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GUIDELINES FOR BASIC SCIENCE

Hepatic expression and cellular distribution of the glucose transporter family

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Abstract

Glucose and other carbohydrates are transported into cells using members of a family of integral membrane glucose transporter (GLUT) molecules. To date 14 members of this family, also called the solute carrier 2A proteins have been identified which are divided on the basis of transport characteristics and sequence similarities into several families (Classes 1 to 3). The expression of these different receptor subtypes varies between different species, tissues and cellular subtypes and each has differential sensitivities to stimuli such as insulin. The liver is a contributor to metabolic carbohydrate homeostasis and is a major site for synthesis, storage and redistribution of carbohydrates. Situations in which the balance of glucose homeostasis is upset such as diabetes or the metabolic syndrome can lead metabolic disturbances that drive chronic organ damage and failure, confirming the importance of understanding the molecular regulation of hepatic glucose homeostasis. There is a considerable literature describing the expression and function of receptors that regulate glucose uptake and release by hepatocytes, the most import cells in glucose regulation and glycogen storage. However there is less appreciation of the roles of GLUTs expressed by non parenchymal cell types within the liver, all of which require carbohydrate to function. A better understanding of the detailed cellular distribution of GLUTs in human liver tissue may shed light on mechanisms underlying disease pathogenesis. This review summarises the available literature on hepatocellular expression of GLUTs in health and disease and highlights areas where further investigation is required.

Key words: Hepatic; Liver; Glucose transporters; Glucose; Transport; Hepatocyte

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INTRODUCTION

Provision of a regular supply of glucose and other carbohydrates for fuel is vital for human survival and these are transported into cells using members of a family of integral membrane glucose transporter (GLUT) molecules[1]. To date 14 members of this family, also called the solute carrier 2A (SLC2A) proteins have been identified which can be divided on the basis of transport characteristics (intrinsic or inducible, specificities) and sequence similarities[2] into several families (Classes 1 to 3)[3,4]. The expression of these different receptor subtypes varies between different species, tissues and cellular

subtypes and each has differential sensitivities to stimuli such as insulin.

The liver is a contributor to metabolic carbohydrate homeostasis and is a major site for synthesis, storage and redistribution of carbohydrates. At its simplest, after a meal hepatocyte GLUTs take up glucose from the portal bloodstream and it is converted to glycogen for storage. In a glucose-depleted state, this glycogen can then be converted back to glucose for fuel with up to 70% of total hepatic glucose production arising *via* this route[5]. Situations in which the balance of glucose homeostasis is upset such as diabetes or the metabolic syndrome can lead metabolic disturbances that drive chronic organ damage and failure, which confirms the importance of understanding the molecular regulation of glucose homeostasis. The liver is the major store of glycogen, regulates the availability of glucose and acute liver failure is associated with profound hypoglycemia. This has led to a large body of work investigating the expression and function of receptors that regulate glucose uptake and release by hepatocytes, the most import cells in glucose regulation and glycogen storage but there is less appreciation of the roles of GLUTs expressed by other cell types within the liver. Thus to date expression of GLUT-1, GLUT-2[6,7], GLUT-9[8] and GLUT-10[9] has been documented on hepatocytes but little is known about their expression or function on other cell types. However all cells require carbohydrate to function and there is evidence that non-parenchymal cells may contribute to glucose disposal. For example sinusoidal endothelial cells bind insulin with high affinity, and endothelial insulin-responses may be rate-limiting for glucose uptake[10]. Thus a better understanding of the detailed cellular distribution of GLUTs in human liver tissue may shed light on mechanisms underlying disease pathogenesis. We begin by discussing the extrahepatic expression and functions of these proteins.

EXTRAHEPATIC EXPRESSION AND FUNCTION OF CLASS I GLUCOSE TRANSPORTERS

This family contains the proteins GLUTs 1 to 4 and 14 (SLC2A1-4, 14). The gene for GLUT-1 (*SLC2A1*) the most ubiquitous transporter is located on chromosome 1p35-p31.3 and generates a 54 Kd protein in humans and rodents[11]. It has a high K_m for glucose (K_m = 1-2 mmol/L) and is mainly responsible for basal glucose and uptake[12], but can also transport other hexose carbohydrates including mannose, galactose, glucosamine, 3-O-methylglucose and 2-deoxy-d-glucose. GLUT-1 is, expressed in most cells[13] at low levels, with highest expression reported on erythrocytes, the blood brain barrier, neuronal membranes, eye, placenta and lactating mammary glands[14-16]. Murine embryonic expression also suggests a developmental role[17,18]. Over expression of GLUT-1 has been documented in a variety of tumours[19] and is associated with increased proliferation rates and increased mortality[20] leading to its use as a diagnostic/prognostic marker in some cancers[21,22].

