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EDITORIAL

Intestinal sugar transport

Laurie Drozdowski, Alan BR Thomson

Laurie Drozdowski, Division of Gastroenterology, Department of Medicine, University of Alberta, 5150 Dentistry Pharmacy Building, Edmonton, AB, T6G 2N8, Canada
Alan BR Thomson, 130 University Campus, Division of Gastroenterology, Department of Medicine, University of Alberta, Zeidler Ledcor Center, Edmonton, AB, T6G 2X8, Canada
Correspondence to: Laurie Drozdowski, 5150 Dentistry Pharmacy Bldg, University of Alberta, Edmonton AB, T6G 2N8, Canada. lad2@ualberta.ca
Telephone: +1-780-4927528 Fax: +1-780-4927964
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Abstract

Carbohydrates are an important component of the diet. The carbohydrates that we ingest range from simple monosaccharides (glucose, fructose and galactose) to disaccharides (lactose, sucrose) to complex polysaccharides. Most carbohydrates are digested by salivary and pancreatic amylases, and are further broken down into monosaccharides by enzymes in the brush border membrane (BBM) of enterocytes. For example, lactase-phloridzin hydrolase and sucrase-isomaltase are two disaccharidases involved in the hydrolysis of nutritionally important disaccharides. Once monosaccharides are presented to the BBM, mature enterocytes expressing nutrient transporters transport the sugars into the enterocytes. This paper reviews the early studies that contributed to the development of a working model of intestinal sugar transport, and details the recent advances made in understanding the process by which sugars are absorbed in the intestine.

Key words: Glucose; Fructose; SGLT1; GLUT2; GLUT5; Transport; Intestine; Enterocytes; Sugar

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INTRODUCTION

It has been known for decades that two different processes existed for intestinal glucose and fructose absorption. In studies using everted sacs of hamster small intestine, Crane and colleagues found that when the serosal and the mucosal side of the tissue were bathed in glucose, glucose accumulated on the serosal side[1]. This was not the case for fructose, and therefore the absorptive process was labelled as non-concentrating. The involvement of sodium (Na+) in glucose absorption was first proposed by Riklis and Quastel (1958)[2], although studies had previously demonstrated that the decrease in sugar absorption seen in adrenalectomized animals was prevented by adding NaCl to the drinking water[3]. The original Na^+/glucose cotransport hypothesis was presented by Crane in the 1960s[4]. This group showed that active glucose absorption by hamster small intestine required sodium (Na^+) in the bathing medium. Glucose transport was also blocked by ouabain that inhibits the Na^+K^+-ATPase in the basolateral membrane (BLM). This protein is responsible for maintaining the Na^+ gradient in the enterocytes, and driving Na^+ dependent transporters such as the sodium-dependent glucose transporter (SGLT1) in the brush border membrane (BBM).

Crane further developed the model of a mobile carrier in the BBM with two binding sites, one for glucose and one for Na^+[5]. He determined that the continuously maintained outward Na^+ gradient accomplished by the Na^+K^+-ATPase on the BLM was the primary asymmetry providing the driving force for active sugar transport. The phenomenon was considered to be "secondary active transport", as the hydrolysis of ATP was indirectly coupled to glucose transport via this electrochemical gradient. This pioneering work provided the framework for the further characterization of not only glucose transport, but also the transport of other co-transported solutes, and this concept is now considered to be a central tenet in cell physiology.

The pioneering work done by Crane was followed by the electrophysiological studies of Curran and colleagues[6-8] that further characterized transcellular Na^+ transport, and increased the understanding of Na^+ coupled co-transport. Further important advances were made in the 1980s. The method of expression cloning, developed by Wright and colleagues, resulted in SGLT1 being the first eukaryote cotransporter to be cloned. This technique takes advantage of the fact that Xenopus oocytes have the unique ability to translate foreign mRNA, and insert functional transporters into their plasma membrane. The researchers injected rabbit polyA RNA into the oocytes, and observed increases in glucose transport. Utilizing molecular techniques, they were able to isolate a single clone, and use it as a probe to identify human SGLT1[9].

With the continuing development of molecular techniques, the process of intestinal sugar absorption was developed further. The cloning and characterization of the sugar transporters GLUT2[10] and GLUT5[11]

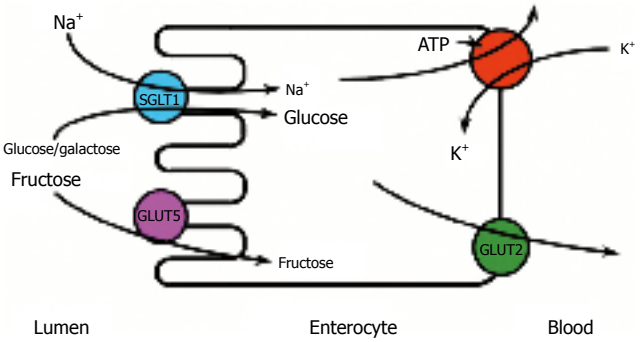

Figure 1 Classical model of intestinal sugar transport (from Wright, 1998). SGLT1 is the sodium dependent glucose/galactose transporter on the brush border membrane (BBM). The Na+K+-ATPase on the basolateral membrane (BLM) maintains the gradient necessary for the functioning of SGLT1. GLUT5 is a facilitative transporter on the BBM which transports fructose into the cell. GLUT2 on the BLM transports glucose, galactose and fructose out of the cell.

Table 1 Affinity constants of sugar transporters

Transporter	Km
SGLT1 (BBM)	Glucose:0.1-0.6 mmol/L (Wright *et al*, 2003)
GLUT2 (BLM)	Glucose:> 50 mmol/L Fructose: 66 mmol/L (Walmsley *et al*, 1998)
GLUT5 (BBM)	Fructose: 6-14 mmol/L (Walmsley *et al*, 1998)

soon followed, and the molecular aspects of the process of sugar absorption across the BBM and BLM were characterized. What is now known as the *"classical model of sugar absorption"* was developed (Figure 1), with SGLT1 actively transporting glucose and galactose across the BBM, and fructose crossing the BBM by facilitative diffusion via GLUT5. GLUT2, a low affinity transporter, was responsible for transporting these sugars across the BLM via facilitative diffusion.

SGLT1

The sodium/glucose cotransporter family (SLCA5) contains more than 200 members found in both animal and bacterial cells. There are 11 human genes expressed in tissues ranging from epithelia to the central nervous system. Hediger *et al* (1987) cloned the SGLT1 gene[9]. The cotransporter is a 73 kDa membrane protein with a Na^+-glucose stoichiometry of 2:1. The transporter has the same affinity for both glucose and galactose (Table 1), and transport is phloridzin sensitive (Ki = 0.1 mmol/L) (Table 2). The membrane topology of SGLT1 was determined using N-glycosylation scanning mutants and hydropathy plots. The transporter contains 14 transmembrane alpha-helices, with an extracellular N and C terminus[12-14]. The transporter contains a single glycosylation site between transmembrane 5 and 6; however, glycosylation is not required for functioning of the protein. Phosphorylation sites have been identified between transmembrane helices 6 and 7, and between transmembrane helices 8 and 9[15]. The importance of SGLT1 phosphorylation will be discussed below. SGLT1 is found in brush border membrane of mature enterocytes in the small intestine, with very small amounts detectable in the kidneys and the heart. Recently, SGLT1 has also been detected in the luminal membrane of intracerebral capillary endothelial cells, where it may participate in the transport of glucose across the blood-brain barrier[16].

