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Chapter

Understanding Taste Using *Drosophila melanogaster*

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Abstract

Taste is a short-range contact chemosensation required by all animals to detect nutrient rich foods and avoid consuming toxic chemicals. In insects, it is also required to select mates and appropriate oviposition sites. Organization of the fruit fly *Drosophila melanogaster* taste system and availability of experimental tool box, makes *Drosophila* gustatory system an ideal model system for studying the perception of taste and taste elicited behaviors. Like humans, fruit flies also respond to wide range of taste chemical and can differentiate between different taste categories including sweet, bitter, sour, umami and salt. This chapter will present a research progress made in the field of taste using neuroanatomical, genetic, behavioral, molecular and cellular biology techniques in the fruit fly. The compiled survey will provide an outlook of taste research done in fruit fly and its comparison with human taste behavior.

Keywords: *Drosophila*, gustation, neurons, taste receptors, taste behavior

1. Introduction

Animals including *Drosophila melanogaster* use their chemosensory system to monitor the chemical world around them. The chemosensory system includes olfactory system to detect volatile chemicals and gustatory system to detect soluble compounds. The olfactory and visual system helps in food detection and the taste system controls the food acceptance or rejection behavior by helping animals detect nutrient-rich food and avoid toxic substances. The quality and concentration of taste compounds help animals to make such an assessment.

Drosophila and mammals are able to detect basic taste modalities including sugars, bitter compounds, salt, acids, and amino acids [1]. The taste qualities are detected by taste cells present in the periphery. The activation of different taste cells provides a simple mechanism to encode modality. Like mammals' fly taste cells also show dose dependent activation providing the potential to encode different concentrations. The taste system of a fly is distributed over the whole-body, proboscis or labial palps being the main taste organ. It is located on the distal end of the labellum. Like other insects, the taste sensilla are present on labellum, legs, wings and on the female genitalia (**Figure 1**) [2].

The simplicity of the gustatory system of flies provides an ideal situation for comparative studies of taste perception and taste-elicited behaviors. The availability of the experimental tool box including high end imaging of neural circuits in the brain, simple behavioral assays, possibility of electrical recordings and ease

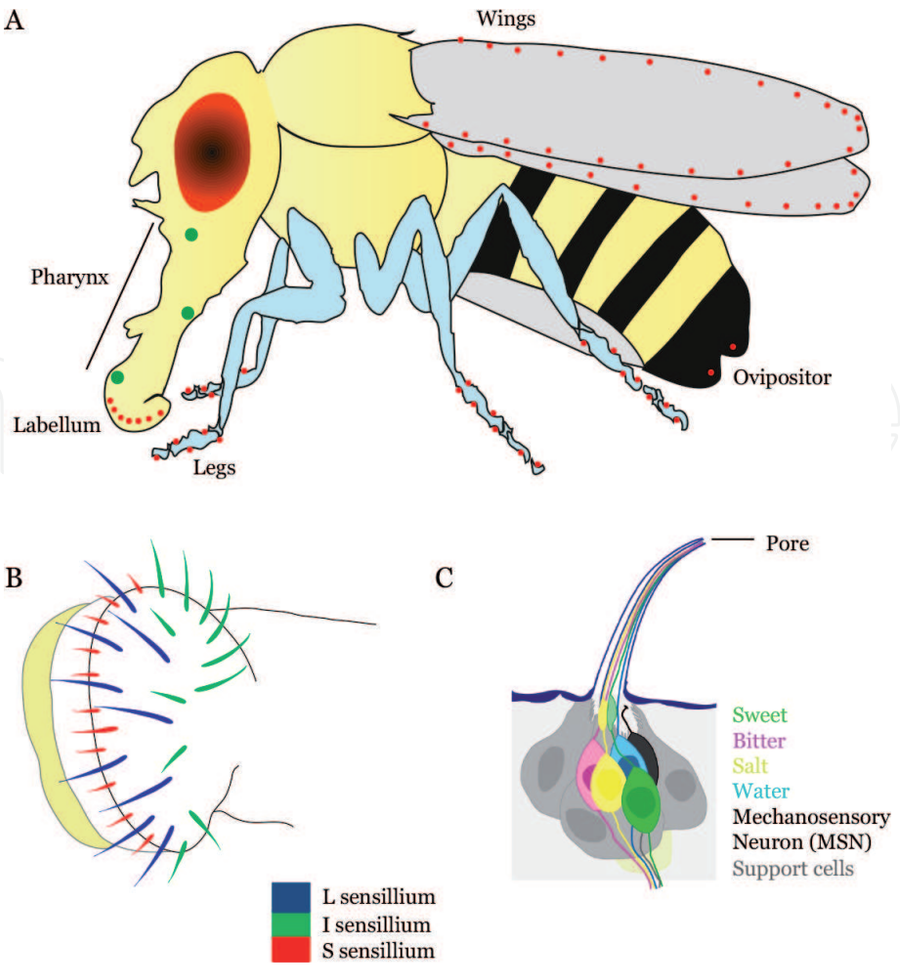


Figure 1.
Taste system of adult Drosophila. (A) Taste neurons are located on different body parts of fly namely labellum, pharynx, legs, wings and ovipositor as shown with red and green dots. (B) Three different types of taste sensillum (Large-L, Intermediate-I and small-S) present on the labellum (mouth part of a fly). (C) Taste sensillum structure showing pore at the tip and different types of taste neurons in a taste sensillum namely sweet (green), bitter (magenta), salt (yellow) and water (sky blue) neurons together with one mechanosensory neuron (black) surrounded by support cells (gray).

of molecular- genetics analyses with the availability of transgenic and mutant flies makes fly a unique system to study taste. In addition, flies share the same molecular logic of taste as mammals.