The *GLUT-2* (*SLC2A2*) gene located on chromosome 3q26-1-q26.2 encodes a 524 amino acid protein. GLUT-2 can efficiently transport sugars due to its high V_{max} and K_m for glucose, and is well suited to managing large bi-directional fluxes of glucose in and out of cells[23]. It also transports other dietary sugars such as galactose, mannose and fructose with a high affinity for glucosamine[11,24,25]. GLUT-2 is highly expressed in the liver, pancreatic beta cells, and on the basolateral surface of kidney and small intestine epithelia[26,27] with expression regulated by sugars and hormones[23,28]. Glycogenosis in the rare autosomal recessive disorder Fanconi-Bickel Syndrome has been associated with mutations in GLUT-2[29], and diabetes mellitus in patients with prolonged hepatitis C virus (HCV) infection has been linked to virally-induced reduction in hepatocyte expression of GLUT-2[30].

GLUT-3 (SLC2A3) was initially identified from muscle cell cDNA[31]. Expression localises to the membrane of slow twitch muscle fibres[32] and it is implicated in muscle regeneration and cell fusion[33]. However its major role is in neurons, supplying the high glucose demands in the brain[11,34] and it is increased in brain tumour cells[35]. The gene for GLUT-3 is located on chromosome 12p13.3 and encodes a 496aa protein[12] which transports glucose with a high affinity (K_m = 1.8 mmol/L) and maltose, xylose, dehydroascorbic acid, mannose and galactose[25]. It is also present in fat, kidney, heart, placenta and liver at lower levels[36], and is vital for the supply of substrate to early post-implanted embryos[37]. White blood cells, which need an increased supply of glucose to fuel immune functions, express several GLUTs including GLUT-3[34] the expression of which is decreased in diabetes[38].

GLUT-4 (SLC2A4) was cloned and sequenced by several groups in 1989[39-41]. It is a 55kDa protein responsible for more than 50% of all body glucose uptake[42]. In the absence of insulin it is sequestered in intracellular vesicles and rapidly translocated to the plasma membrane in response to insulin. GLUT-4 transports glucose (K_m = 5-6 mmol/L), dehydroascorbic acid and glucosamine[11,24]. Highest levels of expression are detected in insulin sensitive tissues such as skeletal and cardiac muscle, brown and white adipose tissue[11] and endothelial cells[43]. Expression has also been documented in monocytes, and like GLUT-3 is reduced in insulin-resistant individuals[44]. Mutations in the gene have been associated with diabetes.

GLUT-14 (SLC2A14) was identified and cloned by Wu X *et al*[45] in 2002. It is located on chromosome 12p13.3, has a high sequence similarity to GLUT-3 and may have arisen as a result of gene duplication. The protein contains sugar transporter signature motifs predicted to exhibit glucose transport activity[45]. Two splice variants have been identified in the testis[45]. Mutations of GLUT-14 and its drosophila homologue have been associated with Alzheimers disease in genome wide as-

sociation studies in patients and insect models[46,47] and may explain the reported brain-specific dyregulation of glucose metabolism seen in this condition.

EXTRAHEPATIC EXPRESSION AND FUNCTION OF CLASS Ⅱ TRANSPORTERS

This family contains the transporters GLUT-5, GLUT-7, GLUT-9 and GLUT-11. GLUT-5 (SLC2A5) mRNA is detected mainly in the small intestine were it is found at both the apical and basolateral membranes and functions to absorb dietary fructose (K_m = 6 mmol/L)[11,48,49]. It is also expressed at lower levels in the human kidney, microglial cells, adipocytes, muscle, brain, and testes[49,50], and in common with other transporters, expression is increased in human malignant tumours[51]. The protein exhibits no activity for glucose transport in humans or mouse[11,52] and its localization is not regulated by insulin[50,53]. There is a growing interest in fructose consumption and its link with the metabolic syndrome, type 11 diabetes and obesity[49] since consuming foods and beverages which contain excessive amounts of fructose has been linked to nonalcoholic fatty liver disease (NAFLD)[54]. The thiazolidinedione drug pioglitazone[55], which is used to treat type Ⅱ diabetes, decreases GLUT-5 mRNA (52%) and protein (40%) in muscle fibres of type II diabetic subjects.