Table 2 Inhibitors of sugar transporters

	Inhibitors
SGLT1	Phloridzin
GLUT2	Cytochalasin B Phloretin
GLUT5	Glyco-1, 3-oxazolidin-2-thiones, -ones (Girniene *et al*, 2003)
Na^+K^+-ATPase	Oubain

The process of intestinal sugar transport has been reviewed by Wright *et al* (2003)[17]. Initially, on the luminal side of the BBM, two Na^+ ions bind to SGLT1 and produce a conformational change that permits sugar binding. Another conformational change allows the substrates to enter the enterocyte. The sugar, followed by the Na^+, dissociates from SGLT1 because the affinity of the cytosolic sites is low, and also because the intracellular concentration of Na^+ is low (10 *vs* 140 mEq/L). Sodium can be replaced by H^+ or Li^+, but the affinity for glucose then decreases (apparent Michaelis affinity constant (Km) = 4-11 mmol/L).

The Na^+K^+-ATPase in the BLM is responsible for maintaining the Na^+ and K^+ electrochemical gradients across the cell membrane. The Na^+K^+-ATPase contains a 110 kDa α_1 catalytic subunit, as well as a highly glycosylated 55 kDa β_1 subunit[18,19]. The Na^+K^+-ATPase is up-regulated in experimental diabetes[20] and experimental ileitis [21], with post-translational modifications playing an important role in its regulation. This up-regulation may influence the functioning of SGLT1 and subsequently alter intestinal sugar uptake in these conditions.

Panayotova-Heiermann and Wright (2001) expressed various cDNA constructs of rabbit SGLT1 in Xenopus oocytes in order to determine the helices involved in sugar transport[22]. They found that helices 10-13 form the sugar permeation pathway for SGLT1, and they speculated that the N terminal region of SGLT1 (helices 1-9) may be required to couple Na^+ and glucose transport.

A number of factors influence the transport function of SGLT1 (Table 3). For example, the regulation of SGLT1 by dietary sugars was examined by Miyamoto *et al* (1993)[23]. Using Northern blotting, they showed that SGLT1 mRNA was increased by feeding rats 55% sugar diets containing glucose, galactose, fructose, mannose, xylose, or 3-O-methylglucose. Because 3-O-methylglucose is transported by SGLT1, but is not metabolized, and because SGLT1 does not transport fructose, mannose or xylose, the up-regulation of SGLT1 does not appear to

Table 3 Factors influencing transporter function

Factors influencing SGLT1 function	Factors influencing GLUT2 function	Factors influencing GLUT5 function
Foxl1 (Katz *et al*, 2004)	PKCbII(Helliwell *et al*, 200b)	cAMP (Mahraoui *et al*, 1994)
AMPK (Walker *et al*, 2004)	p38(Helliwell *et al*, 200b)	p38 (Helliwell *et al*, 200b)
PKA (Wright *et al*, 1997)	ERK(Helliwell *et al*, 200b)	ERK (Helliwell *et al*, 200b)
PKC (Wright *et al*, 1997)	PI3K(Helliwell *et al*, 200b)	PI3K (Helliwell *et al*, 200b)
RS1 (Veyhl *et al*, 1993)	mTOR (Helliwell *et al*, 2003)	TNF-α (Garcia-Herrera, 2004)
HNF-1 (Martin *et al*, 2000)	AMPK (Walker *et al*, 2004)	
Sp1 (Martin *et al*, 2000)		
Hsp 70 (Ikari *et al*, 2002)		
TGF-b (Ikari *et al*, 2002)		

depend on either metabolism or transport of the sugar in question (Table 3).

Wright *et al* (1997) evaluated the role of SGLT1 phosphorylation[24]. They expressed rabbit SGLT1 in Xenopus oocytes, and activated protein kinase A (PKA) or protein kinase C (PKC) using 8-Br-cAMP and *sn*-1, 2-dioctanoylglycerol (DOG), respectively. PKA activation increased glucose transport by approximately 30%, while PKC activation reduced transport by 60%. The change in maximal transport rates (Vmax) was accompanied by alterations in the number of transporters in the plasma membrane, as well as changes in the surface area of the membrane. Since endocytosis and exocytosis alter the membrane surface area, the findings of the effects of PKA and PKC on SGLT1 suggest that these proteins may be involved in the regulation of glucose transport.

Similar increases in Vmax were obtained with activation of PKA in oocytes expressing rabbit, human, and rat SGLT1 isoforms. The effects of PKC, however, may depend on the sequence of the co-transporter, as there are conflicting reports of the effect of PKC on glucose transport. For example, PKC decreases sugar transport in Xenopus oocytes expressing rabbit and rat SGLT1[25,26], and increases sugar transport when human SGLT1 is expressed[27].

Veyhl *et al* (1993) demonstrated the presence of an intracellular regulatory protein (RS1) that may modify the activity of SGLT1[28]. Co-expression of RS1 and SGLT1 in Xenopus oocytes reduced both the Vmax for glucose transport as well as SGLT1 protein levels[26]. Plasma membrane surface area was also reduced, suggesting alterations in the endo- and/or exo-cytosis of membrane vesicles.

To investigate the role of intracellular trafficking in sugar transport, oocytes were injected either with cRNA of wild type, or mutant dynamin. Dynamin is a motor protein involved in receptor-mediated endocytosis, vesicle recycling, caveolae internalization and vesicle trafficking from the Golgi[29]. The inhibition of glucose uptake by RS1 was largely reduced after co-expression of the mutant dynamin protein. The investigators concluded that RS1 modulates dynamin-dependent trafficking to the BBM of intracellular vesicles containing SGLT1.

In order to further characterize the role of the RS1 protein in the regulation of intestinal glucose transport, a knockout mouse lacking the RS1 protein was recently developed: Osswald *et al* (2005) showed that RS1-/- mice developed obesity associated with increases in food intake, glucose transport and SGLT1 expression in the small intestine[30]. The effect of RS1 deficiency was tissue-specific and occurred through post-transcriptional mechanisms, as SGLT1 mRNA abundance was unchanged. These researchers speculated that therapeutic strategies aimed at reducing glucose uptake by increasing RS1 might potentially be used to treat obesity.

Heat shock proteins (hsp) may also play a role in regulating SGLT1 function (Table 3). A study done in renal epithelial cells showed that treatment with hsp70 increased glucose transport, but not the abundance of SGLT1 protein[31]. The increase in sugar transport was inhibited by an antibody directed against transforming growth factor β (TGF- β), leading the investigators to explore the effect of TGF-β on SGLT1: there was an increase in SGLT1 activity, as well as an increase in hsp70 protein when TGF-β was added to the culture media. The researchers speculated that hsp70 might stabilize SGLT1 expression in the membrane. This concept was supported by confocal microscopy studies, which demonstrated that TGF-β appears to move both SGLT1 and Hsp70 near the apical membrane site. However, the mechanism by which TGF-β exerts these effects on Hsp70 and SGLT1 is not known.

It is not known if SGLT1 is localized to specific microdomains within the BBM. In renal proximal tubular cells, SGLT1 was found in detergent-resistant membrane microdomains, also referred to as "lipid rafts"[32]. In this model, the absence of vimentin, an intermediate filament component, decreased glucose transport and caused a reduction in the amount of SGLT1 protein in these membrane microdomains. Furthermore, fluidization of the plasma membrane, or depleting the membrane of cholesterol, dramatically decreased glucose transport. This suggests that the activity of SGLT1 is optimal in a microenvironment characterized by low fluidity. Further research is required to determine if SGLT1 is localized to lipid rafts in the intestinal BBM, if this localization is mandatory for the functioning of SGLT1, and what are the factors that may regulate the localization of SGLT1 to these specialized microdomains.

