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Expression of Class III facilitative glucose transporter genes (GLUT-10 and GLUT-12) in mouse and human adipose tissues☆

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Abstract

We have examined whether GLUT-10 and GLUT-12, members of the Class III group of the recently expanded family of facilitative glucose transporters, are expressed in adipose tissues. The mouse GLUT-12 gene, located on chromosome 10, comprises at least five exons and encodes a 622 amino acid protein exhibiting 83% sequence identity and 91% sequence similarity to human GLUT-12. Expression of the GLUT-12 gene was evident in all the major mouse adipose tissue depots (epididymal, perirenal, mesenteric, omental, and subcutaneous white; interscapular brown). The GLUT-10 gene is also expressed in mouse adipose tissues and as with GLUT-12 expression occurred in the mature adipocytes as well as the stromal vascular cells. 3T3-L1 adipocytes express GLUT-10, but not GLUT-12, and expression of GLUT-12 was not induced by insulin or glucose. Both GLUT-10 and GLUT-12 expression was also found in human adipose tissue (subcutaneous and omental) and SGBS adipocytes. It is concluded that white fat expresses a wide range of facilitative glucose transporters.

Keywords: GLUT-10; GLUT-12; GLUT-4; Glucose transporters; Brown adipose tissue; White adipose tissue; Adipocytes

The movement of monosaccharides across plasma membranes is controlled by proteins encoded from two structurally and functionally distinct gene families, namely the facilitative glucose transporters (gene symbol SLC2A, protein symbol GLUT) and the Na^+-dependent glucose transporters (gene symbol SLC5A, protein symbol SGLT) [1]. Up to 3 years ago, five different GLUTs, GLUT-1 to -5, were known, but the number of members of this gene family has now increased to fourteen [2,3]. These various GLUTs have different functional characteristics and multiple members can be present in a single tissue (e.g., muscle and adipose tissue). Based on sequence similarity, the GLUT family has been subdivided into three different classes, Class I (GLUT-1, -4, and -14), Class II (GLUT-5, -7, -9, and -11) and Class III (GLUT-6, -8, -10, -12, and HMIT) [2,3]. The GLUT family members have all been described for human sequences, but species homologues, including in the mouse, have yet to be shown for all of the recently identified members. Interestingly, no homologue to GLUT-14 could be found in mice [2]; identification of homologues is necessary for the mouse to be utilised as a model for the study of diseases such as diabetes and obesity.

White adipose tissue (WAT), once regarded simply as an energy store, is now recognised to have important endocrine functions, the tissue secreting leptin and a range of adipokines with diverse modes of action, from signalling to the brain to inflammatory responses [4,5]. The transport and metabolism of glucose is central to the function of WAT and the tissue is known to expresses several members of the GLUT gene family; these include GLUT-1, GLUT-4 [6], and GLUT-5 (a fructose transporter) [6,7]. More recently, GLUT-8 expression has been observed in the WAT of mice [8], GLUT-12 in human fat [9], and HMIT (a myo-inositol transporter) in rat adipose tissue [10].

☆ The mouse GLUT-12 cDNA sequence has been deposited in the EMBL database under the Accession No. AJ549317

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Human GLUT-12 was originally detected in a breast cancer cell line, MCF-7 [9]. Several tissues, including heart, skeletal muscle, adipose tissue (unspecified depot), and small intestine have been reported to exhibit GLUT-12 protein expression. Recent studies have also found GLUT-12 expression in human chondrocytes [11], rat mammary gland [12] and fetal rat tissues [13]. A second class III transporter, GLUT-10, has been cloned from humans and mice, and expression of the gene was detected in human skeletal muscle, heart, lung, brain, liver, pancreas, placenta, and kidney [14,15].

We report here the identification and amino acid sequence of GLUT-12 in mice, and demonstrate that both the GLUT-12 and GLUT-10 Class III glucose transporters are expressed in murine adipose tissues (white and brown); these two new GLUTs are both expressed in mature adipocytes. Thus white fat expresses a wide range of facilitative glucose transporters: GLUT-1, GLUT-4, GLUT-5, GLUT-8, GLUT-10, GLUT-12, and HMIT.

