Review

The Glucose Transporter Families SGLT and GLUT: Molecular Basis of Normal and Aberrant Function.

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ABSTRACT. Glucose enters eucaryotic cells *via* 2 different types of membrane associated carrier proteins, the Na^+-coupled glucose transporters (SGLT) and glucose transporter facilitators (GLUT). Three members of the SGLT family function as sugar transporters (SGLT1 and SGLT2) or sensors (SGLT3). The human GLUT family consists of 14 members, of which 11 have been shown to catalyze sugar transport. The individual isotypes exhibit different substrate specificity, kinetic characteristics, and expression profiles, thereby allowing a tissue-specific adaptation of glucose uptake through regulation of their gene expression. Furthermore, some transporters (eg, GLUT4 and GLUT8) are regulated by their subcellular distribution. In addition to catalyzing glucose entry into cells, some isotypes (eg, GLUT2) seem to be involved in the mechanisms of glucosensing of pancreatic β-cells, neuronal, or other cells, thereby playing a major role in the hormonal and neural control. Targeted disruption in mice has helped to elucidate the physiologic function of some isotypes (GLUT1, GLUT2, GLUT4). Furthermore, several congenital defects of sugar metabolism are caused by aberrant transporter genes (eg, the glucose-galactose malabsorption syndrome, SGLT1; the glucose transporter 1 deficiency syndrome; and the Fanconi-Bickel syndrome, GLUT2). In addition, a malfunction of glucose transporter expression or regulation (GLUT4) appears to contribute to the insulin resistance syndrome. (*Journal of Parenteral and Enteral Nutrition* **28**:365–372, 2004)

Glucose is the main source of energy in eucaryotic organisms and plays, therefore, a central role in metabolism and cellular homeostasis. Most mammalian cells are dependent on a continuous supply of glucose, which acts as primary source for the generation of adenosine-5′-triphosphate (ATP).[1,2] Glucose homeostasis is maintained by the coordinated regulation of 3 processes. First, glucose absorption *via* the small intestine (Fig. 1); second, glucose production in the liver (Fig. 3); and third, consumption of glucose by nearly all tissues.[3] Tissues such as the brain need glucose constantly, and low blood glucose concentrations can cause seizures, loss of consciousness, and irreversible cell damage. On the other hand, excessive blood glucose concentrations have a detrimental effect referred to as "glucotoxicity," which can result in blindness, renal failure, cardiac and peripheral vascular disease, and neuropathy.[4,5] As glucose is the main regulator of insulin secretion and production, excessive amounts of glucose over a prolonged period have negative effects on pancreatic β-cell function, resulting in increased sensitivity to glucose, increased basal insulin release, reduced maximal secretory response, and a gradual depletion of insulin stores.[5] Thus, blood glucose concentrations need to be maintained within narrow limits and are therefore kept at a steady level of about 80 to 110 mg/dL. Because the lipid bilayer of the eucaryotic plasma membrane is impermeable for hydrophilic molecules, glucose is transported across the plasma membrane by membrane associated carrier proteins, glucose transporters. There are 2 different types of transporter proteins, which mediate the transfer of glucose and other sugars through the lipid bilayer, a Na^+-coupled carrier system (SGLT) and the facilitative glucose transporters (GLUT).[6,7] Both types of transporters belong to families of the solute carrier gene series (*SLC*), which comprise 43 families (*SLC1–SLC43*), with 298 genes (for an overview, see http://www.pharmaconference.org/slcable.asp). This review summarizes all family members of both classes of glucose transporters and focuses in particular on defects in the glucose transport system and the resulting pathophysiological consequences. Moreover, it discusses the potential role of glucose transporters as part of the glucosensing systems.

