The Mammalian Glucose Transporters

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Glucose is a key metabolic substrate for mammalian cells. Blood glucose is a precursor for the biosynthesis of glycogen and fat as well as various sugar-containing macromolecules, such as glycoproteins, glycolipids, and nucleic acids. Some tissues (*e.g.* brain) require glucose as an energy source, and other tissues (*e.g.* muscle) will preferentially catabolize glucose for ATP production when it is plentiful. The first step in the metabolism of blood glucose is transport across the plasma membrane. This step is carried out by a family of membrane carrier proteins called glucose transporters (1, 2). Surprisingly, a different family of proteins is responsible for the transfer of glucose across the apical membranes of polarized intestinal and renal epithelial cells. These sodium-glucose cotransporters are secondary active transport systems that appear to be evolutionarily unrelated to the facilitative glucose transporters.

One or more glucose transporters are present in nearly all mammalian cells because of the central role played by glucose in cellular metabolism. In most cell types, glucose transporters are only involved in the net uptake of blood glucose for cellular metabolism. However, in some tissues glucose transporters may participate in the net efflux of glucose from the cell into the blood. For example, this process occurs during the absorption or reabsorption of glucose across the intestinal or renal epithelia, where facilitative glucose transporters are present in the basolateral membrane and allow the passive flux of sugar down its concentration gradient into the blood. Additionally, transporters are involved in the net efflux of cellular glucose from cells of the liver or kidney during fasting.

Glucose transporters are thus involved in both increasing and decreasing blood glucose levels and are, therefore, perfectly positioned to participate in the regulation of glucose homeostasis. This review will focus on recent advances concerning the regulation of glucose transporters in several key mammalian tissues. First, we briefly describe some physical properties of the glucose transporter subtypes.

GLUCOSE TRANSPORTER FAMILIES

Sodium-glucose cotransporters. Sodium-glucose cotransporters have been described in rabbit and human small intestine (3–6) and rabbit kidney (7, 8). They are expressed by specialized epithelial cells, *i.e.* the mature enterocytes lining the intestinal microvillus tip (3), and the brush border of the proximal tubule of the kidney (9–11). This cotransporter actively pumps glucose from the intestinal or tubular lumen against its concentration

gradient by coupling the transport of glucose and sodium, the latter being transported down its concentration gradient. The sodium gradient is maintained by the active transport of sodium across the basolateral surface of the brush border cells by the membrane-bound $Na+/K+/ATPase$.

The sodium-glucose cotransporter consists of 662–664 amino acids and is predicted to traverse the cell membrane 11 times, with the NH_2 and COOH termini located on the extracellular and cytoplasmic sides of the cell membrane, respectively (4). The protein is glycosylated at an asparagine residue in the small exofacial loop connecting transmembrane segments M5 and M6. The gene encoding the human intestinal sodium-glucose cotransporter, SGLT1, has been localized to the q11.2 →qter region of chromosome 22 (12).

Facilitative glucose transporters. The second major type of glucose transporter is expressed in nearly all mammalian cells (13, 14). These proteins transport glucose in an energy-independent process down a concentration gradient by stereospecific, saturable, facilitative diffusion. This class of transporters includes five isoforms that are encoded by different genes and exhibit distinct tissue distributions (Table 1), presumably reflecting the unique glucose requirements of various tissues (13, 14).

The facilitative glucose transporters vary in size from 492 to 524 amino acids. They exhibit 39–64% sequence identity and 50–76% sequence similarity in pair-wise comparisons (15–26). These transporters are predicted to traverse the cell membrane 12 times, with the NH_2 and COOH termini, which vary in sequence and length between the different isoforms, located on the cytoplasmic side of the cell membrane. An exofacial loop between transmembrane segments M1 and M2 carries the site for asparagine-linked glycosylation. A large intracellular hydrophilic segment exists between M6 and M7 (Fig. 1) (15). Comparisons between the different isoforms have revealed that the sequences of the transmembrane segments and the short cytoplasmic loops connecting these transmembrane regions are highly conserved. Thus, it is thought that these regions subserve a common function, such as the transport of glucose. The NH_2- and COOH-terminal regions and the exoplasmic segments are less conserved and may contribute to isoform-specific properties, such as the kinetics, hormone sensitivity, and subcellular localization (15, 16, 18–24, 26).

There are two classification schemes for the family of facilitative glucose transporters. One is based on the order of cloning of the different isoforms and the other is based on the tissue or cell-type from which the isoform was first cloned. In this review, we will adhere to the numerical nomenclature. Some characteristics of the different isoforms are compiled in Table 1.

The studies of Bell *et al.* (13) had revealed similarities in the structures of the human glucose transporter genes. All of their exon-intron orientations are very similar. Glucose transporter (Glut) 1 has 10 exons, whereas Glut 2 and 5 have 11 exons. An additional intron subdivides exon 4 of the Glut 1 gene into two

Glut 2 exons (4a and b). Similarly, Glut 5 has an additional intron dividing exon 9 into 9a and 9b. The length of the genes varies from 8 to 35 kb (13).

INSULIN-SENSITIVE TISSUES

Isoform Distribution. The insulin-sensitive tissues, fat and muscle, express the Glut 1 and Glut 4 transporter isoforms (22, 27–29). Glut 4 is at least 10-fold more abundant in fat and skeletal muscle than is Glut 1 (22, 27, 28, 30). Immunolocalization studies in skeletal muscle indicate that Glut 1 expression is concentrated in the perineural sheath and that Glut 4 is the main muscle cell transporter (31). However, these data do not exclude a lower level of expression of Glut 1 in muscle cells than in nerve. The level of Glut 4 expressed in insulin-sensitive tissues of the rat (brown fat > heart > red muscle > white muscle > white fat) parallels the magnitude of the insulin-mediated increase in glucose transport observed in these tissues (22). This suggests that Glut 4 is the isoform primarily responsible for acutely insulin-stimulated glucose transport.

Insulin. Insulin rapidly increases glucose uptake and metabolism in fat and skeletal muscle (32–34). This response, especially in skeletal muscle, is crucial to lowering blood glucose levels in the postprandial state. Transport is rate-limiting for glucose metabolism in these tissues (35, 36) and, thus, insulin exerts its stimulatory effect principally via increasing this initial step in glucose uptake. The cellular mechanism of this effect has been studied most thoroughly in adipocytes (27, 28, 37–43). In the basal state, both Glut 1 and Glut 4 are concentrated in an intracellular storage pool (38, 39). This storage pool corresponds to tubulo-vesicular elements of the trans-Golgi reticulum (40, 41). Essentially all of the Glut 4 is present in intracellular compartments in the basal state, but a proportion of Glut 1 is found in the plasma membrane, where it likely contributes to the low level of basal transport observed in these cells (28, 42, 44).

Insulin induces the redistribution of both Glut 1 and Glut 4 from their intracellular storage sites to the cell surface, resulting in augmented glucose transport (27, 28, 42, 44). This effect occurs within minutes and is rapidly reversible upon insulin withdrawal. Although there is some controversy concerning this point, it appears that most of the insulin-stimulated increase in glucose transport in adipocytes can be attributed to this translocation phenomenon (28, 41, 42). Ultrastructural studies suggest that a similar translocation mechanism exists in skeletal muscle (45).

In addition to its acute effect on glucose transport, insulin alters transporter gene expression after prolonged exposure of insulin-sensitive cells. Chronic treatment of rats with insulin results in an increase in total adipocyte glucose transporters as measured by cytochalasin B-binding (46). This is solely due to an increase in Glut 4 (47). Chronic insulin-induced hypoglycemia in rats results in an increase (48) or decrease (49) in skeletal

muscle Glut 4 protein, depending on the treatment protocol, with little or no change in Glut 1.

