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Review

Facilitative glucose transporters

Mike MUECKLER

Department of Cell Biology and Physiology, Washington University School of Medicine, St Louis MO, USA

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Facilitative glucose transport is mediated by members of the Glut protein family that belong to a much larger superfamily of 12 transmembrane segment transporters. Six members of the Glut family have been described thus far. These proteins are expressed in a tissue- and cell-specific manner and exhibit distinct kinetic and regulatory properties that reflect their specific functional roles. Glut1 is a widely expressed isoform that provides many cells with their basal glucose requirement. It also plays a special role in transporting glucose across epithelial and endothelial barrier tissues. Glut2 is a high-K_m isoform expressed in hepatocytes, pancreatic β cells, and the basolateral membranes of intestinal and renal epithelial cells. It acts as a high-capacity transport system to allow the uninhibited (non-rate-limiting) flux of glucose into or out of these cell types. Glut3 is a low-K_m isoform responsible for glucose uptake into neurons. Glut4 is expressed exclusively in the insulin-sensitive tissues, fat and muscle. It is responsible for increased glucose disposal in these tissues in the postprandial state and is important in whole-body glucose homeostasis. Glut5 is a fructose transporter that is abundant in spermatozoa and the apical membrane of intestinal cells. Glut7 is the transporter present in the endoplasmic reticulum membrane that allows the flux of free glucose out of the lumen of this organelle after the action of glucose-6-phosphatase on glucose 6-phosphate. This review summarizes recent advances concerning the structure, function, and regulation of the Glut proteins.

The ability to transport glucose across the plasma membrane is a feature common to nearly all cells, from the simple bacterium to the highly specialized mammalian neuron. Glucose is required by many cells for oxidative and nonoxidative ATP production and for anabolic reactions that produce various sugar-containing macromolecules (Newsholme and Leech, 1985). Many lower organisms can survive on glucose as their sole carbon source. The ubiquitous use of glucose as the common currency of metabolism is undoubtedly linked to the extreme abundance in nature of glucose units in the form of cellulose and starch, synthesized from the glucose produced by the dark reactions of photosynthesis. Perhaps uniquely, most of the major categories of membrane transport systems have members involved in the transport of glucose. There are examples in bacteria of proton symporters, substrate-binding transporters, and group translocation systems all of which transport glucose, whereas mammalian cells employ Na^+-dependent cotransporters and the simple facilitative uniporters. The latter are the subject of this review.

The facilitative glucose transporters (for recent reviews, see Bell et al., 1990; Gould and Bell, 1990; Mueckler, 1990, 1992; Burant et al., 1991; Devaskar and Mueckler, 1992; Lienhard et al., 1992) are probably the most thoroughly studied of the facilitated diffusion transport systems, which are often called passive carriers. A passive carrier is an energy-independent system that can only transport its substrate down a concentration gradient. A passive transport system is most effective when the cell is exposed to a fairly constant level of the carrier substrate. Conservation of energy is gained at the expense of transport efficiency and flexibility. Thus, passive carriers are largely restricted to multicellular organisms that regulate the composition of their internal medium. The primary function of the facilitative glucose carriers is to mediate the exchange of glucose between the blood and the cytoplasm of the cell. This may involve a net uptake or output of glucose from the cell, depending on the type of cell in question, its metabolic state, and the metabolic state of the organism. For example, most mammalian cells lack significant levels of glucose-6-phosphatase and are therefore incapable of producing free glucose. These cells are only involved in the net uptake and metabolism of blood glucose. The hepatocyte, on the other hand, becomes a net producer of blood glucose in the post-absorptive state. Glycogenolysis and gluconeogenesis combine to increase intracellular free glucose above its concentration in the blood, resulting in net efflux of glucose from the cell. This, of course, is the major mechanism by which higher organisms provide the brain and other glucose-dependent tissues with sugar during the periods in-between food intake. Conversely, in the postprandial state the hepatocyte takes up blood glucose and uses it to replenish its store of glycogen, thus completing the cycle.

The facilitative glucose transporters essentially form selective pathways between three major pools of glucose, i.e. the blood, the extracellular fluids, and the cellular cytoplasm.

Correspondence to M. Mueckler, Department of Cell Biology and Physiology, Washington University School of Medicine, 660 S. Euclid Ave., St Louis, MO 63110, USA

Abbreviations. NIDDM, non-insulin-dependent diabetes mellitus; CHO, Chinese hamster ovary (but CHO = carbohydrate in Fig. 2).

Table 1. Mammalian glucose transporters.

Name	Tissue distribution	Proposed function
Sglt1	kidney, intestine	Na^+-dependent active transport; concentration across apical epithelial membranes
Glut1	many fetal and adult tissues; abundant in human red cells, endothelia, and many immortalized cell lines	basal glucose and increased supply for growing/dividing cells; transport across blood brain barrier and other barrier tissues
Glut2	hepatocytes, pancreatic β-cells, intestine, kidney	high-capacity low-affinity transport; transepithelial transport (basolateral membrane)
Glut3	widely distributed in human tissues; restricted to brain in other species	basal transport in many human cells; uptake from cerebral fluid into brain parenchymal cells
Glut4	skeletal muscle, heart, adipocytes	rapid increase in transport in response to elevated blood insulin; important in whole-body glucose disposal
Glut5	intestine (jejunum), lesser amounts in adipose, muscle, brain, and kidney tissues	intestinal absorption of fructose and other (?) hexoses
Glut7	hepatocytes and other (?) gluconeogenic tissues	mediates flux across endoplasmic reticulum membrane

Theoretically, the appropriate distribution of whole-body glucose could be controlled by the tissue-specific expression and regulation of several glucose transporter isoforms with distinct kinetic properties. This scenario appears to account at least in part for the mechanism by which glucose is properly distributed among the various cells and tissues of the body under different metabolic conditions.

This review will focus on the properties of the mammalian facilitative glucose carriers that account for their tissue-specific expression and function. Over 1000 papers have been published on glucose transport in the past five years. I apologize to my colleagues whose work is not cited in the context of this brief review.

The facilitative glucose transporter family

Six mammalian glucose transporter isoforms have been identified thus far. The human genes encoding these proteins are named *GLUT1–5* and *GLUT7*. *GLUT6* is a pseudogene that is not expressed at the protein level (Kayano et al., 1990). The corresponding proteins will be designated using the lower case Roman type, i.e. Glut1, Glut2, etc. Some major features of the Glut proteins are summarized in Table 1 and are discussed in more detail below. Three general characteristics are worth emphasizing. First, all six of these proteins have been shown to transport glucose using heterologous expression systems. However, they transport glucose and other hexoses with different efficiencies and kinetics. Glut5, for example, appears to be a fructose transporter and may not be involved in the physiological transport of glucose (Burant et al., 1992). Second, the isoforms exhibit a tissue-specific distribution and a single cell-type often expresses two or more different isoforms. Third, the expression of most of the *GLUT* genes is developmentally regulated and in adult tissues at least three of the genes (*GLUT1*, *GLUT2* and *GLUT4*) are known to be subject to regulation by a number of endogenous and xenobiotic factors.

