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Commentary

A fly rhodopsin sheds light on thermal taste

Molly Stanley, Sasha A.T. McDowell, Michael D. Gordon*

Department of Zoology and Life Sciences Institute, University of British Columbia, Vancouver, BC V6T 1Z3, Canada

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ABSTRACT

In their recent paper, Li and colleagues discover that cold food tastes less sweet to flies, in part by activating bitter sensory neurons through a rhodopsin-dependent mechanism [1]. This work establishes temperature as an important variable in understanding fly taste processing and adds diversity to the sensory roles for rhodopsin receptors.

Picture the disappointment upon biting into a slice of fruit pie and finding it room temperature instead of warm from the oven. Temperature clearly has a profound effect on the palatability of food, but we are only beginning to understand "thermogustation" - the impact of temperature on taste [2]. Psychophysical and neural data in mammals suggest thermogustation varies between taste modalities. Generally, warmth can enhance sweet and umami taste while cooling can increase saltiness. Bitter and sour thermogustation remain less clear, with studies indicating effects in either direction [2].

Sweet thermogustation has been a focus in mammals, and the robust positive interaction between temperature and sweetness provides an opportunity to test whether thermogustatory effects are conserved across species. In their recent paper, Li and colleagues examine this phenomenon in *Drosophila*. They find that, as in mammals, fly sweet taste is suppressed by cold temperatures. Cooling stimulates bitter taste sensory neurons and taste-associated mechanosensory neurons, both of which are required for sweet suppression. Interestingly, cold activation of some, but not all, bitter neurons requires a member of the rhodopsin family, adding to the molecular complexity underlying food sensation (Fig. 1).

Rhodopsins, containing an opsin protein with a retinal chromophore, are specialized GPCRs long-considered to function exclusively in light detection. However, an intriguing collection of recent work reveals non-canonical roles for rhodopsins in fly sensory detection. Li and colleagues find that one rhodopsin, Rh6, is necessary for cool-sensing within a subset of bitter taste neurons, but dispensable in other cold-sensitive neurons on the labellum. This fits with a previously described requirement for Rh6 in larval temperature preference, although these two thermosensitive functions apparently employ distinct phospholipase C (PLC) cascades [3]. Interestingly, Rh6 requires retinal for temperature sensing, but not for its reported roles in proprioception and mechanosensation [3,4]. Moreover, three other rhodopsins mediate retinal-independent aristolochic acid detection by bitter sensory neurons, further complicating the molecular mechanisms underlying taste detection [5]. Clarifying bitter neuron expression of cool-sensing Rh6 relative to chemical-sensing rhodopsins will be critical in understanding how this family of receptors mediates distinct molecular responses to different sensory modalities within a single class of neurons.

The channel downstream of Rh6 in cool detection is unknown, as are the molecules underlying Rh6-independent cooling responses in bitter and mechanosensory neurons of the labellum. Several candidates, including TRPA1, were ruled out; however, the authors did not examine TrpM, which is required for noxious cold detection in larvae [6]. Pdk2 and the mechanosensor NompC also play roles in larval cold detection, and could be candidates for future investigation [6]. Alternatively, cool-sensing channels may be found in the form of gustatory receptors (GRs). Gr28b acts as a thermosensor in the arista [7], and both bitter and sweet sensory neurons contain numerous GRs that may have atypical roles. For example, Gr64e is a ligand-gated glycerol receptor, but also has a TRPA1-like function downstream of PLC in fatty acid sensing [8].

An interesting issue that the authors speculate on but do not explore experimentally is the neural circuit mechanism by which cooling inhibits sweet taste. They suggest that GABA, released either directly by mechanosensory neurons or by interneurons receiving bitter input, likely exerts presynaptic inhibition of sweet neuron output. This model fits with prior studies on sweet taste inhibition by bitter and mechanosensory stimuli [9,10], and with the authors' observation that cooling does not affect calcium responses in sweet neuron somas. While their

* Corresponding author.
E-mail address: gordon@zoology.ubc.ca (M.D. Gordon).