The GLUT-7 (SLC2A7), which was originally cloned from a human intestinal cDNA library[56], has considerable sequence similarity to GLUT-5[57] and is involved in uptake of sugars *via* facilitative diffusion mechanisms. Like GLUT-5 it has substrate specificity for both glucose and fructose and a key Ile-314 residue confers hexose specificity and is essential for fructose transport[58]. GLUT-7 mRNA is detected in the small and large intestines at the brush border membrane of enterocytes[11,49]; it is also detected in the prostate and testis[56]. Interestingly, disparities between the localisation of expression within the small intestine and glucose and fructose substrate availabilities suggest that alternate ligands may exist[57].

GLUT-9 (SLC2A9) shares sequence homology[59,60] and substrate specificities[58] with GLUT-5, GLUT-7 and GLUT-11 and, together with GLUT-2, is important for glucose-sensing by pancreatic B-cells[61]. Expression is localised to liver, kidneys, leukocytes[62], pancreas[61], placenta, lung[63], testis and adrenal gland. Two alternate isoforms have been identified, termed GLUT-9a and GLUT-9b[64,65], and alternative splicing results in differential subcellular localisation. Both isoforms have also been reported to transport urate with high affinity[66], and polymorphisms in the *GLUT-9* gene are linked with an increased predisposition to gout[67]. Some polymorphisms have also been associated with an increased incidence of diabetes in Chinese populations[68]. GLUT-9a expression increases in pregestational and gestational diabetes, and GLUT-9b is increased by insulin[59]. In mouse, three isoforms of this transporter are reported, and similarly elevated in diabetes[8].

Three distinct isoforms of GLUT-11 (SLC2A11) have been identified in humans, with distinct but overlapping tissue expression patterns. Thus GLUT-11-A is expressed in skeletal muscle, kidney and heart, GLUT-11-B in adipose tissue, kidney and placenta, and GLUT-11-C in pancreas, heart, adipose tissue and skeletal muscle[69-72]. Muscle expression is localised to slow twitch fibres[73] and appears to be involved in myeloma cell viability and proliferation[74]. All three variants of GLUT-11 exhibit transport activity for both glucose and fructose but not galactose when expressed in Xenopus oocytes[58,70].

EXTRAHEPATIC EXPRESSION AND FUNCTION OF CLASS Ⅲ TRANSPORTERS

This family constitutes the evenly numbered transporters GLUT-6, GLUT-8, GLUT-10, GLUT-12 and GLUT-13. GLUT-6 (SCL2A6)[62] is widely expressed in normal and malignant tissue. mRNA has been detected in peripheral leucocytes, brain[72] and spleen[11] as well as in pancreas, testis, colon[62] and adipose tissue[75]. Subcellular protein expression varies with plasma membrane localisation in renal collecting tubule cells and cytoplasmic localisation in germinal cells of the testis and smooth muscle. GLUT-6 has significant sequence identity with GLUT-3 and may have arisen through insertion of GLUT-3 sequence into another gene on chromosome 5[76].

GLUT-8 (SLC2A8) is a high capacity intracellular GLUT[77] composed of 447 amino acids containing an N-terminal dileucine motif that permits trafficking *via* adaptor proteins to different organelles[77,78]. Expression is highest in the testis and[79], following insulin stimulation increases in the mid-piece of mature spermatozoa and translocates to the acrosome where the spermatozoa take up glucose to drive motility and the acrosome reaction. GLUT-8 may compensate for a lack of GLUT-4 in spermatozoa[80,81] and the preimplantation blastocyst, which demonstrates insulin stimulated glucose uptake *via* GLUT-8 translocation[82]. GLUT-8 is also found in some insulin receptive tissues including adipose tissue, muscle, brain, adrenal glands, spleen, heart and the liver[62,83,84], but not adipocytes[75] or neuronal cells[85].

GLUT-10 (SLC2A10) is a 541aa protein in humans and 513aa in zebrafish[11,86], which transports both glucose and galactose with high affinity[87]. It is expressed in the brain, lungs, adipose tissue[88], heart, placenta, and skeletal muscle with highest expression in the liver and pancreas[9,87]. The *GLUT-10* gene, located on chromosome 20q12-13.1[89] has been linked with type Ⅱ diabetes[9,90]. However other studies do not show any association with a diabetic phenotype[91,92]. Development of the cardiovascular system and TGFb signalling are linked to GLUT-10 function[93] and mutations are associated with altered angiogenesis and arterial tortuosity syndrome[93,94] as a consequence of a loss of regulation of smooth muscle mitochondrial antioxidants production in the absence of functional GLUT-10[89].

