Family of Glucose-Transporter Genes

Implications for Glucose Homeostasis and Diabetes

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Glucose transport by facilitated diffusion is mediated by a family of tissue-specific membrane glycoproteins. At least four members of this gene family have been identified by cDNA cloning. The HepG2-type transporter is the most widely distributed of these proteins. It provides many cells with their basal glucose requirement for ATP production and the biosynthesis of sugar-containing macromolecules. The liver-type transporter is expressed in tissues from which a net release of glucose can occur and in β-cells of pancreatic islets. A genetic defect resulting in reduced activity of this transporter could hypothetically lead to the two principal features of non-insulin-dependent diabetes mellitus, insulin resistance and relative hypoinsulinemia. The adipocyte/muscle transporter is expressed exclusively in tissues that are insulin sensitive with respect to glucose uptake. This protein is an excellent candidate for a highly specific genetic defect predisposing to insulin resistance. *Diabetes* 39:6–11, 1990

The transport of glucose across animal cell membranes is catalyzed by members of two distinct gene families (1). The facilitated-diffusion glucose transporters are ubiquitously expressed in mammalian cells (2), whereas the Na^+/glucose cotransporters appear to be restricted to selected epithelial cells of renal tubules and the intestinal mucosa (3). The Na^+-dependent proteins are secondary active-transport systems that reside in the apical membranes of the epithelia and concentrate glucose from the intestinal contents and the forming urine. The facilitated-diffusion transporters are passive systems that equilibrate sugar across membranes. The latter proteins are responsible for the movement of sugar from the blood into cells, supplying cellular glucose for energy metabolism, and the biosynthesis of sugar-containing macromolecules, e.g., glycoproteins, glycolipids, and nucleic acids. Additionally, facilitated-diffusion glucose transport in certain tissues may play a critical role in organismal glucose homeostasis. The latter function makes these proteins of interest to the diabetologist. I briefly review our knowledge concerning the physiological roles of the facilitated-diffusion glucose transporters and propose possible mechanisms for the involvement of these molecules in the pathogenesis of diabetes. Much of this discussion is highly speculative, and no attempt is made to review the field exhaustively.

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FAMILY OF GLUCOSE-TRANSPORTER GENES

A flurry of activity in several laboratories over the past 5 yr has resulted in a quantum leap in our knowledge of proteins involved in glucose transport. At least four presumed species of glucose transporter have been identified by cDNA cloning thus far, and it is likely that additional members of this gene family will be discovered in the near future (Table 1). The cDNA for the well-characterized human erythrocyte glucose transporter was cloned from HepG2 cells in 1985 (4), and Birnbaum et al. (5) subsequently reported the cloning and sequence of the equivalent protein from rat brain. These two cDNA species have been used to identify and clone novel transporters from liver and pancreatic islets (6–8), embryonic muscle (9), and insulin-sensitive tissues (i.e., heart, fat, skeletal muscle; 10–13). With the exception of the embryonic muscle species, the functional identity of these proteins has been confirmed by expression of cDNAs or mRNAs in heterologous cell types (7,8,11,14).

The HepG2 protein is the most widely distributed of the transporters. It appears to be expressed in most tissues, albeit at low levels in many cases, and is most abundant in placenta, brain (especially microvessels), and erythrocytes (4,5,15,16). This transporter appears to play primarily a "housekeeping" role, i.e., it is involved in the survival of individual cells by providing them with their basal glucose requirement. For example, increased expression of the

TABLE 1
Mammalian glucose transporters

Type	Tissue distribution	Kinetic properties*	Regulatory factors
HepG2	Many tissues; abundant in brain, erythrocytes, placenta, immortal cell lines	Human erythrocytes: asymmetric carrier with accelerated exchange; V_{max}(influx) < V_{max}(efflux); K_m ~5–30 mM (variable)	Oncogenes, tumor promoters, growth factors, glucose deprivation, ATP, insulin, butyrate
Liver	Liver, pancreatic β-cells, kidney, intestine (basolateral membrane)	Liver: simple, symmetric carrier; K_m ~66 mM; intestine: asymmetric carrier; V_{max}(efflux) < V_{max}(influx); K_m ~23–48 mM (variable)	?
Adipocyte/ muscle	Brown and white fat, red and white muscle, heart, smooth muscle (?)	Adipocyte: simple, symmetric carrier; K_m ~2.5–5 mM†	Insulin, exercise, β-adrenergic agonists, streptozocin-induced diabetes
Fetal muscle	Many tissues; abundant in brain, kidney, placenta	?	?

