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Expression during rat fetal development of GLUT12 – a member of the class III hexose transporter family

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Abstract Glucose is an essential molecule for most mammalian cells, and is particularly important during fetal development, when cells are rapidly dividing and differentiating. In rats, GLUT1 is present at high levels in most fetal tissues, with levels decreasing after birth. We used immunohistochemistry to localise GLUT12 protein, a recently identified member of the sugar transporter family, and GLUT1 during rat fetal development. GLUT12 staining was observed in heart muscle from gestational days 15 to 21. GLUT12 staining in skeletal muscle increased from gestational days 17 to 21, and GLUT12 was also detected in brown adipose tissue. The expression of GLUT12 in insulin-responsive tissues supports a potential role for GLUT12 in the provision of glucose to these tissues before the appearance of GLUT4. GLUT12 protein was also expressed in fetal chondrocytes from gestational day 15 onward, in kidney distal tubules and collecting ducts from day 19, and in lung bronchioles from day 19. The specific pattern of expression observed in the rat fetus suggests that GLUT12 may be important in hexose delivery to developing tissues.

Keywords GLUT12 · GLUT1 · Glucose transport · Embryogenesis · Immunohistochemistry

Introduction

Glucose is transported into mammalian cells by two transport systems: via the facilitative glucose transporter proteins or alternatively, in tissues such as small intestine, via the active sodium-glucose co-transporters. Thirteen members of the facilitative glucose transporter family have been described to date, GLUT1 to GLUT12

and HMIT (Joost et al. 2002), though only GLUT1 to GLUT5 are well-characterised. GLUTs demonstrate a tissue-specific pattern of expression. GLUT1 is present at variable levels in many adult tissues, including red blood cells, brain, kidney, heart and placenta (Bell et al. 1990). GLUT2 is expressed in liver, pancreatic β -cells, kidney and small intestine (Bell et al. 1990). GLUT3 is found in brain, placenta, testis, heart and platelets (Haber et al. 1993; Younes et al. 1997). GLUT4 is expressed at high levels only in heart, skeletal muscle, and white and brown adipose tissue (James et al. 1988). GLUT4 is insulin-responsive, as it translocates from intracellular vesicles to the cell membrane in response to insulin (James and Piper 1994). GLUT5, a fructose transporter, is expressed in small intestine, spermatozoa, kidney and skeletal muscle (Kayano et al. 1990; Burant et al. 1992).

The tissue distribution of each glucose transporter is not, however, constant throughout development. High levels of GLUT1 and GLUT3 are present in a wide range of fetal tissues, with expression of these transporters greatly decreased after birth in many of these cell types. In the pre-implantation embryo, GLUT3 is the transporter responsible for the uptake of uterine glucose in mice, though GLUT8 may also play a role (Pantaleon et al. 1997; Carayannopoulos et al. 2000). High levels of GLUT1 protein are also present in pre-implantation embryos, and by day 6.5 to 7.5 glucose is the main substrate consumed (Houghton et al. 1996; Pantaleon et al. 2001). During the early period of organ formation it is believed that GLUT1 is responsible for glucose supply to the dividing and differentiating cells (Matsumoto et al. 1995). In rats, GLUT1 is present at high levels in most fetal tissues, including brain, small intestine, heart, and skeletal muscle (Santalucia et al. 1992; Matsumoto et al. 1995). After birth, GLUT1 expression decreases dramatically in many rat tissues. A decrease of GLUT1 mRNA from gestational day 20 to postnatal day 8 was observed in rat heart, lung, liver, skeletal muscle and stomach, while constant levels were present in kidney (Werner et al. 1989). By 15 days after birth GLUT1 protein levels are

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low in skeletal muscle, heart and brown adipose tissue, while GLUT4 expression is similar to adult levels (Santalucia et al. 1992).

