexts, the sense of taste has evolved to serve as a dominant regulator and driver of feeding behavior. Gustatory systems detect nutritionally relevant and harmful compounds in food and trigger innate behaviors leading to acceptance or rejection of potential food sources. Taste is therefore a powerful system in which to ask the question, how is sensory input transformed and distributed to evoke a specific behavioral output? A first step in this endeavor is to define how tastant identity and concentration are translated into patterns of activity by primary receptor cells. This Review describes recent progress on this problem and illustrates how dissimilar organisms have converged on a common strategy for the encoding of taste information.

The Mammalian Taste System

Humans, and probably most mammals, categorize taste stimuli into a small palette of qualities (Lindemann, 2001; Chandrashekar et al., 2006). The tastes of sweet, bitter, sour, and salty are familiar to all, while umami, a savory taste elicited by certain L-amino acids (Ikeda, 1909), constitutes a fifth “primary” taste modality. Umami and sweet are “good” tastes that promote consumption of nutritive food (such as the building blocks for protein synthesis and energy), whereas bitter and sour are “bad” tastes that alert the organism to toxins and low pH, promoting rejection of foods containing harmful substances (for instance, noxious plants or spoiled or unripe fruits). Salt can taste either “good” or “bad” to us and be attractive or repulsive to mice, depending both on the concentration of sodium and on the physiological needs of the taster (Lindemann, 2001; Bachmanov et al., 2002). The modest breadth of this repertoire, together with the innate relationship of quality to hedonic

*Correspondence: cz2195@columbia.edu.

valence and behavioral response, imply that the task of the taste system is not “subtle discrimination,” or connoisseurship, but rather to drive binary decisions about whether to consume or reject a potential food item.

Although animals, particularly humans, may acquire a taste for an initially unattractive tastant (for example, coffee), taste preferences are at the outset innate (that is, genetically encoded). For example, naive rodents will avidly consume sweet solutions over water and always choose water over bitter, sour, and concentrated salt solutions. In addition the function of the taste system is greatly impacted by olfaction, texture, and the internal state of the organism. Indeed, our own taste perceptions are richly modulated by hunger, satiety, emotion, and expectation.

Appropriate to being gatekeepers for feeding behavior, taste receptor cells (TRCs) are found in the mouth and are concentrated on surfaces of the tongue and palate (Figure 1). TRCs are organized into taste buds, ovoid structures typically composed of 50–100 cells (Delay et al., 1986; Kinnamon et al., 1993; Lindemann, 2001). On the tongue, taste buds are housed within epithelial structures termed papillae, of which there are three types: (1) dozens of taste buds are distributed across the anterior surface of the tongue in fungiform papillae, (2) hundreds are located in the trenches of circumvallate papillae at the back, and (3) dozens to hundreds more localize to the sides of the tongue in foliate papillae. Many isolated taste buds are also distributed on the soft palate.

Taste signals from the fungiform taste buds and palate are transmitted to neurons in the geniculate ganglion via the chorda tympani and greater superficial petrosal nerve, respectively, whereas the circumvallate and foliate papillae are innervated primarily by the glossopharyngeal nerve, composed of fibers initiating from the petrosal ganglion (Figure 1). Notably, TRCs actively regenerate during adult life, with taste cells living an average of only 2 weeks before dying and being replaced by newly born cells (Lindemann, 2001); this poses the interesting challenge of ensuring that the correct newly born TRC connects to the appropriate afferent nerve fibers. Taste information from sensory ganglia converges onto the rostral portion of the nucleus of the solitary tract in the brainstem, from where it is routed through the parabrachial nucleus in mice or directly to the ventral posteromedial nucleus of the thalamus in primates. From the thalamus, projections connect to the primary gustatory cortex in the insula. Local projections from the nucleus of the solitary tract (NST) within the brainstem mediate low-level (i.e., noncortical) behavioral responses, such as salivation and gaping induced by bitter taste (Spector and Travers, 2005).

Taste Receptors

How are tastants detected on the tongue? The pre-Socratic philosopher Democritus suggested that the different taste qualities are generated by the mechanical action of variously shaped “atoms” on the surface of the tongue. This is not too far from our current understanding that taste perception is initiated by the physical interaction of tastant molecules with specific receptor proteins located at the surface of TRCs (Figure 2).

Receptors for Umami and Sweet

The attractive tastes, sweet and umami, are sensed by heterodimeric G protein-coupled receptors (GPCRs) assembled by the combinatorial arrangement of T1R1, T1R2, and T1R3 subunits (Nelson et al., 2001; Li et al., 2002; Nelson et al., 2002; Zhao et al., 2003). The key role of these receptors in mediating mammalian sweet and umami taste was uncovered from a range of studies, including heterologous expression in cell-based assays (Nelson et al., 2001, 2002; Li et al., 2002) and the engineering of mice with ablated or genetically altered T1R subunits (Damak et al., 2003; Zhao et al., 2003). Together, these studies validated

T1R1+3 (a heteromeric receptor composed of the T1R1 and T1R3 subunits) as the mammalian umami receptor (Li et al., 2002; Nelson et al., 2002; Zhao et al., 2003) and T1R2+3 as the mammalian sweet taste receptor (Nelson et al., 2001; Li et al., 2002; Damak et al., 2003; Zhao et al., 2003). The T1R2+3 sweet receptor recognizes simple sugars, a wide range of artificial sweeteners, D-amino acids, and even intensely sweet proteins (Figure 2). How does a single receptor accommodate this broad range of tastants? Recent structure-function studies have begun to dissect the fine-grained details of the T1R receptor complexes and identified several discrete sites on each of the three subunits that participate in ligand binding (Cui et al., 2006; Jiang et al., 2004, 2005; Winnig et al., 2007); the presence of multiple sites in each receptor complex may help explain their remarkable breadth of tuning.

Mammalian taste receptors show markedly more sequence divergence between species than do typical GPCRs (Adler et al., 2000; Nelson et al., 2001). This diversity is the substrate for functional differences reflecting the adaptation of different species to distinct ecological niches and diet. For example, mice and humans display a number of differences in the range of compounds stimulating sweet and umami taste. Umami is strongly stimulated in humans only by L-Glutamate (MSG) and L-Aspartate, whereas mice display robust attraction and neural responses to the majority of L-amino acids (Iwasaki et al., 1985; Nelson et al., 2002; Zhao et al., 2003). Similarly, humans taste as sweet several compounds to which mice are indifferent (e.g., aspartame; Nelson et al., 2001). Notably, these differences in selectivity are perfectly matched by the tuning of the respective T1R subunits, such that exchanging T1R components between the human and mouse receptors generate the corresponding altered taste selectivity both in cell-based assays and in vivo (Nelson et al., 2001, 2002; Li et al., 2002; Zhao et al., 2003). This strict correlation between receptor function and behavioral selectivity and sensitivity across species strongly implies that T1R receptors are a major determining factor in species-specific taste preferences. Indeed, two extreme examples illustrate this principle: (1) introduction of the human T1R2 gene into mice humanizes sweet taste preferences (Zhao et al., 2003), and (2) the Felidae family acquired a loss-of-function mutation in the T1R2 gene early in their evolution and have consequently loss all sweet taste; this nicely explains the behavioral indifference of all cats to sugars (Li et al., 2005).

Orthologs of the three T1Rs are present in the genomes of all vertebrates thus far examined. T1Rs have not been identified in any invertebrate species, including the chordates amphioxus and *Ciona intestinalis*. Importantly, all members of the T1R family are present in fish, where they also function as heteromeric receptors (Oike et al., 2007; Yasuoka and Abe, 2009). However, fish T1R2+3 responds to L-amino acids rather than prototypical sweet tastants (Oike et al., 2007; Yasuoka and Abe, 2009). This suggests that the mammalian T1R2+3 complex was remodeled to recognize sugars at some point during the transition of vertebrates from oceans to land.

