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Hungry Flies Tune to Vinegar

Wolf Huetteroth[1] and Scott Waddell[1,*]
[1]Department of Neurobiology, University of Massachusetts Medical School, 364 Plantation Street, Worcester, MA 01605, USA
*Correspondence: scott.waddell@umassmed.edu
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Many molecular signals that represent hunger and satiety in the body have been identified, but relatively little is known about how these factors alter the nervous system to change behavior. Root et al. (2011) report that hunger modulates the sensitivity of specific olfactory sensory neurons in *Drosophila* and facilitates odor-search behavior.

Smell is an important element of search behavior in many animals. However, the likelihood that a particular smell elicits search behavior depends on a range of factors. Some odors are innately attractive, whereas others are repulsive. In some cases, such as pheromones, chemical quality can account for the respective valence. In other cases, quantity is paramount with low concentrations being attractive and high being avoided. In addition to these innate preferences, odor-evoked behavior in an animal depends on the context of internal state, including hunger, thirst, stress, sex drive, and circadian period. Lastly, innately attractive odors can be conditioned to become repulsive (DasGupta and Waddell, 2008), and vice versa, demonstrating that learning has a profound influence on odor-driven behavior.

In *Drosophila*, olfactory sensory neurons (OSNs) that express the same odorant receptor project to unique target glomeruli in the antennal lobe. Prior work has shown that fruit flies are attracted to low concentrations of apple cider vinegar, and that Or42b-expressing OSNs that project to the DM1 glomerulus are particularly important for this behavioral response (Semmelhack and Wang, 2009). In the current study, attraction to vinegar was found to be strongest in hungry flies when tested in a search arena. Calcium imaging of OSNs and their direct second-order projection neurons in the antennal lobe reveals that hunger enhances vinegar-evoked activity in the DM1, DM2, and DM4 glomeruli but reduces the response in VM2 and VA3. These findings lead to a search for the underlying mechanism.

Some OSNs express small neuropeptide F (sNPF), suggesting that certain odors might evoke sNPF release into the antennal lobe (Carlsson et al., 2010). RNAi knockdown of transcripts for either sNPF or its receptor sNPFR1 in OSNs impairs hunger-enhanced vinegar attraction behavior and vinegar-evoked responses in OSNs. Consistent with earlier work (Semmelhack and Wang, 2009), sNPF function in the DM1 glomerulus, but not in DM4 or DM2, is particularly important for vinegar-search behavior. Therefore, sNPF appears to enhance vinegar-evoked OSN activity via a cell-autonomous positive-feedback loop (Figure 1). How then is this mechanism modified by hunger and satiety?

The insulin-glucagon system is a conserved mechanism of nutritional homeostasis (Teleman, 2010). In insects, insulin and the ortholog of glucagon, adipokinetic hormone (AKH), are released in an endocrine fashion into the hemolymph. Whereas AKH is mainly used to recruit glucose from internal stores, insulin signals the satiated state after food intake and initiates glucose uptake into tissue. Due to the critical role of nutrient balance at every level of the organism, insulin levels affect many processes including feeding, growth, reproduction, and aging. Furthermore, the insulin receptor is broadly expressed, suggesting that insulin might broadcast nutrient status around the body. Root and colleagues (2011) find that some OSNs, including those projecting to DM1, express the insulin receptor, suggesting that insulin might directly relay nutrient status to OSNs. Indeed, hunger was shown to increase the expression level of sNPFR1 in the antennae. This elevation, and hunger-enhanced vinegar search, can be blocked by expressing a constitutively active insulin receptor in OSNs. The data are therefore consistent with a model in which hunger elevates sNPFR1 expression, thereby promoting positive sNPF feedback in specific OSNs. In contrast, satiety has the opposite effect via insulin signaling in OSNs.