Recently, we have reported the identification of a novel glucose transporter like protein, GLUT12 (Rogers et al. 2002). GLUT12 belongs to the newly classified class III sugar transporter sub-family (Joost and Thorens 2001). Class I comprises the well-characterised transporters GLUT1–GLUT4. Class II includes the fructose transporter GLUT5 and GLUT7, GLUT9 and GLUT11. Class III comprises the recently identified transporters GLUT6, GLUT8, GLUT10, GLUT12 and HMIT. The sugar affinities and kinetic parameters for these proteins are still to be defined. In adult human tissue, GLUT12 protein was detected in the insulin-responsive tissues skeletal muscle and adipose tissue, and in small intestine and a breast cancer cell line (Rogers et al. 2002). We have also detected GLUT12 mRNA and protein in human breast tumours (unpublished results). It is known that some fetal genes may be reactivated in cancer cells. For example, fetal haemoglobin (Hb F) is reactivated in a high proportion of red blood cells in juvenile chronic myeloid leukaemia and in other forms of leukaemia (Sheridan et al. 1976).

As one of the cDNA clones of GLUT12 was obtained from a whole embryo library, and as GLUT12 has been detected in breast cancer cell lines and tumours, we thought that GLUT12 may also be expressed in fetal tissues. In the present study we sought to determine the tissue distribution of GLUT12 protein in the rat fetus from gestational day 13 (E13) to E21 using immunohistochemistry. As GLUT1 is the most characterised glucose transporter in the fetus, we compared the GLUT12 immunolocalisation to that of GLUT1.

Materials and methods

Animals

E13, E15, E17, E19, E20 and E21 embryos were collected from 10–12 week old pregnant Sprague-Dawley female rats and immersion fixed in 4% paraformaldehyde (0.1 M phosphate buffer, pH 7.4). All rats were housed in a stable environment (maintained at 22 ± 1 °C with a 12 h light day cycle) and allowed free access to tap water and standard rat chow containing 0.25% Na⁺ and 0.76% K⁺ (GR2, Clark-King, Gladesville, NSW, Australia). Experimental procedures adhered to the guidelines of the National Health and Medical Research Council of Australia's "Code for the Care and Use of Animals for Scientific Purposes" and were approved by the Bioethics Committee of The University of Melbourne.

Antibodies

The following primary antibodies were used: rabbit polyclonal anti-GLUT12, R1396, raised to the 16 C-terminal amino acids of human GLUT12 (Rogers et al. 2002), affinity-purified R1396 (Rogers et al. 2002), rabbit polyclonal anti-GLUT1 (Chemicon International, Temecula, Calif.), and non-immune rabbit serum.

Immunohistochemistry

Rat fetuses were embedded in paraffin and sectioned at 4 µm on a rotary microtome (Leica, Wetzlar, Germany). Sections were deparaffinised and endogenous peroxidase was removed with 5% H₂O₂ in absolute methanol for 30 min. Sections were blocked for 30 min with 10% normal swine serum (Institute of Medical and Veterinary Science, Gilles Plain, SA, Australia), and 5% fetal bovine serum (FBS; CSL Biosciences, Parkville, VIC, Australia) in phosphate-buffered saline (PBS), then incubated overnight at 4 °C in primary antibodies diluted in 5% FBS/PBS – R1396 serum 1:150 and 1:300, GLUT1 1:150 and non-immune 1:150. Washes with 0.1% Tween-20 in PBS were followed by incubation for 1 h with biotinylated swine anti-rabbit IgG (Dako, Carpinteria, Calif.). Amplification of the signal was achieved using the avidin-biotin complex VECTASTAIN (Vecta Laboratories, Burlingame, Calif.), and detected with the chromagen 3,3'-diaminobenzidine (Sigma, St. Louis, Mo.). Sections were then rinsed in tap water, counterstained with haematoxylin, dehydrated, cleared and mounted with Depex (BDH Laboratory Supplies, Poole, UK).