Receptors for Bitter

The role of sweet and umami taste is to help identify food sources rich in sugar and protein. As such, the T1Rs are low-affinity receptors mediating behavioral preference thresholds in the millimolar range (Damak et al., 2003; Zhao et al., 2003); such low affinity helps the receptors distinguish between different potential sugar and protein sources without reaching saturation below nutritionally relevant concentrations. Bitter recognition faces a different challenge. Not only is the chemical diversity of bitter substances orders of magnitude greater, but in addition these toxic compounds must be detected at much smaller concentrations in order to avoid potentially lethal dietary mistakes. To accomplish this task, mammals are endowed with a family of GPCRs encoding the T2R bitter receptors (Adler et al., 2000; Chandrashekar et al., 2000; Matsunami et al., 2000). The T2Rs have a highly

variable structure with few regions of extended conservation; this sequence diversity reflects the need to recognize a disparate chemical universe. T2Rs are both necessary and sufficient for bitter taste. On the one hand, knockout (Mueller et al., 2005) or genetic alterations (Kim et al., 2003; Bufe et al., 2005) of specific T2Rs leads to changes in bitter taste sensitivity and selectivity. On the other, introduction of novel T2Rs expands the bitter taste repertoire (Mueller et al., 2005).

Ligands for several mouse and human T2Rs have been identified in cell-based assays, and as expected, all are bitter to humans or aversive to mice (Chandrashekar et al., 2000; Bufe et al., 2002; Pronin et al., 2004; Meyerhof et al., 2005). Given that there are far fewer T2Rs (ranging from about 10 to 40 members, depending on the species) than chemically distinct bitter-tasting chemicals, it is not surprising that any given T2R actually recognizes a wide repertoire of ligands (Meyerhof et al., 2005). Interestingly, some compounds, for example acesulfame K and saccharin, evoke sweetness at low concentrations but bitter responses at high concentrations. What underlies this duality of response? As it turns out, not only do these two artificial sweeteners activate the sweet taste receptor (Nelson et al., 2001; Li et al., 2002), but in addition they also activate specific T2Rs at high concentration (Kuhn et al., 2004; Pronin et al., 2007). This observation nicely illustrates the concept that a single chemical species may elicit more than one taste (i.e., through the activation of multiple receptors) and may explain the characteristic “aftertaste” associated with these tastants.

Why do chemically diverse compounds generate a common sensation of bitterness? Studies of the expression of *T2R* transcripts in TRCs showed that each bitter-sensing cell coexpressess the majority of the *T2R* genes (Adler et al., 2000; Mueller et al., 2005; Meyerhof et al., 2005). Given this lack of selectivity in the expression of T2Rs, Adler et al. proposed that bitter TRCs detect a wide range of toxic chemicals but do not discriminate between them. Indeed, subsequent behavioral studies demonstrated that rodents are unable to discriminate between bitter compounds (Spector and Kopka, 2002), and molecular studies showed that taste-blind animals engineered to restore bitter taste function under the control of single T2R promoters recovered taste recognition to the entire repertoire of bitters (Zhang et al., 2003; Mueller et al., 2005). We suggest that this is exactly the type of sensor needed to warn against the ingestion of noxious substances and provides a nice biological underpinning to the observation that many human cultures use a single word to define bitter-tasting compounds.

Sour, Carbonation, and Salty Taste

Sour-sensing TRCs are characterized by the expression of PKD2L1, a TRP ion channel proposed to function as a component of the acid-sensing machinery (LopezJimenez et al., 2006; Ishimaru et al., 2006; Huang et al., 2006). Genetic ablation of these cells via targeted expression of diphtheria toxin specifically and completely abolishes taste responses to acids, without affecting the other four taste qualities (Huang et al., 2006).

How might PKD2L1-expressing TRCs sense acid? It has been argued that intracellular acidification is the relevant stimulus for sour taste (Lyall et al., 2001). However, recent experiments demonstrate that specific inhibition of extracellular proton production on the tongue is sufficient to block the activation of sour cells (Chandrashekar et al., 2009), thus suggesting that the sour sensor operates instead as an extracellular receptor (see below). Several candidate receptors have been proposed for sour taste, including PKD2L1, PKD1L3, HCN1, and HCN4 (Stevens et al., 2001; Ishimaru et al., 2006; LopezJimenez et al., 2006; Huang et al., 2006); knockout studies are needed to determine the role, if any, of these putative acid sensors in vivo.

In mammals, carbonation elicits robust chemosensory responses, including activation of gustatory neurons (Komai et al., 1994; Lyall et al., 2001). How does CO_2 activate the taste system? By genetic ablation and silencing of defined populations of taste receptor cells, Chandrashekar et al. recently showed that the sour-sensing taste receptor cells also act as sensors for carbonation. Importantly, taste responses to carbonation can be functionally uncoupled from acid detection, both pharmacologically and genetically. Car4, an extracellular, glycosylphosphatidylinositol (GPI)-anchored carbonic anhydrase, functions selectively as the main CO_2 sensor in the taste system (Chandrashekar et al., 2009). Indeed, gustatory responses to CO_2 are highly sensitive to inhibition of extracellular carbonic anhydrases, and a knockout of Car4 severely affects CO_2 taste detection. Carbonic anhydrases (CAs) reversibly catalyze the conversion of CO_2 into bicarbonate ions and free protons. Given that Car4 is specifically tethered to the surface of sour-sensing cells, it is thus ideally poised to provide a highly localized signal to the sour TRCs.

The taste of salt in rodents is typically divided into two components based on taste preferences to salt-containing solutions and the sensitivity of salt responses to the channel blocker amiloride (Breslin et al., 1993; Spector et al., 1996). At low concentrations (10–150 mM NaCl), mice will consume salt, but the behavior (and neural responses) are largely blocked by amiloride (Bachmanov et al., 2002). At high concentrations of salt, however, mice exhibit innate aversion, and these responses are unaffected by amiloride. Because the epithelial sodium channel ENaC is strongly inhibited by amiloride, it has been proposed to participate in salt taste (Heck et al., 1984; Brand et al., 1985). However, the identity of the salt receptor(s) and the mechanisms mediating salt attraction and aversion remain open. Notably, mice that are blind to sweet, umami, bitter, or sour taste still retain neural and behavioral response to salts (Huang et al., 2006), substantiating the segregation of all taste modalities at the periphery and demonstrating the existence of one or more TRC populations dedicated to salt detection.

Taste Receptor Cells Are Hardwired to Behavioral Output

The expression of bitter, sweet, umami, and sour receptors in segregated TRCs implies that these tastes are mediated by distinct, dedicated receptor cells, each tuned to a single taste modality (Figure 3). Indeed, a series of studies in genetically engineered mice have now substantiated this logic of taste coding and provided definitive evidence of a labeled-line organization for the taste system at the periphery (Chandrashekar et al., 2006). For example, specific taste receptor cell populations can be genetically ablated by expression of the diphtheria toxin alpha subunit, and the resulting animals exhibit a deficit only in that modality while other responses remain intact (Huang et al., 2006; Chandrashekar et al., 2009). In addition, the innate nature of taste preferences strongly suggests that TRCs are hardwired to behavioral programs for acceptance and rejection. If this is true, activation of selective TRC populations should be sufficient to drive taste behavior. For example, expression of a blue light receptor in sweet cells should, in principle, make blue light “taste” sweet. Although this experiment has not been done yet, expression of a non-taste receptor in sweet or bitter TRCs did allow taste cells to be activated, and a strong specific behavior elicited, by an ordinarily tasteless ligand (Zhao et al., 2003; Mueller et al., 2005). As Figure 4 shows, if this receptor (RASSL, Coward et al., 1998) is expressed in sweet-sensing cells under the control of the T1R2 promoter, these mice are strongly attracted to solutions containing the normally tasteless ligand (Zhao et al., 2003). If, on the other hand, the very same RASSL receptor is expressed in bitter cells, these mice now exhibit strong repulsion (Mueller et al., 2005). Similarly, expression of a bitter receptor in sweet-sensing cells produces animals that exhibit strong attraction to the cognate bitter ligand, that is, bitter tastes sweet (Mueller et al., 2005). These behaviors do not involve learning, as receptor expression is absent during development and is induced only immediately prior to the

behavioral tests. Taken together, these experiments demonstrate that behavioral responses to taste stimuli are determined by the identity of the stimulated cell type, and not by the properties of the taste receptor molecule or even the tastants; they also illustrate how the functional segregation of taste modalities endows the taste system with a refined engine to drive innate behaviors. It will be an interesting challenge to understand the genetic program and mechanism(s) by which each taste cell type is hardwired to the appropriate neural circuitry and to explore if one can also alter taste behavior by manipulating the wiring scheme.