The transcription factors hepatocyte nuclear factor-1 (HNF-1) and Sp1 may also regulate SGLT1. Martin *et al*, (2000) characterized the promoter region of the human SGLT1 gene by transfecting reporter constructs into

Caco-2 cells[33]. They demonstrated that three cis-elements, HNF-1, and two sites on the SGLT1 promoter ("GC boxes" to which Sp1 binds are required for maintaining basal transcription of SGLT1. Members of the Sp1 family bind to the GC boxes, and in the presence of HNF-1, synergistically activate the promoter. Some members of the Sp1 family have been implicated in tissue- and developmental- specific regulation of genes[34,35]. HNF-1 alters the expression of many small intestinal genes, including sucrase-isomaltase (SI) and lactase. It has also been implicated in the diurnal regulation of SGLT1 in rodents[36]. If HNF-1 was required for basal SGLT1 expression, glucose-galactose malabsorption would have been expected to be observed. Of interest, HNF-1 knockout mice experience life-threatening effects on the hepatic and renal systems, but no adverse effects on the gastrointestinal tracts were reported.

Katz *et al* (2004) identified a link between a mesenchymal factor and the regulation of a specific epithelial transport process[37]. *Foxl1* is a winged-helix transcription factor expressed in the mesenchymal cells bordering the crypts in the small intestine. Using the everted sleeve method coupled with Western blotting, the researchers showed that homozygous *Foxl1* null mice had decreased intestinal glucose uptake and decreased levels of SGLT1 protein. Growth retardation and abnormal small intestinal architecture were observed, characterized by short, broad and irregular villi. The effect of the loss of Foxl1 on SGLT1 was specific, as no changes in the expression of SI, lactase, GLUT2 or Na^+K^+ATPase were observed.

The transport of water across the intestinal epithelia has always been a subject of curiosity. The discovery of aquaporins by Preston *et al* (1992) renewed interest in this topic[38]. Although aquaporins may account for a portion of water absorption in the intestine, Wright and colleagues investigated the coupling of water transport to active Na^+-glucose cotransport. Overexpression of human or rabbit SGLT1 in Xenopus oocytes revealed that activation of the transporter was associated with an increase in volume of the cell (reflecting water transport), and this effect was blocked by phlorizin. If oocytes expressing SGLT1 were incubated in a sugar-free solution, no change in oocyte volume was observed. The increase in volume could be accounted for by a stoichiometry of two Na+ ions, one glucose molecule, and 249 water molecules[39]. The transport of water was independent of the osmotic gradient across the membrane, and may be a consequence of the conformational changes in SGLT1 that occur during Na^+/glucose transport. A channel formed by five C-terminal transmembrane helices of SGLT1 is thought to transport not only water, but also urea[22,40].

It is important to note, however, that others have suggested that local osmotic gradients fully account for water fluxes. Lapointe *et al* (2002) present evidence from experiments using Xenopus oocytes expressing human SGLT1 that contradicts the water cotransport hypothesis and suggests the passive movement of water across the plasma membrane[41].

Oral rehydration therapy (ORT) was developed in the 1970's to treat diarrheal dehydration[42]. The introduction of this very simple treatment has reduced mortality due to diarrhea in children under five years of age from 5 million in 1978, to 1.3 million in 2002 (http: //www.who.int/child-adolescent-health.2002; Victora *et al*, 2000). This success led to the proclamation that ORT was the most important medical advance of the 20th century, and earned Dr Hirschhorn and colleagues the first Pollin prize for Pediatric Research.

The goals of ORT are to replace fluids and minimize malnutrition. Starting in 1978, solutions containing a mixture of glucose, sodium, chloride, potassium and citrate were being commonly distributed by the World Health Organization. In fact, 800 million packets of ORT were distributed worldwide in 1991-1992[43]. Interestingly, controversy now exists over the optimal formulation, with reduced osmolarity formulas, rice-based formulas, or formulas containing amylase-resistant starch being favored by some researchers. For example, hypoosmolar rice-based formulas produced better results in cholera patients when compared to standard formulas[44]. The advantages of this rice-based formula are that it is cheap, offers more calories than standard ORT, and rice is readily available in many cholera-stricken regions. ORT formulas containing amylase-resistant starches may be favored due to the production of short chain fatty acids, which increase colonic Na+, Cl- and fluid absorption, and reduce colonic secretions[45-47]. These effects counteract the fluid losses and hypersecretion seen with infectious diarrhea.

Several features of carbohydrate digestion contribute to the efficacy of ORT. This life-saving therapy is based on the ability of SGLT1 to co-transport water. Na^+-dependent glucose absorption is not affected by the increased cAMP levels commonly seen with infections such as Cholera, and therefore this physiological fact can be exploited as a means to achieve glucose, Na^+ and water absorption, even in the presence of chloride and water secretion. Also, the oral administration of glucose or carbohydrates up-regulates SGLT1, thereby further increasing the intestinal transport of glucose, Na^+ and water. Since ORT is commonly administered to infants, it is important to utilize a transport system that is expressed and functional early in life. SGLT1 is expressed prenatally[48], and is functional at birth, making it an ideal candidate. In contrast to glucose, the use of fructose in these ORT solutions is contraindicated, as GLUT5 in the BBM is only expressed following weaning[49].

Glucose-galactose malabsorption (GGM) is a very rare autosomal recessive disease characterized by severe life-threatening diarrhea in the neonate, that resolves when the offending sugars (glucose, galactose and lactose) are removed from the diet[15,50]. Normal intestinal mucosal histology is observed, while phlorizin binding studies show reductions in SGLT1 protein in the BBM[51,52]. Electrophysiological studies and freeze fracture electron microscopy showed that this disease is due to a failure of the SGLT1 protein to traffic normally to the BBM[53]. Approximately 300 cases of GGM have been identified worldwide, affecting all racial and ethnic groups. The majority (70%) of patients are female, with two thirds coming from a consanguineous relationship[17]. Unlike genetic diseases like cystic fibrosis, in which a single

mutation accounts for most cases, in GGM each patient appears to have a unique mutation, ranging from missense mutations, to frame-shift mutations, to split-site-conservative mutations which produce truncated protein and mistrafficking of SGLT1 to the BBM[53-56]. This variety of mutations limits the usefulness of genetic testing for GGM, although prenatal diagnosis in a family at risk may be possible.

GGM is a difficult condition to diagnose. If GGM is suspected, the first step is the elimination of glucose, galactose and lactose from the infant's diet. Oral glucose tolerance tests in GGM patients produce a flat glucose response in the blood, as glucose is malabsorbed in the intestine. A hydrogen breath test performed following oral glucose produces abnormally high concentrations of H_2 in the breath (> 20 ppm) indicating glucose malabsorption, while oral fructose tolerance tests produce normal results. GGM is treated by using glucose-, galactose- and lactose-free formulas, and by eliminating the offending sugars from the diet[17]. Normal growth and neurological development are possible if infants receive fructose-based formula, and if dietary counselling is available[15,57].

