Hypothalamic Regulation of Glucose-Stimulated Insulin Secretion

Owen Chan and Robert S. Sherwin

Circulating glucose levels serve as the principal regulator of the rate of insulin secretion from the pancreatic β-cell, which, in turn, is the body's principal mechanism preventing excessive elevation in circulating glucose. The control center for this critical negative feedback loop is generally thought to reside solely within the province of the β-cell. However, in the February issue of *Diabetes*, Osundiji et al. (1) provide evidence that there may be another player involved, namely, the hypothalamus. They observed that raising glucose levels locally or pharmacologically blocking glucose entry into cells close to the third ventricle of the rat altered the acute insulin secretory response to intravenous glucose, presumably by the extensive neural connections that exist between the hypothalamus and islet. As pointed out by the authors, it is now well recognized that a subgroup of hypothalamic neurons, and neurons elsewhere in the brain, have the capacity to sense glucose and influence the secretion of anti-insulin hormones and hepatic glucose production (2–6). Yet, the idea that the glucose-sensing capacity of these neurons may also influence the function of the β-cell has not been appreciated, and if shown to be true under more physiological conditions, could have important therapeutic implications.

It is commonly believed that the K_{ATP}-dependent model of glucose-stimulated secretion coupling is the primary means used by the β-cell to activate insulin secretion (7–10). In this model, glucose enters the β-cell, is phosphorylated by glucokinase to glucose-6-phosphate, and then enters the glycolytic and oxidative phosphorylation pathways to be metabolized. Through this, ATP is generated, causing ATP-sensitive potassium channel closure, plasma membrane depolarization, and activation of voltage-gated calcium channels, which ultimately cause exocytosis of insulin-containing granules. Although the components of this mechanism are expressed in the β-cell and appear adequate to explain most insulin responses to glucose, there is a growing body of data that cannot be solely explained by this K_{ATP}-dependent mechanism of glucose-stimulated insulin secretion (GSIS). As a result, signals other than the ATP/ADP ratio have been postulated in recent years (11–16). These K_{ATP}-independent mechanisms have mainly focused on the mitochondria and generation of second messengers other than ATP. In these models, it is postulated that conversion of pyruvate to oxaloacetate by pyruvate carboxylase leads to generation of a number of intermediary metabolites that are capable of acting as signals to stimulate insulin release (17,18). Some of these messengers, including NADPH (19–21), malonyl-CoA/long-chain CoA (22,23), short-chain CoA (24), glutamate (25), α-ketoglutarate (26), and GTP (27), are thought to act either directly or indirectly to alter the influx of calcium into the β-cell, ultimately affecting insulin secretory kinetics.

While studies examining GSIS have focused on factors that directly affect the β-cell, little attention has been given to the potential role of the brain in this regard. The brain and islet are tightly linked functionally through neural-entero-islet, brain-islet, and islet-brain axes. Thus, secretion of insulin and other islet hormones are clearly influenced by the hypothalamus and other brain areas, and conversely, insulin action in the hypothalamus influences both energy balance and glucose metabolism. The article in the February issue of *Diabetes* (1) presents some novel observations suggesting that hypothalamic glucose sensing may also provide an additional input to β-cells that modulates the first-phase insulin response to a glucose stimulus. In particular, data are presented suggesting that conversion of glucose to glucose-6-phosphate by glucokinase in the hypothalamus may serve to regulate the first phase of insulin secretion in response to glucose. Thirty minutes prior to giving an intravenous glucose tolerance test, the authors administered either glucose to activate glucokinase or one of two pharmacological inhibitors of glucokinase (glucosamine or mannoheptulose) into the third ventricle. When glucose was administered, a greater insulin secretory response occurred, along with a more rapid decline in plasma glucose levels. Conversely, when either of the nonspecific glucokinase inhibitors was administered, the acute insulin response to intravenous glucose was diminished and glucose excursions were slightly greater. The effect was more pronounced with glucosamine. This may be because glucosamine cannot only inhibit glucokinase, but it may also enter cells via glucose transporters, thereby redirecting intermediary metabolites of glycolysis into the hexosamine biosynthetic pathway. It should be noted that the study design employed a time-sequenced exposure of glucose or glucokinase inhibitors to the brain much before peripheral changes in glucose were induced in the experiments. This may have magnified the impact of the hypothalamus relative to what occurs in the physiological setting. Undoubtedly, more specific reductions in glucokinase gene expression within the hypothalamus will be required before the physiological importance of these specific observations can be determined.

Nonetheless, findings implicating the hypothalamus in GSIS are consistent with recent reports examining the role of insulin and glucose transport in the brain. We have reported that chronic knockdown of insulin receptors in

From the Department of Internal Medicine, Section of Endocrinology, Yale School of Medicine, New Haven, Connecticut.
Corresponding author: Robert S. Sherwin, robert.sherwin@yale.edu.
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the ventromedial hypothalamus reduces insulin secretory responses to a standardized hyperglycemic stimulus (28). In addition, data from the laboratories of Simon Fisher and Domenico Accili indicate that deletion of the insulin-responsive glucose transporter, GLUT4, in the brain leads to impairments in glucose sensing and glucose tolerance in mice (29,30). Together, these data support the role of an insulin-responsive glucose-sensing mechanism within the hypothalamus that regulates islet hormone secretion to maintain glucose homeostasis. One can postulate that following meal ingestion, the rapid rise in peripheral glucose levels acts to initiate the insulin response. Subsequent rises in insulin and glucose may work together to stimulate an increase in glucose uptake by hypothalamic glucose-responsive neurons that further augment insulin secretion and increase glucose handling. Under conditions where central insulin resistance develops, it is intriguing to speculate that a reduction in the capacity to take up glucose in the hypothalamus may contribute to a diminution of the GSIS response.

It is becoming increasingly evident that GSIS likely involves several signaling events that converge to activate exocytosis of insulin-containing granules from the β-cell. The study by Osundiji et al. (1) adds yet another dimension to this already complicated story by providing some of the first evidence that a central nervous system glucose-responsive input might be involved in regulating the early insulin secretory response to a glucose stimulus. On the other hand, it should be emphasized that the observed effects were modest and that peripheral signals are still likely to play the dominant role in initiating insulin release. The brain, which is likely delayed in seeing changes in glucose concentrations, most likely provides a later signal to modulate the magnitude of the response. It will be interesting to see whether this response is due solely to a change in glucose levels or whether it is in response to a rapid rise in insulin. As the authors indicated, this may have important implications for the development of therapeutic strategies in the future.

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