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Drosophila chemoreceptors: A molecular interface between the chemical world and the brain

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Abstract

Chemoreception is essential for survival. Feeding, mating, and avoidance of predators depend on detection of sensory cues. *Drosophila* contains diverse families of chemoreceptors that detect odors, tastants, pheromones, and noxious stimuli, including receptors of the Or, Gr, IR, Ppk, and Trp families. We consider recent progress in understanding chemoreception in the fly, including the identification of new receptors, the discovery of novel biological functions for receptors, and the localization of receptors in unexpected places. We discuss major unsolved problems and suggest areas that may be particularly ripe for future discoveries, including the roles of these receptors in driving the circuits and behaviors that are essential to the survival and reproduction of the animal.

Keywords

Odor receptor (Or); Gustatory receptor (Gr); Ionotropic glutamate receptor (IR); Olfactory Receptor Neuron (ORN); Olfaction; Taste

The problem

Animals in their natural environments are immersed in a sea of chemical compounds. Some of these compounds signal the presence of nutrients, while others signify the danger of poisons. Some compounds indicate the proximity of a mating partner, while others warn of a predator. Animals must be able to detect and identify a wide variety of meaningful signals among the vast complexity of their chemical milieu.

In addition to chemical identity, chemical intensity can also be critical to an animal. The quantity of a sugar in a food source reflects its nutritive value, just as the quantity of a bitter compound such as strychnine may reflect its toxicity. Moreover, some stimuli are attractive at low concentrations and aversive at high concentrations. The temporal pattern of the stimulus is also important. For example, it may inform an animal of the proximity of an odor source.

This, then, is the problem: how to detect and interpret a wide variety of chemical signals amidst a cacophony of chemical noise. The signals are enormously diverse in chemical and temporal structure, and the ability to identify and quantitate them may be a matter of life and death.

This review discusses recent progress in understanding chemoreception, which is the foundation of all the perceptual processes and behavioral responses that follow. We focus on the chemoreceptors of *Drosophila*, which provides a powerful genetic model for the study of chemosensory reception. Although there has been great progress in the field, it is clear that critical problems remain to be solved and that major discoveries are in store.

The cellular context of chemoreception

Volatile compounds are sensed by olfactory receptor neurons (ORNs) of the olfactory system, whereas non-volatile compounds are detected by gustatory receptor neurons (GRNs) of the taste system. That said, the conceptual wall dividing olfaction and taste has been increasingly assaulted by a barrage of experimental results that establish new links between the two sensory modalities.

The adult olfactory system

The fly contains two olfactory organs, the antenna and the maxillary palp (Fig. 1). Both are covered with sensilla, sensory hairs that contain the dendrites of up to four ORNs (Fig. 2A) [1, 2]. The shafts of sensilla are perforated by numerous pores, or channels, through which odorants can pass. The ORN cell bodies lie below the sensillar shafts, adjacent to accessory cells. These cells secrete odorant binding proteins (OBPs) into the lymph that bathes the ORN dendrites [3]. OBPs are widely believed to carry odorants to odor receptors in the dendritic membranes, although other functions have been proposed (Box 1). ORNs project axons to the antennal lobe of the brain, where signals are processed and transmitted to higher-order centers [4].

Most olfactory sensilla fall into three morphological classes [2, 5, 6]. Basiconic sensilla are located on the antenna and maxillary palp, and detect many food odors, including esters, alcohols, and aldehydes. Trichoid sensilla are found on the antenna and detect fly odors, including pheromones. Coeloconic sensilla are found on the antenna and respond to many acids and amines.

The adult gustatory system

Drosophila contains GRNs in a variety of locations [1, 7] (Fig. 1). The labellum, on the proboscis, contains gustatory sensilla that have a single, large pore at the tip (Figure 2B). Many labellar sensilla contain four GRNs, and in some cases one neuron is sensitive to sugars, one to bitter compounds and high concentrations of salt, one to low concentrations of salt, and one to water, *i.e*. osmolarity. Shorter structures called taste pegs are also located on the labellum; they house a single sugar-sensitive GRN.

The legs also contain taste sensilla [7–9], allowing the fly to sample potential food sources before making contact with the mouthparts. Some leg sensilla contain a sugar-sensitive

neuron but not a bitter-sensitive neuron, while others contain a bitter-sensitive neuron but not a sugar-sensitive neuron. Other sensilla have both; still others have neither, leaving a large number of “orphan neurons” whose sensitivities and ligands should be a fertile topic of future exploration.

The anterior margin of the wing contains chemosensory sensilla, which were found to respond to tastants in pioneering studies of Marion-Poll and others [5, 10]. Sensilla on the ovipositor of larger flies have been shown electrophysiologically to have gustatory function [11, 12]. In *Drosophila*, sensilla on the distal tip of the female abdomen exhibit morphology and innervation patterns suggestive of taste function [5, 13], but functional data to support this suggestion are sparse.

Flies also contain internal taste cells [14]. For example, the labral, ventral, and cibarial sense organs (LSO, VCSO, DCSO) of the adult pharynx contain sensilla that house up to eight neurons [5]. These neurons project dendrites into pits that open into the esophageal lumen. Post-ingestive nutrient monitoring also occurs in the brain [15, 16], and presumably in enteroendocrine cells of the midgut [17].

