invited review

# Glucose transporters in the regulation of intestinal, renal, and liver glucose fluxes

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**Thorens, Bernard.** Glucose transporters in the regulation of intestinal, renal, and liver glucose fluxes. *Am. J. Physiol.* 270 (*Gastrointest. Liver Physiol.* 33): G541–G553, 1996.—Five functional mammalian facilitated hexose carriers (GLUTs) have been characterized by molecular cloning. By functional expression in heterologous systems, their specificity and affinity for different hexoses have been defined. There are three high-affinity transporters (GLUT-1, GLUT-3, and GLUT-4) and one low-affinity transporter (GLUT-2), and GLUT-5 is primarily a fructose carrier. Because their Michaelis constants ($K_m$) are below the normal blood glucose concentration, the high-affinity transporters function at rates close to maximal velocity. Thus their level of cell surface expression greatly influences the rate of glucose uptake into the cells. In contrast, the rate of glucose uptake by GLUT-2 ($K_m$ = 17 mM) increases in parallel with the rise in blood glucose over the physiological concentration range. High-affinity transporters are found in almost every tissue, but their expression is higher in cells with high glycolytic activity. GLUT-2, however, is found in tissues carrying large glucose fluxes, such as intestine, kidney, and liver. As an adaptive response to variations in metabolic conditions, the expression of these transporters is regulated by glucose and different hormones. Thus, because of their specific characteristics and regulated expression, the facilitated glucose transporters control fundamental aspects of glucose homeostasis. I review data pertaining to the structure and regulated expression of the glucose carriers present in intestine, kidney, and liver and discuss their role in the control of glucose flux into or out of these different tissues.

homeostasis; diabetes; mutagenesis

GLUCOSE HOMEOSTASIS requires the tight quantitative and temporal regulation of glucose flux into and out of different organs. The brain constantly needs a fixed supply of glucose to produce its energy, and this requires that circulating glucose concentrations never drop below a minimal level of ~5 mM. Blood glucose comes from two different sources, either directly, from the absorption of dietary glucose through intestinal epithelial cells, or from liver, where it is stored as glycogen or synthesized by the gluconeogenic pathway. Reabsorption of filtered glucose in the kidney proximal tubule is also an essential process to prevent secretion of glucose in the urine. If hypoglycemia must be avoided, hyperglycemia must also be prevented, since in the long range it can lead to the development of a number of complications characteristic of diabetes. In the postprandial state, buildup of blood glucose concentrations is prevented by a combination of insulin-dependent glucose storage in liver and uptake by adipocytes and muscles. Whereas insulin can stimulate glucose storage and metabolism, glucagon or other counterregulatory hormones, in contrast, are key regulators of glucose efflux from liver. The balanced and glucose-controlled secretion of insulin and glucagon by pancreatic islet cells is an essential part of the control of glucose homeostasis. These secretory events are triggered by glucose, and uptake of glucose is a key step in the function of α- and β-islet cells.

Since the characterization by molecular cloning of the first human facilitative-diffusion glucose transporter, now called GLUT-1, four other hexose transporters have been identified (GLUT-2 to GLUT-5). Their specific role in the different tissues in which they are expressed and their function in the general control of glucose homeostasis are now being rapidly uncovered. These transporters differ in their kinetic properties, sugar specificities, tissue localization, and regulation in states of imbalanced glucose homeostasis. A simple classification of glucose transporters can be based on their affinity for glucose (see Table 1). GLUT-1, GLUT-3,

 

Table 1. *Michaelis constants ($K_m$) for sugar transport by GLUT molecules expressed in Xenopus oocytes measured under different conditions*

| | $K_m$, mM | | | | |
|---|---|---|---|---|---|
| | GLUT-1 | GLUT-2 | GLUT-3 | GLUT-4 | GLUT-5 |
| *Equilibrium exchange* | | | | | |
| 3-*O*-MG[a] | 17 | 42 | 10 | | |
| 3-*O*-MG[b] | 21.3 | | | 1.8 | |
| *Uptake* | | | | | |
| 2-DOG[c] | 5 | 7 | | | |
| Fructose[d] | | | | | 6 |
| 2-DOG[e] | 6.9 | 16.2 | 1.8 | 4.6 | |
| Galactose[e] | 17.1 | 36 | 6.0 | | |

3-*O*-MG, 3-*O*-methylglucose; 2-DOG, 2-deoxy-D-glucose. [a]Human GLUTs (41). [b]Human GLUT-1, rat GLUT-4 (66). [c]Rat GLUT-1 and GLUT-2 (121). [d]Human GLUT-5 (16). [e]Rat GLUT-1 and human GLUT-2, GLUT-3, and GLUT-4 (13).

and GLUT-4 are high-affinity transporters, whereas GLUT-2 is a low-affinity transporter. The high-affinity transporters function well above their Michaelis constants ($K_m$) at normal glucose concentrations of ~5 mM, and the number of transporters on the plasma membrane controls the flux of glucose into the cells. Their level of cell surface expression is therefore critical in determining the further rate of glucose metabolism, and these transporters are usually expressed at high levels in tissues highly dependent on glucose as an energy source. For instance, in the brain, GLUT-1 is present at a high level in the blood-brain barrier, and GLUT-3, which is the transporter with the highest affinity for glucose, is present in neurons. This arrangement thus creates an affinity gradient that may be essential to maximize the efficiency of glucose uptake by neurons. GLUT-1, which is also present in almost every tissue, has a level of expression that correlates very well with the glycolytic activity of the cells in which it is expressed. For instance, the cells forming the different segments of the kidney nephron have widely different glycolytic activities, which are reflected in their varying levels of GLUT-1 expression. In "insulin-sensitive" cells such as adipocytes and muscle fibers, the rate of glucose uptake is acutely controlled by insulin. This is achieved by the translocation to the cell surface of GLUT-4 transporters, which are stored in intracellular vesicles in the basal state. In contrast to these isoforms, the low-affinity transporter GLUT-2 is present in tissues in which high glucose flux takes place, such as in intestine, liver, or the proximal tubule of the kidney nephron. Also, in β-cells, GLUT-2 allows a fast equilibration of glucose inside the cells, a prerequisite for the normal functioning of the glucose sensor, linking elevations in extracellular glucose concentrations to insulin secretion. Because its $K_m$ (~17 mM) is severalfold higher than the normal blood glucose concentration, a rise in glycemia concentration will be followed by a parallel increase in uptake rate even with a constant number of transporters in the plasma membrane.

