GLUTX1, a Novel Mammalian Glucose Transporter Expressed in the Central Nervous System and Insulin-sensitive Tissues*

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Based on homology with GLUT1–5, we have isolated a cDNA for a novel glucose transporter, GLUTX1. This cDNA encodes a protein of 478 amino acids that shows between 29 and 32% identity with rat GLUT1–5 and 32–36% identity with plant and bacterial hexose transporters. Unlike GLUT1–5, GLUTX1 has a short extracellular loop between transmembrane domain (TM) 1 and TM2 and a long extracellular loop between TM9 and TM10 that contains the only N-glycosylation site. When expressed in Xenopus oocytes, GLUTX1 showed strong transport activity only after suppression of a dileucine internalization motif present in the amino-terminal region. Transport activity was inhibited by cytochalasin B and partly competed by D-fructose and D-galactose. The Michaelis-Menten constant for glucose was approximately 2 mM. When translated in reticulocytes lysates, GLUTX1 migrates as a 35-kDa protein that becomes glycosylated in the presence of microsomal membranes. Western blot analysis of GLUTX1 transiently expressed in HEK293T cells revealed a diffuse band with a molecular mass of 37–50 kDa that could be converted to a ~35-kDa polypeptide following enzymatic deglycosylation. Immunofluorescence microscopy detection of GLUTX1 transfected into HEK293T cells showed an intracellular staining. Mutation of the dileucine internalization motif induced expression of GLUTX1 at the cell surface. GLUTX1 mRNA was detected in testis, hypothalamus, cerebellum, brainstem, hippocampus, and adrenal gland. We hypothesize that, in a similar fashion to GLUT4, in vivo cell surface expression of GLUTX1 may be inducible by a hormonal or other stimulus.

Glucose transport across biological membranes requires the presence of specific integral membrane proteins that, in mammals, fall into two classes. These are the Na+/glucose cotransporters, SGLT1 and SGLT2, which are present mainly in the apical membrane of epithelial cells from intestine and kidney (1) and the facilitative glucose carriers, GLUT1–5, which are present in every tissue (2, 3). Much work has been devoted to the study of the GLUTs to determine their role in the control of glucose fluxes in different organs and their respective importance in the control of whole body glucose homeostasis. Key roles for these transporters involve glucose absorption into the body, glucose uptake by the brain, storage in liver, insulin-dependent uptake in muscles and adipocytes, and glucose sensing by pancreatic β cells (4, 5). Defects in any of these mechanisms may have profound pathophysiological consequences, in particular in the development of type 2 diabetes (6, 7).

Structurally, the GLUTs form a family of highly related hexose transport proteins that belongs to a larger sugar transport superfamily consisting of more than 133 members distributed in a wide variety of species (8). These carrier proteins are characterized by the presence of 12 putative transmembrane segments. These may have evolved by duplication of an ancestral structure consisting of six transmembrane domains, as suggested by the presence of repeated structures in both halves of the molecule. These are GRR/K motifs present between TM2 and TM3 and between TM8 and TM9 and the EXR/RK motifs present between TM4 and TM5 and between TM10 and TM11. Within the mammalian glucose transporters, additional motifs have been characterized that are essential for transporter function. For instance, site-directed mutagenesis studies have suggested that a QLS motif present in TM7 of the high affinity glucose transporters GLUT1, 3, and 4 is important in defining binding affinity and selection of the incoming hexose (9). Immediately following this motif is a conserved pair of glutamine residues. The first one, Glu282 of GLUT1, is required for binding of the glucose competitive inhibitor ATB-BMPA on the exofacial glucose binding site (10). Importantly also, the intracellularly located tryptophan residues 388 and 412 of GLUT1, which are conserved in GLUT2–4, participate in the conformational changes required for transport activity and for binding to the competitive inhibitor cytochalasin B (11–13).