The SGLT Family

The SGLT family (sodium dependent glucose transporter; gene name *SLC5A*) comprises Na^+-dependent glucose co-transporters (SGLT1 and SGLT2), the glucose sensor SGLT3, the widely distributed inositol[8] and multivitamin transporters SGLT4 and SGLT6,[9] and the thyroid iodide transporter SGLT5.[10] The model of their secondary structure, which is based on experimental studies of SGLT1[11] and related family members[12,13] and on a computational analysis of SGLT1, SGLT2, and pig SGLT3,[11] contains 14 mem-
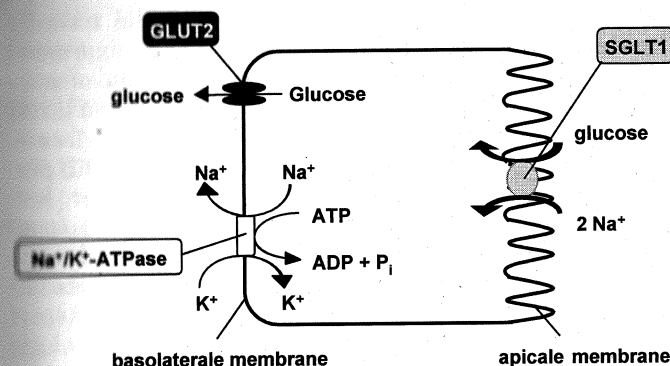
FIG. 1. Transport of glucose in intestinal epithelium. Entry of glucose into epithelial cells is catalyzed by SGLT located in the apical membrane. Glucose leaves the cell *via* a facilitated glucose transporter (GLUT2) located in the basolateral membrane.

brane spanning α-helices with both the hydrophobic N-terminus and the C-terminus facing the extracellular site. Intestinal glucose absorption and renal reabsorption in proximal tubules *via* SGLT1 and SGLT2 can be blocked by phlorizin (phloretin-2′-β-glucoside), a plant product from the bark of the apple tree.[14]

Sodium-dependent glucose cotransporters (SGLT1 and SGLT2). The sodium-dependent glucose transporters, also known as co-transporters or symporters, are integral membrane proteins that mediate the transport of glucose and, with much lower affinity, galactose across the plasma membrane by an active transport mechanism.[15] This transport process is a cotransport of glucose molecules and sodium ions. The energetically favored movement of a sodium ion across the plasma membrane into the cell is driven by a concentration gradient and a membrane potential and is coupled to the movement of the glucose molecule. In the steady state, sodium ions transported into the cells across the apical cell membrane are pumped by a sodium/potassium ATPase across the basolateral membrane. Glucose concentrated inside the cell by the symport moves outward through the basolateral membrane *via* glucose transport facilitators designated GLUT-proteins (Fig. 1).

The SGLT1 (gene name *SLC5A1*)[16] is a high-affinity, low-capacity sodium-glucose symporter with a sodium-to-glucose coupling ratio of 2:1.[17] The transporter is expressed mainly in intestine, heart, and kidney.[18]

The SGLT2 (gene name *SLC5A2*)[19] is in contrast to SGLT1 a low-affinity, high-capacity sodium-glucose symporter with a sodium-to-glucose coupling ratio of 1:1. The protein shows an ubiquitous expression pattern with highest expression levels in kidney,[18] where it mediates the absorption of the bulk of the filtered glucose in the proximal convoluted tubule.[17]

SGLT3, a glucose-sensitive ion channel. Unlike SGLT1 and SGLT2, human SGLT3 (gene name *SLC5A4*) does not transport glucose when expressed in *Xenopus laevis* oocytes.[20] In contrast, pig SGLT3 expressed in *Xenopus* oocytes behaves like a tightly coupled sodium-glucose cotransporter with a lower affinity for glucose and a more restricted sugar specificity than SGLT1.[21–24] Human SGLT3 was mainly detected in intestine, spleen, liver, kidney, and muscle.[25] Recently, Diez-Sampedro and colleges[20] analyzed the expression of human SGLT3 in more detail and could show that SGLT3 is mainly expressed in cholinergic neurons of the small intestine and in skeletal muscle at the neuromuscular junctions.[20] Although human SGLT3 exhibited no glucose transport activity, glucose produced a phlorizin-sensitive inward current that depolarized the membrane potential by up to 50 mV. As a result of the low sugar affinity of SGLT3 at pH 7.5, the depolarization in membrane potential was a linear function of glucose concentration in the physiologic concentration range. Thus, Diez-Sampedro et al[20] suggested that variations in plasma glucose concentration modulate membrane potential in cholinergic neurons in the enteric nervous system and at the neuromuscular junction in skeletal muscle. SGLT3 may therefore act as a glucosensor by conveying information to the cell about external glucose concentration directly through the membrane potential or indirectly coupled through another molecule such as a G protein.