Materials and methods

Isolation of total RNA. Male CD1 mice, aged 10 weeks, were killed by cervical dislocation and WAT depots and various organs collected into either RNAlater (Ambion) or liquid N_2. Human WAT (subcutaneous and omental) was provided by S. Wong from adult obese subjects (body mass index >35) undergoing surgery, with approval from the local Ethics Committee. Tissue was subsequently stored at −80 °C prior to use. RNA was isolated using TRI reagent (Sigma) according to the manufacturer's instructions. RNA quality was assessed by spectrophotometric analysis and denaturing agarose gel electrophoresis.

Adipocyte isolation. WAT from different depots (epididymal, subcutaneous, and perirenal), was placed in albumin buffer (1% BSA, 1× Mixed salts (200 mM NaCl, 100 mM KCl, 100 mM $CaCl_2$, 100 mM $MgSO_4$), and 100 mM Hepes, pH 7.6) immediately on removal from the animal. The tissue was transferred to collagenase buffer (0.5 mg/ml collagenase type II, 2.8 mM D-glucose, 1.75% BSA, 0.5× mixed salts, and 50 mM Hepes, pH 7.6). The tubes containing the adipose tissue were placed in a shaking incubator at 37 °C for 1 h, or until digestion was complete. The digested tissue was passed through a 250 μm mesh and centrifuged at 1000 rpm for 10 min. The mature fat cells floating at the top were then transferred to fresh tubes, excess buffer was removed, and the cells aliquoted and TRI reagent added. Similarly, the resultant pellet, containing the stromal vascular fraction, was resuspended in TRI reagent.

Cell culture. 3T3-L1 cells were obtained from ATCC. The cells were routinely grown as previously described [16]. For studies on glucose and insulin treatment, cells were grown to day 9 (post the induction of differentiation) and switched to either glucose-free or insulin-free medium for 24 h. To investigate the effects of insulin, cells were treated for 24 h with medium containing 0, 0.1, 1, or 10 μM insulin. At the end of this period, the cells were collected in TRI reagent. To investigate the effects of glucose, cells were grown in media containing 0, 5, or 25 mM D-glucose for 0, 24, and 48 h and collected in TRI reagent.

A human preadipocyte cell strain, SGBS [17], was obtained as a gift from M. Wabitsch. Cells were routinely grown as described by Wabitsch et al. [17]; they were collected in TRI reagent and RNA isolated as described above.

Cloning of mouse GLUT-12. Oligonucleotide primers (see below) were derived from the draft sequence of the mouse genome sequence database [18] that aligned to the protein coding region of the human GLUT-12 cDNA sequence [9]. Two-step RT-PCR was employed using single stranded mouse WAT or heart cDNA prepared from 4 μg of total RNA with Superscript II reverse transcriptase (Invitrogen) and 250 ng random hexamers (Promega). The DNA polymerase used in the PCR was Thermostart DNA polymerase (ABgene) which required an initial activation step of 95 °C for 15 min. Reaction conditions used were: 94 °C, 20 s; 65 °C, 20 s; and 72 °C, 45 s for 30 cycles followed by a final extension step of 72 °C for 10 min. The resulting amplicon was ligated into pGEMT-Easy (Promega), custom sequenced (MWG Biotech) and compared to the human GLUT-12 cDNA sequence. The remaining putative protein coding sequence was obtained by the use of Rapid Amplification of cDNA Ends (RACE)-PCR and RT-PCR.

RT-PCR. First-strand cDNA was synthesised from 4 μg of total RNA using Superscript II reverse transcriptase (Invitrogen) with 250 ng random hexamers (Promega). Oligonucleotide primer pairs derived from mouse and human GLUT-12, GLUT-10, GLUT-4, and β-actin cDNA sequences (see below) were used for PCR with Thermostart DNA polymerase (ABgene). The template amount used was the equivalent of 50 ng of total RNA. The cycle number for all primer pairs was optimised to produce products in the exponential phase of amplification. Amplicons were custom sequenced (MWG Biotech) for verification.

