Perspectives in Diabetes

Glucokinase as Glucose Sensor and Metabolic Signal Generator in Pancreatic β-Cells and Hepatocytes

FRANZ M. MATSCHINSKY

This article reviews evidence for a pivotal role of glucokinase as glucose sensor of the pancreatic β-cells. Glucokinase explains the capacity, hexose specificity, affinities, sigmoidicity, and anomeric preference of pancreatic islet glycolysis, and because stimulation of glucose metabolism is a prerequisite of glucose stimulation of insulin release, glucokinase also explains many characteristics of this β-cell function. Glucokinase of the β-cell is induced or activated by glucose in contrast to liver glucokinase, which is regulated by insulin. Tissue-specific regulation corresponds with observations that liver and pancreatic β-cell glucokinase are structurally distinct. Glucokinase could play a glucose-sensor role in hepatocytes as well, and certain forms of diabetes mellitus might be due to glucokinase deficiencies in pancreatic β-cells, hepatocytes, or both. *Diabetes* 39:647–52, 1990

We are searching for the essence that lies behind the fortuitous.

Paul Klee

DEFINITION AND HISTORICAL PERSPECTIVE

Precise blood glucose regulation is crucial for the optimal physiological function of many tissues and is required for longevity of humans. The nervous system is impaired when blood glucose falls below a critical level, and prolonged hyperglycemia severely damages vital tissues, e.g., peripheral nerves, eyes, kidneys, and blood vessels of small and large diameter. An extraordinary system has evolved to maintain blood glucose in the narrow healthy and safe range of 4–7 mM both after meals and during periods of starvation. The homeostatic system in its simplest form comprises seven crucial elements providing effective dual control of blood glucose: four sensors or receptors (i.e., the glucose sensors of α- and β-cells and the receptors for insulin and glucagon) with their associated systems (α-cells, β-cells, hepatocytes, muscle, and adipocytes), the two hormonal messengers insulin and glucagon, and the regulated parameter glucose. The system is capable of lowering or raising blood glucose according to need (1).

The effectiveness of the antagonistic dual-control system maintaining glucose homeostasis is best illustrated by the glucose concentration curves for inhibition of stimulated glucagon release and stimulation of insulin secretion (1). The α-cell is much more sensitive to glucose than the β-cell. Virtually full suppression of stimulated glucagon release is achieved at normoglycemic levels of 4–5 mM glucose, which is close to the threshold for glucose-stimulated insulin release. The crossover of these two opposing glucose dose-response relationships coincides with the level of euglycemia, which beautifully illustrates the physiological significance of the dual-control system. The clear separation of the two glucose dose-response curves also implies that the glucose actions on α- and β-cells are largely independent of each other, strongly suggesting that the effects of the glucose molecule on the two types of endocrine cells are direct. Any proposal about the nature of glucose-sensing devices of α- or β-cells has to be consistent with these fundamental dose-response relationships.

Much is known about the chemistry of the glucose molecule and the biochemical pathways involved in the use or production of glucose, and understanding of the two antagonistic hormones insulin and glucagon and about the structure, molecular biology, and physiological function of their respective receptors is highly advanced (see any modern textbook of biochemistry). However, a generally accepted view of the molecular species of the pancreatic α- and β-cell glucose sensors has progressed slowly. The complexity

From the Department of Biochemistry and Biophysics and the Diabetes Research Center, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.
Address correspondence and reprint requests to Franz M. Matschinsky, MD, Diabetes Research Center, 501 Medical Education Building, 36th and Hamilton Walk, University of Pennsylvania, Philadelphia, PA 19104-6015.
Received for publication 21 November 1989 and accepted in revised form 30 January 1990.

Downloaded from http://diabetesjournals.org/diabetes/article-pdf/39/6/647/357561/39-6-647.pdf by guest on 18 July 2024

of the islet cell glucose-recognition process and the lack of suitable biological study objects are the major reasons the problem has remained elusive. In this brief account, I focus on the loop that involves the β-cells, insulin, and the respective receptors with their metabolism influence spheres. The antagonistic loop composed of α-cells, glucagon, and the glucagon receptor with its target tissues is not discussed. Among the components of the insulin loop, the emphasis is on the β-cell glucose-sensor device and putative analogous glucose-sensor devices in liver.