Here we describe the cloning and functional characterization of a novel glucose transporter identified by data base homology searches using sequences of the known GLUTs. This protein shares the same overall structure as the GLUTs and contains key glucose transporter sequence motifs. However, it shows some distinctive structural features and is most closely related to plant and bacterial sequences, suggesting that it may belong to a novel family of mammalian facilitated glucose transporters.

MATERIALS AND METHODS

Cloning and Sequence Analysis of GLUTX1—Sequences of human GLUTs 1–5 (Swiss-Prot accession numbers P11166, P11168, P11169, P14672, and P22732) were used to screen the EST data base at NCBI using TBLASTN. Novel ESTs were analyzed using the Genetics Computer Group program suite. Primers specific for EST H34451 were used to amplify GLUTX1 cDNA by 5′- and 3′-RACE from rat testis poly(A)+ RNA using Roche Molecular Biochemicals 5′- and 3′-RACE reagents. PCR products were cloned using the TOPO cloning system (Invitrogen). For

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amplification of the full-length GLUTX1 sequence, primers were designed from the 5' and 3' RACE products and PCR amplification performed using the Expand long template PCR system (Roche Molecular Biochemicals). Three independent reverse transcription-PCR reactions were performed from rat testis poly(A)

- RNA, and the resulting products were cloned and sequenced in both directions. Mouse GLUTX1 cDNA was determined by sequencing 5'- and 3'-RACE products and mouse EST clones. Human GLUTX1 cDNA sequence was determined from sequencing human EST and BAC clones (Research Genetics). GLUTX1(II-LL-AA) was constructed from GLUTX1 by mutagenesis using a modified 5' primer. The resulting cDNA was cloned into pcDNA3 (Invitrogen) and pSfS (14) vectors for expression analyses. Sequence compilations and comparisons were made using the best fit, gap, and pileup programs (Genetics Computer Group program suite) and the ClustalX program (15).

GLUTX1 Antibodies—Antibodies were raised against fusion proteins consisting of glutathione S-transferase and either the middle loop (amino acids 203–257) or the carboxyl-terminal tail (amino acids 459–478) of rat GLUTX1. Preparation of fusion proteins by PCR and immunization of rabbits were as described previously (16). Affinity purification of the antibodies was on immobilized fusion proteins consisting of maltose binding protein, and the same regions of rat GLUTX1 were used for immunization (16).

GLUTX1 Protein Analysis—In vitro transcription was performed from a Northern blot using the pSD5 vector containing the GLUTX1 cDNA (Promega). cRNA was in vitro translated in rabbit reticulocyte lysate in the presence or absence of canine microsomal membranes (Promega) and [35S]methionine (NEN Life Science Products). Products were separate on 10% polyacrylamide gels and detected by autoradiography.

For Western blotting, GLUTX1 was transiently transfected in HEK293T cells (17), and cell membranes were prepared and analyzed using specific antibodies following previously published procedures (16). Endoglycosidase H and PNGaseF (New England Biolabs) digestions were performed according to the manufacturer's protocol.

Immunofluorescence microscopic detection of GLUTX1 or GLUTX1(II-LL-AA) was performed following transient transfection of HEK293T cells as described (18) using 10 μg/ml GLUTX1 affinity-purified primary antibody and CY3-conjugated goat anti-rabbit antibody (Jackson Immunoresearch).

Functional Characterization of GLUTX1 in Xenopus Oocytes—Stage V–VI oocytes were injected with 25 ng of RNA prepared from GLUTX1 purified antibody and CY3-conjugated goat anti-rabbit antibody (Jackson Immunoresearch).

Northern Blot Analysis—Total RNA was isolated as described (19). Northern blot analysis was with 10 μg of total RNA, and detection was with a 1.2-kilobase NotI-BglII fragment from the coding sequence of GLUTX1 radioactively labeled by random priming.

