Central Versus Peripheral Glucose Sensing and the Response to Hypoglycemia

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One of the most significant limits in our ability to tightly control blood glucose in patients with diabetes is the occurrence of hypoglycemia. It is now clear that when blood glucose drops in a normal individual, there is a rapid and well-coordinated endocrine response (1). Glucagon, epinephrine, norepinephrine, cortisol, and growth hormone levels rise as the glucose level falls (1). The combination of low blood glucose and elevated hormones limits glucose utilization by the tissues of the body and stimulates glucose production by the liver (2). As a consequence of these metabolic adjustments, the fall in blood glucose is limited and the ensuing hypoglycemia is minimized. In an individual with diabetes, the glucagon response to hypoglycemia begins to diminish relatively early in the disease process (1). Later, even the sympatho-adrenal response may become limited (1). As a consequence, individuals with diabetes, particularly type 1 diabetes, are at increased risk for serious hypoglycemia. Understanding more about the normal response to hypoglycemia and about the failure of the normal response in diabetic individuals is thus of great importance.

A recent debate in this area relates to the site of hypoglycemic sensing. While it has long been known that the brain is involved in detecting low blood glucose, data began to appear in the early 1990s supporting the view that hypoglycemic sensing was also occurring at peripheral sites, particularly within the hepato-portal region. A series of articles by Donovan and colleagues (3–9) showed that infusion of glucose into the hepatic portal vein of the rat or dog during insulin-induced hypoglycemia blunted epinephrine and norepinephrine responses to a low blood glucose even when identical arterial (brain) glucose levels were maintained. Based on their data, these authors suggested that glucose sensing neurons within the hepatoportal region were key determinants of the response of the sympathetic nervous system to hypoglycemia. They went on to show that these neurons lay within the portal vein (6) rather than the liver per se (7) or the hepatic artery (7). They also showed that the response was mediated by spinal rather than vagal afferents (8).

On the other hand, Biggers et al. (10) showed, using the dog, that infusion of glucose to maintain euglycemia in the head (brain) during insulin-induced hypoglycemia eliminated ~80% of the sympathetic nervous system response to hypoglycemia, as well as the entire glucagon response. Additional dog studies by Jackson et al. (11,12) showed that the counterregulatory response to insulin-induced hypoglycemia was not reduced when vagal transmission was inhibited by nerve cooling or when the entire liver was denervated. In line with this, studies in the rat (13–16) identified the ventromedial hypothalamus as a key component in the initiation of the sympathetic response to hypoglycemia. There are thus diverging views as to the significance of central versus peripheral sensing of hypoglycemia. At the same time, it was reported that infusion of glucose into the hepatic portal vein to simulate a feeding signal augmented hepatic glucose uptake under hyperinsulinemic hyperglycemic conditions (17) as a result of decreased sympathetic input to the liver (18). The question thus arose as to whether Donovan and colleagues, by infusing glucose into the portal vein, had simply added a "feeding" signal on top of a "hypoglycemic" signal. However, a report last year by Fujita et al. (9) suggests that this is not the case. These authors showed that knocking out the spinal afferents originating in the portal vein using capsaicin markedly reduced the rise in plasma epinephrine and norepinephrine seen in response to insulin-induced hypoglycemia. The question thus arises as to why these different experimental approaches (brain glucose infusion vs. hepatic portal vein glucose infusion) have led to different conclusions with respect to the dominance of cerebral versus peripheral glucose sensors in defense of a low blood glucose.

The importance of the article by Saberi et al. (19), appearing in this issue of the journal, lies in its finding that the rate of fall of glucose determines the primacy of the site of glucose sensing. In their study, the authors applied capsaicin to the portal vein or to the portal vein as well as the superior mesenteric vein in rats to knockout the glucose-sensing spinal afferent neurons. They then carried out a hyperinsulinemic hypoglycemic clamp to trigger a counterregulatory response. However, they controlled the rate of fall of glucose using a peripheral glucose infusion (80 or 20 min to reach 2.5 mmol/l). Their data showed that when the spinal afferent nerves in the portal vein and superior mesenteric vein were both treated with capsaicin, the epinephrine and norepinephrine responses to hypoglycemia were almost completely absent if the fall in plasma glucose was slow (i.e., when it took 80 min to reach 2.5 mmol/l). On the other hand, the responses were reduced by only 15–30% when the fall in plasma glucose was rapid (i.e., when it took 20 min to reach 2.5 mmol/l). This study thus provides a potential explanation for the apparently conflicting data from earlier studies in that there was a rapid decline in glucose (20–30 min to 2.5 mmol/l) in the studies in which brain glucose was clamped (10–12), while there was a much slower rate of fall of glucose (40–80 min) in the earlier studies of Donovan and colleagues (3–8).

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Taking all of the above data together, it appears that hypoglycemia is sensed both centrally and peripherally. When the fall of glucose is rapid, the central nervous system (CNS) is dominant, whereas when the fall in glucose is slow, portal glucose sensing becomes dominant. The next question is how this hierarchy of response comes about. It is conceivable that when the insulin level is high and the fall in glucose is slow, the glucose sensing cells in the hypothalamus adapt to the changing glucose milieu, thus resulting in a reduced sympathetic response. This would suggest that the portal vein glucose sensors are always functioning but that when the fall in glucose is rapid, their impact in determining the overall counterregulatory response is low. Several key questions remain. It is still not clear whether neural hypoglycemia must be present for input from glucose sensors in the portal region to be effective. Likewise, since all of the studies of Donovan and colleagues were carried out at very high insulin levels, it is not clear whether the insulin level per se has an impact on the site of hypoglycemia sensing. Finally, Donovan and colleagues (4,5) showed that the response of glucagon (the α-cell) to hypoglycemia was not regulated by the portal vein glucose sensors. Biggers et al. (10), on the other hand, showed that it was altered by CNS glucose sensors. It would thus appear that glucagon secretion during hypoglycemia is driven by CNS glucose sensing neurons. Given the importance of glucagon to metabolic counterregulation, this indicates that in the normal individual the brain is the most important hypoglycemic sensing site, regardless of the rate of fall of glucose. This would likely not be the case in individuals with diabetes in whom the α-cell response is deficient.

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