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Glucose-Sensing Neurons Reciprocally Regulate Insulin and Glucagon

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Abstract

A recent paper by Oh *et al. (Nature*, 2019) identified a single pair of neurons in the fruit fly brain that directly senses “blood” glucose levels and reciprocally regulates secretion of insulin and glucagon. This study provides insight into how the brain regulates circulation and storage of glucose.

Keywords

glucose sensing; homeostasis; neuropeptides

Glucose (referring to D-glucose when not specified) is a primary energy source for cells in animals. In mammals including humans, blood glucose levels are tightly regulated and maintained within a narrow range. The interplay of two hormones, insulin and glucagon, is critical for regulating circulating glucose in response to dietary conditions. When blood glucose is high (e.g., after feeding), insulin release from pancreatic β-cells promotes cellular glucose uptake and storage. When blood glucose levels drop (e.g., when fasted), glucagon release from pancreatic α-cells promotes the conversion of stored glucose back into circulating glucose. While glucose levels are sensed by insulin- and glucagon-secreting cells in the pancreas, there are also brain neurons that sense glucose and potentially help regulate glucose homeostasis and feeding. However, the identity and physiological roles of glucose-sensing neurons remain largely unclear.

In *Drosophila* as in mammals, circulating glucose is regulated by *Drosophila* insulin-like peptides (Dilps) and the fly equivalent of glucagon, adipokinetic hormone (AKH). Dilp2 release by neurons in the pars intercerebralis of the fly brain and AKH release by neuroendocrine cells in the corpus cardiacum reciprocally regulate hemolymph (blood) glucose levels. Glucose levels were previously known to be sensed by Dilp2- and AKH-producing cells [1], [2]. A recent study in *Nature* by Oh and colleagues expands our understanding of glucose sensing and regulation in the fly, by demonstrating how neural control of hormonal release regulates glucose availability. Specifically, the authors identified

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a single pair of glucose-sensing neurons in the fruit fly brain that reciprocally regulates Dilp2 and AKH to help maintain glucose homeostasis [3].

To identify neurons that sense glucose based on its nutritional value, the authors screened a library of fly strains in which neural subsets had been silenced for defects in preference for nutritive D-glucose over non-nutritive L-glucose when starved. This screen led to the identification of one pair of neurons that, upon neural silencing, abolished the D-glucose preference. These neurons were named CN neurons, as they expressed two neuropeptides, corazonin and short neuropeptide F (sNPF). Importantly, CN neurons directly responded to sugars present in fly hemolymph, including D-glucose, D-fructose, and D-trehalose, but not to the non-nutritive sugar L-glucose, non-hemolymph sugar sucrose, or non-sugar nutrients such as amino acids. The response to glucose requires glucose transport into the cell and intracellular metabolism of glucose (Figure 1), demonstrating that the CN neurons directly sense glucose.

Do the glucose-sensing CN neurons participate in glucose homeostasis? CN neurons have two axonal branches, with one branch projecting to the Dilp2 cells and the other branch projecting to the AKH producing cells. The authors found that stimulation of CN neurons excites Dilp2 cells while hyperpolarizing AKH cells. Selective silencing of CN neurons results in impaired Dilp2 release, increased AKH release in fed flies, and hyperglycemia. Finally, the authors addressed how CN neurons promote Dilp2 release while inhibiting AKH release. Surprisingly, the release of the neuropeptide sNPF by CN neurons both stimulates the Dilp2 cells and inhibits the AKH cells. Pharmacological experiments suggest that the sNPF receptor, a G protein-coupled receptor, is likely coupled to Gαq to mediate a stimulatory effect in the Dilp2 cells while coupled to Gαi/o to mediate an inhibitory effect in the AKH cells (Figure 1).

This study nicely illustrates how neurons in the brain actively monitor “blood” glucose levels and coordinate hormones that are important for glucose homeostasis. A single neural pair that senses circulating glucose and directly modifies release of Dilps and AKH provides a mechanism for precise temporal control of hormone release. Unlike direct mechanisms for sensing circulating glucose by Dilp2 or AKH producing cells, this indirect neural mechanism may rapidly adjust the relationship between glucose levels and hormone production, and is well-positioned to facilitate the integration of anticipatory cues and drives. For example, in times of high energy demand such as in preparation for flight, CN neurons might anticipate increased energy needs and, in response to other neural signals, decrease Dilp2 and increase AKH release to promote circulating glucose. As another possibility, CN neurons might have increased sensitivity to small glucose changes relative to Dilp2 or AKH cells, providing a mechanism to increase Dilp2 and decrease AKH release to anticipate humeral glucose changes during a meal. While much remains to be discovered about the role of CN neurons, they open exciting avenues to explore brain mechanisms that regulate metabolism based on nutritional state.

The recent study by Oh *et al.* opens up interesting questions about the role of glucose-sensing neurons and neuropeptide release in regulating glucose homeostasis. For example, what is the function of other glucose-sensing neurons in the brain? Work from the same

group previously showed that brain neurons expressing Diuretic hormone 44 (Dh44) directly respond to hemolymph sugars including glucose and are required for the D-glucose preference of starved flies [4]. Although the physiological and behavioral phenotypes of CN neurons and Dh44 neurons are similar, they are not physically connected and therefore seem to represent independent glucose-sensing neural pathways [3]. How Dh44 neurons and CN neurons cooperatively influence feeding decisions awaits further investigation. In addition, what is the function of corazonin in CN neurons? Although corazonin is not required for the D-glucose preference behavior as shown in this paper, corazonin and its receptor in Dilp2 cells appear to have a functional role in regulating carbohydrate and lipid levels and affecting survival under starvation [5]. Finally, in addition to the CN neurons, there are another five to six pairs of neurons that coexpress corazonin and sNPF in the same area of the fly brain [5]. Future work is required to determine if these neurons have similar functions in glucose sensing and endocrine regulation.

