A New Role for Hypothalamic Glucose-Sensing Neurons in Hypoglycemia Unawareness

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The mammalian brain uses glucose for much of its daily energy needs. Neurons have the highest energy demand in the adult brain and thus require continuous delivery of glucose from the blood. As a consequence, tight regulation of glucose metabolism is critical for brain physiology. Understandably, hypoglycemia is a serious threat to the brain, and there is a need to better understand the mechanisms in place to properly detect changes in blood glucose levels. The capacity of the brain to detect such changes in glucose levels is ensured by specialized glucose-sensing neurons, which adapt their electrical activity in response to physiological changes in glucose level (1). Of note, glucose-sensing neurons use glucose not only as fuel but also as a signaling molecule that modulates their electrical activity. It should also be mentioned that these neurons directly detect changes in glucose levels and do not detect changes through indirect presynaptic modulation. Glucose-sensing neurons can be found all over the brain, including in hypothalamic areas (where they have been studied the most) and extrahypothalamic areas. In all these areas, neurons that detect decreased glucose levels are present. Nevertheless, glucose-sensing neurons that detect glucose levels that increase above 2.5 mmol/L, the theoretical brain level (2), seem to be restricted to circumventricular organs of the brain, where the blood–brain barrier is fenestrated (3). On the basis of this statement, it seems that the brain is mostly equipped to sense hypoglycemia rather than hyperglycemia. Glucose-sensing neurons that detect increased glucose level seem to be involved mainly in the control of feeding behaviors (4,5). Nevertheless, an important unanswered question is what are the physiological roles of glucose-sensing neurons that detect decreases in glucose levels?

Since cells in the brain use and depend on glucose as a primary source of fuel, the brain elicits a set of neuroendocrine responses, known as the counterregulatory response (CRR), to hypoglycemia in order to normalize glucose levels. Routh et al. (1) and others have suggested that hypothalamic glucose-sensing neurons are critical for the detection of hypoglycemia and the initiation of the CRR. In addition to triggering the CRR, the brain elicits what is called hypoglycemia awareness. This state of conscientiousness, which includes a variety of symptoms of hypoglycemia (e.g., palpitations, anxiety, and confusion), stimulates behaviors to find energy. One of the most important messages of the article by Patel et al. (6) in this issue of *Diabetes* is that hypothalamic glucose-sensing neurons are involved not only in the control of the CRR but also in hypoglycemia awareness. Patel et al. (6) developed a behavioral model in mice to study hypoglycemia awareness using the conditioned place preference (CPP) paradigm, adapted from Levin and colleagues (7). In this test, animals learn to associate a food cue with a visually discriminated chamber and to develop a preference for that chamber. (Of note, Patel et al. [6] mention that only the use of sweetened cereals as a reward worked, whereas the use of chocolate drops worked to set the CPP paradigm in rats. This raises the question as to whether mice are more attracted to sweet cues than rats.) When exposed to insulin-induced hypoglycemia in the food cue–associated chamber, animals are "aware" of the aversive stimulus and no longer prefer that chamber.

Iatrogenic hypoglycemia is the main issue for patients with diabetes treated with insulin therapy. As nicely highlighted in the introduction of the article by Patel et al. (6), insulin-induced hypoglycemia not only is "acutely life threatening, but recurrent hypoglycemia (RH) impairs the ability of the brain to detect and correct subsequent hypoglycemia." Thus, following RH, both the CRR and hypoglycemia awareness are impaired (7–9). Using animal models, Routh et al. (1) and others have shown that three consecutive days of insulin hypoglycemia impair the CRR and decrease the response of ventromedial hypothalamic glucose-sensing neurons to decreased glucose levels (8,10). By using such "correlation," researchers have made suggestions about the key role of hypothalamic glucose-sensing neurons, i.e., they have found the

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conditions in which the responses of these neurons to decreased glucose and CRR regulation are impaired. Patel et al. (6) show that both the response of perifornical hypothalamus (PFH) orexin glucose-inhibited (GI) neurons and hypoglycemia awareness are impaired after RH. These data suggest that PFH GI neurons are key for the regulation of hypoglycemia awareness. Thus, this study highlights a new role for hypothalamic glucose-sensing neurons. However, two issues that still need to be addressed are *1*) whether PFH orexin GI neurons also play a role in the control of the CRR and *2*) whether other hypothalamic neurons are involved in hypoglycemia awareness. This is the limit of the correlative method used to suggest a role for glucose-sensing neurons. Our group and others have tried to decipher the key molecular mechanism involved in the response of glucose-sensing neurons and to inhibit this mechanism in vivo to understand the roles of these neurons. Several signaling pathways, including AMP-activated kinase, neuronal nitric oxide synthase, the ATP-sensitive potassium channel, the transient potential canonical channel, and others, have been targeted in that sense (11). Thus, in these studies, the authors showed that both the response of glucose-sensing neurons and physiological responses, including the CRR and food intake, are impaired. However, even in such molecular or so-called causal studies, the targeted mechanism is never specific to glucose-sensing neurons, and we cannot rule out that other neurons affected by the inhibition of the signaling pathway targeted can play a role in the studied physiological response. All these studies (correlative and causal) are convincing and a first significant step to understanding the role of glucose-sensing neurons in our search for a specific marker for these neurons. New single-cell sequencing approaches may help to highlight such identification of glucose-sensing neurons and help us further understand the roles of these neurons.

Patel et al. (6) also showed that modafinil reverses both the sensitivity of these neurons and hypoglycemia unawareness after RH. These data convince us even further that PFH GI neurons are involved in hypoglycemia awareness and elegantly suggest that PFH orexin GI neurons can be a therapeutic target for the prevention of hypoglycemia unawareness. In conclusion, in this convincing work, which used a combination of in vivo approaches, pharmacological strategies, and patch-clamp electrophysiology, Patel et al. showed a new role for hypothalamic neurons. We look forward to new elegant studies from this group that highlight new roles of these neurons from the hypothalamus or extrahypothalamic brain areas.

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