The GLUT Family

The human genome contains 14 members of the GLUT family (Fig. 2), which can be divided into 3 subfamilies according to sequence similarities and
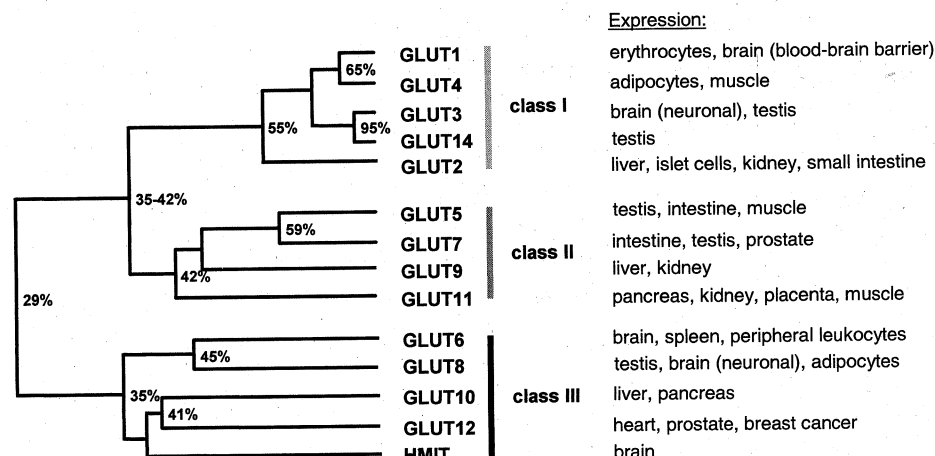

FIG. 2. Dendrogram of the family of human sugar transporter facilitators. The alignment was performed with the CLUSTAL program. Numbers at the branches of the tree indicate percentage of identity.

characteristic elements.[26] The members of the GLUT family (gene name *SLC2A*) exhibit a striking tissue-specific expression.[1,3] Moreover, they differ in their functional characteristics (eg, their substrate specificity, their K_m values, and their binding-affinities to the inhibitory ligands cytochalasin B and forskolin).[26] Furthermore, the function of some transporters (eg, GLUT4) is modified by a regulated redistribution of the protein between the cell membrane and an intracellular compartment. These different characteristics allow a complex and specific regulation of glucose uptake according to the cellular requirements and the physiologic conditions of substrate supply.[26]

As early as 1985, Mueckler et al[27] suggested a structural model of a facilitative glucose transporter according to a hydropathy plot of the GLUT1. This model was later supported by the results of a glycosylation scanning study.[28] According to this model, the GLUT proteins comprise the 12 hydrophobic, transmembrane α-helices arranged in a way that the C-terminus and the N-terminus are facing the cytoplasm. Recently, Lemieux et al[29] succeeded in crystallizing a structurally related protein, the glycerol-3-phosphate transporter of *Escherichia coli*, and obtained a 3-dimensional structure that confirmed the proposed model of the GLUT proteins and of all other related transporters. Sequence comparisons of GLUT1 to 4 and site-directed mutations performed in GLUT1 and GLUT4 allowed the definition of characteristic sugar transporter signatures: (a) 7 conserved glycine residues within the helices, (b) several basic and acidic residues in the surface of the proteins, (c) 2 conserved tryptophan residues, and (d) 2 conserved tyrosine residues.[26]

