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Glucose transporters: Structure, function and consequences of deficiency

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Summary: There are two mechanisms for glucose transport across cell membranes. In the intestine and renal proximal tubule, glucose is transported against a concentration gradient by a secondary active transport mechanism in which glucose is cotransported with sodium ions. In all other cells, glucose transport is mediated by one or more of the members of the closely related GLUT family of glucose transporters. The pattern of expression of the GLUT transporters in different tissues is related to the different roles of glucose metabolism in different tissues. Primary defects in glucose transport all appear to be extremely rare and not all possible deficiencies have been identified. Deficiency of the secondary active sodium/glucose transporters result in glucose/galactose malabsorption or congenital renal glycosuria. GLUT1 deficiency produces a seizure disorder with low glucose concentration in cerebrospinal fluid and GLUT2 deficiency is the basis of the Fanconi–Bickel syndrome, which resembles type I glycogen storage disease.

Glucose transport is of fundamental importance in energy metabolism. The maintenance of a relatively constant blood glucose concentration to sustain cerebral metabolism and the delivery of glucose to peripheral tissues for storage and utilization are key metabolic processes and, in many situations, transport of glucose across cell membranes plays a key role in their regulation and control.

Cell membranes are effectively impermeable to glucose, so movement of glucose into and out of cells must be mediated by protein transporters. This mediated glucose transport can be divided into two forms, secondary active transport and facilitated transport, each involving a different class of glucose transporter. The secondary active transport mechanism is responsible for uptake of glucose into the intestinal mucosa and retention of glucose by the kidney. The distribution of glucose to the various tissues of the body involves a family of glucose transporters, each with different kinetic properties. Most cells express a number of different glucose transporters and the pattern of expression in different tissues is related to specific metabolic requirements. The general properties of the glucose transporters are summarized in Table 1.

Table 1 Summary of the properties of the glucose transporters

Transporter	*Type*	*Tissue distribution*	*Kinetic properties*	*Biological role*	*Disorder*
SGLT1	Na^+-linked secondary active transport	Intestinal mucosa, pars recta of renal proximal tubule	$K_m \sim 0.2$ mmol/L $V_{max} \sim 4$ nmol/min per mg protein	Intestinal glucose absorption, renal reabsorption	Glucose/galactose malabsorption
SGLT2	Na^+-linked secondary active transport	First part of renal proximal tubule	$K_m \sim 10$ mmol/L $V_{max} \sim 10$ nmol/min per mg protein	Major fraction of renal glucose reabsorption	Renal glycosuria
GLUT1	Facilitated transport	Widespread, highest levels in erythrocytes, vascular endothelium	$K_m \sim 20$ mmol/L	General basal glucose transport, transport across blood–brain barrier	Infantile seizures, developmental delay and hypoglycorrhachia
GLUT2	Facilitated transport	Hepatocytes, pancreatic β-cells, basal membranes of intestinal mucosal and renal proximal tubular cells	$K_m \sim 40$ mmol/L	Intestinal absorption, renal reabsorption, pancreatic and hepatic control of glucose homeostasis	Fanconi–Bickel syndrome — hepatic and renal glycogen storage, renal proximal tubular defect
GLUT3	Facilitated transport	Neurons	$K_m \sim 10$ mmol/L	Glucose transport into neurons in brain	Not defined
GLUT4	Facilitated transport	Skeletal muscle, cardiac muscle, adipose tissue	$K_m \sim 3$ mmol/L	Insulin-dependent glucose transport	? Role in insulin resistance
GLUT5	Facilitated transport	Intestinal mucosa		Fructose absorption	None defined — deficiency does not appear to be cause of isolated fructose malabsorption

Secondary active transport of glucose operates in the mucosal cells of the intestine and the proximal tubular cells of the kidney, where it enables the cells to transport glucose against a concentration gradient. This ensures efficient uptake of dietary glucose and minimal urinary loss. The mechanism is cotransport of glucose and sodium ions across the apical surface of the cells and the energy input is provided by the sodium gradient maintained by the Na^+/K^+ ATPase in the basolateral membrane. Efflux of glucose from the cells into the circulation is then mediated by a facilitative transporter in the basal membrane. There are two Na^+-glucose transporters, SGLT1 and SGLT2, which have very closely related amino acid sequences (almost 60% identity) although their properties differ significantly (MacKenzie et al 1994; Turk et al 1994). Sequence analysis suggests that they each have 12 transmembrane segments and a leucine zipper domain on one of the extracellular loops that may be involved in formation of oligomers.