Table 1 Summary of reported hepatic expression of glucose transporters isoforms

Class	GLUT isoform	Hepatic expression	Subcellular expression/localisation	Protein/ mRNA	Ref.
Class Ⅰ	GLUT1	Yes	Sinusoidal membrane of hepatocytes, protein restricted to hepatocytes proximal to the hepatic venule, also expressed on endothelial cells, kupffer cells and cholangiocytes; hepatocyte expression in HCC	Both	[110,113,115,116,120]
	GLUT2	Yes	Hepatocytes	Protein	[124-126]
	GLUT3	Yes	Hepatocytes, bile canalicular membrane more enriched than sinusoidal membrane	Protein	[115,116,132]
	GLUT4	Yes	Stellate cells	mRNA	[115,116,134]
	GLUT14	No			
Class Ⅱ	GLUT5	Yes	Normal liver tissue hepatocytes (cytoplasmic)	Both	[51,115]
	GLUT7	No			[140]
	GLUT9	Yes	Majority of expression in hepatocytes of normal liver and HCC with cytoplasmic expression in pericentral areas	Protein	[51]
	GLUT11	Yes		mRNA	[115]
Class Ⅲ	GLUT6	Yes		mRNA	[76]
	GLUT8	Yes	Perivenous hepatocytes	Both	[115,143]
	GLUT10	Yes		mRNA	[86,115]
	GLUT12	Yes		mRNA	[98]
	GLUT13	No			

The table summarizes the evidence presented within this review to highlight the reported hepatocellular expression of glucose transporter (GLUT) isoforms at message and protein level. Pertinent references are cited in the extreme right hand column. mRNA: Micro RNA; HCC: Hepatocellular carcinoma.

GLUT-12 (SLC2A12) was originally identified in the MCF-7 breast cancer epithelial cell line[95]. It is expressed in insulin sensitive tissues in humans and rodents including adipose tissue, skeletal muscle (major expression in type 1 oxidative fibres) and heart[72,88,96-98] as well as human chondrocytes[99]. GLUT-12 is also found in placenta, small intestine, heart and tumours with a high metabolic and capacity glucose utilisation[100-103]. In normal human muscle GLUT-12 undergoes PI3 kinase dependent translocation from an intracellular region to the plasma membrane[104]. Its expression in insulin sensitive tissues, and evidence that overexpression of GLUT-12 in mice improves glucose clearance rate and whole body insulin sensitivity[105] confirm that this transporter is insulin-sensitive. The *GLUT-13* (*SLC2A13*) gene encodes a 629 amino acid protein, located on chromosome 12q12. It is a H^+/myo-inositol co-transporter[11,106,107] also known as HMIT[108] in neuronal cells[106,108]. Although there are no known reports of glucose activity for GLUT-13[11], the rat gene contains motifs which are important for glucose transport activity (http://omim.org/entry/611036).

LIVER SPECIFIC EXPRESSION OF GLUCOSE TRANSPORTER MOLECULES

The data reviewed above reveal the widespread distribution and diverse function of extrahepatic transporter proteins but much less is known about their expression and function it the liver. Surprisingly, there are few studies documenting changes in expression and function in disease. Defining local expression of GLUTs in tissue will shed light on disease pathogenesis. For example, diabetes is associated with altered expression of GLUT-1, GLUT-2, GLUT-3 and GLUT-8 and GLUT-9 (reviewed in[8]) and abnormal GLUT-1 expression on tumour endothelium in HCC has prognostic and diagnostic significance[109-111]. A good example is the finding that diabetes in HCV is a consequence of virally induced downregulation of GLUT-1 and GLUT-2 on hepatocytes[30]. Similarly, transport of key substrates such as fructose has been linked to NAFLD[54]. Dysregulated glucose homeostasis and insulin resistance in NAFLD is associated with chronic organ damage affecting multiple hepatic cell types. The expression levels of transporters is not only regulated by insulin and glucose levels but also by cytokines including interleukin-6, which is increased in obesity and diabetes and can amplify insulin resistance *via* effects on GLUT-4[112]. The hexose transporters also play important roles in the function of cholangiocytes[113], endothelial cells and stellate cells[114]. Thus we summarise the current state of knowledge regarding hepatocellular expression of the GLUT family of proteins, in order to highlight their potential role in tissue homeostasis and disease (Table 1).