Interpretation of *in vivo* studies involving alterations in insulin levels is complicated by the occurrence of secondary effects, *e.g.* changes in blood glucose or other circulatory factors. Thus, it is not possible to determine the direct mediator of the changes in glucose transporter gene expression from these experiments. However, the effect of insulin on transporter gene expression has also been studied in cultured cells whose environment can be more precisely manipulated. Insulin increases glucose transport via a selective increase in Glut 1 mRNA and protein in 3T3L1 adipocytes (50). The level of total cellular Glut 4 is unchanged by chronic insulin exposure, whereas the amount of Glut 4 on the cell surface actually decreases (51). Apparently, the increase in total cell-surface Glut 1 due to *de novo* protein synthesis is sufficient to compensate for the decrease in Glut 4, resulting in an overall increase in transport activity.

The extracellular glucose concentration also affects glucose transport activity and transporter gene expression in 3T3L1 adipocytes (52). Glucose withdrawal increases transport activity via a complicated series of events involving a pretranslational increase in Glut 1 expression and translocation of preexisting intracellular Glut 4 to the plasma membrane. Interestingly, the level of total cellular Glut 4 protein remains unchanged after 3 d of glucose withdrawal despite a dramatic reduction in the Glut 4 mRNA level. This suggests that glucose starvation enhances the stability of Glut 4 protein in the plasma membrane.

Exposure of L6 myocytes to insulin for 24 h increases glucose transport and results in a selective increase in Glut 1 gene expression (53). Glut 4, under these conditions, is down-regulated at the level of the mRNA. The level of Glut 4 protein increases in the plasma membrane and decreases in intracellular membranes. Apparently, translocation of preexisting intracellular Glut 4 to the plasma membrane occurs concomitant with a suppression in *de novo* Glut 4 synthesis. Glucose starvation of L6 cells results in an increase in transport activity accompanied by a pretranslational increase in Glut 1 expression, and an increase in Glut 4 protein with no change in Glut 4 mRNA (54). It is difficult to evaluate the contribution of each transporter isoform to total transport activity in L6 cells, because the absolute or relative level of expression of the two isoforms in these cells has not been reported.

Thus, in adipocyte and muscle cell lines, both insulin and glucose directly modulate glucose transporter gene expression. Chronic insulin treatment most likely increases glucose transport by stimulating the synthesis of Glut 1, with little or no effect on Glut 4 expression. This contrasts sharply with the long-term *in vivo* treatment of rats with insulin, in which alterations in Glut 4 levels are observed in fat and muscle tissue with little or no change in Glut 1 (46–49). This apparent discrepancy could be due to secondary changes that occur *in vivo* in response to insulin administration or to genuine differences between the response of the cultured cell lines and their tissues of origin. The resolution of this disagreement will depend on additional gene expression

Table 1. *Mammalian facilitative glucose transporters*

| Name	Numerical nomenclature	Tissue distribution	Kinetic properties	Location of human gene
HepG2	Glut 1	Many adult and fetal tissues, abundant in human red cells, placenta, brain microvessels	Erythrocyte: asymmetric carrier with exchange acceleration; Km ~5–30 mM (variable); V_{max} (influx) < V_{max} (efflux)	1p35 → 31.3
Liver	Glut 2	Liver, pancreatic β-cells, kidney, intestine	Liver: simple, symmetric carrier; Km ~60 mM; Intestine: asymmetric carrier; V_{max} (efflux) < V_{max} (influx)	3q26
Fetal muscle	Glut 3	Many adult and fetal tissues, abundant in placenta, brain, kidney	Exchange Km ~10 mM	12p13
Fat/muscle	Glut 4	White and brown fat, skeletal muscle, heart	Adipocyte: simple, symmetric carrier; Km ~2–5 mM	17p13
Intestine	Glut 5	Jejunum, fat, kidney	?	1p31
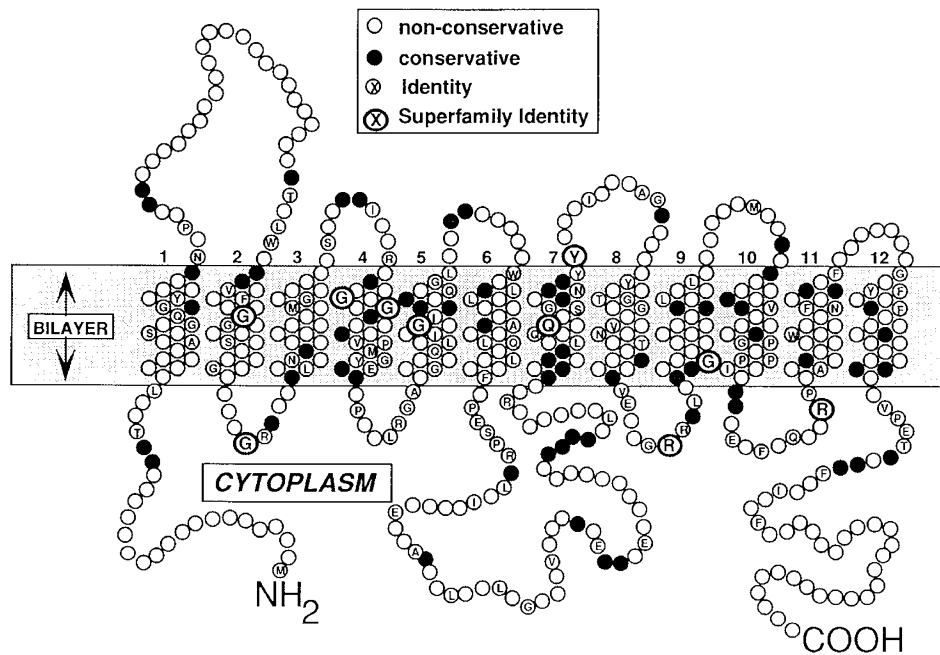
Fig. 1. Predicted topology of the mammalian facilitative glucose transporters. Based on the model proposed in Reference 15. The proteins are predicted to span the membrane in the form of 12 α-helical domains. Residues that are nonconserved among the five known mammalian transporter isoforms are shown as *open circles*. Conserved residues are shown as *closed circles*. The single letter amino acid code is used to indicate residues that are identical among the five mammalian isoforms. Residues that are identical among members of the Sugar Transporter Superfamily are shown as *larger circles*.

studies and, perhaps, characterization of regulatory elements within the glucose transporter genes.

Counter-Regulatory Factors. Counter-regulatory factors are those hormones and other agents that oppose the action of insulin on glucose homeostasis. β-Adrenergic agonists are a classic example of this class of hormone (55, 56). At least some of the effects of β-adrenergic agonists on glucose homeostasis occur at the level of transport. Isoproterenol has been reported to decrease adipocyte glucose transport by affecting a change in the intrinsic activity of glucose transporters without altering their total cellular content (37, 57). Isoproterenol inhibits insulin-stimulated glucose transport by 40% and stimulates phosphorylation of Glut 4 2-fold, without affecting its subcellular distribution in either the basal or the insulin-stimulated state (58). Phosphorylation of Glut 4 by isoproterenol is mediated by an increase in intracellular cAMP, because cAMP analogues mimic the effect (58). These data suggest that Glut 4 phosphorylation may decrease the intrinsic activity of this isoform. The phosphorylation of Glut 4 is confined to a serine/threonine residue in the cytoplasmic carboxy-terminal domain of the protein (59). Studies using okadaic acid, a phosphatase inhibitor, suggest that phosphorylation of Glut 4 may also be involved in triggering the internalization of cell-surface Glut 4 molecules (60). Glucagon, another hormone that increases intracellular cAMP (61) and decreases glucose transport, may also alter glucose transporter intrinsic activity in addition to affecting glucose transporter translocation to the adipocyte plasma membrane (62). The effect of glucagon on Glut 4 phosphorylation as well as the cAMP dependence of its effect on glucose transport have not been reported.