Intestinal glucose absorption is mediated by SGLT1. This is a high-affinity (K_m glucose $\sim$0.2 mmol/L), low-capacity ($V_{max} \sim 4$ nmol/min per mg protein) transporter that transports one Na^+ for each glucose molecule. It is not specific for glucose and transports galactose at a comparable rate. Reabsorption of glucose by the kidney is more complex and is shared between SGLT1 and SGLT2 (Turner and Moran 1982). The major fraction of filtered glucose is reabsorbed in the first part of the proximal tubule by SGLT2, a low-affinity (K_m glucose $\sim$10 mmol/L), high-capacity ($V_{max} \sim 10$ nmol/min per mg protein) transporter. SGLT2 transports two Na^+ for each glucose and is highly specific. Any glucose remaining after passage of the filtrate through the first part of the proximal tubule is reabsorbed by SGLT1 in the luminal surface of the epithelial cells of the pars recta.

Genetic defects in SGLT1 are responsible for the rare condition of glucose/galactose malabsorption (Martin et al 1997). This condition is inherited as an autosomal recessive and patients usually present with severe watery diarrhoea and dehydration in the newborn period. Some patients also have glycosuria. Intestinal morphology and disaccharidase activity are normal. Treatment involves replacement of glucose and galactose in the diet with fructose (Desjeux et al 1995). Congenital renal glycosuria is postulated to be due to defects in SGLT2, although the human gene for this transporter has not yet been characterized and no mutations have been identified. It is usually a benign condition in which there is glycosuria without hyperglycaemia. Renal transport of other sugars is not affected and the uptake and utilization of glucose by other tissues is normal (Desjeux et al 1995).

In all other circumstances, glucose is taken up by one or more of the facilitative glucose transporters. Rapid metabolism of glucose within the cell means that there is always a concentration gradient across the plasma membrane and an active transport mechanism is not required. The facilitative glucose transporters comprise a family of closely related proteins ($\sim$40% overall conservation) with a common molecular architecture (Olson and Pessin 1996). They contain 12 membrane-spanning domains generating both internal and external ligand binding sites, N- and C-terminal cytoplasmic domains and a single glycosylation site on one of the extracellular loops. There are four well-defined glucose transporters in this family, designated GLUT1–4 (Mueckler 1994; Olson and Pessin 1996). A closely related

GLUT5 protein is really a fructose transporter (Burant et al 1992). Two other glucose transporter-related genes, GLUT6 and GLUT7 have been reported; however, GLUT6 is a nonfunctional pseudogene (Kayano et al 1990) and initial suggestions that GLUT7 is an hepatic endoplasmic reticulum glucose transporter have not been confirmed (Waddell et al 1992).

As most cells express a number of different glucose transporters with considerable variation in the proportions in different tissues, many of the properties of the GLUT transporters have been determined by expressing single transporters in the cell membrane of *Xenopus* oocytes and using nonmetabolizable glucose analogues such as 2-deoxyglucose and 3-*O*-methylglucose for kinetic analysis (Gould et al 1991). Consequently, there is little detailed information about the kinetics of glucose uptake in different mammalian cell types. However, the general properties of the GLUT transporters derived from expression studies do relate quite well to the known characteristics of glucose transport in different tissues.

