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PROSPECTS

Tissue-Specific Regulation of Glucokinase Gene Expression

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Abstract Glucokinase contributes to the maintenance of blood glucose homeostasis by catalyzing the high K_m phosphorylation of glucose in the liver and the pancreatic β cell, the only two tissues known to express this enzyme. Molecular biological studies of the glucokinase gene and its products have advanced our understanding of how this gene is differentially regulated in the liver and β cell. The production of an active glucokinase isoform is determined by both transcriptional and post-transcriptional events. Two different promoter regions that are widely separated in a single glucokinase gene are used to produce glucokinase mRNAs in the liver, pancreatic β cell, and pituitary. The different transcription control regions are tissue-specific in their expression and are differentially regulated. In liver, glucokinase gene expression is regulated by insulin and cAMP, whereas in the β cell it is regulated by glucose. The upstream glucokinase promoter region, which gives rise to the glucokinase mRNA in pituitary and pancreas, is structurally and functionally different from the downstream promoter region, which gives rise to the glucokinase mRNA in liver. The use of distinct promoter regions in a single glucokinase gene enables a different set of transcription factors to be utilized in the liver and islet, thus allowing a functionally similar gene product to be regulated in a manner consistent with the different functions of these two tissues. In addition, the splicing of the glucokinase pre-mRNA is regulated in a tissue-specific manner and can affect the activity of the gene product. This is most apparent in the pituitary where an alternately spliced glucokinase mRNA is produced that does not encode a functional enzyme due to an introduced frameshift.

Key words: glucokinase, hexokinase, alternative RNA splicing, gene transcription, islet, liver

Glucose must be phosphorylated at the sixth carbon in order for it to be metabolized. In mammals, this reaction is catalyzed by a multigene family of hexokinases that differ in their functional properties, tissue distribution, and structure. Glucokinase (hexokinase type IV) is a distinctive member of the mammalian hexokinase gene family (Weinhouse, 1976). It differs from the other three hexokinases (types I–III) by its smaller size (~50 kDa vs. ~100 kDa), its greater specificity for glucose, its lack of end product inhibition by glucose-6-P, and its higher K_m (lower affinity) for glucose. These unique kinetic characteristics, particularly a K_m in the 10–15 mM range and the lack of end product inhibition, enable glucokinase to play key roles in the metabolism of glucose in both the liver and pancreatic β cell, the only locations where this activity has been detected (Matschinsky, 1990; Meglasson and Matschinsky, 1984).

The presence of glucokinase in the hepatocyte and β cell enables glucose usage in these tissues to vary as a direct function of the intracellular glucose concentration over a *physiologic* range. Other hexokinases cannot perform this task since their K_ms for glucose are at least tenfold to 100-fold lower and they are inhibited allosterically by the accumulation of glucose-6-P. Furthermore, since glucokinase is situated at the beginning of the glycolytic pathway, the amount of glucokinase activity determines the rate at which glycolysis occurs. The unique role of glucokinase in regulating hepatic and islet glucose metabolism has stimulated interest in the tissue-specific regulation of the glucokinase gene. While the kinetic behavior of the enzyme in these two locations is indistinguishable (Iynedjian et al., 1986), the different roles that the liver and β cell play in maintaining euglycemia necessitates the

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tissue-specific regulation of glucokinase gene expression.