It has long been established that each taste bud is composed of a heterogeneous collection of cell types. Early electron microscopy studies of taste bud structure classified TRCs into four morphological types. Types I, II, and III (also called dark, light, and intermediate cells) make contact with the taste pore, whereas type IV cells are located at the base of the bud (Murray et al., 1969; Delay et al., 1986; Royer and Kinnamon, 1988; Kinnamon et al., 1993). The cloning and characterization of taste receptors has now shown that type II cells include sweet-, bitter-, and umami-sensing cells (Clapp et al., 2004), type III cells are sour-sensing cells (Kataoka et al., 2008), and type IV cells appear to be progenitor cells that divide to regenerate mature TRCs. These molecular studies have brought closure to a long-standing anatomical mystery and suggest that perhaps type I cells correspond to salt-sensing TRCs. But, why are taste receptor cells organized into taste buds? The close proximity of cells responsive to distinct taste qualities may allow lateral interactions to occur while still maintaining segregated outputs. Under this scenario the taste bud is thus a functional unit, an integrated “taste organ.” Indeed, multiple potential neurotransmitters and their receptors are expressed in selective taste receptor cell populations, hinting that intra-taste bud interactions do occur (Herness et al., 2005; Roper, 2006, 2009; Herness and Zhao, 2009). For example, sour-sensing PKD2L1 cells produce serotonin and GABA (Huang et al., 2005; Cao et al., 2009) and have been reported to release serotonin in an activity-dependent manner (Huang et al., 2005). Such release could potentially modulate the activity of sweet, umami, or bitter receptor cells or fibers and in the process alter the saliency, and thus the behavioral output, elicited by taste mixes containing both attractive and aversive tastants.

How do TRCs transmit information to primary afferents? Remarkably, only a few cells in each taste bud, namely the PKD2L1-expressing sour cells, possess conventional synapses as defined by ultrastructural studies (Yang et al., 2000). Yet, ablation of these cells selectively eliminates responses to sour tastants without affecting the other modalities (Huang et al., 2006). This has led to several models of atypical synaptic signaling, including the proposal that sweet, bitter, umami, and salty taste responses are transmitted to primary afferents through some nonconventional connection, such as release from subsurface cisternae (Royer and Kinnamon, 1988) or ATP release through pannexin/connexin hemichannels (Huang et al., 2007; Romanov et al., 2007). Regardless of the mechanism of transmission, it would be extremely useful to be able to follow the connectivity of defined TRCs to second-order and higher neurons. Three groups have reported the transmission of the purportedly transneuronal tracer wheat germ agglutinin from genetically labeled TRCs to higher stations (Sugita and Shiba, 2005; Ohmoto et al., 2008; Damak et al., 2008). Although these approaches have provided limited and somewhat conflicting information about taste pathways, when combined with functional studies, they may help determine how taste signals are transformed, and how the labeled-line organization at the periphery is represented in the higher neuronal stations (ganglia, brain stem, thalamus, and primary cortex).

Taste in Fruit Flies

Given that the fruit fly taste system has evolved quite independently from that of mammals, it detects a remarkably similar range of tastants. Like mice and humans, *Drosophila* are attracted to sugars and low concentrations of salt and are averse to noxious compounds comparable to the mammalian bitters (Amrein and Thorne, 2005). Although we use “sweet” and “bitter” tastes to describe attractive and aversive modalities in flies and mice, it is important to note that these descriptors rely on analogy rather than homology. Indeed, philosophers and neuroethologists have long argued on the meaning of percepts (that is, is your sweet the same as mine, and what does sweet taste like to a fly?); we will avoid this controversy by using the descriptors to refer to detection rather than perception.

Unlike mammals, fruit flies are indifferent to L-amino acids or low pH in their diet. This most likely represents an adaptation to their specialized diet of (often spoiling) fruit, which is typically quite acidic and far more enriched in simple carbohydrates than in protein or amino acids. Unlike mice, flies are much smaller than their food sources, and typically walk along the surface of their food before ingesting it. Thus, in addition to having taste receptors on its mouth parts the fly also has gustatory receptor neurons (GRNs) distributed on its legs and wings (Figure 5).

The fly ingests food through its proboscis, which consists of a muscular tube, the pharynx, gated by two labial palps (labellum). GRNs are housed within 200–300 gustatory sensilla distributed on the proboscis, legs, and wings. In *Drosophila*, each labellum displays 31 taste bristles on each outer surface and about 30 inner taste pegs located between the furrows of pseudotrachea (exposed when the fly begins active feeding). Additional GRNs are located in a series of internal taste organs lining the pharynx. The taste bristles on the proboscis and legs include long, short, and intermediate subtypes, each containing one mechanosensory and either two (intermediate) or four (short and long) gustatory neurons. Each gustatory neuron extends a dendrite to a terminal pore at the tip of the bristle shaft and an axonal process that terminates primarily in the subesophageal ganglion (SOG).

The proboscis is normally stowed at the base of the head, but stimulation of leg or labial taste neurons with an attractive tastant such as sugar causes extension of the proboscis, opening of the labella, and initiation of the feeding program. Expectedly, addition of unpalatable substances to the food source suppresses the proboscis extension reflex (PER) and triggers proboscis retraction; proboscis extension/retraction are robust innate behaviors and are commonly used as behavioral assays for defects in taste system function.

The gustatory bristles of *Drosophila* are amenable to extracellular recordings and simple enough that responses of the gustatory neurons can be reliably discriminated from one another by spike sorting. Early studies utilizing this approach identified several functional classes of GRNs. Short and long gustatory bristles contain one neuron that responds to sugar (S), one to water (W), one to salt (L1), and a fourth that responds to bitter compounds and higher concentrations of salt (L2; Meunier et al., 2003; Siddiqi and Rodrigues, 1980; Thorne et al., 2005). Intermediate bristles contain only two chemosensory cells (Hiroi et al., 2004), one tuned to both low salt and sugars (i.e., attractive tastants) and one to high salt and bitters (i.e., aversive tastants). As expected, different tastants that are sensed by the same cell (such as high salt, caffeine, and quinine) stimulate a common behavioral response. This arrangement is strongly reminiscent of the situation in mammals, in which selectivity to different taste qualities is segregated among a limited number of cell types. As with mice, establishment of the causal relationships between taste neuron activity and behavior required the molecular isolation of taste receptors to dissect the organization of the taste system.

"Sweet" and "Bitter" Pathways in Flies

Fly taste receptors are, for the most part, members of the "Gustatory Receptor" (Gr) family, a group of 68 distantly related genes encoding putative heptahelical transmembrane proteins (Clyne et al., 2000; Scott et al., 2001; Dunipace et al., 2001). Interestingly, although Grs were originally anticipated to function as GPCRs, it is not clear at present whether the Grs signal through G protein-dependent second messenger cascades or operate as ligand-gated ion channels. The closest relatives of the Grs are the insect odorant receptors, which have recently been proposed to function as ion channels (Sato et al., 2008; Wicher et al., 2008).

Just like in mammalian taste, receptor expression in flies also defines strictly segregated populations of GRNs. The trehalose sweet taste receptor, Gr5a (Chyb et al., 2003), is expressed in a population of gustatory neurons that is entirely nonoverlapping with neurons expressing Gr66a (Thorne et al., 2004; Wang et al., 2004), a receptor required for bitter detection (Moon et al., 2006). Each of these receptors is present in a single distinct GRN in nearly all gustatory bristles. In addition, the projections of these neurons to the SOG terminate in spatially segregated domains. The function of Gr5a as a sugar receptor immediately suggests that this class of labeled cells (and projections) represents a labeled line for sweet tastants, whereas Gr66a-expressing neurons may correspond to a labeled line for bitter stimuli. Indeed, a combination of functional imaging, cellular ablation, and activation studies have now shown that all compounds that activate Gr5a neurons are attractive to flies, and all that stimulate Gr66a neurons are aversive (Thorne et al., 2004; Wang et al., 2004; Marella et al., 2006). Thus, these two pathways function as labeled lines for "sweet" (Gr5a) and "bitter" (Gr66a) taste.