Class I sugar transport facilitators. The class I facilitative glucose transporters comprise the thoroughly characterized isoforms GLUT1 to 4 and the recently identified GLUT14. The ubiquitously expressed GLUT1[27] is responsible for the basic supply of cells with glucose. GLUT1 exhibits highest expression levels in erythrocytes and endothelial cells of the brain. GLUT2[30] is a low-affinity glucose transporter with predominant expression in pancreatic β-cells, liver, kidney, and small intestine (basolateral membrane). In all these tissues, the uptake of glucose is not dependent on the number and activity of the glucose transporters but on the blood glucose concentration.[1] Thus, transport activity of GLUT2 cannot be saturated by physiologic blood glucose concentrations. In addition to glucose, GLUT2 is able to transport fructose[31] and, with higher affinity, glucosamine.[32] GLUT3[33] is a high-affinity glucose transporter with predominant expression in tissues with a high glucose requirement (eg, brain). GLUT4[34] is a high-affinity glucose transporter expressed in insulin-sensitive tissues (heart, skeletal muscle, adipose tissue). Insulin stimulates the translocation of GLUT4 from intracellular membranes to the plasma membrane (Fig. 3), resulting in an immediate 10- to 20-fold increase in glucose transport.[35-37] In addition, in skeletal muscle translocation of GLUT4 can be induced by muscle contraction and hypoxia.[38,39] The human gene encoding GLUT14 (*SLC2A14*)[40] appears to represent a duplication of the *SLC2A3* gene, and its amino acid sequence is 95% identical with GLUT3. GLUT14 is exclusively expressed in testis; no ortholog of GLUT14 was found in mice.

GLUT1, GLUT3, and GLUT4 have been described to also transport dehydroascorbic acid (DHAA).[41,42] DHAA a stable oxidation product of ascorbate, which is transported by specific sodium-ascorbic acid cotransporters and mainly stored in skeletal muscle and brain.
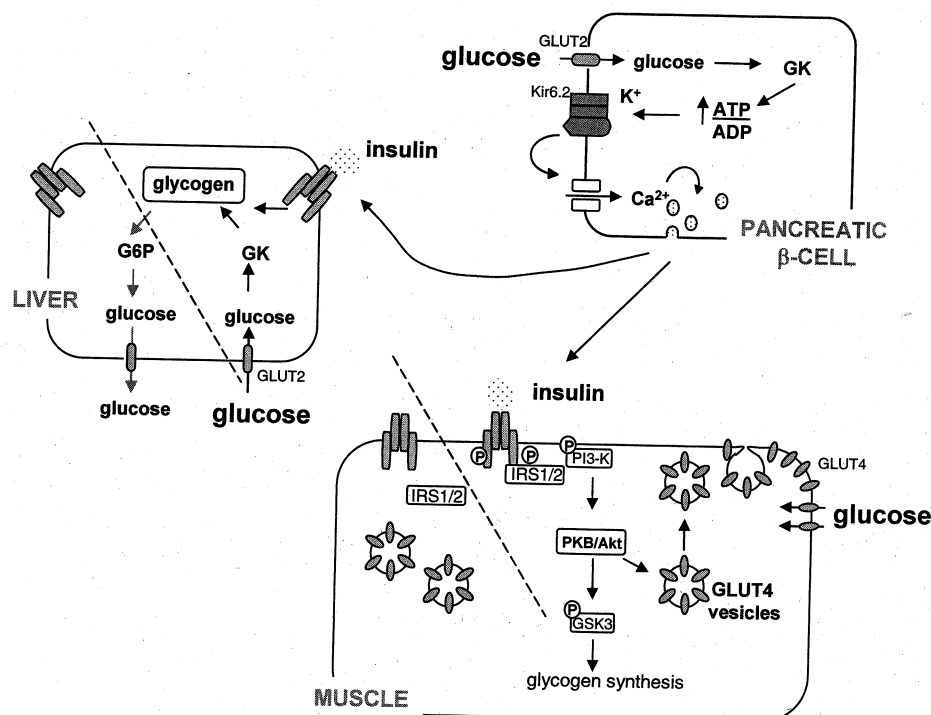

FIG. 3. Mechanism of glucose-induced secretion of insulin in pancreatic β-cells and of its effects in peripheral tissues.