In liver, glucokinase traps glucose in the hepatocyte during periods of hyperglycemia, thereby initiating its conversion to glycogen and other intermediary substrates. By increasing the rate of glucose phosphorylation as its concentration increases, a gradient for the continued entry of glucose into the liver is maintained. However, since glucose flows out of the liver during starvation, the activity of glucokinase needs to be adaptively regulated like other glycolytic and gluconeogenic enzymes of the liver. In the β cell, however, glucokinase functions as the rate limiting step in glucose metabolism, thus serving to couple changes in blood glucose concentration to changes in metabolic activity of the β cell (Matschinsky, 1990). The metabolic activity of this cell is, in turn, tightly linked to the rate of insulin secretion. By acting as the modulator of glucose usage by the β cell, glucokinase functions as the so called "glucose sensor" of the islet (Matschinsky, 1990). It is understandable, therefore, that the regulation of hepatic glucokinase differs from the islet isoform. Liver glucokinase is adaptively regulated to allow a change in activity depending upon the nutritional and hormonal state of the animal, while islet glucokinase must be a more stable determinate of the rate of insulin secretion from the β cell. Thus, while glucokinase is regulated predominantly by insulin and cAMP in the liver, in the β cell it is regulated by glucose (see Table I for list of all agents and actions known to affect expression of this gene).

EFFECTS OF ALTERNATIVE RNA SPLICING ON GLUCOKINASE ISOFORM ACTIVITY

Glucokinase cDNAs were first cloned from rat liver (Andreone et al., 1989; Iynedjian et al., 1987) and shortly thereafter from both rat pancreas and pituitary (Hughes et al., 1991; Liang et al., 1991; Magnuson and Shelton, 1989). Comparison of the glucokinase mRNAs in the liver and β cell showed a substantial size difference with the islet glucokinase mRNA being ~200 bases longer than that in the liver. This difference was found to be due to the presence of different sequences at the 5′ ends, related to the use of alternate promoter regions in the glucokinase gene (Magnuson and Shelton, 1989) that are located at least 12 kb apart (see Fig. 1). The upstream promoter region is transcriptionally active in both the pancreatic β cell and pituitary while the downstream promoter is active only in the liver (Magnuson and Shelton, 1989). The different first exons associated with each promoter region are alternately spliced to common downstream exons. Because the tissue-specific 5′ ends of the hepatic and β cell glucokinase mRNAs contain different translation initiation codons, unique glucokinase isoforms are produced in the liver and islet (Magnuson and Shelton, 1989). The different glucokinase isoforms produced in either the liver or pancreatic β cell differ by 15 amino acids at the amino terminus. When the different glucokinase isoforms (designated L1 and B1, respectively) were expressed in NIH-3T3 cells under control of a cytomegalovirus promoter, their glucose K_ms and V_{max}s were very similar (Liang et al., 1991), thus confirming previous observations that the glucokinase isoforms in the liver and islet are biochemically indistinguishable (Iynedjian et al., 1986).

TABLE I. Differential Regulation of Hepatic and β Cell Glucokinase

	Stimulatory effect	Inhibitory effect
Hepatic glucokinase:	Insulin[a] Biotin[a] Triiodothyronine[a]	cAMP[a]
β cell glucokinase:	Glucose	Exercise training

[a]Regulation at the level of gene transcription has been established.

While the use of alternate first exons in the liver and pancreas does not have any appreciable effect on glucokinase isoform function, other alternative RNA splicing events have been identified that do have an adverse effect on enzyme function (see Table II). In the initial cloning of an islet glucokinase cDNA from rat insulinoma tissue, the first aberrant glucokinase isoform, termed B2, was identified (Magnuson and Shelton, 1989). The mRNA encoding the B2 isoform results from the use of an alternate splice acceptor site in the fourth exon of the gene that deletes 51 bases from the mRNA, thus causing a 17 amino acid in-frame deletion in the protein product. When the glucokinase B2 isoform was expressed in both eukaryotic and prokaryotic cells the protein product obtained was functionally inactive (Liang et al., 1991). Moreover, the nonfunctional glucokinase B2 and analogous L2 isoforms were less stable in NIH-3T3 cells than the functional glucokinase isoforms (e.g., L1

