History of the *Drosophila* Gustatory Receptors

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Taste or gustation is a critical sensory system for animal survival, guiding animals toward beneficial food sources and helping them avoid harmful ones. Many aspects of gustatory systems have been evolutionarily conserved, making it possible to investigate them by genetic model organisms. Due to the ease of its genetic manipulation and the richness of its genetic toolkit, the nature of peripheral taste coding is best understood in the model organism *Drosophila melanogaster*. In this review, we summarize our groups achievements over the past two decades and introduce some current perspectives on the fruit fly *gustatory receptors* (*Grs*).

Keywords: Taste, *Drosophila melanogaster*, Gustatory receptor, Molecular genetics

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Introduction

Taste sensation arises when nonvolatile compounds dissolved in saliva and oral mucus contact the taste organs. The taste or gustatory system provides sensory information that is important for accepting or rejecting food material that enters the first part of the digestive system. To survive, animals must discern beneficial food sources from harmful ones. Thus, gustatory systems are conserved across most animal species, from worms, to insects, to mammals including humans.

Attractive tastants are preferred; aversive tastants are avoided. Although the anatomy and taste-related genes of fruit flies are quite different from those of mammals, the basic logic of peripheral taste recognition is identical. Among insects, the *Drosophila* gustatory system is the most well-studied because of its power as a genetic model organism. We and our colleagues in this field have used the *Drosophila* model system to great effect in studying both gustatory receptor proteins and cells. In this review article, we summarize our accumulated knowledge of the genetic and molecular mechanisms underlying *Drosophila* taste sensation via gustatory receptors.

Anatomy and physiology of fly taste organs

A sensillum is the minimal functional unit for taste detection in insects including *Drosophila*. In *Drosophila*, the sensilla are located on the proboscis, tarsal segments, oviduct, and anterior wing margin [1, 2]. Most sensilla take the shape of taste hairs covered in a layer of cuticle, but some—the taste pegs—lack apical structures and are instead embedded in the surrounding tissue. We know more about the la-

bellar sensilla than those of the other regions because of their experimental accessibility [3].

The *Drosophila* labellum is composed of a bilateral hemispheric structure at the tip of the proboscis, each half of which possesses roughly 30 sensilla [1]. Sensilla are classified according to their size into large-type (L-type), intermediate-type (I-type), and short-type (S-type) [4]. These sensilla arise in stereotyped locations, permitting a specific nomenclature. The initial sensillar nomenclature proposed by the Tanimura group was eventually replaced by one proposed by the Carlson group that better reflected tastant responses and gustatory receptor expression [4, 5].

A sensillum is composed of multiple chemosensory neurons, a single mechanosensory neuron [6], as well as three supporting cells referred to as thecogen, tormogen, and trichogen [2, 7, 8]. L-type and S-type sensilla have four different types of gustatory receptor neurons (GRNs), whereas I-type sensilla have only two. Each GRN in a sensillum shows a characteristic response profile to different tastants [9, 10]. Initial electrophysiologic experiments demonstrated the existence of neurons responding to sugars (the so-called sweet cells, S-cells, or sweet GRNs), neurons responding to hypoosmotic stimuli (the so-called water cells or W-cells), and neurons responding to low or high concentrations of salt (the L1 and L2 cells, respectively) [9]. In I-type sensilla, one neuron seems to respond to sweet tastants and to low concentrations of salt, whereas the other neuron seems to be a standard L2 cell [10]. L2 cells of S-type and I-type sensilla also respond to several bitter compounds, thus they are referred to as bitter GRNs [5, 9-11].

The specific response profile of each GRN is based on the differential expression of receptor molecules [9, 12, 13]. For example, Pickpocket28 (PPK28), an orthologue of the mammalian epithelial sodium channel (ENAC), is required for the detection of hypoosmotic stimuli in W cells [13], whereas ionotropic receptor 76b (IR76b) and IR94e directly mediate depolarization of L1 cells by acting as sodium ion channels themselves [14, 15]. Sweet and bitter GRNs express gustatory receptors (GRs), a subclass of the insect chemosensory receptor family of proteins [12, 16]. We recommend that those interested in other taste-related membrane proteins (e.g., the PPKs, IRs, and TRP (transient receptor potential) channels) read other review articles [17-19]. This review article will focus on the *Drosophila* GRs.