Our view of the β-cell is profoundly influenced by the way we imagine its glucose-sensing element. Several mechanisms by which blood glucose levels could be tracked by the β-cells are theoretically possible. One attractive possibility is a mechanism based on a cell membrane–associated glucoreceptor that recognizes the glucose molecule as such and initiates the secretory response of the β-cell when occupied by high glucose. An equally plausible view proposes that glucose stimulation of insulin secretion results from enhanced glucose metabolism of the β-cell when the blood glucose rises. Our laboratory supports the notion that glucokinase (ATP:D-glucose 6-phosphotransferase [EC 2.7.1.2]) is the constituent enabling the β-cell to recognize and measure the fluctuations of blood glucose (2). This view also implies that catabolism of glucose is a prerequisite for sensing it. We first expressed this idea in 1968 (2):

> The mechanism that has been selected appears to depend on the rapid penetration and transformation of the very molecule which is itself the object of the regulatory process. The scheme of carbohydrate metabolism of the islets of Langerhans has great similarities to the situation found in the liver. The membrane properties of the β-cells, the probable presence of two glucose phosphorylating enzymes with low and high affinity for the substrate and the ability to liberate free glucose from glucose-6-phosphate constitute ideal conditions of rapid adjustments of glycolysis to blood glucose levels.

The idea was more explicitly stated in a review article (3):

> Glucokinase occupies an important role in controlling glucose phosphorylation and metabolism both in the liver and in the pancreatic islets. In the β-cells glucokinase functions as pacemaker of glycolysis at physiological glucose levels. It determines the unique characteristic of islet glucose usage, that is the rate, affinity, cooperativity and anomeric discrimination of glucose metabolism. Because metabolism controls hexose induced insulin release glucokinase is considered the best qualified candidate for the elusive glucose sensor of the pancreatic β-cells. A deficiency of glucokinase would disturb glucose homeostasis. Decreased islet glucokinase would diminish islet glycolysis and would result in a higher set point of β-cells for glucose induced insulin release. Decreased liver glucokinase would cause less efficient hepatic glucose disposal.

The glucokinase glucose-sensor concept has been accepted as useful by many investigators and is best addressed by briefly considering accepted principles of receptor science and judging the merit of the glucokinase glucoreceptor concept on these grounds (5). Some of the sequences linking agonists to the final biological response are very complex. However, a sensor or receptor component is essential for any stimulus-response pathway. The receptor or sensor is aptly described as the lock that allows the gates to intracellular signaling pathways to be opened. The agonist is the key that fits the lock. In the case of the β-cell, glucose is the key, glucokinase is the lock, and glucose recognition and quantitation of its concentration by glucokinase is followed by signal processing that includes *1*) coupling and integration with other metabolic, hormonal, and neural signals; *2*) a transduction step; and *3*) the secretory response (5–7). Coupling and integration refers to the intermediary metabolism of the β-cells that integrates the metabolism of the primary stimulant glucose with metabolism of amino acids, fatty acids, and ketone bodies and results in the generation of putative metabolic coupling factors (e.g., ATP, long-chain acyl-CoA, diacylglycerol, H^+) that impinge on transducing elements (e.g., ATP-sensitive K^+ channels, protein kinase C, ion pumps). Integration also provides for mechanisms by which hormones and transmitters might affect intermediary metabolism and glucose-stimulated insulin release. Transduction refers to the generation of classic second messengers (i.e., cAMP, inositol triphosphate, Ca^{2+}), and insulin release refers to the intricate process of hormone granule extrusion or exocytosis.

From these and other considerations evolved a basic model of stimulus-response coupling in pancreatic β-cells (5–7; Fig. 1). The glucokinase glucose-sensor concept must be viewed in the broader perspective presented by this model in which glucose metabolism occupies center stage.

EVIDENCE FOR GLUCOKINASE GLUCOSE-SENSOR CONCEPT

The glucokinase glucose-sensor concept is based on the assumption that glucose transport into the β-cells is not rate limiting. All available data indicate that this assumption is correct. Extracellular glucose levels and the glucose level of β-cells equalize very rapidly when blood glucose fluctuates, similar to the situation in hepatocytes (2). Strong evidence for this view comes from molecular genetic and immunohistochemical studies that show hepatocytes and β-cells of the islets of Langerhans use the same glucose transporter (8).