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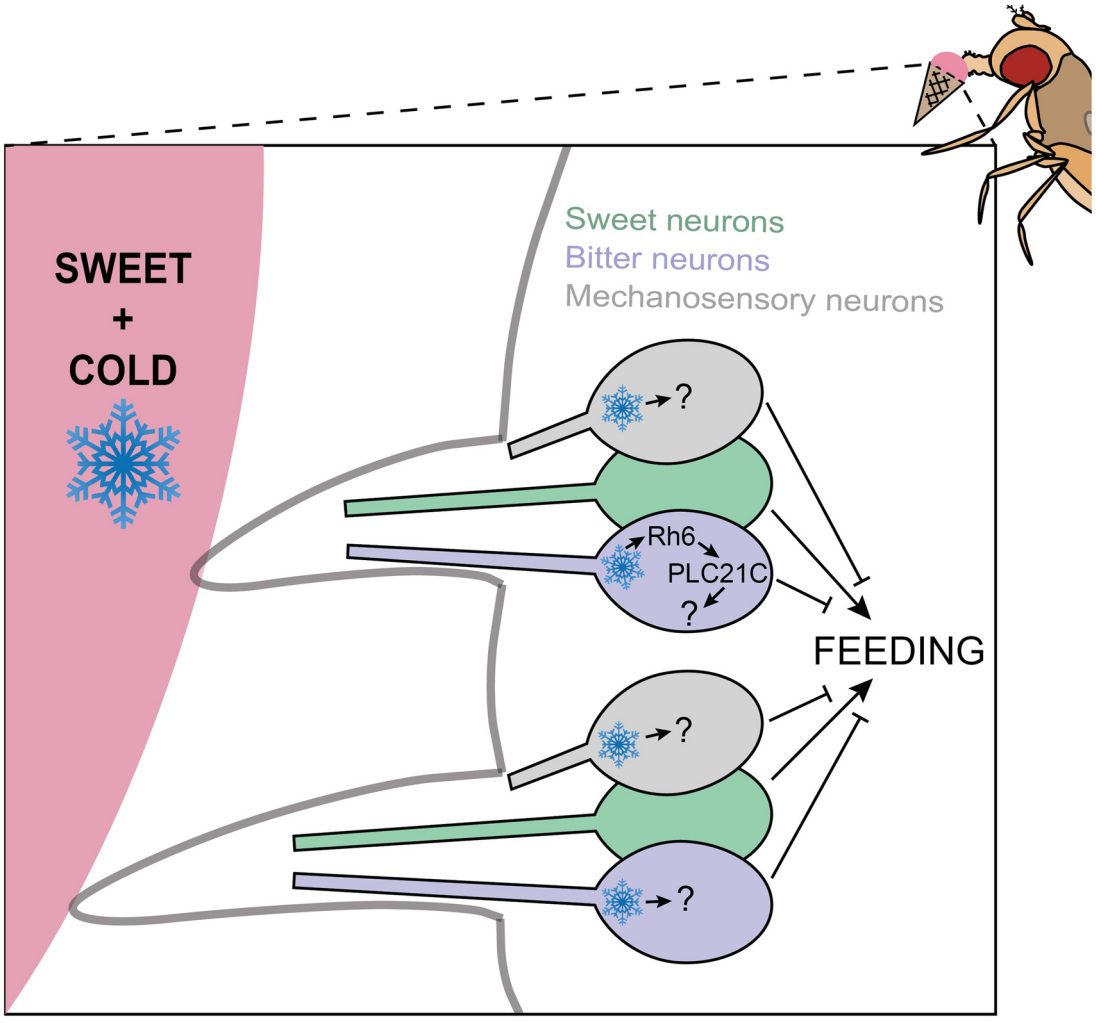

Fig. 1. Sweet taste inhibition by cold. Cold food activates bitter and mechanosensory neurons on a fly's proboscis, which both inhibit appetitive responses to sweetness. Some bitter neurons require Rh6 signaling through PLC21C for cold sensitivity; however, the terminal channel of this cascade and the mechanisms driving cold-evoked activity in other neurons remain unknown.

bath stimulation of labellar taste neurons is uncommon and could suffer from artifacts introduced by the ex vivo preparation, one advantage is that measuring calcium at the soma provides a better estimate of neuronal inputs. Conversely, imaging of taste neuron axon terminals in the brain during cooling could reveal GABA-dependent inhibition of sweet-evoked presynaptic calcium transients.

A number of additional questions remain. One is why the effect of cooling on sweet taste is enhanced in the second and third exposure to cooled sugar. Is this from sensitization of the mechanosensory and/or bitter neurons to cooling, desensitization of the sweet neurons to sugar, or perhaps enhancement of GABA release downstream of the sensory neurons? Further calcium imaging and electrophysiology to measure inputs and outputs of relevant neurons would clarify this issue. Another question is why both bitter and mechanosensory neurons are required for cold-evoked suppression of sweet taste. The authors suggest that perhaps the combination of these two sensory inputs allow discrimination of cold temperatures from bitter or mechanical stimuli. This idea is testable with a learning paradigm, but it is hard to imagine such a discrimination task being mediated by simple inhibitory feedback on sensory neuron output. An alternative explanation is a threshold for inhibition that is only met with activation of both populations under the experimental conditions used.

Future studies will undoubtedly enhance our understanding of thermogustation across species. For now, the work from Li and colleagues establishes an important framework for examining the mechanisms underlying temperature and taste integration in flies, and highlights the possibility that opsins may represent ancestral GPCRs functioning in many sensory modalities outside of vision.

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