These findings raise several important questions. sNPF is broadly expressed in

the brain, including several specific classes of OSN, suggesting that it could have a similar autocrine facilitating role in other neurons and glomeruli (Carlsson et al., 2010). In fact, other classes of OSN with well-defined odor sensitivity express sNPF at much higher levels (Carlsson et al., 2010). These include the Or67d OSNs, which project to the DA1 glomerulus and are activated by the male-specific pheromone 11-cis-vaccenyl acetate (Kurtovic et al., 2007). It will be interesting to determine whether all sNPF-expressing OSNs exhibit autofacilitation and are subject to metamodulation by state, perhaps via the myriad of other neuropeptides present in the antennal lobe (Carlsson et al., 2010). If hunger generally promotes the detection of different food odors, rather than just vinegar, it would seem logical that other food-relevant OSNs might be similarly regulated. For example, the DM2 glomerulus is enlarged in the morinda fruit specialist *Drosophila sechellia* and responds very strongly to hexanoates, a component of morinda odor (Dekker et al., 2006). If sNPF autocrine facilitation is a conserved mechanism for food seeking, one might predict that the *D. sechellia* DM2 glomerulus undergoes sNPF-dependent autofacilitation to hexanoates and is also modulated by hunger.

When a hungry animal finds and consumes food, the drive to seek more food is neutralized. Although the onset of hunger-driven behavior can be slow, satiating effects can be fast. It therefore seems unlikely that transcriptional control of a peptide receptor completely accounts for the cessation of search behavior. A rapid off response would require that the sNPF receptor and its transcript were actively turned over in OSNs of satiated flies, or that sNPF release was inhibited. Alternatively, higher-level modulatory mechanisms could provide fast and flexible control of behavioral output (Krashes et al., 2009).

Odor-driven searching requires the fly to navigate up a concentration gradient toward the source. It is therefore important that the fly simultaneously tracks a change in intensity while maintaining information about odor identity. This task of concentration invariance seems to be achieved by a network of inhibitory and excitatory gain-control mechanisms involving lateral connectivity in the antennal lobe (Yaksi and Wilson, 2010). Given that starvation was reported to increase the amplitude of odor-evoked responses in OSNs and their directly postsynaptic projection neurons (Root et al., 2011), it will be important to understand how this signal amplification is integrated with gain control so that the fly extracts an appropriate orientation signal. Maintaining a constant representation of odor identity is also critical for a fly to benefit from experience. Although hunger might amplify the detection of some food-relevant odors, it is important to remember that some were better than others.

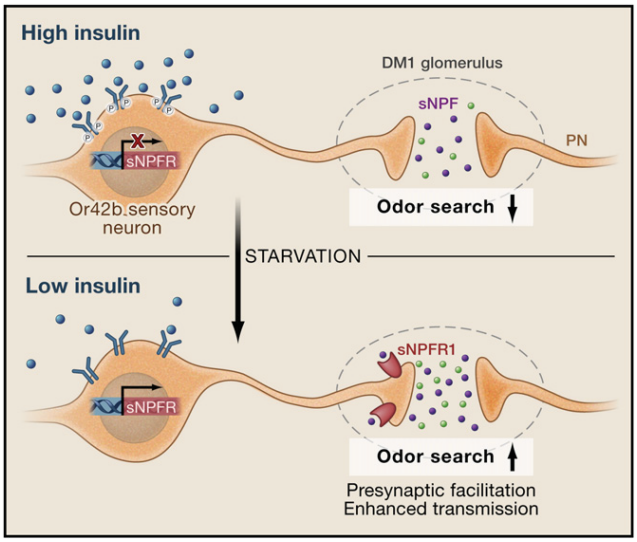

Figure 1. Hunger Facilitates Synaptic Release from Olfactory Sensory Neurons

In starved *Drosophila*, reduced inhibitory insulin (blue) signaling leads to up regulation of sNPF receptor gene (red) expression in Or42b olfactory sensory neurons (left). sNPF (purple) release from the olfactory sensory neurons, presumably driven by odor, leads to presynaptic facilitation via an autocrine positive feedback loop. The result is increased efficacy of transmission (green) from the sensory neuron to downstream projection neurons (PNs), and more effective vinegar search behavior.

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