*For glucose at 20°C.
†For 3-O-methylglucose at 20°C.

HepG2 transporter occurs when cultured cells are starved for glucose (17). Its expression is also induced by factors that stimulate cellular growth and division, e.g., oncogenes (18,19), polypeptide growth factors (20–23), and tumor promoters (18). This response may be important in cells that are mitotically active and require increased levels of glucose for the biosynthesis of proteins and nucleic acids. This may account for the prominant expression of the HepG2 transporter in virtually all immortal cell lines.

The transporter species cloned from liver is also expressed in kidney, intestine, and β-cells of the pancreatic islet (6–8). Cells of the liver, kidney, and intestine share in common the property that net release of glucose into the blood can occur from them under the appropriate metabolic circumstances. The liver is the principal supplier of blood glucose during short fasts, and during prolonged starvation, the kidney becomes a net producer of blood glucose (24). In the intestine, the liver-type transporter is localized to the basolateral membrane of the absorptive cells, where it is involved in the transepithelial flux of glucose from the intestinal lumen to the blood (25). A glucose concentration gradient directed from the cell interior to the blood is formed by the Na^+-dependent cotransporter in the apical membrane (3). A similar situation may exist in the kidney, where the liver-type transporter is likely to be localized to the basolateral membrane of renal tubules.

How is this common property of net glucose release related to the expression of a common transporter protein in these tissues? Most mammalian cells are involved exclusively in the net uptake and metabolism of blood glucose. However, the liver-type transporter appears to be involved in the net release of glucose into the blood during fasting or absorption of intestinal or renal glucose. In tissues responsible for net glucose release, there would appear to be a teleological need for a transporter with different kinetic characteristics (25,26). The liver-type transporter is somewhat unusual in that it exhibits a supraphysiological K_m for glucose of ~66 mM (27). (The measurement of K_m for glucose transport in cultured hepatocytes is complicated by the expression of both the liver-type and HepG2 transporters in these cells [28].) This high K_m indicates that the liver transporter operates in the pseudo first-order region of the substrate-velocity curve, suggesting that glucose flux across the liver, intestine, or β-cell changes in a near-linear fashion with the extracellular (or intracellular) glucose level, ensuring that transport does not become rate limiting for intracellular glucose metabolism (or glucose efflux) as the sugar concentration rises. This is a highly desirable characteristic for those cells responsible for supplying blood glucose during either periods of starvation (i.e., liver, kidney) or absorption of sugar from the intestinal lumen. The high K_m may also reflect the possibility that under certain conditions, splanchnic tissues are exposed to intra- or extracellular glucose levels that are significantly higher than that in peripheral blood. For example, after the ingestion of a high-carbohydrate meal, glucose could conceivably accumulate within absorptive intestinal cells by means of the Na^+-dependent cotransporter to levels approaching the apparent K_m value.

Why is the liver-type transporter expressed in pancreatic islets? As in liver cells, the rate of glucose transport into islet cells is very rapid, and the intracellular sugar concentration approaches the extracellular concentration (29). This is appropriate for β-cells, which are dependent on rapid increases in glucose metabolism for signaling events (30). Orci et al. (31) demonstrated that the liver-type transporter is concentrated in regions of β-cell plasma membrane that face other endocrine cells and is relatively sparse in those regions that face blood capillaries. Thus, the liver-type transporter might be involved in the transcellular flow of glucose within the islet, directing it to regions distal to blood capillaries. Perhaps islet cells adjacent to capillaries are polarized and express a different transporter species at their basolateral membrane that is responsible for the uptake of glucose diffusing out of blood capillaries.

