Diabetic Hyperglycemia: Link to Impaired Glucose Transport in Pancreatic β Cells

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Glucose uptake into pancreatic β cells by means of the glucose transporter GLUT-2, which has a high Michaelis constant, is essential for the normal insulin secretory response to hyperglycemia. In both autoimmune and nonautoimmune diabetes, this glucose transport is reduced as a consequence of down-regulation of the normal β-cell transporter. In autoimmune diabetes, circulating immunoglobulins can further impair this glucose transport by inhibiting functionally intact transporters. Insights into mechanisms of the unresponsiveness of β cells to hyperglycemia may improve the management and prevention of diabetes.

THE EXTRACELLULAR CONCENTRATION OF GLUCOSE IN NORMAL humans is restricted within a very narrow range, despite wide variations in the utilization of glucose and in the availability of exogenous glucose. This homeostatic control is achieved by matching of the rates of glucose flux into and out of the extracellular space through tightly coordinated secretion of insulin and glucagon (*1*). In normal humans, the basal rate of glucose utilization is approximately 10 g $hour^{-1}$; to prevent hypoglycemia, the liver, the sole source of endogenous glucose, replaces glucose at a rate of 10 g $hour^{-1}$. Approximately 75% of hepatic glucose production is driven by the secretion of glucagon, the product of pancreatic α cells (*2*). During exercise, if glucose utilization rises to about 40 g $hour^{-1}$, hepatic glucose production will increase to about 40 g $hour^{-1}$. After a meal, the influx of glucose from the gut is matched by an insulin-mediated increase in glucose uptake by muscle and fat, a consequence of insulin secretion by pancreatic β cells. Simultaneously, hepatic glucose production is suppressed through insulin-induced inhibition of glucagon secretion (*3*) and neutralization of the hepatic actions of glucagon (*4*). The insulin response to glucose limits hyperglycemia after a meal to a maximum of 10 mM and restores it to the 5 mM fasting range within 2 hours.

Dysfunction of the β cells and α cells results in disordered blood glucose homeostasis. If the β cells do not respond to glucose, the result is steady-state hyperglycemia in excess of 10 mM, which is diagnostic of diabetes mellitus (*5*). Conversely, β-cell overactivity, as in insulin-producing tumors, leads to hypoglycemia and the possibility of brain cell injury or death. Here I will consider only the hyperglycemic derangements of glucose homeostasis.

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In the United States, the prevalence of diabetes is estimated to be approximately 2% of the population (*5*). Of this 2%, 10 to 25% is the result of autoimmune destruction of the insulin-secreting β cells of the pancreatic islets. The disorder is known as type 1, or insulin-dependent, diabetes mellitus (IDDM), the latter designation reflecting the need for insulin replacement therapy to prevent diabetic ketoacidosis, coma, and death from insulin deficiency (*5*). In the remaining 75 to 90% of diabetic patients, the hyperglycemia is not the consequence of β-cell destruction but of a failure of seemingly normal β cells to meet an increased demand for insulin. This disorder is called type 2, or noninsulin-dependent, diabetes mellitus (NIDDM). The absence of glucose-stimulated insulin secretion is the only common feature of these two hyperglycemic syndromes (Table 1).

The Glucose Response System in Normal and Diabetic β Cells

The ability of β cells to sense and respond accurately to increments in extracellular glucose concentration can be tested by measurement of insulin 1 and 3 min after an intravenous injection of glucose (*6*). In humans, this response decreases progressively during the preovert stage of both autoimmune (*6*) and nonautoimmune (*7*) diabetes; the response to glucose is invariably absent when fasting hyperglycemia appears. This deterioration in insulin response may be selective for glucose in that insulin responses to β-cell secretagogues other than glucose, such as arginine (*8*) and isoproterenol (*9*), do not decline in parallel. Similar studies of the insulin response to glucose and arginine have been carried out in isolated perfused pancreata of rats with diabetes. During the prediabetic phase of the murine equivalents of autoimmune (*10*) and nonautoimmune (*11*) diabetes, the same selective attenuation of glucose-stimulated insulin secretion as in human prediabetes occurs (Fig. 1). When blood glucose concentrations reach 11 mM or greater, the diagnostic criterion for overt diabetes in the rat, the insulin response to glucose is absent, but the response to arginine persists.

These studies of β-cell function in humans and in rats indicate that steady-state hyperglycemia is invariably associated with an inability of β cells to respond to a further increase in hyperglycemia, and that the glucose-response system of β cells must be, at least in part, distinct from the response system for nonglucose secretagogues other than glucose. Because in humans and in rats two pathogenetically dissimilar hyperglycemic syndromes are each preceded by selective attenuation of glucose-stimulated insulin secretion, which is essential for correction of hyperglycemia, both forms of diabetes appear to begin with an abnormality in the glucose-specific portion of the glucose-response system of β cells.