The arguments in favor of the glucokinase glucose-sensor concept are many and strong (Table 1). Some of these require comment. Most impressive is the coincidence of the glucose-dependency curves of glucose use by intact islets and of glucose phosphorylation by islet tissue homogenate (Fig. 2). However, it is appreciated that a glucokinase-independent low-K_m component of islet glycolysis contributes substantially to the flux when glucose levels are low (≤1–2 mM), and the contribution of this component could vary physiologically. The outcome of model experiments with cultured islet tumor cells and nondiabetic islet tissue is consistent with this view (9–11). The greatest difficulty in interpreting the precise role of the low-K_m glycolysis component arises from the cellular heterogeneity of the islet tissue and the leftward shift of the glucose dose-response curve of α-cell suppression relative to that for glucose stimulation of β-cells. Note that anomeric discrimination for hexoses appears to be lost in β-cells of animals with certain forms of experimental diabetes (12). This result is puzzling and has no plausible explanation. Differential regulation of

Downloaded from http://diabetesjournals.org/diabetes/article-pdf/39/6/647/357561/39-6-647.pdf by guest on 18 July 2024

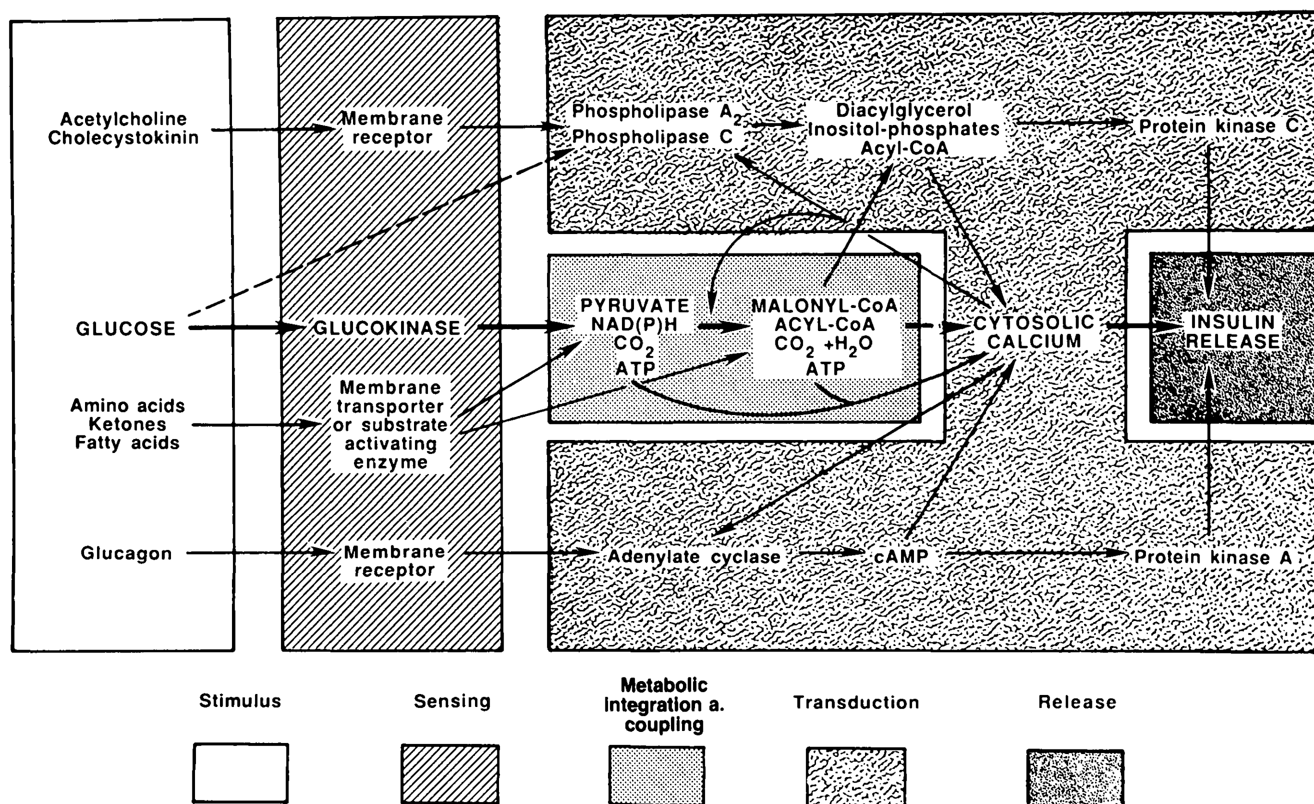

FIG. 1. Signaling in pancreatic β-cells. a., And.

islet tissue and liver glucokinase was proposed on the basis of results of enzyme-activity measurements in tissues obtained from insulinoma-carrying animals during severe hypoglycemia coupled with high serum insulin and during hyperglycemia coupled with serum insulin decline that ensues after tumor removal (13). Molecular geneticists have now provided convincing results that indicate that glucokinase expression from a single gene might be regulated differentially by tissue-specific promoters in liver and islets (14,15). It is also suggested that islets contain a unique glucokinase isoenzyme that differs from the hepatic counterpart by 15 amino acids at the NH_2-terminal (14). The use of alternate tissue-specific promoters could allow differential regulation of the glucokinase gene by insulin in the liver and by glucose in the β-cells, providing the molecular genetic basis for a two-stage feedback cycle that maintains glucose homeostasis involving β-cells and liver, as proposed earlier on the basis of enzyme-activity measurements (13). Islet glucokinase has been found in humans, rats, mice, and hamsters (16). Liver glucokinase is absent in certain species (e.g., ruminants, cats, birds; 17,18). Whether islet glucokinase is also absent in these species is worth investigating.