GLUT5

GLUT5 is a 43 ku protein, with 12 transmembrane domains and intracellular N and C terminals. It was cloned by Burant and colleagues in 1992. GLUT5 was expressed in Xenopus oocytes, and its substrate specificity and kinetic properties were determined using radiolabelled substrates. Northern and Western blotting demonstrated the presence of GLUT5 in human small intestine and testis. Further work by Davidson *et al* (1992) focused on the developmental expression of GLUT5 in the human and fetal small intestine[58]. GLUT5 mRNA levels increase with age, and are highest in the adult small intestine. In adults, GLUT5 was localized to the BBM by Western blotting. Immunohistochemical techniques confirmed this finding, and further localized GLUT5 to only the mature enterocytes populating the upper half of the villus. This luminal localization provided further support for the notion that GLUT5 played a role in the intestinal uptake of dietary sugars.

Rand *et al*, (1993) characterized the expression of GLUT5 in rats[49]. GLUT5 mRNA was detected in the small intestine, kidney and brain by Northern blotting, and in the small intestine, testis, adipose and skeletal muscle using *in situ* hybridization. In the intestine, a proximal-distal gradient was observed, with GLUT5 mRNA levels being higher in the proximal small intestine when compared to the distal small intestine. A distinct pattern of expression was seen along the crypt-villous axis, with mRNA being highest in midvillus region.

The functional domain of GLUT5 was investigated by Buchs *et al*[59]. In order to ensure proper transport and insertion into the membrane, GLUT5-GLUT3 chimeras were created, and included various combinations of the GLUT3 and GLUT5 peptides. These chimeric GLUTs were expressed in Xenopus oocytes. This enabled the researchers to conclude that the regions necessary for fructose transport lie between the amino terminus and the third transmembrane domain, and between the 5th and 11th transmembrane domain.

The response of GLUT5 to dietary sugars was investigated by Miyamoto *et al*[23]. In this study, they fed sugar-enriched diets (55% D-glucose, D-galactose, 3-0-methylglucose, D-fructose, D-mannose or D-xylose) to male Sprague Dawley rats for 5 d. Northern blotting on intestinal samples showed that GLUT5 mRNA was increased only by dietary D-fructose, and was unaffected by the other sugars (Table 3). This was consistent with the suggestion that GLUT5 was a high affinity fructose transporter. Subsequent work by David *et al* (1995) showed that in 16 d old rats, feeding fructose but not glucose increased fructose uptake[60]. Furthermore, while both fructose and sucrose feeding enhanced absorption in older (21-60 d old) animals, glucose alone had no effect.

An interesting study by Castello *et al* (1995) demonstrated that GLUT5 mRNA in rats followed a circadean rhythm, with a 12-fold increase in mRNA at the end of the light cycle as compared to early in the light cycle[61]. BBM GLUT5 protein followed a similar pattern, which is also observed for other small intestinal genes such as BBM SI and lactase[62]. Although this pattern was thought to be a reflection of rodent feeding patterns, Corpe *et al* (1996) found that gene expression is hard-wired, because GLUT5 is up-regulated prior to the onset of feeding, even in the absence of dietary fructose[63]. Shu *et al* (1998) noted that this circadean rhythm was not developed at the time of weaning, possibly because the feeding patterns of suckling rats do not follow the same adult nocturnal patterns[64]. This diurnal variation in adult animals needs to be carefully considered when designing experiments in which levels of GLUT5 are measured, by performing studies in the morning in the early post-prandial period.

The regulation of GLUT5 was studied by Mahraoui *et al* (1994) using Caco-2 cells[65]. Treatment of the cells with forskolin, which stimulates adenylate cyclase and raises intracellular cAMP levels, increased fructose uptake 2-fold, and increased GLUT5 protein and mRNA 5-fold and 7-fold, respectively. Matosin-Matekalo *et al* (1999) used Caco2 cells transfected with a GLUT5 promoter inserted up-stream of the luciferase reporter gene[66]. They found that a region of the GLUT5 promoter binds the thyroid hormone receptor/retinoid X receptor heterodimers, and that both triiodothyronine (T3) and glucose increase GLUT5 mRNA.

Helliwell *et al*[67] looked at the regulation of GLUT5 by a number of signals that have well-established roles in the regulation of sugar transport. Isolated loops of rat jejunum were perfused with activators and inhibitors of the ERK, p38 and PI3K pathways. The findings suggest that the p38 pathway stimulates fructose transport, while the ERK and the PI3K pathways had little effect on fructose transport (Figure 3). Extensive cross-talk occurs between the pathways. For example, inhibiting the ERK pathway with PD98059 increased the sensitivity to anisomysin, which stimulates the p38 pathway. The authors concluded that the three pathways have the potential to regulate fructose transport during the digestion and absorption of a meal. They suggested that future work should focus on

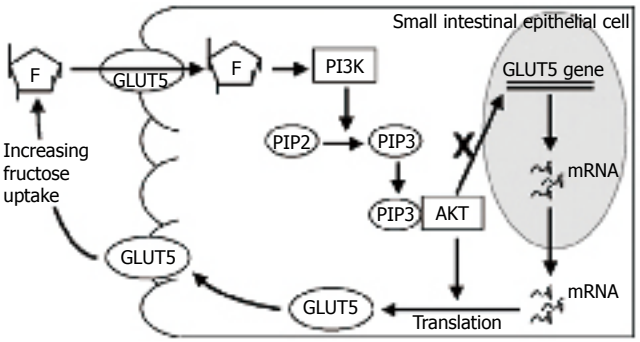

Figure 2 Proposed role of PI3K/Akt signalling pathway in the regulation of GLUT5 synthesis and trafficking (from Cui *et al*, 2005). Abbreviations: *F* = fructose, PIP3 = phosphatidylinositol-3, 4, 5-triphosphate, PIP2 = phosphatidylinositol-4, 5-biphosphate, PI3K = phosphatidylinositol 3-kinase.

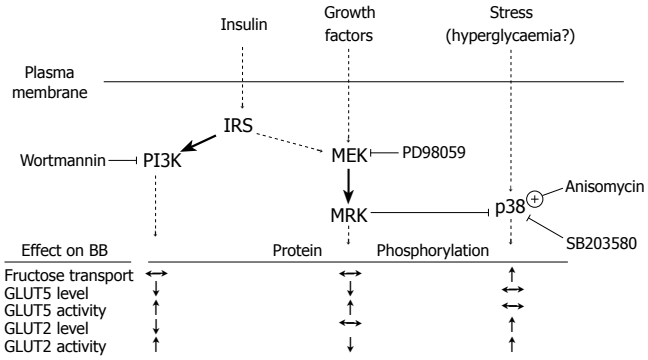

Figure 3 The regulation of BBM fructose transport by the PI3K, ERK and p38 MAPK signalling pathways (from Helliwell et al, 2000). Abbreviations: IRS=insulin regulatory subunit, ERK=extracellular regulated kinase, MEK=mitogen activated kinase kinases, PI3K=phosphatidylinositol 3-kinase, PD98059=ERK/MEK inhibitor, SB203580=p38 MAPK inhibitor, anisomycin=activator of p38 and jun kinase pathways.

determining the hormones that influence these pathways, and the molecular mechanisms that regulate the levels and activities of the sugar transporters.

Gouyon *et al*[68] used Caco-2 cells to investigate the mechanism by which fructose increases GLUT5 expression. Although both glucose and fructose increased the activity of the GLUT5 promoter, the effect of fructose was stronger and associated with higher cAMP concentrations. If cAMP signalling was blocked by a protein kinase A inhibitor, extensive GLUT5 mRNA degradation occurred, suggesting that the mRNA stability was influenced by PKA. A sugar response element was identified in the GLUT5 promoter. PABP-interacting protein 2, which represses translation[69,70], was identified as a component of GLUT5 3'-UTR RNA-protein complex, where it may act to destabilize transcripts. The differences between the effects of glucose and fructose on GLUT5 expression may be attributed to variations in their ability to increase cAMP levels, and to modulate the formation of protein complexes with GLUT5 3'-UTR.

