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Interaction of Islet α-Cell and β-Cell in the Regulation of Glucose Homeostasis in HI/HA Syndrome Patients With the GDH^{H454Y} Mutation

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COMMENTARY

The hyperinsulinemia/hyperammonemia (HI/HA) syndrome—the secondmost common form of congenital hyperinsulinism—is a rare autosomal dominant disease manifested by hypoglycemic symptoms and elevated serum ammonia triggered by fasting or high-protein meals (1). In 1955, Cochrane et al. described a child and her father, both with hypoglycemia that was aggravated by consumption of a low-carbohydrate, high-protein diet (2). Subsequently, another group identified the gene GLUD1. This gene, located on chromosome 10q23.3, is composed of 13 exons and regulates mitochondrial enzyme glutamate dehydrogenase (GDH) (3). The GDH enzyme catalyzes glutamate metabolism and plays important roles in the regulation of amino acid–stimulated insulin secretion in β-cells, modulation of amino acid catabolism in hepatocytes, and ammoniagenesis in the brain (4). A total of 14 amino acid residues affected by GDH-activating mutations has been identified in patients with the HI/HA syndrome (5). GDH activity also is subject to complex regulation by GTP, ADP, and leucine (6). For example, the flux of glutamate into the tricarboxylic acid cycle for energy generation is modulated by the mitochondrial energy potential, which, in turn, is controlled by the ratio of GTP to ADP. When the energy potential is high, amino acid oxidation is not required, and GDH enzyme activity shuts down. When energy potential is low, GDH is activated to sustain energy generation through oxidation of amino acids (4). Interestingly, epigallocatechin gallate, a component of green tea, has been shown to be a potent allosteric inhibitor of GDH enzyme activity (7).

Insulin secretion is upregulated through increased cellular phosphate energy potential, which is manifested as an increase in the ATP/ADP ratio. Elevated ATP/ADP concentrations promote closing of plasma membrane K_{ATP} channels, resulting in pancreatic β-cell membrane depolarization. This voltage change across the cell membrane opens voltage-gated calcium (Ca^{2+}) channels, which promote insulin granule exocytosis (8). For example, in pancreatic β-cells, the elevated levels of ATP promoted by high intracellular α-ketoglutarate lead to hyperinsulinemia and an increased propensity for hypoglycemia. Similarly, a decrease in intracellular N-acetylglutamate leads to inactivity of carbamoyl phosphate synthetase—a ligase mitochondrial enzyme involved in the production of urea—which can cause an overproduction of ammonia (9). Thus in patients with HI/HA syndrome, enhanced insulin secretion by pancreatic β-cells is driven by increased GDH activity in conjunction with available glucose and amino acids (Fig. 1). The importance of enhanced GDH activity is underscored by features of HI/HA syndrome, where a dominant mutation causes loss of inhibition of GDH enzyme activity that is normally exerted by GTP and ATP (10). Indeed, H454Y transgene pancreatic expression was confirmed by increased GDH enzyme activity and decreased sensitivity to GTP inhibition in islets (11). Leucine levels serve as an indicator of increases in amino acid supply following a high-protein feeding in mice with the H454Y mutation of GDH. The activation of oxidation of amino acids through transamination to glutamate and then into the tricarboxylic acid cycle via GDH causes an increase in the ATP/ADP ratio and ultimately triggers insulin release (1) (Fig. 1). This pathway can be activated in the absence of glucose when the phosphate potential is low. This is because a low ATP/ADP ratio

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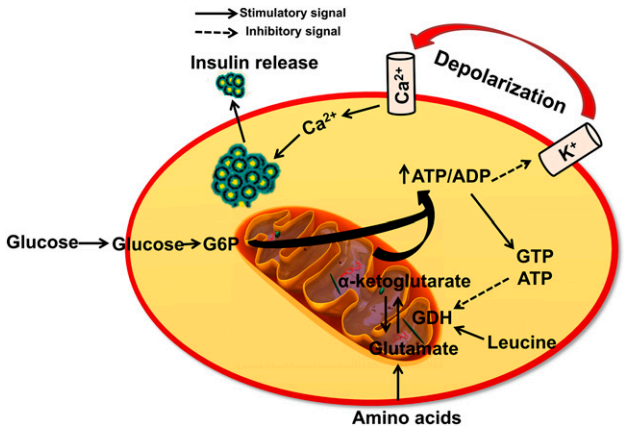