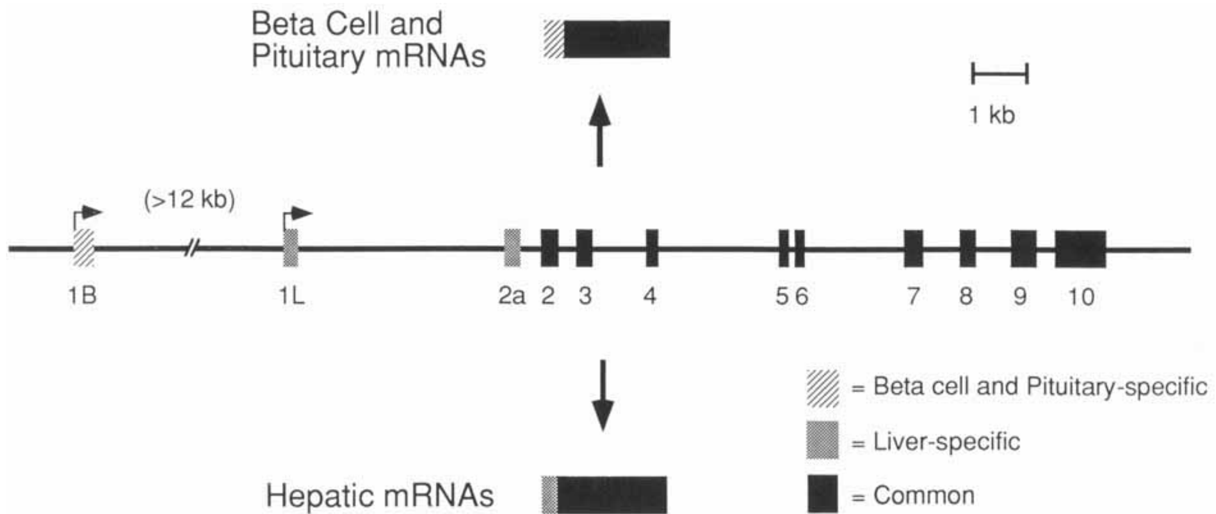

Fig. 1. Structure of the glucokinase gene. The tissue-specific promoter regions are indicated by the arrows. Exon 2a has been found to be utilized only in the liver.

TABLE II. Alternate RNA Splicing Events Involved in the Production of Glucokinase mRNA That Have a Deleterious Effect on Enzyme Activity

Location in gene	Tissues involved	No. nucleotides added or deleted	Frameshift	Size of protein product (aa)
Exon 2A	Liver[a]	+151	Yes	498
Exon 2	Pituitary[b]	−25	Yes	68
Exon 2	Pituitary Liver[a]	−52	Yes	58
Exon 4	β cells Liver Pituitary[b]	−51	No	448

The origin of each splicing variant is discussed in the text.
[a,b]Indicates that two alternative splice sites were utilized in a single mRNA.

and B1), thus arguing against any significant accumulation of the aberrant isoforms in the liver and β cell. Use of the alternate splice site in the fourth exon of the gene that gives rise to the B2 isoform has also been detected in liver RNA (Liang et al., 1991), although in the liver and islet we estimate that less than 10% of all glucokinase mRNAs utilize this splice site (Liang et al., 1991). The infrequent use of the exon splice site may explain why other investigators have not identified these particular RNA variants (Hughes et al., 1991). Indeed, the cloning of glucokinase B2 isoform by Magnuson and Shelton was, in retrospect, probably fortuitous. Studies of this and other glucokinase mRNA splicing variants, however, have heightened awareness of the role that post-transcriptional events play in regulating glucokinase gene expression. These findings have particular relevance in understanding the processes involved in regulating glucokinase expression in the pituitary.

