

Horizons in Nutritional Science

Glucose transporters (GLUT and SGLT): expanded families of sugar transport proteins

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The number of known glucose transporters has expanded considerably over the past 2 years. At least three, and up to six, Na⁺-dependent glucose transporters (SGLT1–SGLT6; gene name SLC5A) have been identified. Similarly, thirteen members of the family of facilitative sugar transporters (GLUT1–GLUT12 and HMIT; gene name SLC2A) are now recognised. These various transporters exhibit different substrate specificities, kinetic properties and tissue expression profiles. The number of distinct gene products, together with the presence of several different transporters in certain tissues and cells (for example, GLUT1, GLUT4, GLUT5, GLUT8, GLUT12 and HMIT in white adipose tissue), indicates that glucose delivery into cells is a process of considerable complexity.

Glucose transporter proteins: Diabetes mellitus: Adipose tissue: Muscle: Sugar transport

Glucose is a key fuel in mammals and an important metabolic substrate. It is obtained directly from the diet, principally following the hydrolysis of ingested disaccharides and polysaccharides, and by synthesis from other substrates in organs such as the liver. Glucose derived from the diet is transferred from the lumen of the small intestine, and both dietary glucose and glucose synthesised within the body have to be transported from the circulation into target cells. These processes involve the transfer of glucose across plasma membranes and this occurs via integral transport proteins. These transporters comprise two structurally and functionally distinct groups, whose members have been identified over the past two decades, namely: (i) the Na⁺-dependent glucose co-transporters (SGLT, members of a larger family of Na-dependent transporters, gene name SLC5A) (Wright, 2001); (ii) the facilitative Na⁺-independent sugar transporters (GLUT family, gene name SLC2A) (Mueckler, 1994; Joost & Thorens, 2001).

In the past 2 years the number of these glucose, and other sugar, transporters identified has expanded considerably, particularly the GLUT, with major implications for the control of the delivery of glucose to mammalian cells. These developments are summarised here.

Sodium-dependent glucose transporters

The SGLT transport glucose (and galactose), with different affinities, via a secondary active transport mechanism. The Na⁺-electrochemical gradient provided by the Na⁺–K⁺ ATPase pump is utilised to transport glucose into cells against its concentration gradient. This form of glucose transport takes place across the luminal membrane of cells lining the small intestine and the proximal tubules of the kidneys. The first of this type of glucose transport protein to be cloned was the high-affinity transporter from rabbit intestine, SGLT1 (Hediger *et al.* 1987). The human analogue soon followed by homology cloning (Hediger *et al.* 1989). Amino acid comparisons of the human SGLT range from 57–71% sequence identity (GAP algorithm, GCG software package). SGLT1 has a limited tissue expression and is found essentially on the apical membranes of small-intestinal absorptive cells (enterocytes) and renal proximal straight tubules (S3 cells).

A second Na⁺-glucose transporter, SGLT2, is of low affinity and is predominantly expressed on the apical membrane of renal convoluted proximal tubules (S1 and S2 cells) (Wells *et al.* 1992; Kanai *et al.* 1994). It is currently accepted that in the kidney, SGLT2 (low affinity, high

capacity) transports the bulk of plasma glucose from the glomerular filtrate. Any remaining glucose is recovered by SGLT1 (high affinity, low capacity) thus preventing glucose loss in the urine. However, controversy exists as to whether SGLT2 is the major renal glucose transporter (Hediger *et al.* 1995; Wright, 2001).

A pig renal amino acid co-transporter (SAAT1) has been reclassified as a low-affinity glucose co-transporter (Mackenzie *et al.* 1994) and finally renamed pSGLT3. However, current studies with the human analogue of SGLT3 (EMBL accession number, AJ133127) suggest that its function may require a re-evaluation (EM Wright, personal communication). Signals have been detected for SGLT3 in the small intestine of pigs by northern blot analysis (Kong *et al.* 1993) and in human subjects by reverse transcription polymerase chain reaction (IS Wood, unpublished data). These findings conflict with collective data indicating that SGLT1 is the only Na⁺-glucose co-transporter expressed in the small intestine.