The larval chemosensory system

Larvae hatch on food sources and then burrow into them, emerging only in the final phase of larval life to pupate. During most of larval life, therefore, chemical stimuli seem likely to reach the larva primarily via fluids rather than air. In experimental paradigms, however, larvae of all instars respond to airborne odorants [18, 19]. The primary olfactory organ, the dorsal organ (DO), contains both ORNs (n~21) and GRNs (n~9)(Fig. 3). Two other external taste organs, the terminal organ (TO) and the ventral organ (VO) also contain GRNs [20, 21]. Internal chemosensory organs line the larval pharynx and contain small numbers of GRNs as well [20, 21]. Interestingly, some of the pharyngeal GRNs are among the few larval sensory neurons to survive remodeling during metamorphosis, being incorporated into some of the adult pharyngeal sensory organs [22].

The largest families of chemoreceptors

Chemoreceptors of the fly are numerous and sundry (Fig. 4). A recurrent source of excitement in the field has been the discovery of new kinds of chemoreceptors. Below we describe the largest classes of chemoreceptors. We also introduce some additional classes of chemoreceptors in Box 2. Other kinds of receptors may well lurk in the genome of the fly, awaiting discovery.

Odor receptors (ORs)

The *Drosophila melanogaster* genome contains 60 *Or* genes, which are predicted to encode 62 seven-transmembrane-domain proteins via alternative splicing [23]. These proteins have little if any sequence similarity to the odor receptors of vertebrates or *C. elegans*, which are G protein-coupled receptors (GPCRs). Moreover, the membrane topology of Ors is distinct from that of GPCRs [24]. Heterologous expression studies have provided evidence that Ors can function as ligand-gated ion channels and can transduce olfactory information independent of G proteins [25–27]; however, a role for G proteins in olfactory signaling has

been supported by several studies, and the mechanism of Or-mediated transduction remains an active topic of investigation [28–30].

Most ORNs of basiconic and trichoid sensilla express a single member of the Or family, which confers the odorant response profile of the neuron [31, 32]. These neurons also express a co-receptor, Orco, which heterodimerizes with the Or and is essential for the targeting of the complex to the dendritic membrane [33].

The response profiles of Ors have been characterized in detail by expressing them in an *in vivo* expression system called the “empty neuron” system [32, 34]. This system is based on a mutant neuron that lacks an endogenous Or and does not respond to odorants. An individual Or may be expressed in this neuron via the *GAL4-UAS* system and the odorant responses that it confers are measured by singleunit electrophysiology. The response profiles conferred by many Ors were found to match closely with the response profiles of specific ORN classes of the wild type antenna, which supported the fidelity of the expression system and allowed construction of a receptor-to-neuron map of the antenna [32]. This map was confirmed and extended by molecular analysis, providing a near-complete map of Or expression in the fly’s olfactory organs [31, 35].

Ectopic expression of *Or* genes revealed that Ors dictate several properties of ORN response [32]. The odor response spectrum, the mode of response (excitation v. inhibition), the termination kinetics, and the level of spontaneous activity all depend on the receptor. An individual receptor can mediate both excitatory and inhibitory responses to different odors in the same cell. Systematic functional analysis of the Or repertoire revealed that some receptors were narrowly tuned and others broadly tuned with respect to a panel of 110 diverse odorants [36]. Tuning depends on concentration: receptors that respond broadly to high concentrations of odorants respond to a narrower range of odorants when tested at lower concentrations. Coding is combinatorial, in that different odors elicit responses from different subsets of receptors.

A particularly exciting area of recent research has extended this primary analysis of odor sensitivity to include compounds of special biological significance to the fly. One receptor, Or56a, is narrowly tuned to geosmin, a compound that alerts flies to the presence of toxic microbes and that activates an aversion circuit [37]. Or19a detects terpenes present in citrus fruits, and activates an oviposition circuit [38]. Or67d, Or47b, Or88a, and Or65a detect fly pheromones that act in sexual, aggression, or social aggregation behaviors [39–44]. These findings illustrate an interesting philosophical problem that transcends the entire field of chemoreception: given the vast dimension of chemical space and our ability to sample only an infinitesimal fraction of it, it is difficult to be certain what ligand any receptor has evolved to bind. That said, it is particularly compelling when low concentrations of a compound from the natural environment of the fly are found to activate a particular receptor, a dedicated circuit, and an adaptive behavior.

The receptor-to-neuron map of the olfactory system raises an intriguing developmental problem. How do individual ORNs select the Ors that they express, from a family of 60 genes? A combinatorial code of transcription factors, including the POU domain

transcription factor Acj6 and the Kruppel-like transcription factor Rotund, underlies much of the process [45, 46]; epigenetic mechanisms also contribute to receptor regulation in ORNs [47]. A code of regulatory elements upstream of *Or* genes acts in specifying their expression patterns [48]. Another puzzle is posed by the spatial distribution of expression. ORNs that express the same receptor are restricted to particular regions of the antenna, but within a given region, ORNs that express one individual receptor are intermingled with ORNs that express other receptors [49]. Intriguingly, this patterning arises in part through mobility: sensilla are initially specified during early pupal development, and then move beneath the surface of the antennal disc during late pupal development to give rise to a scattered pattern [50].