Class II sugar transport facilitators. The class II facilitative glucose transporters include the fructose-specific transporter GLUT5 and 3 related proteins, GLUT7, GLUT9, and GLUT11. GLUT5 mRNA[43] is predominantly expressed in small intestine, testis, and kidney. GLUT5 exhibits no glucose transport activity and is responsible for the uptake of fructose in the mentioned tissues. GLUT7 is a high-affinity transporter for glucose and fructose.[44] GLUT7 mRNA can be detected in small intestine, colon, testis, and prostate; within the small intestine, GLUT7 is predominately expressed in the enterocytes' brush border membrane.[44] GLUT9[45] exhibits highest expression levels in kidney and liver; lower mRNA levels were detected in small intestine, placenta, lung, and leukocytes. Carayannopoulos et al[46] demonstrated expression of GLUT9 in the mouse at a preimplantation stage of development and suggested that GLUT9 is critical for early preimplantation development. Moreover, they identified 3 different isoforms, which seem to be differentially expressed during development. Two of the mouse GLUT9 isoforms showed glucose transport activity when expressed in *X. laevis* oocytes. GLUT11[47] exhibits a low affinity for glucose and a low-affinity cytochalasin B binding. As glucose transport activity can be inhibited by fructose, GLUT11 is suggested to be a fructose transporter with low affinity to glucose. GLUT11 is expressed predominantly in pancreas, kidney, and placenta and exhibits also moderate expression in heart and skeletal muscle. Alternative splicing of the *SLC2A11* gene generates 3 isoforms that differ in their N-terminal sequence.[48] According to data of Gaster et al,[49] GLUT11 immunoreactivity in skeletal muscle was present exclusively in slow-twitch fibers and was predominantly associated with intracellular structures and, to a lesser degree, with the sarcolemma. Thus, the expression pattern of GLUT11 in muscle is strikingly different from that of GLUT4, which is associated almost exclusively with the plasma membrane in all fiber types.[50]

Class III sugar transport facilitators. Class III comprises the transporter isoforms GLUT6, GLUT8, GLUT10, GLUT12, and HMIT. In contrast to class I and II, all members of this class are characterized by a shorter extracellular loop 1 that lacks a glycosylation motif, and by the presence of such a site in the larger loop 9.[26] Because class III sugar transporters show highest homologies with different transporters in yeast, bacteria, and *Drosophila melanogaster*, they were speculated to have evolved earlier than class I and class II transporters; the latter might reflect an evolutionary adjustment to the additional requirements of glucose homeostasis in mammals.[26] The low-affinity glucose transporter GLUT6[51] is predominantly expressed in brain, spleen, and peripheral leukocytes. Like its closest relative GLUT8, the N-terminus of GLUT6 harbors a dileucine motif that directs the protein to intracellular storage compartments when expressed in isolated fat cells and COS-7 cells.[52] GLUT8[53] is a high-affinity glucose transporter whose activity is specifically inhibited by D-fructose and D-galactose, indicating that GLUT8 might be a multifunctional transporter.[54] GLUT8 is predominantly expressed in testis, and lower amounts of GLUT8 mRNA were detected in most other tissues, including insulin-sensitive tissues like heart and skeletal muscle. Moreover, GLUT8 was detected in preimplantation embryos, where it was reported to mediate insulin-stimulated glucose uptake.[55] In testis, the protein was associated with the acrosomal region of mature spermatozoa.[56] In addition, GLUT8 may play a role in glucose uptake of adipocytes; its expression was found to be regulated by the metabolism of these cells.[57] GLUT10[58] is predominantly expressed in the liver and pancreas. The *SLC2A10* gene was mapped to a region (chromosome 20q12-q13.1) that has previously been linked to type 2 diabetes.[58] However, a polymorphism in codon 206 (Ala → Thr) was associated with interindividual variation of fasting and oral glucose–induced serum insulin levels but not with the incidence of type 2 diabetes.[59] GLUT12[60] is predominantly expressed in heart and prostate and exhibits glucose transport activity when expressed in *X. laevis* oocytes. This activity was found to be competitively inhibited by D-galactose and to a lesser extent by D-fructose.[61] In addition, GLUT12 seems to sustain the increased glucose consumption in prostate carcinoma[62] and breast cancer.[63] The H^+-coupled *myo*-inositol transporter HMIT[64] is expressed predominantly in the brain. It specifically transports *myo*-inositol and related stereoisomers but lacks any sugar transport activity.

