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CLINICAL IMPLICATIONS OF BASIC RESEARCH

A Toggle for Type 2 Diabetes?

Bernard Thorens, Ph.D.

Type 2 diabetes mellitus is characterized by a relative deficit in insulin secretion, caused by a decrease in the glucose sensitivity of the pancreatic beta cells, by a reduction in their total number, or a combination of both. Not surprisingly, a great deal of effort is expended in understanding the processes that underlie these events and how they go awry in type 2 diabetes. One line of investigation involves dissection of the mechanisms by which glucose triggers insulin secretion; a recent article by Ohtsubo and colleagues¹ underscores an interesting process.

Glucose-stimulated insulin secretion requires the metabolism of glucose, and consequent events induce an influx of calcium, which, in turn, induces exocytosis of granules containing insulin (Fig. 1). Biochemical studies and genetic analysis of patients with adult-onset diabetes of the young type 2 have shown that the insulin-secretory activity of beta cells — which is proportional to the dose of glucose — is controlled by the kinetics of glucokinase, the enzyme that converts glucose into glucose-6-phosphate.

Before glucokinase can act on glucose, however, glucose must be transported across the beta-cell membrane into the cytoplasm — a process mediated by the glucose transporter 2 (GLUT-2). In physiologic situations, transmembrane transport mediated by GLUT-2 provides glucose with unrestricted access to glucokinase. But GLUT-2 expression is tightly regulated in beta cells and markedly reduced in the diabetic state when glucose-stimulated insulin secretion is impaired. This process can be caused by elevated levels of free fatty acids or glucocorticoids or by a reduction in the level of specific transcription factors, such as pancreas duodenum homeobox1 or hepatocyte nuclear factor 1 α . Whether decreased transporter expression in these contexts is sufficient to suppress glucose-stimulated insulin secretion has been difficult to evaluate because the modified expression of other proteins could co-

operate to deregulate secretion. However, studies of knockout and transgenic mice have shown that impaired glucose-stimulated insulin secretion develops when GLUT-2 is reduced by 80 percent or more.^{2,3}

Ohtsubo et al. described a novel mechanism that controls cell-surface expression of GLUT-2 in beta cells. With the use of transgenic technology, they engineered mice that lack an enzyme that resides in the Golgi apparatus and that transfers the terminal sugar to the oligosaccharide side chains of GLUT-2. (The enzyme, *N*-acetylglucosamine transferase 4a, is encoded by *Mgat4a*.) Strikingly, these mice were hyperglycemic and hypoinsulinemic and had impaired glucose tolerance; in addition, the first phase of insulin secretion was suppressed and the second phase was muted — which is very similar to the defect seen in type 2 diabetes and in *Glut2*-deficient mice. Analysis of the islets of the *Mgat4*-deficient mice revealed very low expression of GLUT-2 at the cell surface of beta cells and a poor capacity for glucose uptake. The authors then showed that the low surface expression of GLUT-2 is due to a modification in the structure of the GLUT-2 N-glycan, which is unable to interact with a cell-surface lectin, galectin-9 (also known as the urate transporter). The investigators showed that this interaction is essential to retain wild-type GLUT-2 (but not other membrane proteins) at the cell surface.

Of particular interest is the discovery by Ohtsubo et al. that feeding normal mice a high-fat diet, which is known to affect insulin secretion negatively, strongly down-regulated the expression of *N*-acetylglucosamine transferase 4a. This was accompanied by the modified GLUT-2 N-glycan structure, diminution of GLUT-2 expression at the cell surface, and impaired glucose-stimulated insulin secretion.

The extent to which *MGAT4A* is relevant to human diabetes may be difficult to evaluate, because human beta cells express other glucose transport-