Although knowledge of the glucose response pathway in the β cell is rudimentary, it is likely that glucose-specificity is confined to the

initial steps (Fig. 2). This would include a glucose-specific transporter, a glucose-specific hexokinase with a high Michaelis constant (K_m), designated glucokinase, and, perhaps, glucose-derived metabolic signals. Although the identity of the putative glucose sensor is still disputed, there is general agreement that its locus is intracellular rather than on the plasma membrane (*12, 13*). Appropriate response of insulin to glycemic change thus requires rapid equilibration of glucose across the plasma membrane (*14*). Because normal β cells readily discriminate between glucose concentrations of 20 and 30 mM (*15*), β cells probably have a facilitative glucose transporter with a high K_m. In fact, normal rat islets have a transport function with a K_m of 17 mM and a maximum velocity (V_{max}) of 32 mmol min^{-1} $liter^{-1}$ (*16*). A low K_m (1.4 mM) glucose transport function with a V_{max} of 5.5 mmol min^{-1} $liter^{-1}$ is also found and accounts for about 20% of the total transport activity in islets. This may in part represent transport into cells other than β cells.

The evidence for a defect in β-cell glucose transport in diabetes came in 1986 when it was reported that glucose transport in islets from BB rats isolated within 24 hours of the onset of autoimmune diabetes was reduced by 90% (*10*). Complete absence of glucose-stimulated insulin secretion was associated with persistence of response to arginine. Advances in the molecular biology of the facilitative glucose transporters (*17–19*) have made it possible to examine the role of the β-cell glucose transporter in this and other forms of diabetes.

The Structure and Function of Facilitative Glucose Transporters

Facilitative transport of glucose across plasma membranes of cells, the initial event in cellular glucose metabolism, is important in all animal cells and essential in some, such as the brain. The complementary DNA (cDNA) of the first of the facilitative glucose transporters was cloned in 1985 (*17*) and, soon thereafter, four other isoforms (*18, 19*) were also cloned. The various isoforms are numbered GLUT-1 through GLUT-5 (*19*).

On the basis of hydropathy plots of their primary sequences, all isoforms have 12 membrane-spanning domains that form six exoplasmic loops, the first of which is the largest and contains an N-linked glycosylation site (*17*). There are five endoplasmic loops, including a large hydrophilic central loop. The NH_2-terminal and COOH-terminal tails are intracytoplasmic. Amino acid identity between the five human isoforms ranges from 39 to 65% whereas up to 98% identity exists between the same isoform in rat and human (*20*). This conservation of isoform structure between species, compared to the divergence of isoform structure between tissues in the same species, implies that tissue-specific specialized function evolved early in the course of phylogenetic development.

The membrane-spanning domains and cytoplasmic loops are the most conserved portions of the isoforms, suggesting that they may contain the active glucose transport site (*20*). The first exoplasmic loop and the NH_2- and COOH-terminal tails are least conserved. They have been proposed as possible determinants of tissue-specific behavior. The COOH-terminal peptide has been used as an antigen to produce isoform-specific antibodies (*18*).

The tissue distribution, apparent K_m, and special features of the five isoforms are listed in Table 2. GLUT-1 and GLUT-3 both have a low K_m that permits glucose uptake in glucose-requiring tissues such as brain and erythrocytes at blood glucose concentrations well below the normal fasting range. GLUT-4, with a K_m of approximately 5 mM, is believed to be the insulin-sensitive isoform of muscle and fat (*21*). A defect in its expression or recruitment could be a factor in insulin resistance (*22*).

GLUT-2, the only known high K_m facilitative glucose transporter, has been found only in cells that participate in regulation of blood glucose homeostasis: liver, pancreatic β cells, and the basolateral aspect of the epithelial cells of the small intestine and renal tubules through which glucose is absorbed. The predicted amino acid sequences of liver and β-cell GLUT-2 are identical (*16*). GLUT-2 is present in β cells by immunocytochemical staining with antibodies to the COOH-terminal hexadecapeptide of the liver transporter (*19, 23*). It is located predominantly in the microvillar portion of the plasma membrane, facing adjacent endocrine cells (*23*). Pancreatic islet cells other than β cells do not contain GLUT-2.