Oligonucleotides. All oligonucleotide pairs, synthesized by MWG Biotech UK, were designed to be exon spanning and were species-specific. Mouse GLUT-12, 616 bp, (F)TGCTGAACCAGAAGGGGAGAGAGG, (R)GCTATTGCTTGCAGAACTCCCAGG; mouse GLUT-10, 473 bp: (F)ACATCCAATGCCAGCCAGCAGGTG, (R)ATGAAAGCCAGGCCAAGGACAGCG; mouse GLUT-4, 317 bp: (F)CCTGCCCGAAAGAGTCTAAAGC, (R)ACTAAGAGCACCGAGACCAACG; mouse β-actin, 463 bp: (F)TGCTGTCCCTGTATGCCTCT, (R)AGGTCTTTACGGATGTCAACG; human GLUT-10, 630 bp: (F)GGTCTTTGTCAGTGCCTTCT, (R)GAGATGTGCAAGTCAATGGG; human GLUT-12, 405 bp: (F)CTGCTGAACCAGAAGGGGACAGCC, (R)GAGGGAGATGGAGACCCCTATGGC; human GLUT-4, 413 bp: (F)GGCATGTGTGGCTGTGCCATC, (R)GGGTTTCACCTCCTGCTCTAA; and human β-actin, 309 bp: (F)TTCAACTCCATCATGAAGTGTGACGTG, (R)CTAAGTCATAGTCCGCCTAGAAGCATT.

Results

A cDNA sequence for human GLUT-12 was recently isolated from a breast cancer cell line, MCF-7 [9]. The cDNA sequence encoding the protein coding region was used to BLAST search the draft mouse genome sequence [18] on both the ensemble (http://www.ensembl.org/) and NCBI (http://www.ncbi.nlm.nih.gov/BLAST/) web sites. An alignment was obtained of between 78% and 86% over four fragments located on chromosome 10, position A3. A pair of overlapping oligonucleotide primers was designed from separate fragments of the highlighted mouse genome sequence and used for two-step RT-PCR against first-strand cDNA synthesised from mouse epididymal WAT RNA. The sequence of the resulting amplicon, 616 bp, was found to be identical to the draft mouse genome sequence. This fragment shares 82% identity with the human GLUT-12 sequence and corresponded to position 35–638 nucleotides

relative to the translational start codon. A minus-RT first-strand synthesis control confirmed that the amplicons were mRNA derived and not a result of genomic contamination.

Rapid amplification of cDNA ends-polymerase chain reaction (RT-PCR) was utilised to complete the putative mouse GLUT-12 cDNA sequence. Amplicons derived from 5′RACE-PCR in both WAT and heart were identical. The amplicon that yielded the greater sequence information extended 223 nucleotides upstream from the 616 bp mouse RT-PCR product isolated above. A 1.1 kb amplicon obtained from 3′RACE-PCR of mouse WAT was identical to the mouse genome sequence. The presence of a polyadenylation signal 16 bp from the end of the RACE product would suggest that this fragment represents the end of a mRNA transcript. The remainder of the mouse GLUT-12 cDNA sequence was completed using RT-PCR with a primer pair designed from the mouse sequence BLAST alignment with the human GLUT-12 cDNA sequence. An amplicon of 1601 bp was obtained which overlapped with the previously obtained fragments. Complete sequencing of this product showed it to be 100% identical to the mouse genome database sequence and the products already isolated here.

The assembled isolated mouse GLUT-12 cDNA sequence consists of 3057 bp and was used to search against the mouse genome database with NCBI Blast server (http://www.ncbi.nlm.nih.gov/BLAST/). The sequence was found to be 100% identical over five fragments corresponding to different exons. The ends of the aligned cDNA and genomic sequences are shown in Table 1 with estimated intronic sequence lengths. The deduced amino acid sequence consisted of 622 amino acid residues and shares an 83% sequence identity and 91% sequence similarity with the human GLUT-12 [9].