Larvae express 25 Ors, of which 13 are larval-specific [19, 31, 51]. For 19 receptors, an odorant that activates it strongly has been identified [52]. Silencing of neurons that express different receptors reduces behavioral response to different odorants [19]. Mutational analysis of two receptors showed that they mediate responses to different concentrations of ethyl acetate [53].

Gustatory receptors (Grs)

The *D. melanogaster* genome contains 60 *Gr* genes, which are predicted to encode 68 proteins via alternative splicing [23]. These proteins are extremely divergent, containing as little as 8% amino acid identity. Grs are weakly related to Ors, which can be viewed as a single lineage within a larger insect chemoreceptor superfamily [23]. The topology of insect Gr proteins is not as clearly established as that of Or proteins [54].

Grs are expressed in the labellum, legs, and pharynx of the adult fly [9, 55–59], the larval taste organs [20], and in a variety of other adult tissues, including the antenna, maxillary palp, enteroendocrine cells of the gut, multidendritic cells of the abdominal body wall, neurons innervating reproductive organs, and the brain [15, 17, 60–63]. Gr expression studies have been constrained by the inability to visualize most tested Gr transcripts by in situ hybridization. Localization of Gr expression has thus primarily been carried out directly using RT-PCR, RNA-Seq, or microarray analysis, or indirectly using transgenic and knock-in reporter techniques, all of which are subject to limitations. That said, expression studies of labellar and leg Grs have in some cases been confirmed by electrophysiological studies of individual taste sensilla [9, 59].

Unlike ORNs, some GRNs coexpress many receptors. One class of bitter-sensitive neurons in the labellum expresses reporter constructs representing 29 different Grs [59], a bitter neuron in the leg coexpresses 18 [9], and a neuron of the larval taste system coexpresses 17 [20]. Expression of Grs in bitter neurons is combinatorial, although some receptors are expressed broadly. Gr33a, for example, is expressed ubiquitously in bitter neurons of the labellum, leg, and larva. Sugar-sensitive neurons also coexpress several receptors [64, 65]. Strikingly, the sets of Grs expressed in bitter and sugar neurons are mutually exclusive [66]. Despite this division of sweet and bitter sensing into separate cells, there is evidence that sugar neurons are both inhibited by bitter compounds and activated by sugars, raising new and exciting questions about how the fly detects and integrates information from stimuli of opposing valence [67, 68].

Loss-of-function experiments have shown that some Grs, such as Gr5a, Gr61a and members of the Gr64a-f cluster are required for responses to various sugars [62, 64, 65, 69]. Reciprocally, all of these genes conferred a sugar response when ectopically expressed in an antennal neuron that has no endogenous sugar responses [70]. All of these genes lie in one clade of the Gr family [23].

Bitter responses also depend on Grs. For example, Gr93a is required for electrophysiological response of one class of taste sensilla to caffeine, but not to several other bitter compounds [71]. Gr8a is required for response to the aversive compound L-canavanine, but not other compounds [72]. Mutation of Gr33a, by contrast, reduced electrophysiological response to a variety of structurally diverse bitter compounds [73]. The breadth of this phenotype and its expression pattern suggested the possibility that Gr33a acts as a co-receptor for other Grs. However, Gr33a differs from Orco in that it is not required for trafficking of other tested Grs to the membrane. Moreover, normal electrophysiological response to caffeine also depends on a third broadly expressed Gr, Gr66a [74], raising the possibility of a signaling complex consisting of three or more Gr subunits.

Some Grs are required for sexual behavior. Mutation or knockdown of *Gr39a* in males led to reduced courtship of females, consistent with the notion that these receptors signal the presence of an excitatory female pheromone [75]. Mutation of *Gr32a* also led males to court other males and previously mated females, as if this receptor signals the presence of an inhibitory pheromone [76]. Remarkably, Gr32a also acts in males of *Drosophila melanogaster* to prevent them from mating with females of different species [77]. We note that mutation of the broadly expressed Gr33a produced elevated male-male courtship [73], consistent with the notion that Gr33a acts as a coreceptor for Gr32a. One study found that knockdown of Gr68a, or silencing of Gr68a-expressing neurons in males, reduced male courtship towards females, suggesting that Gr68a is a receptor for a female pheromone and is required for efficient courtship. [78]. However, a recent investigation found that Gr68a-expressing male neurons sense an anti-aphrodisiac compound produced by males that can inhibit male courtship toward females [79], illustrating that there are still numerous exciting puzzles to be solved regarding the role of Grs in pheromone detection and sexual behavior in *Drosophila*.

Early studies revealed expression of a few Grs in the antenna [60, 63]. Gr21a and Gr63a are coexpressed in one class of antennal ORNs, where together they confer response to CO_2 [80, 81], which is an important cue used in detecting fermenting food sources and is a stress signal in *Drosophila* [82]. Mosquito ORNs that express orthologs of these Ors respond to CO_2 and odorants from human skin, informing mosquitoes of the proximity of human hosts [83]. Gr28b.d is expressed in a specialized structure of the antenna called the arista and plays a critical role in thermosensation [84].

Surprisingly, recent RNA-seq analysis revealed that 12 *Grs* are expressed in the antenna [85], a larger number than previously detected using transgenic *GAL4* reporters or *in situ* hybridization. RNA-seq examines RNA levels directly, unlike transgenic *GAL4* reporters, and its sensitivity is greater than that of conventional *in situ* hybridization. Intriguingly, five

members of the *Gr64a-f* cluster of sugar receptor genes are expressed in the antenna, where their function remains enigmatic [62, 85].