Human Glut1–5 exhibit 39–65% sequence identity and 50–76% sequence similarity in pairwise comparisons (Bell et al., 1990). The sequence of human Glut7 has not yet been reported. Simultaneous comparison of all five isoforms reveals 26% sequence identity and an additional 13% similarity resulting from conservative amino acid differences (see Fig. 1). The individual isoforms vary somewhat in their degree of conservation across species. Glut1 appears to be the most highly conserved isoform. Human Glut1 exhibits $\approx$ 97–98% sequence identity with the analogous rat, mouse, rabbit and pig proteins. Human Glut2, on the other hand, is only $\approx$ 82% identical in sequence to its rat and mouse counterparts, a value that is perhaps more typical for this phylogenetic distance. The high degree of sequence conservation for Glut1 suggests a structurally frugal protein with few non-essential amino acid residues.

The 12 transmembrane segment transporter superfamily

The mammalian *GLUT* genes belong to a large superfamily of genes whose protein products are involved in the transport of a variety of hexoses and other carbon compounds (Marger and Saier, 1993). The members of this superfamily include numerous bacterial sugar-proton symporters, bacterial transporters of carboxylic acids and antibiotics, sugar transporters in various types of yeast and the protozoan parasite, Leishmania, and an energy-dependent glucose transporter in the higher plant, *Arabidosis thaliana*. New members of this superfamily are being reported on a regular basis. Many have been demonstrated to be involved in transport activity by appropriate expression studies, whereas functionality remains to be established for some members of this superfamily.

The most characteristic feature of these proteins is the presence of 12 transmembrane segments as predicted by hydrophathic analysis. Sequence similarity between pairs of family members can be very weak. Maiden et al. (1987) uncovered the presence of a pentameric motif (RXGRR, where X is any amino acid) shared by many members of the sugar transporter superfamily. This motif is present in the cytoplasmic loops connecting predicted transmembrane segments 2 with 3 and 8 with 9. The presence of this motif at symmetric positions in both halves of the transporter molecule suggests that these proteins are descended from a common ancestor comprised of six transmembrane segments whose gene underwent a duplication event. This pentameric motif places the *lac* permease in the 12-transmembrane-segment transporter superfamily, despite the complete absence of any other discernible primary structural similarity with other members of the superfamily.

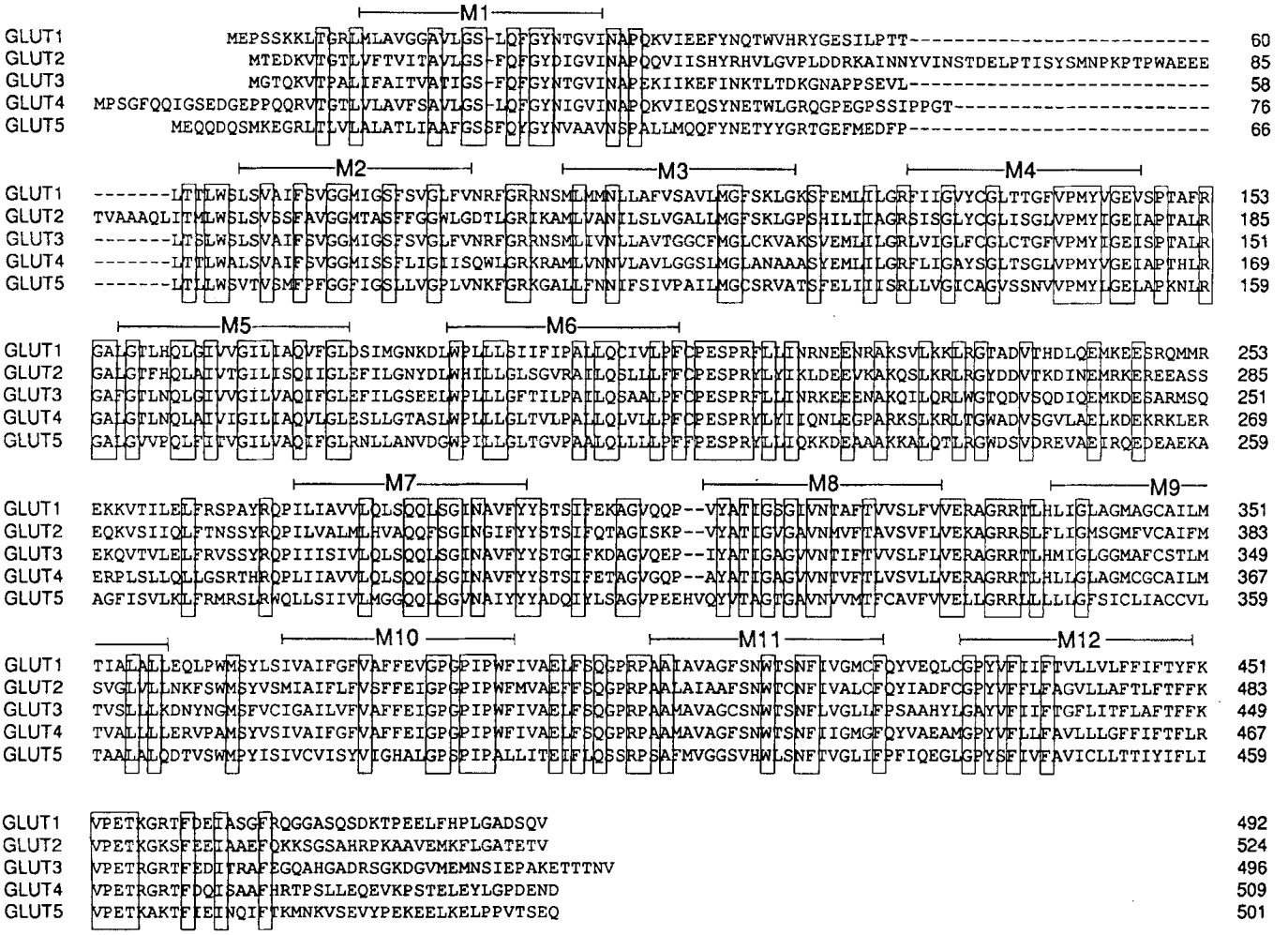

Fig. 1. Alignment of human Glut1–5 deduced protein sequences. Residues that are identical among all five isoforms are boxed. The 12 predicted transmembrane segments are designated M1–M12. Gaps have been introduced to optimize the alignment. Adapted from Kayano et al. (1990).

Interestingly, the mammalian Na^+-glucose cotransporter, also predicted to be a 12-transmembrane-segment protein, bears no other resemblance to members of the superfamily (Hediger et al., 1989). If indeed this protein shares a common ancestor with this superfamily, it is curious that the mammalian facilitative glucose transporters display greater sequence similarity with the bacterial sugar-proton cotransporters than does the mammalian Na^+-glucose cotransporter. Perhaps the common characteristic of 12 transmembrane segments represents functional convergence. The Na^+-glucose cotransporter appears to be the prototype member of a separate superfamily of membrane transporters that includes a number of other sodium symport proteins, including a mammalian nucleoside cotransporter, bacterial cotransporters for proline and pantothenate, and mammalian sodium–amino-acid cotransporters (Pajor and Wright, 1992).