R1396 serum (1:300) and affinity-purified R1396 (10 and 20 µg/ml) were preincubated overnight on ice with 100 µg/ml of either competitive peptide, the peptide used to generate the R1396 antibody, or an unrelated non-competitive peptide.

Table 1 Distribution of immunohistochemical staining of GLUT1 and GLUT12 in rat fetus between E13 and E21. Empty cells indicate that the tissue was not yet differentiated or was not present in the sections. – no staining, +/- weak staining, + moderate to intense staining

Tissue	Gestational day						GLUT isoform
	E13	E15	E17	E19	E20	E21	
Heart	+	+	+	+	+	+	GLUT1
	+/-	+	+	+	+	+	GLUT12
Skeletal muscle			+/-	+/-	+/-	+/-	GLUT1
			+/-	+	+	+	GLUT12
Brown adipose tissue				–	–	–	GLUT1
				–	+	+	GLUT12
Chondrocytes		+	+	+/-	–	–	GLUT1
		+	+	+	+	+	GLUT12
Kidney				–	+	+	GLUT1
				+	+	+	GLUT12
Lung	–	–	–	+	+	+/-	GLUT1
	–	–	–	+/-	+	+	GLUT12
Brain	–	–	–	–	–	–	GLUT1
	–	–	–	–	–	–	GLUT12
Brain microvessels	+	+	+	+	+	+	GLUT1
	–	–	–	–	–	–	GLUT12

Fig. 1 Immunohistochemical staining of R1396 GLUT12 polyclonal antibody in rat E20 cardiac muscle cells (**A, B**), skeletal muscle fibres (**C, D**), brown adipocytes (**E, F**), chondrocytes (**G, H**), kidney (**I, J**) and lung (**K, L**). GLUT12 staining was observed

in these tissues after preincubation of R1396 affinity-purified antibody with non-competitive peptide (**A, C, E, G, I, K**), but was absent after preincubation with competitive peptide (**B, D, F, H, J, L**). *Magnification* $\times 400$

Fig. 1 (continued)

Results

The specificity of GLUT12 staining using the polyclonal antibody R1396 in the rat fetus was demonstrated by comparing the staining pattern produced with R1396 serum to that of affinity-purified antibody. R1396 serum and affinity-purified R1396 demonstrated the same staining pattern in fetal tissues (Fig. 1). The optimal concen-

tration of affinity-purified R1396 for preabsorption experiments was determined to be 10 $\mu\text{g/ml}$ (data not shown). Reduced immunohistochemical staining after preincubation of affinity-purified R1396 with competitive peptide was demonstrated (Fig. 1). R1396 serum was utilised to further determine GLUT12 immunolocalisation during fetal development. The distribution of GLUT1 and GLUT12 proteins in rat fetus is outlined in Table 1.

GLUT12 protein was detected by immunohistochemistry in the heart muscle (Fig. 2A, D), while intense

Fig. 2 Immunohistochemical staining of rat heart in E17 (A–C) and E21 (D–F) fetuses. GLUT12 staining was observed in the cardiac muscle cell sarcoplasm of both E17 and E21 fetuses (A, D), as

was strong GLUT1 membrane and sarcoplasmic staining (B, E). Non-immune rabbit serum (C, F). *Magnification* $\times 400$

Fig. 3 Immunohistochemical staining of rat skeletal muscle in E17 (A–C) and E21 (D–F) fetuses. GLUT12 staining was demonstrated in the skeletal muscle fibres from latissimus dorsi muscles

from E17 (A), and increased in intensity by E21 (D). GLUT1 was also present at E17 (B), though low levels were observed at E21 (E). Non-immune rabbit serum (C, F). *Magnification* $\times 400$

Fig. 4A–C Immunohistochemical staining of rat brown adipose tissue in E21 fetus. GLUT12 protein was present in the plasma membrane of some of the adipocytes (A), while GLUT1 staining was not detected (B). Non-immune rabbit serum (C). *Magnification* $\times 400$

GLUT1 staining was present (Fig. 2B, E). In skeletal muscle, GLUT12 protein was present from E17 onward, though staining was more intense from E19 (Fig. 3A, D). GLUT1 protein appeared to be present only at low abundance in skeletal muscle on all days (Fig. 3B, E).