In contrast to the acute inhibitory effect of cAMP on glucose transport in primary rat adipocytes, a marked stimulation of glucose transport into 3T3L1 adipocytes has been reported in response to long-term cAMP exposure (61, 63). A 70% decrease in Glut 4 mRNA and protein occurs in 3T3L1 adipocytes after 16 h of cAMP exposure. Expression of Glut 1 mRNA and protein increases 3-fold after 6 h of cAMP treatment. These changes are accompanied by an increased basal 2-deoxyglucose uptake and a loss of insulin-stimulated glucose uptake. Although cAMP has no detectable effect on the fractional distribution of Glut 4

protein between the plasma membrane and low-density microsomes, it causes a substantial increase in the fraction of Glut 1 protein at the plasma membrane. The magnitude of Glut 4 depletion *versus* Glut 1 mRNA accumulation is cAMP dose-dependent, the former being due to a decrease in the transcriptional rate alone, while the latter is secondary to a transient transcriptional activation and mRNA stabilization (61). Whether 3T3L1 adipocytes behave differently than primary rat adipocytes, or whether cAMP exerts opposing effects based on the duration of exposure, is not resolved by these studies. The 3T3L1 adipocytes express less Glut 4 and more Glut 1 than do primary rat adipocytes and, thus, subtle effects on Glut 4 intrinsic activity may go undetected in 3T3L1 adipocytes because of the opposing action on the expression of Glut 1.

Growth hormone is known to produce insulin resistance after prolonged therapy (64, 65). Recent investigations demonstrate that, in the basal state, growth hormone suppresses adipocyte Glut 1 expression at a pretranslational level with no effect on Glut 4. Thus, over a period of time, cellular glucose transport is impaired (66).

Steroids, another class of counter-regulatory hormone, alter the insulin-induced recruitment of glucose transporters to the cell surface (67, 68) and decrease Glut 4 expression at the mRNA level (69). Acute and chronic exposure of primary rat adipocyte cultures to dexamethasone leads to a decline in both basal and maximally insulin-stimulated glucose transport. Acute (2-h) exposure of adipocytes to dexamethasone results in a decrease in basal and insulin-stimulated cellular plasma membrane glucose transporters without a change in total cellular glucose transporter content. On the other hand, chronic treatment for 24 h led to depletion of total cellular glucose transporters in both the basal and insulin-stimulated states (69). These alterations may explain some of the steroid-induced perturbations in glucose homeostasis observed *in vivo*.

Thyroxine increases basal glucose uptake in humans (70, 71) and rats (72). Specific studies using the insulin clamp, however, demonstrated no change in basal glucose metabolism, with an increase in insulin-stimulated glucose disposal in hyperthyroid patients (73). The major route of insulin-stimulated glucose

disposal in hyperthyroid patients appears to be glucose oxidation (73). This may account for decreased skeletal muscle glycogen content in hyperthyroid animals (74). A recent report suggested the mechanism for these changes to be a thyroxine-induced increase in skeletal muscle Glut 4 protein (75). However, the effect of thyroxine on the subcellular distribution of Glut 4 was not examined. Based on these observations, it is possible that an increase in Glut 4 could mediate an increase in insulin-stimulated transport in skeletal muscle, thereby facilitating increased glucose oxidation.

Exercise. Physical training in humans and animals enhances insulin sensitivity *in vivo* and has been advocated as an adjunct therapy for diabetes (76–80). Acute exercise increases glucose uptake in perfused rat hind limb and isolated skeletal muscle (81, 82). This stimulation persists after muscle contraction (82) and can be reproduced by electrical stimulation *in vivo* (83–85). Acute exercise induces the recruitment of intracellular Glut 4 to the cell surface with no change in the distribution of Glut 1 (86). However, the exercise-sensitive Glut 4 does not appear to originate from the insulin-sensitive intracellular compartment, suggesting the existence of two distinct intracellular pools of recruitable glucose transporters (86). These studies demonstrate that skeletal muscle glucose transport increases with exercise.

Apart from the short-term studies, prolonged exercise training has been shown to enhance the ability of insulin to stimulate glucose uptake into skeletal muscle. A prolonged exercise program of 6 wk duration results in an increase in the rat plantaris (slow-twitch oxidative fibers) Glut 4 protein, with no significant change in soleus (fast-twitch glycolytic and fast twitch oxidative glycolytic fibers), despite a noticeable hypertrophy of the soleus (87). Thus, in certain muscle types, exercise increases the efficiency of the glucose transport system by increasing the total number of insulin-regulatable glucose transporters. On the other hand, chronic physical inactivity caused a decrease in the gastrocnemius muscle growth, glucose uptake, and total glucose transporters as assessed by cytochalasin B binding (88). Although data on the effect of exercise on insulin sensitivity and glucose homeostasis exist for human subjects (76), studies characterizing the effect of either exercise or physical inactivity on human adipocyte or skeletal muscle Glut 4 have not yet appeared.

Abnormal States. Diabetes mellitus. A number of studies have addressed the effect of non-insulin-dependent diabetes mellitus (NIDDM) in the human and streptozotocin-induced diabetes in the rat on glucose transport. Streptozotocin-induced diabetes in the rat is brought about by selective destruction of pancreatic β-cells, resulting in markedly impaired insulin secretion and insulin resistance in peripheral tissues (89). This metabolic state results in a suppression of insulin-stimulated cellular glucose transport in adipocytes (32). Long-term streptozotocin treatment induces a pretranslational suppression of adipocyte and skeletal muscle Glut 4 with minimal effect on Glut 1 (90). However, milder streptozotocin treatment was reported to decrease adipocyte Glut 4 protein, with no effect on skeletal muscle Glut 1 and Glut 4 protein despite a decrease in the insulin-stimulated glucose uptake (31).

The regulation of Glut 4 in muscle in response to streptozotocin treatment appears to be fiber-type dependent. A week of streptozotocin-induced diabetes results in a significant decline in insulin-stimulated glucose transport in the soleus (type I fibers), pooled deep red quadriceps/gastrocnemius muscles (type I and IIA, slow twitch oxidative fibers), and pooled superficial white quadriceps/gastrocnemius muscles (type IIB, fast twitch glycolytic fibers) (91). A corresponding decrease was noted in red and soleus muscle Glut 4 mRNA and protein, but a significantly diminished down-regulation of Glut 4 was observed in white muscle (91). The physiologic consequences of this regulation may reflect the distinct metabolic properties of these different muscle fibers. It was proposed that diabetes induces a rapid uncoupling of the insulin-stimulated glucose transport system before down-regulating Glut 4 protein and mRNA (91). These

changes may be time-dependent, with sequential defects consisting of either impaired skeletal muscle glucose transporter translocation or intrinsic activity, followed by a decline in Glut 4 protein levels, which may contribute toward the insulin-resistant state of type II diabetes (31).