Glut1

Structure

This isoform is also called the erythrocyte, brain, or HepG2-type glucose transporter. The kinetics of glucose transport via Glut1 have been studied for over four decades, principally in the human red cell (Widdas, 1988). Widdas (1952) first proposed a saturable carrier mechanism for placental glucose transport. He used a simplified application of the Michaelis-Menton equation to correctly predict some of the kinetic properties of sugar transport in erythrocytes and other cell types. However, controversy exists to this day as to whether any type of simple carrier mechanism can account for the detailed kinetics of glucose transport via Glut1 in the human red cell. Some investigators believe that more complex models are required to fit the available data (Carruthers, 1990; Carruthers and Helgerson, 1991), whereas others believe that experimental error and other factors can account for discrepancies between kinetic data and the predictions of the carrier model (Wheeler and Hinkle, 1985; Wheeler and Whelan, 1988; Lowe and Walmsley, 1989).

The biochemical era for the study of glucose transport began in 1977 when Kasahara and Hinkle (1977) purified Glut1 from human erythrocyte membranes. This purification was possible because Glut1 comprises 5% of the total red cell membrane, by far the highest concentration density for any glucose transporter. Erythrocyte Glut1 remains the only glucose transporter isoform that has been purified from its native cell type. The purified transporter is a highly hydrophobic, heterogeneously glycosylated protein that exhibits

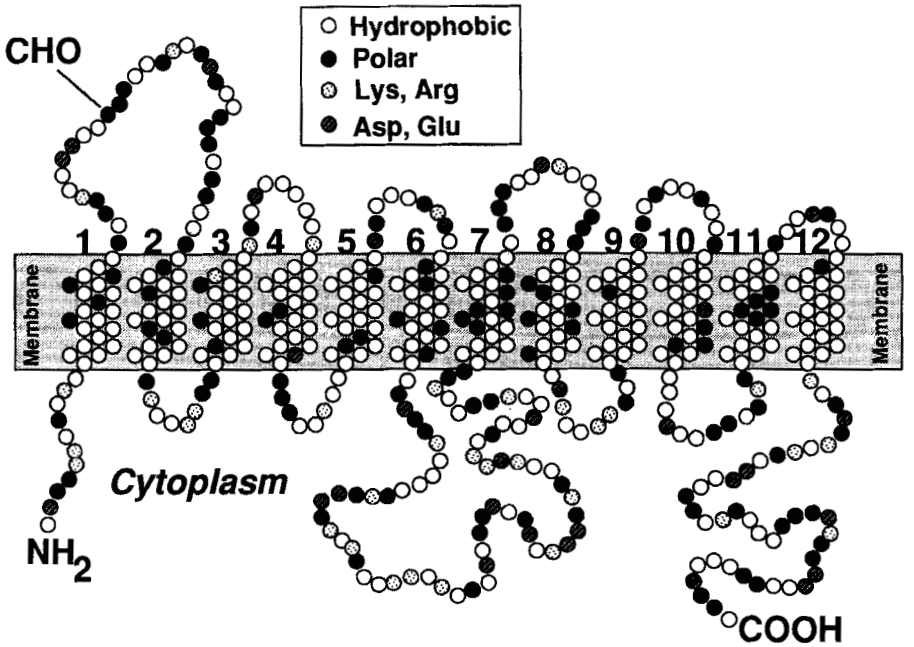

Fig. 2. Predicted topology of Glut1. The 12 predicted transmembrane helices are numbered 1−12. The single N-linked oligosaccharide is designated by CHO.

kinetic properties similar to those observed for glucose transport in the intact red cell (Wheeler and Hinkle, 1981). Preparation of antibodies against the purified red cell transporter facilitated the expression cloning of Glut1 from human HepG2 cells (Mueckler et al., 1985) and rat brain (Birnbaum et al., 1986). The identity of the human clone was verified by fast-atom-bombardment mapping of the purified erythrocyte transporter and the sequencing of tryptic peptides derived from the purified protein. Glut1 cDNA clones have been functionally expressed in *Xenopus* oocytes (Gould and Lienhard, 1989; Keller et al., 1989; Gould et al., 1991; Burant and Bell, 1992), CHO cells (Asano et al., 1989; Harrison et al., 1990b; Oka et al., 1990b), 3T3L1 cells (Gould et al., 1989; Harrison et al., 1990a), COS cells (Schürman et al., 1992), Sf9 insect cells (Yi et al., 1992) and transgenic mice (Marshall et al., 1993a; Ren et al., 1993b).

The 12-transmembrane-segment model (see Fig. 2) originally proposed for Glut1 was based primarily on hydrophathic analysis of the deduced amino acid sequence (Mueckler et al., 1985). This topological model remains unverified but a few details of the model have been confirmed. Baldwin and colleagues have established the cytoplasmic disposition of the carboxyl terminus and the central hydrophilic loop by protease digestion experiments and the use of site-specific antibodies (Cairns et al., 1987; Davies et al., 1987). The results of site-directed mutagenesis experiments involving residue Cys429 are consistent with the predicted exoplasmic distribution of the hydrophilic loop containing this residue (Wellner et al., 1992). Circular dichroic studies on the purified red cell transporter indicate an 82% α-helical content, a finding consistent with the predicted 12-α-helical transmembrane-segment model (Chin et al., 1987).

Little is known about the three-dimensional structure of the transporter. Detailed structural data will require the generation of high-quality protein crystals, a feat that has been achieved for very few membrane proteins. As shown in Fig. 3, our original simplistic suggestion was that several amphipathic helices cluster together in the membrane to form

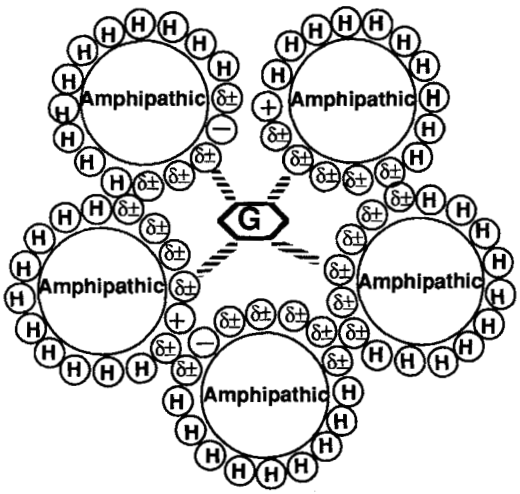

Fig. 3. Hypothetical aqueous tunnel formed by the clustering of at least five amphipathic transmembrane helices. A simplified model for the tertiary structure of the glucose transporter. Hydrophobic amino acid side chains are denoted by H. Polar side chains with the indicated charges are given by +, −, and $\delta\pm$. A glucose molecule is proposed to hydrogen-bond to polar amino acid side chains comprising the wall of the aqueous channel. The helices shown are for illustrative purposes only and do not represent the composition of helices proposed for Glut1. Actual transmembrane helices are likely to be at least 20 residues in length.

the walls of a barrel-like structure containing an aqueous pore (Mueckler et al., 1985). Hydroxyl and amide-containing amino acid side chains could provide hydrogen-bonding sites for sugar substrates. The general kinetic properties of membrane transporters suggest that the 'pore' cannot represent a continuous pathway for substrate across the lipid bilayer, rather substrate passage must be blocked at one end at any instant in time (Stein, 1986). This is the basic assumption of the alternating conformation model for glucose transport

which states that loaded or unloaded substrate binding sites (or a single site) are alternately exposed at one face of the membrane or the other as the molecule undergoes thermally induced conformational changes.