Different members of gustatory receptor (GRs) genes expressed in gustatory neurons mediate the detection of taste compounds such as sugars and bitter compounds [3–7]. Expression patterns of taste receptors is based largely on transgenic GAL4 expression studies and suggest that different GRs are expressed in overlapping but non-identical subsets of sugar- and bitter-sensing neurons [6–8]. In addition, electrophysiological studies from taste neurons suggest heterogeneity among the responses of individual sugar- or bitter-sensing cells [9–11] suggesting diversity among the peripheral cell types that detect sugars or bitter compounds in *Drosophila.* This organization provides the potential for different taste cell types to be activated by different compounds within a taste modality and the possibility for intra modality discrimination.

This chapter will present a research progress made in the field of taste perception in the fruit fly and will describe the anatomical properties of the *fly* gustatory system. We shall then review taste perception mainly from a molecular genetic perspective that includes the results from behavioral, electrophysiological and imaging analyses. The parallels between the flies and human taste system will provide insight into how the detection of taste compounds regulates feeding decisions.

2. Mammalian taste system

In humans, taste receptors cells (TRC's) helps in the detection of taste stimuli. TRC's are present in taste buds and palate epithelium at the back and sides of the tongue (circumvallate and foliate papillae). The taste buds called fungiform are scattered across the front of the tongue and on the palate. Three morphologically distinct cell types (I, II and III) are present in a taste bud and constitute five functional classes of sensory cells, each specialized to detect one of the five basic taste qualities (bitter, sweet, umami, sour and salty). TRCs are epithelial cells that extend a process to the apical surface of the epithelium, where a taste pore allows direct contact with chemicals in the environment. The life of taste cells is short and they replenish from proliferative basal keratinocytes [12]. TRCs can relay information of taste quality independent of cells relaying other taste qualities [13]. Neurotransmitter receptors are present on taste cells. TRC's release various neurotransmitters to communicate among cells in the taste bud to shape the output of the bud [14]. Vertebrate TRCs do not possess an axon, and instead are innervated by pseudo unipolar neurons whose cell bodies reside in the petrosal and geniculate ganglia. The chorda tympani nerve that (innervates the anterior tongue) contain fungiform papillae and the glossopharyngeal nerve, (innervates the posterior tongue and most of the palate) carry most of the taste information. Neurons from taste ganglia project to the nucleus of the solitary tract, and from there information is relayed to the gustatory cortex [15].

3. Gustatory system of *Drosophila*

Although the same taste preferences are shared between *Drosophila* and mammals, the organization of their gustatory systems are rather different. Unlike humans, flies have wide distribution of taste cells over much of the body including many peripheral organs like labellum, legs, wings and genitalia (**Figure 1**). Such a distribution of taste cells enables the fly to gather contact chemosensory information from many reference points that may make contact with their body enabling detection of potential calorie rich foods or toxic compounds [16]. The presence of taste-sensing cells in other tissues provides the safety benefits allowing evaluation of chemicals without the potential hazard of accidental ingestion. The gustatory sensillum or taste bristle are the main sensory unit of all taste organs housing two to four primary gustatory receptor neurons (GRNs) as well as a single mechanosensory neuron (MSN) [2]. The labellum is the main taste organ in *Drosophila* located at the end of the proboscis (equivalent to human tongue). Labial palps contain 31 bristles (sensilla) each that are arranged in a stereotyped pattern. The sensilla are morphologically classified into three types long, intermediate and short (L, I, and S type) based on their shape and location (**Figure 1**) [2, 17, 18]. L- and S-type sensillum house dendrites of four GRNs, and the I type are associated with two GRNs. Electrophysiological investigations suggest each GRN is thought to respond exclusively to either sugar, water, low salt concentration, or high salt concentration and bitter compounds [11, 19–22]. The terminal pore at the tip of the taste bristle (**Figure 1**) allows taste stimuli access to the dendrite of the GRN, which extends into the bristle shaft [23]. In addition to the peripheral taste sensillum on the palps, legs, and wings, taste neurons are also semi-internally or internally located. The first group consists of row of taste pegs that line the inside of the labial palps and are exposed to foods when the fly 'opens' its palps and readies itself for 'sucking up' foods. The internally located group consists of three sensillum clusters that line the pharynx (**Figure 1**). They allow re-evaluation of the food as it passes and enters

the esophagus and the digestive system. Peripheral labial palp GRNs, the internal sensillum, and some leg GRNs project their axons to the sub esophageal zone (SEZ), whereas the wing and a minority of leg GRNs project to the thoracic ganglion (**Figure 2**) [24, 25].

