Glucokinase as Pancreatic β Cell Glucose Sensor and Diabetes Gene

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Introduction

This article is an account of research in physiological chemistry, molecular biology, and human genetics that developed the concept that glucokinase (GK)[1] of the insulin-secreting pancreatic β cells plays the crucial role of glucose sensor in an endocrine feedback cycle that maintains glucose homeostasis, and traced one cause of non–insulin-dependent diabetes mellitus (NIDDM) to mutations of the GK gene. This body of knowledge promises to be significant for the understanding of glucose homeostasis in general and of the etiology of diabetes mellitus, and also for devising new approaches to the management of the disease.

Unique physiological and biochemical design features of glucose metabolism of pancreatic β cells

Physiological considerations. The narrow range of physiological blood glucose concentrations (4–8 mM) is governed by the glucose set points and the secretory capacities of the pancreatic α and β cells (1). This design feature is illustrated by the concentration dependency curves and the opposite effects of glucose on α and β cells showing a physiological crossover point in the fed state at 5 mM glucose (Fig. 1 *A*). The glucose set point and secretory capacity of the β cell play the paramount role in glucose homeostasis, and their physiological or pathological alterations thus influence the average blood glucose levels in a preeminent manner. It cannot be overemphasized that glucose is the only nutrient molecule that stimulates β cells directly at physiological levels, and that blood glucose levels of at least 2.5–3.0 mM need to be maintained to allow the recognition by the β cell of other nutrient molecules (i.e., amino acids and ketone bodies) and of hormones or neurotransmitters that stimulate β cell function (e.g., enteroglucagon or acetylcholine) (2).

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1. *Abbreviations used in this paper:* GK, glucokinase; MODY, maturity-onset diabetes of the young; NIDDM, non–insulin-dependent diabetes mellitus.

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Unique design features of β cell glucose metabolism. Glucose stimulation of insulin secretion is the result of enhanced glucose metabolism of β cells (1, 3–6). Glucose enters the β cells via the high-capacity, high K_m hexose transporter, GLUT-2 (6, 7). The capacity of glucose transport in intact islets is at least 100-fold in excess of actual glycolysis and is sufficient to assure equalization of extra- and intracellular glucose within seconds of any blood glucose level changes, pointing to an intracellular glucose sensing device. Glucose transport reductions of > 90% need to take place to exert a marked impact on physiological islet glucose metabolism (7).

Phosphorylation of glucose is dually controlled by at least one hexokinase (probably hexokinase I) and by GK (3–6, 8). Islet tissue hexokinase has relatively broad substrate specificity, has a low K_m for glucose of 0.05–0.15 mM, and is inhibited "in situ" by > 95% by various phosphorylated intermediates (e.g., glucose-6-phosphate, glucose-1,6-diphosphate, and 6-phosphogluconate [G-6-P, G-1,6-P_2, and 6-GP]), such that flux through hexokinase is relatively slow even when fully saturated at ≥ 1.0 mM glucose (compare Fig. 1, *B* and *C*). However, flux through hexokinase(s) can be regulated indirectly (8), particularly when glucose levels are low and flux through the high K_m system (see below) is relatively slow (4). Future research should elucidate the precise nature and possible role of hexokinases other than GK. GK of the β cell has by far the lowest capacity of all glycolytic enzymes (3, 4). It has an apparent K_m of ~ 10 mM for glucose and shows cooperative kinetics (the Hill coefficient [n_H] = 1.5–1.7) with its substrate glucose (Fig. 2). The inflection point of the sigmoidal glucose dependency curve of GK is at ~ 5 mM, close to the threshold of β cells for glucose stimulation. GK prefers the α anomer of glucose. GK lacks significant feedback inhibition by metabolites in contrast to other hexokinases. The fructose-6-phosphate (F-6-P)-dependent GK inhibitor protein found in liver, although present in islets, appears to be of little importance under normal conditions (9). The actual rate of glucose phosphorylation by GK in the intact cell is thus largely determined by the enzyme content and the concentration of its substrate glucose. Studies with recombinant human liver and β cell GK isoforms showed that the kinetic characteristics of the human enzymes are indistinguishable from those of authentic rat liver enzyme (10, and Liang, Y., P. Kesavan, L. Wang, Y. Tanizawa, M. A. Permutt, and F. M. Matschinsky, manuscript submitted for publication). Most importantly, the apparent K_m is ~ 10 mM and the n_H is ~ 1.7. A K_m of 10, a n_H of 1.7, and an inflection point of 5 mM indicate that glucose may control glycolysis most effectively in the range of 3–15 mM, close to an ideal design for a glucose sensor molecule (Fig. 2). The possibility exists that