In the present review, I concentrate on the mechanisms of glucose transport through intestinal and kidney epithelial cells and into and out of liver. I discuss the structure and function of these tissue-specific glucose carriers and their regulated expression in development and in altered metabolic conditions. Because the transepithelial transport of glucose is initiated by uptake through $Na^+$-dependent glucose transporters (SGLTs), I first briefly describe their structure and function, and when necessary their role and regulation is discussed together with that of the facilitative transporters.

## $Na^+$-DEPENDENT GLUCOSE TRANSPORTERS

Transport of glucose across the apical brush border of intestinal and kidney epithelial cells is an active process that requires the presence of a $Na^+$ gradient between the exterior and interior of the cells. The low intracellular $Na^+$ concentration is maintained by the basolaterally located $Na^+$-$K^+$-adenosinetriphosphatase, which extrudes accumulated $Na^+$. Transport of sodium ions down their electrochemical gradient provides the driving force for glucose cotransport and allows uptake of glucose from a low extracellular concentration into the cells. Initial molecular characterization of the rabbit intestinal glucose symporter, now referred to as SGLT-1, was performed by Hediger et al. (46). Analysis of the deduced primary amino acid sequence predicted a protein with 12 transmembrane domains. Sequence comparison revealed that this protein was homologous to the proline transporter of *Escherichia coli*, the $Na^+$-dependent neutral amino acid transporter, and the $Na^+$-dependent *myo*-inositol transporter. This therefore indicated the existence of a large family of related transporters that have been highly conserved through evolution.

A protein 59% identical to rabbit SGLT-1 was isolated from a human kidney library, using SGLT-1 cDNA as a probe (126). This new molecule (SGLT-2) was demonstrated to be a glucose cotransporter by expression in *Xenopus* oocytes (60). SGLT-1 has a relatively high affinity for glucose ($K_m$ = 0.35 mM), whereas SGLT-2 has a lower affinity ($K_m$ = 1.6 mM). With respect to $Na^+$, $K_m$ values differ even more greatly, with $K_m$ of 35 mM for SGLT-1 and ~280 mM for SGLT-2. Further differences between isoforms are in the $Na^+$-to-glucose ratio, which is 2:1 for SGLT-1 and 1:1 for SGLT-2, and in hexose specificity: SGLT-1 can transport both glucose and galactose, whereas SGLT-2 transports only glucose (see Ref. 47 for review).

Northern blot analysis revealed that SGLT-2 was almost exclusively present in kidney and not in intestine, whereas SGLT-1 was present at a high level in intestine but also at a somewhat lower level in rat, but not human, kidney. Immunocytochemical and in situ hybridization localization of SGLT-1 (68, 108) and SGLT-2 (60) along the nephron indicated a differential localization of these two transporters. The low-affinity transporter SGLT-2 was abundant in the proximal convoluted tubule (S1), whereas the high-affinity

SGLT-1 was present in the straight part (S3) of the proximal tubule.

## FACILITATED DIFFUSION GLUCOSE TRANSPORTERS

Five functional hexose carriers have been described so far and are referred to as GLUT-1 to GLUT-5 (5, 40, 84, 112). Three of these, GLUT-1, GLUT-3, and GLUT-4, have a relatively high affinity for glucose ($K_m$ = 1–3 mM). GLUT-2 is the only low-affinity transporter ($K_m$ = 17–20 mM), and GLUT-5 is a fructose transporter that transports glucose only poorly, if at all. The existence of a GLUT-7 has been reported in a preliminary form and may participate in the glucose-6-phosphatase complex of the hepatic endoplasmic reticulum (122).

### *GLUT-1*

GLUT-1 is the human erythrocyte glucose transporter and was the first glucose transporter to be characterized by molecular cloning (85). This transporter can carry glucose, galactose, and mannose. The $K_m$ for D-glucose uptake, as measured in erythrocytes (18, 104), is ~1–2 mM for D-glucose, whereas $K_m$ for glucose efflux is about an order of magnitude higher (20–30 mM), indicating that the transport process is asymmetrical. The kinetics of glucose transport by each transporter isoform have also been studied by expression from synthetic mRNA injected into *Xenopus* oocytes. For GLUT-1 the $K_m$ for 3-*O*-methylglucose was ~20 mM in equilibrium exchange conditions (41, 66, 88) and 6.9 mM for 2-deoxy-D-glucose uptake (zero-*trans* conditions) (13).

Besides human erythrocytes, GLUT-1 is found in almost every tissue, with varying levels of expression. Particularly important is the high expression of this transporter in blood-tissue barriers, such as the endothelial cells forming the blood-brain barrier (71).

### *GLUT-2*

GLUT-2 is the only low-affinity glucose transporter characterized so far. Cloning of this transporter cDNA was achieved by screening rat (116) and human (38) liver cDNA libraries with a GLUT-1 cDNA probe. The mouse GLUT-2 cDNA has also been cloned (106). GLUT-2 is 55% identical in amino acid sequence to GLUT-1 and has the same predicted topology (see below). GLUT-2 is the predominant facilitated diffusion glucose transporter in the sinusoidal membrane of hepatocytes and in the basolateral membrane of epithelial cells from the intestine and kidney proximal tubules (113) and in pancreatic β-cells (116, 128). It is also found in different regions of the brain (55, 69).

Glucose uptake studies performed on liver (127) or isolated hepatocytes demonstrated that *1*) the $K_m$ for glucose was relatively high, ~15–20 mM (26), *2*) the transport process was symmetrical, i.e., the $K_m$ was the same (~20 mM) for glucose influx or efflux in zero-*trans* or in equilibrium exchange conditions (25, 26), *3*) the concentration of cytochalasin B producing half-maximum inhibition of glucose uptake ($K_i$) by isolated hepatocytes is 1.9 μM, a value about 10-fold higher than the $K_i$ for inhibition of GLUT-1 (4). GLUT-2 was functionally expressed in bacteria (116) and in *Xenopus* oocytes after injection of in vitro synthesized mRNA (121). In *Xenopus* oocytes the $K_m$ for 3-*O*-methylglucose was 42 mM in equilibrium exchange conditions (41) and 16.2 mM for 2-deoxy-D-glucose uptake (13). In transfected AtT-20 cells, the $K_m$ for uptake by GLUT-2 was ~17 mM (50). Gould et al. (41) further determined that GLUT-2 can carry glucose, galactose, mannose, and fructose. The capability to transport fructose is unique to GLUT-2 and GLUT-5, as discussed further below.