In considering the distribution and properties of the GLUT transporters, GLUT1 and GLUT3 will be considered together as they are both particularly involved in delivery of glucose to the brain. As glucose is the obligatory substrate for cerebral metabolism under normal conditions, glucose transport is of fundamental importance in this organ. GLUT1 was the first of the glucose transporters to be clearly defined as it is very abundant in the plasma membrane of erythrocytes. It is widely distributed in fetal tissues, but has a more restricted expression in the adult where, apart from the erythrocyte, it is found mainly in vascular endothelial cells. GLUT1 exists in a number of different isoforms that differ in the composition of the carbohydrate at the glycosylation site; however, the biological significance of these different forms is unclear (Maher et al 1994). Kinetic studies indicate that GLUT1 has a relatively high K_m for glucose (of the order of 20 mmol/L). GLUT3 has a lower K_m for glucose ($\sim$10 mmol/L) and is found particularly in neurons in the central nervous system (Mantych et al 1992).

Glucose transport into the brain is a complex process involving the endothelial cells of small blood vessels, glial cells, particularly astrocytes, and the neurons themselves. GLUT1 is expressed at high level in the endothelial cells of the microvasculature of the brain and is responsible for transfer of glucose across the blood–brain barrier. In these cells, GLUT1 is predominantly present as the 45 kDa glycoform. It is becoming apparent that delivery of glucose to neurons is, at least in part, mediated by astrocytes (Forsyth et al 1996) and these cells also express GLUT1, but in this case mainly as the 55 kDa glycoform. Finally, uptake of glucose into the neurons to support their energy metabolism is mediated by GLUT3.

There have been a number of studies of the development of GLUT transporters in the brain and their regulation under different conditions. In rat brain, levels of both GLUT1 and GLUT3 are very low at birth and increase rapidly to adult levels by the time of weaning, a period that corresponds to rapid development and maturation. The expression of GLUT1 correlates with supply of nutrients and general growth of the brain, while levels of GLUT3 appear to be more related to maturation and cerebral function (Vannucci 1994). GLUT1 expression in the brian is increased under conditions of hypoglycaemia (Simpson et al 1999), but suggestions

of a comparable effect on GLUT3 expression (Uehara et al 1997) have not been confirmed (Simpson et al 1999). Following episodes of cerebral ischaemia/hypoxia, neuronal cell death leads to a reduction in the level of GLUT3 in the affected area and this is accompanied by increased expression of GLUT1 in surrounding vessels and astrocytes (Vannucci et al 1998).

GLUT1 deficiency was first described in two patients in 1991 (De Vivo et al 1991) and since then a further 15 patients have been reported (Klepper et al 1999). The condition usually presents in early infancy with seizures and developmental delay and patients become progressively microcephalic. The most characteristic biochemical abnormalities are a low concentration of glucose in cerebrospinal fluid and a reduced CSF/blood glucose ratio. Usually, no changes are detected on cerebral imaging. The seizures respond well to institution of a ketogenic diet, but patients may continue to experience paroxysmal episodes of ataxia and unresponsiveness and usually manifest neurobehavioural disturbances (De Vivo et al 1995). Glucose transport studies in erythrocytes from the patients reveal a 50% reduction in the rate of uptake compared with parents, unaffected siblings and normal controls. In some cases, a 50% reduction in GLUT1 immunoreactive protein in the erythrocyte membrane has also been demonstrated. Mutation analysis of the GLUT1 gene has revealed either hemizygosity or heterozygosity for missense mutations, indicating that GLUT1 deficiency is inherited as a new dominant condition (Seidner et al 1998).

Deficiency of cerebral glucose transport has also been studied in relation to Alzheimer disease, where it presumably occurs secondarily to the underlying pathogenic processes. In patients with Alzheimer disease, a consistent reduction in the regional metabolism rate for glucose can be demonstrated in the parietal and temporal lobes by positron emission tomography (Friedland et al 1989). This occurs early in the course of the disease and is associated with a significant reduction in both glycoforms of GLUT1 and GLUT3 (Simpson et al 1994). This reduction is not simply a function of loss of neurons, but its role in the course of the disease is unclear.

