

## Commentary

# Glucokinase, glucose sensing, and diabetes

Mike Mueckler

Department of Cell Biology and Physiology, Washington University School of Medicine, St. Louis, MO 63110

The riddle of how pancreatic  $\beta$  cells detect and respond to alterations in the level of blood glucose has occupied endocrinologists for decades. The recent work reported by Epstein *et al.* (1) represents a major step forward in solving this biochemical puzzle. The blood glucose level in mammals is maintained within narrow limits through the concerted effort of three major tissue axes. The peripheral tissues, brain and muscle, are the primary sites of glucose uptake and disposal during the postabsorptive and postprandial states, respectively. The liver plays a unique role in that it is a net producer of blood glucose in the fasted state via glycogenolysis and gluconeogenesis and a primary site for the storage of glucose in the form of glycogen when the sugar is plentiful. The distinct cell types in the pancreatic islets control the rates of glucose disposal and endogenous glucose production via the regulated secretion of polypeptide hormones that exert their effects primarily on the liver and skeletal muscle. Insulin, produced by the islet  $\beta$  cell, is the most potent of these hormones. It lowers blood glucose levels after the ingestion of a meal by stimulating glucose uptake and metabolism in the muscle and liver and by inhibiting *de novo* glucose production by the liver. The proper functioning of the  $\beta$  cell thus depends on its ability to accurately sense changes in the level of blood glucose and to respond with the appropriate increase or decrease in the secretion of insulin.

Two major hypotheses were advanced in the 1960s and 1970s to explain how  $\beta$  cells sense and respond to changes in blood glucose. A glucoreceptor was proposed to bind glucose at the  $\beta$ -cell plasma membrane and transmit a signal to the cytoplasm to provoke insulin secretion (2). Alternatively, an intracellular signal might be generated or triggered as a consequence of glucose uptake and metabolism within the cell (3, 4). The latter hypothesis implies that it is the rate of glucose utilization and the consequent alteration in the level of one or more metabolites that ultimately triggers the secretory response. Matchinsky and colleagues (for review, see ref. 5) have examined this problem through a series of elegant and technically demanding biochemical studies spanning more than two decades. Following the second hypothe-

sis, they reasoned that an identification of the rate-limiting (i.e., nonequilibrium) steps in islet glucose metabolism might lead to an understanding of how  $\beta$  cells sense blood glucose levels. A pioneering study published by Matschinsky and Ellerman in 1968 (6) demonstrated the presence in isolated rat islets of a high- $K_m$  form of hexokinase, subsequently identified as hexokinase IV or glucokinase. The hexokinases catalyze the first step in the intracellular metabolism of glucose—i.e., its phosphorylation to glucose 6-phosphate. Glucokinase activity had previously been identified only in the liver, another tissue that must accurately sense blood glucose levels in order to perform its function. Unlike other hexokinase isozymes, glucokinase has a  $K_m$  for glucose ( $\approx 10$  mM) within the physiologic range of blood glucose levels. As a result of Michaelis–Menton enzyme kinetics, the rate of phosphorylation of glucose by this enzyme will change in direct proportion to physiologic changes in blood glucose, given that the transport of glucose across the membrane is not rate-limiting. Furthermore, if the phosphorylation step is rate-limiting for glycolysis in the  $\beta$  cell, glucokinase might be a key factor in glucose sensing.

This hypothesis has been extremely difficult to test directly because, ideally, it requires the *in vivo* manipulation of glucokinase levels in the  $\beta$  cell. Epstein *et al.* (1) have made elegant use of transgenic technology to confirm the importance of the phosphorylation step in  $\beta$ -cell glucose sensing. They used the rat insulin promoter to drive expression of yeast hexokinase B in the  $\beta$  cells of transgenic mice, resulting in a 2-fold increase in total  $\beta$ -cell hexokinase activity. The mice exhibited increased serum insulin levels and blood glucose levels that were 20–50% below that of controls. Islet cells isolated from the transgenic animals demonstrated increased glucose-stimulated insulin secretion. These results definitively establish the importance of the hexokinase step in the ability of  $\beta$  cells to translate blood glucose levels into the appropriate secretory response.

The results of Epstein *et al.* (1) have important ramifications for the etiology of non-insulin-dependent diabetes mellitus (NIDDM). NIDDM is a heterogeneous genetic disorder that usually oc-

curs after the third decade. Its two key characteristics are the inability of peripheral tissues to properly dispose of a glucose load (insulin resistance) and an inappropriately low insulin secretory response to the ambient glucose level, both of which contribute to hyperglycemia. Although there is considerable controversy as to which of these two pathologic conditions is the initiating event in the disease, it is clear that abnormal insulin secretion is necessary to diagnose NIDDM according to the accepted guidelines. The cloning of the rat (7, 8) and human (9, 10) glucokinase genes paved the way for an investigation of the possible role of this gene in NIDDM. Two groups of investigators have reported an association between polymorphisms at the glucokinase locus and a rare form of NIDDM called maturity-onset diabetes of youth (MODY). Unlike garden-variety NIDDM, MODY is a genetic disease with an autosomal dominant pattern of inheritance and is thus most likely the result of a defect at a single genetic locus. Linkage studies in French (11) and British (12) MODY families established a strong association between the glucokinase locus and the disease. Fifteen distinct mutations within six exons were identified in the French MODY families (13, 14). Most of the alterations were point mutations within the structural gene that predict truncated glucokinase polypeptides. Affected family members were heterozygous for the defective gene, suggesting that fairly modest ( $\approx 2$ -fold) reductions in the level of glucokinase activity can cause diabetes. The results of Epstein *et al.* (1) provide strong experimental support for a cause-and-effect relationship between the glucokinase gene defects and MODY and also suggest an important role of the  $\beta$  cell, as opposed to the liver, in the pathogenesis of the disease.

The work described above is a major breakthrough in understanding the molecular basis of diabetes. However, many questions remain concerning the etiology of the most common forms of NIDDM. Permutt and colleagues (15) have demonstrated an association between NIDDM and the glucokinase locus in African Americans, but no correlation was observed in a family linkage study (14) or population study (16) of Caucasians exhibiting late-onset diabetes.

MODY is a relatively mild form of diabetes and, unlike the more common forms characterized by later age of onset, insulin resistance is usually not observed. It is likely that the more-common severe forms of NIDDM require defects in genes involved in glucose disposal as well as insulin secretion. As NIDDM is clearly a heterogeneous disorder, it is also likely that several, and perhaps many genes, expressed in  $\beta$  cells and the glucose disposal tissues, will be causally involved in the disorders collectively called NIDDM. The work on glucokinase and MODY should provide a strong stimulus to examine the possible role in NIDDM of other enzymes that catalyze nonequilibrium steps in  $\beta$ -cell glucose metabolism. Importantly, the actual signal generated by glucose metabolism that triggers insulin secretion has not yet been identified, and little is known about the molecular defects that cause insulin resistance in liver and skeletal muscle. However, the great attention these problems are receiving will undoubtedly result in major breakthroughs in the near future.

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