### *GLUT-3*

GLUT-3 was originally cloned from a human fetal muscle cDNA library (65). Its mRNA was found to be almost ubiquitously expressed in humans, with a low level of expression in adult muscle. The transporter protein distribution, however, was found to be restricted to brain and testis, in particular with spermatozoa (42). Mouse GLUT-3 is only 83% identical to human GLUT-3 (87). In mouse and rat, GLUT-3 mRNA is detected only in the brain (87). By in situ hybridization (87) and immunodetection (70, 77), GLUT-3 was determined to be mainly expressed in neurons. Kinetic measurement of glucose uptake by *Xenopus* oocytes injected with GLUT-3 mRNA showed a $K_m$ for equilibrium exchange of 10 mM, a value smaller than that for GLUT-1 (~20 mM), and the $K_m$ for 2-deoxy-D-glucose uptake was 1.8 mM (13).

### *GLUT-4*

GLUT-4 is the major glucose transporter of brown and white adipose tissues and of skeletal and cardiac muscles. It has been cloned from human (37), rat (6, 20, 54), and mouse (59) tissues. When measured in adipocytes, the $K_m$ for glucose uptake is ~5 mM (see Ref. 7 for review) and 4.6 mM when measured in *Xenopus* oocytes (13). In adipose and muscle tissues GLUT-4 is mostly present in intracellular vesicles. Upon insulin stimulation, there is a rapid increase in the number of cell surface-exposed transporters, which results from the translocation toward, and fusion with, the plasma membrane of the GLUT-4-containing vesicles (27, 98, 101, 102, 107). The resulting higher density of cell surface-expressed transporters increase the maximal velocity ($V_{max}$) for glucose uptake. Numerous recent excellent reviews have discussed the role of GLUT-4 in glucose homeostasis, its regulated expression in diabetes, and its intracellular traffic in response to insulin stimulation (7, 53, 67, 105).

### *GLUT-5*

GLUT-5 was isolated from human intestinal epithelial cell (64) and rat (95) and rabbit (82) jejunum cDNA libraries. It is only 39–40% identical to the other glucose transporter isoforms. GLUT-5 is expressed primarily in the jejunal region of the small intestine. However, its mRNA is also detected at low levels in human kidney, skeletal muscle, and adipocytes. In brain it has been found in microglial cells and in the

human blood-brain barrier (75). GLUT-5 was also present at a high level in human but not rat spermatozoa, in agreement with the ability of these cells to utilize fructose as a source of energy (16). In human intestine (28) and in Caco-2 cells (73), GLUT-5 immunoreactivity was primarily concentrated in the brush border, although a recent report found GLUT-5 to be also present in the basolateral membrane of human jejunal cells (8).

Recently, using expression of human (16) or rat (95) GLUT-5 in *Xenopus* oocytes, Burant and colleagues have shown that GLUT-5 was primarily a fructose transporter. Fructose transport by rat and human GLUT-5 could not be inhibited by cytochalasin B. However, D-glucose could compete with fructose transport by rat, but not by human, transporters. Miyamoto et al. (82) reported that transport of fructose by rabbit brush-border vesicles was insensitive to the presence of D-glucose or D-galactose, as was transport of fructose in *Xenopus* oocytes injected with jejunal mRNA. In contrast, fructose uptake by oocytes injected with in vitro synthesized rabbit GLUT-5 cRNA was inhibitable by D-glucose. These authors suggested that the differential sensitivity to glucose of fructose transport in these different conditions may be due to proteins interacting with GLUT-5 in the brush-border preparations or in jejunal mRNA-injected oocytes. The $K_m$ for fructose uptake in GLUT-5 mRNA-injected oocytes was determined to be ~6–11 mM (82, 95).

## STRUCTURE OF GLUCOSE TRANSPORTERS

The primary sequence of the protein encoded by the isolated cDNA predicted a topology with 12 transmembrane, amphipathic domains connected by hydrophilic loops (Fig. 1). Both the amino and carboxy tails of the protein are on the cytoplasmic side of the plasma membrane. The first extracellular loop contains the site of N-glycosylation. A large intracellular loop is present between the sixth and seventh transmembrane domains and separates the molecule in two six-transmembrane segments containing homologous amino- and carboxy-terminal domains. This same general structure is conserved for the mammalian GLUTs but is also conserved for a superfamily of transporters including the bacterial $H^+$-sugar cotransporter and other transporters in yeast and plants (48). Experimental evidence for the predicted topology comes from analysis of the structure of GLUT-1, with antipeptide antibodies directed against the amino or carboxy terminal of the protein, together with trypsin and glycosidase digestion studies (2, 29). More recent studies were performed in which the exoplasmic glycosylated domain of GLUT-4 was inserted either in the amino- or carboxy-terminal tail of GLUT-1 or in the different putative cytoplasmic or exoplasmic loops. When expressed in *Xenopus* oocytes, the pattern of glycosylation of the mutants perfectly agreed with the proposed 12-transmembrane domain topology (49). Biophysical measurements showed that GLUT-1 purified from human erythrocytes and reconstituted in liposomes is predominantly in α-helical configuration; thus the transmembrane segments form α-helixes perpendicular to the plane of the lipid bilayer (1, 24).

Transport of glucose across biological membranes by glucose carriers may be described by an alternating conformer model. In this model the transporter has two mutually exclusive sugar binding sites, one on the extracellular and the other on the intracellular face of the transporter. Binding of glucose to one site induces the transporter to switch to the opposite conformation, a process that is accompanied by movement of the substrate across the plasma membrane (see Ref. 18 for review). The presence of two mutually exclusive glucose binding sites has been revealed by the binding of competitive inhibitors on either side of the plasma membrane (104). The bis-mannose compound ATB-BMPA [2-*N*-4-(1-azi-2,2,2-trifluoroethyl)benzoyl-1,3-bis-(D-mannose-4-yl-oxy)-2-propylamine] and 4,6-*O*-ethylidene glucose bind on the external face of the transporter, whereas cytochalasin B and a derivative of forskolin, [$^{125}$I]iodo-4-azidophenetylamido-7-*O*-succinyldeacetyl (IAPS)-forskolin, bind on the cytoplasmic site.