Mutations of human SGLT1 result in the potentially fatal neonatal condition of glucose galactose malabsorption (Turk *et al.* 1991). The severe diarrhoea associated with glucose-galactose malabsorption is corrected by replacing dietary glucose with fructose. The magnitude of this disorder, by the mutation of a single gene, would indicate that alternative luminal glucose transport does not occur to any significant extent. The relevance of SGLT3 intestinal expression needs to be addressed and suggests that care should be taken when transposing structure-function relationships to similar proteins across species. Furthermore, the importance of establishing protein localisation in heterologous tissue types rather than relying on mRNA expression alone cannot be overlooked.

Over recent years, data collected from homology cloning and the Human Genome Project has indicated the presence of additional members of the SGLT-like transporters, which are currently under investigation (Wright, 2001). Additional members, SGLT4–6, have been assigned but await complete functional and structural characterisation (EM Wright, personal communication).

Facilitative glucose transporters

The facilitative transporters (GLUT) utilise the diffusion gradient of glucose (and other sugars) across plasma membranes and exhibit different substrate specificities, kinetic properties and tissue expression profiles. The first transporter to be isolated, GLUT1, was cloned from a HepG2 cell line (Mueckler *et al.* 1985). Identification of other members of the GLUT family followed over a 5-year period to yield four glucose transporters (GLUT1–4) and a fructose transporter (GLUT5). Two further members were briefly included but have since been discarded. One gene, for GLUT6, was deemed to be a pseudogene (Kayano *et al.* 1990) and GLUT7 was found to be a sequencing artifact (Burchell, 1998). The GLUT6 and GLUT7 names have since been assigned to other gene products (see Table 1 and p. 5).

The generation and screening of expressed sequence tag databases, in addition to standard cDNA library screening and the near completion of the Human Genome Sequencing

Project, has led to the identification of eight further members of the GLUT family over the last 2 years (Joost & Thorens, 2001). However, the pace at which these new genes were identified and classified by independent groups initially caused confusion in their terminology. A consensus has since been reached (Joost *et al.* 2002) in which the thirteen members have been named GLUT1–12 and HMIT (H⁺-coupled myo-inositol transporter). It is considered that all members of the family have now been identified (Joost & Thorens, 2001).

The facilitative sugar transporters are predicted to have twelve membrane-spanning regions with intracellular located amino- and carboxyl-termini. Amino acid sequence comparisons of the human GLUT family members range from 28 to 65 % identity (GAP algorithm, GCG software package) measured against GLUT1. Sequence comparisons of all members reveal the presence of 'sugar transporter signatures' (Joost & Thorens, 2001) and these consist of numerous conserved glycine and tryptophan residues, which are regarded as being essential for general facilitative transporter function. Structural and functional characteristics of the individual GLUT members are at varying degrees of completion. Based on a dendrogram (Fig. 1) from a multiple sequence alignment of the extended GLUT family, three subclasses (I–III) are apparent, which also share common sequence motifs (Joost & Thorens, 2001); see Table 1.

Class I facilitative transporters

The class I facilitative transporters contain GLUT1–4, and these have been comprehensively characterised in terms of structure, function and tissue distribution. GLUT1 is expressed particularly in the brain (including the blood-brain barrier) and erythrocytes. Moderate levels of expression are also observed in adipose tissue, muscle and the liver. GLUT2 is expressed primarily in pancreatic β -cells, the liver and the kidneys. In the β -cells, GLUT2 is thought to play a role in the glucose-sensing mechanism, while in the liver it is expressed on the sinusoidal membrane of hepatocytes and allows for the bi-directional transport of glucose under hormonal control. GLUT2 is also found on the basolateral surface of proximal renal tubules and enterocytes, where it forms part of the transcellular pathway for glucose and fructose transport. GLUT3 has a high affinity for glucose and this is consistent with its presence in tissues where the demand for glucose as a fuel is considerable, in particular the brain.