Given the similarity between fly Dilps/AKH and mammalian insulin/glucagon, *Drosophila* offers an attractive model for the study of energy homeostasis. The production and release of Dilps and AKH are under regulation of various factors ranging from dietary nutrition-induced factors, neurotransmitters and neuropeptides, to humoral factors (reviewed in [6]). For instance, Dilp2 and AKH cells respond to signals from metabolic tissues in addition to hemolymph sugar levels. Adipose tissues secrete cytokine Upd2 to stimulate Dilp2 release, whereas the same cytokine secreted by skeletal muscles promotes AKH release [7], [8]. The work by Oh *et al.* will now allow examination of how signals from the central nervous system coordinate with those from peripheral tissues and the bloodstream to dynamically regulate energy availability.

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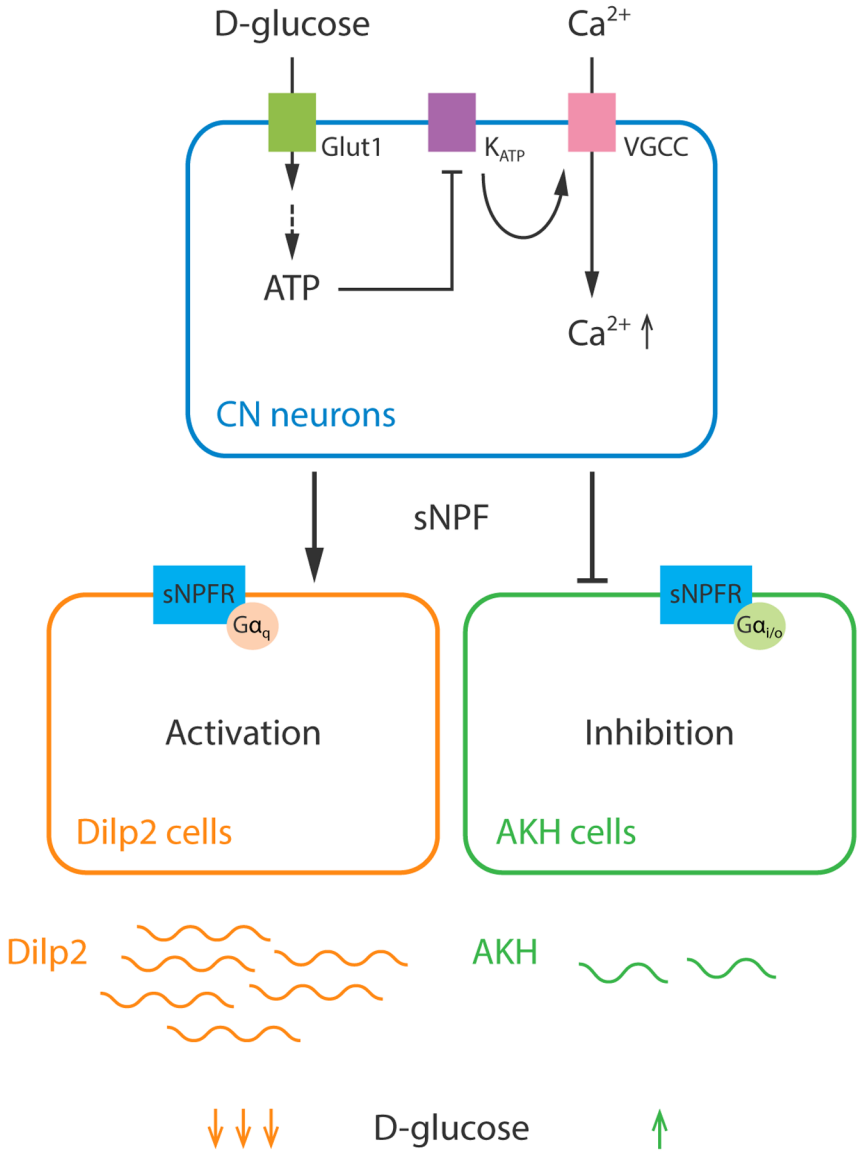

Figure 1. Glucose-sensing CN neurons reciprocally regulate Dilp2 and AKH release in *Drosophila*.

CN neurons are activated by increased levels of hemolymph D-glucose. The response of CN neurons to D-glucose requires glucose transporter 1 (Glut1), glycolysis, ATP-sensitive potassium channels (KATP), and voltage-gated calcium channels (VGCC). This suggests the following model: D-glucose is transported into the CN neurons and metabolized into ATP; ATP then inhibits KATP and causes depolarization; which in turn activates VGCC and leads to calcium influx. CN neurons release neuropeptide sNPF to simultaneously activate Dilp2 cells and inhibit AKH cells, through Gαq and Gαi/o signaling coupled to sNPFR in Dilp2 and AKH cells, respectively. CN activation thus leads to increased Dilp2 release and decreased AKH release, which in turn decreases hemolymph D-glucose levels.