The most recent transporter to be identified through molecular cloning is the major species in tissues that are insulin-sensitive with respect to glucose transport, i.e., fat, skeletal muscle, and heart (10–13). Glucose transport appears to be rate limiting for its metabolism in these tissues (32,33), and skeletal muscle is the major depot for the disposal of glucose

in the postprandial state (34,35). Thus, the regulation of transport into muscle plays a key role in glucose homeostasis. It is generally accepted that insulin-stimulated transport in these tissues occurs in part via the redistribution of transporters from an intracellular membrane compartment to the cell surface (36–38). The most obvious explanation for the expression of a common transporter in fat and muscle tissue is that this protein fulfills a unique role in the acute insulin-mediated increase in transport activity. Is translocation a unique property of the adipocyte/muscle transporter? Studies involving the expression of the human HepG2 transporter in 3T3-L1 adipocytes suggest that this is not the case (39). The human HepG2 transporter, which is not insulin responsive in HepG2 cells, is capable of translocating from an intracellular membrane compartment to the cell surface in response to insulin when expressed in adipocytes. Thus, translocation is dependent on cell-specific factors and is not unique to the adipocyte/muscle transporter.

What then is the basis for the expression of a distinct transporter species in fat and muscle? Acute regulatory events other than translocation distinguish the fat/muscle and HepG2 transporters. Translocation alone cannot quantitatively account for the acute increase in transport mediated by insulin in adipocytes (40–42). It is likely that insulin induces an increase in both the quantity and intrinsic activity of the transport system in the adipocyte plasma membrane. Transport in adipocytes is also acutely regulated by β-adrenergic agonists, which decrease the intrinsic activity of the transporter (43). Modulation of the intrinsic activity of the adipocyte-transport system by glucose regulatory and counterregulatory hormones may be a unique property of the adipocyte- /muscle-specific transporter. The fat/muscle transporter, unlike the HepG2 species, is phosphorylated in response to β-adrenergic agonists. Thus, phosphorylation is a potential mechanism by which β-agonists inhibit the intrinsic activity of this transporter (44).

Chronic regulatory events also differentiate the HepG2 and fat/muscle transporters. Several recent studies have shown that induction of streptozocin-induced diabetes in rats results in a decrease in the level of the fat/muscle-transporter protein and mRNA in adipose tissue, with no change in the level of the HepG2-type transporter (45–47). These studies suggest that the reduction of transporter expression observed in fat is relevant to the mechanism of insulin resistance in diabetes. However, the results must be interpreted with caution, because fat is an inconsequential sink for glucose disposal (48), and the adipocyte/muscle transporter may undergo differential regulation in these two tissues. The streptozocin studies also suggest that insulin per se regulates expression of the fat/muscle glucose-transporter gene, at least in fat cells. Curiously, however, insulin has no direct effect on expression of the fat/muscle transporter gene in cultured 3T3-L1 adipocytes (23). Murine 3T3-L1 adipocytes express both the HepG2 and fat/muscle transporters, as do normal rat adipocytes. Prolonged treatment of these cells with either insulin or sulfonylureas augments glucose transport by a selective increase in the expression of the HepG2-type mRNA and protein, whereas these agents may actually decrease expression of the fat/muscle transporter gene. Thus, either the transporter genes are regulated differently in 3T3-L1 adipocytes than in rat adipose tissue, or changes in insulin levels are not directly responsible for regulation of the fat/muscle transporter in vivo. It is impossible to resolve this issue because of the complexity of the changes that occur in streptozocin-treated rats. Carefully conducted studies utilizing glucose and insulin clamps are necessary to resolve this controversy.

GLUCOSE TRANSPORTERS AND NON-INSULIN-DEPENDENT DIABETES MELLITUS (NIDDM)

There is considerable interest in the possible involvement of glucose transporters in the pathogenesis of NIDDM. NIDDM is clearly a heterogeneous genetic disease, the development of which is influenced by environmental factors (49,50). It is also highly likely to be polygenic in nature (51). There are at least two possible ways in which glucose transporters could be involved in this disease. Specific alleles at one or more glucose-transporter loci could predispose to NIDDM, and/or other genetic loci whose products regulate transport activity could be involved. In the following discussion, a "defect" in a glucose transporter refers to either of these two possibilities.