Grs are also expressed in pharyngeal organs and in enteroendocrine cells of the gut [17, 55–58]. These cells may regulate food intake and other functions. Gr43a is expressed in the brain, where it functions as a fructose receptor and controls feeding responses [15].

The mechanism of Gr-mediated transduction is in great need of further investigation. Of 11 Grs of the silkmoth *Bombyx mori* expressed in *Xenopus* oocytes, one, BmGr-9, conferred response to a tastant, D-fructose [86]. This receptor and its *Drosophila* ortholog, Gr43a, also conferred responses when expressed in cultured cells. Analysis of these responses was consistent with the hypothesis that BmGr-9 is a ligand-gated ion channel; evidence to support a role for G protein-mediated signaling was not found. By contrast, *in vivo* studies of taste responses to sugars have found a requirement for G protein signaling, but different studies implicated different G proteins (Goα, Gqα, or Gsα, as well as Gγ1) [7], and the roles of some G proteins may be modulatory or indirect. Moreover, different Gr proteins may signal through different mechanisms.

Ionotropic receptors (IRs)

The *D. melanogaster* genome also contains ~60 *IR* genes, which are related to ionotropic glutamate receptor genes (iGluRs) [87]. *IR* genes are predicted to encode ligand-gated cation channels with three transmembrane domains [88].

Antennal IRs—Approximately 17 IRs are expressed in the antenna, mostly in ORNs of coeloconic sensilla [85, 87, 89], which typically do not express Ors [31]. These IRs confer response to many organic acids and amines [89, 90]. IR92a is required for response to particular amines [91], whereas IR64a is acid-sensitive [92]. Like Ors, the trafficking and function of these IRs depend on the expression of widely expressed co-receptors, including IR8a or IR25a [93]. For example, IR64a and IR8a are physically associated *in vivo* and form a functional channel when coexpressed in Xenopus oocytes [94].

Some antennal IRs play interesting behavioral roles. IR84a is activated by food odors, and this activation increases levels of male courtship behavior [95]. Evidently the ORN expressing IR84a influences a male courtship circuit. *D. melanogaster* mates primarily on food sources, and thus IR84a appears to provide a neural link between food and sex. Another intriguing role for an IR concerns the avoidance of the insect repellent DEET: in *Drosophila* this aversion is mediated in part via IR40a, which is expressed in neurons within a three-chambered pit on the antennal surface [87, 96]. Like Gr28b.d, IR21a expresses in the arista of the *Drosophila* antenna [87]; it will be interesting to investigate whether IR21a also plays a role in thermosensation.

Gustatory IRs—Some IRs are expressed in gustatory organs of adult or larval *Drosophila* [88, 97, 98], where investigations into their roles in taste perception have only recently been initiated. A large clade of IRs, the IR20a clade, consists of ~35 members that are more distantly related to the iGluRs. *GAL4* drivers representing genes of the *IR20a* clade were recently found to be expressed in taste neurons of all gustatory organs of the fly, including

the labellum, the legs, the pharynx, and the anterior wing margin [98]. Neurons expressing these drivers project to taste centers in the CNS. Eleven drivers are expressed in the larva, mostly in single pairs of pharyngeal neurons [97].

Some gustatory *IR* drivers are coexpressed with *Gr* drivers in bitter- or sugar-sensitive neurons of the labellum, suggesting that some of these IRs function in detection of aversive or appetitive stimuli, respectively [98]. The IRs may detect stimuli not recognized by Grs; alternatively, activation of one class of receptor may lead to modulation of another.

Other gustatory IR drivers are expressed in “orphan” taste neurons that do not express Grs or other known receptors, and that do not respond to canonical food sources [9, 98]. Analysis of *IR52c* and *IR52d* has shown sexually dimorphic expression in such neurons of the male foreleg, which makes contact with females during courtship behavior, and genetic analysis has verified that *IR52c* and *IR52d* play roles in sexual behavior [98]. The neurons in which they are expressed are activated by exposure to virgin *D. melanogaste*r females, but not by exposure to males or virgin females of a sibling species, *D. simulans*, suggesting a role in recognition of a species-specific female pheromone.

Another IR that is not a member of the IR20a clade, IR76b, has been proposed to be a detector of appetitive, low concentrations of salt, based on molecular, genetic, and physiological evidence [99]. IR76b has also been proposed to be a co-receptor with other IRs [93]. IR25a may be a co-receptor in both olfactory and taste systems [88, 93, 97], providing another interesting link between the two sensory modalities.

Concluding Remarks and Future Perspectives

Great progress has been made in understanding the receptors that constitute the basis of all of chemosensory perception. However, critical boxes remain black, key principles remain controversial, and major topics remain unexplored. It is as if a new continent has been discovered but only the coastline has been mapped.

Ors and Grs are currently represented as squiggles through cartoon membranes, with much uncertainty in the case of Grs. A 3D structure of Ors and Grs and their co-receptors, with and without ligands, is urgently needed. Although experimental determination of Ors and Grs has remained elusive, a recent 3D modeling study provided evidence that the packing of Or transmembrane helices is distinct from that of canonical GPCRs [100]. In the case of Grs, we need to know whether receptors assemble as complex multimers, possibly of three or more subunits. We also need to know whether any of these receptors interact directly with G proteins, and to clarify the potential roles of various G proteins in signaling.