Infection may also regulate fructose transport. Intravenous administration of Tumor necrosis factor-α (TNF-α) in rabbits significantly reduced jejunal fructose transport and GLUT5 protein[71]. This inhibition was related to the secretagogue effect of TNF-α, and both nitric oxide and prostaglandins were implicated in the inhibition of fructose uptake. Adaptive immunity also influences the expression of a number of developmentally regulated genes. In mice lacking in adaptive immunity (B cell deficient recombination-activating gene [RAG] mice), RNase protection assays demonstrated that GLUT5 was increased[72].

Recent advances have been made in understanding the signalling pathways involved in the regulation of GLUT5. Cui *et al*[73] have demonstrated that cAMP stimulates fructose transport in the neonatal rat intestine. Perfusing fructose (100mM) plus 8-bromo-cAMP in 22-d-old rats increased fructose uptake rates, while an inhibitor of adenylate cyclase abolished this effect. Despite the presence of two cAMP response elements in the human GLUT5 promoter region[65], GLUT5 mRNA was not affected by cAMP treatment. Interestingly, inhibitors of PKA did not prevent the fructose-associated increases in transport, suggesting that cAMP modulates fructose transport independent of PKA (Table 3).

Subsequent work by the same group has shown that fructose-induced increases in neonatal rat intestinal fructose uptake involve the PI3K/Akt signalling pathway[74]. In this study, PI3K inhibitors (wortmannin and LY94002) and an Akt inhibitor (SH-5) abolished the increase in fructose uptake, as well as the abundance of GLUT5 protein (but not mRNA) seen following fructose (100 mmol/L) perfusions in neonatal rats. Fructose perfusion increased phosphatidylinositol-3, 4, 5-triphosphate (PIP3), the product of PI3K, in the mid to upper regions of the villus, where most of the GLUT5 was located. The authors suggest that the PI3K/Akt pathway may be involved in the synthesis and/or recruitment of GLUT5 to the BBM in response to luminal fructose (Figure 2).

GLUT2

GLUT2 is a low affinity, high capacity facilitative transporter in the BLM that transports glucose, fructose, galactose and mannose[10,63,75-77]. It has 12 transmembrane domains, with intracellular N and C terminals. Using immunohistochemistry, Thorens *et al*[75] showed that GLUT2 expression increases as enterocytes migrate up from the crypt to the villous tip. Amino acid sequences in transmembrane segments 9-12 are primarily responsible for GLUT2's distinctive glucose affinity, whereas amino acid sequences in transmembrane segments 7-8 enable GLUT2 to transport fructose[78].

Luminal sugars[23,79] or vascular infusions of glucose or fructose[80,81] stimulate GLUT2 expression and activity. The response of GLUT2 to dietary sugars was investigated by Miyamoto *et al*[23]. In this study, they fed sugar-enriched diets to male Sprague Dawley rats for 5 d. GLUT2 mRNA was up-regulated by glucose, fructose and galactose. GLUT2 modulation required intracellular metabolism of the sugar, as it was unaffected by 3-O-methyglucose, a non-metabolized glucose analog.

In a study by Cui *et al*[82], the jejunum of 20-d-old anaesthetized rat pups was perfused with 100 mmol/L glucose or fructose. Increases in GLUT2 mRNA were

observed, and this effect was inhibited by actinomycin D, an inhibitor of transcription. Cycloheximide, an inhibitor of translation, did not block the enhanced expression of GLUT2 mRNA, suggesting that the synthesis of new proteins is not necessary for increases in GLUT2 mRNA. Because levels of GLUT2 mRNA and protein are tightly correlated, the regulation of GLUT2 may be transcriptional[83].

PASSIVE UPTAKE

For years there has been considered to be a "passive" component to sugar absorption. This traditional view has been challenged, with the suggestion that the kinetic characteristics of sugar uptake could also be described by a second high affinity, high capacity BBM transporter[83]. In order to better understand the new "GLUT2 trafficking model", we need first to consider the classic "passive permeation" model.

The fact that SGLT1 saturates at 30-50 mmol/L glucose was inconsistent with the observation that intestinal glucose absorption increases linearly with increases in luminal glucose concentrations up to several hundred millimolar[85]. This finding suggests the presence of two components: an active, phloridzin-sensitive component, and a phloridzin-insensitive, possibly passive component that does not appear to be saturable. Some studies have suggested that the "passive" component played a large role in glucose transport at high glucose concentrations, in some models contributing 3-5 times as much as the active component[86,87].

The passive component of glucose transport was characterized by Pappenheimer and Reiss (1987)[88]. The observation that high rates of water absorption accompany glucose absorption[89] provided a rationale for proposing that glucose in the intercellular spaces provided an osmotic force that resulted in bulk flow of nutrients. Pappenheimer and Reiss (1987) perfused isolated segments of hamster small intestine with 10-25 mmol/L glucose[88]. Structural studies using electron microscopy and freeze fracture analysis revealed large dilatations within junctions following glucose perfusion. They concluded that Na^+-coupled transport of solutes from the intestinal lumen to the cytosol of the enterocytes provides the driving force for the absorption of fluid and nutrients, and triggers the widening of intercellular junctions, thereby promoting the bulk absorption of nutrients by solvent drag. They calculated that the contribution of solvent drag exceeds that of active transport at luminal glucose concentrations greater than 250 mmol/L. Madara and Pappenheimer (1987) further demonstrated that the transport of glucose via SGLT1 caused dilatation of the tight junctions[90]. They concluded that passive glucose absorption is a result of paracellular solvent drag, and is indeed SGLT1 dependent. Therefore, like the more recent model suggested by Loo et al (2002)[39], these investigators suggest that the transport of water is SGLT1-dependent. However, this theory suggests the presence of a non-specific route, which could potentially allow passage of several solutes.

Ferraris and Diamond proposed an alternative theory, in which paracellular flow is negligible[91,92]. Based on the determination of up-dated kinetic constants for glucose absorption, and the determination of the usual free glucose concentrations in the intestinal lumen, they concluded that SGLT1 fully accounts for glucose absorption. Much of their work is based on studies examining long-term dietary adaptations, from which they concluded that BBM transporters are matched to dietary intake. Their model is supported by the findings of Lane *et al*[93], who demonstrated that paracellular flow in unanaesthetized dogs did not account for more than 2%-7% of total absorption.

Much of the controversy surrounding the role of the paracellular pathway stems from the discrepancies between the estimated concentrations of glucose in the intestinal lumen. Pappenheimer and Reiss[88] based their calculations on luminal glucose concentrations of 300 mmol/L, whereas Ferraris *et al*[92] did a detailed analysis of luminal glucose concentrations and concluded that physiological luminal values ranged from 0.2-48 mmol/L. Pappenheimer[94] used the rate of membrane hydrolysis of maltose to indirectly measure luminal glucose concentrations. They also point out that the techniques used by Ferraris *et al* (1990)[92], which involve glucose analysis of luminal contents, will underestimate the concentration found at the membrane following hydrolysis by disaccharidases. The actual physiological levels of glucose in the lumen remain a subject of debate.