The presence of a high-K_m glucose transporter in β cells assures that their uptake of glucose will be proportional to the highest physiologic extracellular glucose concentrations. The extracellular glucose concentration thus governs glucose usage in β cells and hence the magnitude of the insulin response (*13*). It follows that a defect in high K_m glucose transport function, irrespective of cause, will impair the β-cell response to hyperglycemia and thus prevent its correction.

Because it is possible to down-regulate the expression of GLUT-2 in rat β cells by inducing chronic hyperinsulinemia (*24*), we could test this assumption by measuring the glucose transport kinetics of islets that were virtually devoid of GLUT-2 messenger RNA (mRNA) (Fig. 3). In control rat islets, 3-*O*-CH_3–glucose uptake was not saturated at concentrations of up to 30 mM, whereas in islets in which GLUT-2 mRNA had been markedly decreased by a continuous 12-day insulin infusion, 3-*O*-CH_3–glucose uptake was saturated at 5 mM (Fig. 3B). The K_m was 2.5 mM and the V_{max} was 5 mmol min^{-1} $liter^{-1}$ in GLUT-2–deficient islets, compared to 17 mM and 32 mmol min^{-1} $liter^{-1}$ in the controls. Thus, glucose transport in islets at glucose concentrations above 5 mM, which is the normal fasting glucose concentration, was restricted by down-regulation of GLUT-2 expression. This result implies that absence or impairment of GLUT-2 would render β cells incapable of sensing and responding to increments of blood glucose in excess of 5 mM and that postprandial hyperglycemia would therefore go uncorrected.

Table 1. Comparison of IDDM and NIDDM.

Characteristic	IDDM	NIDDM
Age at onset	Childhood and young adulthood	Middle and old age
Race	Predominately Caucasians	All races
HLA linkage	Yes	No
Discordance in monozygotic twins	Yes	No
Mechanism	Autoimmune destruction	Unknown
Initial pathology	Insulitis; reduction in β-cell mass	Little or none
Late pathology	Absence of β cells; increase in α and δ cells	Amyloid deposition; fibrosis; β-cell mass normal or moderately reduced
First functional abnormality	Decrease in glucose-stimulated insulin secretion	Decrease in glucose-stimulated insulin secretion

Glucose Transport and GLUT-2 Expression in IDDM

Type 1 diabetes or IDDM, an autoimmune-mediated destructive disease of β cells, affects children and young adults with an inherited susceptibility linked to a class II major histocompatibility complex molecule (*25*). The destruction occurs gradually over a variable period of time averaging 3 years in duration (*26*), but a clinically apparent metabolic abnormality does not appear until at least 80% of the β cells have been destroyed. During the clinically silent prediabetic phase, the only known functional derangement of β cells is the attenuation of the first-phase insulin response to intravenously injected glucose (*26*). Several antibodies to β-cell antigens may be present during this prodromal phase of the disease, including antibodies to a 64-kD islet protein (*27*) [believed to be glutamic acid decarboxylase (*28*) and heat-shock protein 65 (*29*)], as well as unidentified β-cell surface antibodies (*30*), insulin autoantibodies (*31*), and cytoplasmic islet-cell antibodies (*32*). All of these antibodies are regarded as epiphenomenal rather than pathogenic, probably representing an immune response to β-cell antigens released during the destruction of β cells.

Immunoglobulins from patients with new-onset IDDM interfere with high K_m glucose transport of rat islet cells (*33*) and with glucose-stimulated insulin secretion (*34*). When dispersed islet cells isolated from normal rats were incubated for 15 min with purified immunoglobulin G (IgG) from patients with recent-onset IDDM, 3-*O*-CH_3–glucose uptake was significantly reduced compared to islet cells incubated with IgG from either normal controls or patients with NIDDM. This inhibitory effect was entirely the consequence of a reduction of high K_m glucose uptake, the V_{max} averaging 12.5 mmol min^{-1} $liter^{-1}$, compared to 32 mmol min^{-1} $liter^{-1}$ when control IgG from nondiabetic subjects was used (Fig. 4). Leucine uptake by islet cells was not affected by incubation with diabetic IgG. The inhibitory activity could be completely abolished by incubation of the IgG from diabetic patients with cells or cell membranes that display GLUT-2, such as hepatocytes and β cells. Incubation with cells or cell membranes that do not express GLUT-2 (for example, erythrocytes or preparations of kidney brush border) did not affect the inhibition. Although these findings suggest an antibody reaction with either GLUT-2 or a putative β-cell protein that influences GLUT-2 function, this has not yet been established by standard immunologic techniques.