In addition to the glucokinase B2 variant, other aberrant glucokinase cDNAs have been isolated from liver, pancreas, and pituitary that do not encode functional isoforms. A variety of alternative RNA splicing events are involved in the production of these glucokinase gene products. For instance, Hayzer and Iynedjian cloned a rat liver glucokinase cDNA that uses a cassette exon represented in about 5% of hepatic glucokinase mRNA (Hayzer and Iynedjian, 1990). Exon 2a, which is located immediately upstream of the normal exon 2 (see Fig. 1), adds 151 bases to the length of this variant RNA. However, in the clone studied from rat liver exon 2a was used in conjunction with an alternate splice donor site in exon 2 which removes 52 bases from the mRNA. Together, these combined insertion and deletion events add 87 new residues to the reading frame of glucokinase, resulting in a unique 498 amino acid glucokinase isoform. Since all of the sequences normally derived from exon 2 have been altered, it is not surprising that this glucokinase isoform does not phosphorylate glucose when expressed in bacteria (Quaade et al., 1991).

Recently, an analogous cassette exon of 124 bp has been identified as a component of human liver glucokinase mRNAs (Tanizawa et al., 1991).

In humans, glucokinase mRNAs containing the cassette exon are more abundant than those mRNAs without it. Furthermore, in humans the use of exon 2a is not associated with the use of alternate downstream splice sites. Surprisingly, human liver glucokinase mRNAs containing exon 2a sequences encode an active glucokinase isoform that is initiated from a second translation start site (Tanizawa et al., 1991). This finding provides further support for the notion that the amino terminal sequences of the enzyme can be varied without any deleterious effects on enzyme activity, as suggested by the different 15 N-terminal amino acids in the rat liver and β cell glucokinase isoforms.

Expression of the glucokinase gene in the pituitary is especially intriguing because of the lack of a function for the enzyme in this gland. While glucokinase mRNA has been identified in both the anterior pituitary and in mouse corticotroph-derived AtT-20 cells (Hughes et al., 1991; Liang et al., 1991), a high K_m glucose phosphorylating activity cannot be detected in pituitary gland extracts, even after a chromatographic purification step (Liang et al., 1991). The discrepancy between the expression of a glucokinase mRNA and the lack of glucokinase activity in the pituitary appears to be due to tissue-specific alternate RNA splicing of the glucokinase pre-mRNA. Two different pituitary-derived glucokinase cDNAs have been reported. Hughes et al. (1991) found that the same alternate splice donor site in exon 2 as described by Hayzer and Iynedjian (1990), which removes 52 bases from the mRNA, was also utilized in rat pituitary. However, Liang et al. found that two different alternate splicing sites had been utilized in the pituitary cDNA they obtained (Liang et al., 1991). In the latter cDNA, both an alternate splice donor site in exon 2 that removes 25 bases, and an alternate splice acceptor site in exon 4 that removes 51 bases, were identified. The alternate splice site in exon 4 was the same as previously detected in pancreas and liver (Liang et al., 1991). Frameshifts, due to the deletion of either 52 or 25 bases from exon 2 sequences, result in the premature termination of translation on either mRNA template, thereby producing peptides of only 58 or 68 amino acids, neither of which is long enough to encode a functional enzyme. Thus, while it is not clear which of several alternate splice sites is preferentially used in the pituitary, the consequences are the same.

DIFFERENTIAL REGULATION OF GLUCOKINASE GENE EXPRESSION BY TWO PROMOTERS

The rat glucokinase gene has been characterized and the DNA sequence of the two different promoter regions have been determined (Magnuson et al., 1989; Magnuson and Shelton, 1989). Little sequence similarity is observed between these widely separated DNA regions, thereby suggesting that different transcription factors are involved in the regulation of each promoter region. In liver, where the downstream promoter is transcriptionally active, insulin exerts the major regulatory influence on the rate of synthesis of glucokinase. In liver and primary hepatocyte cultures, insulin has been shown to stimulate glucokinase expression by increasing transcription of the gene (Iynedjian et al., 1988, 1989a; Magnuson et al., 1989). Within 45 min of insulin administration to a streptozotocin-diabetic rat, glucokinase gene transcription in the liver increases at least 20-fold, as measured by a run-on transcription assay. An increase in the amount of glucokinase mRNA and protein follows. Studies performed in primary hepatocytes have shown that the effect of insulin is mediated via the insulin receptor (Iynedjian et al., 1989). Furthermore, the effect of insulin is not dependent upon the concentration of glucose (Iynedjian et al., 1989a). As is the case with other hepatic genes regulated by insulin, the effect of glucagon acts opposite to that of insulin (Iynedjian et al., 1989a). Glucagon, acting via cAMP, is a potent inhibitor of glucokinase gene transcription, acting within 30 min of its addition to primary hepatocytes to shut off transcription (Iynedjian et al., 1989a).