RESULTS

Structure of GLUTX1—Amino acid sequences of GLUTs 1–5 were used to screen the public EST data base and novel ESTs showing significant homology to the GLUTs were identified. Human EST clones 50147 and 46121 (accession numbers H18721 and H09414, respectively) encoding the carboxyl terminus and 3'-untranslated region of GLUTX1 were used as probes on rat multiple tissue Northern blots and identified a 2.5-kilobase transcript that was strong in testis. A 2087-base pair cDNA encoding a protein of 478 amino acids was cloned from rat testis poly(A)

- RNA, and the resulting mRNA by RACE as described under "Materials and Methods." The amino acid sequence of GLUTX1 compared with eight other mammalian glutamate transporters and the sugar transporter from sugar beet, termed integral membrane sugar transporter (XYLT), and between 29 and 32% with the other mammalian glucose transporters. Importantly, sequences that have been reported to be critical for the glucose transport function are present in GLUTX1 at conserved locations. These include the two repeated sequence motifs GRR(K) and EX(F/R)(K) (see Introduction) and two tryptophan residues, Trp395 and Trp419, corresponding to Trp398 and Trp412 of GLUT1. Interestingly, a dileucine motif is found in the amino-terminal cytoplasmic domain of the protein. Human, rat and mouse GLUTX1 sequences have been determined (Fig. 1B). Mouse and rat GLUTX1 are most similar, showing 91% identity at the nucleotide and 94% identity at the amino acid sequence level; human GLUTX1 is more divergent, showing 85% identity with both the nucleotide and the protein sequence of rat and mouse GLUTX1.

GLUTX1 Functional Studies—To determine whether GLUTX1 was a functional glucose transporter, synthetic mRNAs were transcribed in vitro from the full-length rat cDNA and injected in Xenopus oocytes, and 2-DG uptake was measured 3 days later. As shown in Fig. 2, 2-DG uptake by oocytes injected with the wild-type GLUTX1 mRNA was not significant. We suspected that the lack of transport activity was due to the dileucine motif present at the amino-terminal end of the protein, which could serve as an internalization signal preventing sufficient surface expression of GLUTX1. We therefore mutated these two leucines into alanosines and injected oocytes with the corresponding mutant mRNA. Transport activity by these injected oocytes was now strongly stimulated (Fig. 2A).

Fig. 2B shows that a 100-fold excess of d-glucose could completely block radioactive 2-DG uptake, whereas l-glucose was not a competitor. D-Fructose and d-galactose could also inhibit glucose uptake, although with a reduced efficacy as compared with d-glucose. Uptake could also be blocked by cytochalasin B, a specific inhibitor of all the mammalian glucose transporter isoforms. Finally, the affinity of the transporter for glucose was determined (Fig. 2C). Michaelis-Menten analysis of the fitted curve indicates a Km for 2-DG of approximately 2.4 mM.

GLUTX1 Protein—GLUTX1 synthetic mRNA was in vitro translated in reticulocyte lysate in the presence or absence of canine pancreas microsomal membranes. Fig. 3A shows that the primary translation product migrated as a 35-kDa band, a higher electrophoretic mobility as compared with the predicted molecular mass of 51 kDa. In the presence of microsomal membranes, a part of the 35-kDa band was converted to a higher molecular mass of 37 kDa. This was due to N-glycosylation of the protein as demonstrated by the susceptibility of this band to digestion by both endoglycosaminidase H and PNGaseF. This modification probably takes place at the unique N-glycosylation site present in the exoplasmic loop between TM9 and TM10.

To further characterize the protein, antibodies were raised against either the middle intracellular loop of the transporter or against its carboxyl-terminal tail. The antibodies were characterized by Western blot using membrane fractions prepared from HEK293T cells transfected with GLUTX1. Fig. 3B shows that no reactive bands were detected in mock-transfected cells, whereas two prominent bands were detected in GLUTX1-expressing cells: a laddering band extending from approximately 37 to 50 kDa, and a band with a molecular mass of greater than 70 kDa. The same two bands were seen using either the middle