Of 28 immunoglobulin samples from patients with recent-onset NIDDM 27 (95%) inhibited 3-*O*-CH_3–glucose uptake by at least 1 SD of the mean of nondiabetic controls, whereas samples from only 16 patients (60%) were positive for islet cell cytoplasmic antibodies. If this accurately reflects the relative prevalence of GLUT-2 and islet cell cytoplasmic antibodies in such patients, IgG-mediated inhibition of high K_m glucose transport is the more sensitive index of β-cell destruction.

GLUT-2 function is not only inhibited by circulating IgG: the amount of immunodetectable GLUT-2 is also reduced in β cells undergoing autoimmune destruction. In BB rats, a rodent model of autoimmune diabetes, at the onset of diabetes only 48% of the surviving β cells express GLUT-2 (*35*). Because only 20% of the normal complement of β cells are still present (*10*), this represents a 90% reduction in the number of GLUT-2–positive β cells. The reduction in glucose uptake by such islets to about 10% of normal (*10*) can therefore be accounted for entirely by the reduction in the number of GLUT-2–positive β cells. If a reduction in GLUT-2 expression of this magnitude also occurs in human autoimmune diabetes, it alone could account for the loss of glucose-stimulated insulin secretion even in the absence of inhibition of high K_m glucose transport by immunoglobulins.

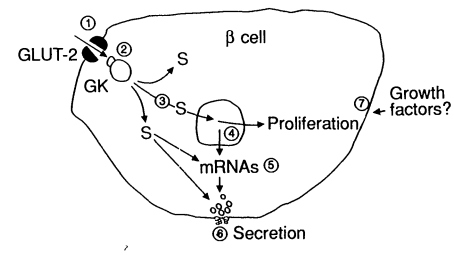

Fig. 2. Components of a putative glucose response system through which glucose can stimulate the release of stored insulin, insulin biosynthesis, and β-cell proliferation. Only steps 1 and 2 are unquestionably glucose-specific components, although glucose-derived metabolites might have specific functions as signals (*5*) (GK, glucokinase; S, unidentified signals).

Glucose Transport and GLUT-2 Expression in NIDDM

Type 2 diabetes or NIDDM is by far the most common form of human diabetes, afflicting at least 2% of middle-aged and older Americans (*36*), close to half of the Pima Indians of Arizona (*37*), and 34% of the natives of Nauru (*38*). Unlike in autoimmune diabetes, there is no consistent reduction in β-cell number in NIDDM (*39*), although late in the disease there may be loss of islet mass, and amyloid deposits may encroach on β cells (*40*). No morphologic lesion of β cells has ever been identified by either light or electron microscopy. These facts led to the suggestion that loss of glucose-stimulated insulin secretion at the onset of fasting hyperglycemia, without parallel loss of the response to arginine, could be the result of defective high K_m glucose transport.

Because this hypothesis cannot be tested in pancreata from living diabetic patients, animal models of NIDDM have been employed. One such model is a partially inbred colony of glucose-intolerant Zucker fatty (*fa/fa*) rats [ZDF/Drt-*fa*(F10)] (*41*). All male *fa/fa* rats become obese and develop overt NIDDM between 7 and 9 weeks of age. Neither the *fa/fa* females, which are as obese as the *fa/fa* males, nor the lean male and female heterozygotes (*fa*/+) develop hyperglycemia.

Insulin secretion by the isolated perfused pancreas of diabetic male ZDF rats responds to 10 mM arginine but not to 20 mM glucose, whereas age-matched nondiabetic female littermates respond to both (*11*). Young, prediabetic, male ZDF rats with normal fasting glucose concentrations have intact glucose-stimulated insulin secretion that begins to be impaired as their morning glucose levels approach 11 mM. When hyperglycemia exceeds 11 mM (200 mg/dl), glucose-stimulated insulin secretion is invariably absent. Immunofluorescent staining of the perfused pancreata from these animals with an antibody to the COOH-terminal hexadecapeptide of GLUT-2 (*11*) permitted quantitation of GLUT-2–positive immunofluorescence (*42*). In prediabetic ZDF rats, GLUT-2 was normal, but it became virtually undetectable in animals with late, severe diabetes (*11, 42*). This was confirmed by immunoblot

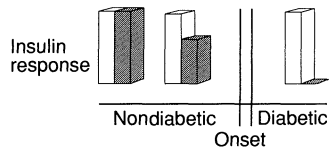

Fig. 1. Representation of the insulin response to glucose (hatched bars) and arginine (open bars) before (left two bars) and at the onset (right two bars) of fasting hyperglycemia (blood glucose greater than 11 mM). In both IDDM and NIDDM, glucose-stimulated insulin release decreases before overt diabetes without a parallel reduction in the arginine response (middle two bars).