Adipocytes isolated from human NIDDM subjects exhibit decreased insulin-stimulated glucose transport, decreased total cellular transporters as measured by cytochalasin B binding, decreased insulin-induced translocation of intracellular transporters to the plasma membrane, and a pretranslational suppression of Glut 4 expression (92, 93). Insulin-mediated glucose uptake into leg muscles is decreased in NIDDM patients when compared with lean and obese controls (94). Pederson *et al.* (95) reported no difference in the level of Glut 4 in vastus lateralis muscle of diabetics *versus* controls, whereas Dohm *et al.* (96) reported a decrease in Glut 4 in rectus abdominis and vastus lateralis in obese insulin-resistant diabetics and nondiabetics relative to nonobese controls. Further studies are clearly necessary to resolve these differences. It is possible that the patient populations in the two studies represented subgroups with distinct characteristics.

Insulin therapy of streptozotocin-treated diabetic rats normalizes the defective insulin-stimulated translocation of intracellular glucose transporters to the cell surface in adipocytes (32). Insulin therapy of greater than 7 d duration causes an initial overcompensation, resulting in a pretranslational increase above control in Glut 4 expression followed by a return to the prediabetic control level (90). Insulin-induced normalization of Glut 4 expression occurs in both adipocytes and skeletal muscle of streptozotocin-treated diabetic rats (31, 91). Although insulin therapy alone reverts Glut 4 expression back to normal, the correction of hyperglycemia per se by increasing renal tubular excretion of glucose by phlorizin administration fails to revert Glut 4 gene expression back to the normal prediabetic state (97). A change in Glut 4 intrinsic activity was proposed as a mechanism for correcting the diabetic hyperglycemia-induced decrease in cellular glucose transport (97). However, it should be noted that phlorizin is a toxin, and its effects on the animal are almost certainly not limited to reversal of hyperglycemia.

Sulfonylureas are oral hypoglycemic agents that are used in the treatment of NIDDM (98). These drugs increase the secretion of insulin from the pancreas (99, 100) and also appear to augment glucose disposal in peripheral tissues by a mechanism unrelated to their effect on insulin secretion (102, 102). The mechanism of the so-called extrapancreatic effects of the sulfonylureas may involve an alteration in glucose transport. Glyburide appears to have no effect on glucose transport in basal primary rat adipocytes, but enhances the insulin-induced recruitment of intracellular glucose transporters to the cell surface (103). Tolazamide enhances insulin-stimulated glucose transport into L6 rat skeletal muscle cells by increasing the expression of Glut 1 (104). Similarly, tolbutamide increases glucose uptake into 3T3L1 adipocytes by selectively increasing Glut 1 expression with no effect on the steady state level of Glut 4 (50). Thus, it is feasible that part of the hypoglycemic action of these drugs *in vivo* is the result of their effects on glucose transport in tissues expressing Glut 1.

Vanadate, a trace element, is a potent insulin-mimetic agent that normalizes hyperglycemia (105). Unlike the effect of sulfonylureas in cultured cells, but similar to that of insulin in whole animals, vanadate acts to relieve diabetic hyperglycemia by inducing expression of skeletal muscle Glut 4 at a pretranslational level (106).

Obesity. Glucose transport is markedly impaired in tissues from obese humans (107) and animals (108). Glut 4 has been extensively studied in this abnormal metabolic state. Relative to its lean littermates, the spontaneously obese, hyperglycemic, hyperinsulinemic, and insulin-resistant db/db mouse exhibits decreased Glut 4 mRNA levels in skeletal muscle (quadriceps) but normal levels in other insulin-sensitive tissues (29). However, the level of Glut 4 protein is unaffected in all the insulin-sensitive

tissues, suggesting that an alternate mechanism is involved in the inhibition of insulin-stimulated glucose disposal in these animals (29). Goldthioglucose-induced obese mice expressing hyperinsulinemia and slight hyperglycemia at 4 to 6 mo of age exhibit a decrease in brown and white adipose tissue Glut 4 protein, with no change in skeletal muscle Glut 4 protein (109). An 18-d treatment with a thermogenic agent, BRL 26830A, which normalizes blood glucose without affecting the hyperinsulinemia of the obese state, results in an increase in brown and white adipose tissue Glut 4 protein close to lean controls, with no change in skeletal muscle Glut 4 (109). Consistent with this observation is a report describing the effect of 4 d of hyperinsulinemia with accompanying hypoglycemia or glucose-clamped euglycemia on lean, heterozygous, Zucker rats (49). Similar alterations in Glut 4 expression were observed in both hyperinsulinemic groups when compared with the control group. Hyperinsulinemia of a short duration caused a differential tissue response, with an increase in white adipose tissue Glut 4 mRNA and protein and a decrease in skeletal muscle Glut 4 mRNA and protein.

Collectively, these studies indicate that there is no simple relationship between blood glucose/insulin levels and expression of the major insulin-responsive glucose transporter in fat and muscle. This could be, in part, due to the fiber-type specificity of Glut 4 regulation in muscle, effects on gene expression that change with time, and differences in the response of genetically distinct groups of animals used in the different experiments. It should also be noted that the direct physiologic mediator(s) of the alterations in glucose transporter expression associated with perturbations in glucose and insulin homeostasis *in vivo* has not been identified. In the context of obesity, these studies suggest that high circulating insulin levels may be responsible for diverting glucose utilization from skeletal muscle into adipose tissue, resulting in obesity. Once a larger white adipose tissue mass is established, an insulin-resistant state sets in with decreased activity of the adipocyte transport system.

Obesity in humans results in impaired insulin-mediated translocation of glucose transporters in adipocytes (92), along with a decrease in adipocyte Glut 4 mRNA and protein relative to lean controls (94). Pederson *et al.* (95) reported no change in Glut 4 expression in vastus lateralis muscle of obese patients compared to lean controls, whereas Dohm *et al.* (96) observed a decrease in Glut 4 in rectus abdominis and vastus lateralis muscle of obese patients relative to lean controls. The reason for this discrepancy is not known, but it may relate to the extent of obesity as assessed by the body mass index or some other distinct characteristic of the patient groups used in the two studies.

Starvation. Starvation induces a state in which insulin-stimulated glucose transport into adipocytes is diminished, while insulin hyperresponsiveness is observed in skeletal muscle (34, 110). Insulin resistance in adipocytes is due to a decrease in the total intracellular pool of glucose transporters and to a diminished translocation of glucose transporters from the intracellular pool to the cell surface (110). A decrease in Glut 4 and, to a lesser degree, in Glut 1 mRNA and protein occurs in adipocytes after 2–4 d starvation (34, 111, 112). A similar state of starvation results in an increase in skeletal muscle Glut 1 and Glut 4 mRNA and protein (34, 48). The differential effect on adipose and skeletal muscle Glut 4 during starvation is opposite from that observed in the case of obesity (see above) (49). Refeeding for a period of 6–8 d results in an increase in insulin-stimulated transport in adipocytes that overshoots the control values (34). Refeeding reverses the starvation-induced changes in adipose and muscle Glut 1 and Glut 4 gene expression (34).

Similar studies have not been conducted in humans. Based on the rat investigations, it appears that acute starvation results in a self-preservation phenomenon in which insulin responsiveness is maintained in skeletal muscle. However, prolonged starvation ultimately leads to an insulin-resistant state *in vivo* (113, 114).

Other insulin-resistant states. Other insulin-resistant states that have been studied include high fat/low carbohydrate feeding

(115) and aging (108), where a basal intracellular depletion of glucose transporters, along with a diminished insulin-stimulated translocation of glucose transporters to the adipocyte plasma membrane, were observed. Aging is associated with a decrease in adipocyte Glut 4 protein with no change in Glut 1 (116, 117). An insulin-resistant chronic uremic state was examined in partially nephrectomized rats (118). Both basal and insulin-stimulated glucose transport into isolated adipocytes were decreased because of a decline in total cellular glucose transporters and a resultant diminution in insulin-induced translocation to the cell surface.

