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Regulation of the fructose transporter GLUT5 in health and disease

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Douard V, Ferraris RP. Regulation of the fructose transporter GLUT5 in health and disease. *Am J Physiol Endocrinol Metab* 295: E227–E237, 2008. First published April 8, 2008; doi:10.1152/ajpendo.90245.2008.—Fructose is now such an important component of human diets that increasing attention is being focused on the fructose transporter GLUT5. In this review, we describe the regulation of GLUT5 not only in the intestine and testis, where it was first discovered, but also in the kidney, skeletal muscle, fat tissue, and brain where increasing numbers of cell types have been found to have GLUT5. GLUT5 expression levels and fructose uptake rates are also significantly affected by diabetes, hypertension, obesity, and inflammation and seem to be induced during carcinogenesis, particularly in the mammary glands. We end by highlighting research areas that should yield information needed to better understand the role of GLUT5 during normal development, metabolic disturbances, and cancer.

cancer; diabetes; diet; hypertension; inflammation; metabolic syndrome

FOR THOUSANDS OF YEARS, humans consumed about 16–24 g of fructose each day, mainly as fruits and honey obtained from foraging and agricultural activity. Recent modernization and specialization in agricultural and food processing methods initiated in Europe and North America have altered consumption patterns. Today, the per capita amount of fructose consumed each day ranges from 8 to 100 g, and the average is ~80 g/day in the United States (16, 56, 86, 130). Most of the increase in consumption is derived from refined or processed fructose (63).

The chemical process for the rapid commercial conversion of glucose to fructose was developed in 1957 (99), and this technological advance led to the gradual increase in the manufacture and consumption of high-fructose corn syrup (HFCS) (11). HFCS typically contains 42, 55, or 90% fructose (68). Fructose is the sweetest of all natural sugars, and this is the primary reason why glucose is converted to fructose and why HFCS is used in the formulation of food and beverage products. About 330–380 kcal/day of the energy intake of average Americans (corresponding to 17–20% of daily energy intake) is derived from fructose (48). Recent studies have shown that there seems to be a direct relationship between increases in consumption of fructose and increases in incidence of obesity and type 2 diabetes (12, 69, 114, 120). High-fructose diets may also lead to the development of "metabolic syndrome," which precedes the onset of type 2 diabetes and is a cluster of symptoms associated with insulin resistance, including dyslipidemia, insulin resistance, impaired glucose homeostasis, increased body fat, and high blood pressure [per reviews (8, 48, 78, 86, 130)].

The myriad effects of fructose are possible only if fructose reaches physiologically significant concentrations in the plasma and extracellular fluids and if subsequently transported into cells of various organ systems, thereby potentially altering normal metabolism in those organs. There are marked variations in estimates of blood fructose concentrations arising from differences in methods of collection and analysis. In normal humans, serum fructose concentration was estimated to be 0.008 mM (80), while plasma fructose was 0.030 mM (92). These variations can also arise from differences in fructose consumption, which is a potent regulator of intestinal fructose transport. In rats fed a diet containing glucose as the only carbohydrate source, serum fructose concentrations were <0.01 mM, but in those consuming fructose or sucrose, serum fructose concentrations reached 0.10–0.30 mM (19). In healthy humans consuming high-fructose or -sucrose diets, serum fructose can reach 0.2–0.5 mM (92), but this concentration is still very low compared with normal blood glucose levels (5.5 mM). This low fructose level results from rates of intestinal absorption lower than that of glucose and from efficient clearance of blood fructose mainly by the liver (50–70%) and, to a lesser extent, (20%) by the kidneys (103).

The Main Fructose Transporter GLUT5

How does fructose move from the intestinal lumen to the blood and from there to various tissues? Fructose is transported passively across membranes by a member of the facilitative glucose transporter (GLUT) family, named GLUT5 (19, 20, 72, 98, 137). The GLUT family consists of 14 members divided into three major classes based on sequence homology and substrate selectivity, as described in recent reviews (97, 149). The structure and kinetic properties of GLUT5 and other GLUTs will not be reviewed here, nor will fructose transport studies not clearly linked to GLUT5 and GLUT2. Among the seven members able to transport fructose, GLUT5 is the sole transporter specific for fructose with no ability to transport glucose or galactose. It is also insensitive to phloretin and cytochalasin B (79, 97). The second major fructose transporter

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is GLUT2, a low-affinity transporter that is also capable of recognizing glucose and galactose, and is inhibitable by phloretin and cytochalasin B (97). GLUT2 in a bidirectional manner is involved mainly in fructose uptake across the hepatic plasma membrane into the liver (154) and in the basolateral membrane of the intestinal and renal epithelial cells (88). Five other GLUTs may possess varying degrees of fructose selectivity based on sequence homology with GLUT5: GLUT7, GLUT9a/b, GLUT8, GLUT11, and GLUT12 (43, 90, 96).