Clustered helices in the transporter could be of an intra- or inter-molecular nature, the latter necessitating an oligomeric structure. There is convincing evidence that detergent-solubilized Glut1 exists in dimeric and tetrameric forms (Pessino et al., 1991; Hebert and Carruthers, 1992). However, it is very difficult to prove that these oligomeric forms exist *in situ*. Additionally, expression studies in *Xenopus* oocytes (Burant and Bell, 1992) and one-transporter/one-vesicle reconstitution studies (Baldwin et al., 1981) suggest that Glut1 functions as a monomer. Perhaps the transporter does exist in an oligomeric state in the membrane, but the oligomerization is important for some aspect of transporter maturation or regulation rather than catalytic activity *per se*.

Most structure/function studies concerning facilitated glucose transport have been conducted on Glut1. Generalizations about important functional regions of Glut1 are not yet possible because this exploration is still in its infancy. However, a few interesting details have appeared in the literature. Tryptophan is the rarest and most highly conserved amino acid residue in soluble proteins and frequently plays an important role in structure and catalytic activity. Of the six tryptophan residues in Glut1, three are conserved in Glut1–5 (Trp65, Trp186 and Trp412) and a fourth (Trp 388) is conserved in four of these five isoforms. Mutations at Trp412 severely impair transporter specific activity in mammalian cells (Katagiri et al., 1991) and *Xenopus* oocytes (Garcia et al., 1992), whereas mutations at Trp388 have a modest affect on specific activity but also inhibit maturation of the transporter to the oocyte plasma membrane. All other Trp mutations tested in these experiments were without effect. A particularly interesting mutation was reported at Gln282 by Hashiramoto et al. (1992): a Gln282→Leu mutation was shown to have minimal affect on transport activity or labeling by cytochalasin B but it did decrease the binding of an exofacial ligand by more than tenfold. This important result clearly shows that substrate binding is not rate-limiting for transport, and it suggests that the inward-facing and outward-facing substrate binding sites may be distinct. Substitution of aspartate for Asn415 reduces activity of Glut1, and inhibitor studies are consistent with the involvement of this residue in forming the inward-facing substrate binding site (Ishihara et al., 1991).

Tissue distribution and physiologic function

Glut1 appears to be the most ubiquitously distributed of the transporter isoforms. It is expressed in many fetal and adult mammalian tissues and cell types, although frequently at low levels and in conjunction with more tissue-restricted glucose transporter isoforms. Glut1 mRNA was detected at every stage of the early mouse embryo, from the oocyte to the blastocyst (Hogan et al., 1991; Aghayan et al., 1992). The pattern of Glut1 expression throughout later stages of development varies considerably, depending on the tissue. However, interpretation of many of these studies is complicated by the expression of Glut1 in erythroid cells present in fetal tissues. In the adult, Glut1 is expressed in the heptatocytes immediately surrounding terminal hepatic venules (Tal et al., 1990). This illustrates one of the specialized roles of Glut1, which is to provide glucose transport in various cells comprising a barrier between a body tissue and the blood supply. Thus, endothelial or epithelial-like barrier cells of the brain, eye, peripheral nerve, and placenta all express relatively high levels of Glut1 (Takata et al., 1990). The best characterized example is the very high expression of Glut1 in the brain capillaries that comprise the blood-brain barrier (Pardridge et al., 1990; Koranyi et al., 1991a). This is an especially important physiological function as brain parenchymal cells are completely dependent on blood glucose as an energy source under normal conditions. An example of the cooperative action of two glucose transporter isoforms occurs in the insulin-sensitive tissues, fat and muscle. In these tissues Glut1 is present constitutively in the plasma membrane, where it presumably provides the low level of glucose required for basal cellular activity (Zorzano et al., 1989; Marette et al., 1992). The tissue-specific Glut4 isoform is present in a special intracellular membrane compartment in the basal state and is recruited to the plasma membrane in response to insulin or other stimuli that signal the need for higher levels of cellular glucose transport. This phenomenon is discussed in more detail below.

Regulation

A large number of studies have been published on the regulation of Glut1. Most of these concern the regulation of Glut1 in cultured cell lines. Glut1 is almost invariably the major glucose transporter isoform expressed in cultured cells. This probably reflects the dedifferentiation or fetalization that most cell lines undergo relative to their cells of origin, coupled with the fact that Glut1 is the major fetal glucose transporter isoform. It may also reflect the observation that Glut1 expression in general is induced by growth stimuli, a consequence of the increased energy and biosynthetic requirements of dividing cells. Glut1 expression has been shown to be altered by phorbol esters (Hiraki et al., 1988), sulfonylureas (Tordjman et al., 1989), vanadate (Mountjoy and Flier, 1990), butyrate (Takano et al., 1988), glucose (Walker et al., 1988, 1989; Tordjman et al., 1990; Wertheimer et al., 1991), hypoxia (Loike et al., 1992), cAMP (Hiraki et al., 1989), thyroid hormone (Weinstein et al., 1990), serum (Hiraki et al., 1988), insulin (Tordjman et al., 1989), insulin-like growth factor-I (Maher et al., 1989), platelet-derived growth factor (Rollins et al., 1988), fibroblast growth factor (Hiraki et al., 1988), tumor necrosis factor α (Stephens et al., 1992), growth hormone (Tai et al., 1990), transforming growth factor-β (Kitagawa et al., 1991), oncogenes (Birnbaum et al., 1987; Flier et al., 1987) and a number of other factors. All of these factors increase Glut1 expression, with the exception of glucose, whose concentration in culture media varies inversely with Glut1 protein and mRNA levels. Most of these studies have simply demonstrated steady-state changes in Glut1 protein or mRNA, although a few have looked at transcriptional effects or apparent effects on intrinsic activity. Surveying the current literature, it appears to be more difficult to find an agent that does not alter Glut1 expression in a cultured cell line than to find one that does.

Far fewer studies have examined the regulation of Glut1 in the whole animal. There is an inverse correlation between Glut1 expression in brain and the level of blood glucose in the rat, consistent with the rate-limiting role of transport across the endothelium for glucose utililization in brain (Koranyi et al., 1991a; Boado and Pardridge, 1993). Thus, a reduction in blood glucose evokes an increase in Glut1, resulting in an increased flux of glucose across the blood brain

barrier. Glut1 expression either increases or appears anew in human tumors (Yamamoto et al., 1990), consistent with the observations in cultured cells described above. Hypothyroidism increases Glut1 protein levels in rat heart (Weinstein and Haber, 1992) and denervation increases the Glut1 content of skeletal muscle (Coderre et al., 1992). At present it is unclear whether the small number of papers dealing with the *in vivo* regulation of Glut1 reflects a relative lack of such regulation or lack of experimental attention.