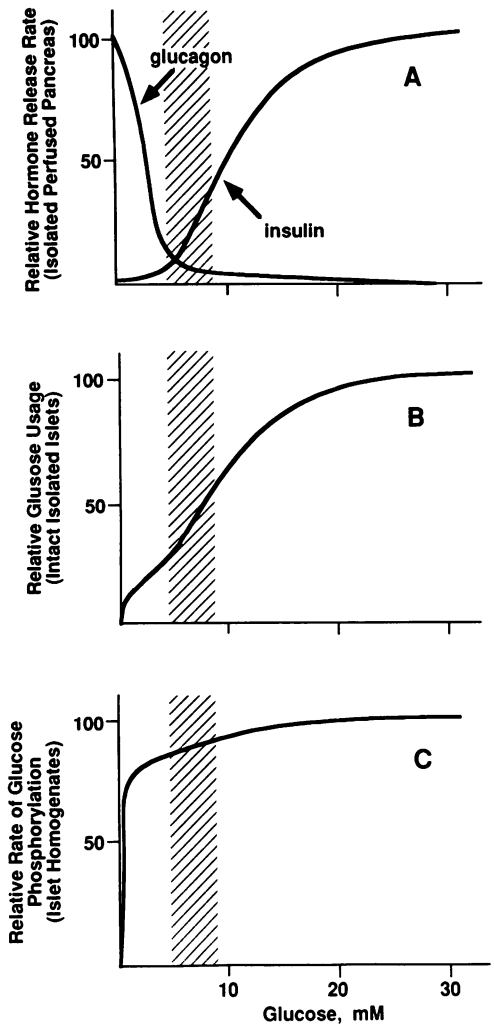

Figure 1. Glucose phosphorylative capacity, glucose usage, glucose set points, and secretory capacities of pancreatic islet cells. Relative rates of hormone secretion as a function of glucose concentration are shown (*A*). When glucose usage of intact isolated pancreatic islets is studied (*B*) low and high K_m components are visible, however, the high K_m component greatly predominates in the intact cells. The glucose phosphorylative capacity of islet homogenates is shown (*C*). A low K_m component predominates but a minor high K_m component can be recognized. The graphs are idealized renderings based on many concordant reports in the literature. The cross-hatched band brackets the physiological blood glucose range.