malian glucose transporter proteins. GLUTX1 protein sequence shows the highest degree of homology with nonmammalian sugar transporters. Identity is 36% with a putative sugar transporter from sugar beet, termed integral membrane protein (20), 35% with Escherichia coli galactose-proton symport (GalP), 32% with Lactobacillus brevis xylose proton symport (XYLT), and between 29 and 32% with the other mammalian glucose transporters. Importantly, sequences that have been reported to be critical for the glucose transport function are present in GLUTX1 at conserved locations. These include the two repeated sequence motifs GRR(K) and EX(F/R)(K) (see Introduction) and two tryptophan residues, Trp395 and Trp419, corresponding to Trp398 and Trp412 of GLUT1. Interestingly, a dileucine motif is found in the amino-terminal cytoplasmic domain of the protein. Human, rat and mouse GLUTX1 sequences have been determined (Fig. 1B). Mouse and rat GLUTX1 are most similar, showing 91% identity at the nucleotide and 94% identity at the amino acid sequence level; human GLUTX1 is more divergent, showing 85% identity with both the nucleotide and the protein sequence of rat and mouse GLUTX1.
FIG. 1. A, alignment of GLUTX1 with *B. vulgaris* integral membrane protein (IMP) (Swiss-Prot accession number Q39416), *E. coli* galactose proton symport (GALP) (Swiss-Prot accession number P37021), *L. brevis* xylose proton symport (XYLT) (Swiss-Prot accession number O52733), and rat GLUTs 1–5 (Swiss-Prot accession numbers P11166, P11168, P11169, P14672, and P22732). Alignment was made using the pileup (Genetics Computer Group) and ClustalX programs. Black shading indicates identical residues, and gray shading indicates amino acids belonging to the same conservation group. The approximate positions of the transmembrane domains are marked. The position of a dileucine motif in GLUTX1 sequence is indicated by a horizontal bar, and the position of a putative glycosylation site is indicated by an asterisk. Four regions of conservation between GLUTX1 and integral membrane protein are marked with boxes. B, alignment of GLUTX1 mouse, rat, and human amino acid sequences.
loop (Fig. 3) or the carboxyl-terminal antibodies (not shown). After treatment of the membranes with PNGaseF, the 37–50-kDa band shifted toward a well defined band centered at approximately 35 kDa. The migration of the upper band was, however, only slightly affected. This band may represent non-specific dimer aggregates of the lower band, because it is also sometimes visible in the reticulocyte lysates (Fig. 3 A), and its intensity relative to the 37–50-kDa band depends in part on the cell lysis conditions, in particular on the addition of reducing agents.

To determine the cellular localization of GLUTX1, its cDNA was transiently expressed in HEK293T fibroblasts, and immunostaining was performed using the affinity-purified antibody directed against the cytoplasmic loop of GLUTX1. GLUTX1 showed a strong intracellular staining (Fig. 4 A) but no surface expression. Because mutation of the amino-terminal tail dileucine motif to alanines leads to detection of transport activity when the corresponding mRNA was injected into oocytes, we expected that the same mutant would be expressed at the cell surface. Fig. 4 B indeed shows that most of the GLUTX1(LL-AA) is expressed on plasma membrane of transfected HEK293T cells. This therefore confirms the importance of this signal on the intracellular retention of GLUTX1.

GLUTX1 Tissue Distribution—GLUTX1 tissue distribution was assessed by Northern blot analysis of adult rat tissues total RNA. The strongest expression was seen in testis, with moderate expression in the cerebellum, brain stem, hippocampus, hypothalamus, adrenal gland, liver, spleen, brown adipose tissue, and lung (Fig. 5). A low level of expression was detected in white adipose tissue, muscle, kidney, tongue and was barely detectable in intestine and stomach. No GLUTX1 expression was detected in thyroid.