GLUT5 was cloned almost 20 years ago and was initially described as a glucose transporter (9) until its specificity for fructose in the intestine and sperm was clearly demonstrated (20). Modest to significant levels of GLUT5 mRNA and/or protein have now been demonstrated in kidney, fat, skeletal muscle, and brain (55, 65, 66, 76, 81, 91, 101, 135).

Paralleling the increasing concern about the role of fructose in various diseases, the number of studies on GLUT5 has increased dramatically in the last three years (~70 studies from 2004 to 2007). Here, we review the evidence demonstrating the presence of GLUT5 in an increasing variety of organs and tissues and then describe its regulation under physiological and pathophysiological conditions.

Physiology and Function

Small intestine. The small intestine regulates fructose absorption from dietary sources and, therefore, the availability of fructose to other tissues. It is also the organ system expressing the greatest amount of GLUT5 in human (13, 20, 47, 79, 81), rat (24, 35–38, 45, 72, 75, 84, 108, 112, 113, 139, 140, 147), mouse (22, 33, 83, 107), rabbit (109), chicken (60), and horse (104). In cattle, GLUT5 expression in the intestine is significantly lower than in skeletal muscle (159), probably because this species is a foregut fermenter, and it is possible that fructose-like cellulose and other carbohydrate products are fermented in the stomach and little sugar reaches the intestinal lumen.

After apical transport mediated by GLUT5, fructose is transported across the basolateral membrane by GLUT2. Recent work by Kellett and Brot-Laroche (82) proposes that GLUT2 is also involved in the apical transport of fructose (see also 5, 15, 136). The K_m for fructose measured in oocytes expressing the human isoform of GLUT5 or in the brush border membrane vesicles from rat and human intestine ranges from 11 to 15 mM (20, 79, 100). This K_m is therefore similar to daytime intestinal luminal fructose concentrations in rats fed dietary fructose, ~26 mM (75). The V_{max} for GLUT5 measured in brush border membrane vesicles from rat intestine is ~200 pmol/s per milligram of protein (100). In rodents, cattle, and horses, the distribution of GLUT5 is greater in the proximal (duodenum and proximal jejunum) compared with the distal segments (distal jejunum and ileum) (104, 160). In addition to regional expression patterns, GLUT5 gene expression appears to be tightly regulated by developmental, nutritional, hormonal, and circadian influences. The mechanisms involved in these regulatory processes are detailed in the following paragraphs.

Developmental patterns. Under normal conditions, in the prenatal and suckling periods of rat, rabbit, and human development (<14 days in rodents), intestinal GLUT5 mRNA levels and fructose transport rates are very low (17, 51) (Fig. 1).
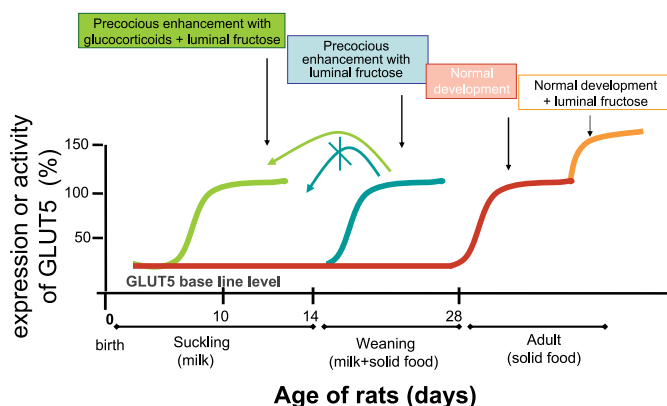

Fig. 1. Under normal conditions (red line), the intestinal fructose transporter GLUT5 is expressed at low baseline levels throughout suckling (0–14 days of age) and weaning (14–28 days) stages in neonatal rats. GLUT5 expression and activity increase normally after weaning has been completed and then can be enhanced by increases in consumption of dietary fructose (orange). Between 14 and 28 days old (blue), GLUT5 expression and activity are dramatically enhanced by precocious introduction of its substrate fructose into the intestinal lumen. GLUT5 cannot be enhanced by luminal fructose in rats <14 days old unless the gut is primed with dexamethasone (green).

Consumption of honey and fruit juice containing much fructose elicit marked increases in breath hydrogen (a marker of carbohydrate malabsorption) in children less than 1 yr of age, but not in those 2 or more yr old, suggesting fructose-induced intestinal malabsorption in very young humans possibly expressing low GLUT5 levels (116). Fructose malabsorption in 5-mo-old infants is associated with infantile colic (46) and increases their energy requirements (150). In rats, baseline GLUT5 expression and activity remain low (51, 75) throughout postnatal development until the weaning stage (Fig. 1) and then increase only after completion of weaning when solid foods are consumed. The increase in activity at 28 days of age is thought to be hardwired (148) and may not require the presence of luminal fructose. This increase in GLUT5 expression and activity can be advanced developmentally in younger, weaning pups. Between 14 and 28 days of age, GLUT5 is dramatically stimulated by early introduction of dietary fructose or by gavage feeding fructose solutions into the gastric lumen (35, 42, 45, 75, 112, 139). At this age range, the nutritional regulation of GLUT5 by fructose is clearly genomic (75) and requires the presence of fructose in intestinal lumen (140). GLUT5 response to luminal fructose occurs rapidly as the mRNA abundance in all enterocytes lining the villus increases simultaneously within 4 h (74). In contrast to GLUT5, both intestinal GLUT2 and SGLT1 (the Na$^+$-dependent glucose transporter) are expressed at high levels throughout development, even in the prenatal stage of mammals (17). From the prenatal to the weaning stages, rat SGLT1 does not seem to be regulated by sugars (139), whereas rat GLUT2 appears to be regulated by luminal and systemic glucose or fructose (36).