Glucose Transporters as Components of the Glucosensing Machinery

A constant monitoring of blood glucose concentrations by specific glucosensing mechanisms is required for the maintenance of the whole-body glucose homeostasis. The best described glucose detection system is that of pancreatic β-cells, which control the insulin secretion (Fig. 3). This sensor machinery includes glucose transporters (GLUT2),[65] the enzyme glucokinase,[66] and the ATP-sensitive K^+ (K_{ATP}) channel.[67] When the extracellular glucose concentration increases, more glucose enters the β-cell *via* the low-affinity glucose transporter GLUT2 and is phosphorylated by glucokinase. Glycolytic and oxidative metabolism of glucose raises the ATP-to-ADP ratio, causing ATP to bind to the K_{ATP} channel complex. This inactivates the channel and leads to membrane depolarization, influx of calcium, and insulin secretion.

A second glucosensing system is present in the brain, which is particularly vulnerable to hypoglycemia. It consists of neurons that directly sense changes in glucose levels and respond in alteration of their firing rate system,[68] triggering counterregulatory impulses (eg, activation of the sympathic nervous systems). The existence of specialized glucosensing neurons has been known for many years.[69] As brain glucose levels rise, glucose-responsive (GR) neurons increase and glucose-sensitive (GS) neurons decrease their firing rate. Little is known about the mechanism by which GS neurons sense glucose. GR neurons appear to function much like the pancreatic β-cell, with glucokinase modulating the K_{ATP} channel, leading to membrane depolarization, calcium influx, and increased cell firing.[68,70] The glucose transporter involved in the neuronal glucosensing unit is still not known. Possible candidates

are the high-affinity glucose transporter isoforms GLUT3 and GLUT8 because of their distinct expression in neurons of the hypothalamus, but also the low-affinity transporter GLUT2.[71]

Recently, a member of the SGLT family (SGLT3) was predicted to be a glucosensor rather than a Na^+/glucose cotransporter.[18] In cells expressing SGLT3, glucose caused a specific Na^+-dependent depolarization of the membrane potentia, whereas no sugar transport could be detected. The authors concluded that SGLT3 might be involved in glucosensing in both the central nervous system and the gastrointestinal tract.

Pathophysiology of Glucose Transport

Glucose transporters and insulin action. Insulin stimulates glucose uptake in muscle and adipose tissue by recruiting the insulin-sensitive glucose transporter isoform GLUT4 from an intracellular storage pool to the plasma membrane.[35–37] When GLUT4 expression is reduced or fully disrupted, the ability of these peripheral tissues, in particular muscle, to adequately respond to insulin is impaired.[72] Insulin resistance of muscle tissue is a characteristic symptom of type 2 diabetes mellitus and appears to precede the decompensation of glucose homeostasis because of islet cell failure. In type 2 diabetic patients, insulin resistance of muscle glycogen synthesis has been shown to be secondary to defective glucose transport.[73] Thus, GLUT4 expression and trafficking may play a major role in the pathogenesis of insulin resistance.

More recently, the importance of glucose homeostasis through insulin—and consequently through the glucose transporter GLUT4—has been demonstrated in nondiabetic patients. Van den Berghe et al[74] hypothesized that hyperglycemia or relative insulin deficiency during critical illness may directly or indirectly confer a predisposition to complications, such as severe infections, polyneuropathy, multiple-organ failure, and death. The authors performed a clinical study to determine whether normalization of blood glucose levels with intensive insulin therapy has a positive effect on the state of health in critically ill patients. Indeed, the use of exogenous insulin to maintain blood glucose at a level no higher than 110 mg/dL reduced morbidity and mortality among critically ill patients, regardless of whether they had a history of diabetes.[74]