Discovery of the Gustatory Receptors

The completion of the fly genome project predicted a group of genes encoding membrane proteins that are expressed in taste organs. These genes are referred to as *gustatory receptors* or Grs [12, 16, 20, 21]. The *Gr* family is composed of 60 genes encoding 68 proteins because of alternative splicing [16, 21]. Among these genes, *Gr5a*, *Gr61a*, and 6 *Grs* in the 64 cluster are referred to as sweet *Grs* because they are expressed in sweet GRNs [22-24]. Most of the remaining family members are considered bitter *Grs* because of their expression in the bitter GRNs of the adult and larval taste organs [5, 12]. Several bitter GRs are referred to as commonly expressed receptors (CERs) because they are expressed in all the S-type and I-type sensilla of the adult labellum. These CERs include *Gr32a*, *Gr33a*, *Gr39a.a*, *Gr66a*, *Gr89a*, and

Gr93a [5, 25]. Expression outside the taste organs has been also reported: *Gr43a* is an internal sensor of blood fructose [26], *Gr21a* and *Gr63a* are olfactory receptors for carbon dioxide [27, 28], and *Gr28b* is a nociceptor for physical stimuli [29-31].

Initially, GRs and the related odorant receptors (OR) were considered G-protein coupled receptors (GPCRs) because they were predicted to possess seven transmembrane domains [32]. Later investigations revealed the membrane topology of GRs and ORs is opposite that of conventional GPCRs [33, 34], calling their classification into question. Moreover, electrophysiologic experiments revealed that ORs and *Bombyx mori* GR9, paralogues and orthologues of fly GRs, respectively, trigger ion conductance upon ligand application [35-37], suggesting they may function as ligand-gated ion channels rather than GPCRs.

A functional reconstitution of GRs in a heterologous expression system is necessary to prove their true molecular identity because this would allow them to be subjected to whole-cell and single-channel patch clamping. Unfortunately, this has proven to be a considerable technical challenge. In contrast to ORs, which function as heterodimers comprising the odorant receptor co-receptor (Orco, formerly known as OR83b) with a specialized OR [35, 36], GRs require more than two receptors to detect tastants. To this day, no one has characterized the mechanism of action underlying GR function, in part because we still do not know what constitutes a functional receptor complex.

Bitter Gustatory Receptors

The ease with which fly mutants can be generated has allowed us to evaluate loss-of-function mutations for most of the *Grs*. *Gr66a* was the first *Gr* subjected to such a molecular genetic approach [11]. Flies lacking *Gr66a* show disrupted behavioral avoidance and neuronal responses to caffeine (CAF), a bitter-tasting compound. Later, *Gr66a* was implicated in the detection of most bitter compounds, not just CAF [38, 39]. Similarly, *Gr33a*, the *Gr* most closely related to *Gr66a*, was also found to be required for the detection of most bitter compounds [40]. In contrast, *Gr93a* is only required for the detection of a narrow spectrum of bitter compounds, including CAF and theophylline (TPH). This discovery divided bitter GRs into two groups: broadly tuned receptors important for signal transduction and narrowly tuned receptors that provide ligand specificity to the receptor complex [41]. Nevertheless, misexpression of *Gr33a*, *Gr66a*, and *Gr93a* in sweet GRNs did not confer ectopic responses to CAF or other bitter compounds, indicating the existence of a missing component.

Our group was the first to successfully recapitulate a gustatory response to a bitter compound, L-canavanine [38, 42]. In an RNA interference screen against all the *Grs,* we found that the broadly tuned receptor GR66a and the narrowly tuned receptors GR8a and GR98b were necessary for L-canavanine responses. Moreover, we found the misexpression of these three bitter GRs conferred on sweet GRNs responses to L-canavanine, but not to other bitter compounds. We also observed ion conductance in response to L-canavanine in *Drosophila* S2 cells expressing GR8a, GR66a, and GR98b [42].