Role of glucocorticoid and thyroid hormones. In suckling rats younger than 14 days, gavage feeding or perfusion in vivo of fructose has no effect on the already low levels of GLUT5 expression and activity (Fig. 1) (38, 45, 74). This is understandable since milk is fructose free and there is no luminal signal that can stimulate GLUT5. However, GLUT5 in weaning rats (>14 days old) with no access to solid food, or even

those with access to fructose-free pellets, can be enhanced by fructose. What developmental factors control the dramatic difference in GLUT5 regulation between suckling and weaning stages? Cui et al. (38) and Douard et al. (45) used microarray approaches to identify in vivo intestinal regulatory genes that modulate fructose sensitivity by tracking changes in expression as a function of age and of perfusion solution. When the microarray results revealed that a significant number of age- and fructose-responsive genes were modulated by glucocorticoids, they hypothesized that corticosteroids play a major role in regulating intestinal GLUT5. By priming the gut with dexamethasone (a glucocorticoid analog), fructose was suddenly able to markedly stimulate GLUT5 even in suckling pups younger than 14 days (45). Dexamethasone also has similar stimulatory effects on the development of another intestinal membrane protein, sucrase-isomaltase, in similar-age pups, except that dexamethasone can directly upregulate sucrase-isomaltase without its substrate sucrose (2).

The glucocorticoid receptor, which binds dexamethasone, may be one of the transcription factors involved in the glucocorticoid-mediated enhancement of GLUT5 by fructose (44). Another candidate transcription factor discovered by microarray as significantly and simultaneously fructose and dexamethasone responsive is karyopherin-α2 (45), a nuclear importin known to be involved in the trafficking of nuclear factors stimulating the transcription of sugar-responsive genes (23). The expression of karyopherin-α2 is stimulated by fructose at 20 days, an age when fructose can stimulate GLUT5, but not at 10 days, when fructose alone does not stimulate GLUT5 (45).

In older pups, ∼20–28 days of age, glucocorticoids may no longer be involved in the fructose stimulation of GLUT5, since adrenalectomy of pups at 10 days of age does not prevent dietary fructose from enhancing GLUT5 expression (112). However, in this experiment, adrenalectomized pups received aldosterone every day to prevent salt wasting. Because aldosterone and corticosterone can both bind the glucocorticoid receptor with high affinity, this receptor may have mediated the effect of aldosterone on GLUT5 in the presence of fructose and confounded the effect of adrenalectomy on GLUT5 development.

The role of thyroid hormones, known to mediate the development of hydrolytic enzymes in the intestine, in the developmental regulation of GLUT5 has also been examined. L-triiodothyronine enhances GLUT5 expression in Caco2 cells (102, 110, 111). In fact, thyroid hormone response elements were identified in the −338/−272 bp promoter region of GLUT5 (102, 111). However, the role of thyroid hormones in GLUT5 regulation so clearly demonstrated in cell culture may not be physiological because in vivo studies suggest that thyroxine does not regulate GLUT5. In normal pups, thyroxine concentrations increase significantly during the transition from suckling to weaning, and thyroxine may therefore be an ideal regulator of GLUT5 development (70). However, in weaning pups made hypothyroid from birth, dietary fructose can still enhance intestinal fructose uptake and GLUT5 mRNA expression even though thyroxine levels in the serum are very low (113).

Diurnal rhythm. In adult rats, GLUT5 mRNA and protein expression follow a distinct diurnal rhythm not found in neonatal rats (140). The rhythm occurs independent of food and fructose intake (34, 146), which in rats occur mostly and naturally at night (52). This diurnal rhythm consists of an anticipatory fourfold induction of intestinal GLUT5 mRNA and protein expression occurring 3–4 h before the onset of peak feeding. Thus, GLUT5 can be regulated by factors not associated with feeding or with changes in luminal fructose concentrations. The same diurnal rhythm was also observed for intestinal GLUT2 (34, 146). Diurnal regulation of GLUT5, like fructose regulation of GLUT5 in weaning rats, seems modulated by paracrine and endocrine signals in the intestine, because diurnal variation of GLUT5 expression is independent of the vagus nerve. In contrast, GLUT2 diurnal expression is controlled by vagal signals (146).