The concept of more than one transport system for glucose was suggested by Malo[95]. Using human fetal and adult BBM vesicles, curvilinear Eadie-Hofstee plots and sodium activation curves were obtained when glucose concentrations were varied in the medium. These findings, coupled with determinations of phloretin-sensitive and -insensitive components, and the ability of the BBM vesicles to transport 3-O-methylglucose, suggested the presence of two transport systems: a high-affinity low-capacity system and a low-affinity high-capacity system[95,96]. This agrees with the observation that Na^+/glucose cotransport saturates at 30-50 mmol/L, yet absorption is linear from 50 mmol/L to several hundred mmol/L[85].

Although this concept was proposed many years ago, it was not until recently that interest in the area has re-emerged due to an alternative model of intestinal glucose transport proposed by George Kellett and his colleagues at the University of York, and by Edith Brot-Laroche and her colleagues at the University of Paris. Let us briefly explore this fascinating "voyage of discovery".

GLUT2 IN BBM

Several years ago, GLUT2 was detected in the BBM of enterocytes in diabetic animals, although at the time this was interpreted to be a pathological event[63]. More recently, Kellett and his colleagues proposed a model by which BBM SGLT1, in the presence of luminal glucose, promotes the rapid insertion of GLUT2 into the BBM via PKCβII and the MAP kinase-dependent signal transduction pathways[67,97,98]. PKCβII is located in the terminal web of mature enterocytes in the upper part of the intestinal villus[99]. Interestingly, these are the same cells that are responsible for glucose absorption.

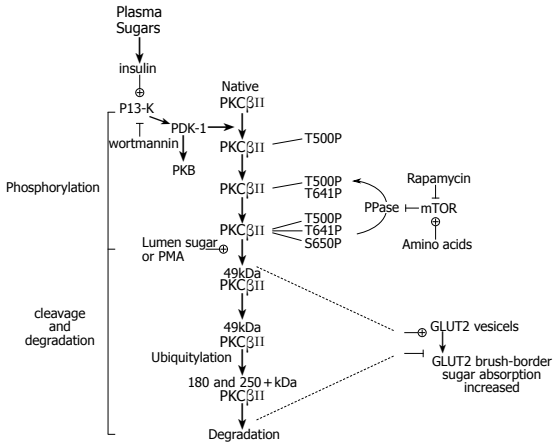

Figure 4 Potential signaling pathways for the regulation of GLUT2-mediated sugar absorption by insulin and amino acids through the control of PKC βII activity. (from Helliwell et al, 2003). Abbreviations: PMA= phorbol 12-myristate 13-acetate, PDK-1=protein-dependent kinase-1, PI3K=phosphatidylinositol-3-kinase, PKB=protein kinase B, mTOR=mammalian target of rapamycin, PKCβII=protein kinase C βII.

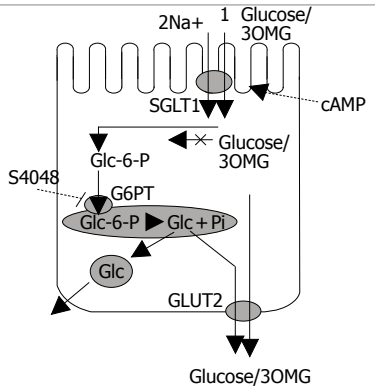

Figure 5 Proposed alternative mechanism for intestinal glucose transepithelial transport (from Stumpel et al, 2001). Abbreviations:Glc=glucose, Glc-6-P=glucose-6-phosphate, G6PT=glucose-6-phosphate translocase, 3-OMG=3-O-methylglucose, S4048=inhibitor of glucose-6-phosphate translocase, Pi=phosphate.

Using a luminal perfusion model, Kellett and coworkers measured the phloretin-insensitive (SGLT1) component and phloretin sensitive component (GLUT2) of glucose transport. They also showed using Western blotting that BBM GLUT2 increased 2.2 fold when the concentration of glucose in the perfusate increased from 0 to 100 mmol/L. Similarly, the BBM level of PKCβII increased with increasing glucose concentrations. This finding, coupled with the observation that PKCβII shows a saturation response and has a Km similar to that of SGLT1 (21-27 mmol/L), suggests that PKCβII is an important signal in the recruitment of GLUT2 to the BBM. PKCβII levels also correlate with levels of GLUT2 in the BBM, and this association offers further support for its role in the recruitment of GLUT2 to the BBM. The ability of the PKC inhibitor "chelerythrine" to block phorbol 12-myristate 13-acetate (PMA)-stimulated fructose transport and GLUT2 abundance in the BBM also supports this mode l[97].

Kellett's working hypothesis proposes that before a meal, when luminal concentrations of glucose are low, GLUT2 levels in the BBM are also low, which would minimize the escape of glucose from the cell (any glucose that did escape would be recycled by SGLT1, which can transport it against the glucose gradient). Once a meal is ingested and BBM enzymes hydrolyse disaccharides, luminal glucose concentrations increase. Glucose uptake via SGLT1 causes increases in enterocyte volume due to a rise in osmolarity (and the co-transport of water molecules by SGLT1), and may trigger the entry of Ca+, activating PKCβII and promoting the insertion of GLUT2 in the BBM. The involvement of SGLT1 in the recruitment of GLUT2 to the BBM agrees with observations that phloridzin (an SGLT1 inhibitor) fully blocks glucose uptake, and that patients with defective SGLT1 suffer from glucose-galactose malabsorption. Trafficking of GLUT2 is thought to be rapid, with a $t_{1/2}$ of less than 5 minutes. A rounding of the apical surface, due to a contraction of the peri-junctional actomyosin ring, allows luminal glucose to have increased access to the BBM enzymes and transporters. The authors recognize that there may also be an activation of the small amount of GLUT2 that is already present in the BBM.

Helliwell *et al*[67] investigated the role of several signalling pathways in intestinal fructose absorption. Using an *in vivo* perfusion model, they showed that fructose transport was mediated by both GLUT5 and GLUT2. Using PMA to stimulate a 4-fold stimulation of fructose transport, they saw a 4-fold increase in GLUT2 protein in the BBM that correlated with PKCβII activation. Only minor changes in GLUT5 levels were observed, suggesting that recruitment of GLUT2 to the BBM represents a mechanism by which absorptive capacity is matched to dietary intake.

Helliwell *et al*[100] also established a role for the PI-3K and the mTOR pathways in the phosphorylation, turnover and degradation of PKCβII. Using an *in vivo* perfusion model, they showed that inhibitors of these pathways (wortmannin and rapamycin, respectively) block GLUT2 trafficking to the BBM and inhibit sugar absorption. A role for insulin in the regulation of intestinal sugar absorption is suggested. In their model, they suggest that as sugar absorption increases, the plasma sugar concentration increases, stimulating the release of insulin, which activates PI 3-kinase, resulting in the phosphorylation of PKCβII (Figure 4).

They also proposed a model by which amino acids promote the formation of competent PKCβII by activating the mTOR pathway, which prevents dephosphorylation of PKCβII (Figure 4). Thus, the dynamic control of intestinal sugar absorption may be achieved by the rapid turnover and degradation of PKCβII.

Why haven't previous investigators been able to detect GLUT2 in the BBM? *In vivo* endogenous hormones and nutrients activate PKCβII. Kellett's group points out that the process of harvesting tissue for *in vitro* preparations causes the inactivation of PKCβII and the rapid trafficking of GLUT2 away from the BBM. This observation may help to explain why the passive component was more apparent in the *in vivo* studies, as compared to *in vitro* experiments. In order to minimize the loss of GLUT2 from the BBM, Kellett's group perform all stages of tissue harvesting and membrane vesicle preparations at 0-4℃

after perfusing the intestine with a sugar load.