By site-directed mutagenesis, a number of amino acids involved in the binding of these inhibitors have been mapped. A region in helix 7 that is highly conserved in all the mammalian transporters, $Q^{282}$QXSGXNXXFY$Y^{293}$ (see Fig. 1), has been proposed to be important for the binding of the exofacial inhibitors (40, 44), and mutation of glutamine-282 to leucine decreases binding of ATB-BMPA to ~5% of wild-type values and increased the $K_i$ for 4,6-*O*-ethylidene glucose from 12 to >120 mM. Mutation of tyrosine-293 to isoleucine, but not mutation of tyrosine-293 to phenyl-

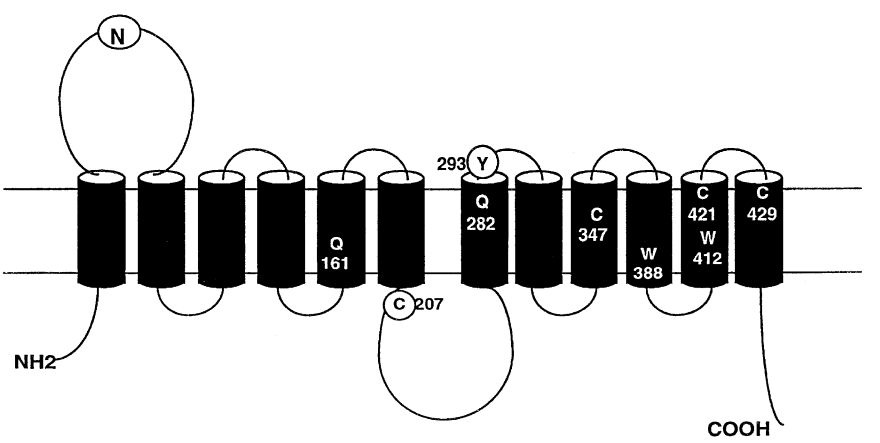


Fig. 1. Structure of the GLUT-1 molecule with the predicted 12 transmembrane helixes. Both amino- and carboxy-terminal ends of molecule are on cytoplasmic side of plasma membrane. The N-glycosylation site (N) is present on the first extracytoplasmic loop. The approximate position of selected amino acids is shown as their role in the sugar transport and inhibitor binding is discussed in the text. C, cysteine; Q, glutamine; W, tryptophan; Y, tyrosine.

alanine or of tyrosine-292 to isoleucine or phenylalanine, blocked transport activity without impairing ATB-BMPA binding, but decreased cytochalasin B affinity by ~300-fold. This suggested that the mutation blocked GLUT-1 in an outward-facing conformation (83). The above data thus indicate that the region of helix 7 is important for glucose binding to the external site. Gould and Holman (40) also proposed that the QLS sequence present on the amino-terminal side of glutamine-283, which is present only in the high-affinity glucose transporters GLUT-1, GLUT-3, and GLUT-4 and not in GLUT-2 or GLUT-5, may be important for determining the affinity of D-glucose for the outward-facing site (40). Binding of ATB-BMPA was also reduced in a GLUT-1 mutant in which proline-385, located on the internal side of helix 10, was mutated to isoleucine. However, this mutant had a normal binding for cytochalasin B. It was suggested that deficient binding of the exofacial inhibitor resulted from an inability of the transporter to adopt an outward-directed conformation (111). Substitution of glutamine-161 with asparagine in GLUT-1 led to a strong reduction of transport activity and an 18-fold increased $K_i$ for 4,6-*O*-ethylidene glucose, indicating that glutamine-161 may also participate in the exofacial substrate binding site (86).

Binding of cytochalasin B and IAPS-forskolin to GLUT-1 appears to involve interaction with a region located on the internal side of helixes 10 and 11. Mutations of tryptophan residues 388 and 412 present in these helixes, but not of tryptophan residues 48, 65, 186, and 363, led to decreased transport activity (39). Cytochalasin B labeling was reduced in either the 388 or 412 mutant and completely suppressed in the double mutant while binding was decreased to ~30 percent of that of the wild-type transporter (52). This suggests that cytochalasin B binds in a region formed by helixes 10 and 11 and that coupling by photoactivation requires tryptophan-388 or tryptophan-412. However, IAPS-forskolin still binds normally to the tryptophan-412 mutant but binds with a ~70% reduced efficiency to the tryptophan-388 mutant. When expressed in oocytes, the tryptophan-412 mutant does not transport, whereas the tryptophan-388 mutant does, suggesting that glucose and forskolin binding require different tryptophan residues (99).

GLUT-2 binds cytochalasin B with a 10-fold lower affinity than GLUT-1 (4, 56) but binds the exofacial reagent ATB-BMPA with the same affinity as GLUT-1 or GLUT-4 (57). This suggests that the relatively low affinity for glucose of GLUT-2 is caused by the difference in glucose binding at the internal site. However, the above mutagenesis data provide no simple explanation for this difference in affinity, since tryptophan-388 and tryptophan-412 and the important proline residues present in this region of helixes 10 and 11 are conserved between GLUT-1 and GLUT-2. However, some other, primarily conservative, differences are present in the amino acid sequence of this region and may be of functional importance.

An important role of the carboxy tail in determining the catalytic activity of the transporters has been demonstrated. Deleting the last 37 carboxy-terminal amino acids of the GLUT-1 carboxy tail generates a mutant that is unable to transport glucose and is apparently locked in an inward-facing conformation (90). By progressively shortening the carboxy tail of GLUT-1 it was further shown that deletion of up to 24 amino acids has no consequence on the catalytic activity of the transporter, but that further deletion of 25–27 amino acids blocked the transport function (12). Substitution of the carboxy tail of GLUT-1 with that of GLUT-2 produced a chimera with increased $K_m$ and $V_{max}$ but similar binding affinity for cytochalasin B (62). However, Buchs et al. (12) have demonstrated, using GLUT-4/GLUT-2 chimeras, that helixes 7–12 and the carboxy tail of GLUT-2 were required to confer to the chimera the same $K_m$ as GLUT-2. They further showed that substitution of only the carboxy tail of GLUT-2 for that of GLUT-4 increased the $K_m$ of the chimera by twofold (~14 mM under equilibrium exchange), a value much lower than that of GLUT-2 (31.8 mM).