In mice, activation of selective TRCs robustly drives behavior, irrespective of the source of activation (see Figure 4). Does the same logic extend to flies? Scott et al. expressed the mammalian capsaicin receptor, TrpV1, in fly gustatory neurons and proved that expression in Gr5a neurons produces a dose-dependent preference for capsaicin whereas expression in Gr66a neurons results in aversion (Marella et al., 2006). Analogous experiments in which odorant receptors are expressed in Gr5a and Gr66a neurons confer attraction or repulsion, respectively, to the cognate odorant (Hiroi et al., 2008). Finally, a recent study shows that expression and activation of the light-activated channel rhodopsin-2 reporter in Gr5a neurons is sufficient to induce robust initiation of the feeding program upon stimulation with blue light (Gordon and Scott, 2009). Thus, just as in mammalian taste, distinct populations of taste receptor cells are hardwired to elicit appropriate behavioral responses.

How do taste inputs control behavior? The fly brain is several orders of magnitude smaller than the mammalian brain; this makes the dissection of circuits controlling behavior (e.g., from the mouth to the sensory and integration centers of the brain to motor outputs) a far more tractable problem than in mice. For instance, a recent study in flies identified a motor neuron within the SOG (E49; Gordon and Scott, 2009) that appears to act as an integrator of bitter and sweet inputs to control proboscis extension. Notably, this neuron is stimulated by activity in Gr5a neurons and inhibited by Gr66a activity; thus the "bitter" and "sweet" labeled lines ultimately come together to choreograph antagonistic responses in neurons gating the behavior to food.

The Tastes of Salt, Water, and Carbonation

Like mammals, flies are attracted to salt at low concentrations and averse at high concentrations. Both Gr66a- and Gr5a-expressing neurons display functional responses to NaCl (Marella et al., 2006). Whereas Gr5a GRNs respond to concentrations as low as 10 mM NaCl, bitter-responsive Gr66a neurons require much higher stimulus concentrations, consistent with thresholds for behavioral aversion. Ablation of Gr5a neurons greatly

diminishes the PER to low salt concentrations (Wang et al., 2004). Surprisingly, ablation of Gr66a neurons does not significantly affect salt avoidance (Wang et al., 2004), suggesting that additional pathways may contribute to high salt aversion (such as L1 salt-sensitive neurons). Candidates for salt receptors in flies include members of the Degenerin/ENaC (pickpocket) family of ion channels (Liu et al., 2003). However, definite data linking a specific receptor to salt taste function or dysfunction are still missing.

Flies display a robust PER to water, particularly when they are water deprived (Inoshita and Tanimura, 2006). This response corresponds to the sensitivity of the gustatory W neuron, which is stimulated by pure water and inhibited by rising concentrations of salts or other solutes. Notably, a recently characterized *Drosophila* enhancer trap line, NP1017, drives reporter expression in a single neuron in each of the water-sensitive long and short labial sensilla. Silencing of these neurons abolishes the PER to water, without affecting response to sugars (Inoshita and Tanimura, 2006). These cells now provide the means to isolate and characterize a putative water receptor, a most exciting prospect.

In addition to taste bristles, flies possess approximately 30 taste pegs on the inner surfaces of each labial palp. Approximately, six of the taste peg neurons express Gr5a (Thorne et al., 2004), but the remaining ones do not express any known Gr. What is the function of these putative gustatory neurons? An anatomical screen of enhancer trap lines for expression in taste tissue identified one line, E409, that labels all of the non-Gr5a-expressing taste peg neurons (Fischler et al., 2007). Using this driver line, Scott and coworkers elegantly demonstrate that the E409 cells function as CO_2 sensors, activated by growing yeast, beer, carbonated water, dry ice, and even gaseous CO_2 (Fischler et al., 2007). In food preference assays flies like to feed from solutions containing CO_2. However, this preference is greatly reduced by genetically silencing the E409 neurons (Fischler et al., 2007). In addition, expression of the TrpV1 channel in E409 cells produces animals that exhibit robust taste attraction to capsaicin (Fischler et al., 2007). Together these data argue persuasively that flies have a dedicated pathway for CO_2 taste detection and suggest that CO_2 is an important driver of food choice (for example, fermented fruits).

Aftertastes and Afterthoughts

Flies and mice diverged from a common ancestor in the Cambrian period 550 million years ago. Yet, each species possesses a gustatory system sharing the same fundamental principles of organization. Both systems categorize a diverse array of nutritionally relevant compounds using a relatively small number of labeled inputs: sweet, sour, salty, bitter, and umami in mice, and “sweet,” “bitter,” water, CO_2, and (probably) salt in flies. These inputs correspond to segregated populations of receptors cells at the periphery, each responsible for detection of a single taste quality. The “taste” of a food item is thus a reflection of the ensemble of activated TRC types.

Important questions remain with regard to the peripheral representation of taste in both flies and mice: Is primary taste information processed or transformed within “taste organs” (buds in mice and sensory bristles and pegs in flies)?. How are signals transmitted between TRCs and afferent nerves? Are there taste receptors for fat or other orosensory stimuli? How is wiring specificity maintained despite constant TRC turnover? Are all Gr66a neurons in the fly functionally equivalent, or does the fly use distinct subclasses of “bitter” neurons to behaviorally discriminate between toxins? How do flies use information from the different gustatory organs distributed along the body plan for selective behaviors? Is tastant location encoded along with quality?

What about the central representation of taste? The role of our senses is to create an internal representation of the physical and chemical features of the outside world. In the case of taste, this question can be reduced to how does the brain know what the tongue knows? Given our new understanding of the organization of the taste system at the periphery, it is reasonable to speculate on strategies to encode tastant identity (and intensity) in the primary taste cortex. Current models of taste coding propose that neuronal lines for each taste converge into common targets, even at the earliest of neuronal stations (see Roper, 2007). However, if the spatial segregation seen in the periphery is largely preserved through the central stations, we may instead discover a chemotopic map of taste qualities, reminiscent of the logic seen in the somatosensory, visual, and auditory systems. Recent advances in multi-electrode recording and imaging techniques now provide a venue to answer this question.

Finally, although taste is the only sense strictly devoted to feeding behavior, all senses play a role in influencing dietary choices. To humans, a dish that is sweet, savory, and perfectly salted may be rendered unappetizing due to foul odor, unexpected color, or bad association with a particular experience. As we follow taste information upwards from the primary taste cortex, two exciting challenges will be to identify the sites where information from different sensory modalities converges onto decision centers to control feeding behavior and to determine how taste and odor representations are bound to create perceptions of “flavor.”

Acknowledgments

We thank J. Chandrashekar, K. Scott, and W. Fischler for their helpful suggestions. We also thank members of our labs for their dedication, commitment, and brilliant efforts in our past and present studies in the biology of mammalian taste. D.A.Y. was a graduate student in the Division of Biological Sciences at UCSD and is now in the Biochemistry and Molecular Biophysics program at Columbia University. C.S.Z. is an HHMI Investigator (HHMI); N.J.P.R. is an investigator in the Intramural Research Program of the National Institute of Dental and Craniofacial Research (NIDCR)/NIH. C.S.Z. is a scientific cofounder of Senomyx and a member of its scientific advisory board.

References

Adler E, Hoon MA, Mueller KL, Chandrashekar J, Ryba NJ, Zuker CS. A novel family of mammalian taste receptors. Cell. 2000; 100:693–702. [PubMed: 10761934]

Al-Anzi B, Tracey WD Jr, Benzer S. Response of *Drosophila* to wasabi is mediated by painless, the fly homolog of mammalian TRPA1/ANKTM1. Curr Biol. 2006; 16:1034–1040. [PubMed: 16647259]

Amrein H, Thorne N. Gustatory perception and behavior in *Drosophila melanogaster*. Curr Biol. 2005; 15:R673–R684. [PubMed: 16139201]

Bachmanov AA, Beauchamp GK, Tordoff MG. Voluntary consumption of NaCl, KCl, CaCl2, and NH4Cl solutions by 28 mouse strains. Behav Genet. 2002; 32:445–457. [PubMed: 12467342]

Brand JG, Teeter JH, Silver WL. Inhibition by amiloride of chorda tympani responses evoked by monovalent salts. Brain Res. 1985; 334:207–214. [PubMed: 3995317]

Breslin PA, Kaplan JM, Spector AC, Zambito CM, Grill HJ. Lick rate analysis of sodium taste-state combinations. Am J Physiol. 1993; 264:R-12–R318. [PubMed: 8430872]

Bufe B, Hofmann T, Krautwurst D, Raguse JD, Meyerhof W. The human TAS2R16 receptor mediates bitter taste in response to beta-glucopyranosides. Nat Genet. 2002; 32:397–401. [PubMed: 12379855]

Bufe B, Breslin PA, Kuhn C, Reed DR, Tharp CD, Slack JP, Kim UK, Drayna D, Meyerhof W. The molecular basis of individual differences in phenylthiocarbamide and propylthiouracil bitterness perception. Curr Biol. 2005; 15:322–327. [PubMed: 15723792]

Cao Y, Zhao FL, Kolli T, Hivley R, Herness S. GABA expression in the mammalian taste bud functions as a route of inhibitory cell-to-cell communication. Proc Natl Acad Sci USA. 2009; 106:4006–4011. [PubMed: 19223578]

Chandrashekar J, Mueller KL, Hoon MA, Adler E, Feng L, Guo W, Zuker CS, Ryba NJ. T2Rs function as bitter taste receptors. Cell. 2000; 100:703–711. [PubMed: 10761935]

Chandrashekar J, Hoon MA, Ryba NJ, Zuker CS. The receptors and cells for mammalian taste. Nature. 2006; 444:288–294. [PubMed: 17108952]

Chandrashekar J, Yarmolinsky D, von Buchholtz L, Oka Y, Sly W, Ryba NJP, Zuker CS. The taste of carbonation. Science. 2009; 326:455–458.