TABLE 1
Arguments in favor of glucokinase (GK) as β-cell glucose sensor

GK serves as major determinant of the high-K_m component of islet glycolysis and glucose oxidation (i.e., it explains the V_{max}, K_m, and n_H of the high-K_m component).
GK properties explain the hexose specificity of the high-K_m component of glycolysis.
GK serves as discriminator of hexose anomers.
GK generates hexose-6-phosphate, ADP, and H^+ at a rate proportional to blood glucose level as first signals that could initiate the β-cell response.
GK is the site of mannoheptulose and pseudo-D,L-glucose inhibition of glycolysis and glucose-stimulated insulin release.
GK is a target of alloxan and ninhydrin.
GK is regulated differently in islet tissue and liver (by glucose and insulin, respectively), consistent with the proposed unique roles of the enzyme in these organs.
GK is present in the islet tissue of many species, including humans.

UNRESOLVED ISSUES

It is important to design experiments that allow direct testing of the hypothesis that proposes differential regulation of glucokinase genes by insulin in the liver and by glucose in the pancreatic β-cells. The insulin induction of liver glucokinase based on enhanced gene expression is well established. However, islet glucokinase mRNA levels are low and more difficult to study, and there was no effect of starvation on its levels (19). Glucose levels change little in the feeding-starvation-refeeding paradigm used in the above study. Broader ranges of glucose levels must be tested, preferably with the help of an islet-culture system.

Glucokinase was found in microdissected β-cell–depleted islets from uncontrolled chronically diabetic rats (20). The results indicate that glucokinase is a constituent of α-cells of diabetic animals. Whether glucokinase is present in significant amounts in the α-cells of euglycemic animals is not known. The issue is important for understanding the role of the β-cell glucokinase glucose receptor. A possible role for glucokinase in δ-cells needs to be considered.