Figure 1—GDH regulates insulin secretion in pancreatic β-cells in HI/HA syndrome. The elevated ATP concentration in the β-cell induced by amino acids closes the plasma membrane K_{ATP} channels, resulting in the depolarization of the membrane potential. This voltage change across the membrane opens voltage-gated Ca^{2+} channels and then leads to insulin release. However, ATP production from glucose metabolism inhibits the GDH activity, which is involved in the glutamate metabolism and plays important roles in the regulation of amino acid–stimulated insulin secretion in pancreatic β-cells. G6P, glucose-6-phosphate.

increases glutaminolysis and sensitizes GDH to stimulation by leucine (12). As noted above, the H454Y transgene in islets resulted in higher insulin secretion in response to glutamine alone as well as a twofold greater GDH flux. High glucose inhibited both glutaminase and GDH flux, and leucine could not override this inhibition (1). Li et al. suggested that their results indicate that GDH functions predominantly in glutamate oxidation rather than glutamate synthesis in islets, and that this flux is tightly controlled by glucose (1). These data also suggest that patients with HI/HA syndrome should consume carbohydrates preferentially to protein to prevent the protein-induced hyperinsulinism and hypoglycemic symptoms.

In this issue of *Diabetes*, Kibbey et al. (13) examine the effects of fasting and amino acids on glucose, insulin, and glucagon levels in mice with mitochondrial GTP (mtGTP)-insensitive mutations in GDH^{H454Y}. This study convincingly demonstrates that the H454Y mice had fasting hypoglycemia despite the fact that their plasma insulin concentrations were similar to controls. Both glucose- and glutamine-stimulated insulin secretion were severely impaired, and the lack of a glucagon response during hypoglycemic clamps showed impaired counterregulation in the mutated H454Y mice. Conversely, acute pharmacologic inhibition of GDH activity restored both insulin and glucagon secretion and normalized glucose tolerance in perfused islets isolated from these mice. These in vivo studies identify a physiologically relevant role for GDH in the β-cell mitochondria that controls α-cell release of glucagon. Furthermore, the relevance of this model is supported by the observation that hypoglycemia may occur as a consequence of diminished glucagon release from mtGTP insensitivity in children with GDH^{H454Y} mutation.

Overall, these new and interesting data highlight a central role of the mtGTP-GDH-glucagon axis in glucose homeostasis, and they have the potential to be a translationally relevant rodent model. One caveat with respect to the clinical utility of this model is the fact that insulin concentrations are not always elevated in HI/HA patients, even during hypoglycemia. In support of the utility of their model, the authors cited work (ref. 24 in [13]) supporting their notion that hypoglycemia could develop without increases in insulin secretion. Indeed, in that study, insulin secretion increased under protein tolerance test conditions. As discussed above, GDH^{H454Y} transgenic islets manifested decreased leucine- and glutamine-stimulated insulin secretion with glucose stimulation; this is discordant with the low insulin response following glutamine stimulation in the current study (13). A second caveat concerns studies supporting the concept that amino acids, especially branched-chain amino acids such as leucine, may enhance the mammalian target of rapamycin (mTOR) signaling pathway. This may act as a double-edged sword in the maintenance of β-cell function and glucose metabolism (14). Initially, mTOR signaling positively regulates β-cell function and insulin secretion (15). However, chronic activation of mTOR signaling increases insulin resistance in islets via feedback reductions of insulin receptor substrate 1/2 metabolic signaling (15). It is possible that mTOR activation promotes GDH-regulated insulin release from β-cells in patients with HI/HA syndrome. Finally, Kibbey et al. did not address the complex cross talk between islet α- and β-cells in the reciprocal regulation of insulin and glucagon release. The α-cell is electrically active, which allows opening of Ca^{2+} channels and glucagon exocytosis under physiological conditions of hypoglycemia. However, the ability of low glucose to stimulate α-cell secretion of glucagon requires an initial increase in insulin levels from the β-cell followed by insulin deprivation in presence of low glucose (16). This may help explain the role of the mtGTP-GDH-glucagon axis in glucose homeostasis.

Despite these limitations, the new study by Kibbey et al. (13) identifies a physiologically relevant role for the mitochondrial GDH enzyme in β-cell modulation of α-cell secretion of glucagon. It also identifies a putative mechanism by which hypoglycemia may occur as a consequence of diminished glucagon release. Obviously, further studies are warranted to further elucidate cellular and molecular mechanisms involved in the cross talk of α- and β-cells among patients with the HI/HA syndrome and the GDH^{H454Y} mutation.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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