Nutrient sensing

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No sugar, just protein please — says the fly

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Malita, Kubrak et al. identify a circuit that drives food-specific appetites in *Drosophila* orchestrated by gut-derived Neuropeptide F.

Who hasn't chosen something sweet over something savoury and vice versa? Choosing what to eat is part of our everyday life. This is true not only for humans but for all animals, because hunger for specific foods is how our metabolism communicates the specific nutrients it needs. Food-specific appetites have evolved to align metabolic needs with the consumption of specific nutrients so that nutritional homeostasis is maintained. In other words, if internal glucose or amino acid levels are low, animals, including humans, prefer eating foods high in sugar or protein, respectively. As a result, conserved sensors that detect the internal nutritional state and signalling pathways that translate the nutritional state to feeding decisions control the animal's feeding behaviour[1–3]. Even though great progress has been made in understanding the diverse circuits and inter-organ signals that regulate hunger and satiety, the homeostatic mechanisms that drive food-specific hungers remain poorly understood.

Drosophila has emerged as a powerful genetic model to study feeding behaviour[2]. In this issue of *Nature Metabolism*, an elegant study by Malita, Kubrak et al.[4] sheds light on the complex circuits that control food-specific hungers in flies (Fig. 1). Building on work from previous studies, together with sophisticated genetic interaction and behavioural experiments, the groups led by Halberg and Rewitz provide evidence for the importance of gut-derived Neuropeptide F (NPF) signalling in suppressing sugar preference and in promoting protein feeding.

NPF is the homologue of mammalian Neuropeptide Y (NPY), one of the most potent orexigenic peptides in the mammalian brain, which triggers food consumption and preferential intake of carbohydrates[5,6]. NPF is expressed in both the *Drosophila* brain and gut enteroendocrine cells (EEs). While brain-derived NPF promotes sugar sensitivity and increases feeding in female flies, reminiscent of NPY, gut-derived NPF has different functions[2,7]. Previous work by Yoshinari et al. found that in virgin female flies, sugar-dependent metabolism is controlled by gut-derived NPF, which promotes lipid anabolism and starvation resistance by regulating glucagon-like and insulin-like hormones[7]. Expanding on this work, Malita, Kubrak et al.[4] found that reduction of NPF in EEs leads to high sugar intake not only in virgin flies but also in mated females, whereas male flies have opposing feeding behaviour. Additionally, different feeding assays together with several genetic perturbations, like genetically increasing NPF release from gut EEs and testing the feeding behaviour of the fly, further established the sugar-satiety roles of gut NPF in females.

An interesting aspect of the female fly feeding behaviour is that their food-specific appetites change after mating, reminiscent of the food cravings in pregnant women[8,9]. Mated female flies increase their food preference for protein-rich food, like yeast, due to the metabolic demands of egg production[8]. The bias for protein-rich food that mated females have is controlled by the sex peptide (SP)[8], which is transferred

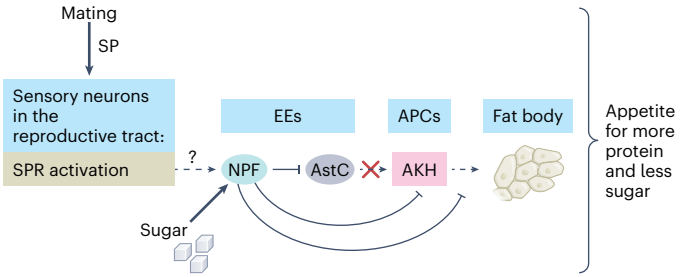

Fig. 1 | Gut-derived hormonal circuit driving food-specific appetites in *Drosophila*. Malita, Kubrak et al. propose that gut-derived NPF suppresses sugar intake and promotes protein preference in mated female flies. SPR activation in sensory reproductive neurons and sugar consumption promote NPF release from EEs in the *Drosophila* gut. NPF signalling then suppresses the release of the glucagon-like AKH in three ways: 1) by signalling directly to APCs; 2) by blocking AstC-dependent release of AKH and 3) by counteracting AKH signalling in the fat body (*Drosophila* liver and adipose tissue). Together, these lead to reduction of further sugar intake and increase in protein-rich food choices.