The β-cells of the streptozocin-induced model of type II (non-insulin-dependent) diabetes lose the anomeric discrim-

Downloaded from http://diabetesjournals.org/diabetes/article-pdf/39/6/647/357561/39-6-647.pdf by guest on 18 July 2024

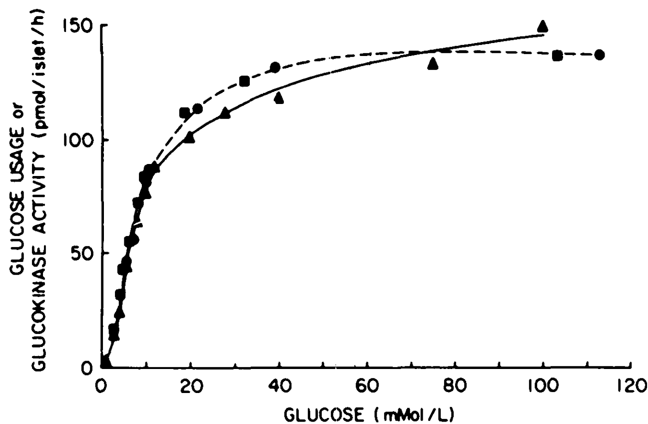

FIG. 2. Comparison of low-affinity glucose usage (▲) by isolated rat islets with glucokinase activity in intact islets. Low-affinity glucose usage was determined by subtraction of high-affinity glucose usage from total glucose usage by iterative calculations. Glucokinase activity was computed based on maximum activity of glucokinase measured in supernatants of homogenates of rat islets and activity of glucokinase purified from islets or insulinomas as function of glucose concentration. Glucokinase activity was corrected for partial saturation by ATP based on K_m for ATP measured for islet glucokinase and estimated cytosolic ATP concentration of 3 mM. Factors other than substrates that may regulate glucokinase were considered to have negligible effect. Glucokinase activity was computed based on glucose saturation plots for glucokinase purified from islets (●) or insulinomas (■). From Meglasson and Matschinsky (4).

ination of α- and β-D-glucose, as judged from insulin-release studies with the isolated perfused pancreas (12). A first step toward resolving this puzzling result would be studying isolated pancreatic islets to assess whether loss of anomeric discrimination is also observed for glucose phosphorylation and glycolysis, which provides the metabolic basis of glucose-induced insulin release.

The creation of a model β-cell that might under- or overexpress functional glucokinase would go a long way to test the proposed glucoreceptor role of this enzyme. The transgenic mouse system appears to be suitable for creating such conditions (21).

RAMIFICATIONS

Classic textbooks of physiology and biochemistry teach that liver glucokinase is sufficiently active to allow effective nearly quantitative hepatic removal of alimentary glucose from the portal vein and that this enzyme constitutes the first rate-limiting step in the pathway that results in the storage of nutrient glucose in the form of liver glycogen (22). However, this view is changing radically (22–24). It has been proposed in the last decade that liver glucokinase activity is insufficient to serve this role and that most of the postprandial surge of liver glycogen is due to enhanced gluconeogenesis from lactate and other precursors. It also follows that glucokinase activity of the liver is much too low to generate sufficient lactate to serve as substrate for the gluconeogenic or indirect pathway of glycogenesis. It appears that the major fraction of lactate is generated by extrahepatic tissue, e.g., intestine and muscle. Thus, glucokinase seems to be losing its proposed pivotal role as the regulator of liver glucose metabolism. However, a secondary role of this enzyme in liver glucose metabolism seems unlikely considering its teleologically plausible distribution among different species (17,18) and in view of the exquisite hormonal control mechanisms that have evolved to regulate its activity (14). Instead of serving as a major flux-generating enzyme, liver glucokinase may play the role of a metabolic signal generator in hepatocytes, allowing blood glucose levels to influence hepatic intermediary metabolism activity in addition to the well-established indirect route via insulin or glucagon. In a way, the situation would be similar to what is proposed for the pancreatic β-cell. Glucokinase could play a glucose-sensor role by coupling hepatic intermediary metabolism to the minute-by-minute fluctuation of blood glucose without being quantitatively important for pathway fluxes. It could play a role analogous to that of hepatic phosphorylase *a*, which has a glucose-binding site rendering it a more suitable substrate for phosphoprotein phosphatase that inactivates the glycogenolytic enzyme and activates glycogen synthase (25). Phosphorylase *a* has indeed been called the hepatic glucoreceptor (26).