Kidney. After the small intestine, the kidney expresses the most GLUT5 in human, rat, and rabbit (4, 20, 28, 40, 81, 109, 126). GLUT5 mRNA is abundant in the cytosol, and protein is present in the apical plasma membrane of S3 proximal tubule cells (28, 145), where GLUT5 can potentially recapture fructose lost from glomerular filtration. Renal GLUT5 of rats has a V_{max} of 106 pmol/s per milligram of protein and a K_m of 12.6 mM, values relatively similar to those in the small intestine (101). The K_m, however, seems much higher than physiological fructose concentrations in the blood (∼0.008–0.03 mM) and, presumably, glomerular filtrate. Fructose concentration in the urine of normal nondiabetic humans is 0.035 mM (personal communication, T. Kawasaki). Differences in fructose concentration between filtrate and intracellular compartment will determine the direction of fructose flux mediated by GLUT5. GLUT2 is also in the basolateral membrane of proximal tubular cells, and the role of these two relatively low-affinity GLUTs in renal fructose transport, in light of relatively low, apparently similar fructose concentrations in the blood and urine, needs to be elucidated. The transcript size and molecular weight of the protein are similar to those determined for GLUT5 in the intestine (33), in accord with the resemblance in kinetic features of this transport system from the two organs. Moreover, during the prenatal period, the levels of renal GLUT5 mRNA and protein are low but then rapidly increase during weaning when its expression is also inducible by the fructose diet (19, 126), suggesting similar mechanisms of developmental regulation as those in the small intestine.

Testes and sperm. GLUT5 has consistently been found in the spermatozoa of many species: human (3, 20), mouse (3, 33), rat (3), bull (3), pig (133, 134), and dog (127). Even if its role in sperm metabolism remains uncertain, it may confer to the spermatozoa the ability to use fructose as an energy source or as an activator of the fertilization process (3, 127). In humans, GLUT5 is expressed only in mature spermatids, suggesting a selective upregulation of GLUT5 expression during germ cell development, from immature spermatogonia expressing low levels of GLUT5 through to elongated spermatids expressing high levels of GLUT5 (3, 20).

Testicular GLUT5 levels are also influenced by age as are those in the small intestine. Interestingly, changes in GLUT5 expression in the whole testis as a function of ontogenetic development parallels changes in GLUT5 expression as a function of spermatogenetic development. Testicular GLUT5 expression increases threefold in 6-wk-old adults compared with that in 1-wk-old prepubertal mice (33). This implies a reproductive function for fructose and suggests that, even in a tissue that does not deal with or perceive the diet change at

weaning, an intrinsic factor with wide-ranging effects seems to be responsible for the developmental regulation of GLUT5.

The pubertal timing for the increase in GLUT5 expression in the testis reinforces the postulated relationship between steroid hormones and GLUT5 as previously described in the small intestine. The total transcript size of testicular GLUT5 is 2.8 kb and is significantly larger than the 2.1 kb size of intestinal and renal GLUT5 (33). The difference in transcript size may result from the existence of two distinct promoters, one type controlling GLUT5 transcription in somatic cells like intestinal epithelia and another type controlling transcription in germ cells, where GLUT5 contains an additional exon (33). The GLUT5 promoter in the intestine/kidney contains binding sites for the caudal homeobox gene (CdxA, a transcriptional factor involved in development of gastrointestinal tissues) (33). In addition to CdxA, the GLUT5 promoter in the testis also contains binding sites for the sex-determining region of Y (SRY, a transcriptional factor essential for the development of the testis), whose influence prevails over or supplements that of CdxA. These findings show how differences in promoter regions or in promoter activity may be responsible for the tissue-selective expression of GLUT5.

Muscle/fat tissue. GLUT5 is expressed in skeletal muscle of human (14, 40, 41, 66, 71, 81, 125, 137, 143, 144), rat (40), and mouse (131). In fact, GLUT5 is, along with GLUT4 and GLUT12, one of the more significantly expressed GLUTs in human skeletal muscle compared with the other members of the GLUT family (144). However, GLUT5 mRNA and protein levels in skeletal muscle are low compared with those of the intestine in humans (81) and rats (40). Adipocytes of rats (65, 91) and humans (137) also express GLUT5, but expression seems less compared with that of the small intestine (81). GLUT5 expression is strictly confined to the plasma membrane of adipocytes and to the sarcolemma of skeletal muscle where it is responsible for facilitating fructose uptake from the blood into these tissues (40, 65, 137). Since GLUT5 is facilitative and extracellular fructose concentration seems quite low (probably 69, 161). In human adipocytes, a recent study demonstrated, hypoxia increases GLUT5 expression (9-fold) (155). Because hypoxia becomes more common during the progression of obesity, it can be one of the factors leading to increases in GLUT5 expression in adipocytes of young obese *fa/fa* rats (91).

In contrast to the intestine and kidney but like the testis, GLUT5 expression is not substrate dependent in muscle (40) but may be modulated by hormones. Insulin is capable of increasing the abundance and functional activity of GLUT5 in skeletal muscle cells, and the insulin effect is most likely mediated via activation of the GLUT5 promoter (66). The contribution of skeletal muscles and of adipocytes in the clearance from the blood and in metabolism of fructose is minor compared with that of the liver and the kidney.

