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Hedgehog-mediated gut-taste neuron axis controls sweet perception in *Drosophila*

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Dietary composition affects food preference in animals. High sugar intake suppresses sweet sensation from insects to humans, but the molecular basis of this suppression is largely unknown. Here, we reveal that sugar intake in *Drosophila* induces the gut to express and secrete *Hedgehog* (*Hh*) into the circulation. We show that the midgut secreted Hh localize to taste sensilla and suppresses sweet sensation, perception, and preference. We further find that the midgut Hh inhibits Hh signalling in the sweet taste neurons. Our electrophysiology studies demonstrate that the midgut Hh signal also suppresses bitter taste and some odour responses, affecting overall food perception and preference. We further show that the level of sugar intake during a critical window early in life, sets the adult gut Hh expression and sugar perception. Our results together reveal a bottom-up feedback mechanism involving a "gut-taste neuron axis" that regulates food sensation and preference.

Sugar is a major energy source for most animals, and thus sweet taste typically mediates attraction (i.e., has a positive valence). This innate drive to consume sugar must be fine-tuned to avoid insulin resistance and type 2 diabetes. Sugar metabolism and energy status in the muscles, gut, and adipose tissue regulate insulin release[1], which then balances the metabolic requirements of the periphery. In mice and humans, dopaminergic mesolimbic neurons reshape sugar responses and their activation produces an intense desire for sugar[2]. Accumulating evidence suggests sugar reward is suppressed by insulin, which passes through the blood brain barrier and suppresses dopamine pathways[3,4]. Therefore, insulin resistance in the reward circuits leads to sugar overconsumption and obesity in humans[5–7]. Thus, in both mice and humans, peripheral sugar metabolism can act through insulin to reduce the central drive for sugar consumption, reducing sugar intake.

In *Drosophila*, the insulin producing cells (IPCs) are localized in the brain and thus communicate central energy status[8]. IPCs are regulated by *Gr43a* taste receptor-expressing neurons in the fly brain that sense internal sugar status. They then promote feeding in food-deprived flies and suppress feeding in fed flies[9,10]. Energy status also regulates the activity of dopaminergic taste interneurons that control food consumption[11], suggesting that feeding in flies may also be regulated at the level of taste perception. Ingested sugar also regulates sweet perception in *Drosophila*[12], with low sugar intake increasing sweet sensation and high sugar intake suppressing sweet perception[12–15]. This suggests that the periphery in *Drosophila* uses signals other than insulin to balance sugar intake. However, the circuitry and signals that communicate peripheral sugar metabolism to regulate sweet taste sensitivity remain unknown.

Sugar suppression of sweet sensation also occurs in mice and humans[16]. We therefore hypothesized that the same sweet suppressive signal may regulate sugar metabolism in both *Drosophila* and mice. In both species, Hedgehog (Hh) signalling regulates sugar metabolism[17,18]. Interestingly, dysfunctional sugar metabolism increases the release of the vertebrate Hh orthologue Sonic hedgehog (Shh) into the blood[19]. In *Drosophila* larva, the midgut secretes Hh into the haemolymph[20]. After its release, Hh binds and inhibits its

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