The literature contains scattered evidence that can be used in favor of such a speculative function of hepatic glucokinase. It has been demonstrated that glucose is an effective potentiator of glycogenesis from lactate, alanine, and glutamine. The concentration-dependency curve of this effect is consistent with a regulatory role of glucokinase (27,28). However, the glucose effect is usually explained by glucose inactivation of glycogen phosphorylase *a* (25). The effect on glycogen phosphorylase *a* is apparently direct and does not require glucose phosphorylation. The reported K_m values of this glucose effect (3.9–33.0 mM) are in accord with its glucose-sensor function (26). However, to our knowledge, whether the potentiator action of glucose on glycogen synthesis from smaller precursors is indeed independent of its metabolism has not been tested thoroughly and critically. A similar potentiator action of glucose has been observed for lipogenesis from a mixture of lactate, pyruvate, and glutamine (29). The potentiator action of glucose on lipogenesis is paralleled by an accumulation of malonyl-CoA and a curbing of fatty acid oxidation. This glucose effect is usually attributed to its stimulatory action on glycogenesis. Here again, it has not been ascertained that the glucose effect is direct and unrelated to phosphorylation as the hypothesis implies. Lack of insulin in diabetes blocks the effect of glucose on glycogenesis and at the same time causes a loss of hepatic

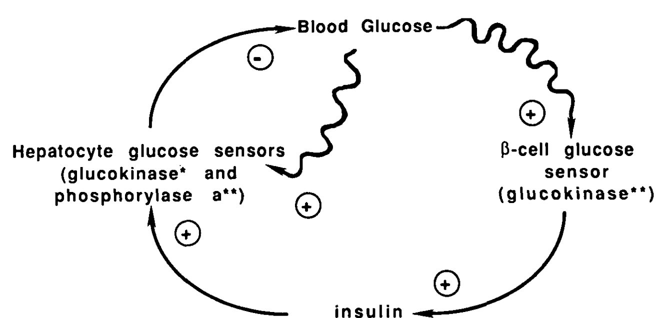

FIG. 3. Blood glucose as messenger or signal molecule stimulating pancreatic β-cells in insulin-independent way and hepatocytes in manner both independent (**) of (phosphorylase *a*) and dependent (*) on (glucokinase) insulin. Glucose insensitivity or refractoriness would lead to hyperglycemia. Analogous feedback loop could exist involving α-cells and glucagon.

Downloaded from http://diabetesjournals.org/diabetes/article-pdf/39/6/647/357561/39-6-647.pdf by guest on 18 July 2024

glucokinase that could imply an involvement of the enzyme in glycogenesis (30). Also consistent with the proposed role of glucokinase as signal generator is the situation in ruminants (17). Liver glucokinase is absent in ruminants, and glucose appears to be incapable of stimulating glycogen synthesis (17,18). It would be important to know whether the hepatic phosphorylase *a* of ruminants is glucose sensitive. Admittedly, evidence for the present proposal of glucokinase as liver glucose sensor and signal generator is slim, but the proposal could be useful and lead to new avenues of experimentation. Two mechanisms of glucokinase involvement might be considered. One is based on the generation of metabolic coupling factors: glucose-6-phosphate, ADP, H^+, and related downstream molecules. Another involves the glucokinase molecule itself as messenger: ternary complexes of glucokinase (ATP/glucose/enzyme or ADP/glucose-6-phosphate/enzyme) may have distinct messenger roles, e.g., they could mediate inhibition of glucose-6-phosphatase or activate glucogen synthase. Such speculative ideas can be tested readily because sufficient amounts of glucokinase will undoubtedly become available in the near future.

PATHOPHYSIOLOGICAL IMPLICATIONS

A pivotal role of glucokinase isoforms in pancreatic β-cells and liver cell intermediary metabolism and function is the underlying theme of this brief discussion. It should be obvious that alterations of the structure, function, and regulation of liver and β-cell glucokinase could have a drastic influence on the glucose homeostasis of the organism. We calculated that even very modest diminution of β-cell glucokinase activity could significantly reduce the glucose sensitivity of the pancreatic β-cell (3). Considering the preceeding discussion, it is not unreasonable to extrapolate from the β-cell to the hepatocyte. Because of the apparent differential regulation of liver and β-cell glucokinase gene expression, liver- and islet-specific defects are conceivable, or the enzyme might be affected in both organs. Subtle or drastic changes in the K_m or V_{max} of this enzyme in β-cell, liver, or both might occur in humans. A first step in exploring such a possibility would be to study restriction-fragment–length polymorphisms of the glucokinase gene and its tissue-specific promoter regions with families in which type II diabetes is found in several generations. This is now feasible because suitable reagents are becoming readily available (14,15).