HEPATIC EXPRESSION OF CLASS Ⅰ TRANSPORTERS

The widespread expression of GLUT-1 includes the liver although the precise cellular distribution remains controversial. Because hepatocytes are capable of gluconeogenesis their need for glucose uptake is modest. GLUT-1 is expressed on the sinusoidal membrane of rat and porcine[115,116] hepatocytes, and may be expressed to a greater extent than GLUT-2 during early post-natal development[117]. Expression of both GLUT-1 and GLUT-2 by foetal hepatocytes allows for efficient glycogenesis at low plasma glucose concentrations[118]. In adult animals, expression is strongest in the central acinar zones[119]. Transcription and microsomal expression of GLUT-1 is detected in periportal and perivenular hepatocytes but membrane localisation is restricted to hepatocytes

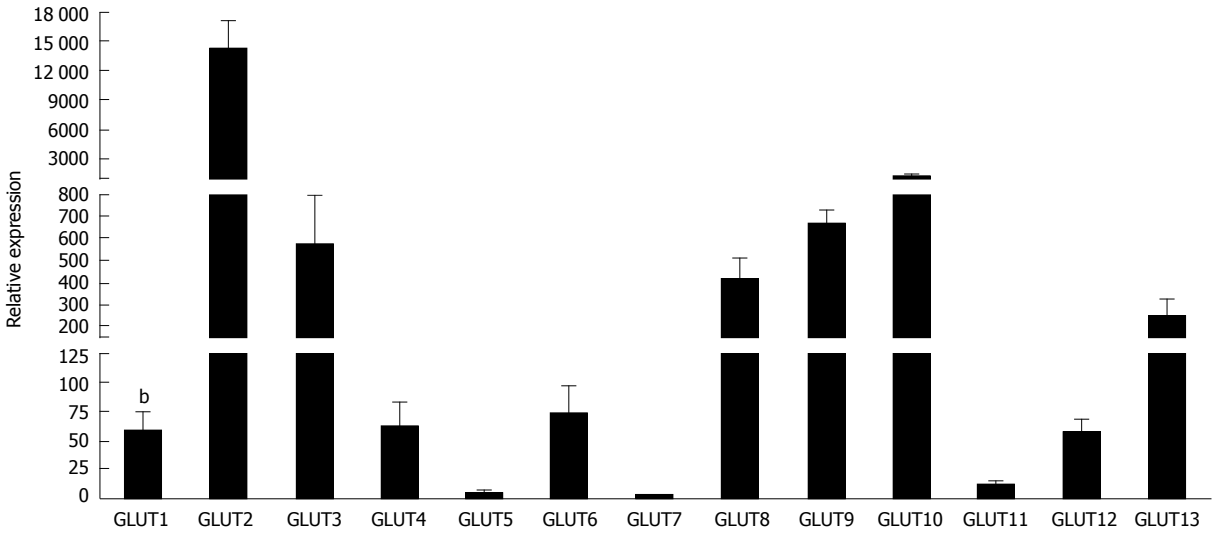

Figure 1 Expression of glucose transporter glucose transporters 1-13 micro RNA in normal human livers. This figure contains unpublished data generated by the authors. Livers were collected from patients at the Liver Unit, Queen Elizabeth Hospital, Birmingham, United Kingdom with appropriate informed written consent and local ethics committee approval. Micro RNA was extracted using standard protocols and integrity was confirmed using an Agilent 2100 Bioanalyser. Transcriptome analysis was carried out for all samples using Agilent Human Whole Genome Oligo Arrays (G4112F) in accordance with Agilent one colour microarray gene expression analysis protocol. Results are expressed as means of five normal livers ± SE, and were run on triplicate plates. Data were normalized to pooled endogenous controls and differential expression is represented as power $2^{-\Delta CT}$. $^{b}P < 0.01$ *vs* glucose transporters (GLUT) 2.

proximal to the hepatic venule[120] under basal conditions. Our own microarray analysis of human normal livers confirms expression of GLUT-1 and GLUT-2 in total liver mRNA (Figure 1). In hepatocellular carcinoma, variable cytoplasmic GLUT-1 is detected and is has been used to distinguish between cholangiocarcinomas and hepatocellular carcinomas (HCC)[109] and has even been proposed as a therapeutic target for HCC[110]. Exposure of rodents to alcohol and high fat feeding results in increased GLUT-1 and decreased GLUT-2 expression in hepatocytes which presumably reflects changes in energy metabolism in response to the dietary changes[121].