**Fig. 2.** A, 2-DOG uptake in *Xenopus* oocytes injected with 25 ng of GLUTX1 wild-type (WT) RNA and GLUTX1(LL-AA) RNA compared with noninjected control oocytes. The concentration of 2-DOG was 2 mM. Each bar represents the average for 10 oocytes. B, effect of competitors and inhibitors on uptake of 2-DOG in GLUTX1(LL-AA)-injected oocytes. For all conditions 2-DOG concentration was 2 mM. 8–10 oocytes/condition were incubated with 250 mM D-glucose, 250 mM L-glucose, 250 mM D-galactose, 250 mM D-fructose, or 50 μM cytochalasin B. Results are expressed as percentages of average 2-DOG uptake in nontreated oocytes (top bar). The results shown are an average of two experiments performed with two different batches of oocytes. C, dose curve for uptake of 2-DOG in GLUTX1(LL-AA)-injected oocytes fitted using the Michaelis-Menten equation. 2-DOG uptake was measured at varying concentrations from 0.07 to 10 mM. Each point represents the average uptake from 8 to 10 oocytes.

**Fig. 3.** A, *in vitro* translation of GLUTX1 cRNA using rabbit reticulocyte lysate in the presence (+MM) or absence (−MM) of canine pancreatic microsomal membranes as described under “Materials and Methods.” In the reaction without microsomal membranes, only one band of approximately 35 kDa is present. An additional band of approximately 37 kDa is present in the reaction with microsomal membranes, indicating that this is the glycosylated form of GLUTX1. This was confirmed by sensitivity of the 37-kDa band to EndoH or PNGaseF. B, Western blot of membrane proteins from HEK293T cells transiently transfected with wild-type GLUTX1 and control 293T cells. Membrane protein preparations from transfected cells were incubated at 37 °C for 2 h in the presence or absence of PNGaseF as described under “Materials and Methods.” Each lane contains 20 μg of protein. Immunodetection was with the affinity purified GLUTX1(203–257) antibody as described under “Materials and Methods.”
DISCUSSION

We used database screening to identify a novel glucose transporter GLUTX1. This has the same predicted topology and contains sequences motifs that are signatures of members of the sugar transport family. Expression in *Xenopus* oocytes confirmed that GLUTX1 is a glucose transporter. This transporter is expressed at different levels in a wide variety of tissues. Immunocytochemical analysis revealed that GLUTX1 is an intracellular protein whose location depends on the presence of a dileucine internalization motif.

Sequence comparison indicated that rat GLUTX1 was 29–32% identical to the GLUTs, whereas the GLUTs are between 40 and 70% identical to each other. Highest sequence identity (36%) was with a putative sugar transporter (integral membrane protein) cloned from sugar beet (20) and with bacterial galactose/xylose/proton cotransporters (35%). Four small regions of GLUTX1 (45–49, 70–74, 181–188, and 398–403) show almost perfect conservation with integral membrane protein sequences that are only very distantly related to sequences at the same locations in GLUTs (indicated in Fig. 1A). These regions imply differences in evolutionary origin and/or differences in structural requirements for GLUTX1 compared with the GLUTs. Interestingly, one unique feature of GLUTX1 is the long exoplasmic loop present between TM9 and TM10 that contains the only N-glycosylation site of the molecule. This sequence has no counterpart in the GLUTs or in the related plant or bacterial transporters mentioned above. By using Smith-Waterman sequence similarity search (21) using rat GLUTX1, we, however, found that this sequence contains a stretch (amino acids 341–362) that is similar (54% identical over 22 residues) to a segment (amino acids 333–354) of the *msmF* multiple sugar receptor/transporter of *S. mutans*. The *msmF* protein has six putative transmembrane domains and forms part of a system responsible for the uptake and metabolism of multiple sugars (22) and is closely related to the maltose transport system of *E. coli*. This similarity is at present of unknown functional importance but may point to a structure that participates in sugar binding.

Chimeric and mutant glucose transporters have been widely used for the study of the structure/function of the GLUTs (reviewed in Ref. 13). A recent study has identified the QLS sequence in transmembrane domain 7 of GLUT1,3,4 as a motif critical for hexose selection at the exofacial binding site. Replacing this sequence with that of human GLUT2 led to fructose, in addition to glucose, transport activity of the mutated transporter (9). GLUTX1 has MVF at this position instead of QLS. This suggests that it may transport other hexoses beside glucose. Our oocyte uptake experiments indeed show that both fructose and galactose can compete for 2-DOG transport.