GLUCOSE AS NUTRIENT SIGNAL MOLECULE

I close this perspective with a brief but bold speculation. The preceding discussion of pancreatic β-cell and liver glucose-sensor molecules leads logically to the complementary concept of glucose as a nutrient signal molecule (Fig. 3). Physiologists have all along toyed with the notion of a unique messenger role for glucose. Claude Bernard has called glucose a nutritive stimulator (22). The term implies that glucose has a role over and above being a fuel and substrate molecule for energy metabolism of the cell. This concept captures the essence of the material discussed in this essay and could be useful for understanding normal glucose homeostasis and explaining the pathogenesis of hyperglycemic states. Type II diabetes is in part attributed to peripheral insulin resistance (31). It is apparent from the preceeding discussion that glucose exerts hypoglycemic actions that appear to be partly independent of insulin. It could be instructive to assess to what extent glucose resistance or glucose insensitivity might play a part in hyperglycemia syndromes. Primary glucose refractoriness involving glucose-sensor molecules in pancreatic islet cells and hepatocytes (e.g., glucokinase, phosphorylase *a*, glucose-6-phosphatase, and other molecules to be discovered) might play a role.

REFERENCES

1. Matschinsky FM, Bedoya F: Metabolism of pancreatic islets and regulation of insulin and glucagon secretion. In *Endocrinology*. Vol. 2. DeGroot LJ, Ed. Philadelphia, PA, Saunders, 1989, p. 1290–303
2. Matschinsky FM, Ellerman JE: Metabolism of glucose in the islets of Langerhans. *J Biol Chem* 243:2730–36, 1968
3. Meglasson MD, Matschinsky FM: New perspectives on pancreatic islet glucokinase. *Am J Physiol* 246:E1–13, 1984
4. Meglasson MD, Matschinsky FM: Pancreatic islet glucose metabolism and regulation of insulin secretion. *Diabetes Metab Rev* 2:163–214, 1986
5. Matschinsky FM, Meglasson MD, Schimizu T, Prentki M, Garfinkel D, Achs M, Erecinska M, Najafi H, Parker J, Weik H: Glucose metabolism, glucose sensing and stimulus response coupling in insulin release by pancreatic β-cells. In *Pathogenesis of Non-Insulin-Dependent Diabetes Mellitus*. Grill V, Efendic S, Eds. New York, Raven, 1988, p. 61–78
6. Prentki M, Matschinsky FM: Ca^{2+}, cAMP and phospholipid derived messengers in coupling mechanisms of insulin secretion. *Physiol Rev* 67:1185–245, 1987
7. Matschinsky FM, Corkey BE, Prentki M, Meglasson MD, Erecinska M, Shimizu T, Ghosh A, Parker J: Metabolic connectivity and signalling in pancreatic β-cells. *Proc Int Diabetes Fed, Sydney, Australia, 1988*. Larkins R, Zimmet P, Chisholm D, Eds. Amsterdam, Elsevier, 1989, p. 17–26 (Excerpta Med. Int. Congr. Ser.)
8. Thorens B, Saka HK, Kafack HR, Lodish HF: Cloning and functional expression in bacteria of a novel glucose transporter present in liver, intestine, kidney, and β-pancreatic islet cells. *Cell* 55:281–90, 1988
9. Shimizu T, Knowles BB, Matschinsky FM: Control of glucose phosphorylation and glucose usage in clonal insulinoma cells. *Diabetes* 37:563–68, 1988
10. Shimizu T, Parker JC, Najafi H, Matschinsky FM: Control of glucose metabolism in pancreatic β-cells by glucokinase, hexokinase and phosphofructokinase: model study with cell lines derived from β-cells. *Diabetes* 37:1524–30, 1988