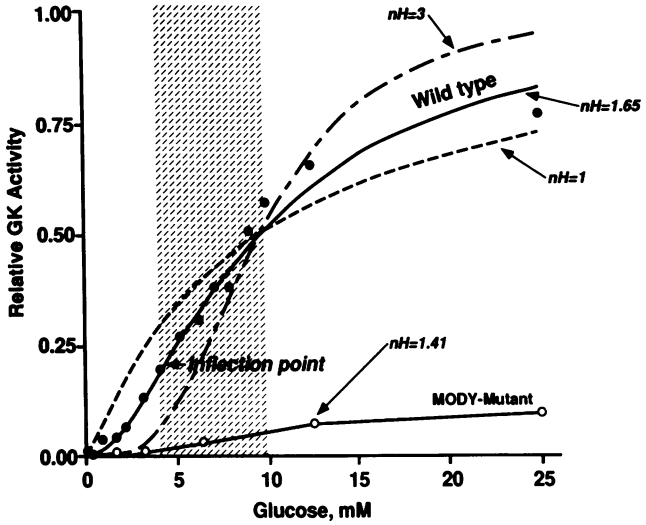

Figure 2. Glucose-dependent cooperation of recombinant wild-type and mutant human islet glucokinase: glucokinase as β cell glucose sensor and diabetes gene. Three theoretical glucose dependency curves of glucose phosphorylation by wild-type glucokinase with a K_m of 10 and Hill coefficients of 1.0, 1.65, and 3.0 are shown. The sigmoidal relationship between velocity (V) and substrate level (S) of glucokinase can be described by an equation of the following general form: $V = S^{nH}V_{max}/S^{nH} + K'$, where $K' = [K_m]^{nH}$. The actual data with the recombinant β cell isoform (o) fits best the plot that was generated with a Hill coefficient of 1.65. Data for one human mutant (families 114 and 331 of Table I) are shown for comparison (10, and Matschinsky, F. M., Y. Liang, P. Kesavan, L. Wang, K. Niswender, and M. A. Magnuson, unpublished results).

factors in the β cell, yet to be discovered, could modify GK such that the K_m or n_H for glucose are modified, resulting in a shift of the glucose dependency curve of metabolism and insulin release. Glucose-6-phosphatase, glucose-6-P dehydrogenase, and the glycogen apparatus are other enzyme systems that impinge on G-6-P levels (11, 12). Quantitating precisely the actual rates of all processes governing the level of G-6-P is a difficult task and has not been accomplished. Subtleties aside, it appears that GK is the principal determinant of altered flux through the G-6-P pool when glucose levels change in the physiological range of 4–8 mM. The most convincing evidence in support of this view stems from comparisons of the high K_m components of glucose phosphorylation of islet cell homogenates with the glucose use of intact pancreatic islets, which are virtually identical and show identical cooperativity, suggesting that GK is the main determinant of glucose usage by β cells (1, 4, 5). Moreover, GK activity of islet tissue extracts and glucose usage rates of intact islets changed concordantly over a fivefold range in cultured pancreatic islets maintained at 3–30 mM glucose (13). Another outstanding feature of pancreatic β cell metabolism is the high activity of mitochondrial α-glycero-*P*-dehydrogenase, an enzyme that shuttles hydrogen unidirectionally from the cytosol into mitochondria (14). Glucose stimulates oxygen consumption of islets effectively (15). Yet the molecular basis of enhanced O_2 consumption remains to be elucidated. It may be explained, in part, by the effectiveness of the hydrogen and substrate shuttles that connect cytosol and mitochondria and by the redundancy of enzymes involved in pyruvate metabolism: pyruvate dehydrogenase, malic enzyme, and pyruvate carboxylase. Effective generation of oxalacetate and acetyl-CoA may enhance citrate production, probably augmenting the citric acid cycle. Citrate efflux from the mitochondria may increase and facilitate the generation of malonyl-CoA, which could redirect β cell metabolism from lipid oxidation during fasting to nearly exclusive glucose use during feeding (16, 17).

Coupling of metabolic events to membrane electrical and secretory events of the β cells is probably mediated through the cytosolic levels of adenine nucleotides, which are known to alter the conductance of a particular K^+ channel (18). ATP is an inhibitor and ADP an activator of this K^+ channel. Since islet levels of total ATP are not changed whereas levels of free ADP seem to fall when glucose is high, free ADP stands out as the most plausible candidate metabolic coupling factor (19). When free ADP falls, K^+ channels close, the cell membrane is

depolarized, Ca^{2+} influx is enhanced, and insulin release commences.

GK as glucose sensor and diabetes mellitus candidate gene

GK as critical determinant of β cell intermediary metabolism and glucose sensor. As a result of the remarkable overall metabolic design of β cells, even small physiological alterations of blood glucose levels are recognized and quantitated, and this information is then transmitted through the metabolic machinery to the nucleotide-sensitive K^+ channels, the primary determinants of the membrane potential. GK serves as pacemaker of glucose catabolism and thus as "glucose sensor" of this process, and the downstream enzymatic steps of glycolysis and the citric acid cycle are automatically activated due to mass action and by various complex mechanisms of feedforward or feedback modification (3–6, 8). This mass action effect probably explains increased electron transport and oxidative phosphorylation as well (20). Because of the formidable network of metabolic pathways and the many ways to regulate them, it should be expected that intermediary metabolism of β cells, and thus insulin release, can be modified by nutrients, the nervous system, and by endocrine factors leading to intricate control of β cell functions. Our understanding of the control mechanisms that are involved remains fragmentary.