The second example of bitter receptor reconstitution showed responses to a restricted but broader spectrum of bitter compounds than that of the L-canavanine receptor. We focused on reconstituting the responses of I-a sensilla because I-a sensilla show narrow tuning to specific bitter compounds, such as lobeline (LOB), berberine (BER), and denatonium (DEN). In addition, the number of *Grs* expressed in I-a sensilla is more restricted than in other sensilla [5]. Thus, we hypothesized that the 6 *Grs* (i.e., *Gr32a*, *Gr33a*, *Gr39a.a*, *Gr59c,* and *Gr66a*) expressed in I-a sensilla mediate the characteristic bitter responses of I-a sensilla to LOB, BER, and DEN. Indeed, we found misexpression of all 6 I-a sensilla *Grs* confers on sweet GRNs responsiveness to LOB, BER, and DEN. By omitting each of the 6 *Grs* one by one, we finally determined that the combination of *Gr32a*, *Gr66a*, and *Gr59c* represents the minimal requirement for responses to LOB, BER, and DEN. The restricted expression pattern of *Gr59c* in I-a and S-a type sensilla implied the existence of another receptor combination in S-b type sensilla. We additionally found S-b type sensilla express GR22e instead of GR59c to form a receptor complex with GR32a and GR66a. Interestingly, the misexpression of *Gr22e*, *Gr32a*, and *Gr66a* conferred on sweet GRNs, not only to responsiveness to LOB, BER, and DEN, but also to strychnine, which is not the normal ligand for the *Gr59c* combination. These results suggested to us that GR22e and GR59c determine the ligand specificity of the receptor complex. As with the L-canavanine receptor, the heterologous expression of both combinations of receptors in *Drosophila* S2 cells led to inward current upon application of LOB, BER, or DEN. Thus, these *Grs* may also function as

ligand-gated ion channels [39].

Recently, the Carlson group discovered the last missing component of the functional CAF receptor, GR39a [25]. Among the CERs, *Gr39a* was difficult to identify because its antiparallel gene, *Mondo,* interfered with the process of generating a *Gr39a* mutant via homologous recombination. The Carlson group bypassed this problem using CRISPR genome editing technology, and then determined that GR39a is necessary for the detection of the GR93a ligands CAF and TPH [43, 44]. Moreover, they demonstrated that misexpression of *Gr39a*, along with the other requirements for CAF sensing—*Gr33a*, *Gr66a*, and *Gr93a*—confers on sweet GRNs responsiveness to CAF, TPH, and UMB, but not to other bitter compounds. The receptor complex comprising *Gr33a*, *Gr39a*, *Gr66a*, and *Gr93a* has not yet been tested with an electrophysiologic approach in a heterologous expression system, so the mechanism of its signal transduction remains unclear.

Sweet Gustatory Receptors

Given that the GRs and tastants associated with sweet taste than bitter, you might expect research on sweet taste to be easier than research on bitter taste. Unfortunately, the reality is considerably more complicated. Of the eight sweet *Grs*, all but *Gr5a* and *Gr61a* are concentrated at the 64 cluster, being transcribed into a single polycistronic mRNA [24]. Generation of a mutant fly covering just one of the sweet *Grs* in the 64 cluster would likely affect the expression of neighboring genes, making it easy to misinterpret the resulting phenotype. In fact, there are several examples in which the phenotypes of

different mutant strains covering the same sweet *Gr* seem to differ from one another [22-24, 45-47]. Thus, it is difficult to infer the function of sweet GRs based on canonical loss-of-function studies. Nevertheless, it does seem that multiple sweet GRs are required for the detection of at least one sweet compound. Deletion of all the *Grs* located in the 64 cluster blocks the detection of trehalose [46, 47], the first known ligand for a specific sweet GR (i.e., GR5a) [22, 23]. Although no one has yet achieved functional reconstitution of sweet GRs in a heterologous system, this still implies sweet GRs function as heteromeric receptors.