The GLUT-1 transporter has been shown to exist in a tetrameric form, which can be recognized by a conformation-specific antibody (45). Tetramerization appears to increase the catalytic activity of the complex by a mechanism in which binding of one glucose molecule to one carrier increases the rate of interconversion of adjacent transporters to the outward-facing conformation. The formation of the tetrameric structure can be reversibly inhibited by reducing agents that act on intrachain disulfide bonds and lead to a dimeric form of the transporter. The cysteine residues involved in the formation of the disulfide bonds are present in the carboxy-terminal domain of the transporter and are most probably cysteine-347 and cysteine-421 (130). In transfected Chinese hamster ovary cells, a GLUT-1 chimera in which the carboxy tail was replaced by that of GLUT-4 could be shown to oligomerize with endogenous GLUT-1 (91). No heterooligomer formation between GLUT-1 and GLUT-4 could be observed, however. Dimerization of GLUT-1 requires structures present in the first 199 amino acids of the transporter, whereas tetramerization requires the carboxy-terminal domain of the transporter. The role of cysteines in increasing the catalytic activity of GLUT-1, however, has not been observed in *Xenopus* oocytes expressing GLUT-1 molecules with mutations of each individual cysteine (125). This study demonstrated that the impermeant mercurial reagent *p*-chloromercuribenzenesulfonate reacts on the external surface with cysteine-429 and reacts with cysteine-207 when added on the cytoplasmic side, in agreement with the proposed topology of the transporter.

## TRANSEPITHELIAL GLUCOSE TRANSPORT

### *Intestine*

In intestine, the vectorial transport of hexoses from the lumen to the interstitial space is a two-step process (Fig. 2*A*). Uptake of glucose and galactose through the apical brush border is catalyzed by SGLT-1, the high-affinity $Na^+$-glucose cotransporter, whereas uptake of

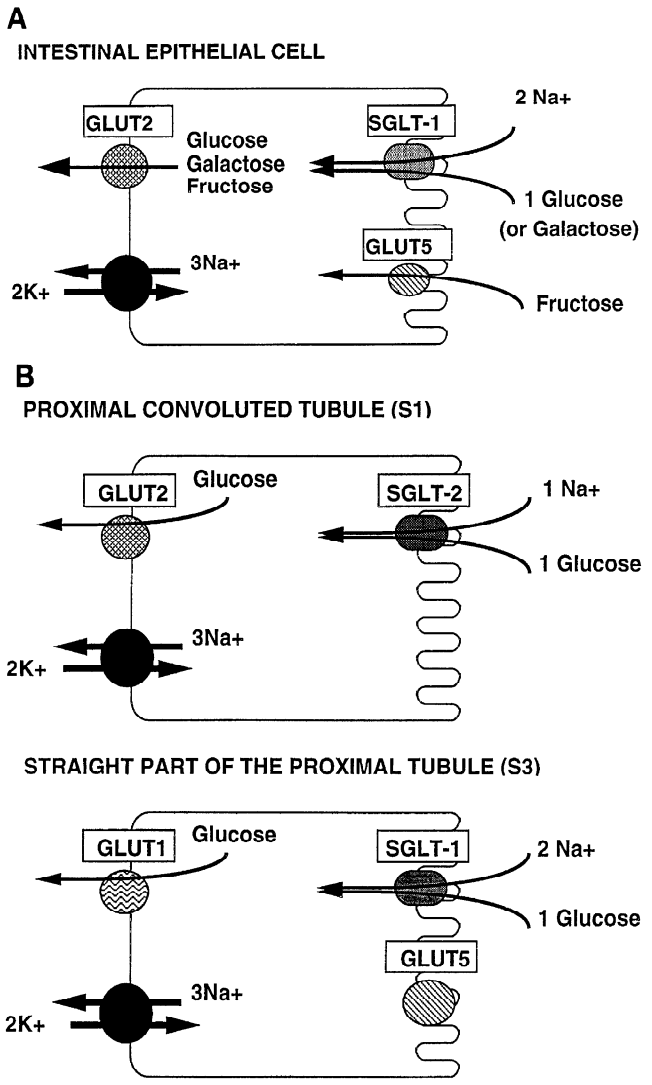


Fig. 2. Transepithelial transport of hexoses. *A*: in intestine, glucose (or galactose) is transported through the apical brush-border membrane by the high-affinity $Na^+$-glucose cotransporter SGLT-1, and fructose enters epithelial cells by facilitated diffusion through GLUT-5. Hexoses are then released in the interstitial region close to blood capillaries by GLUT-2, which can carry glucose, galactose, and fructose. A recent report, however, has indicated that GLUT-5 is also present in the basolateral membrane (see text). *B*: in kidney, transepithelial reabsorption of glucose proceeds differently in the convoluted (S1) and in the straight (S3) parts of the proximal convoluted tubule. The bulk of glucose reabsorption takes place in S1 and is catalyzed by the low-affinity SGLT-2 cotransporter, and glucose is released through the basolateral membrane by GLUT-2, although GLUT-1 has also been detected in this region and may also be functionally important (see text). In S3, reabsorption of the remaining glucose is catalyzed by the high-affinity, high-energy (two $Na^+$ for one glucose) cotransporter SGLT-1. Release across the basolateral membrane is through the high-affinity glucose transporter GLUT-1. The role of GLUT-5 in kidney has not yet been established. In all situations, the activity of the basolaterally located $Na^+$-$K^+$-adenosinetriphosphatase is required to maintain a low intracellular $Na^+$ concentration and to drive the apical cotransport process.

fructose is catalyzed by the GLUT-5 fructose carrier. In these cells, GLUT-2 is the major carrier detected in the basolateral membrane, although a recent publication indicates that in human jejunum, GLUT-5 is also present in the basolateral membrane (8). Diffusion of glucose, galactose, and fructose in the interstitial tissue in close proximity to blood capillaries is thus catalyzed by GLUT-2 and, in humans, also by GLUT-5.