Brain. Glucose is the principal substrate used by and is considered sufficient for the metabolic needs of the brain (142), so there is no requirement for additional energy sources. However, GLUT5 has been identified in different cell types such as human microglia (122), cerebellar Purkinje cells in human fetus (117), mouse cerebellum (55), human blood-brain barrier (98), and rat hippocampus (138). Because the GLUT5 transporter is commonly found in tissues that metabolize fructose (20), these brain cells may be capable of utilizing fructose

as an energy substrate. However, the utility of fructose and function of GLUT5 remains uncertain in the brain. Since it is unlikely that the brain secretes fructose, the presence of GLUT5 in the blood-brain barrier indicates that fructose enters the brain, but radioalabeled fructose injected into rat arteries resulted in minimal accumulation of radio-labeled fructose in the brain, suggesting insignificant transport across the blood brain barrier (119) that is likely mediated by GLUT1. GLUT1 typically transports glucose across the blood brain barrier but has a very low affinity for fructose (39). In contrast to the finding that fructose does not enter the brain, a modest and transient upregulation of GLUT5 mRNA and protein levels in the brain has been demonstrated in rats consuming a high fructose diet (138) and following schemia (151). This suggests that fructose enters the brain because it is a potent and specific stimulator of GLUT5 transcription (51). Consistent with the controversial nature of this subject, a more recent study found that high fructose diets do not upregulate GLUT5 in the brain (106). Hence, the physiological role of GLUT5 and the effect of high-fructose diets in the brain still need to be investigated.

Regulation of Intestinal GLUT5 by Its Own Substrate

Regulation in vivo. Here, we will focus primarily on the intestinal regulation of GLUT5 in adults or weaning pups older than 14 days in which GLUT5 responds to luminal fructose. GLUT5 expression and function in weaning and postweaning rats can be enhanced markedly in vivo by consumption of high-fructose diets (42), gavage-feeding of fructose solutions (74), perfusion in vivo of the intestine with fructose (75), or incubation in vitro of isolated everted intestines in fructose solutions (85). Intestinal GLUT5 is therefore remarkably responsive to its substrate fructose. The response of GLUT5 is quite specific, as SGLT1 or GLUT2 expression is similar among fructose, glucose, and nonmetabolizable glucose analogs. Fructose metabolism, partial or total, may be a key factor in the regulatory process because of the modest effect of the nonmetabolizable fructose analog 3-*O*-methylfructose on GLUT5 upregulation in 20-day-old rats (75). Fructose is supposedly metabolized via either of two pathways, the fructose 1-phosphate and/or the fructose 6-phosphate pathway. Although the fructose 1-phosphate pathway using fructokinase and aldolase B seems to be prominent in the liver, it is not clear whether intestinal cells are capable of fructose metabolism and, if they are, which of the two pathways would prevail (49, 103).

Along with GLUT5, the mRNA expression of key gluconeogenic enzymes, glucose-6-phosphatase (G-6-Pase) and fructose-1,6-bisphosphatase (FBPase), increased significantly in fructose-perfused intestines, suggesting a link between gluconeogenesis on the one hand and fructose transport as well as intracellular fructose on the other (38). However, only the inhibition of FBPase activity using vanadate prevents the fructose-induced increase in GLUT5 mRNA expression and fructose uptake (84). FBPase activity is indirectly regulated by cAMP, which increases in vivo in the intestinal mucosa (35) or in vitro in Caco2 cells (94) exposed to fructose compared with those exposed to glucose. It had been demonstrated in vivo that cAMP modulates fructose transport induced by fructose without affecting GLUT5 mRNA abundance (35), whereas in vitro, cAMP affects GLUT5 mRNA expression levels (62). The reasons for these different effects of cAMP on the transcrip-

tional and posttranscriptional regulation of GLUT5 by fructose remain unknown and may underlie the difference between in vitro and in vivo models. In fructose-perfused rats, the phosphatidylinositol 3-kinase/protein kinase B system (PI 3-kinase/Akt) also mediates the fructose-induced increase in fructose uptake but still has no effect on GLUT5 transcription (37). The signaling pathways in vivo related to the dramatic and specific fructose-induced increase in GLUT5 mRNA and activity remain to be elucidated, although several fructose-responsive genes identified from microarray comparisons of fructose- and glucose-perfused intestines suggest that *1*) intracellular phosphate metabolism or transport, *2*) several regulatory genes in the gluconeogenic pathway, and *3*) alterations in ATP/ADP levels, may be involved (38).