GLUT12 was observed in brown adipose tissue from E20 (Fig. 4A), while GLUT1 was not detected (Fig. 4B). GLUT12 immunostaining was pronounced in proliferating and maturing chondrocytes (Fig. 5A, D). GLUT1 was also present in these cells as well as in upper hypertrophic chondrocytes (Fig. 5B), though GLUT1 staining was not detected from E20 (Fig. 5E). In the kidney, GLUT12 was localised to distal tubules and collecting ducts from E19 (Fig. 6A). GLUT1 staining was also observed in distal tubules and collecting ducts from E20 (Fig. 6B). In lung, GLUT12 staining was observed in bronchiolar columnar epithelial cells from E19 onwards (Fig. 7A, D), and GLUT1 protein was also present from E19 (Fig. 7B), though staining intensity was weak by E21 (Fig. 7E).

In brain, GLUT12 staining was not observed (Fig. 8A), while GLUT1 protein was present in the endothelial cells of brain microvessels on all days examined (Fig. 8B).

Discussion

Glucose is an essential molecule for most mammalian cells, being particularly important as an energy source during fetal development, when cells are rapidly dividing and differentiating. In adult human tissues, expression of the recently described glucose transporter like protein GLUT12 is restricted to skeletal muscle, white adipose tissue and small intestine (Rogers et al. 2002).

Our study has shown that in the rat fetus GLUT12 is expressed in insulin-responsive tissues, specifically heart, skeletal muscle and brown adipose tissue. This result is consistent with previous findings in human adult tissues that GLUT12 protein is expressed in skeletal muscle and white adipose tissue, and GLUT12 mRNA is present in heart muscle (Rogers et al. 2002). GLUT1 has been shown previously to be the primary glucose transporter expressed in rat fetal heart, skeletal muscle and brown adipose tissue, with levels declining after birth, while GLUT4 expression increases during late gestation (Santalucia et al. 1992; Schroeder et al. 1997). GLUT3 is expressed in fetal skeletal muscle, but is not present after birth (Gaster et al. 2000). We have also shown that GLUT1 is expressed in fetal heart and skeletal muscle, although expression was low in skeletal muscle, and no GLUT1 expression was observed in brown adipose tissue. It is possible that GLUT1 was not detected in brown adipose tissue due to a lack of sensitivity of the GLUT1 antibody using our immunohistochemical method. The only other immunohistochemical study of glucose transporter expression in brown adipose tissue determined GLUT4 expression in adult rats (Slot et al. 1991).

GLUT12 protein is expressed in chondrocytes. As cartilage and bone are derived from the same mesenchymal progenitors as muscle and adipose tissue (Grigoriadis et al. 1988), glucose uptake by chondrocytes may be regulated via the same mechanisms as in insulin-respon-

Fig. 5 Immunohistochemical staining of rat chondrocytes in E15 (A–C) and E21 (D–F) fetuses. GLUT12 staining was present from the first appearance of chondrocytes at E15, in the vertebrae

(A), and remained at E21, as observed in the femur (D). GLUT1 was also present at E15 (B), but was absent by E21 (E). Non-immune rabbit serum (C, F). *Magnification A–C* ×200, *D–E* ×400

Fig. 6A–C Immunohistochemical staining of rat kidney in E20 fetus. GLUT12 protein was expressed in the epithelial cell membrane of distal tubules and collecting ducts (A), as was GLUT1 (B). Non-immune rabbit serum (C). *Magnification* $\times 200$

sive tissues. In support of this hypothesis, GLUT4 protein is expressed in juvenile mouse chondrocytes, and is likely to be regulated by insulin-like growth factor I (IGF-I) (Maor and Karnieli 1999; Wang et al. 1999). GLUT1 protein is also present in the chondrocytes of fetal rats, a finding supported by the expression of

GLUT1 in juvenile mouse chondrocytes (Maor and Karnieli 1999).