A single MSN and several support cells are also present in the taste sensilla together with the GRNs (**Figure 1**) [26]. These MSNs translate mechanical forces into electrical signals and mediate hearing, positional awareness, and the coordination of movements [27, 28]. The MSNs sense the hardness and viscosity of food [29] similar to the ability of the human tongue to determine the consistency and texture of foods.

3.1 Gustatory receptors of *Drosophila*

Like mammals, GRs in *Drosophila* also detect taste compounds. *Drosophila* utilize ion channels (Ionotropic receptors) to detect salts and sour (acid) compounds. Putative gustatory receptors in *Drosophila* and mammals were discovered almost simultaneously and detect sugars and bitter substances. Mammalian taste receptors belong to the large super family of GTP-binding (G) protein-coupled receptors (GPCRs), but fly GRs share no significant sequence similarity with them [4, 30–38]. A total of 68 *Gr* genes were found in *Drosophila* by analyzing the *Drosophila* genome database using algorithms that identify multi-transmembrane proteins or by performing reiterated Basic Local Alignment Search Tool searches with *Drosophila* olfactory receptor proteins as query sequences [4, 32, 38, 39]. The *Gr* genes are remarkably diverse having similarity between most receptor pairs only 20% or less

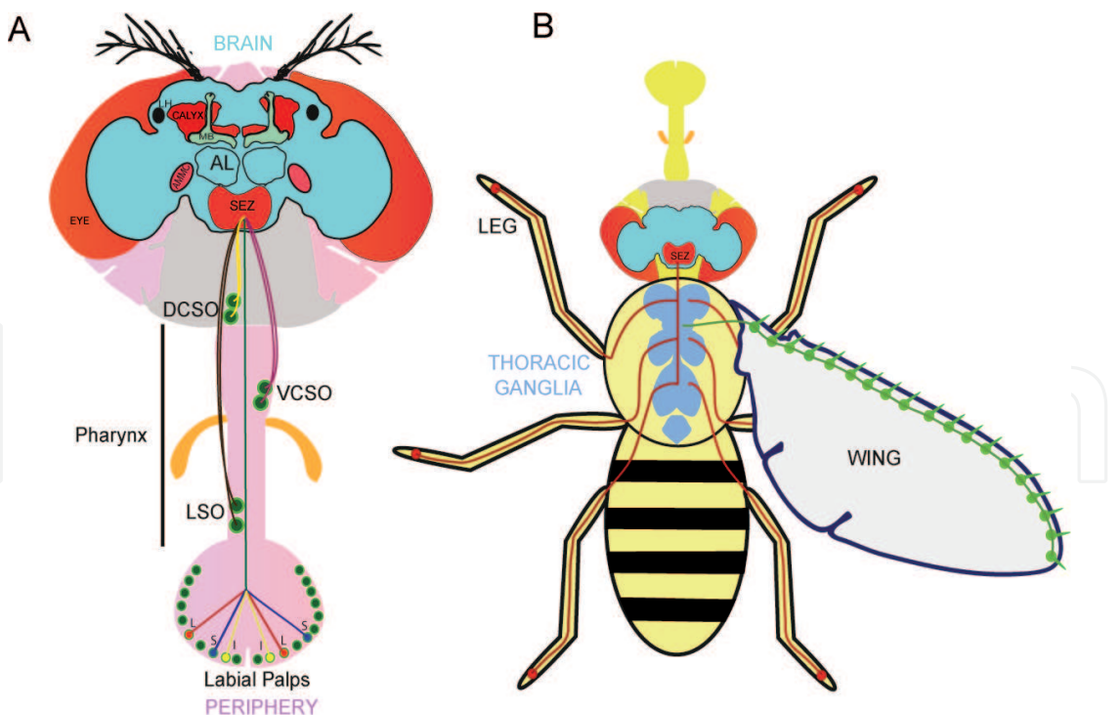


Figure 2.
(A) Taste neurons send projections from the periphery (neurons from different taste sensilla L,I and S) including pharyngeal areas (LSO-labral sense organ, VCSO-ventral cibarial sensory organ, and DCSO-dorsal cibarial sensory organ) to sub esophageal zone (SEZ) in the brain which is the main taste processing center. The taste information flow from SEZ to the antennal and mechanosensory motor center (AMMC). Mushroom body (MB), calyx and lateral horn (LH) are learning and memory centers. Antennal lobes (AL) get information from the olfactory neurons present on antennal surface in Drosophila. (B) GRNs from the legs of an adult fly (Red) send projections to SEZ and some GRNs project to thoracic ganglia only (shown in light blue). GRNs from the wing margins send axonal projections to thoracic ganglia (taste cells present in the wing shown in Green).