to females through the seminal fluid during mating before activating the G-protein-coupled SP receptor (SPR), which is expressed in sensory neurons along the reproductive tract[8,10]. In addition, SP–SPR signalling during mating triggers NPF release from EEs to induce germline stem cell proliferation in the ovaries[11]. Based on these findings, the authors investigated whether the SP-dependent change in food choices in females and the concurrent SP-dependent stimulation of gut-derived NPF signalling are linked. Using automated feeding assays to test the preference for yeast or sugar, and by performing clever perturbations such as genetically reducing SPR signalling while injecting NPF into the hemolymph of mated females, they found that gut NPF acts downstream of SPR signalling to increase the fly's preference for protein and to reduce sugar consumption. Altogether, these studies unravelled how a reproductive signalling pathway stimulates a gut-derived hormone to align food-specific appetites with post-mating nutritional requirements.

What are the cellular mechanisms that regulate NPF in EEs? They discovered that the sugar transporter 2 (Sut2) in EEs triggers the NPF sugar-satiety response following sugar intake. Interestingly, Yoshinari et al.[7] previously reported that in virgin females, NPF release in response to sugar is controlled by Sut1, a paralogue of Sut2. Given that feeding behaviour depends on metabolic needs, which are influenced by the reproductive state, and that NPF is involved in driving feeding choices during reproduction, perhaps these different findings highlight the complex mechanism governing the release of NPF from EEs.

An essential hunger-inducing signal in *Drosophila* is adipokinetic hormone (AKH), the fly analogue of mammalian glucagon, which is released by AKH-producing cells (APCs). Even though any roles of AKH in food-specific appetites remain unexplored, previous work by

Yoshinari et al.[7] found that gut NPF suppresses AKH to regulate lipid metabolism in virgin females, thus linking sugar-responsive release of NPF to AKH signalling[7]. Here, the authors further explored the NPF–AKH axis in mated females and unravelled the multifaceted suppression of AKH signalling by NPF. Specifically, they found that NPF blocks AKH release directly via the G-protein coupled NPF receptor (NPFR) in APCs, as well as indirectly by blocking Allatostatin C (AstC) release in EEs[12] and by counteracting the stored energy mobilization effects of AKH signalling in the fat body[13] — the fly organ analogous to liver and adipose tissue. Moreover, a plethora of different genetic interaction experiments between NPFR and AKH signalling showed that, after mating, the gut derived NPF–AKH axis promotes protein-rich food preference and suppresses sugar intake.

Altogether, through a diverse array of elegantly performed experiments, the team led by Halberg Rewitz have described a gut hormonal circuit that drives food-specific appetites. Their findings strongly support that in mated females, sugar responsive NPF signalling from EEs inhibits AKH to suppress further sugar intake and to increase protein preference. Nevertheless, some questions remain, including a better understanding of the SPR–gut axis. For example, how do SPR-expressing neurons promote NPF release from EEs? Does signalling from SPR-expressing neurons regulate the release of other gut hormones? In addition, this study focuses primarily on the interorgan circuit controlling post-mating feeding choices. Given that feeding decisions exhibit sexual dimorphism and differ based on the reproductive state, more work is needed to dissect the mechanisms that drive food-specific appetites in male and virgin female flies.

Finally, the mammalian NPY family includes several peptides that regulate food-seeking behaviour, besides NPY itself. One of them is peptide YY (PYY), which is produced by gut-endocrine L cells and functions as a satiety signal. Low PYY circulation is associated with obesity, and PYY is being considered as a therapeutic for weight management[14], yet it remains unclear if PYY regulates food-specific appetites. These findings suggest that perhaps gut-derived NPF in *Drosophila* fulfils similar functions to PYY, which may help characterize the role of PYY in aligning metabolic needs to food-specific hungers, which could be of noteable therapeutic value.

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Competing interests

All authors declare no competing interests.