Where does the brain detect hypoglycemia?

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IN 1953, JEAN MAYER PROPOSED a glucostatic hypothesis for the regulation of food intake (12). A pivotal construct was the hypothesized existence of glucoreceptors in the brain that transduced extracellular glucose concentration into ion movements and ultimately action potentials. The primary role of such receptors presumably would be to detect shortages of available energy (viz hypoglycemia) and to organize appropriate physiological and behavioral responses. It was not until 11 years later that such cells were identified in the hypothalamus and, subsequently, in many other brain regions, as well as in the periphery (see Ref. 11 for a recent review). This diversity of types of glucose sensors and locations leads to new and more complex questions, such as, are their activities integrated and, if so, how and where? For example, all sites may contribute to both physiological and behavioral responses, or there may be anatomical segregation of effector function (7, 16). In the present issue of American Journal of Physiology: Regulatory Integrative and Comparative Physiology, de Vries et al. (6) report that norepinephrine (NE) release in the ventromedial hypothalamus (VMH) of rats during insulin-induced hypoglycemia was prevented by local infusion of glucose and the concurrent sympathoadrenal response was greatly attenuated. This study uses a classic experimental design of global removal (of glucose) and local restoration to show that glucose replacement in the VMH is sufficient for this outcome.

Hypoglycemia became a substantial clinical problem with the introduction of insulin as a treatment for diabetes. Insulin-induced mental confusion or coma is the product of either insufficient or overwhelmed endogenous counterregulatory responses to hypoglycemia. Cannon et al. (5) were the first to show that insulin-induced hypoglycemia was associated with an increase in secretion from the adrenal medulla, and this was dependent on sympathetic outflow via the splanchic nerves. From cross-circulation studies, La Barre and DeCespedes (10) showed that the detection of hypoglycemia in the vascular territory supplied by the carotid arteries resulted in the secretion of gastric acid, a vagally mediated response. Both Cannon et al. (5) and Armin and Grant (1) noted that a critical, substantial level of hypoglycemia, typically a 50% reduction in plasma glucose, had to be achieved to activate these counter-regulatory responses. In 1968, Himsworth (9) summarized these and other data as follows.

The inference from these studies is that there exists somewhere in association with the nervous system a receptor that is sensitive to the presence of glucose and which responds when the blood glucose falls below a certain minimum concentration by promoting the secretion of adrenaline.

The question addressed by de Vries et al. (6) extends an important experiment by Borg et al. (3) to the level of neurotransmitter release in the brain. Borg et al. (3) studied the effect of VMH glucose replacement in fasted rats subjected to gradual reduction in plasma glucose using a hypoglycemic clamp. Concurrent infusion of 100 mM (but not 15 mM) glucose through bilateral dialysis probes in the VMH abolished the appearance of sympathoadrenal and glucagon counter responses to hypoglycemia. Further demonstrating the enormous physiological impact of those responses, they found that 3–4 times more peripherally infused glucose was needed to maintain the clamp when the responses were prevented by VMH dialysis of glucose. Borg et al. (3) concluded that the VMH is a key glucose-sensing region of the brain for physiological counterregulation to hypoglycemia.

De Vries et al. (6) extend this result by concurrent measurement of NE release in the VMH, using nonfasted rats given a bolus injection of insulin. Previous studies have shown that hypoglycemia and/or neuroglucopenia increase release or turnover of NE in the VMH (2, 13), but it has not been shown that this results from either hypoglycemia within the VMH and/or arises from afferents to the VMH from glucose sensors located elsewhere in the brain or periphery. The de Vries et al. (6) result establishes clearly that the NE release is due to local hypoglycemia and is prevented by reverse dialysis of 100 mM glucose unilaterally into the VMH. Because the probe efficiency for glucose transport was ~2.5%, it was estimated that the infusion maintained extracellular glucose near its basal level (~1.7 mM) during systemic hypoglycemia. Furthermore, because the infusion was unilateral and diffusion away from the probe is thought to be quite limited (4), the glucose-infused side of the VMH would have been euglycemic, yet the uninfused side presumably remained hypoglycemic, suggesting that onset of unilateral hypoglycemia in the VMH is insufficient to trigger a substantial sympathoadrenal response.

What then is the role of peripheral glucoreceptors? Hevener et al. (8) showed that hypoglycemia activates afferents from the portal vein because denervation of this region reduced the sympathoadrenal response by ~50%. Furthermore, infusion of glucose into the portal vein of intact rats treated with insulin reduced the sympathoadrenal response by ~50% without altering the level of hypoglycemia systemically and presumably in the VMH. The contribution of receptors in the brainstem also seems to be important; Frizzell et al. (7) argued that the vascular regions served by carotid (forebrain) and vertebral (hindbrain) arteries has an approximately equally contribution to counterregulation in dogs. Similar arguments for the involvement of hindbrain sites have been made in rats. For example, Ritter et al. (15) examined the occurrence of hyperglycemia, indicative of a glucose-mobilizing sympathetic outflow in the absence of antecedent systemic hypoglycemia, following injections of a glucose antimetabolite 5-thio-D-glucose unilaterally into various regions of the brain. They found hyperglycemia from 0 of 61 sites in the hypothalamus but in 49 of 142 sites in the ventrolateral and dorsomedial medulla. These sites overlapped the C1-C3 groups of catecholamine neurons. However, another study found that infusion of 2-deoxy-D-glucose into the VMH did trigger a sympathoadrenal response (4). Whereas local injection of glucose antimetabolites has been useful in localizing brain regions of interest, Levin et al. (11) noted that it is impossible to know quantitatively the degree of cellular glucoprivation achieved by a
particular dose of an antimetabolite. Given that different regions of the brain have different resting extracellular concentrations of glucose (11), it will be especially important in future work to reach a quantitative plane for local manipulation of glucose levels analysis, exemplified in the approach used by de Vries et al. (6).

This method can be applied to examining the interrelationship between sites. For example, would glucose infusion in site A alter hypoglycemia-related transmitter release in site B, and if so, what are the critical extracellular glucose concentrations for these effects? This “wiring diagram” approach, coupled with ongoing advances in the molecular components of glucose transduction (11) will lead to a much more complete view of glucoreceptor function at the organismic level. This science is proceeding by using mainly physiological counterresponses rather than behavior as the dependent variable. While purely “glucostatic” theories of food intake have been cast aside, there is little doubt that glucose sensing contributes to regulation of intake, and, within that context, many of the neuropeptide mechanisms currently studied in relation to food intake or obesity are located close to the VMH, suggesting a key metabolic sensing role for these neurons (11, 14).

REFERENCES