(at the amino acid sequence level). There are several gene clusters containing up to six genes, exhibit significantly higher similarity to each other (up to 70%). *Gr* genes with greater than 30% sequence similarity have been grouped into several subfamilies [32]. The domain that is most conserved among all *Gr* genes is located in the region encoding the putative seventh transmembrane domain at the carboxy terminus, a domain that is also shared with the olfactory receptors (ORs) genes this domain was used as a signature motif in one study that lead to the discovery of the fly taste receptors [32].

GRs within a subfamily detect structurally similar taste compounds. For example, the sugar receptor *Gr5a* subfamily consisting of *Gr5a* encoding a trehalose receptor [3, 40, 41] *Gr61a*, and *Gr64a–f* share sequence similarity in the range of 60% and detect diverse sugars [18]. Bitter compounds cover a vast chemically much more diverse structural space than sugars and majority of remaining GRs are devoted to the detection of bitter-tasting and toxic compounds.

Well established GAL4/UAS system, transgenic expression methods helped visualizing the expression of various *Gr* genes [42]. *Gr* gene promoters drive the expression of the yeast transcription factor GAL4 (regulate genes induced by galactose) and GAL4 in turn activates transcription with high specificity via the cis-regulatory element upstream activating sequence (UAS), cloned upstream of green fluorescence protein (GFP), or β-galactosidase reporter genes [42]. Expression analyses of *Gr* genes suggest that they are expressed in distinct subpopulations of GRNs, supporting their role as chemosensory receptors and providing first insights into their complex cellular expression [6, 7, 32, 38].

3.2 Types of taste receptors in mammals and *Drosophila*

The three tastes, bitter, sweet and umami taste are mediated by taste-specific GPCRs, which are expressed in distinct subsets of taste receptor cells in mammals [13]. These three taste employ a canonical G protein phosphoinositide-based pathway, where receptors activate a taste cell-specific G protein that activates PLCβ2, generating second messengers IP_3, DAG and H^+. IP_3 acts on the IP_3 receptor (IP_3R_3) to release Ca^{2+} from intracellular stores, and Ca^{2+} gates the membrane channel TRPM5 [43].

Drosophila taste receptors bear no sequence relationship to mammalian taste receptors. The majority of bitter and sweet taste receptors in insects are members of a large protein superfamily of gustatory receptors [4, 32, 38, 39]. The 68 members of *Drosophila* taste receptors have seven transmembrane domains, but they share no sequence relationship to GPCRs. Rather, they are distantly related to *Drosophila* olfactory receptors (ORs), which have an opposite membrane topology from GPCRs and form ligand-gated ion channels [44–46]. Insect GRs including *Drosophila* have an inverted topology like ORs relative to GPCRs [47] and may form ionotropic receptors [48].

3.2.1 Sweet receptors

Highly concentrated sugars (100–500 mM), artificial sweeteners, and small number of sweet-tasting proteins elicit the sweet taste in mammals. The heterodimer of T1R2 and T1R3 constitutes the sweet receptor [49]. Animals also sense energy-rich foods and various sugars through a mechanism similar to that used by pancreatic β-cells to detect blood glucose [50]. According to this hypothesis, the metabolism of sugars by sweet cells produces ATP, which closes ATP-sensitive K^+ channels leading to membrane depolarization [50].

Flies are attracted to many of the same sugars as humans [9, 51] although they respond most robustly to disaccharides (such as sucrose and maltose) and

oligosaccharides [8]. The fly sweet receptors belong to the same superfamily of receptors that includes most of the bitter receptors. In adult flies the three key receptors required for sensing sugars, except for fructose, are Gr5a, Gr64a and Gr64f [8, 40, 52–54]. These three receptors are co-expressed in the sugar-responsive GRNs in the labellum, along with five other related GRs that comprise the *Gr*-Sugar (*Gr*-S) clade [8, 52].

Gr5a and Gr64a sense structurally different sugars. Gr64a participates in the response to sucrose and maltose [8, 52], while Gr5a detect trehalose and melezitose [8, 40, 41]. Gr64f might act as a co-receptor for the responses for all sugars tested except fructose, and functions in concert with Gr5a and Gr64a [53]. Gr43a is the only receptor known to detect fructose [55].

3.2.2 Bitter receptors

Bitter taste allows animals to detect toxins in the environment and avoid consuming them. Compounds such as caffeine, cycloheximide (a protein synthesis inhibitor), denatonium (added to rubbing alcohol to discourage consumption), and quinine (a component of tonic water) taste bitter to humans, mice and flies. In vertebrates, bitter chemicals are detected by a small family of receptors (T2Rs), which are structurally related to rhodopsin, and range in number from 3 to 49, depending on the species [31, 34, 56]. In general, each bitter responsive taste receptor cell expresses multiple types of bitter receptors [57], but not all bitter receptors are expressed by every bitter cell [58], leading formally to the possibility that there are subclasses of bitter cells, as is the case in flies [59]. The chemical receptive field of the bitter receptors fall into two classes—"specialists" that detect one or a few bitter chemicals and "generalists" that detect many [60].