SGLT1 and SGLT2 deficiency. SGLT1 deficiency results in the development of glucose-galactose malabsorption (GMM) through the intestinal brush border, an autosomal recessive disease characterized by neonatal onset of severe watery and acidic diarrhea, which is fatal within a few weeks unless nutrients containing glucose and galactose, including polycose and products derived from corn syrup, are removed from the diet.[75,76] The mutations responsible for GMM include missense, nonsense, frame shift, splice site, and promoter mutations of the *SLC5A1* gene.[75,77] Most mutations result in either truncated SGLT1 protein or in mistargeting of the transporter in the cell.[76]

Congenital defects in SGLT2, which is located in the apical membrane of the S1 segment in proximal renal tubule cells, lead to a primary renal glucosuria.[78]

Patients with this disease have normal blood glucose levels, normal oral tolerance test results, and persistent glucosuria. In the most severe cases, patients may excrete a major portion of the filtered glucose.[79]

GLUT1 and GLUT2 deficiency. Glucose transporter type 1 deficiency syndrome defines a group of disorders resulting from impaired glucose transport across blood-tissue barriers. In 1991, de Vivo et al[80] described 2 children with infantile seizures, developmental delay, and acquired microcephaly. Analysis of the cerebrospinal fluid (CSF) showed an unexplained hypoglycorrhachia (low glucose concentration in CSF) in the presence of normoglycemia (CSF/blood glucose ratio <0.4), whereas lactate concentrations were low to normal in the CSF, suggesting intact intracellular pathways for glucose use. According to these findings, a defect in GLUT1-mediated glucose transport across the blood-brain barrier was assumed. Since 1991, >70 patients and numerous heterozygous mutations resulting in GLUT1 haploinsufficiency have been identified.[81–83] Clinical features are variable and include seizures, delayed development, acquired microcephaly, hypotonia, and motor disorders including elements of ataxia, dystonia, and spasticity.[83] The disease is treated effectively with a ketogenic diet because ketone bodies easily penetrate the blood-brain barrier and serve as an alternative fuel for the brain.[84,85]

A congenital defect within the *SLC2A2* gene is the basis of the Fanconi-Bickel syndrome (FBS), a rare autosomal-recessive inborn error of metabolism, which resembles type I glycogen storage disease.[78,86] One hundred twelve FBS patients and 34 different GLUT2 mutations have been reported in the recent literature. Because GLUT2 is the predominant glucose transporter in hepatocytes, pancreatic β-cells, enterocytes, and renal tubular cells, a loss of GLUT2 leads to a typical combination of hepatorenal glycogen accumulation, glucose and galactose intolerance, fasting hypoglycemia, a characteristic tubular nephropathy, and severely stunted growth.[87] Although no specific therapy is available for FBS patients, the symptomatic treatment is directed toward a stabilization of glucose homeostasis and compensation for renal losses of various solutes.[87]

Transgenic mice lacking GLUT1, GLUT2 or GLUT4. So far, 3 genes encoding members of the GLUT family, GLUT1, GLUT2, and GLUT4, have been inactivated in mice by either a gene knockout approach or an antisense-based technique in order to study their *in vivo* functions.

Maternal diabetes is known to reduce GLUT1 expression and glucose uptake in preimplantation embryos, resulting in apoptosis,[88] which is potentially involved in diabetic embryopathy. Therefore, using an antisense-based method, Heilig et al[89] generated transgenic mice (GT1AS) in which GLUT1 is suppressed in a range observed in embryos of diabetic mothers. Although the homozygous GT1AS genotype was lethal during gestation, heterozygous GT1AS embryos exhibited an impaired development from the earliest stages on, leading to developmental malformations and embryonic demise in those with lowest GLUT1 levels. In animals with reduced GLUT1

expression, multiple organs (eg, kidney, brain, liver, intestine) were found to be affected.[89] These data indicate that the GLUT1 is essential for development in most cells and tissues.