The insulin-responsive glucose transporter, GLUT4, is found in heart, skeletal muscle and adipose tissue, where it is responsible for the reduction in the postprandial rise in plasma glucose levels; it is also found in the brain (Rayner *et al.* 1994). Insulin acts by stimulating the translocation of specific GLUT4-containing vesicles from intracellular stores to the plasma membrane resulting in an immediate 10–20-fold increase in glucose transport (Shepherd & Kahn, 1999; Bryant *et al.* 2002). Various animal and human models of 'diabesity' (Astrup & Finer, 2000) exhibit reduced expression levels of GLUT4 in adipose tissue, but not muscle, suggesting that this decline is not

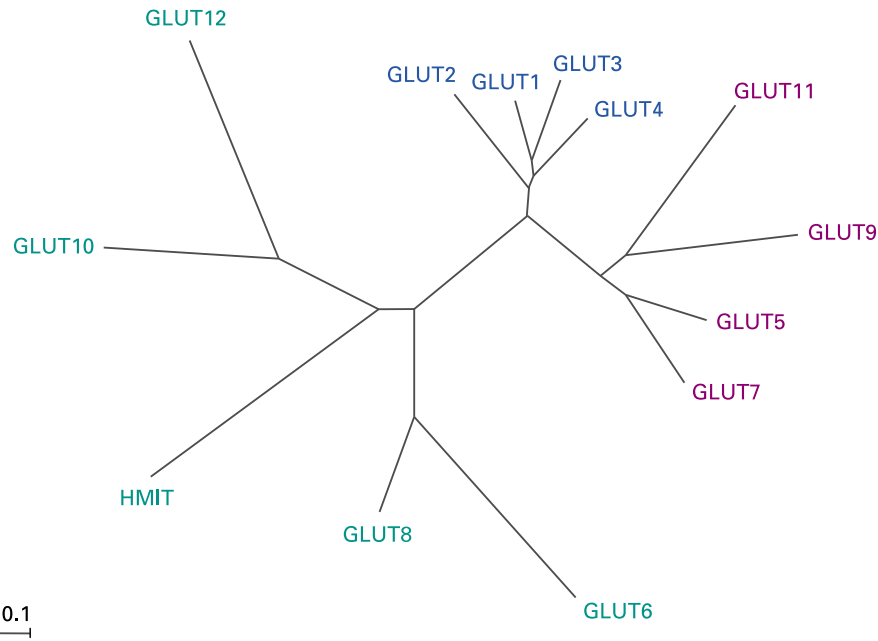


Fig. 1. Dendrogram of the glucose transporter (GLUT) family. An unrooted radial phylogram was drawn from a multiple sequence alignment of the thirteen members of the human GLUT family. The tree was constructed using neighbour-joining analysis of a distance matrix generated with PHYLIP software (Felsenstein, 1989). The three classes of GLUT proteins are colour-coded as: blue, class I; red, class II; green, class III. The scale bar represents 0.1 substitutions per amino acid position. HMIT, H⁺-coupled myo-inositol transporter.

the causative factor of insulin resistance (Shepherd & Kahn, 1999).

Global or tissue-specific GLUT4 knockout mouse models (Katz *et al.* 1995; Stenbit *et al.* 1997; Zisman *et al.* 2000; Abel *et al.* 2001) exhibit a varying degree of pathophysiology relating to type II diabetes. Charron and colleagues (Katz *et al.* 1995, 1996) have suggested that, amongst other factors, the expression of additional but unknown glucose transporters may have a role in the observed phenotypes. Compensatory expression of the recently identified GLUT family members in GLUT4 knockout mice has yet to be demonstrated.

Class II facilitative transporters

The class II facilitative transporters are headed by the fructose transporter GLUT5, and include GLUT7, GLUT9 (neither of which has been functionally characterised) and GLUT11. GLUT5 is expressed predominantly in the small intestine, testes and the kidneys. GLUT7 is the least-known member of the family; the uncharacterised gene for it was identified on the basis of a genome-wide homology search and has been mapped to chromosome 1 but the sites of expression are currently unknown (Joost & Thorens, 2001). GLUT9 expression is evident in the liver and the kidneys.