It seems clear that new pheromone receptors await identification. The pheromonal profile of the fly has recently been found to be much richer than previously thought and may include 58 hydrocarbons [101, 102]. Many of these compounds appear to be transferred from males to females, and some in the opposite direction, during sexual behavior. The number of pheromones thus appears to greatly exceed the number of known pheromone receptors. It has also become clear that larvae signal to each other via pheromones [103]. Beyond pheromones, the natural environment is teeming with signals – from predators, a cornucopia

of food sources, and the chemical arsenal of microbes and plants that do not want to be eaten. Receptors for many signals await identification.

In addition to these “orphan ligands” for which receptors have not been identified, there are “orphan receptors” for which no ligands have been identified. The future may well see some happy unions between these ligands and receptors; in any case there are clearly many inviting opportunities for ligand and receptor de-orphanization. We note also that there are many “orphan neurons”, such as in the legs and the larva, for which neither ligands nor receptors have been identified.

The establishment of neural circuits depends critically on the expression of the receptors that drive them. Receptors that signal mates, nutrients, and toxins must be expressed in neurons that drive mating, consumption, and avoidance. Much remains to be learned about the genetic and epigenetic mechanisms by which individual neurons select the Ors they express, and virtually nothing is known of how neurons select Grs or IRs.

Finally, how does the pattern of receptor expression serve the behavior of the animal? Does the combinatorial pattern of Gr and IR expression in taste organs allow for combinatorial coding of taste information and thereby enhance the specificity or discriminatory power of the system? How does it allow a single bitter compound to have both a positive and a negative valence, *i.e.* to suppress feeding but activate egg-laying [57, 104]? The behavior of *Drosophila* is governed by the function of more than 180 receptors, and an understanding of how behaviors are activated depends critically on an understanding of the receptors that activate them.

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Box 1

A large and diverse family of soluble chemosensory proteins

Large families of soluble proteins called Odorant binding proteins (Obps) have been identified in many insects, originally in a moth [105, 106]. Obps are small proteins (~14kDa) that are highly divergent in sequence but that share six cysteines. They bind odorants, with different degrees of binding selectivity reported for different Obps [107, 108]. Obps are reminiscent of Ors in their number (52 genes in *D. melanogaster*), sequence divergence, and diversity of expression patterns. Intriguingly, some are expressed at exceedingly high levels [85, 109].

Obps have been proposed to bind and transport hydrophobic odorants across the hydrophilic sensillum lymph to odor receptors in the dendrites of ORNs [106]. However, Obps have also been proposed to act in the termination of odor response, perhaps by removing odorants from receptors or from the sensillar lymph [105, 106, 110]. Odor receptors expressed in heterologous systems such as Sf9 cells respond to odors in the absence of Obps. The response profiles of Ors appear not to depend on Obps, in some if not all cases [111]. Obps increase the sensitivity of responses *in vitro* [112, 113], but in one system the sensitivity could be increased equally well by the addition of a non-specific protein [114]. These results leave open the question of why olfactory organs express large families of diverse Obps, in diverse patterns.

A variety of studies support a role for Obps in olfactory perception *in vivo.* RNAi knockdown of Obps led to abnormalities in olfactory behavior in *Drosophila* [109] and decreased physiological responses in mosquito antennae [115, 116]. Mutation of an Obp reduced the response of an ORN to the pheromone cVA in *Drosophila*, although the mechanism has been controversial [117, 118]. Some Obps are also expressed in the taste system, and mutations of some of them altered responses to tastants; interestingly, one of the responses that was altered was inhibitory [68], rather than excitatory [117, 119].

In summary, enormous biological resources are devoted to the synthesis and regulation of these abundant and diverse proteins, but much remains to be learned about their mechanism of action and role in chemosensory coding.

Box 2

Other chemoreceptors in the fly: Ppks and Trps

Pickpocket (Ppk)/Degenerin-Epithelial sodium Channels (Deg/ENaCs) also play interesting roles in chemoreception. There are 31 *ppk* genes in *Drosophila*, and they are predicted to encode two-transmembrane-domain proteins [120]. Ppk28 is required for the sensing of water and osmolarity, and misexpression of *ppk28* in bitter-sensitive neurons confers water sensitivity to them [121, 122]. *ppk23* and *ppk29* are expressed in male forelegs, among other chemosensory tissues, and are required for male courtship behavior toward females [123–125]. *ppk23* mutant males also showed abnormally high courtship toward other males, suggesting that the gene can function in both excitatory and inhibitory circuits. Both *ppk* genes are required for responses to identified fly pheromones.

Trp proteins are six-transmembrane-domain proteins that act in a variety of sensory modalities. A number of Trps are expressed in taste and olfactory organs of the fly [7, 85]. Two of them, TrpA1 and Painless, act in thermosensation [126] but are also expressed in taste organs. TRPA1 is required for the response to noxious electrophiles, and is activated by electrophiles when expressed in *Xenopus* oocytes [127]. TRPA1 also functions in the response to aristolochic acid, a bitter compound [128], as does TRPL in the response to camphor [129] and Painless in the behavioral aversion to isothiocyanate, the pungent ingredient of wasabi [130]. Interestingly, the mechanisms of action in these three latter cases differ from that by which TRPA1 detects electrophiles.

