GLUT7: a new intestinal facilitated hexose transporter

Chris Cheeseman
Membrane Protein Research Group, Department of Physiology, University of Alberta, Edmonton, Alberta, Canada
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Cheeseman CI. GLUT7: a new intestinal facilitated hexose transporter. Am J Physiol Endocrinol Metab 295: E238–E241, 2008. First published May 13, 2008; doi:10.1152/ajpendo.90394.2008.—The very last member of the SLC2A gene family of facilitated hexose transporters to be cloned was SLC2A7 (hGLUT7). It has been assigned to the class II of the GLUT family on the basis of sequence similarity, and its closest family member is GLUT5, an intestinal fructose transporter. GLUT7 is primarily expressed in the small intestine and colon, although mRNA has been detected in the testis and prostate as well. The protein is expressed in the apical membrane of the small intestine and colon, and it has a high affinity (<0.5 mM) for glucose and fructose. The abundance of the protein in the small intestine does change in parallel with the dietary carbohydrate. However, the distribution of GLUT7 along the small intestine does not entirely match with the availability of glucose and fructose, suggesting that the physiological substrate for this transporter has yet to be identified. Unlike GLUT13, the proton-coupled myoinositol transporter (HMIT), there is no evidence for the coupling of protons to the hexose movement via GLUT7. One area of study in which GLUT7 has provided useful comparison with GLUT1 has been in the development of the hypothesis that the facilitated hexose transporters may have a selectivity filter at the exofacial opening of the translocation pore, which helps to determine which hexoses can be transported. If substantiated, the elucidation of this mechanism may prove useful in the design of hexose analogs for use in cancer imaging and therapeutics.

Functional Activity

Injection of hGLUT7 cRNA into Xenopus oocytes resulted in a significant amount of the protein being expressed in the plasma membrane but the induction of a relatively low rate of hexose transport. Both glucose and fructose appeared to be substrates, while galactose, 2-deoxyglucose, and xylose were not. The kinetic analysis of the glucose and fructose transport showed a remarkably high affinity of the transporter for these substrates, with the $K_m$ as low as 200–300 μM. This is in sharp contrast with GLUT5, which has a $K_m$ for fructose of ~5–15 mM when expressed in oocytes or Chinese hamster ovary

Address for reprint requests and other correspondence: C. Cheeseman, Membrane Protein Research Group, Dept. of Physiology, Univ. of Alberta, Edmonton, Alberta, T6G 2H7, Canada (e-mail: chris.cheeseman@ualberta.ca).
CHO cells (3, 11). The transport of hexoses by GLUT7 is not affected by the mycotoxin cytochalasin B (CB) or by phloretin, both of which can inhibit the activity of the class I and some of the class III GLUTs. Subsequent characterization of the other class II GLUTs indicates that none of them are sensitive to CB (19). Other substrates for this transporter have been screened, including short-chain fatty acids and urate (see Future Research below), but none have yet been found to be taken up by this protein (unpublished observations).

Sites of Expression

Northern blotting of human tissues indicated that the major sites of expression of GLUT7 mRNA appear to be in the small intestine and colon, with some RNA expressed in the testis and the prostate. Immunohistochemistry of rat tissue localized the protein to the apical membrane of the small intestinal epithelium in the upper (jejunum) and lower (ileal) regions, but apparently not in the colon. The duodenum has not been tested for expression. However, Western blotting of brush-border membranes showed expression of GLUT7 in all three regions, with similar levels of the protein in the jejunum and ileum and a little less in the colon (Fig. 2). Also, there was no evidence for the expression of mRNA or protein in the intestinal muscle. These findings were surprising given that the majority of carbohydrate digestion and absorption is achieved in the jejunum and completed by the end of the ileum. Thus, luminal concentrations of free hexoses in the ileum should be quite low and negligible in the colon. Furthermore, as a facilitative transporter, GLUT7 would be unlikely to move substrate against a concentration gradient from the lumen into the epithelial cells. However, the affinity for both glucose and fructose is extremely high, which would fit with the predicted low substrate concentrations in the ileal lumen.

Control of Expression

The expression of hexose transporters in the small intestine changes in parallel with the abundance of their hexose substrates in the diet, so that both the facilitative (GLUTs) and concentrative [sodium-dependent glucose transporters (SGLTs)] increase or decrease when the carbohydrate intake is held at a particular level for several days (2, 7, 10). This also proved to

![Fig. 1. Sequence alignment for hGLUT5 and hGLUT7. The two sequences were aligned using CLUSTALX software. Red highlights indicate the 12 putative transmembrane domains (TMs). Blue areas indicate the QQLS motif common to class I and II GLUTs in TM7; yellow indicates the hydrophobic NAI motif postulated to form part of an exofacial selectivity filter; green region shows the unique COOH-terminal sequence used to generate a specific GLUT7 polyclonal antibody.](http://ajpendo.physiology.org/)