GK as candidate diabetes mellitus gene. Because of the unique regulatory role of GK as pacemaker of β cell glucose and energy metabolism, it was recognized that even small reductions of β cell GK activity (e.g., as little as 15–20%) might elevate the set point of β cells for glucose recognition, thus creating a diabetes mellitus–like state for the organism, and the possibility that GK could be a diabetes gene was proposed (3–5). Sensitive methods were designed that allowed the quantitation of picogram amounts of GK in fragments of single human islets and were readily applicable to biopsy samples of human liver (21). GK was found in normal human islets and the measured GK activity and the kinetic characteristic accounted for the glycolytic rate of isolated intact human islets (21). These methods are suitable to determine GK in microscopic hepatic and islet samples from individuals with diabetes mellitus.

β cell–liver feedback loop in glucose homeostasis and differential regulation of GK in hepatocytes and β cells. The presence of GK in the pancreatic β cells and recognition of its function as glucose sensor suggested a broader role of this enzyme in a two-stage feedback loop involving the liver as one of the organs and the β cells as the other (22) (Fig. 3). It was soon discovered that regulation of GK in hepatocytes and β cells was fundamentally different, with glucose governing the level of β cell GK and insulin regulating that of hepatocyte GK (23). Attempts to assess the relative importance of the two components in this feedback loop of glucose homeostasis are problematic because of the cyclic nature of the process. However, the β cell GK link appears to be the component with the highest control strength because there appears to be little or no redundancy, contrasting with the hepatic GK link. After a meal liver GK participates in the removal of elevated blood glucose and its deposition as liver glycogen. However, as much as three-fourths of the glycogen may be synthesized by an indirect gluconeogenic pathway from lactate and pyruvate generated in liver, the splanchnic organs, and muscle, in large part independent of GK (24). A partial reduction of liver GK might therefore be compensated by other processes, as opposed to the case of a β cell GK deficiency. Furthermore, glucose uptake by muscle that is stimulated by insulin participates in glucose disposal.

Cellular heterogeneity of hepatic and islet GK distribution and intracellular compartmentation of GK in β cells. Pancreatic β cells are heterogeneous, as manifest in remarkably different GK contents of individual β cells (25). Some β cells are nearly devoid of immunoreactive enzyme (Fig. 4). This cellular heterogeneity of β cell GK may be paralleled by cellular heterogeneity of insulin contents and of secretory glucose responsiveness, although a correlation between GK content and insulin-secreting ability has not been established (26). The significance of cellular heterogeneity of GK distribution for the glucose set point and the nature of the glucose dependency curve of insulin secretion remain elusive because individual β cells do show a graded response to glucose as well, rather than responding in an all or none fashion.

It has been proposed that GK might be compartmentalized within the β cell by association with the GLUT-2 transporter at the cell membrane, thus constituting a higher level organization, which might establish a unique metabolic signaling pathway in the β cells (27). This possibility remains to be fully investigated.

Glucokinase gene structure and regulation

Tissue-specific GK isoforms. The biochemical and physiological studies that served to define the function of GK in the pancreatic β cell and the liver provided a framework for molecular genetic studies. The cDNA sequence of rat hepatic GK was the first to be determined (28, 29), and soon thereafter the sequence of rat β cell GK was elucidated (30, 31). Both hepatic and β cell GK were found to be 465 amino acid polypeptides

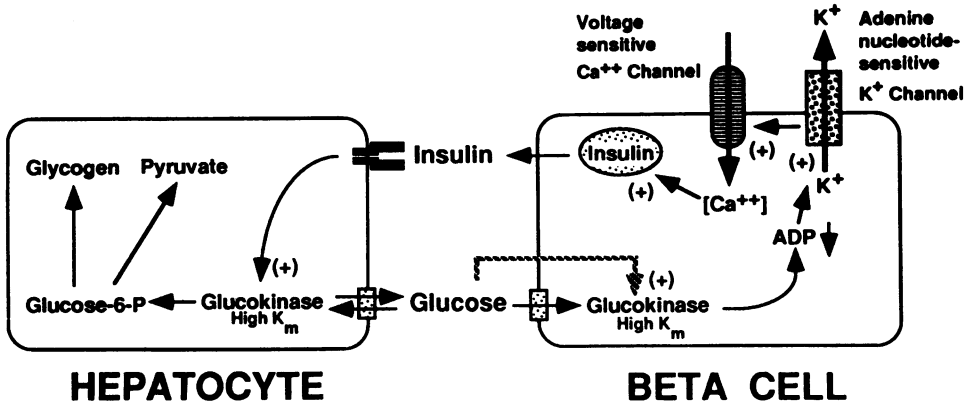

Figure 3. Feedback loop for glucose homeostasis involving β cell and hepatic GK.

