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Letter to Editor

The Role of the Sucrose-Responsive IR60b Neuron for *Drosophila melanogaster*: A Hypothesis

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Abstract

In a recent paper, Joseph and colleagues (Joseph et al. 2017) have characterized an IR60b receptor-expressing neuron in *Drosophila*. They showed that it responds to sucrose and serves to limit sucrose consumption, and proposed that it may thereby act to prevent overfeeding. Here, we propose an alternative hypothesis for the functional role of sucrose feeding control, and for how this limitation of sucrose uptake is accomplished. Adult fruit flies feed by excreting saliva onto the food, and imbibing the predigested liquefied food, or by filling the crop, where the food is predigested. Enzymes in the saliva hydrolyze starch and disaccharides into absorbable monosaccharides. Premature ingestion into the midgut would not give the enzymes in the saliva enough time to predigest the food. Thus, IR60b neurons might serve as a sensor to monitor the digestive state of external food or crop content: when disaccharides (sucrose) concentration is high, ingestion to the gut is inhibited, keeping a low concentration of starch and disaccharides in the midgut.

Key words: insects, nutrition, obesity, sugar sensing, taste receptor

Taste is an essential sense for most animals, as it is needed for detecting palatable food, keeping nutrient balance, and rejecting spoiled food. In *Drosophila*, the gustatory receptors GR64a-f and GR5a are expressed in neurons in taste sensilla on the labial palp and legs and mediate the "sweet" perception of multiple sugars and promote feeding in hungry flies (Dahanukar et al. 2007; Jiao et al. 2007; Fujii et al. 2015), whereas GR43a-expressing neurons in the brain sense hemolymph fructose and regulate feeding in a satiation-dependent manner (Miyamoto et al. 2012). In a recent paper, Joseph and colleagues (Joseph et al. 2017) have characterized an additional sugar-responsive neuron which expresses the receptor IR60b (Koh et al. 2014). These neurons are located in the labral sense organ in the pharynx, where they have direct contact with ingested food. IR60b neurons are selective to sucrose, which is a ubiquitous sugar in fruit and is a disaccharide composed of glucose and fructose. Surprisingly, IR60b neurons have the opposite effect on feeding as the previously known sugar-responsive GR64a-f- and GR5a-expressing neurons: activating IR60b neurons reduces feeding, whereas silencing them increases feeding (Joseph et al. 2017). Therefore, the authors propose that IR60b neurons could be part of a circuit that prevents fruit flies

from food overconsumption to maintain homeostasis and balance nutrients. Interestingly, IR60b is under strong stabilizing selection, indicating that protection from overfeeding would exert a strong evolutionary pressure. In this commentary, we propose an alternative function for this receptor. Rather than preventing overfeeding, we propose that IR60b neurons delay the ingestion of undigested sucrose into the gut, thereby providing enough time for its predigestion externally or inside the crop.

Insects have evolved a great variety of mouth parts: piercing, cutting, sucking, etc. Fruit flies, similar to their closely related house flies, have sponging mouthparts (Smith 1985). The labellum is sponge-like at the end, with many food channels. The digestive tract in *Drosophila* is similar to that of other dipterans (Lemaitre and Miguel-Aliaga 2013). Blow flies (*Calliphora*) feed by releasing saliva or crop content onto their food to liquefy and predigest it (Hansen Bay 1978). The saliva contains digestive enzymes, including amylase to hydrolyze starch into disaccharides (Boer and Hickey 1986) and sucrase (Hansen Bay 1978) to hydrolyze the disaccharide sucrose into the monosaccharides glucose and fructose. On a starch-rich diet, mutant flies with no amylase activity can only survive when

kept with wildtype flies, relying on their external starch digestion (Haj-Ahmad and Hickey 1982). In the midgut, transport proteins move monosaccharides into the hemolymph (Lemaitre and Miguel-Aliaga 2013), where the glucose concentration is kept low by conversion to trehalose (Treherne 1958).

Predigestion of starch and disaccharides makes foodborne bacteria more susceptible to bactericidal activity in the midgut (Dare et al. 1972; Espinoza-Fuentes and Terra 1987). Therefore, we propose that it may be important for a fly that, after releasing its saliva onto, say, the surface of a banana or ingesting the content into the crop, it waits sufficiently long for the enzymes to hydrolyze starch and disaccharides into monosaccharides. A high concentration of sucrose, as the main disaccharide in the food, would indicate that the predigestion process has not proceeded sufficiently—therefore ingestion should be delayed. When the enzymes have fulfilled their digestive action, sucrose concentration drops while glucose raises, and the fly should now ingest the food into the midgut. In this scenario, IR60b neurons would mediate the "stop" signal: a receptor with high selectivity for disaccharides and low response to monosaccharides, at the very beginning of the alimentary canal. It is also conceivable that IR60b neurons control the digestive state of crop regurgitates, and control whether food is directed to the crop or to the midgut. The more generalist sugar sensing neurons (neurons that express GR5a and GR64a-f) would mediate a positive driving force. Joseph and colleagues (Joseph et al. 2017) show that IR60b neurons respond to both sucrose (at low concentrations) and glucose (at high concentrations) at concentrations that are consistent with our proposal. Banana is one of the fruits with the highest sugar concentration (Widdowson and McCance 1935). It contains 322 mM glucose (IR60b would not respond) and 193 mM sucrose (IR60b would respond). After complete predigestion the crop content would contain 515 mM glucose, which is below the 900 mM glucose that elicited a response in IR60b (Joseph et al. 2017). More complete dose-response curves would be needed to address this point. Likewise, more research is needed to understand the time-scales of IR60b-mediated feeding inhibition and the role of other sensory modalities in controlling crop filling and emptying (Stoffolano and Haselton 2013). Furthermore, the role of physiological conditions in crop and intestinal tracts needs to be addressed: it is known that the pH value of different gut segments is tightly controlled and adapted to the local enzymes (Lemaitre and Miguel-Aliaga 2013). We note that *Drosophila* larvae lack a crop and use external digestion: they live in their food and engage in social digestion as they feed collectively (Gregg et al. 1990; Dombrovski et al. 2017) and actively regulate external digestion (Sakaguchi and Suzuki 2013). Larvae express IR60b in their dorsal pharyngeal sensilla (Stewart et al. 2015).

Control of digestive steps is an important task for all animals: the alimentary canal is divided into different stages, and food is passed from one stage to the next in a carefully controlled manner. For example, in humans the pylorus controls the passage of food from the stomach into the duodenum, and similarly the ileocecal valve controls the passage from the ileum (last section of the small intestine) into the colon (large intestine). In humans, as in flies, predigestion of starch and disaccharides into monosaccharides is the first step in digestion. It is accomplished in the alkaline mouth by enzymes including amylase, and according to some dietologists swallowing into the acidic stomach should be delayed until a food bolus has been completely insalivated, and mouth pre-digestion has occurred. In humans, the osmotic effects of non-absorbable oligo- and disaccharides and their fermentation through intestinal bacteria causes

intestinal harm (Shepherd et al. 2013). The pharyngeal reflex is only activated when the food bolus has a texture that indicates sufficient salivation, but we are not aware of a chemosensory component that would signal when to swallow, and would inhibit precocious swallowing. It is conceivable that a downregulation of pharyngeal reflex control, for genetic or cultural reasons (e.g., "fast food" habits), might contribute to dietary problems, including obesity. Thus, studying IR60b neurons (Joseph et al. 2017) in fruit flies can contribute to understanding how digestive steps are organized in animals.

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