Helliwell and Kellett [101] looked at perfusion conditions in order to determine if the so called passive component was SGLT1-dependent, as suggested by their work, or was SGLT1-independent, as suggested by earlier work by Debnam and Levin[102]. They concluded that the passive component is independent of the active component in high mechanical stress perfusions, suggesting that SGLT1-dependent recruitment of GLUT2 did not occur under these conditions. This may be related to the restrictions in blood flow and supply of endogenous nutrients and hormones caused by the high stress perfusions.

However, under conditions of low mechanical stress, inhibition of SGLT1 with phloridzin does decrease GLUT2 levels in the BBM. Clearly, the perfusion conditions affect the results of the experiment, and this may explain the discrepancies between various studies. Finally, Kellett and colleagues suggest that the term "facilitated" should be used rather than "passive" to more accurately describe the GLUT2 mediated component of sugar uptake.

The antibody used to detect GLUT2 is also critically important in being able to detect GLUT2 in the BBM. Currently, there are two commercially available antibodies that recognize GLUT2: one that recognizes the extracellular loop between transmembrane 1 and 2 (Biogenesis, Poole, England); and another that recognizes a portion of the C- terminus (Research Diagnostics, Flanders, NJ). The choice of antibody is important, as Au *et al* (2002) demonstrated that the biotinylation procedure they used to detect surface proteins interfered with the ability of the GLUT2 antibody to recognize the extracellular loop, forcing them to use the C-terminus antibody[103]. However, Thorens *et al*[103] were unable to detect GLUT2 in the BBM by immunohistochemistry using an antibody that recognizes the C-terminus[75]. In contrast, when using the antibody directed against the extracellular loop, Cheeseman's group was able to detect BBM GLUT2**.** In contrast, when using Western blotting on BBM vesicles, they were able to detect GLUT2 using either of the antibodies. Clearly, the choice of antibody depends on what method of detection is used.

Although earlier studies established a role for GLP-2 in modulating GLUT2 activity in the BLM[63,104], more recently Au *et al*[103] investigated the effect of GLP-2 on the transient expression of GLUT2 in the BBM. Using an *in vivo* perfusion model in rats, they showed that a one hour vascular infusion of GLP-2 (800 pM) doubled the rate of fructose absorption, and this enhanced absorption of fructose could be blocked by phloretin, an inhibitor of GLUT2. Immunohistochemistry localized GLUT2 to both the BBM and BLM, and identified a pool of transporter located just under the microvilli in the terminal web region. This raises the possibility that the cytoskeleton structure is involved in the insertion of GLUT2 into the BBM. Luminal glucose perfusion (50 mmol/L) or vascular GLP-2 infusion (800 pmol/L) increased GLUT2 in the BBM two-fold as determined by Western blotting of biotinylated surface proteins. Both Kellett and Cheeseman suggest that in addition to the insertion of GLUT2 in the BBM, the intrinsic activity of apical GLUT2 may also be regulated[103,105]. The concept of intrinsic activity and its regulation will be discussed in subsequent sections.

Gouyon *et al*[68] used confocal microscopy and immunofluorescence in mice to confirm the presence of GLUT2 in the BBM following five days of feeding a 65% sugar meal, or following an oral bolus of either fructose or glucose. Wild type and GLUT2 null mice were fed fructose, glucose or sucrose (65% glucose, fructose or sucrose)-rich diets for five days, or were fasted and then received a 40% fructose, glucose or sucrose bolus. The absence of GLUT2 did not significantly affect fructose absorption in animals fed a low-carbohydrate diet, suggesting that under these conditions GLUT5 is soley responsible for fructose uptake into the enterocyte.

In animals fed a high fructose diet, cytochalasin B (an inhibitor of GLUT2) inhibited fructose uptake 60% in wild type mice, whereas GLUT2 null mice were unaffected. A 40% reduction was observed in animals fed a high glucose diet. This suggests that under these conditions fructose enters the cell by both a cytochalasin B dependent process (GLUT2) and a cytochalasin B independent process (GLUT5). The trafficking of GLUT2 to the BBM may represent a mechanism by which sugar absorptive capacity is matched to dietary intake.

When GLUT2 null mice were challenged with oral fructose, transport was 60% lower than in wild type animals, indicating firstly that the absence of GLUT2 limited fructose uptake, and secondly that this could not be fully compensated for by GLUT5. Still, some compensatory changes were noted, as GLUT5 mRNA was found to be increased three-fold in the ileum, possibly indicating some fructose malabsorption in the GLUT2 null mice. Therefore, Gouyon's study demonstrates that while under control conditions GLUT5 is solely responsible for BBM fructose uptake, BBM GLUT2 may be responsible for 40%-60% of sugar uptake when the luminal sugar concentrations are high.

The role of AMP-activated kinase (AMPK), an intracellular energy sensor, in the regulation of intestinal sugar uptake has also been examined. Walker *et al*[106] demonstrated that the activation of AMPK resulted in the recruitment of GLUT2 to the BBM and a down-regulation of the energy-requiring SGLT1-mediated glucose uptake. The importance of this phenomenon, particularly in models of intestinal damage or stress, warrants further investigation.

The presence of GLUT2 in the BBM of humans has not been confirmed. Dyer *et al*[107] found GLUT2 expression was restricted to the BLM in humans, although critics of this work have speculated that this may be a result of the methods used to obtain and process biopsies, and the lack of feeding a high sugar diet or giving an oral sugar test prior to obtaining the biopsies[68].

In summary, the role of GLUT2 in the transport of sugars across the BBM remains controversial. The most recent data suggests that in specific situations, such as when luminal sugar concentrations are high, GLUT2 is recruited to the BBM and contributes to sugar uptake from the lumen. This may explain the discrepancies between studies and the inability of many researchers to detect GLUT2 in the BBM in their experimental models.

INTRINSIC ACTIVITY AND TRANSPORTER TRAFFICKING

A number of factors are involved in the regulation of intestinal sugar transport. These factors may modify sugar transport by altering the abundance of sugar transporters in the intestine. Alternatively, sugar transport may be regulated at an entirely different level. The intrinsic activity of the transporters (amount of substrate transported per unit of transporter protein) may be altered, in the absence of detectable changes in transporter abundance. Indeed, there has been a long history of reports of discrepancies between glucose uptake and the protein abundance of glucose transporters both in skeletal muscle[108], adipose[109] and in the intestine[67,103,110-114]. Changes in the intrinsic activity of glucose transporters have observed with hyperglycemia[110], diabetes[63], low luminal glucose concentrations[98] and following the activation of MAPK and PI3K[67]. The post-translational mechanism by which intrinsic activity is regulated is not known, but may involve phosphorylation or dephosphorylation of the transporter or the activation or inhibition of the transporter by a regulatory protein.

Kellett and his colleagues have shown that the PI3K pathway is involved in the modification of the intrinsic activity of GLUT2 and GLUT5[67]. Control of transport by the modulation of both the levels and activities of the transporters occurred as a result of extensive cross-talk between the extracellular signal-regulated kinase (ERK), p38, and phosphatidylinositol 3-kinase (PI 3-kinase) pathways. Activation of the p38 pathway stimulates fructose transport by increasing GLUT2 levels in the BBM, as well as increasing the intrinsic activity of GLUT2. In contrast, the ERK or PI 3-kinase pathways have regulatory effects on transporter trafficking and intrinsic activity, without having significant effects on fructose transport (Figure 3). However, these results are derived from independently modulating these pathways, when clearly there is extensive cross-talk. For example, when the ERK pathway is inhibited, fructose transport stimulated by the activation of the p38 pathway increases 50-fold, suggesting that the ERK pathway restrains the p38 pathway.