Expression of GLUT-12 and GLUT-10 in mouse adipose tissue depots

Two-step RT-PCR was used to examine the expression of the GLUT-12 and GLUT-10 genes in mouse adipose tissues. The epididymal, subcutaneous, perirenal, omental, and mesenteric WAT depots, interscapular brown adipose tissue (IBAT), together with other organs (heart, skeletal muscle, kidney, brain, spleen, lung, small intestine, and liver) were examined. Fig. 1 shows that GLUT-12 mRNA was detected in all six adipose tissue depots screened, the identity of the PCR product being confirmed by sequencing (similarly for GLUT-10 below). Furthermore, GLUT-12 expression was observed in skeletal muscle, heart, brain, kidney, spleen,

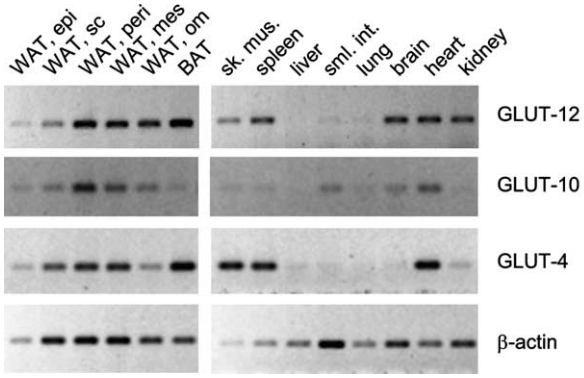

Fig. 1. Tissue specificity of GLUT-12 and GLUT-10 gene expression. First-strand cDNA synthesis and subsequent PCR of various mouse tissues was performed. These included six adipose tissue depots and eight other tissues, as indicated. Amplification cycle numbers were as follows: GLUT-12, ×30; GLUT-10, ×31; GLUT-4, ×27; and β-actin, ×21. WAT, white adipose tissue; BAT, interscapular brown adipose tissue; epi, epididymal; sc, subcutaneous; peri, perirenal; mes, mesenteric; om, omental; sk. mus., skeletal muscle; and sml. int., small intestine. A representative gel is shown.

Table 1
Proposed exon–intron organisation of mouse GLUT-12 gene

Exon	Exon size (bp)	5′ Splice donar	3′ Splice acceptor	Estimated intron size (bp)
		38	40	
1	>302	A C A G*[G]*	P S M F	19,084
		TGCCTGCGCGGGA*ggtaacg*	*taggt*CCCAGCATGTTT	
		486	488	
2	1344	G L G P*[M]*	P W L V	26,965
		GGTCTGGGACCC*agtaagta*	*tagtg*CCTTGGTTGGTG	
		527	529	
3	123	L T V T*[D]*	L I G L	1738
		CTGACAGTGACT*ggtaagaa*	*tagat*CTTATTGGTTTG	
		571	573	
4	132	E L A K*[A]*	N Y V K	8071
		GAGCTAGCAAA*Ggcgtaagt*	*cagg*AACTATGTGAAA	
5	>1156			

Proposed gene structure using the Wise2 program from the EBI sequence analysis toolbox (http://www.ebi.ac.uk/Wise2/index.html). The accession number of the genomic DNA contig sequence was NT_039492.1, nucleotides 125966–273231. Exon sequences are depicted in capital letters. Intronic sequences are depicted in lower case italics. The numbers above the sequence refer to amino acid residues. Interrupted amino acid residues are indicated in square brackets.