Non-parenchymal cells, which cannot carry out gluconeogenesis, rely on glucose uptake rather than endogenous generation. GLUT-1 is the dominant receptor on both endothelial cells and Kupffer cells and levels increase in response to even brief exposure to LPS[122]. Interestingly, acute liver failure has been associated with increased GLUT-1 expression on cerebral vasculature in response to elevated circulating ammonia levels[123]. Cholangiocytes demonstrate basolateral expression of GLUT-1[113] which facilitates absorption of glucose from bile.

GLUT-2 fulfils the major glucose transport role in hepatocytes[36,124] (Figure 1). The protein localises to the sinusoidal plasma membrane of normal[23,125] and malignant hepatocytes. Historical reports suggest a K_m for glucose transport of up to 66 mmol/L in intact rat hepatocytes[126] although contribution from other transporters likely contributes in this study since others report lower values between 10 mmol/L and 20 mmol/L[23]. GLUT-2 promotes rapid glucose efflux following gluconeogenesis. In the fasting state the liver produces glucose *via* glycogenesis or glycogenolysis with the conversion of glucose 6 phosphate into glucose preceding release *via* GLUT-2[23]. However in the fed state glucose and insulin levels rise and inhibit endogenous glucose production through effects on enzymes involved in gluconeogenesis. This is associated with removal of membrane GLUT-2 and a subsequent fall in GLUT-2 mediated release[23]. Excess glucose is stored as glycogen or converted to lipids and hepatocyte GLUT-2 and the insulin receptor are internalised together into endosomes in response to insulin[23,127,128]. In mice lacking GLUT-2 the rate of hepatic glucose production is not impaired indicating the presence of a facilitated diffusion-independent mechanism for glucose release[129]. Thus the major role of hepatocyte GLUT-2 is to regulate efflux rather than uptake of glucose. However, in obesity insulin resistance drives an increase in GLUT-2 levels that may further exacerbate metabolic dysfunction in NAFLD[130].

Much less is known about the hepatic expression and function of GLUT-3. GLUT-3 is expressed in porcine livers[115] and localised to the plasma membrane of rat hepatocytes. Expression is focussed on the bile canalicular membrane rather than the sinusoidal membrane[116]. Mice with GLUT-3 haploinsufficiency develop obesity and insulin resistance associated with hepatic steatosis, possibly as a consequence of foetal glucose insufficiency[131]. GLUT-3 expression is increased on both primary and metastatic hepatic tumours, which might reflect an increased need for glucose uptake in cancer[132]. Low levels of GLUT-3 have been reported in the human liver[36] and are supported by our microarray analysis but detailed human studies are lacking and little is known about changes in disease.

Whilst the liver is generally considered to lack significant expression of GLUT-4[133], a recent study reports expression of GLUT-4 mRNA in porcine liver[115]. Al-

though there is little evidence for expression in hepatocytes, GLUT-4 has been detected in sinusoidal endothelial cells and stellate cells where it can mediate glucose uptake by semicarbazide sensitive amine oxidase mediated effects on insulin receptor signalling[134] which explains our findings of expression at mRNA level in humans (Figure 1). Expression on stellate cells is enhanced by leptin signalling[114] leading to HSC activation that may contribute to fibrogenesis in NAFLD. In contrast, in murine models of diet-induced obesity GLUT-4 mRNA is decreased in the liver[135] and cirrhosis is associated with decreased extrahepatic GLUT-4 mRNA[42]. Deletion of skeletal muscle GLUT-4 results in redirection of excess circulating glucose to the liver where is becomes fuel for conversion to lipid storage[136-138]. Thus glucose homeostasis is maintained by a complex relationship between intra- and extra hepatic levels of GLUT-4 regulated by metabolic activity and dietary intake. To date there are no published reports concerning expression of GLUT-14 in the liver.