One of the receptors in the 64 cluster, GR64e, shows dual functionality, being required both for the detection of the simplest sugar alcohol, glycerol [48], and several fatty acids, such as hexanoic acid and oleic acid [46]. The modalities in which GR64e participates in each of these signaling pathways depend on the ligand. For the detection of glycerol, GR64e serves as a receptor together with GR64B, as previously suggested [48]. In contrast, GR64e does not seem to serve as the receptor for free fatty acids [46]. Rather, it transduces the intracellular signals downstream of phospholipase C (PLC) [49]. This is reminiscent of dTRPA1, which also has a dual mode of action. dTRPA1 acts in bitter GRNs as a ligand-gated ion channel for various electrophiles, such as N-methyl maleimide, allyl isothiocyanate, and benzyl isothiocyanate, as well as nucleophiles like dithiothreitol and benzyl thiocyanate [50-52]. dTRPA1 serves as a downstream effector of GPCR signaling, mediating Ca^{2+} influx under the control of PLC activation upon detection of aristolochic acid [53]. Indeed, our group found dTRPA1 expression

can compensate for a loss of GR64e in the detection of free fatty acids [46]. These data raise the possibility of that GRs may have multimodal mechanisms of action.

Gustatory Receptors Beyond Taste

Although *Grs* were first discovered in the taste organs, some are also expressed elsewhere [26-29]. This suggests GRs may cover more sensory modalities than simple taste. For example, rather than being expressed in GRNs, *Gr21a* and *Gr63a* are expressed only in the ab1A neurons of the third antennal segment, the fly's primary olfactory organ. Genetic mutation of either *Gr21a* or *Gr63a* impairs olfactory detection of carbon dioxide, indicating that they are the olfactory carbon dioxide receptor [27, 28]. GR43a in the brain serves as an internal sensor of fructose, a sugar constituent of fly blood, to estimate the hunger and satiety state of the organism [26]. It is also possible that, in addition to chemical ligands, physical stimuli, such as light or temperature may activate GR family members. *Gr28b* encodes five GR28b protein isoforms (A to E) through alternative splicing. Among these isoforms, *Gr28b.d* is expressed in the hot cell neurons of the antennal arista that detect short-term increases in temperature. GR28(D) also complements the function of dTRPA1 in the anterior cell neurons of the brain where it mediates long-term thermal preference for temperatures above 25 ℃ [30]. An unidentified *Gr28b* isoform is also expressed in the class IV multidendritic neurons that innervate the surface of the larval body wall. The loss of *Gr28b* reduces the firing of these neurons in response to short wavelength (i.e., UV and blue)

light [29]. Given that both light and thermal stimuli are noxious, and that other *Gr28b* subfamily members are expressed in bitter GRNs [5, 54], the response spectrum of bitter GRs has clearly expanded from noxious chemical ligands to noxious physical stimuli.

Conclusion—Future Directions

Many experiments suggest GRs function as ligand-gated ion channels rather than as GPCRs, but more experiments are required to clarify their molecular physiology. The ion channel pore region of the GRs has not yet been mapped, nor is their ion selectivity known. We do not even know whether GRs show any voltage dependency. In the case of the ORs, a recent cryo-EM structural study identified the S7b segment of Orco as the gating pore region [55]. This implies that the analogous region of GR66a, the most coreceptor-like GR, may have a similar function. Still, it is possible that GRs other than GR66a possess the gating pore. Whatever the truth, the complexity of the GRs make them more difficult to study.

Even the number of GRs that constitute a functional receptor complex for tastants differs on a case-by-case basis (Fig. 1). Three GRs are necessary and sufficient for detection of L-canavanine [38, 42] whereas four GRs are required for detection of the GR93a ligands CAF, THE, TPH, COU, and UMB [11, 40, 41, 43, 44]. For the receptor complex in which GR32a participates, four GRs are necessary but three are sufficient; the complex is still functional even in the absence of GR33a [39, 40]. These data raise questions about the exact stoichiometry of GR complexes. A recent cryo-EM structural analysis of