Glut2

Tissue distribution and physiological function

Glut2 is the major glucose transporter isoform expressed in hepatocytes, pancreatic β cells, and absorptive epithelial cells of the intestinal mucosa and kidney (Fukumoto et al., 1988; Thorens et al., 1988; Thorens, 1992). In the epithelial cells Glut2 is expressed exclusively in the basolateral membrane, where it works in conjunction with the sodium-glucose cotransporter of the apical membrane to facilitate the absorption or reabsorption of glucose from the intestinal lumen or forming urine into the blood (Thorens et al., 1990a, c). The most distinguishing feature of this isoform is that it is a low-affinity high-turnover transport system. The exchange K_m reported for Glut2 expressed in the *Xenopus* oocyte is 42 mM versus 18–21 mM for Glut1 (Gould et al., 1991). The supraphysiological K_m for transport via Glut2 is the key to understanding the functional niche occupied by this isoform. Coupled with the kinetically similar high-K_m hexokinase IV isozyme ('glucokinase') in hepatocytes and β cells, Glut2 forms part of a glucose-sensing apparatus that responds to subtle changes in blood glucose with corresponding alterations in the rate of glucose uptake into the cell (Unger, 1991). This 'sensing' ability is a simple consequence of a coupled transport-phosphorylation system operating within the quasi-linear region of a Michaelis-Menton velocity/substrate concentration curve. Transport capacity via Glut2 is present in vast excess of the glucokinase trapping reaction (German, 1993). Thus, it is the glucokinase reaction that is 'rate-limiting' for glucose uptake in these cells. In the intestine and kidney, the high-capacity low-affinity transport system is probably required to handle the large transepithelial substrate flux that may occur after a high carbohydrate meal.

Glut2 and diabetes mellitus

Glut2 has garnered a great deal of attention as a molecule that could be involved in the pathogenesis of diabetes mellitus. Reductions in β-cell Glut2 have been observed in several animal models of diabetes, including the autoimmune diabetic BB rat (Orci et al., 1990a) and the Zucker diabetic fatty rat (Johnson et al., 1990; Orci et al., 1990b). The reductions in Glut2 in these models is associated with a loss in glucose-stimulated insulin secretion. These were striking observations, from which it was very tempting to conclude that a cause and effect relationship exists between these parameters. However, subsequent experiments argue against a reduction in Glut2 being the cause of reduced β-cell glucose sensitivity in these rodent models. An association between reduced β-cell Glut2 and decreased glucose-stimulated insulin secretion was also noted in the obese, diabetic, db/db mouse (Thorens et al., 1992) and in the streptozotocin-treated rat (Thorens et al., 1990d). However, experiments in which islets from diabetic db/db mice and normal db/+ mice were cross-transplanted under kidney capsules indicated that the loss of β-cell Glut2 was a consequence of the diabetic state rather than a preceding factor (Thorens et al., 1992). Glucose-stimulated insulin release could be restored in perfused pancreas from streptozotocin-treated rats by perfusion in buffer lacking glucose, with no increase in β-cell Glut2 (Chen et al., 1992). Transgenic mice overexpressing a *ras* oncoprotein in β cells also exhibit a dramatic decrease in β-cell Glut2 expression (Tal et al., 1992). However, these mice are euglycemic and their β cells exhibit normal glucose-sensitive insulin secretion. Isolated islets from these transgenic mice displayed normal glucose phosphorylation and oxidation, consistent with the non-rate-limiting role of Glut2 in β-cell glucose metabolism. The predominant role of glucokinase in glucose sensing has been amply demonstrated by the existence of glucokinase mutations in MODY (maturity onset diabetes of the young) diabetes (Froguel et al., 1993; Girth et al., 1993) and experiments in which a yeast hexokinase gene was overexpressed in the β cells of transgenic mice (Epstein et al., 1992). There would appear to be little support at present for a causative role for Glut2 in the pathogenesis of diabetes.

Autoantibodies against Glut2 have been detected in the sera of newly diagnosed type I diabetics (Inman et al., 1993). These antibodies may prove to be useful in the diagnosis of type I diabetes. Additionally, the possible role of the autoimmune reaction involving this transporter isoform in the pathogenesis of type I diabetes needs to be explored.

Regulation

Aside from its down-regulation in the β cells of diabetic rodents, Glut2 expression may be modulated under other conditions. The levels of Glut2 mRNA in β cells was reported to vary directly with blood glucose levels in glucose- or insulin-infused rats (Chen et al., 1990). A similar correlation was observed in rat islets (Yasuda et al., 1992) and HIT-T15 cells (Inagaki et al., 1992) cultured for several days in media containing different glucose concentrations. In all of these studies alterations in Glut2 mRNA were expressed on a per islet basis. However, in a fourth study little if any change in whole pancreatic Glut2 mRNA was observed in fasted hypoglycemic rats, insulin-injected hypoglycemic rats, or dexamethasone-injected hyperinsulinemic (insulin-resistant) rats (Koranyi et al., 1992). In freshly isolated islets, the Glut2 mRNA level was reportedly higher in the two hypoglycemic groups. In this study insulin-injection was correlated with a 39% decrease in islet Glut2 protein, but fasting had no effect on the steady-state level of the protein. The reason for these discrepancies is not apparent and it remains unresolved as to whether and to what extent perturbations in glucose homeostasis *in vivo* actually affect β-cell Glut2 expression.

The effect of altered glucose homeostasis on liver Glut2 expression is also somewhat controversial. Streptozotocin-induced diabetes has been reported to either increase expression of liver Glut2 mRNA and protein (Oka et al., 1990a) or to have little or no effect (Thorens et al., 1990b). However, in the most comprehensive published study, liver Glut2 expression was analyzed at several time points after a single injection of streptozotocin (Burcelin et al., 1992). Glut2 mRNA was dramatically reduced 6 h after streptozotocin administration, remained low until 30 h post-injection, and then increased to above control levels by 48 h. The reduction in Glut2 mRNA observed at early time points was correlated

with the initial phase of hyperinsulinemia that occurs following streptozotocin treatment. Normalization of glucose levels by phlorizin administration restored liver Glut2 mRNA to control levels and insulin infusion reduced Glut2 mRNA to 25% of the control level. Similar results were observed for Glut2 protein. The authors concluded that portal hyperinsulinemia decreases Glut2 gene expression and that hyperglycemia induces expression of this gene. These results are consistent with a subsequent study in which hyperinsulinemia and hyperglycemia had opposing effects on liver Glut2 expression *in vivo* and in cultured hepatocytes (Postic et al., 1993b). Perhaps all of the discrepancies among the Glut2 gene expression experiments can be attributed to complex time-dependent effects of various treatment regimens.

A single study has appeared examining the regulation of Glut2 in epithelia (Miyamoto et al., 1992). Glut2 protein expression was elevated in purified intestinal basolateral membranes from streptozotocin-treated diabetic rats and rats fed a high-carbohydrate diet, but was unaltered in rats made hyperglycemic by glucose infusion. Glucose transport activity was elevated under all three conditions.