Chyb S, Dahanukar A, Wickens A, Carlson JR. Drosophila Gr5a encodes a taste receptor tuned to trehalose. Proc Natl Acad Sci USA. 2003; 100(Suppl 2):14526–14530. [PubMed: 14523229]

Clapp TR, Yang R, Stoick CL, Kinnamon SC, Kinnamon JC. Morphologic characterization of rat taste receptor cells that express components of the phospholipase C signaling pathway. J Comp Neurol. 2004; 468:311–321. [PubMed: 14681927]

Clyne PJ, Warr CG, Carlson JR. Candidate taste receptors in Drosophila. Science. 2000; 287:1830–1834. [PubMed: 10710312]

Coward P, Wada HG, Falk MS, Chan SD, Meng F, Akil H, Conklin BR. Controlling signaling with a specifically designed Gi-coupled receptor. Proc Natl Acad Sci USA. 1998; 95:352–357. [PubMed: 9419379]

Cui M, Jiang P, Maillet E, Max M, Margolskee RF, Osman R. The heterodimeric sweet taste receptor has multiple potential ligand binding sites. Curr Pharm Des. 2006; 12:4591–4600. [PubMed: 17168764]

Dahanukar A, Lei YT, Kwon JY, Carlson JR. Two Gr genes underlie sugar reception in *Drosophila*. Neuron. 2007; 56:503–516. [PubMed: 17988633]

Damak S, Rong M, Yasumatsu K, Kokrashvili Z, Varadarajan V, Zou S, Jiang P, Ninomiya Y, Margolskee RF. Detection of sweet and umami taste in the absence of taste receptor T1r3. Science. 2003; 301:850–853. [PubMed: 12869700]

Damak S, Mosinger B, Margolskee RF. Transsynaptic transport of wheat germ agglutinin expressed in a subset of type II taste cells of transgenic mice. BMC Neurosci. 2008; 9:96. [PubMed: 18831764]

Delay RJ, Kinnamon JC, Roper SD. Ultrastructure of mouse vallate taste buds: II. Cell types and cell lineage. J Comp Neurol. 1986; 253:242–252. [PubMed: 3793992]

Dunipace L, Meister S, McNealy C, Amrein H. Spatially restricted expression of candidate taste receptors in the *Drosophila* gustatory system. Curr Biol. 2001; 11:822–835. [PubMed: 11516643]

Fischler W, Kong P, Marella S, Scott K. The detection of carbonation by the Drosophila gustatory system. Nature. 2007; 448:1054–1057. [PubMed: 17728758]

Gordon MD, Scott K. Motor control in a *Drosophila* taste circuit. Neuron. 2009; 61:373–384. [PubMed: 19217375]

Heck GL, Mierson S, DeSimone JA. Salt taste transduction occurs through an amiloride-sensitive sodium transport pathway. Science. 1984; 223:403–405. [PubMed: 6691151]

Herness S, Zhao FL. The neuropeptides CCK and NPY and the changing view of cell-to-cell communication in the taste bud. Physiol Behav. 2009; 97:581–591. [PubMed: 19332083]

Herness S, Zhao FL, Kaya N, Shen T, Lu SG, Cao Y. Communication routes within the taste bud by neurotransmitters and neuropeptides. Chem Senses. 2005; 30(Suppl 1):i37–i38. [PubMed: 15738183]

Hiroi M, Meunier N, Marion-Poll F, Tanimura T. Two antagonistic gustatory receptor neurons responding to sweet-salty and bitter taste in Drosophila. J Neurobiol. 2004; 61:333–342. [PubMed: 15389687]

Hiroi M, Tanimura T, Marion-Poll F. Hedonic taste in *Drosophila* revealed by olfactory receptors expressed in taste neurons. PLoS One. 2008; 3:e2610.10.1371/journal.pone.0002610 [PubMed: 18612414]

Huang YJ, Maruyama Y, Lu KS, Pereira E, Plonsky I, Baur JE, Wu D, Roper SD. Using biosensors to detect the release of serotonin from taste buds during taste stimulation. Arch Ital Biol. 2005; 143:87–96. [PubMed: 16106989]

Huang AL, Chen X, Hoon MA, Chandrashekar J, Guo W, Trankner D, Ryba NJ, Zuker CS. The cells and logic for mammalian sour taste detection. Nature. 2006; 442:934–938. [PubMed: 16929298]

Huang YJ, Maruyama Y, Dvoryanchikov G, Pereira E, Chaudhari N, Roper SD. The role of pannexin 1 hemichannels in ATP release and cell-cell communication in mouse taste buds. Proc Natl Acad Sci USA. 2007; 104:6436–6441. [PubMed: 17389364]

Ikeda K. On a new seasoning. J Tokyo Chem Soc. 1909; 30:820–836.

Inoshita T, Tanimura T. Cellular identification of water gustatory receptor neurons and their central projection pattern in Drosophila. Proc Natl Acad Sci USA. 2006; 103:1094–1099. [PubMed: 16415164]

Ishimaru Y, Inada H, Kubota M, Zhuang H, Tominaga M, Matsunami H. Transient receptor potential family members PKD1L3 and PKD2L1 form a candidate sour taste receptor. Proc Natl Acad Sci USA. 2006; 103:12569–12574. [PubMed: 16891422]

Iwasaki K, Kasahara T, Sato M. Gustatory effectiveness of amino acids in mice: behavioral and neurophysiological studies. Physiol Behav. 1985; 34:531–542. [PubMed: 4011734]

Jiang P, Ji Q, Liu Z, Snyder LA, Benard LM, Margolskee RF, Max M. The cysteine-rich region of T1R3 determines responses to intensely sweet proteins. J Biol Chem. 2004; 279:45068–45075. [PubMed: 15299024]

Jiang P, Cui M, Zhao B, Snyder LA, Benard LM, Osman R, Max M, Margolskee RF. Identification of the cyclamate interaction site within the transmembrane domain of the human sweet taste receptor subunit T1R3. J Biol Chem. 2005; 280:34296–34305. [PubMed: 16076846]

Jiao Y, Moon SJ, Wang X, Ren Q, Montell C. Gr64f is required in combination with other gustatory receptors for sugar detection in *Drosophila*. Curr Biol. 2008; 18:1797–1801. [PubMed: 19026541]

Kataoka S, Yang R, Ishimaru Y, Matsunami H, Sevigny J, Kinnamon JC, Finger TE. The candidate sour taste receptor, PKD2L1, is expressed by type III taste cells in the mouse. Chem Senses. 2008; 33:243–254. [PubMed: 18156604]

Kim UK, Jorgenson E, Coon H, Leppert M, Risch N, Drayna D. Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. Science. 2003; 299:1221–1225. [PubMed: 12595690]

Kinnamon JC, Henzler DM, Royer SM. HVEM ultrastructural analysis of mouse fungiform taste buds, cell types, and associated synapses. Microsc Res Tech. 1993; 26:142–156. [PubMed: 8241550]

Komai, M.; Bryant, BP.; Takeda, T.; Suzuki, H.; Kimura, S. Olfaction and Taste. Tokyo: Springer-Verlag; 1994. The effect of topical treatment with a carbonic anhydrase inhibitor, MK-927, on the response of the chorda tympani nerve to carbonated water; p. 92