Two splice variants have been described for GLUT11, through the skipping of exon 2, which results in long and short forms of the protein consisting of 503 and 493 amino acid residues, respectively (Doege *et al.* 2001;

Sasaki *et al.* 2001). The two splice variants are expressed in a tissue-specific manner. Low-affinity glucose transport is demonstrated by the short form of GLUT11, and is competed for by fructose, with the transporter being expressed predominantly in heart and skeletal muscle (Doege *et al.* 2001). The long form of GLUT11, which is not expressed in heart or skeletal muscle but is detected in liver, lung, trachea and brain, was shown to increase fructose transport when expressed in Chinese hamster ovary cells (Wu *et al.* 2002). Collectively, it is tempting to speculate that fructose may indeed be the main transported substrate for GLUT11.

Class III facilitative transporters

The class III facilitative transporters comprise five members: GLUT6, GLUT8, GLUT10, GLUT12 and HMIT. One feature of this class is the location of the characteristic glycosylation site on loop 9. This glycosylation site, which has been shown to be functionally important for GLUT1 (Asano *et al.* 1991), is found on loop 1 in the other two classes. A second feature is that all members of this class (also GLUT7 and GLUT9) contain targeting motifs. The intracellular localisation of both GLUT6 and GLUT8 is due to single dileucine motifs present in their N-termini, and in both cases insulin treatment has been reported not to induce protein translocation to the cell surface (Lisinski *et al.* 2001). The significance of these and other targeting motifs in this group, with regard to hormonal regulation, remains to be determined. GLUT6

Table 1. The glucose transporter (GLUT) family of facilitative sugar and polyol transporters (gene name SLC2A)

Isoform	Previous name	Class	Main tissue localization	Insulin sensitive?	Functional characteristics (transport)	Present in skeletal muscle?*	Present in white adipose tissue?*	Primary references
GLUT1	-	I	Erythrocytes, brain, ubiquitous	No	Glucose	Yes	Yes	Mueckler <i>et al.</i> 1985; Gould <i>et al.</i> 1991
GLUT2	-	I	Liver, pancreas, intestine, kidney	No	Glucose (low affinity); fructose	No	No	Fukumoto <i>et al.</i> 1988; Gould <i>et al.</i> 1991
GLUT3	-	I	Brain	No	Glucose (high affinity)	No	Yes (m)	Kayano <i>et al.</i> 1988; Gould <i>et al.</i> 1991
GLUT4	-	I	Heart, muscle, WAT, BAT, brain	Yes	Glucose (high affinity)	Yes	Yes	Fukumoto <i>et al.</i> 1989; James <i>et al.</i> 1989
GLUT5	-	II	Intestine, testes, kidney	No	Fructose; glucose (very low affinity)	Yes	Yes	Kayano <i>et al.</i> 1990; Davidson <i>et al.</i> 1992
GLUT6	GLUT 9	III	Brain, spleen, leucocytes	No	Glucose	No	n.d.	Doerge <i>et al.</i> 2000a; Lisinski <i>et al.</i> 2001
GLUT7	-	II	n.d.	n.d.	n.d.	n.d.	n.d.	Joost & Thorens, 2001
GLUT8	GLUT X1	III	Testes, brain and other tissues	No (yes in blastocytes)	Glucose	Yes (m)	Yes (m)	Carayannopoulos <i>et al.</i> 2000; Doege <i>et al.</i> 2000b; Ibberson <i>et al.</i> 2000; Lisinski <i>et al.</i> 2001
GLUT9	GLUT X	II	Liver, kidney	n.d.	n.d.	No	n.d.	Phay <i>et al.</i> 2000
GLUT10	-	III	Liver, pancreas	No	Glucose	Yes (m)	n.d.	Dawson <i>et al.</i> 2001; McVie-Wylie <i>et al.</i> 2001
GLUT11†	-	II	Heart, muscle	No	Glucose (low affinity); Fructose (long form)	Yes (m)	No	Doege <i>et al.</i> 2001; Wu <i>et al.</i> 2002; Sasaki <i>et al.</i> 2001
GLUT12	GLUT 8	III	Heart, prostate, muscle, small intestine, WAT	Yes	n.d.	Yes	Yes	Rogers <i>et al.</i> 2002
HMIT	-	III	Brain	n.d.	H ⁺ -myo-inositol	No (m)	Yes (m)	Uldry <i>et al.</i> 2001

WAT, white adipose tissue; BAT, brown adipose tissue; m, mRNA only; n.d., not determined; HMIT, H⁺-coupled myo-inositol transporter.