Glut3

Glut3 is the most prominent glucose transporter isoform expressed in parenchymal cells of adult brain (Kayano et al., 1988; Nagamatsu et al., 1992). Its expression is restricted to nervous tissue in the mouse, but the mRNA and protein have been detected in several other human tissues, including placenta, liver, and kidney (Gould et al., 1992). Glut3 is a major transporter isoform in rat placenta, where it is localized to the labyrinthine syncitiotrophoblast and is probably involved in glucose transfer to the embryo (Zhou and Bondy, 1993). Although Glut3 protein is present in several cell types in human brain, it is enriched in neurons as opposed to glial or endothelial cells. The most distinctive characteristic of this isoform is its low K_m for glucose (Gould et al., 1991). This is frequently interpreted to indicate that Glut3 has a high 'affinity' for glucose. This is incorrect in that binding of glucose to the transporter is not rate-limiting for transport (Wang et al., 1986) and thus the K_m is not a measure of substrate affinity. Rather, the K_m simply corresponds to the substrate concentration at which transport activity is half-maximal under a specific set of conditions. However, one can infer that Glut3 evolved to operate more efficiently at lower substrate concentrations than the other isoforms. This presumably reflects the lower glucose concentration to which it is exposed in the brain interstitium relative to the blood.

There is relatively little information available about Glut3. It is, like Glut1, expressed in several cultured cell lines. For example, Glut3 is expressed in the skeletal-muscle-derived L6 cell line (Bilan et al., 1992). This may reflect the normal expression of this transporter isoform in fetal muscle and the dedifferentiation exhibited by cultured muscle cells. Although Glut3 protein was enriched in an L6 plasma membrane fraction, a portion of the protein was detected in an intracellular membrane fraction and this was observed to partially redistribute to the plasma membrane fraction after insulin or IGF-1 treatment. This is similar to the behavior of Glut1 and Glut4 in insulin-sensitive cells (see below).

Glut4

Tissue distribution and physiological function

Glut4 is expressed only in adipocytes and muscle cells (Birnbaum, 1989; Charron et al., 1989; Fukumoto et al., 1989; James et al., 1989; Kaestner et al., 1989). These are the 'insulin-sensitive' cell types, so-called because they respond to insulin with a rapid and reversible increase in glucose transport. Glut4 is expressed at highest levels in brown fat, followed by heart, red muscle, white muscle, and white fat (James et al., 1989). Although these tissues express other glucose transporter isoforms, most notably Glut1, several lines of evidence indicate that Glut4 is responsible for insulin-stimulated transport: (a) it is by far the most abundant isoform in fat and muscle (Holman et al., 1990; Marette et al., 1992); (b) its expression during the differentiation of 3T3L1 adipocytes correlates with the onset of insulin-stimulated transport (Tordjman et al., 1989); (c) its level of expression in various muscle and fat cell types generally corresponds to the magnitude of insulin-stimulated glucose disposal in that cell type (James et al., 1989; Henriksen et al., 1990); (d) transfected L6 muscle cell lines overexpressing Glut4 exhibit increased insulin-stimulated glucose transport (Lawrence et al., 1992).

Glucose transport in the insulin-sensitive tissues has received considerable attention because of the importance of this process in the maintenance of whole-body glucose homeostasis. Glucose disposal via skeletal muscle in the human, for example, accounts for $\approx 20\%$ and $\approx 75-95\%$ of whole-body glucose disposal under basal and hyperinsulinemic conditions, respectively (Baron et al., 1988). Nearly all of the glucose metabolized in muscle under hyperinsulinemic conditions is converted to glycogen (Shulman et al., 1990). The transport step is rate-limiting for glucose uptake into muscle under most conditions (Ziel et al., 1988). Thus, glucose transport in muscle would appear to be an important step in whole-body glucose disposal. This hypothesis is supported by recent glucose clamp experiments in humans that indicate a direct correlation between muscle Glut4 levels in normal individuals and the rate of whole-body glucose disposal (Koranyi et al., 1991b; Eriksson et al., 1992). It is supported further by observations with transgenic mice overexpressing Glut1 in skeletal muscle (Marshall et al., 1993a; Ren et al., 1993b). These mice are hypoglycemic relative to their non-transgenic litter mates, demonstrating that an alteration in glucose transport in skeletal muscle can, by itself, alter the blood glucose set point. Additionally, skeletal muscles of the transgenic mice have a tenfold increase in glycogen content and a twofold elevation in lactate, demonstrating directly that transport is rate-limiting for muscle glycogen synthesis and glycolysis.

Acute regulation by insulin

Evidence was first presented over a decade ago that insulin augments glucose transport in isolated rat adipocytes via the redistribution of transporter molecules from an intracellular membrane compartment to the cell surface (Cushman and Wardzala, 1980; Suzuki and Kono, 1980). Since these initial observations, the translocation phenomenon has been established as the major mechanism by which insulin acutely stimulates glucose transport in fat and muscle cells (reviewed by Birnbaum, 1992). Other agents known to increase transport via translocation include cAMP (Kelada et al., 1992), phorbol esters (Holman et al., 1990; Vogt et al., 1991), and muscle contraction (Douen et al., 1990). Insulin and muscle contraction are the only known mediators of translocation under physiological conditons. An increase in the intrinsic activity of Glut4 may occur in parallel to translocation, although its contribution to increased transport activity is still uncertain.

Early experiments demonstrating translocation employed either reconstitution of transport activity from subcellular membrane fractions (Suzuki and Kono, 1980) or cytochalasin B as an affinity ligand (Cushman and Wardzala, 1980) to follow the steady-state redistribution of transporter molecules. More recently developed tools that have contributed to increased understanding of Glut4 regulation include isoform-specific antibodies (James et al., 1989; Birnbaum, 1989) and impermeant transporter-specific ligands (Holman et al., 1990; Jhun et al., 1992).

An important and elegant series of experiments using glucose transporter antibodies has been published by Slot and colleagues. These investigators employed immunogold labeling of frozen ultrathin tissue sections to visualize the redistribution of Glut4 from a *trans*-Golgi membrane compartment to the cell surface in brown adipocytes (Slot et al., 1991b), heart (Slot et al., 1991a) and skeletal muscle (Rodnick et al., 1992). Smith et al. (1991) reported that intracellular Glut4 is present in morphologically distinct invaginations of the plasma membrane in white adipocytes. It is unclear whether these disparate results reflect a fundamental difference in the intracellular storage compartment in different cell types or are due to some technical or procedural differences. Little is known about the intracellular Glut4 membrane compartment(s) *per se*. The compartment in adipocytes has been shown to contain members of the VAMP (Cain et al., 1992) and SCAMP (Laurie et al. 1993) families, proteins of unknown function that are residents of synaptic vesicles. Low-molecular-mass GTP-binding proteins have been detected in Glut4-immunoenriched low-density vesicles from adipocytes (Cormont et al., 1991). These proteins are members of the *ras* superfamily, are widely distributed throughout the secretory pathway and appear to be involved in nearly every stage of membrane trafficking. Baldini et al. (1991) have presented evidence for the involvement of GTP-binding proteins in insulin-stimulated translocation of Glut4 to the plasma membrane in permeabilized rat adipocytes. The identification of other protein constituents of the Glut4 vesicles is of obvious importance in understanding the structure and function of this organellar compartment.