Outstanding Questions Box

What are the 3D structures of Ors and Grs? What are their multimeric compositions? Where do ligands bind? What are the transduction mechanisms?

How do individual neurons select which chemoreceptor genes to express, from an enormous repertoire?

What circuits and behaviors are driven by individual Ors, Grs, IRs, and other chemoreceptors?

Do IRs and Grs detect different classes of tastants or different features of the same gustatory stimuli?

How are signals from IRs and Grs integrated in the brain?

How are olfactory and taste signals integrated with each other and with other sensory inputs?

Does combinatorial coding of taste information by IRs and Grs enhance discrimination or memory of taste stimuli?

How is signaling via chemoreceptors modulated by experience, and how is it shaped through evolution?

Trends Box

- Odorant receptors (Ors) have been found to activate an increasing number of behavioral circuits.
- Gustatory receptors (Grs) are expressed in a wide diversity of organs. Emerging results reveal roles in an expanding repertoire of functions, extending beyond chemoreception.
- Ionotropic receptors (IRs) are expressed not only in olfactory organs but in taste organs. A large clade has recently been found to be expressed in all taste organs of the fly.
- Ors, Grs, and IRs all have roles in the sexual behavior of the fly.

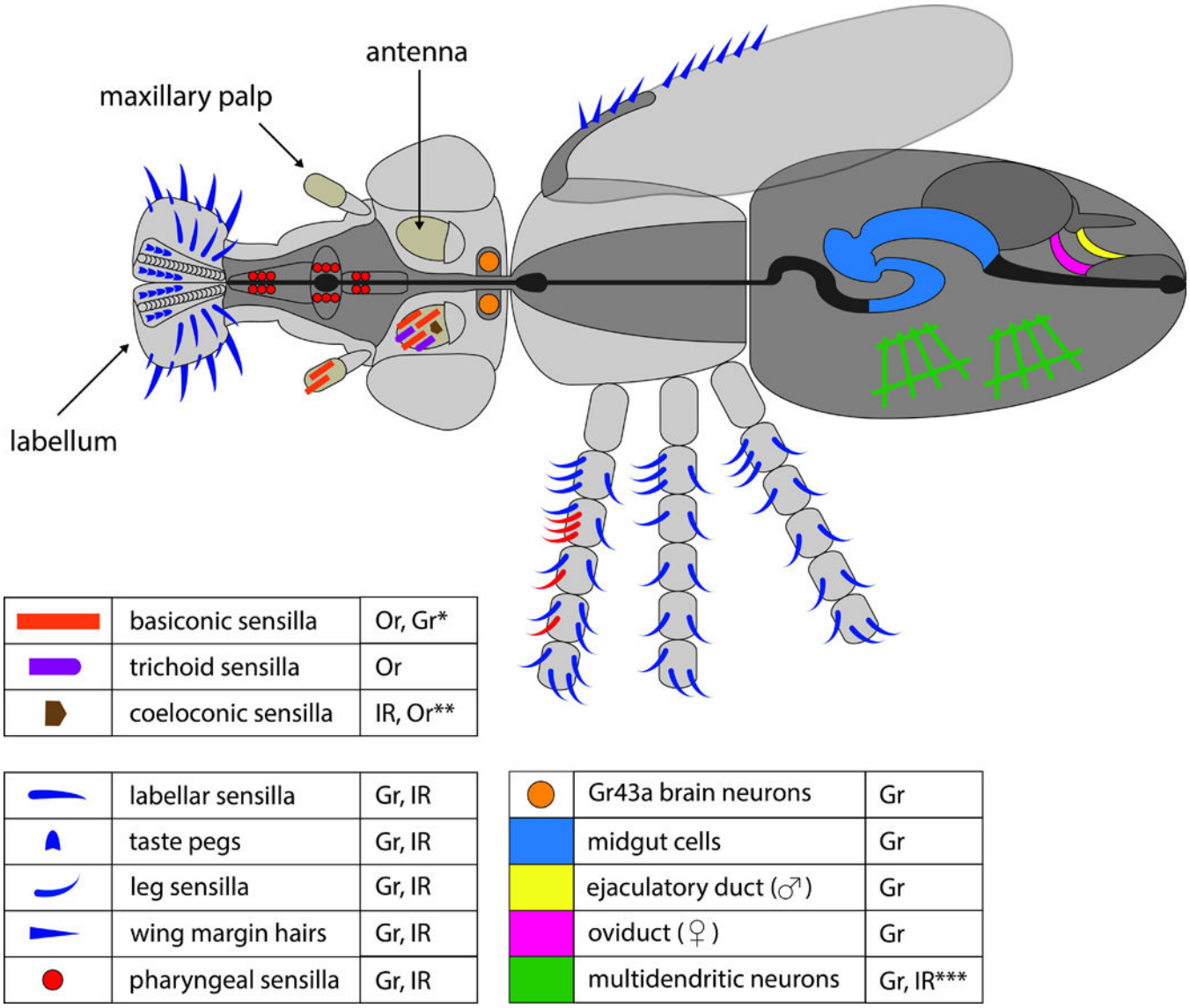


Fig. 1.

