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 1-arginine and reduced when NO synthesis is inhibited in 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. (2a) further examine NO regulation of GI neurons in the VMH prior to the fourth episode (6). Clearly, sensory neurons located in 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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