Which glucose transporter is the most likely candidate for a defect predisposing to NIDDM? The HepG2 transporter is widely distributed and appears to be the major transporter expressed in brain. It is likely that severe genetic defects in this protein or its expression would be lethal in utero, and that more mild defects would result in nondiabetic phenotypes. Although it is conceivable that a decrease in the activity of this protein or its expression could affect whole-body glucose disposal, it is unlikely to be directly involved in the pathogenesis of NIDDM because of its tissue distribution.

The liver/islet transporter is perhaps unique among known proteins in that a defect in this single gene product could hypothetically give rise directly to the two principal characteristics of NIDDM—relative hypoinsulinemia and insulin resistance (Fig. 1*A*). (The argument that follows could just as well be applied to glucokinase.) Although transport is not normally rate limiting for glucose uptake into either islets or hepatocytes, a defect in this transporter could give rise to reduced insulin biosynthesis and secretion by β-cells and reduced uptake and metabolism of glucose in liver. The defect would have to reduce the velocity of transport to a level that diminished the steady-state concentration of intracellular glucose to affect the velocity of the glucokinase reaction and thus alter the overall rate of glucose metabolism in either the β-cell or hepatocyte. Such a defect would be reasonably specific for a diabetic phenotype, because glucose transport into most other tissues would be unaffected. However, there are at least two problems with this hypothesis. First, the fraction of whole-body glucose disposal that occurs via the splanchnic bed is insufficient to account quantitatively for insulin resistance in NIDDM. Second, the available data indicate that hepatic glucose uptake is not abnormal in NIDDM subjects (52). Thus, if the liver/islet transporter is involved in the pathogenesis of NIDDM, its effect is most likely at the level of the β-cell.

There is strong evidence that the major site of insulin resistance in NIDDM is skeletal muscle (52–54). The existence