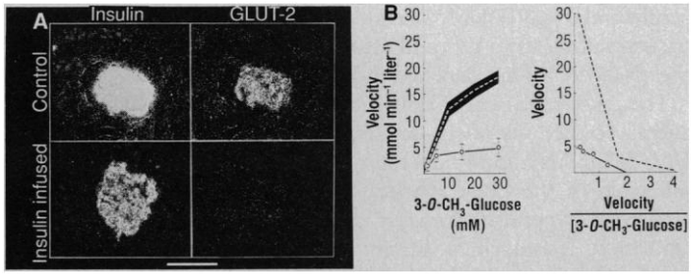

Fig. 3. Effect of down-regulation of β-cell GLUT-2 on kinetics of glucose transport by islets. (**A**) Dark-field photomicrographs of a typical islet from the pancreas of a control rat (upper panels) and a rat continuously infused with insulin (lower panels) for 12 days. Pancreas was hybridized in situ with ^{35}S-labeled antisense RNA probes for insulin or GLUT-2. [Reprinted from (*24*) with permission.] (**B**) Kinetic characteristics of glucose uptake by normal rat islets or islets isolated from rats after a continuous 12-day infusion of insulin. (Left) Concentration dependence of 3-*O*-CH_3–glucose uptake in islets isolated from insulin-infused rats (—) and normal rats (- -). (Right) Eadie-Hofstee plot of data on the left comparing infused rats (—) and normal rats (- -). The steep portion of the plot in normal rats represents the high K_m, high V_{max} glucose transport function, believed to represent β cells (see text and Fig. 4). Velocity is the initial velocity in millimoles per minute per liter of islet space and concentration is in millimolar. [Adapted from (*24*) with permission.]

analysis, by blot hybridization (*11*), and by protein A–gold immunocytochemistry with electron microscopy, which revealed a 75% reduction in GLUT-2 in β cells of severely diabetic rats (*42*). There was a significant negative correlation between the final glucose concentration before pancreatic perfusion and the percent of β cells displaying immunodetectable GLUT-2 (*11*) (Fig. 5). In every rat with fewer than 60% GLUT-2–positive β cells in its pancreas, the insulin response to glucose was absent and the final glucose concentration was 11 mM or greater. By contrast, there was no relation between arginine-stimulated insulin secretion and the abundance of GLUT-2–positive β cells; the response was as brisk in rats with 10% of β cells positive for GLUT-2 as it was in controls.

GLUT-2 mRNA in diabetic ZDF rats was quantitated by in situ hybridization and by blot hybridization and was found to be reduced by 50 to 75% as compared to concentrations in obese nondiabetic female ZDF animals and in lean nondiabetic controls (*11*). The decrease in GLUT-2 expression in β cells of diabetic ZDF rats predicts a reduction in the high K_m glucose transporter. Indeed Johnson and co-workers found that the uptake of 15 mM 3-*O*-

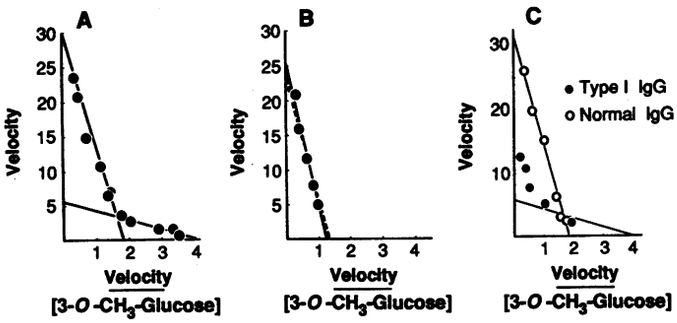

Fig. 4. Kinetic characteristics of glucose uptake by normal rat islets showing the effect of preincubation of islets with (**A**) buffer only, (**B**) 0.4 μM cytochalasin B, or (**C**) purified IgG from nondiabetic normal controls or new-onset diabetics with IDDM on the V_{max} of high and low K_m 3-*O*-CH_3–glucose transport in normal rat islets. In (A), K_m = 17 mM, V_{max} = 32 mmol min^{-1} liter^{-1} for the steeper curve and K_m = 1.4 mM, V_{max} = 5.5 mmol min^{-1} liter^{-1} for the flatter curve. In (B), K_m = 18 mM, V_{max} = 24 mmol min^{-1} liter^{-1}. Velocity is the initial velocity in units of millimoles per minute per liter of islet space and concentrations are millimolar. [Adapted from (*16*) with permission of the *Journal of Biological Chemistry* and from (*31*) with permission of the *New England Journal of Medicine*.]