GLUT2 has the highest K_m for glucose of the GLUT transporters ($\sim$40 mmol/L) and is expressed predominantly in the liver, kidney, β-cells of the pancreas and intestinal mucosal cells. Unlike the other glucose transporters, which function to deliver glucose to cells for utilisation, GLUT2 is primarily involved in glucose homeostasis through its role in glucose uptake from the intestine, reabsorption by the kidney, sensing in the pancreatic β-cells and uptake and release by liver. Glucose taken up in the intestine and reabsorbed in the proximal tubule by the Na^+-glucose transporters is released into the circulation via GLUT2 in the basal membrane of the epithelial cells. The high K_m for glucose of GLUT2 means that glucose transport by pancreatic β-cells and hepatocytes is proportional to the blood glucose concentration (Gould et al 1991). This permits the cells to sense the prevailing glucose concentration via the activity of glucokinase, and this in turn leads to control of insulin secretion by the pancreas and the uptake or release of glucose by hepatocytes as required to regulate the blood glucose. GLUT2 is not completely specific for glucose and is probably also involved in galactose transport.

Altered expression of GLUT2 has been studied particularly in relation to the pathogenesis of diabetes. Reduced GLUT2 expression is found in association with defective glucose-stimulated insulin release in animal models of diabetes such as the autoimmune BB rat (Orci et al 1990); however, this appears to be a consequence of the diabetes in these animals, rather than part of the cause (Chen et al 1992; Thorens et al 1992). Variation in the expression of GLUT2 in pancreatic β-cells in response to the prevailing blood glucose concentration has been reported (Chen et al 1990), but has not been confirmed in subsequent studies (Koranyi et al 1992). Animal studies suggest that GLUT2 expression in the liver is increased in response to hyperglycaemia and suppressed by hyperinsulinaemia (Postic et al 1993). GLUT2 expression in intestinal mucosal cells has been reported to be increased following introduction of a high-carbohydrate diet (Miyamoto et al 1993).

Genetic defects in GLUT2 are responsible for the Fanconi–Bickel syndrome, a rare autosomal recessive condition that presents during infancy with failure to thrive, rickets and enlargement of the liver and kidney due to glycogen accumulation (Santer et al 1998). Later sequelae include short stature, doll face and abdominal distension similar to type I glycogen storage disease. There is a general renal proximal tubular defect with glycosuria, amino aciduria, renal tubular acidosis and hyperphosphaturia. Biochemical abnormalities include postprandial hyperglycaemia, fasting hypoglycaemia and hypergalactosaemia. A mechanism for these biochemical characteristics has been proposed by Santer and colleagues (1998). It is proposed that after meals a modest reduction in intestinal glucose absorption is counteracted by a more significant defect in insulin secretion and hepatic glucose uptake, leading to hyperglycaemia. Impaired hepatic glucose release and renal reabsorption would be responsible for the glycogen accumulation and fasting hypoglycaemia.

In addition to information gained from studies on patients with Fanconi–Bickel syndrome, mice with targeted disruption of the GLUT2 gene have also contributed to our understanding of the biological role of this transporter. The most significant result from biochemical studies of these mice is that, although they have only minimal facilitated glucose transport across hepatocyte cell membranes, liver glucose release and the response to glucagon are normal (Guillam et al 1998). These observations suggest that there may indeed be an endoplasmic reticulum glucose transporter, such as the postulated GLUT7, specifically for the release of glucose generated by the glucose-6-phosphatase system.

GLUT4 is the insulin-sensitive glucose transporter and is most abundant in the cell membranes of insulin-responsive tissues such as skeletal and cardiac muscle and adipose tissue (James et al 1989). In these tissues, GLUT4 is responsible for most of the glucose uptake, even though they also express other GLUT transporters. GLUT4 has the lowest K_m of all of the members of the GLUT family (Nishimura et al 1993) and glucose transport is the rate-limiting step for skeletal muscle uptake and glycogen synthesis (Ziel et al 1988). The most striking aspect of GLUT4-mediated glucose transport is its acute regulation in response to insulin stimulation. Under nonstimulated conditions, the density of GLUT4 transporters in the cell membrane is relatively low and most of the transporter molecules are present in the

membranes of cytoplasmic vesicles. Upon insulin stimulation, these transporters are translocated to the cell membrane and glucose uptake is increased (Cushman and Wardzala 1980; Suzuki and Kono 1980).