Development and Cellular Differentiation. The most prominent fetal glucose transporter is Glut 1, which is expressed by almost all fetal tissues examined, including those tissues that fail to express it significantly in the adult. Most fetal cells exhibit rapid growth and development necessitating an enhanced requirement for various metabolic substrates, including glucose. This is not unlike cellular growth observed *in vitro* (119). Thus, ontogenic studies in most tissues have revealed a higher expression of Glut 1 in fetal tissues when compared with the corresponding neonatal and adult tissues (120, 121). On the other hand, fetal tissues are more resistant to the acute metabolic action of insulin when compared with the adult (122). Of the different insulin-responsive tissues, skeletal muscle and heart have been examined in the fetal rat (120, 121). In skeletal muscle, a higher molecular mass fetal form (~50–55 kD) was observed in addition to the lower molecular mass adult form (~45–50 kD) (120). The significance of the two forms in fetal tissues is not clear, because it reportedly cannot be explained by glycosylation differences alone (120). However, preliminary observations from our laboratory are highly suggestive of red cells within vascular spaces of fetal tissues contributing to the increased abundance of the Glut 1 isoform in certain tissues at this developmental stage (123). Thus, studies using whole tissues may not be able to distinguish between the fetal red cell and the tissue-specific Glut 1 transporter. In contrast, Glut 4, which is abundant and vital to the adult insulin-responsive tissues, is expressed at a much lower abundance in the fetus (our unpublished observations) and preweaning newborn (124). Thus, it appears that although basal glucose requirements necessary for cellular growth and proliferation are high in the fetus, the specialized insulin-responsive glucose transport needs do not develop until later in life.

The neonatal period is a transitional stage during which various changes in glucose metabolism take place. Glut 1 tends to decline in most tissues examined during the early neonatal period and either remains low in the adult or increases again in the young adult, depending on the tissue (121). Glut 4 increases in adipocytes and skeletal muscle during the stage of weaning to reach adult levels by a few weeks of age (124). Investigations designed to determine the factors that regulate this developmental increase in the expression of glucose transporters in insulin-responsive tissues are limited. A recent report suggested that weaning from a high-fat milk diet to a high-carbohydrate diet is a critical factor in inducing Glut 4 expression in both adipocytes and skeletal muscle, thereby conferring insulin sensitivity at the age of weaning (124).

The expression of Glut 1 and Glut 4 has been examined during the differentiation of 3T3L1 cells from the fibroblast-like preadipocytes to the adipocyte stage (50, 125). The preadipocytes express only Glut 1. During differentiation, the level of Glut 1 progressively decreases concomitant with the appearance and increased expression of Glut 4. The decrease in Glut 1 parallels a decrease in basal transport activity in the differentiating cells, whereas the increase in Glut 4 parallels the increase in insulin-stimulated transport activity. The turn-on of Glut 4 expression is likely mediated by the nuclear transcription factor, CCAAT/enhancer binding protein (C/EBP) (125).

Genetics. The glucose transporters of insulin-sensitive tissues (22) are logical targets for genetic defects predisposing to insulin-resistance (92, 93, 95, 96). The detection of restriction fragment

length polymorphisms in the Glut 1 and Glut 4 genes has led to genetic linkage studies involving NIDDM populations. Positive associations between polymorphisms at the Glut 1 locus and NIDDM have been reported in some racial groups (126), but not in Afro-Americans (127, 128) or Chinese Americans (129). Glut 4 cDNA clones were also used to evaluate DNA polymorphisms in genomic DNA from American blacks with NIDDM (130). A single polymorphism was identified. However, the allelic, genotypic, and haplotypic frequencies of the DNA polymorphism did not differ in frequency between diabetic and control populations. It appears unlikely that specific alleles at the Glut 1 and Glut 4 genes contribute in a major way to the genetic susceptibility to NIDDM observed in Afro-Americans. However, these data do not exclude the possible involvement of these genes in the predisposition to insulin-resistance of NIDDM in a subpopulation of diabetics.

LIVER AND PANCREATIC β-CELLS

Isoform Distribution. Glut 2 is the major transporter isoform expressed in hepatocytes and β-cells of the pancreatic islets (18–20). Perivenous hepatocytes do express detectable levels of Glut 1 (131). Glut 2 appears to be a high-turnover/low-affinity transporter (132). Transport is not rate-limiting for glucose uptake into either β-cells or hepatocytes, and the intracellular sugar concentration approaches the extracellular concentration (14, 133). This is in sharp contrast to the situation in muscle and fat cells, where transport is clearly rate-limiting for glucose metabolism (35, 36). The high Km exhibited by Glut 2 in these tissues may reflect the fact that splanchnic tissues can be exposed to a higher glucose concentration than is present in peripheral blood. The operation of this transport system at low substrate concentrations relative to its Km suggests that the rate of transport should vary linearly with the sugar concentrations (14). This is a desirable situation for both the hepatocytes and the β-cells. The rate of glucose transport into hepatocytes will thus increase when portal blood sugar rises in the postprandial state, ensuring that transport does not limit the net uptake and storage of excess glucose (14).

β-Cells are essentially glucose homeostats that are designed to react to changes in blood glucose by varying their rates of insulin biosynthesis and secretion. A high-Km transporter in this cell-type ensures accurate sensing of blood glucose levels (20, 133). Interestingly, in rat islets, Glut 2 is concentrated in those regions of the β-cell membrane that face other endocrine cells rather than membrane surfaces that face blood capillaries (134). The functional significance of this is not known, but perhaps Glut 2 is involved in the transcellular flux of glucose through β-cells, directing it to regions distal to blood capillaries.

Abnormal States. Diabetes mellitus. Streptozotocin-induced diabetes results in an increase in liver Glut 2 mRNA levels in the rat (135, 136). Conversely, underexpression of Glut 2 was reported in pancreatic islets of the Zucker diabetic fatty rat compared to its lean littermates (137). It was proposed that the decrease in islet Glut 2 is responsible for the diminished glucose-stimulated insulin secretion observed in these animals. Similarly, in the case of new onset autoimmune diabetes mellitus in the BB/Wor rat, a reduction in Glut 2 expression paralleled the loss of glucose-stimulated insulin secretion that usually precedes profound β-cell depletion (138). However, unlike the situation in adipocytes and skeletal muscle, transport is not rate-limiting for islet or liver glucose metabolism (14, 133) and, thus, the functional consequences of these changes, if any, is not known.

In distinct contrast to the state of diabetes, prolonged hyperglycemia alone in the presence of a normal pancreas results in an increase in the rat β-cell Glut 2 mRNA by 46%, along with an increase in proinsulin expression (139). Thus, under different conditions, β-cell Glut 2 expression seems to parallel insulin secretory function. However, it is unclear, at present, whether

this correlation represents any type of cause-and-effect relationship between these two parameters.

The serum of insulin-dependent diabetic human subjects has been reported to contain an IgG directed against β-cell Glut 2 (140). Although a controversial finding, this IgG reportedly inhibits glucose transport into rat β-cells and, thereby, impairs glucose-stimulated insulin secretion.

