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NEUROENDOCRINOLOGY

More nutritious than delicious

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Food-deprived *Drosophila melanogaster* show a preference for nutritive sugars (which can be metabolized) over non-nutritive sugars (which offer no nutritive benefit) independently of taste; however, the mechanisms that mediate this preference are unknown. In a recent study, Suh and colleagues show that, in *D. melanogaster*, neurons expressing Diuretic hormone 44 (Dh44; a homologue of mammalian corticotropin-releasing hormone (CRH)) respond selectively to nutritive sugar and signal to promote the preferential ingestion and digestion of nutritive sugars.

The authors demonstrated that just 5 minutes after starting to feed in a two-choice test, starved flies show a preference for eating solution containing a nutritive sugar, such as D-glucose, over eating a more concentrated (and thus more tasty) solution of a non-nutritive sugar, such as L-glucose, implying that flies need no training to develop this preference. By contrast, starved Dh44-mutant flies show a strong preference for the tastier, but non-nutritive, solution. Specific artificial inactivation or activation of Dh44-expressing neurons (via targeted expression of a hyperpolarizing channel or a depolarizing channel, respectively) also impaired the preference for the nutritive sugar. Therefore, the activity of Dh44-expressing cells mediates the preferential consumption of nutritive sugars.

The authors found that Dh44 is expressed by six neurons in the pars intercerebralis (which is functionally homologous to the hypothalamus) and, using calcium imaging of brain preparations, found that nutritive, but not non-nutritive, sugar solutions induced calcium oscillations in these cells. Moreover, levels of Dh44 in these neurons decreased following exposure to nutritive sugars — suggesting that, when activated, these cells may secrete the neuropeptide. Furthermore, this nutritive-sugar-induced reduction in intracellular Dh44 was abolished when sugar transporters or the glucose-metabolizing enzyme hexokinase were pharmacologically inhibited, indicating that these cells may release Dh44 only in response to sugars that can be transported from the haemolymph into the cell and metabolized.

Dh44-positive neurons were found to project to the suboesophageal zone (SEZ) in the brain and to the gut, and the two Dh44 receptors, Dh44R1 and Dh44R2, were expressed in neurons innervating the SEZ and in cells in the gut, respectively. In the two-choice test, starved Dh44R1- or Dh44R2-mutant flies showed no preference for D-glucose over L-glucose, implying that these receptors are also necessary for nutritive discrimination. Strikingly, artificial activation of Dh44R1-expressing cells promoted feeding and digestion: this activation increased the frequency of proboscis extension, the rate of gut muscle contractions and the numbers of excreta produced.

Altogether, these results provide evidence for a taste-independent system for nutrient detection and selection in flies. The authors propose a model whereby Dh44-positive neurons metabolize nutritive sugars taken up from the haemolymph and release Dh44, which binds to Dh44Rs in the SEZ and gut to upregulate feeding behaviours and digestion. Furthermore, the authors suggest that CRH, which is expressed by the hypothalamus, might be involved in a similar system in mammals.

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