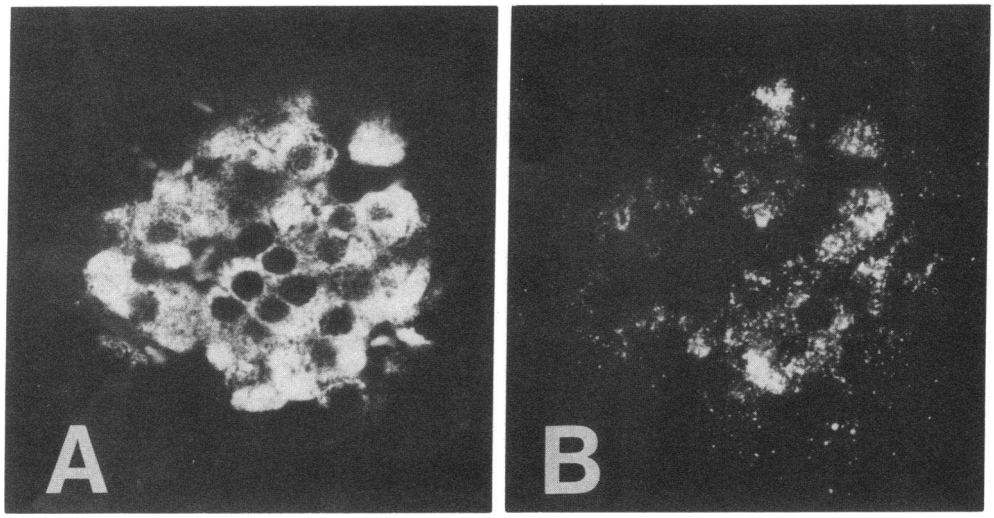

Figure 4. GK heterogeneity in pancreatic β cells. Immunofluorescent staining of a rat pancreatic islet with antibodies to either insulin (*A*) or glucokinase (*B*). GK immunoreactivity colocalizes with that of insulin in pancreatic β cells. GK immunoreactivity is heterogeneous compared with that observed with insulin.

whose sequences were homologous to both yeast hexokinase and mammalian hexokinase I (53 and 33%, respectively). Although of the same length, the sequence of β cell GK differed from the hepatic isoform in the 15 amino acids at the NH_2 terminus. When the different rat isoforms were expressed in cultured cells, the V_{max} and K_m of both isoforms were similar (32). Further confirmation of the kinetic similarity of these isoforms has recently been obtained by analysis of recombinant human GK isoforms (10, and Liang, Y., P. Kesavan, L. Wang, Y. Tanizawa, M. A. Permutt, and F. M. Matschinsky, manuscript submitted for publication).

Alternate promoters in the GK gene and differential regulation of hepatic and β cell GK gene. An explanation for the origin of the different GK isozymes was found when the structure of the GK gene was determined. Alternate first exon sequences of a single GK gene were found to be used in a tissue-specific manner to produce the different hepatic and pancreatic β cell isoforms (31). The different first exons each encode a translation initiation codon and 14 additional amino acids that are alternately spliced to 9 common downstream exons (see Fig. 5). The upstream GK promoter is active in the pancreatic β cell while the downstream promoter is active in hepatocytes. The two promoters are widely separated in the GK gene. In the rat they lie at least 15 kb apart. Judging from the lack of sequence similarity and from different patterns of transcription initiation, the two different promoters appear to be functionally distinct.

Identification of alternate promoters in the GK gene was an observation that supported the GK regulation studies, which established the differential regulation of GK in the liver and β cell (see above and reference 23) and strengthened the model of a regulational feedback loop, involving GK in the liver and the β cell (Fig. 3).