Expression of the three largest chemoreceptor families in *Drosophila*. Light gray coloring indicates the exterior of the fly; dark gray coloring indicates the interior. Tan highlights the antenna and maxillary palp, which primarily house olfactory neurons. Leg sensilla indicated in red are male specific. Gr expression in the gut occurs in enteroendocrine cells as opposed to neurons. Multidendritic neurons are subcuticular. Expression of Grs and IRs is based in most cases on expression of *Gr-GAL4* and *IR-GAL4* drivers. Expression of Ors is based on *Or-GAL4* drivers and *in situ* hybridizations. Classes of receptors that have been identified in each corresponding sensillum type or tissue are indicated at right of labels. *Antennal Grs include *Gr21a* and *Gr63a* in basiconic sensilla neurons and others [62, 85]. **A single Or has been localized to one neuron of one coeloconic sensillum. ***A single IR has been localized to multidendritic neurons in the abdomen

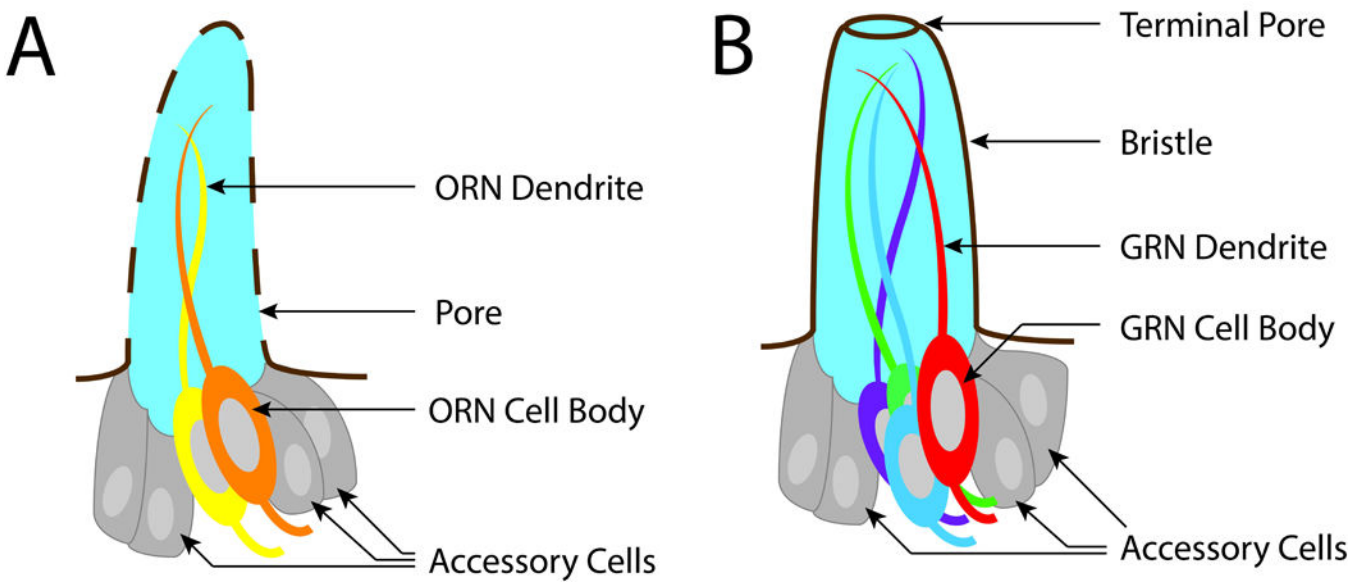


Fig. 2.

Chemosensory sensilla. (A) olfactory and (B) gustatory sensilla in adult flies. The dendrites are bathed in sensillar lymph (light blue). The shaft of the olfactory sensillum is perforated by small pores, while the shaft of the gustatory sensillum contains a single pore, located at the tip. Both olfactory and gustatory sensilla contain non-neuronal accessory cells, which secrete OBPs into the lymph.