Tri-iodothyronine (T_3) also stimulates glucokinase gene transcription, but its effect is more permissive in nature. In rats, T_3 is necessary for the induction of glucokinase by refeeding but it has no effect by itself in a starved animal (Hoppner and Seitz, 1989). However, in primary hepatocytes obtained from neonatal rats, T_3 has a more striking effect. A dose-dependent induction of glucokinase mRNA of a magnitude comparable to the effect of insulin has been observed (Narkewicz et al., 1990). Furthermore, the effect of T_3 and insulin on glucokinase mRNA expression in the neonatal hepatocyte culture system is additive. Biotin, a water soluble vitamin, has also been shown to induce transcription of the hepatic glucokinase gene in rats. A

20-fold increase in transcription occurs within 1 h of administration of this vitamin to a starved rat although this peak of transcription decays rapidly (Chauhan and Dakshinamurti, 1991).

The *cis*-regulatory elements that mediate the effects of insulin, cAMP, T_3, and biotin on glucokinase gene transcription in the liver have not been defined. Furthermore, the enhancer elements that target expression of the downstream promoter to liver have not been identified. When transfected into primary hepatocytes, glucokinase-chloramphenicol acetyltransferase (CAT) fusion genes containing 5.5 kb of 5′ flanking DNA do not respond to insulin (Noguchi et al., 1989). However, weak promoter activity was observed when hepatic glucokinase promoter DNA fragments as short as 88 bp were transfected (Noguchi et al., 1989). Whether these results indicate that the insulin response element in the glucokinase gene is outside the 5.5 kb fragment tested, or whether the primary hepatocytes used fail to recapitulate the inductive effect of insulin, is not known. The upstream promoter region which is active in the β cell and pituitary lies at least 12 kb upstream of the liver-specific downstream promoter region. It is possible, therefore, that this wide separation is due to various hormone response elements and/or liver-specific enhancer elements in the intervening region.

The differential regulation of glucokinase in the pancreatic islet was first observed by Bedoya et al. (1986), who found a reduction in islet glucokinase activity when insulin-secreting tumors were transplanted into normal rats. When glucokinase cDNA probes were developed, Iyndejian et al. (1989b) found that while the amount of hepatic glucokinase mRNA varied with fasting and refeeding, the amount of islet glucokinase mRNA remained constant, thus confirming the differential regulation of this gene in islets and liver. The finding of two different promoters in a single glucokinase gene by Magnuson and Shelton strengthened this notion and provided a conceptual framework for understanding how the dual regulation of this gene might occur (Magnuson and Shelton, 1989). Insulin does not have an effect on glucokinase expression in cultured rat islets whereas glucose does (Liang et al., 1990). In islets cultured for 7 days in different glucose concentrations, glucokinase activity varied by about fivefold and the magnitude of the effect was concentration dependent. The regulation of glucokinase by glucose in the islet and by insulin in the liver has led to the proposal of a feedback loop involving the different transcription control regions in the glucokinase gene (Magnuson and Shelton, 1989). However, the mechanism involved in the regulation of glucokinase activity by glucose may actually involve translational control, possibly related to the unique 5′ untranslated region of the glucokinase mRNA in the β cell (Liang et al., 1990). The high degree of cross-species sequence conservation between the 5′ untranslated regions of rat and mouse glucokinase RNAs suggests a possible role in translational regulation (Hughes et al., 1991).