HEPATIC EXPRESSION OF CLASS Ⅱ TRANSPORTERS

GLUT-5 protein has been detected in human hepatocytes[51] although low to undetectable RNA levels in pigs[115] imply species-specific differences in GLUT-5 expression. Hepatic metastases from lung and breast cancer are GLUT-5 positive[132] but under normal conditions liver expression is minimal (Figure 1). A mechanistic link between elevations in GLUT-5 expression in small intestine and alterations in hepatic metabolism[139] has been suggested.

GLUT-7 was initially reported as a hepatic microsomal GLUT found in the endoplasmic reticulum, which facilitated the release of glucose formed in the process of gluconeogenesis and glycogenolysis for export into the blood[36,140]. However this has recently been challenged by studies showing that neither human nor rat livers contain GLUT-7 mRNA[141] and our data in Figure 1, suggesting that the previous findings were due to a cloning artefact. Definitive studies need to be performed to clarify the situation.

GLUT-9 has been detected in the cytoplasm of pericentral hepatocytes in normal human liver and in HCC[51]. The receptor appears to be functional for glucose transport because plasma membrane expression of GLUT-9 correlates with glucose influx in HepG2 cells[142] and GLUT-9 inactivation in mouse hepatocytes leads to hyperuricosuria[143]. Although GLUT-11 mRNA has been detected in porcine liver[115], there are no studies documenting expression of GLUT-11 in the human liver.

HEPATIC EXPRESSION OF CLASS Ⅲ TRANSPORTERS

Little is known about the hepatic expression of the recently identified Class Ⅲ transporters although our microarray data (Figure 1) is indicative of some degree of expression. Presence of mRNA for GLUT-6 has been described in hepatoma cell lines but has not been detected in normal human liver[76]. GLUT-8 mRNA has been detected in perivenous hepatocytes in pig[115] and mouse[144] livers where it may regulate glycolytic flux. Mice with type I diabetes show decreased expression whereas expression increases in insulin resistance and type Ⅱ diabetes suggesting that expression is regulated by insulin[144]. Hepatic expression of GLUT-10 has been reported in pigs[115] and zebrafish[86] but we are unaware of any data in humans. GLUT-12 mRNA has been documented in all bovine tissues including the liver where levels are low compared to spleen and skeletal muscle[98], but again detailed cellular expression data is currently lacking. There are no known reports of GLUT-13 expression in the liver.

CONCLUSION

Systemic carbohydrate homeostasis is maintained by a complex relationship between organs such as the pancreas, intestine, muscle and liver. Intra- and extra hepatic levels of GLUT molecules are regulated in part by metabolic activity, dietary intake, and disease state. For example, diabetes is associated with altered expression of GLUT-1, GLUT-2, GLUT-3 and GLUT-8 and GLUT-9[8] and abnormal GLUT-1 expression on tumour endothelium in HCC[109-111] permits efficient glucose uptake by tumour cells even at low blood glucose concentrations. Chronic fructose intake drives glucose and glycogen storage, lipogenesis and production of lipogenic intermediates as well as promoting production of very-low-density lipoproteins[145]. This suggests that the reported hyperlipidaemic and hyperuricaemic effects of fructose, coupled with macrovesicular steatosis and lobular inflammation patterns[146] characteristic of human NAFLD seen in rodents fed high fructose diets, may be enhanced in the context of altered expression of fructose transporters within the hepatic parenchyma and especially so for individuals with high fructose intake or pre-existing hyperlipidaemia or metabolic syndrome. New data is increasingly suggesting the merits of targeting members of the GLUT family therapeutically. Thus overexpression of GLUT-1 in tumours, particularly those with poor prognosis has been suggested as a possible means to selectively inhibit tumour cell metabolism[147], although expression of GLUT-1 red blood cells will likely preclude use therapeutically. Similarly targeting of GLUT-3, which is involved in neovascularisation in glioblastoma has been suggested to prevent resistance to conventional therapy[148], and GLUT-4 is of particular interest in the context of diabetes and insulin resistance, with efforts underway to design therapeutics to enable appropriate glucose uptake independently of insulin stimulation[149]. Alterations in hepatic expression of GLUT transporters have been described in response to

insulin resistance and hyperlipidaemia, alcohol consumption, viral infection and carcinogenesis, with diverse functions including biliary transport, fibrogenesis, urate transport and angiogenesis executed by family members in extraparenchymal cells. Combined with the central role of the liver in regulation of circulating carbohydrate therefore, future definition of the spatial, temporal and disease-specific expression of GLUTs within the liver microenvironment is key to understanding disease pathogenesis and potential hepatic complications of systemic inhibition.

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