GK gene transcription in liver is affected by several glucose-regulating hormones and other agents, in contrast to the more constitutive expression of the upstream promoter in β cells. This allows hepatic GK to be adaptively regulated in response to changes in nutritional and hormonal status, while islet GK remains a more stable determinant of the rate of glucose metabolism and insulin secretion from the β cell. Among hormones affecting expression of hepatic GK the effect of insulin is the most pronounced (33, 34). Both biotin and triiodothyronine also stimulate transcription of the GK gene in liver, while glucagon, acting via cAMP, has an opposing effect, both inhibiting GK gene transcription and decreasing the half-life of GK mRNA (35). The regulatory elements mediating transcription of the hepatic GK gene have not been identified.

The activity of GK in the pancreatic β cell is induced by glucose and appears to be regulated at a posttranscriptional level (13). We speculate that glucose itself controls the rate of GK degradation and thus the enzyme activity.

A detailed fusion gene analysis of the elements responsible for transcriptional activity in insulinoma cells showed that multiple regions in the proximal portion (−280 to +14) of the

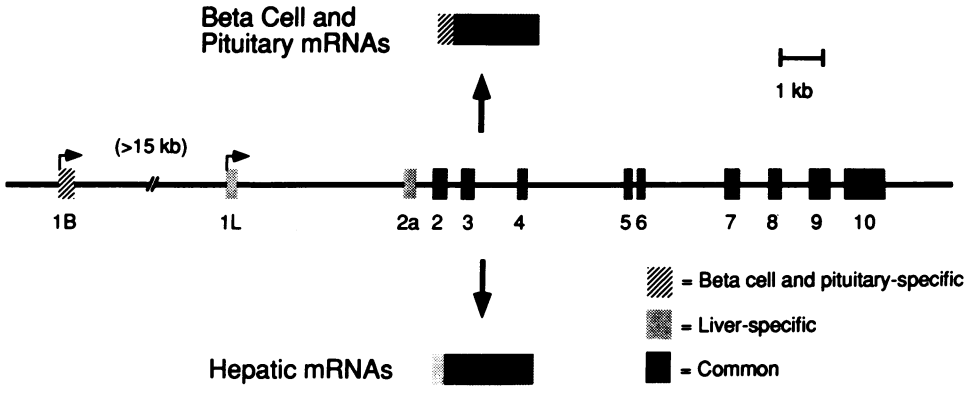

Figure 5. GK gene structure. The structure of the rat GK gene was the first to be determined and is shown. The human GK gene has the same number of exons, which are distributed in a similar manner.

upstream promoter are necessary (36). Within this 294-bp fragment of the GK gene are three copies of an element (CAT(T/C)A(C/G) that binds a factor that also binds to both the rat and human insulin genes. The presence of the same element in both the insulin and GK promoters that binds a β cell–specific nuclear factor suggests that certain aspects of gene expression in the pancreatic β cell may be, at least in part, coordinately regulated.

Human GK gene and polymorphisms. Structurally, rat and human GK are 97% identical although there are two different hepatic isoforms that differ at the amino terminus in a way similar to the differences between the rat hepatic and islet isoforms (37). Moreover, the human gene is organized in a manner similar to that of the rat with dual promoters that are separated by at least 20 kb (38). The remainder of the exons, including an alternate cassette second exon, are scattered over 16 kb. The human GK gene exists as a single copy in the genome and is located on chromosome 7p (38). Highly polymorphic microsatellites have been identified at three positions in the gene, facilitating an analysis of diabetic human pedigrees using PCR-based assays, for GK gene mutations.

Genetic GK Defects as cause of familial early-onset NIDDM

Definition of the MODY syndrome and linkage studies with candidate genes. Maturity-onset diabetes of the young (MODY) is a form of NIDDM characterized by an early age of onset and by autosomal dominant transmission with high penetrance, and appears to be a heterogeneous disorder (39). The autosomal dominant transmission of diabetes in MODY families made these pedigrees attractive for analysis of GK gene mutations.