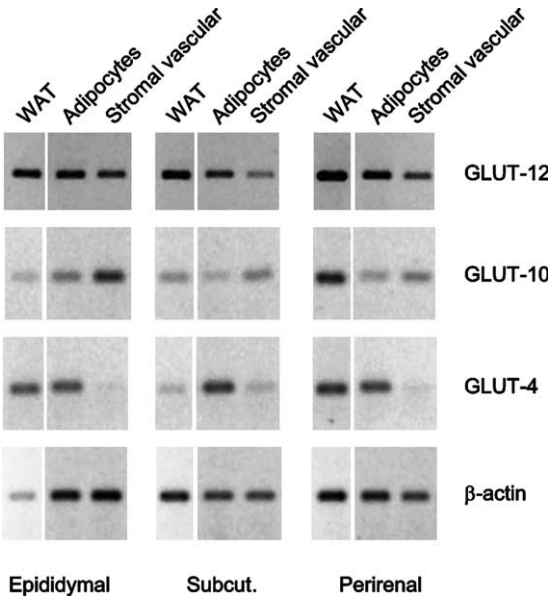

Fig. 2. Cellular expression of GLUT-12 and GLUT-10 genes in WAT. Adipocytes were separated from the stromal vascular fraction of three mouse WAT depots by collagenase digestion and RT-PCR performed; a representative gel is shown. Amplification cycle numbers were as follows: GLUT-12, ×35; GLUT-10, ×31; GLUT-4, ×27; and β-actin, ×21. Subcut, subcutaneous.

and to a lesser extent in small intestine and lung. GLUT-12 mRNA was not detected in the liver.

The expression of GLUT-10 reflected that of GLUT-12 in its widespread distribution. However, the relative abundance of the mRNA did appear to vary from that of GLUT-12. With respect to adipose tissue, the abundance appeared consistently less in IBAT compared to the WAT depots. As with GLUT-12, GLUT-10 gene expression was not detected in the liver.

Adipose tissue is heterogeneous at a cellular level, adipocytes comprising about 50% of the total cell content. To establish whether GLUT-10 and GLUT-12 are expressed in adipocytes, white fat from three depots (epididymal, subcutaneous, and perirenal) was fractionated into mature adipocytes and the stromal vascular fraction. Two-step RT-PCR was performed and the results are shown in Fig. 2. Signals for GLUT-10 and GLUT-12 were observed in both the adipocyte and stromal vascular fractions in all three depots examined. By comparison, an established adipocyte reference marker, GLUT-4 [19], was expressed almost exclusively in adipocytes (Fig. 2).

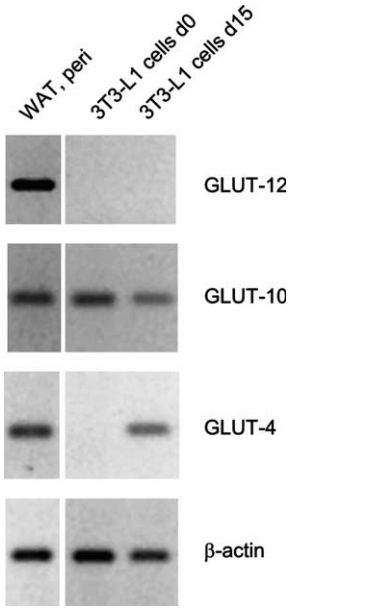

Fig. 3. Expression of GLUT-12 and GLUT-10 genes in 3T3-L1 cells. 3T3-L1 cells were harvested at day 0 and day 15 after the induction of differentiation. Total RNA was isolated and two-step RT-PCR performed; a representative gel is shown. Perirenal WAT was included as a reference. Amplification cycle numbers were as follows: GLUT-12, ×35; GLUT-10, ×31; GLUT-4, ×27; and β-actin, ×21.