Starvation. Perivenous hepatocytes in normal rat liver express Glut 1, whereas the remaining hepatocytes express primarily the Glut 2 isoform (131). During starvation, a 3- to 4-fold increase in the expression of Glut 1 was observed in these cells. The increase correlated with the expression of Glut 1 in an increased number of hepatocytes. The increased expression of Glut 1 was reversed after glucose refeeding (131). Similar experiments examining Glut 2 expression showed that 2 d of fasting decreases Glut 2 mRNA by 45% and 24-h refeeding increases Glut 2 mRNA levels 5-fold. Starvation did not affect the level of Glut 2 protein in liver; however, refeeding increased the level of Glut 2 protein 75% above the prestarvation control level (136).

Hypoglycemia. The effect of insulin-induced hypoglycemia on glucose transporter gene expression has been studied in both the liver and pancreas (139). Although a significant reduction in Glut 2 mRNA in pancreatic islet β-cells was observed along with a decrease in proinsulin mRNA, a relatively slight reduction occurs in liver Glut 2 mRNA. These results are consistent with an adaptive response in which hypoglycemia results in a diminished pancreatic secretion of insulin, but not necessarily a diminished output of hepatic glucose. However, the actual physiologic consequences of these changes in Glut 2 expression are not known.

Normal Development. Glut 1 appears to be the predominant glucose transporter isoform expressed in fetal liver (120, 121). Although specific studies determining the presence of Glut 2 in fetal liver have not been reported, D-glucose-inhibitable cytochalasin B binding has been studied in rabbit liver. Fetal liver possesses fewer low-affinity (Glut 2) (141) sites compared to that of the adult (142). These findings along with reports on the abundance of Glut 1 in fetal liver (120, 121), suggest that Glut 2 is expressed in negligible amounts at this stage. The neonatal period is a transitional stage during which the newborn begins to rely on endogenous production of glucose via glycogenolysis (143) and gluconeogenesis in the liver (144). In the neonate, liver Glut 1 expression is low, mimicking the adult levels (121), and Glut 2 levels are intermediate between the fetal and adult concentrations (141). The expression of glucose transporter isoforms in β-cells during ontogeny has not been reported.

Genetics. The detection of restriction fragment length polymorphisms in the human Glut 2 gene has led to genetic linkage studies involving NIDDM populations. Three highly polymorphic sites were identified within the Glut 2 gene, one of which (*EcoRI-Hae*III) appeared to be due to an insertion and/or deletion of 200 bp of DNA (130). Significant linkage disequilibrium between these sites over ~30 kb of genomic DNA suggested that these polymorphisms could be in linkage disequilibrium with mutations at this locus, if they existed. The frequencies of these polymorphisms did not differ between diabetics and controls. Therefore, it appears that mutations at this locus may not contribute in a major way to the genetic susceptibility to NIDDM observed in Afro-Americans (130). Once again, however, the power of these studies is not sufficient to eliminate this locus as a contributor to the NIDDM phenotype in a subpopulation of diabetics.

KIDNEY AND SMALL INTESTINE

Isoform distribution. A property shared by the kidney, small intestine, and liver is that the net release of glucose from these tissues into the blood can occur under appropriate metabolic situations (14). Although the liver is the principle supplier of blood glucose during short fasts, the kidney can also become a

net producer of blood glucose during prolonged starvation (145). During the postprandial phase, the small intestine catalyzes the transepithelial flux of glucose into the bloodstream. The initial step of lumen to intracellular transport is accomplished by the sodium-glucose cotransporter that is situated on the lumenal surface of brush border cells of the proximal tubule of the kidney (7–11) and the enterocytes lining the intestinal microvilli (3–6). The second step of transepithelial transport involves the high Km Glut 2 that is localized to the basolateral membrane of the epithelial cells lining the renal tubules and intestinal microvilli (146, 147). Glut 2 is involved in the net release of glucose into the blood during absorption of renal and intestinal glucose, ensuring that the glucose flux across these absorptive cells changes in a near-linear fashion with the intracellular glucose concentrations.

Glut 5 is expressed at high levels in the jejunum, but little is known concerning its function (26). Localization of this isoform to the apical or basolateral surface of specific cell types will facilitate the elucidation of its function. It is tempting to speculate that this isoform may be involved in the transepithelial flux of sugar substrates other than glucose.

Regulation. Few studies are available concerning the regulation of renal and intestinal glucose transporters. Glucose deprivation induces a selective accumulation of Glut 1 protein in the plasma membrane of cultured normal rat kidney cells, thereby increasing glucose transport (148). Streptozotocin-induced diabetes increases the activity of the sodium-glucose cotransporter in rat small intestine by increasing transporter number (149). Insulin therapy normalizes this change, whereas starvation-induced normoglycemia fails to have an effect on the diabetes-induced effect (149).

Normal development and cellular differentiation. The sodium-glucose cotransporter is present at lower abundance in fetal than in adult kidney (150). The glucose transporter system in the intestinal enterocyte is a marker for enterocyte maturity, developing in the fully differentiated cells present only at the tip of the microvillus (3). Developmental regulation of Glut 2 and Glut 5 in the kidney and small intestine has not been reported.

Genetics. The identification of an *EcoRI* restriction fragment-length polymorphism within the human sodium-glucose cotransporter gene should facilitate studies investigating the involvement of this sodium-glucose cotransporter in genetic disorders, such as benign renal glycosuria and the glucose-galactose malabsorption syndrome (12, 13). Recent studies involving sequence analysis of polymerase chain reaction-amplified sodium-glucose cotransporter cDNA and genomic DNA obtained from members of a family affected with the autosomal recessive glucose-galactose malabsorption syndrome revealed a single missense mutation in the sodium-glucose cotransporter gene. This mutation cosegregates with the glucose-galactose malabsorption phenotype and results in complete loss of sodium-dependent glucose transport in *Xenopus* oocytes injected with the mutant mRNA (151).

BRAIN

Isoform distribution. Glucose is an essential substrate for oxidative metabolism in brain (152). Circulating glucose crosses the blood-brain barrier and enters brain parenchymal cells via facilitative transport. The adult mammalian brain expresses Glut 1 and Glut 3 (16, 21). The other facilitative glucose transporters appear to be absent from adult human cerebrum (18, 22–26).

In rat and human adult brain sections, Glut 1 is predominantly localized to the brain microvasculature (153–156). Electron microscopic examination revealed ~40% of Glut 1 on the ablumenal surface of the endothelial cells, with another 40% in the cellular cytoplasm and 10% on the lumenal surface (157). A report on the adult rat brain microvasculature suggested that nearly all D-glucose inhibitable cytochalasin B binding sites corresponded to Glut 1 (158). Thus, it appears that in adult rat brain, Glut 3 is not localized to the microvasculature but to brain

parenchymal cells (158). Glut 1 and 3 are both expressed in cultured rabbit neonatal glial cells (Figs. 2 and 3) (159). Cultured neonatal neurons, on the other hand, which exhibit a relatively high glucose requirement (160–162), express very low levels of the Glut 1 isoform and no detectable Glut 3 (Figs. 3 and 4) (159). This suggests the possibility of an as yet unidentified neuronal type of glucose transporter during the newborn period. However, inasmuch as cross-species probes were used in these studies, it is possible that the expression of some rabbit glucose transporter isoforms went undetected. Whether a similar cellular distribution of glucose transporter isoforms exists in the adult brain is not known.