Molecular genetic, metabolic, and clinical studies were carried out in 32 families with MODY, collected in France. Candidate genes for a pancreatic β cell defect (e.g., insulin, GLUT-2, and GK) were investigated, in addition to the ADA region on chromosome 20 (40). Negative results were found for insulin, GLUT-2, and ADA. In contrast, tight linkage was demonstrated between MODY and DNA polymorphisms near the GK gene. The availability of three microsatellites increased the genetic information on the families and together allowed for a maximum lod score between diabetes and GK of more than +25 over all MODY families at a recombination fraction of 0.00. This indicates that the odds in favor of linkage are $> 10^{25}$:1. Some MODY families showed exclusion of linkage with GK, implying the presence of at least one additional diabetes susceptibility gene, however, the proportion of families in which MODY is linked to the GK locus is estimated to be 60%.

Mutations of the GK gene in MODY families. The 12 coding exons of the GK gene of the affected individuals were scanned by single-strand conformation polymorphism analysis. Direct sequencing of the amplified exons identified 16 different mutations present only in affected individuals of 18 of the 32 early-onset NIDDM families as compiled in Table I (41). Two of the gene mutations were identical in different kindreds. 50% of the nucleotide substitutions occur in a CpG dinucleotide known to be a hot spot for mutations, findings that argue against a founder effect. In all cases the mutations (nonsense, missense mutations, or deletion) altered the sequence of GK or resulted in the synthesis of a truncated protein either by premature termination or by changing the sequence at an exon–intron junction that affected splicing.

Mutations were detected in all the affected young individuals in the MODY pedigrees, however, none of the unaffected individuals showed evidence of mutation. In addition to the French families, linkage to the GK locus has been found in a British MODY family (42). Glucokinase mutations were also identified in $\sim$ 5% of subjects with gestational diabetes mellitus (43). 10 of the > 20 known mutant human glucokinases have been expressed in *Escherichia coli* and have been studied kinetically (10, 43, and Matschinsky, F. M., Y. Liang, P. Kesavan, L. Wang, K. Niswender, and M. A. Magnuson, unpublished results). These mutations dramatically decrease the activity and/or the affinity for glucose of this enzyme, vital to hepatocyte and β cell glucose metabolism (Table I).

Pathophysiological consequences of mutations in the GK gene. An insulin secretion defect consistent with the β cell GK defect has been identified in MODY patients carrying mutant GK alleles (44). In the typically heterogeneous MODY patients β cell GK is probably reduced by 50%. Therefore, glycolysis and glucose oxidation in β cells are likely to be decreased in parallel, resulting in a release profile equivalent to a profile of normal individuals with blood sugar levels one-half to two-thirds that of patients. This may explain the autosomal dominant inheritance of MODY. A presumed reduction of GK activity may result from a gene dosage effect.

These MODY data contrast with those in the commonest form of NIDDM with late age of onset, where the first-phase insulin secretory response is characteristically lost when fasting plasma glucose concentration rises to 6.4–6.7 mmol/liter (45). The insulin secretory profile also seems to be different from profiles of MODY patients linked to DNA markers in chromosome 20 (46), in whom first-phase insulin secretion seems to be drastically reduced.

Perspective

The β cell GK glucose sensor concept and the recognition that GK is a significant diabetes mellitus gene greatly expand our understanding of glucose homeostasis both normally and in the pathogenesis of the disease. The significance can be appreciated best by considering the topic at increasing levels of organizational complexity.

At the molecular level it can be anticipated that clarification of the mechanism of catalysis of glucose phosphorylation will be more effectively sought because of the availability of ample recombinant enzyme protein with specific, functionally significant mutations, and that the unique positive cooperative effect of glucose resulting in a n_H of 1.5–1.7 will be intensively studied. The possibilities of allosteric and covalent modifications of the enzyme need to be studied carefully. Recombinant human liver and β cell GK isoforms can now be produced in milligram quantities, which will allow the crystallographic analysis of the enzyme and its mutant forms.

