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Gustatory receptors: not just for good taste

Craig Montell

Neuroscience Research Institute and the Department of Molecular, Cellular and Developmental Biology, University of California Santa Barbara, Santa Barbara, CA, 93106, USA

Craig Montell: craig.montell@lifesci.ucsb.edu

Summary

A recent study demonstrates that a member of the Drosophila gustatory receptor family is required for thermotaxis. Since other fly gustatory receptors function in the detection of CO_2, nutrients in the brain, and light, the roles of the so-called "gustatory receptors" go way beyond peripheral detection of non-volatile chemicals.

There is a long and celebrated tradition of using fanciful, even irreverent names for Drosophila genes. Some of my favorites include *methuselah*, *rutabaga*, *van gogh* and *cheap date*. This custom is not simply to show off the uncanny humor that abounds in the Drosophila research community. The somewhat cryptic names seem less shortsighted when additional, unexpected gene functions are uncovered. Unfortunately, it is not always practical to apply levity to nomenclature. A case in point is the collection of 60 Drosophila "gustatory receptor" genes encoding 68 proteins, which were identified on the basis of sequence homology [1-3]. The first few members of this gene family that were molecularly characterized appeared to be expressed exclusively in gustatory receptor neurons, so the family name ("gustatory receptors") made sense. Indeed, many of the gustatory receptor proteins, which are unrelated to mammalian taste receptors, are now known to function in the detection of sugars, bitter compounds and non-volatile pheromones [4]. Then, the surprises started. These proteins are not just for contact chemosensation in peripheral gustatory receptor neurons. In the latest demonstration of this concept, Paul Garrity and colleagues report that GR28b(D) is required for thermotaxis, and represents a new class of thermosensor [5].

The first functional evidence that gustatory receptors do more than endow afferent neurons with the capacity to sense tastants was the finding that *Gr21a* and *Gr63a* are expressed in fly olfactory receptor neurons, where they collaborate to promote detection of CO_2 [6, 7]. This is important not least of which because homologs of these receptors are expressed in the CO_2-sensing organ of the insect vector for malaria (*Anopheles gambiae*), and CO_2 oozing from skin enhances the attraction of anthropophilic mosquitoes to humans. Another gustatory receptor (GR43a) is expressed in a small subset of neurons in the fly brain, where it serves as a nutrient sensor, through detection of dietary fructose in the hemolymph [8]. GR43a is also expressed in the uterus [8], raising the possibility it plays a role in reproduction or mating [9]. Most unexpectedly, a worm protein related to Drosophila GR28b called LITE-1 is a light receptor that initiates a phototransduction cascade [10]. One of the five GR28b proteins also appears to be a light detector [11]. It is expressed in class IV

dendritic arborization neurons in the larval body wall, and helps the animals avoid intense ultraviolet, violet and blue illumination [11]. The *Gr28b* locus is complex. It encodes five genes (*Gr28b.a – Gr28b.e*), each with a unique transcriptional start site and exon, joined to two common exons (Figure 1) [5, 12]. The specific GR28b protein that is expressed and in the class IV neurons, and which responds to bright light avoidance is unclear.

The recent study from the Garrity group reports the intriguing discovery that the repertoire of functions that depend on Drosophila gustatory receptors includes thermosensation. The *Gr28b.d* reporter is expressed in warm-activated peripheral neurons in an appendage known as the arista, which extends out from the antenna (Figure 2) [5, 12]. The three so-called “hot cell neurons” in the arista are adjacent to “cold cell neurons” and are activated with a threshold just above the ideal temperature of 25°C [13]. As the heat gradually increases above this preferred temperature, the flies elicit progressively stronger aversive responses. *Gr28b.d* functions in the peripheral hot cell neurons and is necessary for avoidance of temperatures that exceed 25°C by just a few degrees. This observation is quite unexpected since the Garrity laboratory showed previously that flies employ the TRPA1 channel in a separate group of warm-activated “anterior cell neurons” in the brain to avoid warm temperatures in the same range [14] (Figure 2).