Exercise training has also been identified as a regulator of glucokinase gene expression (Koranyi et al., 1991). A 68% reduction in the amount of glucokinase mRNA was observed in poly A(+) RNA from total pancreas when rats were subjected to 3 weeks of an exercise regimen. The reduction of glucokinase mRNA was similar in magnitude to that observed for proinsulin mRNA (78%), whereas no change was seen in the expression of GLUT 2 mRNA. Exercise is known to diminish glucose-stimulated insulin secretion; thus, the finding that exercise decreases the amount of glucokinase mRNA offers a sensible mechanism by which this occurs. It is not yet known, however, whether this regulation occurs by a change in the rate of glucokinase gene transcription or by altering the stability of glucokinase mRNA.

PROSPECTS

The tissue-specific regulation of glucokinase gene expression occurs at multiple levels. Strong evidence for differential regulation at the transcriptional level was obtained with the finding of alternate promoter regions in the glucokinase gene. Alternate RNA splicing, a post-transcriptional event, plays an important role in determining whether an active glucokinase isoform is generated from the transcribed glucokinase mRNA. In addition, the effect of glucose on β cell glucokinase activity may also involve regulation at the translational level. It will be necessary to decipher the different mechanisms involved in these multiple levels of control in order to understand fully the role of glucokinase in maintaining glucose homeostasis.

The reason for the use of alternate promoter regions in the liver and β cell seems clear when the dual functional roles of glucokinase are considered. The use of two different promoter re-

gions enables the gene to be differentially regulated in the two tissues that express active glucokinase isoforms. The reason for the post-transcriptional regulation of glucokinase gene expression, as is evident in the pituitary, is more mysterious. At first glance, transcription of this gene without production of a functional enzyme product seems wasteful. However, we do not yet understand the molecular mechanisms involved in regulating transcription in the islet and pituitary. It is possible, therefore, that a conserved transcriptional mechanism involved in other aspects of the function of these endocrine cell types has led to the evolution of a post-transcriptional control mechanism. The apparent panoply of alternative RNA splicing events that can adversely affect isoform activity is otherwise unexplained. In any event, the use of alternate tissue-specific promoters, coupled to the use of tissue-specific alternate RNA splicing mechanisms that can affect glucokinase activity (see Table III), reveals a greater degree of complexity in the expression of the glucokinase gene than was previously suspected.

It is necessary to establish new experimental systems that mimic the in vivo regulation of this gene for further progress to be made in studying the molecular mechanisms involved. While the molecular genetic reagents necessary to study the regulation of this gene are largely in hand, various difficulties in studying both islet and hepatic glucokinase regulation are retarding progress. For instance, while the established β cell lines tested to date all express the glucokinase gene, these cells appear to have diminished expression of GLUT 2, the high K_m glucose transporter of the β cell (Thorens et al., 1988), and do not respond normally to glucose. Thus, established β cell lines are of limited use in studying the effect of glucose. While intact islets do maintain a glucose response, they are not currently amenable to transfection techniques, thereby suggesting that it may be necessary to utilize other approaches, such as transgenic mice, in future studies. Furthermore, the absence of established hepatic cell lines that express glucokinase has also hampered studies of the regulation of the downstream glucokinase promoter region. While primary hepatocytes are likely to be useful, it may also be necessary to use transgenic mice as an experimental system to study the regulation occuring in liver. Thus, it seems likely that a variety of advanced experimental approaches will be needed in order to learn the secrets underlying the tissue-specific regulation of the glucokinase gene.

TABLE III. Both Transcriptional and Post-Transcriptional Events Affect the Production of Glucokinase Activity

Tissue or cell type:	β cell	Pituitary	Liver
Active promoter:	Upstream	Upstream	Downstream
Enzyme activity:	Yes	No	Yes

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