Regulatory studies. Hypoglycemia increases and hyperglycemia decreases glucose uptake into adult rat brain (163, 164). These changes appear to be due to alterations in Glut 1 gene expression. Streptozotocin-induced hyperglycemia increases Glut 1 mRNA (165) while down-regulating the transporter protein (166) in adult rat brain microvessels. Conversely, insulin-induced hypoglycemia increases Glut 1 protein levels in whole rat brain (167). Thus, there appears to be an inverse correlation between blood glucose levels and the expression of Glut 1 in brain microvessels. This may be a compensatory response to
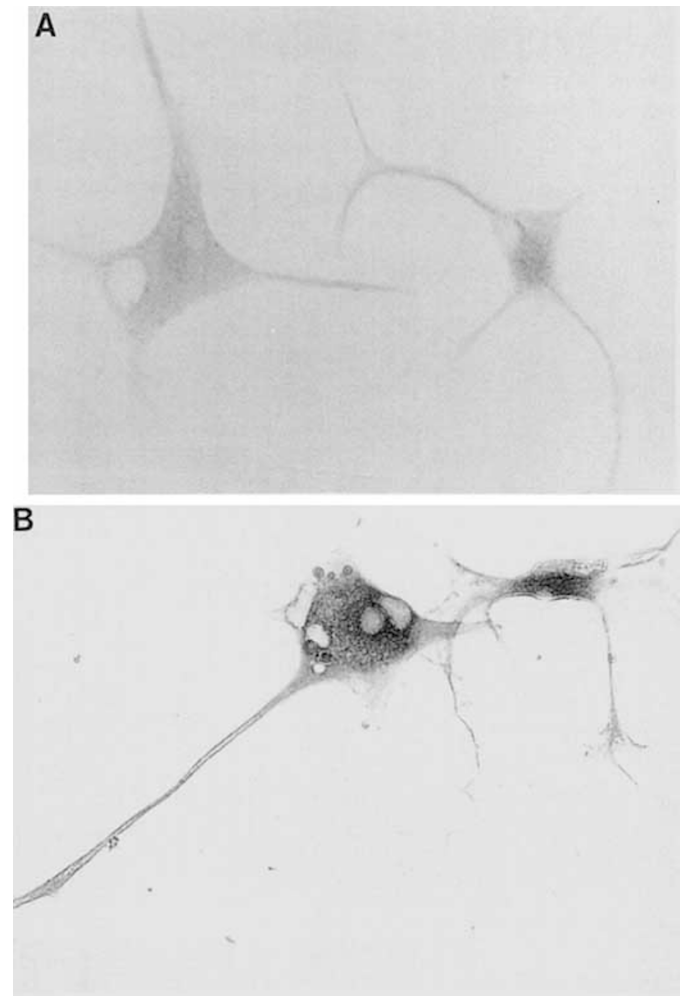

Fig. 2. Immunohistochemistry of rabbit glial cell cultures. *A*, Control treated with a 1:500 dilution of normal rabbit serum/preimmune serum (×400 magnification) demonstrating control staining with 3′,3′-diaminobenzadine. *B*, A 1:500 dilution of the anti-rat brain glucose transporter antibody (Ref. 22) (×400 magnification) demonstrating the perinuclear cytoplasmic and plasma membrane distribution of the glucose transporter immunoreactivity (Ref. 159). (Reproduced with permission from Williams & Wilkins, Baltimore, MD, and Plenum Press, New York, NY.)
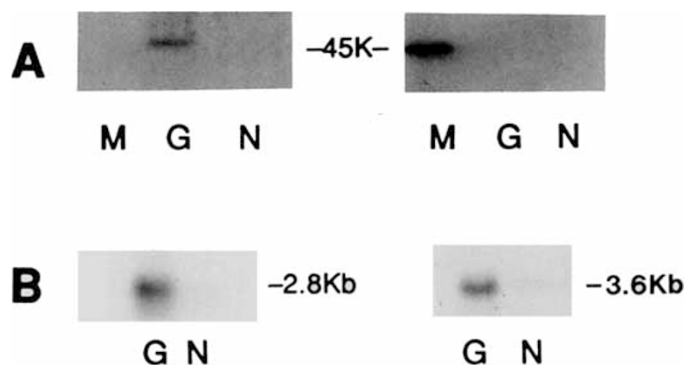
Fig. 3. Autoradiographs of Western blots demonstrating the Glut 1 (*left panel*) and Glut 4 (*right panel*) proteins (~45 kD) in muscle (*M*), glia (*G*), and neurons (*N*). *B*, Autoradiographs of Northern blots demonstrating the Glut 1 (~2.8 kb; *left panel*) and Glut 3 (~3.6 kb; *right panel*) mRNA in glia (*G*) and neurons (*N*) (Ref. 159). (Reproduced with permission from Williams & Wilkins, Baltimore, MD.)

ensure that transport of glucose across the blood-brain barrier does not become rate-limiting for glucose utilization in brain cells during a prolonged decrease in blood glucose levels. Consistent with this hypothesis, in cultured glial cells, Glut 1 protein and mRNA vary inversely with the level of glucose in the medium, *i.e.* high glucose suppresses Glut 1 expression and glucose starvation increases expression (168). This is similar to the effect of glucose availability on transporter gene expression in 3T3L1 adipocytes (52) and L6 myoblasts (53). The mechanism of the glucose-mediated alterations in glucose transporter gene expression is not known.

Insulin and IGF-I increase glucose transport in isolated glial cells by increasing expression of the Glut 1 gene (169). IGF-I appears to increase Glut 1 expression and glucose uptake only in neonatal rat glial cells, with no such effect in adult cells despite the greater abundance of IGF-I receptors (170).

Normal development. The Glut 1 transporter is developmentally regulated in rat and rabbit brain (121, 159, 171). Its expression is highest in adult brain, followed by fetal and neonatal brain, respectively. This finding is consistent with the observation that glucose transport in adult brain is higher than that in neonatal rat brain (172, 173). Detailed examination of Glut 1 protein in fetal rat brain revealed a 55-kD species along with the 45-kD adult form (120). This size difference reportedly cannot be explained by differential glycosylation alone (120). An examination of isolated microvessels from rat brain demonstrated a gradual increase in total glucose transporters, composed mainly of Glut 1, from the fetal to the adult stage of development (174). Glut 1, which is primarily expressed in brain vasculature at most stages of development, is preferentially expressed in brain parenchymal cells during the neonatal phase of brain development (174). Only Glut 1 and Glut 3 appear to be expressed in the rabbit CNS (159). The ontogenic expression of Glut 3 in rabbit brain follows a reciprocal pattern to that of Glut 1. The lowest expression is found in the fetal brain, followed progressively by the adult and late neonatal stages (159).

LUNG

Glucose is an important metabolic substrate in the lung (175). An intricate relationship has been suggested between lung glucose-glycogen metabolism and surfactant phospholipid synthesis (176-178). Circulating glucose enters lung epithelial cells and contributes to pulmonary glycogen (179, 180) and, thereby, the glycerol backbone of disaturated phosphatidylcholine (178, 181). High circulating glucose results in a derangement of lung phosphatidylcholine synthesis and flux (182), thus causing the clinical syndrome of respiratory distress (183).