In contrast to vertebrate bitter detection, flies employ a much more complex strategy to sample bitter chemicals. In flies, bitter sensitive GRNs have distinct sensitivities. Based on the response profile to a panel of 16 bitter compounds, the L-, I- and S-type sensilla on the labella are classified into five groups, four of which are sensitive to bitter chemicals (**Figure 1**) [59]. Out of the four, two groups are narrowly tuned to distinct sets of bitter compounds (I-a and I-b). The other two groups respond broadly to bitter tastants but have variable patterns of activity (S-a, S-b). Analysis with a larger panel of bitter compounds may reveal more additional subgroups.

In flies, 33 out of 38 *Gr* genes that express in the labellum are found to be localized to bitter GRNs [59]. The roles of only a few of the bitter GRs have been dissected genetically so far. A minimum of 28 *Gr*s can be expressed by some GRNs in the labellum in adult fly. One of the larval GRN classes expresses at least 17 *Gr*s [59, 61]. Many GRs act as co-receptors responding to large numbers of aversive chemicals. *Gr32a*, *Gr33a* and *Gr66a* are needed for detection of most bitter chemicals [62, 63]. These three *Gr*s with additional *Gr*s (*Gr89a* and *Gr39a.a*) are expressed in all bitter responsive GRNs making this group of five GRs to be the "core-bitter GRs" [59]. Other GRs are very narrowly tuned and confer ligand specificity. These receptors are critical in defining the chemical specificity of the GRs, in combination with other GRs. Different combinations of complex sets of GR receptors may explain how a limited number of bitter GRs confer the capacity to respond to a vast collection of structurally diverse bitter compounds. Three TRP channels expressed in the labellum GRNs also contribute to the sensation of aversive compounds through mechanisms that are independent of GRs. TRPA1 show behavioral avoidance to aristolochic acid [64], a related TRPA channel Painless, is required for the behavioral avoidance to isothiocyanates (AITC;

wasabi) [65] and TRP-Like (TRPL) is both necessary and sufficient to confer sensitivity to camphor [66].

3.2.3 Salt taste receptors

Moderate levels of salt is necessary to maintain the important physiological functions such as muscle contraction, action potentials and many other functions while excessive salt intake is deleterious and can lead to hypertension. Salty taste is elicited by Na^+ concentrations ranging from 10 to 500 mM. In humans, salt taste is amiloride-insensitive. The amiloride sensitive component of salt taste is selective for Na^+ and Li^+ over other monovalent cations such as K^+, is sensitive to low concentrations of salts (<100 mM), and is generally appetitive [67]. Amiloride-sensitive salt taste occurs only in the front of the tongue [68]. Based on taste nerve recordings, there is a population of broadly tuned high-salt fibers that are insensitive to amiloride and activated by KCl and NaCl [69]. These fibers innervate both the front and back of the tongue, in contrast to the amiloride-sensitive fibers that innervate only the front of the tongue. Epithelial Na^+ channels (ENaCs) are composed of three subunits—α, β and γ and α subunit is absolutely essential and forms part of the pore [70]. ENaC α has been suggested to be a component of the low salt sensor since a taste-cell specific knockout eliminates sensitivity and behavioral attraction to low concentrations of salt [71].

The cells that mediate the behavioral responses to high salts are not specifically dedicated to sensing high salt, but instead comprise at least two populations of cells with previously identified functions in sensing bitter and sour [72]. Inactivation of TRPM5 or PLCβ2, expressed by bitter cells, eliminates a component of the high salt response, while silencing PKD2L1-expressing sour cells eliminates the remaining components [72]. Remarkably, mice in which PKD2L1-expressing cells are silenced and TRPM5 is inactivated find high salt concentrations attractive, presumably due to activation of the amiloride-sensitive ENaC channels by high salt [72].

Salt taste preferences in *Drosophila* are similar to those in mammals. Both larvae and adult fruit flies prefer low-salt foods, while they reject high-salt concentrations. Two ENaC channels family members, *ppk11* and *ppk19* are reported to be expressed in the terminal organ and required for sensing low salt [73] in *Drosophila* larvae. However, these channels do not appear to function in the salt response in adults [74]. A member of the ionotropic glutamate receptor (IR) family member, Ir76b, is required for low salt sensing in adult flies [74]. IRs were identified originally as a new class of olfactory receptor [75]. However, several IRs are also expressed in GRNs [76]. Ir76b is expressed in GRNs distinct from those that respond to sugars and bitter compounds, and the Ir76b GRNs extend their projections into a unique region of the SEZ [74]. Most recently combined activity of most of all GRN classes encoding salt taste has been proposed [77].

3.2.4 Sour taste

Acidic pH and organic acids such as acetic acid evokes sour taste in the tongue. A subset of taste receptor cells in the tongue and palate epithelium that respond to acidic pH and weak organic acids with electrical activity detects the sour taste [78, 79]. PKD2L1-expressing cells respond are required for sensory response to acids [72, 78, 80] which is mediated by an unusual proton-selective ion channel [80]. Proton selectivity allows the cells to respond to acids without interference from Na^+, which may vary independently in concentration. The taste of carbonation (CO_2) is also detected by PKD2L1-expressing cells. This response is

dependent on a membrane anchored carbonic anhydrase isoform 4, Car4 [81], which interconverts $CO_2 + H_2O$ to $H^+ + HCO_3^-$. How Car4 contributes to the activation of sour cells is still not known.