One distinguishing feature of GLUTX1 as compared with the GLUTs is its relatively short carboxyl-terminal cytoplasmic tail, which has a predicted length of 20 amino acids as compared to 42–45 amino acids for GLUTs 1–5. Deletion studies of GLUT1 have suggested that its carboxyl-terminal tail was important for allowing conformational changes that accompany glucose transport. Removing 37 amino acids of the GLUT1 tail suppressed glucose transport by locking the transporter in an inward facing conformation (23). However, shorter truncations, up to 24 amino acids (leaving an 18-amino-acid-long carboxyl-
terminal tail), did not affect on transport activity or cytochalasin B binding (13). Therefore, by analogy, the short cytoplasmic tail of GLUTX1 should still permit normal transport activity. This was indeed confirmed by oocyte expression studies. These functional experiments were, however, successful only after mutation of the dileucine motif present in the amino-terminal tail of the molecule. Transport was not inhibited by an excess of \( L \)-glucose, suggesting stereospecificity of the transport mechanism. Transport was cytochalasin B-sensitive, which is compatible with the presence of tryptophan at positions 395 and 419, which correspond to Trp\(^{386} \) and Trp\(^{112} \) of GLUT1. Transport was also indicated for fructose and galactose as assessed by competition experiments. The \( K_m \) for 2-DOG, as determined in zero-trans experiments, was \( -2.4 \) mm. This value is similar to that of GLUT3, which is the highest affinity transporter of the GLUT family (3).

A possible physiological role for GLUTX1 can be suggested based on both its tissue and cellular localization. First, its intracellular location suggests that it is not involved in basal cellular glucose uptake. However, similarly to GLUT4, GLUTX1 contains a dileucine internalization motif. In GLUT4, this motif, located in the carboxyl-terminal cytoplasmic tail, functions as signal for re-endocytosis following surface expression, which occurs either as part of a basal recycling process or following stimulation by insulin (24, 25). In GLUTX1, the dileucine motif appears essential for maintaining the intracellular localization of the transporter as assessed both in transfected HEK293T cells and in neuroendocrine cells and as inferred from Xenopus oocytes functional studies. This therefore suggests that in its normal life cycle, GLUTX1 recycles between an intracellular site and the plasma membrane. Therefore, one possible role for this transporter may be to increase cellular glucose uptake in response to certain stimuli. Those could be hormones such as insulin or neurotransmitters but also other factors such as stresses induced by, for instance, hypoxia or hypoglycemia.

The high level of GLUTX1 expression in testis suggests that this glucose transporter could function to promote glucose and fructose transport in the developing spermatocyte alongside GLUT3 and GLUT5, which are also known to be expressed in testis (26, 27). GLUTX1 expression is relatively high in the brain stem and hypothalamus where glucose-sensing neurons are located and that respond to hyperglycemia or hypoglycemia by increasing or decreasing their firing rates (28–30). It is therefore possible that GLUTX1 plays a role in some of these glucose-sensing mechanisms or in some adaptive functions. Finally, recent studies performed with knockout mice have revealed the existence of glucose transport activity that could not be accounted for by any of the known GLUTs. This was the case in the pancreatic \( \beta \) cells of GLUT2-null mice, which are characterized by a loss of first phase insulin secretion but which have a preserved second phase. This remaining glucose secretory activity still depends on glucose uptake and metabolism (31). Glucose uptake, however, cannot be accounted for by any other known GLUTs. This was also the case in some muscles of GLUT4-null mice in which glucose uptake can still be stimulated by an insulin-dependent mechanism (32) that does not appear to involve GLUT1–5. Further localization studies, at the tissue and cellular levels, as well as evaluation of a mechanism that may induce GLUTX1 surface expression will ultimately be required to more fully elucidate the physiological role of this transporter.

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