*Regional expression of hexose transporters.* Intestinal epithelial cells are produced from dividing stem cells present in the crypts of Lieberkühn and differentiate into mature absorptive cells as they migrate toward the tip of the villi. GLUT-2 (113) and GLUT-5 (28) are expressed only in enterocytes present well above the base of the villi. A similar increase in SGLT-1 mRNA and protein along the crypt-villus axis has been described (51), indicating that active transepithelial transport of glucose and other hexoses is restricted to the mature enterocytes. Along the intestinal axis in the rat, GLUT-2, in one report, was found at the highest level in the first two-thirds of the intestine and was almost absent from the distal one-third, whereas SGLT-1 was present in all segments (32). In contrast, Rand et al. (95) found GLUT-2, GLUT-5, and SGLT-1 in both rat jejunum and ileum, although GLUT-5 was less abundant in distal small intestine (95). In humans, there appears to be no change in GLUT-2 and GLUT-5 levels in the different segments of the small intestine (28), and GLUT-5 is not present in colon epithelial cells (73).

*Developmental regulation.* Levels of GLUT-2 mRNA are low in human fetuses (28) and newborn rats (79) but increase progressively until the adult stage. A similar pattern of developmentally regulated expression of GLUT-5 is observed both in rats and humans, with highest levels observed in adults (19, 28, 79). In contrast, GLUT-1, which is present in fetal intestine, progressively disappears until it is undetectable in adults (28).

*Regulation by environmental changes.* Glucose flux across the intestinal mucosa can be altered in response to changes in environmental conditions, including periods of hyperglycemia and diabetes mellitus, or by high carbohydrate feeding.

HYPERGLYCEMIA. Hyperglycemia maintained for 12 h by intravenous injection of glucose in guinea pigs leads to a higher rate of transport across epithelial cells (36). Karasov and Debnam (61) provided evidence that the increase in glucose flux achieved shortly (within 3 h) after induction of hyperglycemia by intravenous infusion of glucose resulted primarily from an increase in transport through the basolateral membrane. This conclusion is in agreement with data of Cheeseman and Maenz (22), who measured, after 2 h of glucose infusion, a 3.5-fold increase in the $V_{max}$ for glucose uptake in vesicles prepared from the basolateral membrane of jejunal epithelial cells (22). Interestingly, this increased rate of glucose uptake was not paralleled by an increase in the number of glucose transporters, and cycloheximide injection before glucose infusion decreased glucose uptake rates by 80%, with no change in the number of cytochalasin B binding sites (22). This suggested the possible involvement of a short-lived protein in the control of transporter activity. A similar conclusion was reached in another study in which glucose transport rates in basolateral membrane vesicles and GLUT-2 expression were measured: 12 h of

high glucose infusion increased the rate of glucose transport three- to fourfold, with no detectable change in GLUT-2 protein (81).

DIABETES, STARVATION, AND CIRCADIAN RHYTHM. An increase in glucose transport rate has also been demonstrated associated with diabetes mellitus (33). In rats made diabetic by streptozocin treatment, an increase in the expression of SGLT-1, GLUT-2, and, to a lesser extent, GLUT-5 was observed after different periods of diabetes (14, 81), although in one study GLUT-5 levels were significantly decreased at 30 and 60 days of diabetes (80). The increase in the three transporters was observed both at the protein and mRNA levels. By in situ hybridization it appeared that cells at an earlier stage of their migration along the crypt-villus axis became positive for each transporter mRNA, suggesting recruitment of additional cells for transepithelial hexose transport. All of these modifications were reversible upon insulin therapy (14). Binding of [$^3$H]phlorizin, which binds specifically to the $Na^+$-glucose cotransporter, was also shown to be increased after 60 days of diabetes in the jejunum, whereas in the ileum an increase in phlorizin binding was already measurable after 14 days of diabetes, and phlorizin binding was further increased after 60 days (34).

The observed increase in GLUT-5 expression in diabetes indicates that insulinopenic diabetes may also stimulate the flux of fructose, as well as glucose. Interestingly, expression of GLUT-5 has also been reported to be regulated by circadian rhythm, with up to 12-fold higher mRNA levels observed at the end of the light cycle and with a concomitant 78% increase in protein levels. However, it is not clear whether these diurnal variations are really regulated by a circadian rhythm rather than by food intake, since no comparison of GLUT-5 expression with fasted rats was made in these experiments. Increased GLUT-5 expression has also been reported after starvation in the rat (19).

TRANSPORTER SUBSTRATES. A number of studies have demonstrated that the expression of intestinal transporters could be increased by elevated dietary levels of their substrates (21). Solberg and Diamond (103) showed that the rate of sugar transport was increased in brush-border membrane vesicles prepared from mice fed diets containing 55% of either glucose, galactose, fructose, maltose, or 3-*O*-methylglucose. In similar experiments performed in rats, it has been demonstrated that SGLT-1, GLUT-2, and GLUT-5 mRNA levels could be modulated specifically by different hexoses (78, 81). The D-isomers of glucose, galactose, fructose, mannose, and xylose, as well as the nonmetabolizable analogue 3-*O*-methylglucose, induce SGLT-1 expression. However, increased GLUT-2 levels can only be obtained by high-glucose, -galactose, or -fructose diets, and increased GLUT-5 levels can only be obtained by a high-fructose diet. At the protein level, fructose feeding increased GLUT-5 fivefold and eightfold at 1 and 7 days, respectively, with a much less pronounced effect seen at the mRNA level, suggesting that fructose increases its transporter expression primarily by a stabilization of the protein (15). These effects are rapidly reversible by reverting to the normal diet. Interestingly, GLUT-5 expression was not modified by fructose feeding in an intestinal loop severed from the rest of the intestine but still vascularized by the mesenteric blood vessels, indicating that direct contact of the sugar with the epithelial cells is necessary for the regulatory effect to take place.

In Caco-2 cells, a human colon carcinoma cell line, differentiation into epithelial cells is induced when cells reach confluence. The differentiation program is accompanied by an increased expression of SGLT-1, GLUT-5, and, at later time points, GLUT-2 (72). In these cells GLUT-5 gene transcription and protein accumulation are strongly upregulated by adenosine 3′,5′-cyclic monophosphate (74).