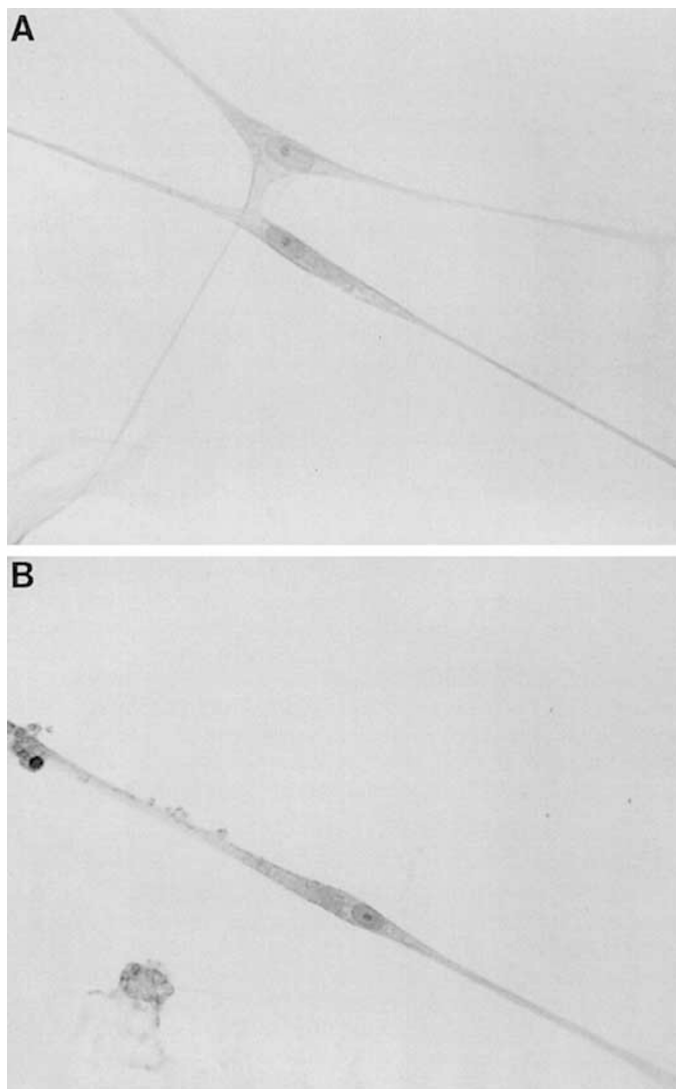Studies defining the glucose transport system in lung are

Fig. 4. Immunohistochemistry of rabbit neuronal cell cultures. *A*, Control cultures were treated with a 1:500 dilution of a normal rabbit serum/preimmune serum (×400), and the cells were counterstained with hematoxylin. *B*, A 1:500 dilution of the anti-rat brain glucose transporter antibody demonstrating a rather slight immunoreactivity (above control staining) within the cytoplasm (×400) (Ref. 159). (Reproduced with permission from Williams & Wilkins, Baltimore, MD.)

limited. Glucose within the alveolar lumen is absorbed by the alveolar epithelial cells via a saturable mechanism that is linked to sodium transport (184, 185). In confirmation of these observations, the sodium-glucose cotransporter system has been detected in adult rat alveolar cells (186). Thus, in the adult, the sodium-glucose cotransporter may play a role in removing solutes and water from the alveolar spaces (185), but in the fetus its role appears to be insignificant (187). On the other hand, the system involved in transporting glucose from the bloodstream into the alveolar cells is unknown. The presence of a facilitative glucose transport system was detected in adult rat lung type II alveolar epithelial cells maintained *in vitro* (188). Glut 1 mRNA is abundantly expressed in fetal lung when compared with that of the newborn and adult (121). In mouse lung sections, Glut 1 protein appears to be expressed in fetal red cells, accounting for the greater fetal lung Glut 1 expression, with the alveolar epithelium being distinctly negative (123). In adult mouse lung, Glut 1 is not expressed by either the adult red cells trapped in lung tissue or the alveolar epithelial cells, but is abundant in Schwann cells that form the perineural sheath (123). Thus, the major

alveolar epithelial cell facilitative transport system remains to be defined.

PLACENTA

Glucose transport across the placenta is an insulin-independent facilitative diffusion process (189, 190). A number of studies have been reported on glucose transport in normal placenta (191). Further, it has been determined that Glut 1 and Glut 3 are the predominant placental isoforms (13, 21). Glut 1 is mainly localized to the ectoplacental fenestrated epithelial cells lining the maternal vascular spaces and serving as a materno-fetal barrier (192).

A decrease in the fractional clearance of 3-O-methyl glucose across the placenta was observed in the streptozotocin-induced diabetic pregnant rat model, indicating a decrease in materno-fetal transfer of glucose (193). Although other studies have examined the effect of maternal diabetes on placental glycogen metabolism (194, 195), there are no studies, to date, describing the placental transport system in a diabetic state.

Intrauterine growth retardation does not affect glucose transport across the placenta in the guinea pig (196) or alter placental glucose utilization in the rat (197). Insulin-induced hypoglycemia in rats also does not change glucose uptake by the placenta (198). Therefore, in the absence of specific studies examining the regulation of placental glucose transporters, it appears that there may be no long-term change in placental glucose transporters as the result of a hypoglycemic insult.

GROWTH AND REGENERATION IN MISCELLANEOUS TISSUES

Various malignant states are associated with an increased expression of Glut 1 or Glut 3 (199, 200). Liver regeneration, as the result of partial hepatectomy, results in a 2- to 3-fold increase in Glut 2 expression in hepatocytes (201). These observations suggest that normal and abnormal cellular growth result in an increased expression of glucose transporters to increase the supply of glucose for growing and dividing cells. In support of this hypothesis, experiments undertaken *in vitro* have demonstrated that cells transformed by certain oncogenes (*src* and *ras*) (202, 203) and growth factors, such as fibroblast growth factor, epidermal growth factor, platelet-derived growth factor (119), insulin, and insulin-like growth factors (54, 169), enhance the expression of Glut 1 and, thereby, increase cellular glucose uptake. Although the intracellular signaling pathway between insulin/IGF-I and the Glut 1 transporter is unknown, in L6 myocytes both of these factors increase Glut 1 transcription and mRNA stability (54).

Phorbol esters increase Glut 1 expression in some cultured cells by activation of protein kinase C (204). Additionally, in nonregenerating cells, phorbol esters phosphorylate Glut 1 and, thereby, covalently modify the protein rather than alter its expression (205). However, the phosphorylation of Glut 1 by phorbol esters is substoichiometric and has no known functional significance.

Tumor necrosis factor, a pluripotent endotoxin-induced macrophage secretory protein, is cytotoxic or cytostatic to many tumor cells. This monokine, however, increases the growth of nontransformed cells. Coordinate with tumor necrosis factor α-induced mitogenesis of 3T3L1 fibroblasts is the transcriptional induction of immediate early protooncogenes that are involved in the regulation of the cell cycle. Glucose transport increases as the result of translocation of Glut 1 to the cell surface, an apparent change in the glucose transporter intrinsic activity, and an increase in Glut 1 mRNA due to an increase in its stability. Glut 4 is unaffected by tumor necrosis factor-α (206).

As a whole, these data indicate that mitogenesis, in general, is associated with an induction of Glut 1 expression, resulting in increased glucose transport.

SUMMARY

We have described the properties of glucose transporters expressed in several mammalian tissues and have summarized some of the adaptations that take place involving these molecules in various normal and abnormal states. With the exception of a few cell types, such as adipocytes and skeletal muscle, glucose transport is not a rate-limiting step in cellular glucose metabolism, and other substrates may be equally important for cellular metabolism. Nevertheless, an understanding of the mechanisms behind the regulation of glucose transport in individual tissues may facilitate an understanding of *in vivo* glucose utilization and clearance processes as they relate to normal and disease states. Although adult studies provide an impetus toward a mechanistic approach in preventing and treating various disease states involving derangements in glucose homeostasis, there remains a need for similar studies in the fetus and newborn. These developmental studies should help unravel the fetal/neonatal responses to normal and abnormal hormonal and substrate milieu.

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