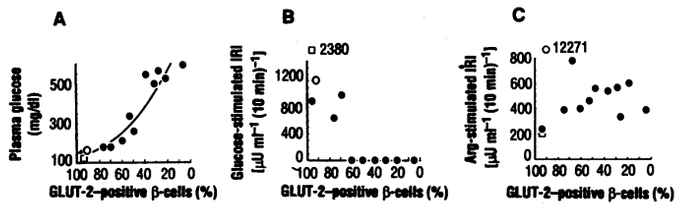

Fig. 5. Relation between β-cell functions and the percentage of GLUT-2–positive β cells in male ZDF rats with and without overt diabetes, nondiabetic female ZDF rats, and nondiabetic lean controls. (**A**) The relation between the final blood glucose concentration before the experiment and the percent of GLUT-2–positive β cells in diabetic ZDF rats (●), nondiabetic female ZDF rats (○), and lean male control rats (□) ($P < 0.001$, $r = -0.98$). (**B**) The relation between glucose-stimulated immunoreactive insulin (IRI) release and the percent of GLUT-2–positive β cells. (**C**) The relation between arginine-stimulated IRI release and the percent of GLUT-2–positive β cells. [Adapted from (*11*) with permission, © 1990 AAAS.]

CH_3–glucose in ZDF males was less than 40% of that in nondiabetic ZDF females and 20% of that in lean control rats (*11*). Thus, equilibration of high concentrations of glucose into GLUT-2–deficient β cells is seriously impeded in islets of diabetic ZDF rats.

It was surprising that incomplete reduction in GLUT-2 protein and glucose transport was associated with essentially complete loss of glucose-stimulated insulin secretion. This raised the possibility that there was another abnormality of the next glucose-specific point in the glucose response pathway, glucokinase (Fig. 2). The abundance of highly charged amino acid residues in the NH_2-terminal region of the β-cell isoform of glucokinase (*43*) suggested to Newgard and co-workers that there might be electrostatic interactions between the enzyme and other islet proteins, of which GLUT-2 would be an ideal partner for an efficient glucose-sensing apparatus (*44*). If GLUT-2 were required for optimal function of the enzyme (that is, if free glucokinase were functionally less efficient than glucokinase in a GLUT-2–bound state), a moderate reduction in GLUT-2 would reduce glucose phosphorylation and glucose transport and thus would cause disproportionately greater reduction of glucose usage than could be explained on the basis of the reduction of glucose transport alone.

In view of the pronounced effect of experimental down-regulation of β-cell GLUT-2 on high K_m glucose transport (*24*), a causal relationship linking the reduction of GLUT-2, the loss of glucose-stimulated insulin secretion, and the steady-state hyperglycemia of the diabetic ZDF rats seems plausible, provided that the loss of immunodetectable GLUT-2 is not secondary to the hyperglycemia. To examine this question, the effects of sustained hyperglycemia and its prevention on β-cell GLUT-2 expression were studied in vivo and in vitro (*42*). Hyperglycemia of approximately 11 mM was maintained for 7 days in two normal rats by continuous infusion of 50% glucose; in these rats, the percent of GLUT-2–positive β cells was 96 and 98%, compared with 97 and 100% in two normoglycemic controls infused with 5% glucose (*42*). In β cells cultured for 5 weeks in a medium with a glucose concentration of 33.4 mM, GLUT-2 abundance was determined by electron microscopy by means of the protein A–gold technique, and it did not differ from controls; there were 1.6 ± 0.1 gold particles per micrometer of plasma membrane in these β cells, compared to 1.0 ± 0.1 particles per micrometer in β cells from islets cultured in 5.5-mM glucose (*42*).

Finally, it was determined whether prevention of hyperglycemia throughout the lifetime of male ZDF rats would prevent loss of β-cell GLUT-2. Acarbose was administered to the rats daily, beginning at 7 weeks of age, approximately 1 week before the onset of hyperglycemia (*42*). Acarbose is an α-glucosidase inhibitor that prevents hyperglycemia by blocking the absorption of ingested

Table 2. The facilitative glucose transporter family (*20*).

Glucose transporter	Tissue distribution	K_m	Features
GLUT-1	Ubiquitous, red blood cells, brain	1–2	Induced in transformed cells (Hep G2, RIN m5F)
GLUT-2	β cells, liver, kidney, small bowel	~17	Glucose homeostatic roles
GLUT-3	Brain, fat	<1	
GLUT-4	Muscle, fat	~5	Insulin-recruitable
GLUT-5	Small bowel, kidney	1–2	

carbohydrate; it is not known to affect β cells directly (*45*). At 26 weeks of age, untreated male ZDF diabetic rats had an average glucose concentration of 33 mM and only 9% of β cells were positive for GLUT-2. In acarbose-treated male ZDF rats, glucose levels dropped to 7.2 mM, but only 20% of β cells were positive for GLUT-2. In nondiabetic controls with a slightly higher glucose concentration, 94% of the β cells were positive for GLUT-2 (*42*). GLUT-2 down-regulation in male ZDF rats is therefore not secondary to hyperglycemia.