Fruit flies reject foods that are too acidic and prefer the ones which are slightly acidic, such as carbonated water. Carbonated water triggers Ca^{2+} influx in the region of the SEZ innervated by taste peg GRNs, suggesting these neurons are involved in CO_2 detection [82]. Fruit flies avoid many carboxylic acids with a low pH. Behavioral and physiological analysis reveals that the avoidance to carboxylic acid is mainly mediated by a subset of bitter GRNs [83]. The ionotropic receptor Ir7a has been shown for rejecting foods laced with high levels of acetic acid suggesting flies discriminate foods on the basis of acid composition rather than just pH [84].

3.2.5 Amino acid receptors

Umami (amino acid taste) is the sensation elicited by glutamate. In humans, umami is only elicited by glutamate, while mice are sensitive to a wider range of L-amino acids [1]. Addition of the nucleotides IMP or GMP potentiates the umami response, distinguishing it from a more general sensing of glutamate [85]. T1R1/T1R3 is widely recognized as the umami receptor [1].

Fruit flies can taste amino acids too, although their preference is enhanced when raised on a food source devoid of amino acids [86]. Female fruit flies show greatest preference for cysteine, phenylalanine, threonine and tyrosine, while males prefer leucine and histidine. None of the 18 standard amino acids tested stimulates action potentials in GRNs in sugar responsive sensilla [8] raising the possibility of taste pegs in sensing amino acids. Another amino acid, L-canavanine is toxic and elicits an avoidance response in flies [87] and is sensed by GRNs in a subset of S-type sensilla [88]. Gr8a and Gr66a are both required for L-canavanine avoidance [88]. An ionotropic receptor Ir76b has been shown recently for amino acid taste in flies [89].

Activation of fly GRNs by sweet substances, bitter compounds and the amino acid, L-canavanine occur through direct activation of ion channels and G-protein signaling pathways. G proteins subunits Gγ, $G_o\alpha$, $G_s\alpha$ and $G_q\alpha$ are implicated in sugar signaling [90–93]. PLCβ is an effector for $G_q\alpha$. Knockdown in sugar-responsive GRNs of *plcβ21c* or any of the genes encoding TRPC channels (TRP, TRPL and TRPγ) alters the behavioral response to trehalose [92]. Role of G-protein coupled signaling pathways in sensation of bitter tastants has also been suggested for example AC78C is required for the response to caffeine [94], and the PLCβ encoded by *norpA* is required in *trpA1*-expressing GRNs for the behavioral and electrophysiological responses to the bitter compound, aristolochic acid [64] suggesting a role of Gq/PLC/TRPA1 pathway functions in the detection of aristolochic acid. $G_o\alpha$47A is needed for detection of L-canavanine [95]. The predicted role of G-protein coupled signaling pathways in insect taste is to enhance the responses to low concentrations of ligands, as seen for photo transduction cascade in amplifying the response to a photon of light.

3.3 Taste coding

Taste in flies and mammals use labeled line model of coding (in which each cell represents a distinct taste quality and communicates essentially without interruption to the central nervous system). Single taste neurons in flies can detect multiple taste qualities having the same valence (behavioral output) supported by the results that some GRNs are activated by sugars, and low levels of fatty acids,

both of which promote feeding [96] while other GRNs are activated by bitter compounds and high concentrations of salt and suppress feeding [20]. In addition, a subset of bitter GRNs is also activated by low pH carboxylic acids, which are feeding deterrents [83]. A complex model for salt coding in flies that combinatorially integrates inputs from across cell types to afford robust and flexible salt behaviors [77].

The taste system of mice also uses a variant of the labeled line model. In mice, taste receptors are segregated into distinct populations such that bitter, sweet, sour and low concentrations of salt are detected by non-overlapping sets of cells [1, 58]. Whether this principle applies to sweet and umami is presently unclear. Recent evidence suggest that aversive high concentrations of salt are not detected by a separate subset of cells, but are instead detected by the populations of cells that detect bitter and sour [72] suggesting that the mammalian taste system is relatively hard-wired to behavior, as is the case in flies.