![Fig. 2. Effect of dietary carbohydrate on jejunal and ileal expression of GLUT7 in the rat. Animals were fed for 1 wk on normal rat chow (control), a low-carbohydrate (LC, 23%), or a high-carbohydrate (HC, 44%) diet. Isolated brush-border membranes were prepared from mucosal scrapings, and equivalent amounts of protein were loaded into SDS-PAGE gels. An antibody raised against the unique COOH-terminal sequence of GLUT7 (PTASPAKETSF) was used to detect the protein. A: Western blots of protein isolated from rat jejunum, ileum, and colon detecting GLUT7. B: relative abundance of GLUT7 determined by scanning Western blots and quantified using Un-Scan-It software. All data were normalized against the expression level of protein in the ileum from animals on the control diet. Error bars represent SE; *P < 0.05.](http://ajpendo.physiology.org/)
be the case for GLUT7, the expression of which increased in the small intestine of rats when their dietary carbohydrate was increased using an isocaloric diet (Fig. 2). After 1 wk on a low- or a high-carbohydrate diet, in which the caloric content was kept constant by reciprocally changing the fat content, realtime PCR, Western blotting, and immunohistochemistry all indicated that both GLUT7 message and protein increased in animals on the high-carbohydrate diet. This would suggest that one or more of the recently published mechanisms for sensing luminal carbohydrate could also be responsible for the increase in transcription and subsequent translation of GLUT7 in the small intestine (16, 17, 20). In contrast, the expression of GLUT7 in the colon was unaffected by dietary carbohydrate, as would be expected given that normally no hexoses would reach that far down the GI tract. In the case of GLUT2 it has been shown that increased expression in the basolateral membranes (BLM) can be induced by either glucose or fructose in the diet, whereas nonmetabolized hexoses failed to induce a response (4). This induction appears to be controlled at the level of transcription in the small intestine (8). However, GLUT5 expression in the enterocyte apical membrane responds specifically to luminal fructose and not glucose (8). Currently, the control of GLUT7 expression in the intestine is limited to overall carbohydrate levels, and there have been no reported studies on the specificity of the signals involved (Fig. 3).

Some hexose transporters in the small intestine can also be acutely regulated. GLUT2 activity in the BLM responds to increases in plasma and luminal glucose within 60 min (5, 22), and it has been proposed that this is mediated by the enteric peptide hormones gastric inhibitory polypeptide (GIP) and glucagon-like peptide-2 (GLP-2) (6). GLP-2 has also been implicated in the rapid insertion of GLUT2 into the apical membrane (1), although this response appears to involve a complex set of signaling pathways including taste receptors, SGLT1, and apical calcium channels (14). Again, there is no information available on whether GLUT7 activity is also acutely responsive to vascular or luminal glucose levels or the hormones GIP and GLP-2.

**Protein Structure**

Like all the other GLUTs, hydropathy analysis indicated 12 membrane-spanning domains for GLUT7. The likely glycosylation site appears on the first extracellular loop between TMs 1 and -2, which is common for all of the class I and II GLUTs. Comparison of the sequence alignment of the other GLUT proteins indicated that, in the region predicted to form TM7, where a number of residues key to hexose transport had already been identified, there is a hydrophobic sequence that might correlate with substrate specificity. GLUT2, -5, -7, and -9 all transport fructose and express an isoleucine close to the exofacial end of TM7, whereas the non-fructose-transporting GLUTs GLUT1, -3, and -4 have a valine at this position. Expression of a GLUT7 mutant in which the isoleucine had been replaced with a valine resulted in a loss of fructose transport capacity, whereas glucose mediation was unaffected (18). This substitution was also found to result in the same loss of fructose transport, and the authors suggested that this residue (isoleucine or valine) might form a hydrophobic interaction across the exofacial opening of the translocation pore with a tryptophan in TM2. Furthermore, this structure might in some way form a substrate selectivity filter restricting hexose access to the translocation mechanism. Computer modeling of the structure of GLUT1 and -7 supported this contention, but in the absence of a crystal structure for these proteins it will be difficult to confirm whether this model is correct. However, it does raise interesting questions as to how this family of proteins recognizes their substrates and interacts with them during the transport cycle. Prior to the introduction of this hypothesis, it had been assumed that substrate specificity was determined solely by the substrate binding site(s) associated with the translocation mechanism. The conservation of this hydrophobic region at this position in the GLUT orthologs throughout numerous phyla suggests that this is an important structural component of facilitated hexose transporters (19).

**Future Research**

To date, the functional activity of GLUT7 has only been determined using the oocyte expression system, and its ability to mediate hexose transport in intestinal epithelial cells still needs to be assessed. The use of short interfering RNA to knock down the expression of GLUT7 or, alternatively, a mouse knockout model could provide useful insights into the contribution that this transporter makes to hexose absorption in the small intestine.

The physiological regulation of this transporter in the small intestine still remains to be elucidated. Is the transport activity or levels of expression regulated by the same or different signals and pathways from those for SGLT1, GLUT2, or GLUT5?

The very low capacity for glucose and fructose transport exhibited by GLUT7 does raise the possibility that the physiological substrate for this transporter is something other than a hexose. This transporter could exchange another organic compound for glucose or fructose. Recent findings with GLUT9 (23a), indicate that this closely related class II GLUT is a glucose-urate exchanger, and so GLUT7 may also interact with an as-yet-unidentified substrate.

Although Northern blotting has indicated the presence of GLUT7 message in the testis and prostate, the expression of the protein has not yet been measured in either of these tissues. Given the important metabolic role of fructose in these tissues,
GLUT7 may well play an important role in providing metabolic substrate.

The structure-function studies with GLUT7 and, subsequently, other class II members, have raised an interesting possibility that GLUT proteins may have a substrate selectivity filter at the exofacial opening of their translocation pore. This putative structural element deserves further investigation because it could well have important implications for the design of hexose analogs used either for cell imaging with positron emission tomography (PET) or for possible cancer chemotherapeutic agents.

REFERENCES