Transfection studies have demonstrated that Glut4 is targeted to intracellular compartments in a number of non-insulin-sensitive cell types (Haney et al., 1991; Hudson et al., 1992; Kotliar and Pilch, 1992; Shibasaki et al., 1992). The Glut4-enriched intracellular compartment in transfected 3T3L1 fibroblasts morphologically resembles the intracellular Glut4 compartment in insulin-sensitive cells, and the Glut4-containing vesicles present in cellular homogenates obtained from these different cell types exhibit a similar profile on sucrose density gradients (Haney et al., 1991). These data suggest that the apparatus responsible for the intracellular sequestration of Glut4 is present in many different cell types and that this sequestration is determined solely by some structural feature of the Glut4 molecule. Two groups have employed heterologous expression of Glut1/Glut4 chimeric molecules in Chinese hamster ovary (CHO) cells to identify the regions of the Glut4 molecule that specify intracellular targeting. Piper et al. (1992, 1993) reported that the N-terminal cytoplasmic tail of Glut4 is both necessary and sufficient for its intracellular sequestration in Sindbis-virus-infected CHO cells, and that Phe5 forms part of a motif important for the clustering of Glut4 in clathrin-enriched membrane domains. Asano et al. (1992) reported a contradictory finding that two distinct domains of Glut4, exclusive of the N-terminus, contribute in an additive fashion to the intracellular sequestration in permanent lines of transfected CHO cells. These disparate results appear to be mutually exclusive and cannot be attributed to cell-specific targeting factors. Three groups, using entirely different expression systems, subsequently reported that sequence information within the C-terminal cytoplasmic domain of Glut4 is both necessary and sufficient for intracellular sequestration of chimeric Glut1/Glut4 transporters. Verhey et al. (1993) localized the intracellular targeting domain to the C-terminal 30 amino acid residues of Glut4 by analysis of permanently transfected lines of NIH 3T3 fibroblasts. Czech et al. (1993) identified the C-terminal 30 residues of Glut4 as important for the sequestration of chimeric transporters in transiently transfected COS cells. Finally, Marshall et al. (1993b) found that the C-terminal tail of Glut4 is sufficient to confer intracellular sequestration of chimeric transporters in *Xenopus* oocytes. It should be noted that none of the identified targeting domains has been shown to be involved in the intracellular trafficking of Glut4 in the native environment of a fat or muscle cell. A resolution of these disparate results may thus require functional expression of chimeras in an insulin-responsive cell line, such as 3T3L1 adipocytes, or expression in transgenic animals. Our preliminary results indicate that a small region within the C-terminus of Glut4 is capable of conferring intracellular sequestration of Glut1 in the skeletal-muscle-derived L6 cell line (P. Haney and M. Mueckler, unpublished observations). The theoretical problems involved in the interpretation of these targeting studies have been discussed by Marshall et al. (1993b).

Several recent studies have begun to address the mechanism and pathway of Glut4 trafficking in adipocytes. After insulin treatment, immunogold labeling revealed the presence of Glut4 in early endosomes of brown adipocytes, suggesting that this protein participates in an endosomal recycling pathway (Slot et al., 1991a). Studies in isolated white adipocytes (Jhun et al., 1992; Czech and Buxton, 1993) and 3T3L1 adipocytes (Yang and Holman, 1993) indicate that Glut4 recycles constitutively between a low-density membrane compartment and the cell surface, and that insulin induces redistribution of the protein by altering the kinetics of the endocytic and exocytic steps (see Fig. 4). The studies disagree, however, on the magnitude of the insulin-induced changes in the internalization and externalization rate constants. Two of the these studies involved analysis of transporters that were photolabeled with substrate analogs and it is not known what effect, if any, the presence of the photoactivatable tag has on the recycling process.

Long-term regulation

Many studies have examined the effect of altered metabolic states, especially those associated with insulin resistance, on Glut4 gene expression. Streptozotocin-induced diabetes is associated with dramatic decreases in Glut4 mRNA and protein in rat adipose tissue (Berger et al., 1989; Garvey et al., 1989; Sivitz et al., 1989). The reduction in adipocyte Glut4 expression is due to a decrease in the rate of transcription of the Glut4 gene (Gerrits et al., 1993). This reduction accounts for the insulin resistance observed in adipocytes isolated from streptozotocin-treated rats. A similar reduction in adipocyte Glut4 expression is responsible for the insulin resistance displayed by adipocytes isolated from non-insulin-dependent diabetes mellitus (NIDDM) patients (Garvey et al., 1991). Although streptozotocin treatment is also associated with a modest reduction in rat skeletal muscle Glut4

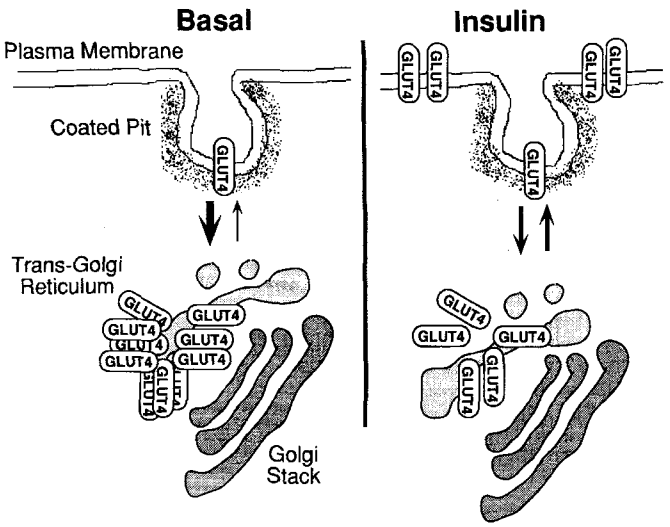

Fig. 4. Insulin-stimulated translocation of Glut4 to the plasma membrane in adipocytes. Glut 4 is targeted to a subcompartment of the *trans*-Golgi reticulum in the absence of insulin. It may recycle through the plasma membrane via coated pits in this state, but the rate of endocytosis is much greater than the rate of exocytosis, so that very few transporters are present at the cell surface. Insulin increases the rate of entry of intracellular Glut4 into the exocytic route and/or decreases the rate of entry of cell-surface Glut4 into the endocytic route, bringing about a steady-state increase in the level of plasma membrane Glut4. The thickness of each arrow represents the relative magnitude of the endocytic or exocytic step.

mRNA and protein (Bourey et al., 1990), this reduction can be temporally dissociated from the streptozotocin-induced decrease in whole-body insulin sensitivity (Richardson et al., 1991). There appears to be little if any reduction in the Glut4 content of skeletal muscle obtained from NIDDM patients compared to controls (Pedersen et al., 1990; Eriksson et al., 1992). Thus, a simple reduction in the total muscle Glut4 content is unlikely to be an important factor in the insulin resistance associated with human NIDDM. It is unclear at present how much of the streptozotocin effect on Glut4 expression in fat and muscle is due to insulinopenia, hyperglycemia, or some other effect of the drug, although hyperglycemia appears to play some role. Normalization of blood glucose in streptozotocin diabetic rats by treatment with phlorizin restores insulin-sensitivity in adipocytes without affecting Glut4 protein levels (Kahn et al., 1991). A similar normalization regimen was shown to reverse the effects of streptozotocin treatment on Glut4 expression in the skeletal-muscle plasma membrane (Dimitrakoudis et al., 1992).

