Nitric oxide’s role in glucose homeostasis

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NEARLY 40 YEARS AGO, A TYPE of neuron was identified that responds to changes in local glucose availability. These neurons were unique in that they appeared to use glucose as an intracellular signaling molecule to regulate their membrane potential and firing rate rather than as a fuel source (8). Since then much work has been done to identify their location and sensing mechanisms as well as a possible role for their dysfunction in metabolic diseases. Although originally called glucose sensing, these neurons have been shown to respond to other metabolites, such as lactate, fatty acids, and ketone bodies, as well as hormones and neurotransmitters (13). Several subsets of glucose-responsive neurons have now been distinguished and are generally classified based on whether their firing rates increase [glucose excitatory (GE) neurons] or decrease [glucose inhibitory (GI) neurons] as glucose increases (1). The ventromedial hypothalamus (VMH) is a key site for control of whole body homeostasis, and metabolic sensing neurons are ideally situated there to regulate glucose and energy balance. Of the glucose-responsive neurons located in the VMH, 14–19% are GE and 3–14% are GI (4, 11).

Changes in activity and responsiveness of glucose-sensitive neurons have been observed in several clinically relevant conditions. VMH GI neurons are critical for the detection of hypoglycemia and activation of the counterregulatory response (CRR). Prior episodes of hypoglycemia reduced the sensitivity of GI neurons to subsequent decreases in glucose, indicating a possible role in hypoglycemic unawareness and the defective counterregulation seen in insulin-treated diabetics (12). Rats predisposed to develop diet-induced obesity also have impairments in central glucose sensing, including a reduction in number of glucose-responsive neurons in the VMH and a decrease in the KATP channel sensitivity of GE neurons (5, 11).

Nitric oxide (NO) activity in the brain is modulated by both insulin and leptin, and its synthesis is affected by diabetes and obesity. Food intake is increased when NO synthesis is stimulated by l-arginine and reduced when NO synthesis is inhibited by obesity-prone rats (7, 10). In diabetic rats, hippocampal neuronal NO synthase (nNOS) expression is reduced and NO-mediated inhibition of sympathetic outflow from the paraventricular nucleus is impaired (9, 14). Recently, Canabal et al. (2) reported a novel pathway of GI neuron regulation involving NO synthesis. Using NO-sensitive dyes, they demonstrated that glucose and leptin suppress the nNOS-dependent production of NO in VMH GI neurons via inhibition of AMP-activated protein kinase (AMPK). In contrast, insulin stimulated NO synthesis through the phosphatidylinositol 3-kinase/Akt pathway (2). Since NO readily diffuses to surrounding areas, local NO production in VMH GI neurons could affect the activity and sensitivity of adjacent neurons, including GE neurons. Similarly, downstream effectors of NO signaling, such as protein kinase G and cGMP, may also affect ion channel activity. Thus, changes in NO production in GI neurons are potentially an important link to the regulation of other neurons involved in energy balance and glucose homeostasis. In the current issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology Canabal et al. (2a) further examine NO regulation of GI neurons in the diabetic hyperglycemic condition. Elevated glucose concentrations impaired NO production and prevented membrane depolarization in VMH GI neurons. Previously, it was demonstrated that nNOS-dependent NO synthesis in GI neurons increased as glucose levels were reduced. Hyperglycemia significantly attenuated the NO production in response to decreasing glucose. Likewise, insulin-stimulated NO production was greatly reduced in hyperglycemic conditions. Similar results were obtained using neurons from streptozotocin-induced diabetic rats and from nondiabetic rats cultured in hyperglycemic conditions, confirming that high glucose was responsible for the observed effects, rather than other diabetes-associated pathologies. Increased NO production in response to both insulin and decreasing glucose were restored in hyperglycemia by the addition of an AMPK activator (AICAR) or a mammalian target of rapamycin (mTOR) inhibitor (rapamycin).

A common pathway for glucose and insulin signaling through AMPK and mTOR in GI neurons also has implications for energy balance regulation. Activity of mTOR in the brain is related to energy availability. Increased mTOR signaling, by central administration of leucine or leptin, decreased food intake, and conversely, when energy stores were low following a fast, mTOR signaling decreased (3). The inhibition of membrane depolarization by hyperglycemia in GI neurons is of interest in relation to glucose sensing and the defective CRR seen in diabetics. Previously, it was shown that the CRR to recurrent hypoglycemia was amplified by administration of AICAR in the VMH prior to the fourth episode (6). Clearly, sensory neurons within the VMH are critical to regulation of energy and glucose homeostasis but are influenced via many complex systems that are not fully understood. Insight into the mechanisms of glucose-responsive neurons and their alteration by disease, such as provided here by Canabal et al. (2a), is essential to improve therapeutic approaches to diabetes and obesity.

REFERENCES


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