Mechanism of Diabetic Hyperglycemia

The above studies suggest the following scheme for the pathogenesis of hyperglycemia in male ZDF rats: Unidentified primary event → reduced β-cell GLUT-2 mRNA → reduced β-cell GLUT-2 → loss of glucose-stimulated insulin secretion → uncorrected hyperglycemia = NIDDM. The alterations of blood glucose homeostasis resulting from this and associated glucose transporter anomalies of NIDDM are depicted in Fig. 6.

The cause of GLUT-2 down-regulation is not clear. Hyperinsulinemia caused by a 12-day insulin infusion diminishes β-cell GLUT-2 mRNA in normal rats (*24*) and the endogenous hyperinsulinemia of the obese diabetic ZDF rats is in a similar range. However, hyperinsulinemia is an unlikely cause of the down-regulation, inasmuch as insulin levels were even higher in the nondiabetic females with normal β-cell GLUT-2 expression.

Another possibility is that expression of GLUT-2 is determined by the intracellular demand for glucose and its availability from plasma glucose concentrations. Transformed β cells (*46*) and hepatoma cells (*17*) express low K_m GLUT-1 rather than GLUT-2, as if in response to increased demand for glucose during rapid proliferation. Normal hepatocytes from animals subjected to starvation also exhibit a reduction in GLUT-2 and an increase in GLUT-1 (*47*), although the changes are small. Perhaps when β cells are forced to increase their secretory activity or when their access to glucose is jeopardized, they abandon their functional role as sensors of hyperglycemia, which requires GLUT-2, and express a low K_m glucose transporter to maximize glucose influx at lower glucose levels. In both forms of diabetes, the functional demands on β cells are increased: as β cells are progressively depleted by autoimmune destruction in IDDM, the workload of the remaining β cells rises progressively, whereas in NIDDM the underlying peripheral insulin resistance imposes an increase in workload. Loss of GLUT-2 and, presumably, its replacement by an unidentified low K_m transporter, may be the molecular explanation of what has been referred to as β-cell "exhaustion" or failure (*48*).