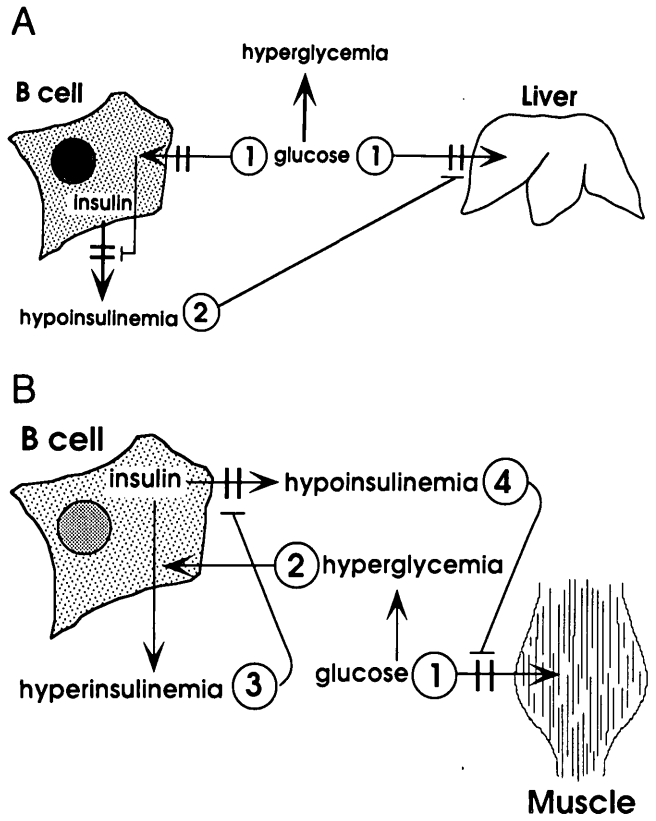

FIG. 1. Hypothetical role of liver/islet and adipocyte/muscle glucose transporters in pathogenesis of non-insulin-dependent diabetes mellitus (NIDDM). *A*: ①, primary genetic defect in liver/islet glucose transporter could give rise directly to both insulin resistance at level of liver, resulting in postprandial hyperglycemia and relative hypoinsulinemia due to diminished uptake and metabolism of glucose in pancreatic β-cells. ②, Protracted hypoinsulinemia could further exacerbate insulin resistance at liver, e.g., by decreasing expression of hepatic glucokinase. Glucose transport into these tissues is not normally rate limiting for its metabolism, and thus, defect would have to be of sufficient magnitude to noticeably reduce steady-state intracellular concentration of free glucose to affect rate of phosphorylation reaction and subsequent metabolism. There appears to be no evidence for defect in hepatic glucose uptake in NIDDM (52,53). See text for additional discussion. *B*: ①, primary genetic defect in adipocyte/muscle glucose transporter would be highly specific for insulin-resistant phenotype at level of muscle and fat. ②, Resulting postprandial hyperglycemia would initially lead to transient bouts of hyperinsulinemia. ③, Continued overstimulation of β-cells could, in susceptible individuals, result in eventual β-cell damage and consequent reduced synthesis and secretion of insulin. ④, Resulting absolute hypoinsulinemia might further exacerbate insulin resistance in muscle, e.g., by reducing expression of glucose transporter gene in this tissue. This scenario is reasonably consistent with clinical data on NIDDM subjects and their first-degree relatives (56,57).

of a glucose transporter specific to skeletal muscle and other insulin-sensitive tissues makes this protein an excellent candidate for a defect giving rise to insulin resistance for the following reasons. *1*) Transport of glucose appears to be rate limiting for its utilization in muscle. Thus, any reduction in the rate of transport would give rise to a proportional decline in muscle glucose disposal. *2*) A defect in the fat/muscle transporter would be specific to these tissues, and thus, the only direct consequence would be insulin resistance. *3*) Reductions in transporter activity and protein have been detected in adipocytes obtained from NIDDM subjects (55). However, the latter point must be interpreted with caution, because the adipocyte/muscle transporter may be subject to differential regulation in these two tissues. A reduction in adipocyte transport may therefore not be indicative of similar changes in skeletal muscle. *4*) The expected phenotypic progression resulting from a genetic defect in this transporter is similar to that which can be inferred from a revealing study of NIDDM subjects and their first-degree relatives (Fig. 1*B*; 56).

It has been argued that transport per se cannot be the primary site of insulin resistance, because transport defects should affect glucose disposal via the oxidative and non-oxidative pathways equally, contrary to what is observed in NIDDM subjects (57). However, this would only be the case if the velocity of the rate-limiting steps in each pathway was affected equally by a reduction in the velocity of transport. This would depend on the actual kinetic parameters of the rate-limiting enzymes in the pathways and the changes in the steady-state concentrations of their respective substrates and that of any regulatory factors. It is not possible to determine or predict all of these values in vivo with any degree of confidence. Thus, the adipocyte/muscle glucose transporter remains an excellent candidate for a defect predisposing to insulin resistance and NIDDM. However, it is imperative that future studies address the role of this transporter species in skeletal muscle from healthy and NIDDM subjects.

Is there genetic evidence associating glucose-transporter genes with NIDDM, insulin resistance, or any other pathologic condition? There is a single study indicating an association between restriction-fragment–length polymorphisms at the HepG2 glucose-transporter locus (*GLUT* [58]) and NIDDM (59), but no association was observed in two other studies (60; Kaku et al., this issue, p. 49). Genetic studies are underway in many laboratories throughout the world investigating the possible association of the other transporter genes with NIDDM. Unfortunately, the interpretation of these new studies and the studies mentioned above may be a formidable problem because of the extraordinary difficulty involved in the analysis of complex human genetic traits (61). If NIDDM is both polygenic and heterogeneous, population studies may be of little practical value. The relatively late age of onset of diseases such as NIDDM makes it very difficult to acquire good pedigrees for family studies, and sophisticated genetic analyses with the human linkage map will undoubtedly be required (62).

The battle continues over what constitutes the primary defect in NIDDM. The top two contenders appear to be a β-cell defect resulting in reduced insulin secretion and a skeletal muscle defect causing insulin resistance. The argument may be moot. It is perhaps most likely that inheritance of specific alleles at genetic loci involved in both processes is necessary for the development of this disease. The family of glucose-transporter genes merits attention, because its members can hypothetically be involved in either or both processes. Regardless of whether glucose transporters are directly involved in the genetic predisposition to NIDDM, a thorough knowledge of glucose transport and its regulation in insulin-sensitive tissues is likely to be an important part of unraveling the molecular basis of insulin resistance.

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