At the cellular level the nature of metabolic control by GK as pacemaker enzyme of glucose metabolism in pancreatic β cells governing ATP generation by the mitochondria needs to be more fully explored. Germ line–altered mouse models of the dominantly inherited familial MODY type of NIDDM need to be generated to study the influence of GK mutants on β cell function. This will also allow an extensive evaluation of the relative importance of GK in hepatic and β cell metabolism and glucose homeostasis. Moreover, the glucokinase glucose sensor paradigm, which has been useful for the understanding of pancreatic β cell function, may also be applicable to other glucose-sensing cell types that appear to exist in the intestine and in the central nervous system (Jetton, T. L., Y. Liang, E. C. Zimmerman, C. C. Pettephen, F. G. Cox, U. Horrath, F. M.

Table I. Mutations in the GK Gene in Families with MODY

MODY family	Exonic location, codon number	Nucleotide change	Amino acid change	Relative GK activity at 16.7 mM glucose (wild type:100)*
F392	Exon 2, 70	GAA → AAA	Glu → Lys	ND*
F393	Exon 3, 98	CAG → TAG	Glu → Stop codon	NA*
F423	Exon 4/intron 4,161	15-gp deletion at splice donor site		ND
F386	Exon 5, 175	GGA → AGA	Gly → Arg	14.2
F114, F331	Exon 5, 182	GTG → ATG	Val → Met	19.7
F446‡	Exon 5, 186	CGA → TGA	Arg → Stop codon	NA
F442	Exon 6, 203	GTG → GCG	Val → Ala	6.1
F85	Intron 6/exon 7, 227	Mutation of splice acceptor site		ND
F391‡	Exon 7, 228	ACG → ATG	Thr → Met	0.6
F388, F390‡	Exon 7, 261	GGG → AGG	Gly → Arg	0.0
F8‡	Exon 7, 279	GAG → TAG	Glu → Stop codon	NA
F28‡	Exon 8, 300	GAG → AAG	Glu → Lys	1.9
F51‡	Exon 8, 300	GAG → CAG	Glu → Gln	40.5
F160	Exon 8, 309	CTC → CCC	Len → Pro	0.3
F385	Exon 8, 414	AAA → GAG	Lys → Glu	8.0
F397	Intron 9/exon 10, 418	Mutation of splice acceptor site		ND

Adapted from reference 10 and F. M. Matschinsky, Y. Liang, P. Kesara, L. Wang, K. Niswender, and M. A. Magnuson (unpublished results). * The activity of human recombinant glucokinase (wild type and nine mutants) was determined spectrophotometrically. Samples of 0.1 μg of wild-type glucokinase or 0.5–6 μg of mutant glucokinase were used in the assay. The relative GK activity is governed by V_{max}, K_m, and n_H. ‡ Mutations occurring in the context of a cytosine-phosphate-guanosine dinucleotide. ND, not determined; NA, not applicable.

Matschinsky, and M. A. Magnuson, manuscript submitted for publication). The concept of intracellular compartmentation of GK offers another fruitful experimental field.

At the tissue and organ level the nature of differential regulation of GK gene expression will continue to be an important topic of research aimed at understanding the mechanisms of insulin induction of hepatic GK and of glucose induction of the β cell isoform of the enzyme. The question of cellular heterogeneity of GK expression observed both in the acinar unit of the liver and in the islet of Langerhans requires attention to explore the biochemical basis and the functional significance of these striking cellular heterogeneities. Glucose has a priming action on hepatic glycogenesis and lipogenesis from nonglucose precursors. Thus, it remains to be explored whether GK and thus glucose catabolism play a role in this glucose effect and whether genetic GK deficiencies, e.g., in MODY patients, have a functional hepatic manifestation.

At the whole body level it will be possible to exploit the various GK mutants in humans to better understand glucose homeostasis, for example, the nature of the β cell set point, the modification of the β cell set point by neuro-endocrine factors, and the role of the liver in the regulation of blood glucose. The defined GK lesion in MODY patients will make it possible to reassess the contribution of glucose toxicity and insulin deficiency in the genesis of long-term diabetic complications. The role of glucose toxicity in impaired β cell function is also ammenable to reexamination.

At the highest level of organization, the family and population level, the evolution of the GK defect will need to be explored. And, finally, it needs to be investigated whether GK is the target of toxic environmental factors and whether its activity can be beneficially modified by pharmacological and therapeutic intervention.

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