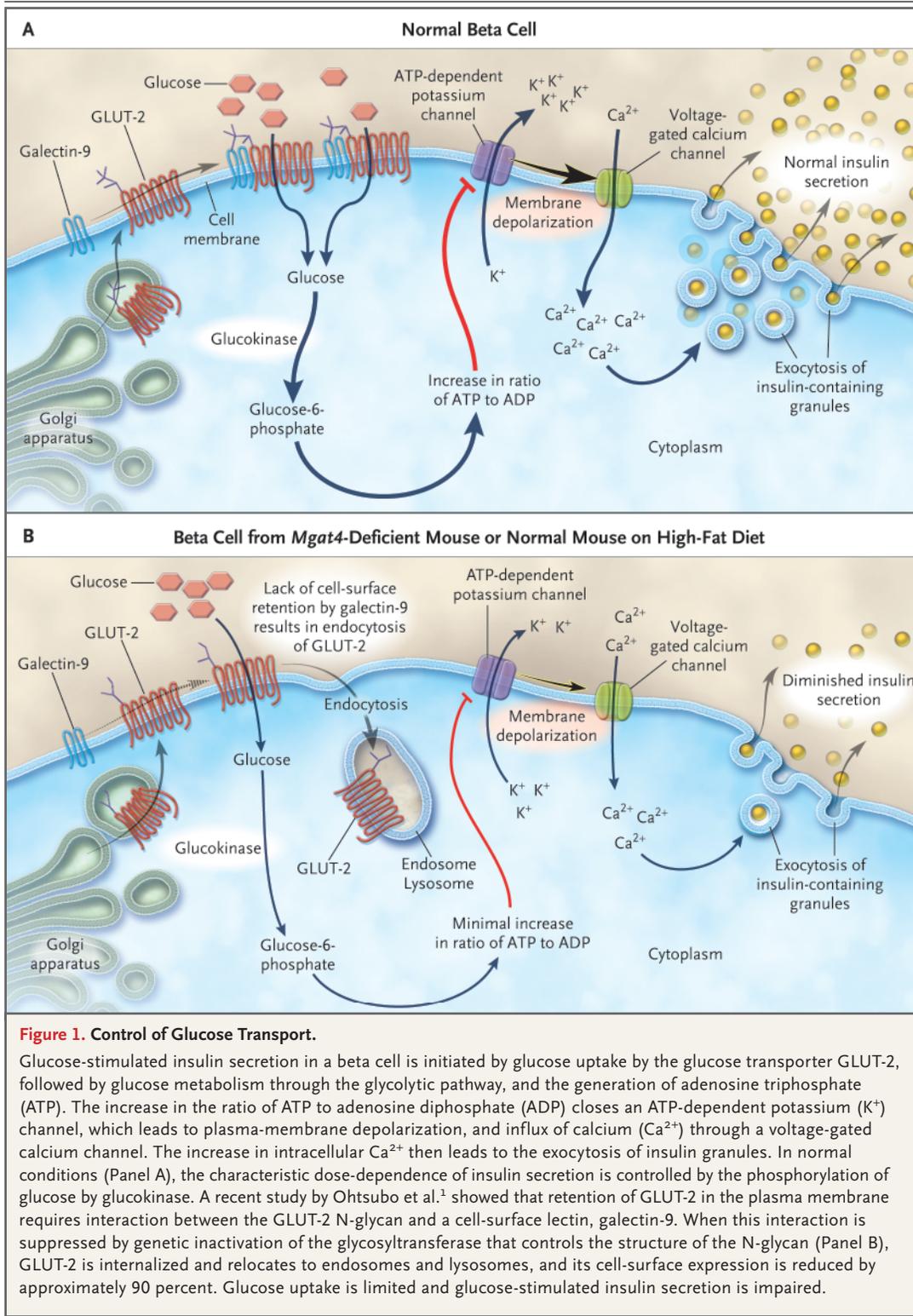


Figure 1. Control of Glucose Transport.

Glucose-stimulated insulin secretion in a beta cell is initiated by glucose uptake by the glucose transporter GLUT-2, followed by glucose metabolism through the glycolytic pathway, and the generation of adenosine triphosphate (ATP). The increase in the ratio of ATP to adenosine diphosphate (ADP) closes an ATP-dependent potassium (K⁺) channel, which leads to plasma-membrane depolarization, and influx of calcium (Ca²⁺) through a voltage-gated calcium channel. The increase in intracellular Ca²⁺ then leads to the exocytosis of insulin granules. In normal conditions (Panel A), the characteristic dose-dependence of insulin secretion is controlled by the phosphorylation of glucose by glucokinase. A recent study by Ohtsubo et al.¹ showed that retention of GLUT-2 in the plasma membrane requires interaction between the GLUT-2 N-glycan and a cell-surface lectin, galectin-9. When this interaction is suppressed by genetic inactivation of the glycosyltransferase that controls the structure of the N-glycan (Panel B), GLUT-2 is internalized and relocates to endosomes and lysosomes, and its cell-surface expression is reduced by approximately 90 percent. Glucose uptake is limited and glucose-stimulated insulin secretion is impaired.

ers in addition to GLUT-2, such as GLUT-1 and GLUT-3, which may, at least in part, compensate for the absence of GLUT-2. Nevertheless, linkage studies have shown an association of DNA sequence variants in or near GLUT-2 with diabetes in some groups. Moreover, patients with the Fanconi–Bickel syndrome — caused by mutation of GLUT-2 — often present with postprandial hyperglycemia and reduced insulin levels suggestive of beta-cell secretion defects. If the mechanism described by Ohtsubo et al. operates in human islets, it may represent a link between a high-fat diet and the development of type 2 diabetes. Furthermore, mutations in *MGAT4A* or other glycosyltransferase genes, the protein products of which modify the normal structure of the

GLUT-2 N-glycan, may also lead to impaired insulin secretion and thereby cause type 2 diabetes.

No potential conflict of interest relevant to this article was reported.

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