The above data thus indicate different requirements for SGLT-1-, GLUT-2-, and GLUT-5-regulated expression by dietary sugars. For SGLT-1, increased expression does not require the sugars to be metabolized (3-*O*-methylglucose) or even to be transported substrates (mannose, fructose, xylose). For GLUT-2 and GLUT-5, on the other hand, only the transported substrates regulate transporter expression (glucose, galactose, and fructose for GLUT-2 and fructose for GLUT-5). Regulation of SGLT-1 expression may therefore involve a direct signaling pathway for the control of this gene expression. Experiments by Ferraris and Diamond (35) provided strong evidence that the hexose signals inducing SGLT-1, as detected by changes in phlorizin binding sites in the brush border, were perceived by the crypt cells, which then committed their progeny to an increased or decreased transporter expression in response to an increased or decreased dietary level of each substrate. For GLUT-2 or GLUT-5, since only the transported sugars regulate their expression, the regulatory mechanisms may take place in more mature enterocytes already expressing the transporters.

Glucose flux across intestinal epithelium has been shown for many years to be a highly regulatable process. The recent data described here indicate that the basis for regulation of glucose flux lies in great part in the control of individual transporter molecule expression and that apical and basolateral transporters are regulated in all the situations studied. The molecular basis for this regulation is, however, still largely obscure. In particular, it is not known whether the changes in expression result from transcriptional or posttranscriptional mechanisms and why there is a sugar specificity in the control of transporter expression. For SGLT-1, it is intriguing that neither transport nor metabolism is required for the control of expression and there may thus be a direct interaction of the sugars with the plasma membrane to signal increased production or to stabilize the transporter. This last hypothesis would be consistent with the observed dissociation between the stronger effect of sugars on transporter protein than on mRNA abundance (35).

What is the role of the increased glucose flux through the intestinal epithelium? Increased hexose absorption in response to high carbohydrate feeding is probably an adaptive response favoring a better absorption of the

sugars present in the diet. However, in diabetes, the increased transport capability observed may lead to an aggravation of postprandial hyperglycemia. Control of higher transporter gene expression may thus be a way to prevent excessive sugar uptake in the postprandial state.

*Kidney*

In kidney, ~90% of the glucose is reabsorbed in the cells forming the S1 segment, or convoluted part, of the proximal tubule. The rest of the glucose is then completely reabsorbed in the S3 segment, or straight part, of the proximal tubule. As determined by immunocytochemical methods and schematized in Fig. 1*B*, glucose reabsorption in the S1 part is catalyzed by high-$K_m$, low-affinity transporters: SGLT-2 in the apical (60) and GLUT-2 in the basolateral membrane (113, 115). However, GLUT-1 was also detected by Western blot analysis in the proximal convoluted tubule (31). In the S3 region, where the luminal glucose concentration is lower, reabsorption depends on the combined action of the high-affinity, high-energy (2 $Na^+$ for 1 glucose) SGLT-1 for glucose uptake in the cells (68, 108) and GLUT-1 in the basolateral membrane (108, 115). As described above, GLUT-1 transport kinetics are asymmetric, with a higher $K_m$ for glucose efflux than for influx. GLUT-1 may thus provide an efficient efflux mechanism for glucose. However, S3 cells, in contrast to cells of the S1 segment, are also glycolytic (97, 118). The presence of GLUT-1 may thus allow efficient glucose uptake when these cells need to take up glucose across the basolateral membrane for use as an energy source.

GLUT-5 expression in rat kidney has been found by in situ hybridization to be restricted to the straight part of the kidney tubule (23). The exact role of this transporter in kidney physiology is not yet known. GLUT-1 is also present in more distal parts of the nephron, where it may be required for the cellular uptake of glucose and the generation of metabolic energy. It is indeed found at levels that correlate with the glycolytic activity of the different cell types. For instance, it is present at intermediate levels in the thin and thick ascending limbs and at highest concentrations in the connecting segment. High expression of GLUT-1 is also observed in the intercalated cells of the collecting duct and at a lower level in the principal cells. In the papilla, only intercalated cells express GLUT-1 (115). GLUT-4 has been detected by in situ hybridization in the thick ascending limb (23), although others have found GLUT-4 at the mRNA and protein level in the kidney microvessels and glomerular mesangial and epithelial cells (11). Expression of GLUT-4 was considerably decreased in microvascular and glomerular cells from diabetic rats (76).

*Regulated expression.* In uncontrolled diabetes the flux of glucose through the proximal tubule is increased. Dominguez et al. (30) have demonstrated that GLUT-2 expression at the mRNA and protein levels was increased after 2–4 wk of streptozocin diabetes, and that this increased expression correlated with higher glucose uptake by proximal tubules. This effect was completely reversed by insulin normalization of the induced diabetes. Interestingly, the level of $Na^+$-glucose cotransporter detected by Western blotting was unchanged in the same animals. However, from the published data it is not clear whether the antibody used recognized only SGLT-1 or SGLT-2, or both SGLT-1 and SGLT-2. Finally, GLUT-1 protein and mRNA were decreased in the diabetic rats and returned to normal after insulin treatment. These data provide evidence that an increase in GLUT-2 expression is a major correlate of elevated glucose flux in the proximal nephron of diabetic animals.

As in intestine, GLUT-2 and GLUT-5 levels can also be increased by high dietary sugars, and glucose stimulates GLUT-2 but not GLUT-5 expression, whereas fructose increases GLUT-5 but not GLUT-2 levels (15).

*Liver*

In conditions of high blood glucose, insulin stimulates the storage of glucose in the form of glycogen or its metabolism via the glycolytic pathway. In contrast, when blood glucose decreases, glucagon or other counterregulatory hormones stimulate glycogen breakdown and activate the gluconeogenic pathway, so that the output of glucose from hepatocytes maintains the blood glucose to a minimal level of ~5 mM. The flux of glucose into or out of liver can reach up to 50 g/h (119). These fluxes are not controlled by acute modifications of transporter function but rather by hormone-mediated alterations in the enzymes catalyzing rate-limiting steps in glycolysis, gluconeogenesis, and glycogen synthesis or degradation (92). However, chronic regulation of transporter expression may be of importance to favor these glucose fluxes, especially glucose output, as described below.