Kuhn C, Bufe B, Winnig M, Hofmann T, Frank O, Behrens M, Lewtschenko T, Slack JP, Ward CD, Meyerhof W. Bitter taste receptors for saccharin and acesulfame K. J Neurosci. 2004; 24:10260–10265. [PubMed: 15537898]

Lee Y, Moon SJ, Montell C. Multiple gustatory receptors required for the caffeine response in Drosophila. Proc Natl Acad Sci USA. 2009; 106:4495–4500. [PubMed: 19246397]

Li X, Staszewski L, Xu H, Durick K, Zoller M, Adler E. Human receptors for sweet and umami taste. Proc Natl Acad Sci USA. 2002; 99:4692–4696. [PubMed: 11917125]

Li X, Li W, Wang H, Cao J, Maehashi K, Huang L, Bachmanov AA, Reed DR, Legrand-Defretin V, Beauchamp GK, et al. Pseudogenization of a sweet-receptor gene accounts for cats' indifference toward sugar. PLoS Genet. 2005; 1:e3.10.1371/journal.pgen.0010003

Lindemann B. Receptors and transduction in taste. Nature. 2001; 413:219–225. [PubMed: 11557991]

Liu L, Leonard AS, Motto DG, Feller MA, Price MP, Johnson WA, Welsh MJ. Contribution of *Drosophila* DEG/ENaC genes to salt taste. Neuron. 2003; 39:133–146. [PubMed: 12848938]

LopezJimenez ND, Cavenagh MM, Sainz E, Cruz-Ithier MA, Battey JF, Sullivan SL. Two members of the TRPP family of ion channels, Pkd1l3 and Pkd2l1, are co-expressed in a subset of taste receptor cells. J Neurochem. 2006; 98:68–77. [PubMed: 16805797]

Lyall V, Alam RI, Phan DQ, Ereso GL, Phan TH, Malik SA, Montrose MH, Chu S, Heck GL, Feldman GM, et al. Decrease in rat taste receptor cell intracellular pH is the proximate stimulus in sour taste transduction. Am J Physiol. 2001; 281:C1005–C1013.

Marella S, Fischler W, Kong P, Asgarian S, Rueckert E, Scott K. Imaging taste responses in the fly brain reveals a functional map of taste category and behavior. Neuron. 2006; 49:285–295. [PubMed: 16423701]

Matsunami H, Montmayeur JP, Buck LB. A family of candidate taste receptors in human and mouse. Nature. 2000; 404:601–604. [PubMed: 10766242]

Meunier N, Marion-Poll F, Rospars JP, Tanimura T. Peripheral coding of bitter taste in Drosophila. J Neurobiol. 2003; 56:139–152. [PubMed: 12838579]

Meyerhof W, Behrens M, Brockhoff A, Bufe B, Kuhn C. Human bitter taste perception. Chem Senses. 2005; 30(Suppl 1):i14–i15. [PubMed: 15738079]

Mitri C, Soustelle L, Framery B, Bockaert J, Parmentier ML, Grau Y. Plant insecticide L-canavanine repels *Drosophila* via the insect orphan GPCR DmX. PLoS Biol. 2009; 7:e1000147. [PubMed: 19564899]

Montell C. A taste of the Drosophila gustatory receptors. Curr Opin Neurobiol. 2009; 19:345–353. [PubMed: 19660932]

Moon SJ, Kottgen M, Jiao Y, Xu H, Montell C. A taste receptor required for the caffeine response in vivo. Curr Biol. 2006; 16:1812–1817. [PubMed: 16979558]

Mueller KL, Hoon MA, Erlenbach I, Chandrashekar J, Zuker CS, Ryba NJ. The receptors and coding logic for bitter taste. Nature. 2005; 434:225–229. [PubMed: 15759003]

Murray RG, Murray A, Fujimoto S. Fine structure of gustatory cells in rabbit taste buds. J Ultrastruct Res. 1969; 27:444–461. [PubMed: 5803342]

Nelson G, Hoon MA, Chandrashekar J, Zhang Y, Ryba NJ, Zuker CS. Mammalian sweet taste receptors. Cell. 2001; 106:381–390. [PubMed: 11509186]

Nelson G, Chandrashekar J, Hoon MA, Feng L, Zhao G, Ryba NJ, Zuker CS. An amino-acid taste receptor. Nature. 2002; 416:199–202. [PubMed: 11894099]

Ohmoto M, Matsumoto I, Yasuoka A, Yoshihara Y, Abe K. Genetic tracing of the gustatory and trigeminal neural pathways originating from T1R3-expressing taste receptor cells and solitary chemoreceptor cells. Mol Cell Neurosci. 2008; 38:505–517. [PubMed: 18539481]

Oike H, Nagai T, Furuyama A, Okada S, Aihara Y, Ishimaru Y, Marui T, Matsumoto I, Misaka T, Abe K. Characterization of ligands for fish taste receptors. J Neurosci. 2007; 27:5584–5592. [PubMed: 17522303]

Pronin AN, Tang H, Connor J, Keung W. Identification of ligands for two human bitter T2R receptors. Chem Senses. 2004; 29:583–593. [PubMed: 15337684]

Pronin AN, Xu H, Tang H, Zhang L, Li Q, Li X. Specific alleles of bitter receptor genes influence human sensitivity to the bitterness of aloin and saccharin. Curr Biol. 2007; 17:1403–1408. [PubMed: 17702579]

Romanov RA, Rogachevskaja OA, Bystrova MF, Jiang P, Margolskee RF, Kolesnikov SS. Afferent neurotransmission mediated by hemichannels in mammalian taste cells. EMBO J. 2007; 26:657–667. [PubMed: 17235286]

Roper SD. Cell communication in taste buds. Cell Mol Life Sci. 2006; 63:1494–1500. [PubMed: 16732426]

Roper SD. Signal transduction and information processing in mammalian taste buds. Pflugers Arch. 2007; 454:759–776. [PubMed: 17468883]

Roper SD. Parallel processing in mammalian taste buds? Physiol Behav. 2009; 97:604–608. [PubMed: 19371753]

Royer SM, Kinnamon JC. Ultrastructure of mouse foliate taste buds: synaptic and nonsynaptic interactions between taste cells and nerve fibers. J Comp Neurol. 1988; 270:11–24. [PubMed: 3372732]

Sato K, Pellegrino M, Nakagawa T, Nakagawa T, Vosshall LB, Touhara K. Insect olfactory receptors are heteromeric ligand-gated ion channels. Nature. 2008; 452:1002–1006. [PubMed: 18408712]

Scott K, Brady R Jr, Cravchik A, Morozov P, Rzhetsky A, Zuker C, Axel R. A chemosensory gene family encoding candidate gustatory and olfactory receptors in *Drosophila*. Cell. 2001; 104:661–673. [PubMed: 11257221]

Siddiqi O, Rodrigues V. Genetic analysis of a complex chemoreceptor. Basic Life Sci. 1980; 16:347–359. [PubMed: 6779799]

Slone J, Daniels J, Amrein H. Sugar receptors in *Drosophila*. Curr Biol. 2007; 17:1809–1816. [PubMed: 17919910]

Spector AC, Kopka SL. Rats fail to discriminate quinine from denatonium: implications for the neural coding of bitter-tasting compounds. J Neurosci. 2002; 22:1937–1941. [PubMed: 11880524]

Spector AC, Travers SP. The representation of taste quality in the mammalian nervous system. Behav Cogn Neurosci Rev. 2005; 4:143–191. [PubMed: 16510892]

Spector AC, Guagliardo NA, St John SJ. Amiloride disrupts NaCl versus KCl discrimination performance: implications for salt taste coding in rats. J Neurosci. 1996; 16:8115–8122. [PubMed: 8987836]

Stevens DR, Seifert R, Bufe B, Muller F, Kremmer E, Gauss R, Meyerhof W, Kaupp UB, Lindemann B. Hyperpolarization-activated channels HCN1 and HCN4 mediate responses to sour stimuli. Nature. 2001; 413:631–635. [PubMed: 11675786]

Sugita M, Shiba Y. Genetic tracing shows segregation of taste neuronal circuitries for bitter and sweet. Science. 2005; 309:781–785. [PubMed: 16051799]