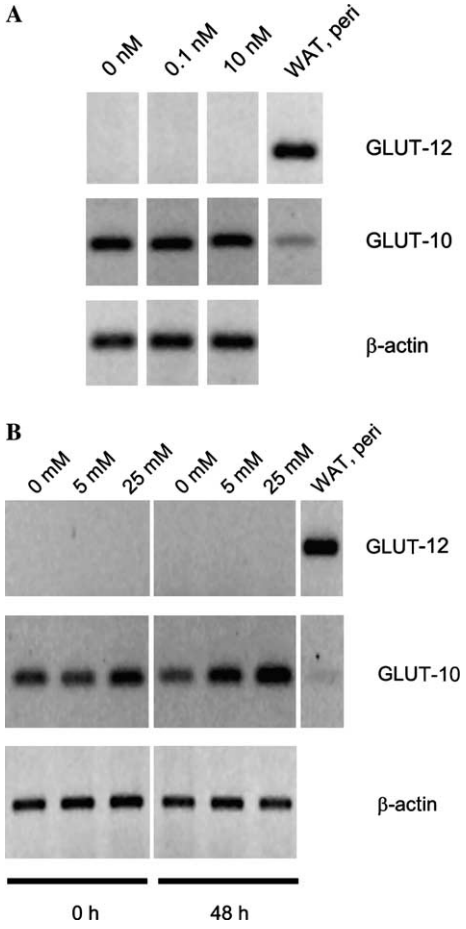

Fig. 4. Effect of insulin and glucose on GLUT-10 and GLUT-12 expression in 3T3-L1 cells. Treatment of cells began at day 9 post-differentiation with a 24 h incubation in insulin or glucose-free medium. Different amounts of either insulin or glucose were added to the medium and cells incubated for the required time. Total RNA was isolated and two-step RT-PCR performed with cycle numbers as follows: GLUT-12, ×35; GLUT-10, ×31; and β-actin, ×20. (A) Insulin treatment. (B) Glucose treatment. Perirenal (peri) WAT was used as a reference. A representative gel is shown.

Expression of GLUT-12 and GLUT-10 in 3T3-L1 cells

RT-PCR was used to determine whether GLUT-12 and GLUT-10 are expressed in the mouse 3T3-L1 cell line. Cells were harvested at day 0 (before differentiation) and at day 15 (following differentiation). Fig. 3 shows that no detectable product for GLUT-12 was present (despite exhaustive efforts), but products for GLUT-10 were observed both before (day 0) and after (day 15) differentiation. This compares to GLUT-4, which was used as a reference marker, where expression was evident at day 15, but not at day 0 (Fig. 3); a similar pattern of expression was found for leptin and resistin (results not shown).

To investigate whether GLUT-12 expression can be induced in 3T3-L1 cells, the effects of incubating with different concentrations of insulin (0, 0.1, and 10 nM) and glucose (0, 5, and 25 mM) were examined. The results of two-step RT-PCR are shown in Fig. 4. Altering either insulin (Fig. 4A) or glucose (Fig. 4B) levels for 48 h (or 72 h; results not shown) did not result in the appearance of GLUT-12 mRNA. Furthermore, no major effects were seen on GLUT-10 expression following treatment with either insulin or glucose (Fig. 4), even allowing for the non-quantitative nature of the RT-PCR procedure.

GLUT-10 and GLUT-12 expression in human adipose tissue and SGBS cells

The expression of GLUT-10 and GLUT-12 was also examined in human adipose tissue and a human adipocyte cell strain, SGBS cells [17]. Fig. 5 shows that products of the expected size for GLUT-12 and GLUT-10 mRNA were detected in the omental and subcutaneous WAT depots; however, in the subcutaneous tissue the signal for GLUT-12 was very weak. The same sized products were also observed in human SGBS cells (Fig. 5). Both GLUT-10 and GLUT-12 were present before (day 0) and after differentiation into mature adipocytes. GLUT-4 expression was used as a reference, and a strong signal was observed in the differentiated cells studied at day 15 (Fig. 5).

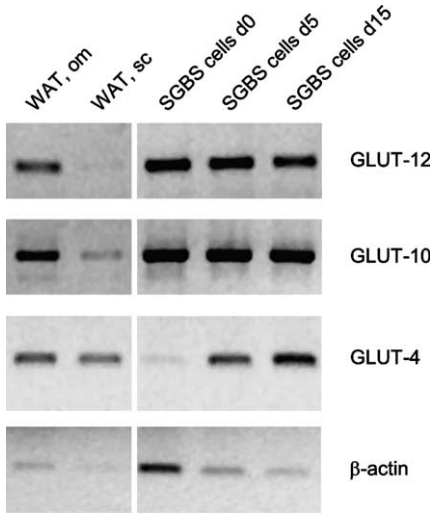

Fig. 5. Expression of GLUT-12 and GLUT-10 genes in human WAT depots and SGBS cells. Total RNA was isolated from human omental (om) and subcutaneous (sc) WAT depots. SGBS cells were harvested at day 0, day 5, and day 15 after the induction of differentiation and total RNA isolated. Two-step RT-PCR performed with cycle numbers as follows: GLUT-12, ×35; GLUT-10, ×35; GLUT-4, ×35; and β-actin, ×25. A representative gel is shown.