Fasting is another condition associated with whole-body insulin resistance. Glut4 protein and mRNA are decreased in the adipocytes of fasted rats, but are elevated in skeletal muscle (Berger et al., 1989; Bourey et al., 1990; Charron and Kahn, 1990). The elevated Glut4 levels in skeletal muscle may explain the paradoxical observation that muscles isolated from fasted rats actually exhibit increased glucose transport activity *in vitro* (Brady et al., 1981). Once again, there appears to be little correlation between total muscle Glut4 levels and *in vivo* insulin sensitivity in this altered metabolic state.

Glut4 gene expression has been examined in animal models of genetic obesity and diabetes. No alterations in Glut4 protein levels were observed in fat or muscle tissues obtained from obese, insulin-resistant, db/db mice relative to their lean litter mates (Koranyi et al., 1990). Adipocytes of young, obese, fatty Zucker rats have increased Glut4 mRNA and protein relative to adipocytes from lean Zucker rats (Hainault et al., 1991) but this is may be due to a nonspecific increase in total cellular protein and RNA (Pedersen et al., 1992). This increase correlates well with the hyperinsulin responsiveness observed on a per cell basis in isolated adipocytes from young fatty Zucker rats. No change was observed in Glut4 gene expression in the skeletal muscle of insulin-resistant fatty Zucker rats (Ying et al., 1992). Results of this latter study suggest that translocation of Glut4 from an intracellular compartment to the plasma membrane is defective in the skeletal muscle of the fatty Zucker rat. Thus, there is no evidence at present in humans or animals that whole body insulin resistance can be attributed to simple reductions in the level of Glut4 gene expression in skeletal muscle. Technical problems make it very difficult to accurately quantitate the plasma membrane content of glucose transporters in skeletal muscle, especially in the human. However, this measurement will be necessary to ascertain the possible contribution of altered glucose transporter subcellular trafficking and insulin responsiveness to insulin resistance. Hexokinase II activity and mRNA have recently been shown to be regulated by insulin in rat skeletal muscle (Postic et al., 1993a). It will be interesting to explore the possible role of this muscle enzyme in various insulin-resistant states.

The effects of several other metabolic perturbations on Glut4 gene expression have been studied. Chronic exercise training increases skeletal muscle Glut4 protein levels in the rat (Rodnick et al., 1990) and human (Ebeling et al., 1993). The observed increases correlate with augmented insulin-stimulated glucose uptake in isolated muscles and improved insulin sensitivity *in vivo*. Chronic creatine deficiency caused by feeding rats β-guanidinopropionic acid coordinately induces expression of Glut4, several mitochondrial oxidative enzymes, and hexokinase in muscle (Ren et al., 1993a). Insulin resistance caused by denervation is associated with decreased muscle Glut4 expression (Coderre et al., 1992). Glucose deprivation of cultured 3T3L1 adipocytes increases glucose transport in part by stabilizing and increasing the plasma membrane content of Glut4 protein, despite the fact that total cellular Glut4 protein remains unchanged and Glut4 mRNA is dramatically decreased (Tordjman et al., 1990). Glucose deprivation of skeletal-muscle-derived L6 cells also increases the plasma membrane content of Glut4 (Koivisto et al., 1991).

Glut5

Glut5 exhibits the weakest inter-isoform homology of any of the members of the Glut family (Kayano et al., 1990). This is consistent with its identity as a fructose, rather than a glucose, transporter (Burant et al., 1992). It is expressed at relatively high levels in the apical membrane of intestinal enterocytes and may be the major route of dietary fructose uptake (Davidson et al., 1992; Mahraoui et al., 1992). It is also expressed at high levels in the plasma membrane of mature spermatozoa, consistent with the known ability of sperm cells to utilize fructose in seminal fluid (Burant et al., 1992). Interestingly, fructose transport mediated by Glut5 is insensitive to inhibition by cytochalasin B, a well-characterized inhibitor of facilitative glucose transport. Glut5 is also expressed in brain endothelium (Mantych et al., 1993) and muscle and fat cells (Hundal et al., 1992; Shepherd et al., 1992), although its physiological role in these tissues is not

clear. In muscle and fat cells it is constitutively expressed in the plasma membrane and is not subject to acute insulin regulation as are Glut1 and Glut4.

Glut7

Glut7 is the most recently discovered glucose transporter isoform and little is known about it at present. It shares 68% sequence identity with Glut2 and was cloned from a rat liver cDNA expression library using antibodies raised against a 52-kDa rat liver microsomal protein (Waddell et al., 1992). Interestingly, it contains a six-amino-acid extension at its carboxyl-terminus relative to Glut2 that corresponds to a consensus motif for retention of membrane proteins in the endoplasmic reticulum. Thus, Glut7 appears to correspond to the glucose transporter that allows the diffusion of free glucose out of the endoplasmic reticulum of gluconeogenic tissues after the action of microsomal glucose-6-phosphatase on glucose 6-phosphate. The identification of this protein should assist with the further dissection of the role of the glucose-6-phosphatase system in the control of hepatic glucose metabolism.

Concluding remarks

Great advances have been made in the past few years in our understanding of glucose transport. This progress has been catalyzed by the development of antibody, DNA and affinity-labeling reagents that have made it possible to directly address questions concerning the structure and function of these difficult-to-study membrane proteins. The Glut proteins are not only important to our understanding of glucose metabolism but have proved to be ideal model proteins to study membrane transport in general and the structure, biosynthesis, and intracellular trafficking of multi-spanning membrane proteins. The increased interest in the study of glucose transporters is reflected in the explosion of papers published in this area over the past five years. Despite the impressive progress that has been made, we have barely penetrated the surface of information that will come from the study of the glucose transporters. The determination of the three-dimensional structure of these proteins is a future achievement that will undoubtedly lead to a quantum leap in our understanding of transporter function. Virtually nothing is known at present about the molecular mechanism of glucose transport or the transport of any solute across the membrane. The detailed mechanism by which Glut4 is regulated by insulin is being intensively studied and may yield new insights into intracellular protein trafficking and insulin action. The possible involvement of Glut4 in insulin resistance associated with non-insulin-dependent diabetes has yet to be fully explored. Work in progress involving Glut2 may aid in the development of artificial β cells to be used for the treatment of diabetes. Studies on Glut1 and Glut3 may yield fundamental insights into energy metabolism in the brain and the possible role of glucose transporter defects in various neurological disorders. The next decade of research on glucose transport should prove to be even more interesting than the last.

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