Transgenic mice lacking the glucose transporter GLUT2 (GLUT2^{-/-} mice) develop diabetes early and show an abnormal postnatal pancreatic islet development. They are characterized by hyperglycemia, hypoinsulinemia, hyperglucagonemia, and glucosuria and die within the first 3 weeks of life. Moreover, their endocrine pancreas exhibits a loss of first-phase glucose-stimulated insulin secretion and an increased α- to β-cell ratio.[90,91] Although transgenic re-expression of GLUT2 in pancreatic β-cells of GLUT2^{-/-} mice restores their normal secretory function and rescues the mice from early death, the reexpression has no effect on peripheral tissues where GLUT2-dependent glucose sensors control glucagon secretion and glucose use.[65] These data indicate that GLUT2 is essential for glucosensing and function of the pancreatic β-cells.

The *in vivo* function of GLUT4 was studied by disruption of the *Slc2a4* gene in mice either in the whole organism (total knockout mouse) or in a tissue-specific pattern exclusively in skeletal muscle, heart, or adipose tissue (Cre/loxP-recombination system). In order to determine the importance of glucose uptake into skeletal muscle for glucose homeostasis, Zisman et al[92] disrupted the *Slc2a4* gene selectively in mouse muscles. The resulting mice were characterized by a profound reduction in basal glucose transport and a marked reduction of the effects of insulin and contraction. In contrast to total GLUT4 null mutants (see below), muscle-specific GLUT4^{-/-} mice showed severe insulin resistance and glucose intolerance from an early age, highlighting the essential role of GLUT4-mediated glucose uptake in muscle for the maintenance of normal glucose homeostasis. Moreover, the primary defect in muscle glucose transport of muscle-specific GLUT4-knockout mice leads to secondary effects resulting in a reduction of insulin's ability to stimulate glucose uptake in adipose tissue and to suppress hepatic glucose production. These effects are thought to be caused by glucose toxicity and to contribute to insulin resistance and to the development of diabetes.[93]

The heart-specific GLUT4^{-/-} mouse generated and characterized by Abel et al[94] exhibits a normal life span and normal serum concentrations of insulin, glucose, free fatty acids, and lactate. The insulin-stimulated glucose transport in the heart is abolished, compensated by modest cardiac hypertrophy and a 3-fold increase of basal cardiac glucose transport and GLUT1 expression.

Abel et al[95] generated mice with adipose-selective interruption of the *Slc2a4* gene in order to determine the role of adipose GLUT4 in glucose homeostasis and in the pathogenesis of insulin resistance and diabetes. Despite markedly impaired insulin-stimulated glucose uptake in adipocytes, these mice exhibit normal growth and adipose mass. Although expression of GLUT4 is preserved in muscle, fat tissue–specific GLUT4^{-/-} mice develop secondarily induced insulin resistance in muscle and liver, resulting in the development of glucose intolerance and hyperinsulinemia. Thus, an adipose-specific disruption of GLUT4 increases the risk of developing diabetes.[95]

In contrast to the specific effects on glucose homeostasis observed in the tissue-specific GLUT4 null mutants, conventional GLUT4^{-/-} mice were growth-retarded and exhibited decreased longevity associated with cardiac hypertrophy and severely reduced adipose tissue. Although these GLUT4 null mice were less sensitive to insulin action, they showed only mild disturbance in glucose homeostasis and exhibited nearly normal blood glucose levels. Thus, it was concluded that GLUT4 is not required for maintaining glucose homeostasis but is absolutely essential for sustained growth.[96] However, the effects of GLUT4 disruption on growth and development may have obscured specific effects on glucose homeostasis in tissues.

Concluding Remarks and Future Perspectives

Glucose transporters of the SGLT and the GLUT family are critical regulators of glucose use, glucose storage, and also—as part of glucosensing systems—the hormonal control of metabolism. Their heterogeneity allows a complex and specific fine tuning of glucose transport activity that is based on variable expression or subcellular distribution of individual isotypes. In spite of considerable progress in recent years, there is still much to be learned about the substrate specificity, the kinetics, and the physiologic function of some isotypes. Furthermore, future research will expand our knowledge as to the association of single nucleotide polymorphisms in transporter genes or in genes regulating their function, with diseases of carbohydrate metabolism (eg, insulin resistance and diabetes mellitus).

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