On a slower time scale, expression of GLUT4 is altered in response to changing metabolic conditions. A high-fat diet leads to reduction in GLUT4 levels in both skeletal muscle and adipose tissue and this is associated with decreased glucose utilization (Kim et al 1994; Pedersen et al 1991). In rats, fasting results in reduced GLUT4 expression in adipose tissue, but increased expression in skeletal muscle (Charron and Kahn 1990). Sustained exercise training is associated with an increase in GLUT4 expression in skeletal muscle (Ebeling et al 1993).

Much of the work on GLUT4 has focused on its possible role in insulin resistance. These studies have been performed both in patients with non-insulin-dependent diabetes (NIDDM) and in animal models such as the streptozotocin-treated rat. Overall, the results of these studies remain inconclusive and controversial, but there are some consistent findings. In adipose tissue cells of diabetic patients and animals and in cardiac muscle of diabetic animals, there is a reduction in transcription of the GLUT4 gene and a subsequent decrease in GLUT4 protein (Garvey et al 1989, 1991; Kainulainen et al 1994). However, in skeletal muscle of patients with NIDDM, GLUT4 levels are not reduced significantly (Eriksson et al 1992) and it is thought that impaired glucose uptake is more likely to be due to a defect in translocation of the transporter from cytoplasmic vesicles to the plasma membrane. The general conclusion from studies of GLUT4 expression and insulin resistance must be that there is no simple correlation between the two.

No mutations in the human GLUT4 gene leading to deficiency of GLUT4 protein have been identified, nor is there clear evidence of association between specific polymorphisms in the GLUT4 gene and NIDDM (Bjorbaek et al 1994; Lesage et al 1997). Consequently, it has not been possible to study the biological role of GLUT4 in humans by analysing the consequences of simple deficiency. Instead, a number of laboratories have generated transgenic mice overexpressing GLUT4 transporters or knockout mice with targeted disruption of the GLUT4 gene.

Homozygous GLUT4 knockout mice are small, with enlarged hearts and no adipose tissue (Katz et al 1995). They do not develop diabetes, but they do have evidence of insulin resistance (Rossetti et al 1997). By contrast, heterozygous GLUT4 knockout mice more closely approximate a model of NIDDM, with hyperglycaemia, hyperinsulinaemia and reduced muscle glucose uptake (Stenbit et al 1997). Transgenic mice overexpressing GLUT4 have low blood glucose, increased sensitivity to insulin and increased mobilization of fatty acids from adipose tissue (Katz et al 1996; Treadway et al 1994). Overexpression of GLUT4 in db/db diabetic mice results in increased insulin sensitivity, increased insulin-stimulated GLUT4 translocation and a reduction in blood glucose, suggesting a potential therapy for insulin-resistant states (Gibbs et al 1995).

There has been a significant increase in our understanding of glucose transport in recent years as a result of cloning and expression of the genes for the various transporters and studies of the biological properties of the protein products in transgenic and knockout mice. Kinetic properties and tissue distribution of the different trans-

porters correlate well with the variations in glucose utilization in different organs. The importance of glucose transporters in normal energy metabolism is emphasised by observations of genetic defects in human glucose transporters. Deficiencies have been described only for SGLT1 and SGLT2 and for GLUT1 and GLUT2, and all of these are extremely rare. The regulatory role of glucose transporters is most clearly seen in the case of GLUT1, where a 50% reduction is sufficient to cause significant cerebral dysfunction. The apparent rarity of glucose transporter defects may simply reflect the fact that complete deficiency is incompatible with normal development and there may still be unrecognized conditions resulting from partial deficiencies. Increasing information from studies of animal models of GLUT deficiencies may provide clues as to how such defects might present and lead to their recognition.

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