Orco revealed that the OR complex is a heterotetramer [55]. Given that no one has reported a case in which five or more individual GRs are required for tastant detection, it is possible that most GR complexes are heterotetramers like the ORs. Still, the exact stoichiometric ratio of a functional GR complex should be further investigated.
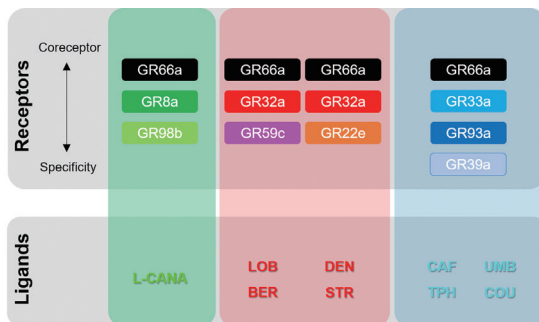

Fig. 1. Functional combinations of gustatory receptors for the detection of bitter tastants. For these bitter ligands, the coreceptor GR66a always seems to participate in the gustatory receptor complex, while other bitter GRs provide ligand specificity. For L-CANA, GR8a and GR98b are required (green box). For LOB, BER, DEN, and STR, GR32a and either GR59c or GR22e are required (red box); For CAF, UMB, TPH, and COU, GR33a, GR93a, and GR39a are required (blue box). Abbreviations: L-CANA (L-canavanine); LOB (lobeline); BER (berberine); DEN (denatonium); STR (strychnine); CAF (caffeine); TPH (theophylline); UMB (umbelliferone); COU (coumarin).

Most of our knowledge of GR expression patterns comes from the expression of *Gr-GAL4* drivers [3, 5, 12, 31, 40]. There are some cases, however, in which the *Gr-GAL4* drivers do not recapitulate the endogenous *Gr* expression patterns [25, 41, 56]. For example, it recently became clear from a mutant analysis and from immunohistochemistry experiments that *Gr93a* is a CER, and the expression of the

Gr93a-GAL4 driver is not as broad as would thus be expected [5, 25, 41]. Such discrepancies will surely degrade our inferences about GR physiology. To better understand the genetics of *Grs*, we need a more precise expression map. We expect the construction of just such a map will become much more feasible with the development of new technologies, such as single cell RNA sequencing, spatial sequencing, and in situ hybridization chain reaction.

Finally, because insect GRs have no mammalian orthologs, they may prove to be novel targets for the development of better insect repellents or insecticides. Although the ease with which we can manipulate *Drosophila* genetics has helped us clarify our understanding of insect GR function, to apply our knowledge in ecologically and agriculturally safe ways, we need more information about the GRs of authentic pest insects, such as mosquitos. Recently, the Vosshall group used the CRISPR/Cas9 system to generate mosquito strains lacking AaOrco, confirming the importance of the olfactory system in blood-feeding [57, 58]. Similar genome editing techniques can also be applied to the GRs of other important species. Yet despite all the potential benefits of studying other insects, we still have a lot to learn about the logic of insect chemosensation from *Drosophila* and its GRs. We expect a broad range of strategies will guide us into the future—hopefully helping us to mitigate all sorts of insect-related problems, from crop crises caused by locusts to mosquito-borne diseases like yellow fever, dengue fever, and malaria.

Conflict of Interest

The authors declare no conflicts of interest.

Acknowledgments

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한글초록

초파리 미각 수용체의 역사

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미각은 적합한 음식에 대한 동물 개체의 섭식행동을 유도하므로 생존에 필수적이다. 동물 대다수의 종에 걸쳐 보존되어 있는 특성으로 말미암아 미각 시스템의 본질을 연구하기 위해 많은 유전학적 모델 동물들이 활용되었다. 그 중에서도 초파리 모델은 유전적 조작이 용이하고 유전학적 도구가 풍부하므로, 말초 미각 감지가 가장 잘 연구된 동물 모델이다. 본 종설에서는 초파리 미각수용체를 대상으로 지난 20년간 본 연구실에서 성취한 결과들을 요약하고, 현재의 관점을 소개하고자 한다.

주제어: 미각, 초파리, 미각수용체, 분자유전학