Do conclusions based on a special colony of Zucker rats apply to

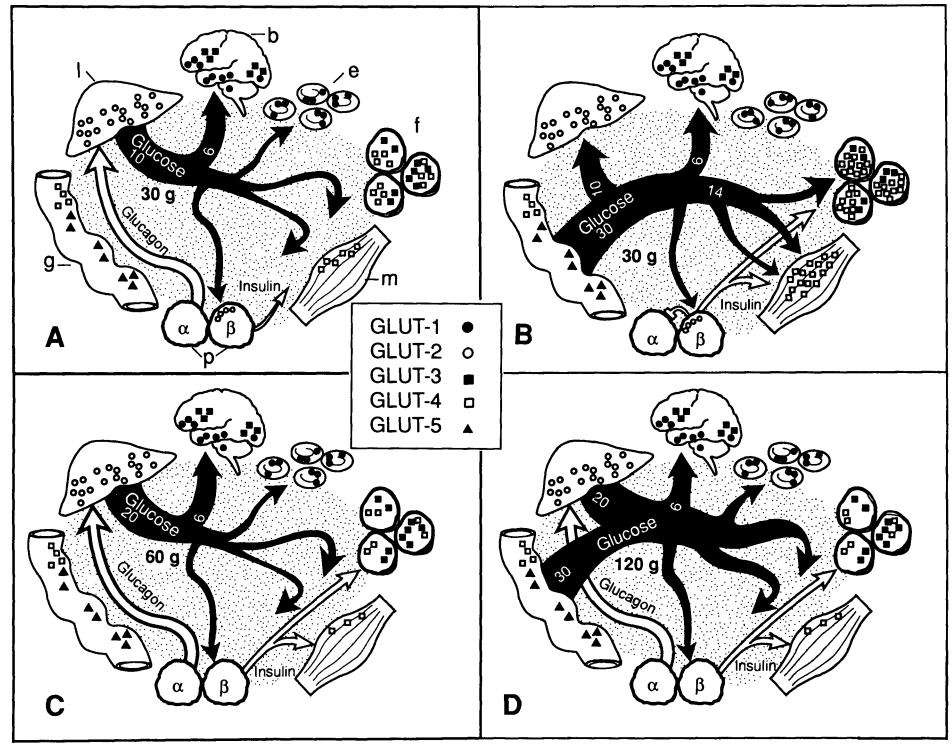

Fig. 6. Glucose homeostasis in a normal human and a human with NIDDM, depicting extracellular glucose movement into and out of tissues. The numbers on the black arrows represent grams per hour. The numbers under the block arrows represent the size of the extracellular glucose pool. (**A**) Normal basal state. Total body glucose utilization is 10 g hour^{-1}, 6 g of which go to the brain, which expresses low K_m GLUT-1 and GLUT-3. Little glucose enters the insulin-sensitive muscle or fat cells because of the small amounts of insulin secreted by β cells when the blood glucose concentration is in the fasting range. Glucagon secretion by α cells causes most of the 10 g hour^{-1} replacement of glucose by the GLUT-2–expressing liver, which maintains the extracellular glucose pool at 30 g and the blood glucose at 5 mM (b, brain; e, erythrocytes; f, fat cells; g, gut; l, liver; m, muscle; p, pancreatic islet cells). (**B**) Normal fed state. After a meal, glucose from the gut may enter the extracellular space at a rate of 30 g hour.$^{-1}$. The rise in insulin secretion by glucose-sensitive, GLUT-2–expressing β cells will increase GLUT-4 on the surface of muscle and fat cells and enhance their uptake of glucose so that total body uptake increases to about 30 g hour^{-1}, thereby limiting and correcting postprandial hyperglycemia. Simultaneously, insulin suppresses glucagon secretion and opposes glucagon's hepatic action, suppressing hepatic glucose production and converting the liver to an organ of glucose uptake. The increased glucose pool will be rapidly restored to about 30 g. (**C**) NIDDM basal state. A reduction in GLUT-4 in insulin-sensitivemuscle and fat cells coupled with an increased rate of glucose production by the liver, leads to an increase in the extracellular glucose pool (60 g) and fasting glucose concentration. GLUT-2 on β cells is reduced, rendering them insensitive to increments in blood glucose above 5 mM. (**D**) NIDDM fed state. A meal with an influx of 30 g hour^{-1} of glucose will increase the glucose pool (120 g) and the glucose concentration, as a consequence of insensitivity of GLUT-2–deficient β cells to the hyperglycemia and insensitivity of insulin target cells to insulin. Because secretion of insulin does not increase, glucose uptake by muscle and fat is not enhanced; because glucagon secretion is not suppressed, glucose production by the liver continues despite the hyperglycemia. The result is uncorrected cumulative postprandial hyperglycemia.

human NIDDM? Because pancreatic tissue cannot be obtained from living patients, this question cannot be answered directly. GLUT-2 on β cells is also reduced in glucose-insensitive β cells of rats with NIDDM induced by neonatal injection of streptozotocin (*49*) and in other rat models of NIDDM. Preliminary studies by Orci and co-workers indicate that the GK rat, a nonobese model of NIDDM, and the Wistar Kyoto rat, an example of NIDDM with extreme insulin resistance, both exhibit β-cell GLUT-2 deficiency (*42*). GLUT-2 is profoundly reduced in normal Wistar rats made diabetic by the administration of steroids (*50*). If these observations are substantiated, a β-cell deficiency of GLUT-2 will have been documented in every form of NIDDM thus far examined, suggesting that underexpression of GLUT-2 is an underlying feature of all forms of NIDDM in rodents. It would seem likely that the same defect could be present in NIDDM of other species, including humans.

Summary

Steady-state hyperglycemia, the criterion on which the diagnosis of diabetes is based, represents a failure of β cells to secrete the insulin required to restore normoglycemia at the prevailing level of insulin sensitivity of target tissues. Because the spectrum of insulin sensitivity in diabetes may vary from normal to extreme resistance, the amount of net insulin output by failing β cells will vary from very low, as in new-onset IDDM, to very high, as in obesity-associated NIDDM. Yet at both extremes of this spectrum, GLUT-2–positive β cells and high K_m glucose uptake by islets are reduced, and glucose-stimulated insulin secretion is absent. This seems to point to GLUT-2 as an essential component of the glucose-response apparatus of β cells required for correction of hyperglycemia and to identify the paucity of GLUT-2–positive β cells as a common lesion in hyperglycemic syndromes caused by entirely different pathogenic processes. The underexpression of GLUT-2 appears, at least in part, to be pretranslational, but its cause is unknown. These insights into the molecular pathophysiology of β-cell failure may open the way to new strategies and capabilities for the management of diabetes.

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