* The presence of each transporter in skeletal muscle and WAT is shown since these are the major sites of insulin-stimulated glucose uptake.

† GLUT11 occurs in two splice variants: a short form (low-affinity glucose transport) and a long form (which may be a fructose transporter).

is expressed in the spleen, leucocytes and the brain (Doege *et al.* 2000a), while GLUT8 is present in the testis, brain and adipose tissue (Doege *et al.* 2000b; Ibberson *et al.* 2000).

Although GLUT10 does not contain a dileucine motif (but does contain an alternative C-terminus motif), its reported expression in the insulin-sensitive tissues of skeletal muscle and heart, and its association with a known type II diabetes mellitus susceptibility locus on chromosome 20 (Dawson *et al.* 2001; McVie-Wylie *et al.* 2001) makes it a particularly interesting target of study. GLUT10 has also been reported as being expressed in the liver and pancreas (Dawson *et al.* 2001; McVie-Wylie *et al.* 2001). Functional glucose transport has been demonstrated for GLUT6 (Doege *et al.* 2000a), GLUT8 (Ibberson *et al.* 2000) and GLUT10 (Dawson *et al.* 2001). However, HMIT has been shown to be an H⁺-coupled myo-inositol transporter, expressed predominantly in the brain (Uldry *et al.* 2001).

It is now apparent that the choice of substrate of the GLUT family members is widening (analogous to the large SGLT family) (Turk & Wright, 1997), which highlights the dangers of assuming functionality based on sequence motifs or comparisons alone. This raises the question as to the primary substrate identity for the uncharacterised GLUT12 transporter expressed in heart, small intestine, prostate and insulin-sensitive tissues (Rogers *et al.* 2002).

Perspective

The presence of a large number of different sugar transporters, and in particular the thirteen distinct facilitative transporters, each with its own characteristics, indicates that the uptake of glucose into cells is highly complex and much more so than was considered up to the last 2 years. The expression of several sugar transporter isoforms in individual tissues, and indeed cells, is a reflection of the different characteristics of each of the various transporters, and provides a high degree of specificity in the control of glucose uptake under different physiological conditions (i.e. a wide range of glucose concentrations).

A number of examples exist, in both polarised cells such as enterocytes and non-polarised cells such as adipocytes, of the simultaneous presence of different glucose transporters. The enterocyte sugar transport system is well characterised and expresses both SGLT1 (glucose transport) and GLUT5 (fructose transport) on the apical (brush-border) membrane. The basolateral facilitative transporter is GLUT2, which is able to transport both glucose and fructose into the circulation. It is clear that the polarity of the two membrane domains lends itself to the need for specialised transporter function.

In the case of adipocytes, these cells express the constitutive transporter, GLUT1, for basal glucose transport, but also express the specialised insulin-responsive transporter, GLUT4. It is the latter isoform that adds to the unique properties exhibited by adipose tissue and muscle in terms of the insulin-stimulated disposition of glucose following a meal. Expression of the fructose transporter, GLUT5, has also been demonstrated in adipose tissue

(Shepherd *et al.* 1992) and is probably responsible for the observed transport of fructose across the adipocyte plasma membrane (Froesch, 1972; Halperin & Cheema-Dhadli, 1982; Hajduch *et al.* 1998). The recent extension of the GLUT family has shown that some of these new transporters are also expressed in adipocytes (GLUT8, GLUT12 and HMIT) and in skeletal muscle (GLUT8, GLUT10, GLUT11 and GLUT12).

The role that this multitude of transporters plays in the function of those tissues in which glucose transport is responsive to insulin remains to be established. However, there is clearly a possibility that the new transporters may be implicated in the development of type II diabetes. Both diabetes, and obesity with which it is associated, are of growing concern. There are, for example, currently 1.4 million diagnosed diabetics in the UK alone (perhaps 150 million worldwide) with the incidence expected to double in the next decade or so as a consequence of the rapid rise in obesity (DiabetesUK, 2000).

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