So why do flies bother with two distinct sets of cells and thermosensory molecules to promote thermal avoidance of uncomfortably warm temperatures? The authors demonstrate that this dual system provides the wherewithal to respond to either steep or shallow temperature gradients. The GR28b(D) protein in the hot cell neurons acts as the sentinel—allowing the flies to quickly sense a rapid rise in temperature (5 °C/cm), and thereby avoid an excessively warm and undesirable thermal landscape. TRPA1 is dispensable for this “rapid negative thermotaxis.” Expression of the TRPA1 thermosensor in the internal anterior cell neurons enables the flies to respond to a more gradual rise in temperature (0.5 °C). This latter sustained strategy is particularly important in a poikilothermic organism, such as the fly, which equilibrates its body temperature to the environment.

A critical but not fully resolved question is whether GR28b(D) is a direct thermosensor, as has been shown for the Drosophila TRPA1 channel [15]. It is plausible that GR28b(D) might be a cation channel since gustatory receptors are structurally related to olfactory receptors, which are cation channels [16, 17]. In addition, GR43a and its silkworm homolog (BmGR-9) form fructose-activated cation channels in heterologous expression systems [18]. Olfactory and gustatory receptors are predicted to be comprised of seven membrane-spanning segments. However, unlike G-protein coupled receptors, their topologies are reversed, with a cytoplasmic N-terminus [19, 20]. Despite this flipped arrangement, some studies nevertheless suggest that gustatory and olfactory receptors might still serve as GPCRs [10, 11, 17].

In support of the proposal that GR28b(D) is a cation channel, ectopic expression of GR28b(D) in transgenic flies confers novel heat sensitivity to cells [5]. Introduction of GR28b(D) in most cells caused incapacitation of the flies when they were placed at 37 °C for 3 minutes. Misexpression of GR28b(D) in sugar responsive gustatory receptor neurons, or motor neurons enabled these cells to display warm activated electrical responses, with a

threshold of ~26°C. Using whole-cell patch clamping of the GR28b(D)-expressing motor neurons, Ni et al. showed that the currents were highly thermosensitive (Q_{10}~25; i.e. a 25-fold increase in current over a 10°C rise in temperature). However, it was not possible to solidify the conclusion that GR28b(D) was a thermosensitive channel, since functional expression studies of the protein either in Xenopus oocytes or HEK cells were not successful. Nevertheless, transgenic flies expressing GR28b(D) in anterior cell neurons in place of TRPA1, rescues the thermotaxis over a shallow gradient, arguing that GR28b(D) represents a new type of thermosensor.

The work by Ni et al. raises many new questions. What are the functions of the other GR28b isoforms, all of which contain unique N-termini and common C-termini? Why does ectopic expression of GR28b(D) confer thermosensitivity to Drosophila cells *in vivo*, but not when it is introduced *in vitro* in Xenopus oocytes or mammalian tissue culture cells? If there exists a required but ubiquitously expressed co-factor that is specific to flies, perhaps Drosophila S2 cells would provide a rationale cell type to express GR28b(D) and perform patch clamp experiments. Because GR28b(D) can substitute *in vivo* for TRPA1, and vice versa, why are these unrelated proteins employed for responding to steep and shallow temperature gradients? If GR28b(D) were to be functionally expressed *in vitro*, it might turn out that it has biophysical properties distinct from TRPA1, and provide guidance for identifying behavioral differences when one channel is expressed in place of the other.

Finally, the question arises as to nature of additional non-canonical functions of gustatory receptors, especially the GR28b proteins. Because a member of the *Gr28b* locus functions in light-sensation (although the isoform is not yet defined) [11], do any of the other four GR28b proteins play unexpected sensory roles distinct from contact chemosensation? Introduction of either GR28b(D) or GR28b(E) transgenes rescues the thermotaxis phenotype resulting from mutation of the entire *Gr28b* locus [5]. Thus, GR28b(E) might also be a thermosensor. Can GR28b(E) substitute for TRPA1 in anterior cell neurons? GR28b(E) does not appear to be expressed in hot cell cells, suggesting that it plays a thermosensory role in some other cell type. Both the *Gr28b.e* and *GR28b.d* reporters are expressed in bitter-responsive taste neurons [12], raising the appealing possibility that one or both proteins function in integrating taste and temperature sensation. The *Gr28b.c* reporter is expressed in the antennal Johnston's organ, which functions in hearing, and *Gr28b.b* and *Gr28b.c* are expressed in a cell of unknown function in the maxillary palp, which is an olfactory organ. Do these proteins participate in hearing or olfaction? In addition, several of the *Gr28b* genes are expressed in abdominal neurons. Additional gustatory receptors are also expressed in a variety of cell types that are not peripheral neurons. In view of wide-range of sensory function for these proteins, which will likely increase over the next few years, the name of this protein family (gustatory receptors), appears to be humorous after all.