3.4 Taste modulation in *Drosophila*

Modulation of taste neuron activity prior to the first relay has been suggested. Presence of multiple molecular and cellular mechanisms by which tastant information is integrated in primary taste neurons has been proposed [97]. Various studies suggest that aversive tastants such as bitter compounds and acids, can inhibit the activity of appetitive taste circuits in adult flies and larvae [83, 98, 99]. The reduction of the firing rate of sweet neurons in mixtures of sucrose and the aversive tastants is independent of the activity of the deterrent neuron [83, 98, 99]. Bitter compounds suppress feeding by activating bitter—GRNs and by inhibiting sugar—sensitive GRNs [11]. The suppression of sugar GRNs depends on a odorant binding proteins" (OBP), OBP49a, which is expressed in gustatory organs or indirectly via GABAergic interneurons that connect bitter taste neuron activity to that of sweet taste neurons [100, 101]. Accessory cells synthesized OBP49a and release it into endolymph fluid bathing the GRNs, which then acts non-cell autonomously on sugar activated GRNs. OBP49a binds directly to bitter compounds, and later interacts with the sugar receptor, Gr64a, on the cell surface of the GRNs to suppress its activity [101]. Such non-cell autonomous modulation of the sugar response ensures that bitter compounds in sugar-laden foods are not consumed. Low concentrations of acid tastants have also been observed to modulate detection of bitter compounds in the context of both sweet and deterrent neurons, suppressing their inhibitory effect in the former and their excitatory effect in the latter [102]. Although the mechanisms by which carboxylic acids or low pH inhibit taste neurons remains to be determined.

Internal state can change the gustatory sensitivity as well: starvation potentiates the responses of sweet GRN and suppresses bitter GRN responses; mating increases taste peg GRN sensitivity to polyamines and behavioral responses to low salt in females; and protein deprivation sensitizes taste peg GRNs to yeast and increases behavioral sensitivity to amino acids [86, 103–108]. Taste neuron sensitivity is also modulated by prior dietary experience. Response to camphor (non-toxic bitter compound) decrease after exposing flies to camphor for long [66]. An E3 ubiquitin ligase-regulated decline in the levels of Trpl caused the change in sensitivity. No calories diet also cause increase activity in the *Gr5a+* sweet taste circuit [104, 109] and reduce sensitivity in the bitter taste circuit [105]. In the former case, dopamine signaling acting on the both primary and secondary neurons in the sweet circuit caused the change in sensitivity [104, 109]. The latter is dependent on sNPF acting via GABAergic interneurons [105]. A significant modulation of fly salt taste behavior by salt deprivation has been shown recently [77].

3.5 Non-canonical taste qualities

3.5.1 Fats

Vertebrates can sense a variety of other important taste qualities such as wetness and fattiness. Olfaction and somatosensation helps in the detection of fats, and they elicit post-ingestive effects that promote consumption. It has been shown that mice prefer water spiked with free fatty acids supports a role for the taste system in detecting this rich source of calories [110]. A fatty acid transporter (CD36) and two fat-sensitive GPCRs—GPR40 and GPR120 are putative receptors for fat taste including K^+ channels that are sensitive to polyunsaturated fatty acids [111]. GPR120 is required for preference to fatty acids in mice [112] and is expressed in human TRCs as well [113].

In flies, sweet GRN activation requires the function of the three *Ionotropic receptor* genes *Ir25a*, *Ir76b* and *Ir56d*. *Ir25a and Ir76b* are expressed in several neurons per sensillum, while *IR56d* expression is restricted to sweet GRNs. *Ir25a* and *Ir76b* mutant flies loose appetitive behavioral responses to fatty acids. The phenotype can be rescued by expression of respective transgenes in sweet GRNs [114].

3.5.2 Calcium taste

Ca^{2+}, an ion is required for a vast array of cellular functions. Ca^{2+}-deprived animals show attraction and Ca^{2+}-sated animals show rejection. The aversive response to Ca^{2+}requires a functioning T1R3 receptor, a subunit of the umami and sweet receptor [115]. In human subjects an attenuation of the taste of Ca^{2+} by the T1R3 blocker lactisole has been shown [116].

Fruit flies avoids toxic levels of calcium. This repulsion is mediated by two mechanisms—activation of a specific class of GRNs that suppresses feeding, and inhibition of sugar-activated GRNs, which normally stimulates feeding. The distaste for Ca^{2+}, and electrophysiological responses to Ca^{2+} require three members of the variant ionotropic receptor family Ir25a, Ir62a and Ir76b. The high concentrations of Ca^{2+} show decrease survival in flies [117].

3.5.3 Water

No water receptor has been identified in vertebrate so far. The somatosensory system of animals can detect wetness across their body and also contribute to the sensing of aqueous solutions in the oral cavity. Various tastes have been ascribed to distilled water, from bitter to salty and sweet. Notably, application of water after exposure to some artificial sweeteners, such as saccharin, elicits a sweet taste [118].

A member of the Degenerin/Epithelial Sodium Channel family, ppk28 (an osmosensitive ion channel) mediates the cellular and behavioral response to water in flies. *ppk28* is expressed in water-sensing neurons and loss of *ppk28* abolishes water sensitivity [119].

3.6 Taste signal processing and taste sensory maps in the *Drosophila* brain

In flies, after evaluation of taste input, the information translates into an appropriate behavioral response such as feeding, cessation of feeding, search for alternative food source, courtship, or egg-laying. Detection of sweet compounds by labellum GRs induces a sucking response and sugar detection by the tarsi induces extension of proboscis. It is a requirement to understand the flow of information

from peripheral activation of GRNs to behavioral output to gain insight into the neuronal wiring of the taste at each level of information processing.