It is not known if PI3K/Akt modifies the intrinsic activity of SGLT1. However, a study by Alexander and Carey (2001) showed that orogastric IGF-1 treatment increased glucose uptake in piglets without increasing SGLT1 abundance, suggesting an effect on intrinsic activity of the transporter[115]. Inhibiting Akt blocked the increase in glucose uptake, possibly by modifying the activity of the transporter.

PI3K has also been implicated in the regulation of GLUT4 trafficking to the plasma membrane in adipocytes or muscle[108]. Despite this possibility, several studies have demonstrated that the trafficking of transporter protein to the BBM cannot fully explain changes in intestinal sugar uptake seen after IGF-1, GLP-2 or glucose administration [103,115,116]. Nevertheless, both alterations in trafficking and intrinsic activity may contribute to the changes seen in sugar uptake. Further work is required to further characterize the relative contributions of each of these mechanisms.

ALTERNATIVE THEORIES

The previously well-accepted role of GLUT2 as the sole BLM glucose transporter is also a subject of debate. The role of GLUT2 was originally based on it being immunolocalized to the BLM. However, this does not exclude the possibility of other basolateral transport pathways. Recently, GLUT2 null mice were developed, in which GLUT1 or GLUT2 was re-expressed in pancreatic β cells to enable survival. This was an important step in investigating the role of GLUT2 in sugar transport. In these animals, normal rates of glucose appearance in the tail vein blood were seen following an oral glucose load, suggesting that GLUT2 was not required for transepithelial glucose transport[117]. It is important to note that this paper has limitations, as the appearance of glucose in the tail vein is not a direct measure of intestinal sugar transport. Further work by Stumpel *et al*[118] using an isolated intestinal perfusion model demonstrated normal glucose transport kinetics despite a lack of GLUT2. This finding was noted under control conditions and following cAMP perfusion, which is known to increase glucose absorption via SGLT1[119]. Even with this accelerated apical uptake of glucose into the enterocyte, the basolateral transport of glucose did not appear to be rate-limiting.

Interestingly, sugar transport was dose-dependently inhibited by an agent that inhibits the glucose 6-phosphate translocase located in the endoplasmic reticulum (ER) membrane. Glucose 6-phosphate translocase transports glucose-6-phosphate from the cytosol into the lumen of the ER, where the active site of glucose-6-phosphatase is located. Furthermore, 3-O-methylglucose, which cannot be phosphorylated by the hexokinases, was not transported, despite the fact that it is a known substrate for both GLUT2 and SGLT1. Taken together, these findings suggest that a distinct pathway exists that involves glucose phosphorylation, transport to the ER, dephosphorylation, and release via a membrane-traffic based pathway (Figure 5). Interestingly, the expression of the glucose-6-phosphatase and the glucose-6-phosphate translocase, as determined by Northern blotting, were not increased in the GLUT2 null animals. This contrasts with the work of Gouyon *et al*[68], who used RT-PCR to demonstrate that GLUT2 null mice had increased mRNA expression of glucose-6-phosphatase.

Stumpel and colleagues[118] also noted that GLUT5 mRNA expression was increased in the GLUT2 null mice, while the expression of all other known GLUT transporters did not change. Human studies have demonstrated the presence of GLUT5 in the BLM of enterocytes[120]. The finding that fructose absorption was unaffected by GLUT2 status suggests that GLUT5 may have been present in the BLM, contributing to fructose release on the serosal surface of the enterocyte. However, the authors dismissed the possibility that fructose and glucose shared a common serosal transport system based on the observation that the release of glucose, but not fructose, was blocked by an inhibitor of the glucose 6-phosphate translocase.

Stumpel *et al*[118] also performed fructose perfusion experiments in GLUT2 null mice. The results showed

that intracellular fructose was not converted to glucose, further supporting the notion that this alternative pathway does not contribute to fructose efflux. The authors also discounted the possibility that the paracellular pathway significantly contributed to glucose absorption, as the SGLT1 inhibitor phloridzin greatly reduced glucose absorption. They concluded that a microsomal membrane traffic-based mechanism may be an important component of transepithelial glucose transport.

The investigators point out that the concept of a microsomal membrane-trafficking transport system is supported by the following observation: genes for glucose-6-phosphate translocase (G6PT1)[121] and glucose-6-phosphatase (G6PC)[122] are expressed in human intestinal cells, despite the fact that only minimal amounts of glycogen are found in jejunal biopsies[123]. Similarly, the high levels of hexokinase activity in intestinal cells [124] support the concept of an alternative transport system characterized by glucose phosphorylation and subsequent microsomal transport and trafficking.

Santer *et al*[125] re-evaluated the role of GLUT2 in intestinal sugar absorption in one patient with Fanconi Bickel syndrome (FBS). FBS is characterized by congenital GLUT2 deficiency. Oral glucose tolerance tests performed on this patient failed to demonstrate differences in breath hydrogen concentrations when compared to control subjects, indicating that sugar was not being malabsorbed, at least within the sensitivity limits of hydrogen breath testing. These findings also suggest that other mechanisms are in place to transport sugars across the basolateral membrane of enterocytes.

RECENT DISCOVERIES

The model of intestinal sugar transport is an ever-changing story. Recently, a new facilitative glucose transporter, GLUT7, has been cloned and characterized[126]. GLUT7 has a high affinity for glucose (Km = 0.3 mmol/L) and fructose (IC50 = 0.060 mmol/L), but not for galactose. GLUT7 mRNA is present in the human small intestine, colon, testis and prostate. GLUT7 protein was found in the intestine, mostly in the BBM. The transporter's high affinity led the researchers to speculate that it may be important in fructose absorption at the end of the meal, when concentrations of fructose in the intestinal lumen are low. The physiological relevance of GLUT7 is unknown, as it doesn't appear to compensate for the loss of SGLT1 in glucose-galactose malabsorption.

Tazawa *et al*[127] have also cloned SGLT4, a sodium-dependent sugar transporter found in the intestine, liver, and kidney. COS-7 cells expressing SGLT4 exhibited Na+-dependent α-methyl-D-glucopyranoside (AMG) transport activity (Km = 2.6 mmol/L), suggesting that SGLT4 is a low affinity transporter. Several sugars were able to inhibit AMG transport (D-mannose > D-glucose > D-fructose > D-galactose), suggesting that these sugars may also be substrates. However, only mannose was confirmed to be a substrate by studies demonstrating direct uptake of mannose into the cell. Because mannose is elevated in diabetes[128] and in the metabolic syndrome[128], the authors suggest that SGLT4 may be a potential therapeutic target for patients afflicted with these disorders. Further characterization of these novel intestinal transporters will add to understanding of intestinal sugar transport.

CONCLUSION

The process of intestinal sugar absorption remains a controversial topic. An increased understanding of this process will enable the development of better therapeutic strategies in conditions where the modulation of intestinal sugar transport could improve health. For example, reducing sugar absorption may be beneficial with regards to the treatment of diabetes or obesity. Conversely, stimulating sugar absorption may be desirable in patients with short bowel syndrome, or in malnourished elderly patients. Furthermore, the targeted delivery of drugs to tumour cells expressing glucose transporters is an exciting area of research that warrants further exploration.

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