Regulation in vitro in Caco2 cells. The molecular regulation of GLUT5 in the intestine has also been studied using mostly Caco2 cells as a model. Among the numerous clones of Caco2, GLUT5 is expressed endogenously only in those clones exhibiting low rates of glucose consumption (Caco2-PD7, -TB10, -TC7, -TF3, or -TG6) and only in those cells that are differentiated (94). It is not clear why these clones have low rates of glucose metabolism, but endogenous expression of GLUT5 suggests that they may be attempting to obtain additional sources of sugars. Interestingly, by use if glucokinase activity as an indicator of the rate of glucose metabolism, the intestine can be categorized more like a low-glucose-metabolizing tissue compared with the liver, brain, or adipose tissue in rats fed a carbohydrate diet (1). Although glucose under in vivo conditions does not alter GLUT5 mRNA and protein levels in enterocytes, both glucose and fructose are potent activators of GLUT5 in Caco2 cells (93, 94, 102, 105). Hence, under most conditions, GLUT5 regulation in Caco2 cells does not distinguish between glucose and fructose. Only if postconfluent cells are grown in culture media containing dialyzed fetal bovine serum and only in Caco2/PD7 or Caco2/TC7 clones can fructose modestly induce GLUT5 expression to a greater extent than glucose (105).

Because fructose, compared with glucose, does not increase the activity of the human GLUT5 promoter in vitro, the modest fructose-induced increase of GLUT5 mRNA abundance in Caco2 cells appears to result from increased mRNA stability (62). Since cAMP is involved in GLUT5 regulation in Caco2 cells (93, 94, 105), increased mRNA stability may result from an inhibitory effect of cAMP on the formation of a complex between the GLUT5 3′ UTR area and PABP (polyadenylate-binding protein)-interacting protein (Paip2). PABP proteins are found in all eukaryotes and are implicated primarily in mRNA maturation, export, and turnover (141). Specifically, Paip2, a partner of PABP, is involved in the destabilization of the transcripts, and inhibition of Paip2 enhances mRNA stability. Two cAMP potential response elements had been identified in the GLUT5 promoter and now localized to −365/−358 and −332/−325 regions (94). Interestingly, GLUT5 expression is also cAMP sensitive in primary cultures of rabbit proximal tubule cells (121).

Pathology and GLUT5

Diabetes/hyperinsulinemia. It is not clear whether diabetes alters serum fructose concentration. Serum fructose concentration and urinary fructose excretion increased markedly in diabetic Japanese patients (80). On the other hand, serum fructose concentrations were similar among healthy Finnish volunteers and those with type 1 or 2 diabetes (124). What is clearer is that fructose may be profoundly involved in the development of metabolic syndromes important in the pathogenesis of diabetic complications (56, 63, 86, 120). Fructose is now the major sweetener in Western diets, and for a while was used in diabetes therapy because it did not result in acute hyperglycemia. GLUT5 is expressed in insulin-sensitive tissues like skeletal muscle and adipocytes of humans and rodents and may participate in the management of glycemia involving insulin. Despite the importance of dietary fructose in the development of diabetes, and that of GLUT5 in fructose transport, very few studies have investigated the link between diabetes and GLUT5 in these insulin-sensitive organ systems. The few studies that did so found interesting but inconsistent correlations between this transporter and diabetes, with inconsistencies arising from the fact that although GLUT5 may be affected by diabetes, GLUT5 is also particularly affected by levels of dietary fructose that may vary markedly among diabetes patients.

Patients with type 2 diabetes exhibited dramatic increases in GLUT5 mRNA and protein abundance in skeletal muscle (143). These increases were specific, because expression of GLUT1, GLUT3, GLUT4, GLUT8, GLUT11, and GLUT12 did not change with diabetes and could be reversed if diabetic patients were treated for 8 wk with pioglitazone, a drug enhancing insulin action.

Several studies have also linked GLUT5 expression in fat tissue of rodent models with diabetes or with diabetic complications. In rats with streptozotocin-induced diabetes, there was a dramatic, insulin-insensitive, glycemia-regulated decrease in levels of GLUT5 mRNA and in rates of fructose uptake in adipose cells (65). Type 2 diabetes may have different effects on GLUT5, and those effects may be age or insulin dependent. GLUT5 protein abundance and activity increased two- to fourfold in young obese *fa/fa* rats that were normoglycemic and hyperinsulinemic compared with lean controls. When insulin resistance (hyperinsulinemia and hyperglycemia) became established in aged obese *fa/fa* rats, GLUT5 protein and the rate of fructose uptake in adipocytes decreased 12-fold (91). These reductions in site density of adipocyte GLUT5 can contribute to increases in plasma fructose concentrations in diabetes. Because GLUT5 abundance and fructose transport in adipocytes are upregulated in highly insulin-responsive rats but are downregulated dramatically when these rats age and become insulin resistant, this suggests that changes in GLUT5 expression in adipocytes of type 2 diabetics are dependent on insulin sensitivity. However, the exact role of insulin needs further study.

In the same aged *fa/fa* rats, there was no effect of insulin resistance on GLUT5 protein levels in the kidney (91), suggesting that the effect of insulin resistance on GLUT5 was primarily in adipocytes. However, two studies observed an increase of GLUT5 mRNA and protein levels in rat kidney after onset of streptozotocin-induced diabetes (4, 28). Streptozotocin-induced diabetes results in increases in levels of GLUT5 in the apical membrane of mesangeal cells in the glomerulus and of proximal convoluted tubular cells in the renal cortex. Changes in the levels of GLUT5 in the membrane of tubular cells may affect rates of fructose transport to/from the filtrate, depending on concentration gradi-

ents. Increases in levels of renal GLUT5 may mediate the three-fold increase in urinary fructose excretion observed in type 2 diabetic patients (80).