GLUT12 is expressed in the fetal kidney, specifically in distal tubules and collecting ducts, and GLUT1 is also expressed in these regions. One previous study investigating glucose transporter mRNA expression in rats showed that GLUT1 and GLUT5 were expressed in E20 kidney, while GLUT4 was expressed only from postnatal day 16 (Chin et al. 1993). GLUT12 expression is also observed in fetal rat lung bronchioles, as is GLUT1. Previous studies have determined that GLUT1 is not present in fetal mouse or human lung (Mantych et al. 1991; Devaskar and deMello 1996). GLUT1 is expressed in fetal rat lung alveolar and bronchial epithelial cells, though expression declines after birth (Hart et al. 1998). As neither GLUT1 nor GLUT12 are expressed in rat fetal brain, GLUT3 or one of the other glucose transporters must be responsible for glucose uptake in this tissue.

What is the functional significance of GLUT12 protein in fetal insulin-responsive tissues? As mentioned earlier, GLUT1 is the predominant fetal glucose transporter in these tissues, though low levels of GLUT4 are also present in later fetal stages. We have observed that GLUT12 translocates to the cell membrane after long-term stimulation of a breast cancer cell line with insulin (Rogers et al. 2002). The presence of potential targeting motifs and the pattern of GLUT12 expression in adult tissues suggest that GLUT12 could be part of a second insulin-responsive transport system (Rogers et al. 2002). It is therefore possible that GLUT12 can act as a substitute for GLUT4 in fetal tissues and allow increased uptake of glucose into cells in the presence of insulin or IGF-I. In adult GLUT4 global knockout mice, glucose homeostasis is essentially normal and glucose uptake is normal or increased in soleus muscle (Katz et al. 1995; Stenbit et al. 1996). It was suggested that expression of another glucose transporter protein compensated for the lack of GLUT4. It is possible that GLUT12 fulfills the glucose transport requirements in both adult and fetal tissues that lack or have low levels of GLUT4. Although GLUT12 was found at the cell surface in some cell types, we cannot conclude from this study whether GLUT12 translocates in response to hormonal stimuli.

Sugars are required in fetal tissues as energy sources and as precursors for other molecules. In the present study we demonstrated that GLUT12 expression is developmentally regulated in the rat fetus. GLUT12 protein is expressed predominantly in heart, skeletal muscle, brown fat, chondrocytes, kidney and lung. GLUT12 belongs to class III of the glucose transporter family. Some members of this class are known to transport glucose but may also transport other sugars (Joost and Thorens 2001). It is possible that GLUT12 is involved in the uptake of hexoses other than glucose, thus explaining the expression of several GLUT isoforms in a single cell type. The specific pattern of GLUT12 expression in the rat fetus suggests that this glucose transporter protein may be important in hexose delivery to developing tissues.

Fig. 7 Immunohistochemical staining of rat lung in E19 (**A–C**) and E21 (**D–F**) fetuses. Weak GLUT12 staining was first observed at E19 in the epithelial cell membrane of bronchioles (**A**), and in-

creased in intensity by E21 (**D**). GLUT1 staining was also observed at E19 (**B**), though intensity was low at E21 (**E**). Non-immune rabbit serum (**C**, **F**). *Magnification* $\times 400$

Fig. 8A–C Immunohistochemical staining of rat brain in E19 fetus. No GLUT12 staining was observed in the cerebral neurones or microvessels (A), while GLUT1 staining (B) was present in endothelial cells of microvessels (arrow and see inset). Non-immune rabbit serum (C). *Magnification* $\times 400$

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