Discussion

The present study shows that the genes encoding two of the recently identified Class III facilitative glucose transporters, GLUT-12 and GLUT-10, are expressed in mouse adipose tissues. The sequence information for mouse GLUT-12 indicates that it is closely related to its human homologue in both gene structure and protein similarity. Initial isolation of the mouse GLUT-12 616 bp RT-PCR product was made possible by the release of the mouse genome draft sequence [18]. Consequently, during the course of this study, three overlapping EST sequences from separate mouse cDNA libraries (RIKEN Genomic Sciences Centre, Japan Accession Nos.: AK028970, AK031659, and AK035972) were found to contain an unnamed protein product containing hypothetical sugar transporters motifs. These putative translated sequences matched exactly the deduced amino acid reported in this paper. Whilst our cDNA sequence data extended upstream beyond that from the EST database sequences, the nature of the 5′RACE-PCR procedure means that the obtained products may not necessarily indicate the transcriptional start site and would therefore require further confirmatory experiments such as primer extension analysis and/or S1 nuclease mapping.

The glucose transporter synonymous with adipose tissue is the extensively characterised, insulin-responsive, GLUT-4 [19]. Furthermore, the expression of the family members GLUT-1 and GLUT-5 [6,7] is well established. The nine genes added to the facilitative glucose transporter family over the last three years are still in the process of functional and structural characterisation. The widespread tissue distribution of GLUT-12 and GLUT-10 gene expression does not of itself give a clear indication of any specialised functional role. However, both these genes are expressed in all adipose tissue depots analysed, brown as well as white, in addition to other insulin sensitive tissues. The stromal vascular expression of both these GLUTs in addition to isolated adipocytes (and pre-differentiation cell cultures), as opposed to the adipocyte specific expression of GLUT-4, is intriguing and may indicate an additional supportive

role to the adipocyte. Indeed, it has been suggested that GLUT-12 may provide glucose to cells of insulin sensitive tissues prior to GLUT-4 expression [13]. However, the substrate specificity for GLUT-12 is yet to be established.

The fact that the GLUT-12 gene was not expressed in 3T3-L1 adipocytes, either before or after differentiation, means that in contrast to GLUT-10 this cell line cannot be used to explore GLUT-12 function. GLUT-12 expression was not induced by treatment with either insulin or glucose, but it is not known whether in practise the GLUT-12 gene is responsive to these stimuli. A human adipocyte cell strain, SGBS cells, were found to express both GLUT-12 and GLUT-10 transcripts, however, and these may therefore represent a useful in vitro system for studies on Class III facilitative glucose transporters in adipocytes.

It appears from the present work and from previous studies that the adipocyte has the potential to express seven transporters from the GLUT gene family, four of which are from the Class III sub-group. It is reasonable to assume that the expression of multiple family members is a reflection of their different functional characteristics. The recent expansion of the GLUT family has revealed a greater diversity of substrate specificity and may be another explanation for the presence of GLUT-12. The expression of many GLUTs is also observed with some other cell types such as chondrocytes [11], albeit with a different expression profile from adipocytes. Interestingly, adipocytes and chondrocytes originate from the same multi-potent mesenchymal cells (which also include myocytes, osteoblasts, and fibroblasts) [11].

From studies on GLUT-4 knockout mice, which surprisingly are not diabetic, it has been suggested [20,21] that additional, but unknown, glucose transporters may be sensitive to insulin. Compensatory expression in GLUT-4 knockout mice of some of the recently identified GLUT family members is clearly a possibility.

Acknowledgments

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