*Regional distribution of glucose transporters in liver.* GLUT-2 is the major transporter isoform present in the sinusoidal membrane of hepatocytes (113), and its level of expression is higher in periportal than in perivenous hepatocytes (43). In the perivenous region, GLUT-1 is also present in the sinusoidal membrane of hepatocytes, which form a few rows around the terminal hepatic venules and also express GLUT-2 (110). It is not clear why these cells have GLUT-1 on their plasma membrane, but this may be related to functional differences between hepatocytes present at different locations along the periportal-perivenous axis. The periportal hepatocytes are more gluconeogenic than the perivenous hepatocytes, which are more glycolytic (58). It is thus striking that, as in kidney, a correlation between GLUT-1 expression and the glycolytic activity of the cells exists, and GLUT-2 is present in higher amounts in cells with higher gluconeogenic enzyme content. The expression in hepatocytes of GLUT-2 is certainly necessary to permit bidirectional glucose flux, although GLUT-1 may provide some advantages for the efficient functioning of the glycolytic pathway. GLUT-2 may also be required for fructose uptake and metabolism in liver, since hepatocytes do not express GLUT-5 but metabolize fructose efficiently.

*Developmental regulation of glucose transporter expression.* In the development of the rat, GLUT-2 can first be observed at the end of fetal life, with very low levels detected at *day 15* and increasing thereafter. After birth, the levels of GLUT-2 rise to reach their maximal levels at adult age (94, 117). Glucokinase, the high-$K_m$ hexokinase isoform that is the main glucose phosphorylating enzyme of adult liver, is not observed until 2 wk after birth and rises until *day 60*. In contrast, GLUT-1 is high in the fetal and neonate periods and starts to decline 2 wk after birth to become very low in the adult. Hexokinase I varies in parallel with GLUT-1; it is high in fetal liver and decreases after birth until low levels are reached in the adult. The switch in transporter expression in early life can be altered by weaning the pups on different diets. For instance, weaning on high-carbohydrate diet has a stimulatory effect on GLUT-2 expression, whereas a high-fat diet leads to only a very small increase in this transporter expression (94). Thus the developmental program leading to change in transporter expression can be strongly modulated by nutrient composition.

*Regulation in altered metabolic conditions.* Regulation of GLUT-2 expression in streptozocin diabetic rats has been reported to be either unchanged (114) or elevated (89). In more recent works, the kinetics of GLUT-2 expression after injection of streptozocin into rats was precisely followed (17). Shortly after treatment (6 h) there was a 90% decrease in GLUT-2 mRNA, which correlated with the transient hyperinsulinemia and hypoglycemia induced by the destruction of the pancreatic β-cells. After 48 h, however, GLUT-2 mRNA reached levels twofold higher than in controls, and the protein levels were increased by two- to threefold after 48–72 h. As expected, the mRNA for phospho*enol*pyruvate carboxylase (PEPCK) was modified exactly in parallel, whereas that for glucokinase underwent the inverse modification with slightly higher levels after 6 h and decreased expression at 48 h. With the use of hyperinsulinemic, euglycemic clamps, glucose was shown to partially prevent the effect of high insulin on GLUT-2 expression. In isolated hepatocytes the inhibitory effect of insulin on GLUT-2 expression could be reversed by glucose. It was further demonstrated that glucose by itself has a stimulatory action on GLUT-2 mRNA accumulation, which was dominant over the inhibitory action of insulin (93). The effect of glucose on GLUT-2 in isolated hepatocytes could also be observed with mannose and fructose but not with the nonmetabolizable substrates 3-*O*-methylglucose and 2-deoxy-D-glucose or with the nontransported disaccharide sucrose (3). The increase in GLUT-2 expression observed in streptozocin-diabetic rats could also be reversed by decreasing the blood glucose concentrations in the absence of insulin treatment either with phlorizin (10) or by treatment with vanadate, which is an insulinomimetic substance (9, 120).

Control of GLUT-2 expression in isolated hepatocytes is at the transcriptional level and requires glucose metabolism initiated by phosphorylation either by hexokinase or by glucokinase (96). The GLUT-2 gene *cis*-regulatory elements required for this glucose control of transcription are located within the first 338 nucleotides upstream of the transcription initiation site and do not show any homology with the glucose regulatory elements of other genes such as those for insulin or L-type pyruvate kinase (96, 123).

In obese animals, such as the Zucker or Wistar fatty rats (129) or the viable yellow mouse (100), there is also an increase in GLUT-2 expression compared with the appropriate controls. Expression of GLUT-1 by perivenous hepatocytes is also increased in diabetes and during fasting (114), primarily as a result of expression in additional rows of hepatocytes around the terminal hepatic venules, an effect that may be due to low levels of circulating insulin rather than to changes in glycemia (109, 110).

The GLUT-2 transporter is a bidirectional transporter that has the same $K_m$ for glucose uptake and efflux. It is striking that its expression is augmented in situations in which hepatic glucose output is increased, such as in streptozocin diabetes, and that it is present at highest levels in periportal hepatocytes. There is thus a correlation between high GLUT-2 expression and high levels of key gluconeogenic enzymes such as PEPCK. Thyroid hormone, which is known to increase hepatic glucose output, also increases GLUT-2 protein expression (124). Existing data thus suggest that even though no acute regulation of transporter expression is required in hepatocytes to control glucose utilization, GLUT-2 upregulation may be required for efficient glucose output in specific conditions.

## CONCLUSIONS

The past 10 years have seen an extraordinary development of our understanding of the molecular control of glucose flux into and out of different organs. This was made possible by the initial characterization by molecular cloning of GLUT-1, the human erythrocyte glucose transporter. The following characterization of the different members of the glucose carrier family, as well as, independently, that of the $Na^+$-dependent glucose cotransporters, has further enabled the study of the molecular basis of glucose transport in almost all tissues. It is now clear that each transporter isoform fulfills a particular role in the general control of glucose homeostasis based on its specific kinetic property, sugar specificity, and regulated expression by glucose or other hexoses and by different hormones.

Much remains to be learned, however. A few specific points are *1*) understanding of the basis for the regulated expression of these transporters by different hexoses, *2*) characterization of the glucose binding sites and the path of glucose across the transporter molecules, and *3*) identification of the signals targeting GLUT-1 and GLUT-2 to the basolateral membrane, GLUT-5 to the apical brush border, and GLUT-4 to the insulin-responsive intracellular vesicles. Also, as reported recently, mice made homozygous for a GLUT-4-inactivating mutation have an almost normal glucose homeostasis (63). This indicates that even though GLUT-4 appears to be critical for glucose handling by

insulin target tissues, it is not essential for survival. Similar genetic approaches should be taken to inactivate other GLUT genes to study their role in the control of glucose homeostasis. This may lead to a much better understanding of the control of energy balance and may also lead to the discovery of new ways to utilize glucose and other nutrients.

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