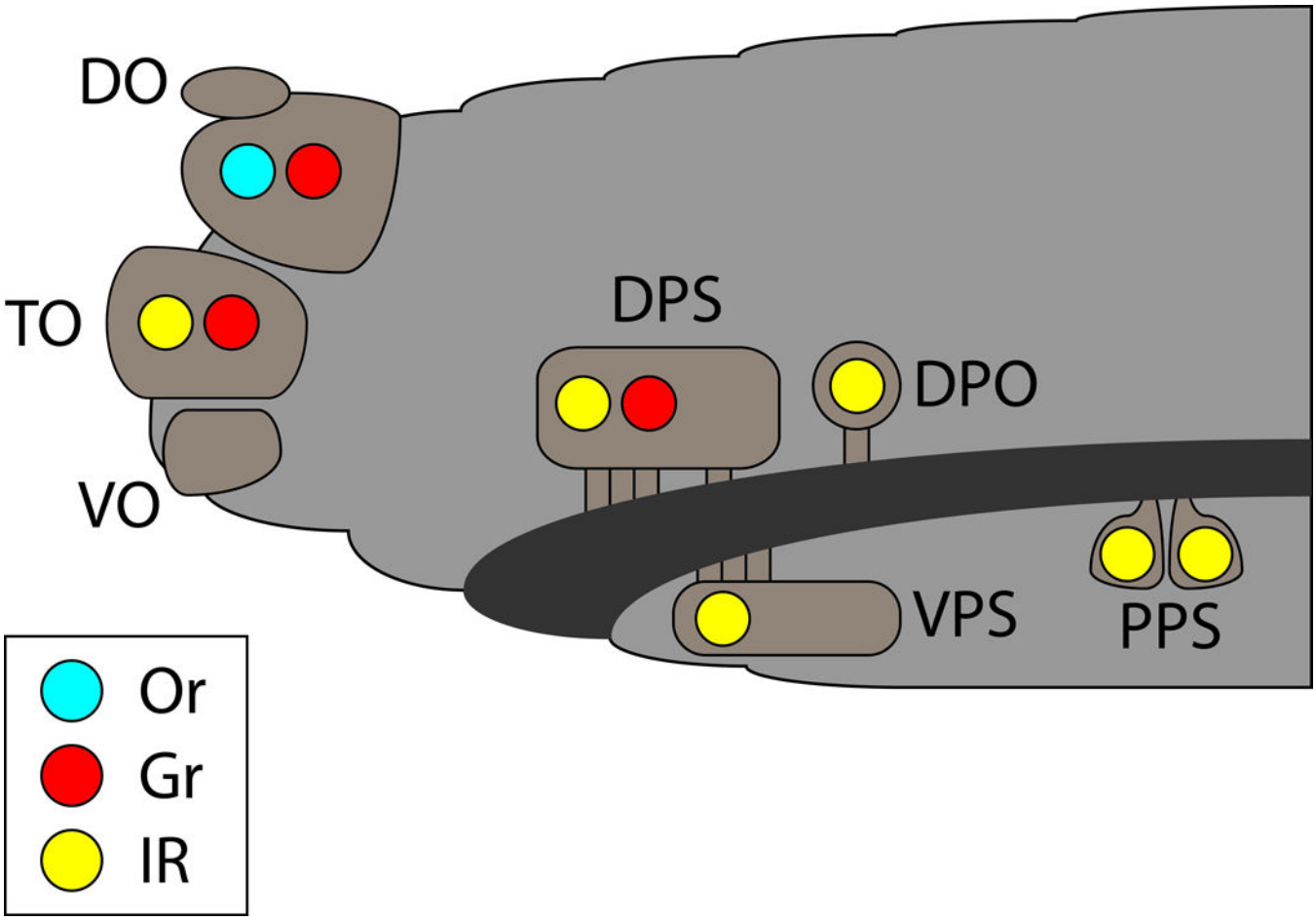


Fig. 3.

Chemosensory organs of the larval head. The dorsal organ (DO), terminal organ (TO), and ventral organ (VO) are external; the dorsal pharyngeal sensilla (DPS), ventral pharyngeal sensilla (VPS) and dorsal pharyngeal organ (DPO) are internal and line the gastrointestinal tract (dark gray) of the larva. Colored circles indicate the expression of at least one receptor of the indicated category in the indicated organ. Mapping of Grs and IRs is based primarily on analysis of *GAL4* drivers.

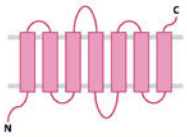
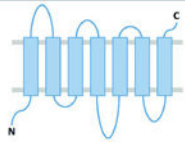
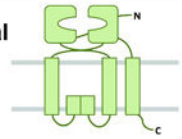
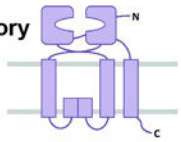
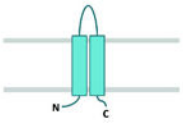
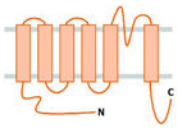
Receptors	Examples	Ligands	Behavioral Output
Ors 	Or56a Or47b Or19a Or67d	Geosmin (toxic microbes) Methyl laurate (pheromone) Terpenes (citrus fruits) cis-Vaccenyl acetate (pheromone)	Activates an aversion circuit Promotes male courtship of females Activates oviposition circuit Drives sexual and aggression behaviors
Grs 	Gr5a Gr93a Gr39a Gr63a	Trehalose (sugar) Caffeine (bitter compound) Presumptive female pheromone CO_2, stress pheromone	Promotes feeding Inhibits feeding Promotes male courtship of females Promotes avoidance
Antennal IRs 	Ir64a Ir92a Ir84a Ir40a	Acids Ammonia and amines Phenylacetic acid (food odor) DEET	Activates avoidance responses Activates Attraction Stimulates courtship on food sources Activates aversion circuit
Gustatory IRs 	Ir52c	Presumptive pheromone	Promotes male courtship behavior
Ppks 	Ppk23 Ppk25 Ppk28	7,11-Heptacosadiene (♀pheromone) Multiple pheromones Water	Activates male courtship behavior Stimulates receptivity to courtship Promotes fluid intake
TRPs 	TRPA1 Painless TRPL	Aristocholic acid (bitter compound) Isothiocyanate (wasabi) Camphor (bitter compound)	Inhibits feeding Activates aversion circuit Inhibits feeding

Fig. 4.

Classes of chemoreceptors. The predicted topologies of the different receptor classes are indicated. The topology of Grs is not well-established and may vary among Grs. Examples of receptors in each class are provided, along with presumptive stimuli and behaviors activated by each receptor. We note that TRPA1 also responds to heat and acts in thermotaxis behavior, while TRPL responds to light and acts in phototaxis behavior.