Diabetes also profoundly affects GLUT5 expression in the small intestine. Duodenal GLUT5 mRNA and protein levels increase three- to fourfold in type 2 diabetic subjects (47). Lowering hyperglycemia in certain patients reversed this intestinal upregulation of GLUT5, suggesting that blood glucose level or its consequences are involved in the GLUT5 regulation in the intestine of diabetic subjects (47). In contrast, in Zucker rats, considered a model of type 2 diabetes, the mRNA and protein levels of the intestinal sugar transporters SGLT1, GLUT5, and GLUT2 remained the same as those of lean controls (31). These differences may arise from species differences or from the different composition of diets consumed by control and diabetic patients in the human study. Interestingly, treating the diabetic rats with troglitazone (another drug enhancing insulin action) specifically downregulates GLUT5 protein levels, consistent with previous observations (143).

In streptozotocin-induced type 1 diabetes, findings on intestine are also contradictory. In streptozotocin-diabetic rats, dramatic increases in levels of GLUT5 mRNA, cytosolic protein, and brush border protein were demonstrated in the jejunum and ileum (18, 32). Diabetes also increased intestinal size and caused a premature expression of hexose transporters by enterocytes along the crypt-villus axis, thereby causing a cumulative increase in enterocyte transporter protein during maturation. GLUT5 protein levels increased in parallel with a diminution of GLUT5 activity (32), suggesting less fructose transported per GLUT5. Unfortunately, in the same model of type 1 diabetic rats, another study observed a diabetes-induced reduction in intestinal GLUT5 expression (108). In summary, the regulation of intestinal GLUT5 in diabetic subjects seems to be complex, and no clear picture has emerged due to contradictory findings. This multifaceted regulation also reflects the complexity of diabetes-induced metabolic changes (e.g., hyperinsulinemia, hyperglycemia, insulin-resistance, obesity, inflammation) that can affect GLUT5 expression.

Arterial hypertension and obesity. Metabolic disorders like impairments in glucose metabolism and insulin resistance have also been reported in humans and mammals exhibiting arterial hypertension. In the ileum of spontaneously hypertensive (SHR) rats, the capacity to absorb fructose was reduced and levels of GLUT5 mRNA and protein decreased, suggesting a transcriptional downregulation of GLUT5 in the intestine of these rats (100). Levels of GLUT5 protein in renal brush border membrane vesicles of hypertensive rats compared with those from normotensive rats also decreased with hypertension (101). It is interesting to note that there exists another animal model for hypertension: young rats fed high levels of fructose. These young rats increase intestinal GLUT5 expression and then eventually develop glucose intolerance and high blood pressure (10).

The mechanism by which dietary fructose induces hypertension is being investigated. In rodents, fructose, unlike other sugars, induces hyperuricemia (115, 132) which is a major risk factor for hypertension (50). Recent clinical studies using patient data from the Third National Health and Nutrition Examination Survey confirm the link not only between hyperuricemia and hypertension in particular but also between serum concentrations of uric acid and the prevalence of metabolic syndrome in general (29, 53). In turn, consumption of sugar-sweetened soft drinks is substantially correlated with increasing levels of serum uric acid and frequency of hyperuricemia (30). This increase in levels of blood uric acid can result from fructose-induced reduction in the renal excretion of uric acid and from the stimulation of nucleotide catabolism (67). However, little else is known about GLUT5 regulation and its physiological significance in fructose induced hypertension in animal models or humans.

Intestinal inflammatory and infectious diseases. Inflammatory or infectious conditions also lead to adaptive changes in intestinal absorptive function, including fructose transport. The link between inflammation or infection and fructose has been poorly explored, maybe because no inherited disorders of intestinal fructose transport have yet been reported. Isolated fructose malabsorption is rare and is not linked to protein-altering mutations in GLUT5, and the inheritance pattern is unknown (153). As a consequence, there are few studies on GLUT5 expression and function under pathological conditions in the intestine. In general, GLUT5 expression and activity decrease in inflammatory diseases. A patient with *Helicobacter pylori* infection exhibited a decrease in intestinal GLUT5 expression (87). In rats, 2–8 days after iodoacetamide-induced colitis, GLUT5 protein and mRNA levels decreased in noninflamed small intestine, thereby paralleling the time course of inflammation manifested in the large intestine and suggesting that GLUT5 in noninflamed tissues may be sensitive to inflammation inducers or to inflammatory signals in the blood (77). In the case of sepsis induced by lipopolysaccharide (LPS) or tumor necrosis factor-α (TNF-α) in rabbit, fructose absorption also decreased in the jejunum (57, 59). When injected intravenously, LPS, which is a component of the membrane of gram-negative bacteria, stimulates cytokine (including TNF-α) and glucocorticoid production. The decrease in rate of fructose absorption can be prevented by an inhibitor of TNF-α and can be explained mostly by decreases in GLUT5 protein levels in the enterocytes, indicating that the effect of inflammatory factors on GLUT5 is mainly specific. LPS treatment decreased GLUT5 levels by proteasome-dependent degradation. The regulatory mechanism underlying the inhibition of fructose absorption by LPS and TNF-α may involve cross talk among various protein kinase signaling pathways because specific inhibitors of PKC, PKA, and MAP kinases, p38 MAPK, JNK, and MEK1/2, protected fructose uptake from adverse LPS effects (58).