Unlike mammalian taste cells, fly GRNs from labellum and pharynx send projections of axons directly to the SEZ area of the brain. GRNs in the ovipositor, wings, and some leg sensilla send projections to the thoracic ganglia [24, 25]. Taste neurons send their axons to loosely defined, widely circumscribed zones in the SEZ or thoracic ganglia [32]. Labial palp *Gr5a* positive GRNs project to large areas in the lateral and anterior region of the SEZ, whereas the *Gr66a*-expressing GRNs project to the medial part of the SEZ [6, 7]. Information from GRNs of the legs activates non-overlapping areas of the SEZ than GRNs of the labial palps, suggesting different behavioral outputs of neurons responding to the same ligand but located in different taste tissues. Functional domains of taste have been mapped in the brain using live flies expressing the calcium-sensitive indicator G-CaMP [120] (G-CaMP protein is a fusion of the calmodulin-binding domain from the myosin chain kinase (M13 peptide), permutated EGFP and the calmodulin) in response to sugars and bitter compounds suggesting different taste compounds activate distinct neural ensembles in the SEZ. In terms of their taste quality, organ location, and in some cases sensillar type, at least 10 categories of patterns have been defined in the SEZ and nine in the thoracic abdominal ganglia. Each category is a unique combination of discrete patterns elements that define taste neurons [97].

The SEZ is a primary gustatory center, the higher brain centers where taste information is conveyed from the SEZ are unknown. Recently, sweet second order projection neurons that relay sweet taste information from the SEZ to the antennal and mechanosensory motor center (AMMC) in the deutocerebrum were described [109]. The results support the role of AMMC (generally receives input from mechanosensory and olfactory neurons) in processing multisensory information. Various other studies have identified interneurons that impinge on taste circuits and feeding behavior routines, including a feeding promoting command neuron, feeding promoting dopaminergic neurons, bitter sensitive projection interneurons, feeding restrain GABAergic neurons and neurons in the ventral nerve cord that balance feeding and locomotion [121–126].

The taste representations in the mushroom bodies (MB) (sites for associative learning) examined recently and found that input to the main calyx continues to be segregated according to taste modality and the location that taste information originates from. The bitter and sweet stimuli activate distinct areas, and stimuli from different taste organs activate partially overlapping but distinct patterns [127]. The information about water and sweet qualities, as well as nutritive and non-nutritive sugars is also separated in MB [128, 129]. Unraveling taste circuits, therefore, will be important not only for understanding how sensory input is translated to behavioral output, but also how taste associations are formed in reward and aversive learning [97].

4. Conclusions

Drosophila Grs, IRs, Trp, and ppk receptors underlie detection of various categories of tastants but a lot remains undetermined about the composition and response properties of taste receptors. How combinations of GRs and IRs belonging to different receptor families (e.g. Gr and IR), coordinate within the neurons that house them is a subject of investigation. Feeding behavior is root cause of metabolic disorders. A better understanding of the biology of metabolic disorders in association with GRs, IRs, Trp, and ppk receptors is a need of the hour because of the burden of metabolic disorders, high incidences of cardiovascular diseases, faster

aging, dependence on readymade food and consumption of unhealthy junk food in kids. A better understanding of the IRs and other receptors, neural circuits, higher order neurons involved in taste modulation as well as food regulation could provide us with a better understanding about human metabolic disorders and lead to a subsequent development of treatment strategies ultimately benefitting mankind. Recent reports invite exciting new avenues of investigation to determine the higher brain locations that receive taste input from the AMMC, and to trace the circuits by which information is relayed to motor neurons and neurons of the mushroom body to control feeding behavior and associations with appetitive and aversive learning.

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Conflict of interest

The authors declare no conflict of interest.

Criteria for authorship

SK and PK both substantially contributed to the conception and design of the work. Both participated in drafting and revising the work, made the figures, wrote the chapter and approved the final version for publication.

Abbreviations

GRs	Gustatory receptors
TRCs	Taste receptors cells
GRNs	Gustatory receptor neurons
MSN	Mechanosensory neurons
SEZ	Sub esophageal zone
IRs	Ionotropic receptors
GPCRs	G-protein coupled receptors
OR genes	Olfactory receptor genes
GFP	Green fluorescence protein
UAS	Upstream activating sequence
TRP	Transient receptor potential
TRPL	Transient receptor potential-like
ENaCs	Epithelial Na^+ channels
OBP	Odorant binding proteins
AMMC	Antennal and mechanosensory motor center
MB	Mushroom bodies
IP_3 receptor	Inositol 1,4,5-triphosphate receptor
DAG	Diacylglycerol
norpA	No receptor potential A
plc	Phospholipase C
PKD2L1	Polycystic kidney disease 2-like 1
Car4	Carbonic anhydrase isoform 4

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sNPF	Short neuropeptide F
GABA	Gamma-aminobutyric acid
ATP	Adenosine triphosphate
IMP	Inosine monophosphate
GMP	Guanylate monophosphate
ppk	Pickpocket

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