Controlling carbs and fat: Learning from the fruit fly

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Incretins are hormones secreted by intestinal cells that regulate pancreatic insulin and glucagon to control sugar metabolism in mammals. Although counterparts of insulin and glucagon have been identified in invertebrates, no hormone equivalent to incretin has been described. Now, researchers at the University of Tsukuba demonstrate that Neuropeptide F (NPF), a hormone produced by the midgut, performs this complex role in the fruit fly.

Life processes are orchestrated by diverse neuroendocrine feedback systems that retain fundamental similarities across the animal kingdom. In response to dietary sugars, incretins from the mammalian gut stimulate pancreatic cells to produce insulin and to suppress its counter-regulatory hormone glucagon. Together, they antagonistically fine-tune sugar levels: Insulin clears circulating carbohydrate and promotes fat storage while glucagon plays a modulatory role.

Having earlier discovered the reproductive function of NPF in the fruit fly, Drosophila melanogaster, the research team wondered about its role in other biological processes, particularly in energy homeostasis. Their research strategy included advanced genetic engineering to generate mutant flies of specific gene knockout strains (in which genetic expression has been inactivated or deleted) and knock-in strains (in which a one-for-one substitution of a genetic sequence has been created at a particular location). Cutting-edge laboratory techniques were used to reveal the genetic and molecular signaling pathways and underlying cellular mechanisms.

The researchers were able to demonstrate that NPF is secreted by intestinal endocrine cells in response to dietary sugar. It signals NPF receptor in the corpora cardiaca, a gland-like organ in insects, and stimulates insulin producing cells in the insect brain to suppress glucagon-like hormone while enhancing insulin-like peptide production. This increases the glucose level in the hemolymph (the circulatory fluid in the insect's body cavity) and promotes lipid accumulation in body fat.

"Our investigations showed that loss of midgut NPF or disordered

NPF/NPFR signaling in the fruit fly produced metabolic disorders similar to incretin loss in mammals, such as lipodystrophy (loss of healthy fat), hypoglycemia and hyperphagia (overfeeding)," Professor Ryusuke Niwa, main author of the study, explains. "Significantly, although NPF is also produced by the brain, we proved that brain-derived NPF lacks this function, and that Drosophila NPF is structurally distinct from mammalian incretins. However, further research to investigate the role of NPF in other potential target tissues is necessary."

This study highlights the underlying similarities of sugar-dependent metabolic processes between insects and mammals. Better understanding of the functional role of incretins may inform therapeutic strategies for medical disorders associated with their dysfunction such as obesity and type 2 diabetes.

More information: Yuto Yoshinari et al, The sugar-responsive enteroendocrine neuropeptide F regulates lipid metabolism through glucagon-like and insulin-like hormones in Drosophila melanogaster, *Nature Communications* (2021). DOI: 10.1038/s41467-021-25146-w

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