Thorne N, Chromey C, Bray S, Amrein H. Taste perception and coding in *Drosophila*. Curr Biol. 2004; 14:1065–1079. [PubMed: 15202999]

Thorne N, Bray S, Amrein H. Function and expression of the Drosophila gr genes in the perception of sweet, bitter and pheromone compounds. Chem Senses. 2005; 30(Suppl 1):i270–i272. [PubMed: 15738152]

Wang Z, Singhvi A, Kong P, Scott K. Taste representations in the *Drosophila* brain. Cell. 2004; 117:981–991. [PubMed: 15210117]

Wicher D, Schafer R, Bauernfeind R, Stensmyr MC, Heller R, Heinemann SH, Hansson BS. Drosophila odorant receptors are both ligand-gated and cyclic-nucleotide-activated cation channels. Nature. 2008; 452:1007–1011. [PubMed: 18408711]

Winnig M, Bufe B, Kratochwil NA, Slack JP, Meyerhof W. The binding site for neohesperidin dihydrochalcone at the human sweet taste receptor. BMC Struct Biol. 2007; 7:66. [PubMed: 17935609]

Yang R, Crowley HH, Rock ME, Kinnamon JC. Taste cells with synapses in rat circumvallate papillae display SNAP-25-like immunoreactivity. J Comp Neurol. 2000; 424:205–215. [PubMed: 10906698]

Yasuoka A, Abe K. Gustation in fish: Search for prototype of taste perception. Results Probl Cell Differ. 2009; 47:239–255. [PubMed: 19145412]

Zhang Y, Hoon MA, Chandrashekar J, Mueller KL, Cook B, Wu D, Zuker CS, Ryba NJ. Coding of sweet, bitter, and umami tastes: Different receptor cells sharing similar signaling pathways. Cell. 2003; 112:293–301. [PubMed: 12581520]

Zhao GQ, Zhang Y, Hoon MA, Chandrashekar J, Erlenbach I, Ryba NJ, Zuker CS. The receptors for mammalian sweet and umami taste. Cell. 2003; 115:255–266. [PubMed: 14636554]

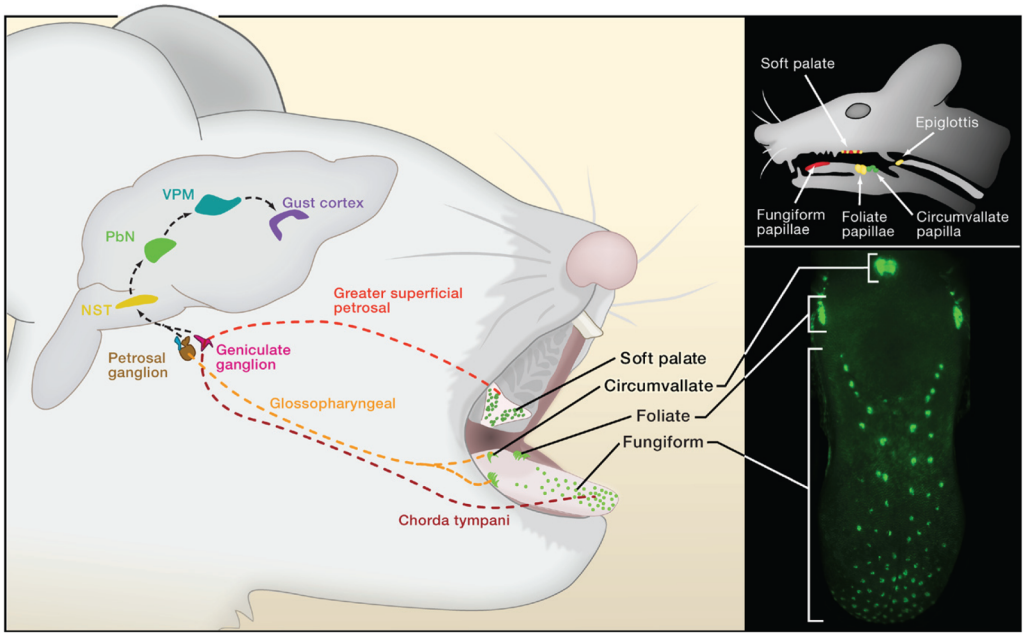

Figure 1. The Anatomy of Taste

Taste buds are broadly distributed on the tongue and soft palate. On the tongue, taste buds are localized to three classes of papillae: In mice, the single circumvallate papilla is found at the very back of the tongue; foliate papillae are at the posterior lateral edge, and fungiform papillae are distributed over the anterior two thirds of the tongue; these three classes of paplilae can be highlighted in mice engineered to express green fluorescent protein in taste bud areas (lower right panel). The taste buds on the tongue and palate are innervated by three afferent nerves: the chorda tympani, greater superficial petrosal, and glossopharyngeal. These nerves carry taste information from the taste receptor cells to the nucleus of the solitary tract (NST) in the brain stem. From the NST, taste responses are transmitted (and processed) through the parabrachial nucleus (PbN) and the thalamus (VPM) to the primary gustatory cortex in the insula. Behavioral responses to food (and perceptions of flavor) are ultimately choreographed by the integration of gustatory information with other sensory modalities (such as olfaction, texture, etc.)

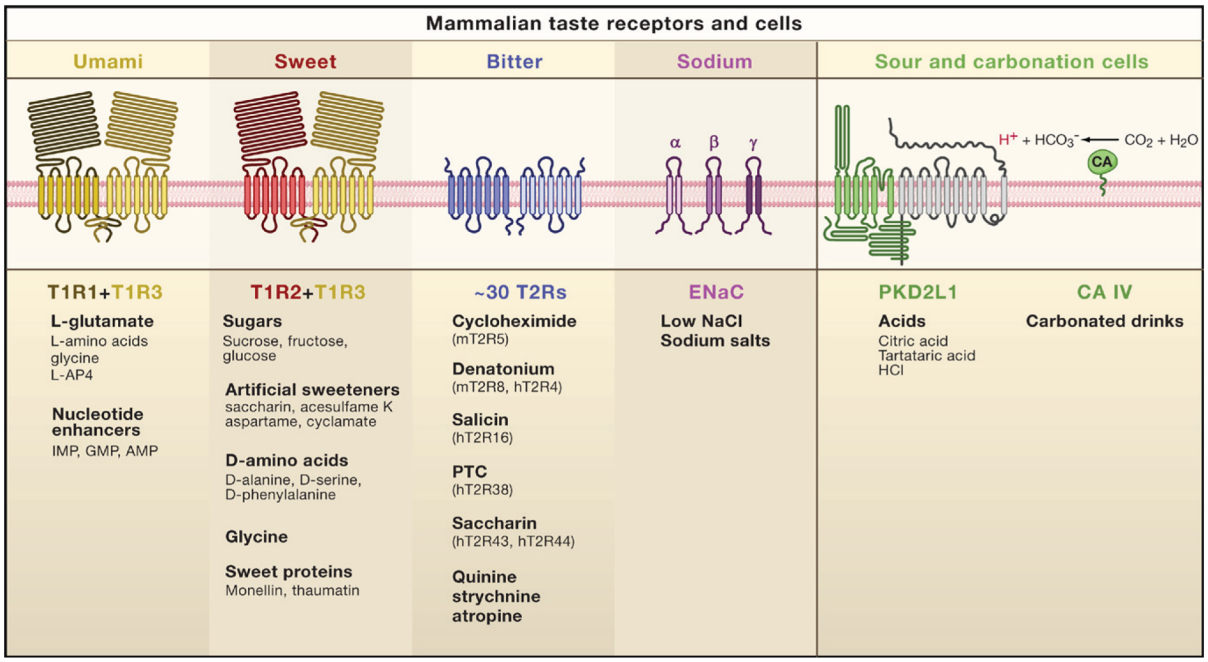

Figure 2. Mammalian Taste Receptors, Cells, and Ligands

Detection of the gustatory world is mediated by several distinct classes of taste receptors and taste receptor cells. Sweet and umami compounds are sensed by T1R heterodimers (Nelson et al., 2001, 2002; Li et al., 2002), while bitter compounds activate T2R receptors (Chandrashekar et al., 2000; Mueller et al., 2005; Meyerhof et al., 2005). Salt is detected via several mechanisms, one of which is thought to rely on the sodium channel ENaC (Heck et al., 1984). Sour-sensing cells are defined by the expression of PKD2L1 (Huang et al., 2006), whereas gustatory responses to carbonation are mediated by the membrane-tethered carbonic anhydrase CA IV (Chandrashekar et al., 2009).