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Figure 1.

Gr28b locus. *Gr28b* includes five transcriptional start sites and 5′ exons (A – E), which are joined by mRNA splicing to two common 3′ exons (ce). Shown at the bottom are the RNAs produced following mRNA splicing. Consequently, *Gr28b* encodes five different proteins with different N-termini, but the same C-termini. The illustration is by Peter Allen and Ryan Allen.

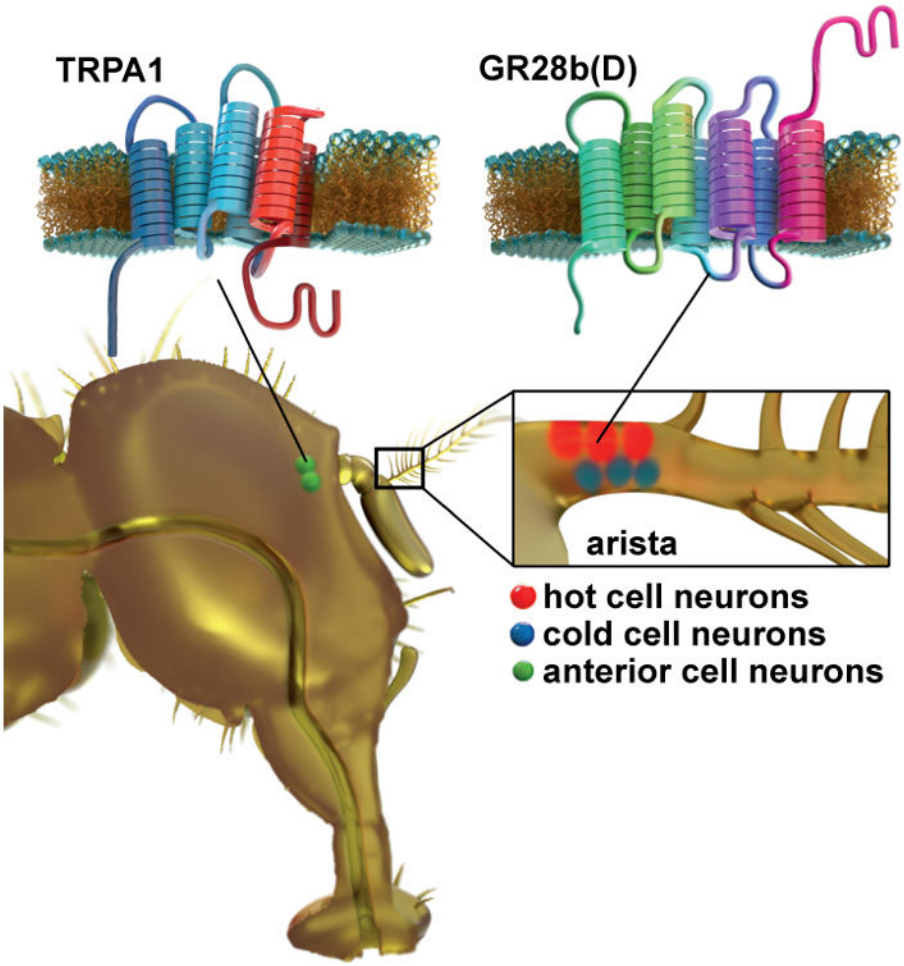

Figure 2.

Peripheral and internal neurons both respond to warm temperatures. Shown are the positions of the anterior cell neurons in the brain (green cells) that express TRPA1 and respond to a shallow temperature gradient (0.5 °C/cm) as the temperatures rise over 25°C. The hot cell neurons (red cells) in the arista express GR28b(D) and are adjacent to the cold cell neurons (blue cells). The hot cell neurons and GR28b(D) are required for the response to a steep temperature gradient above 25 °C (5 °C/cm). The box indicates a magnified portion of the arista, which is shown to the right. The illustration is by Peter Allen and Ryan Allen.