11. Meglasson MD, Najafi H, Matschinsky FM: Acetylcholine stimulates glucose metabolism by pancreatic islets. *Life Sci* 39:1745–50, 1986
12. Niki A, Niki H, Niki I, Kunoh Y: Insulin release by glucose anomers in a rat model of non-insulin-dependent diabetes. *Diabetologia* 31:65–67, 1988
13. Bedoya FJ, Matschinsky F, Shimizu T, O'Neil JJ, Appel MC: Differential regulation of glucokinase activity in pancreatic islets. *J Biol Chem* 261:10760–64, 1986
14. Magnuson MA, Andreone TL, Printz RL, Koch S, Granner DK: Rat glucokinase gene: structure and regulation by insulin. *Proc Natl Acad Sci USA* 86:4838–42, 1989
15. Magnuson MA, Skelton KD: An alternate promoter in the glucokinase gene is active in the pancreatic β-cell. *J Biol Chem* 264:15936–42, 1989
16. Bedoya FJ, Wilson JM, Ghosh AK, Finegold D, Matschinsky FM: The glucokinase glucose sensor in human pancreatic islet tissue. *Diabetes* 35:61–67, 1986
17. Ballard FJ: Glucose utilization in mammalian liver. *Comp Biochem Physiol* 14:437–43, 1965
18. Pilkis SJ, Hansen RJ, Krahl MD: Hexose-ATP phosphotransferase: comparative aspects. *Comp Biochem Physiol* 25:903–12, 1968
19. Milburn JL, Quaade C, Iynedjian P, Alam T, Newgard CB: Expression of a unique islet glucokinase mRNA in islets, islet cell tumors, and rat insulinoma cell lines (Abstract). *Diabetes* 38 (Suppl. 2):6A, 1989
20. Bedoya FJ, Oberholtzer JC, Matschinsky FM: Glucokinse in β-cell–depleted islets of Langerhans. *J Histochem Cytochem* 35:1089–93, 1987
21. Efrat S, Linde S, Kofod H, Spector D, Delamoy M, Grant S, Hanahan D, Baekcheskov S: Beta-cell lines derived from transgenic mice expressing a hybrid insulin gene-oncogene. *Proc Natl Acad Sci USA* 85:9037–41, 1988
22. McGarry JD, Kuvoajima M, Newgard CB, Foster DW: From dietary glucose to liver glycogen: the full circle round. *Annu Rev Nutr* 7:51–73, 1987
23. Foster DW: Banting Lecture 1984: from glucogen to ketones—and back. *Diabetes* 33:1188–99, 1984
24. Katz J, McGarry JD: The glucose paradox: is glucose a substrate for liver metabolism? *J Clin Invest* 74:1901–909, 1984
25. Hers HG: Control of glycogen metabolism in the liver. *Annu Rev Biochem*

Downloaded from http://diabetesjournals.org/diabetes/article-pdf/39/6/647/357561/39-6-647.pdf by guest on 18 July 2024

45:167–89, 1987
26. Stalmans W, Laloux M, Hers HG: The interaction of liver phosphorylase *a* with glucose and AMP. *Eur J Biochem* 49:415–27, 1974
27. Hems DA, Whitman PD, Taylor EA: Glycogen synthesis in the perfused liver of the starved rat. *Biochem J* 129:529–38, 1972
28. Bontemps F, Hue L, Hers HG: Phosphorylation of glucose in isolated rat hepatocytes. *Biochem J* 174:603–11, 1978
29. Boyd ME, Albright EB, Foster DW, McGarry JD: In vitro reversal of the fasting state of liver metabolism in the rat: reevaluation of the roles of insulin and glucose. *J Clin Invest* 68:142–52, 1981
30. Weinhouse S: Regulation of glucokinase in liver. *Curr Top Cell Regul* 11:1–50, 1976
31. Bogardus C, Lillioja S, Howard BV, Mott DM, Bennett PH: Cross-sectional and longitudinal studies of carbohydrate metabolism in Pima Indians. In *Pathogenesis of Non-Insulin-Dependent Diabetes Mellitus*. Grill V, Efendic S, Eds. New York, Raven, 1988, p. 285–301

Downloaded from http://diabetesjournals.org/diabetes/article-pdf/39/6/647/357561/39-6-647.pdf by guest on 18 July 2024