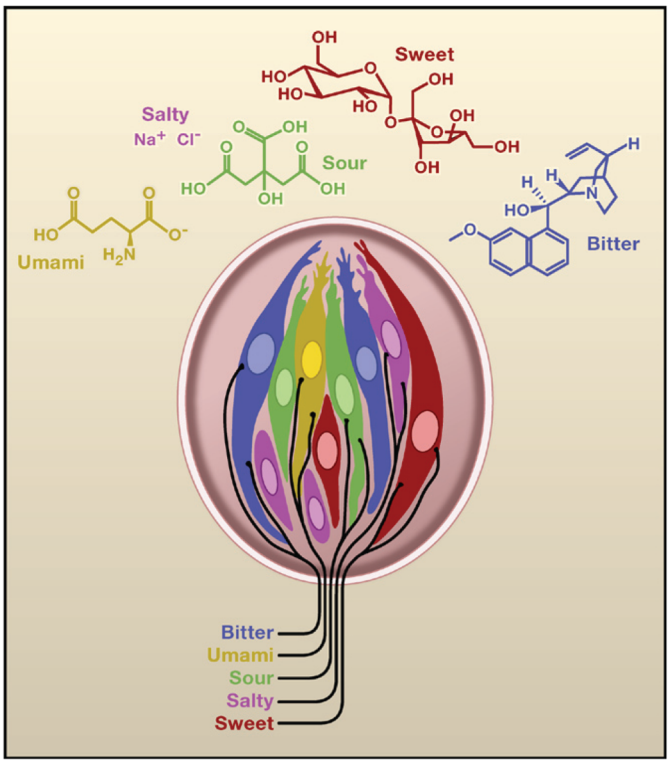

Figure 3. Labeled Lines Mediate Taste Sensation

It is now known that tastes to sweet (red), bitter (blue), sour (green), umami (yellow), and sodium (purple) are mediated by separate populations of selectively tuned taste receptor cells. Notably, taste buds from all regions of the oral cavity contain cells that respond to the five basic modalities. Thus, contrary to popular belief, there is no topographic map (i.e., a tongue map) of taste qualities on the tongue.

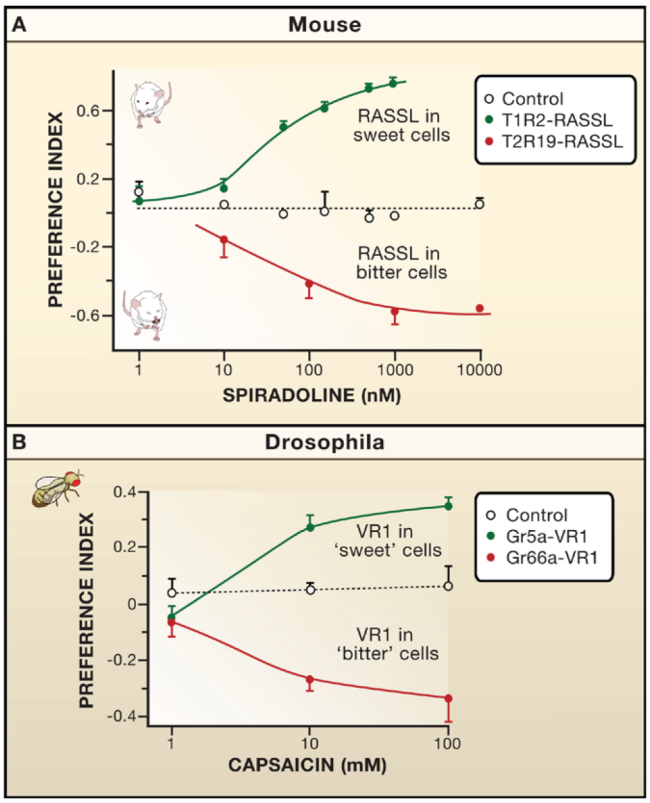

Figure 4. Behavioral Attraction and Aversion Are Hardwired

Mice and flies have converged on a similar organization of taste coding at the periphery. In both cases, dedicated cells tuned to selective taste qualities are hardwired to trigger specific behavioral responses. The synthetic opiate spiradoline is normally tasteless to mice (A, open circles). However, after targeted expression of the spiradoline receptor (RASSL) to sweet cells, mice exhibit dose-dependent attraction to spiradoline (Zhao et al., 2003). In marked contrast, directing expression of the very same RASSL receptor to bitter cells results in strong aversion to the ligand (Mueller et al., 2005). Similarly, activation of selective populations of gustatory receptor neurons in flies (B) mediates robust innate behavioral responses (Marella et al., 2006). Expression of the mammalian ion channel TrpV1 in sugar-sensing GRNs (Gr5a-TrpV1) results in strong behavioral preference for capsaicin. In contrast, expression of TrpV1 in the “bitter-responsive” Gr66a cells makes capsaicin an aversive tastant. Normal flies do not respond to capsaicin (open circles); preference index = (tastant − control)/total.

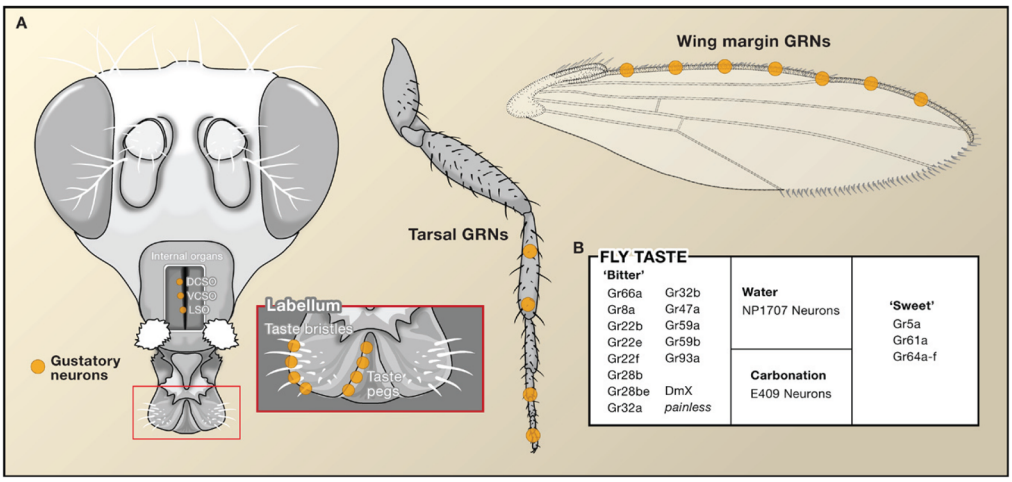

Figure 5. Fly Taste Reception

(A) Flies detect tastants via gustatory receptor neurons (GRNs) housed in sensilla distributed across the mouth parts (labella), legs, and wings. Stimulation of GRNs by appetitive tastants elicits extension of the proboscis to initiate feeding. Upon intake, food contacts GRNs in the taste pegs of the inner labellum and in the internal taste organs lining the pharynx (lateral sensory organ, ventral cibarial organ, and dorsal cibarial sensory organ).

(B) Like mammals, fly gustatory receptors are expressed into dedicated classes of GRN detecting distinct classes of attractive or aversive tastants. Most, but not all, sugar and bitter receptors are members of the “Gustatory Receptor” (Gr) gene family (Montell, 2009; Al-Anzi et al., 2006; Mitri et al., 2009). To date, several Grs have been linked to detection of specific attractive or aversive tastants. For example, mutants for Gr66a and Gr93a both show defective behavioral and physiological responses to caffeine (Lee et al., 2009); logically, as fruit flies are not normally exposed to caffeine, this receptor must be activated by ligands sharing structural features with caffeine. As for sugar detection, Gr64f is a candidate receptor required for responses to a wide range of sugars, including sucrose, maltose, glucose, and trehalose (Dahanukar et al., 2007; Jiao et al., 2008; Slone et al., 2007). In contrast, Gr5a is a narrowly tuned receptor for trehalose alone (Chyb et al., 2003). Thus, many receptors may recognize the same sugars, and a given sugar may act on several receptors (or receptor complexes). Carbonation and water are sensed by different subpopulations of GRNs (Fischler et al., 2007; Inoshita and Tanimura, 2006).