The role of bacteria and the adaptive immune responses it generates also seem to affect GLUT5 expression. Under nonpathological states but in the absence of both passive and adaptive immunity, a dramatic increase in expression of GLUT5 is observed in the proximal small intestine of 18-, 21-, and 25-day-old rats (73). This increased expression of GLUT5 in the immunodeficient host could be an adaptive response limiting the nutrients available for intestinal microflora in the more distal regions of the gut and indicate that when the immune system is compromised GLUT5 expression is upregulated.

GLUT5 is also found in immune cells like the mature macrophages of peripheral organs (54, 95) and in the microglia of the brain (26, 128, 135, 151). When human monocytes differentiate into macrophages, differentiation is accompanied by marked changes in intracellular location of GLUT5 and by dramatic increases in GLUT5 mRNA levels and protein abundance and in fructose uptake rate (54, 95).

Breast cancer. GLUT5 mRNA and protein expression are affected by the development of tumors in certain organ systems. This surprising finding is not only consistent among different organ systems and cell types but also seems independent of associated metabolic or inflammatory diseases. In general, oncogene-transformed cells that portray cancerous characteristics will also exhibit an increase in glucose transport by overexpressing specifically sugar transporters like GLUT1 in breast, colorectal, lung, and ovarian carcinoma (21, 64, 118, 156), GLUT12 in breast cancer (129), or GLUT3 in lung, ovarian, and gastric cancers (157). This increase in glucose transport and metabolism may reflect a requirement by these rapidly growing cells for more sources of energy (27). Although GLUT5 is poorly expressed in normal mammary epithelial cells, the breast carcinoma cell lines MCF-7 and MDA-MB-231 possess high amounts of GLUT5 mRNA and protein and exhibit high rates of fructose transport (158). This finding from an earlier study was later on confirmed a number of times in later studies. In fact, GLUT5 knockdown by antisense oligonucleotide decreases rates of fructose uptake, thereby inhibiting the proliferation and the growth of MCF-7 and MDA-MB-231 cells, which are, respectively, models of early- and late-stage breast cancer (25). A large-scale screening of the GLUT family of transporters in malignant vs. normal human tissues and cells showed that GLUT5 was highly overexpressed in 27% of cancerous tissues tested, including tumors in brain, breast, colon, liver, lung, testis, and uterus (61). In situ RT-PCR and ultrastructural immunohistochemistry confirmed GLUT5 expression in breast cancer. In contrast, GLUT6 and -9 are clearly not overexpressed in human cancer of various tissues, whereas GLUT1 is expressed in cancers of a wide range of tissues but expression in each tissue is modest. The extensive expression of the glucose/fructose transporter GLUT2, and the fact that in most of the tumor cells overexpressing GLUT5 the rate of fructose uptake is exacerbated,

indicate that fructose may be a preferred substrate providing energy required for the growth and proliferation of tumor cells (61, 89). This increase of GLUT5 could indicate preferential utilization of fructose by cancer cells. However, the link between fructose and tumor cell growth remains unclear. Interestingly, it was observed over 50 years ago that cancer cells maintain a high rate of glycolysis even in the presence of oxygen, a phenomenon called the Warburg effect (7, 123, 152). One of the major regulatory steps in glycolysis involves conversion of fructose 6-phosphate to fructose-1,6-bisphosphate by phosphofructokinase-1 (PFK-1). The activity of PFK-1 is allosterically controlled by fructose-2,6-bisphosphate, the product of the enzymatic activity of a dual kinase/phosphatase family of enzymes (PFKFB1–4) that is also increased in a significant number of tumor types (6). Fructose is known to stimulate the intestinal expression of PFKFB1 (38), but it is not known whether fructose leads to increased levels of fructose 2,6-bisphosphate. However, it is clear that the rate of glycolysis can be stimulated by fructose because its entrance into glycolysis skips the two main regulatory enzymes (glucokinase and PFK-1) (67). Either the presence of GLUT5 leads to a greater use of fructose by neoplastic cells, or increased usage of fructose leads to a higher abundance of GLUT5. Clearly, the role of fructose in enhanced glycolysis observed in cancer cells requires further study.

Future Research

GLUT5 is found in many tissues, and its expression and activity are clearly regulated under normal and are altered under pathological conditions (Fig. 2). The increasing importance of fructose in human nutrition and disease calls for additional studies that hopefully will increase our understanding of the role of the fructose transporter GLUT5 in health and disease.
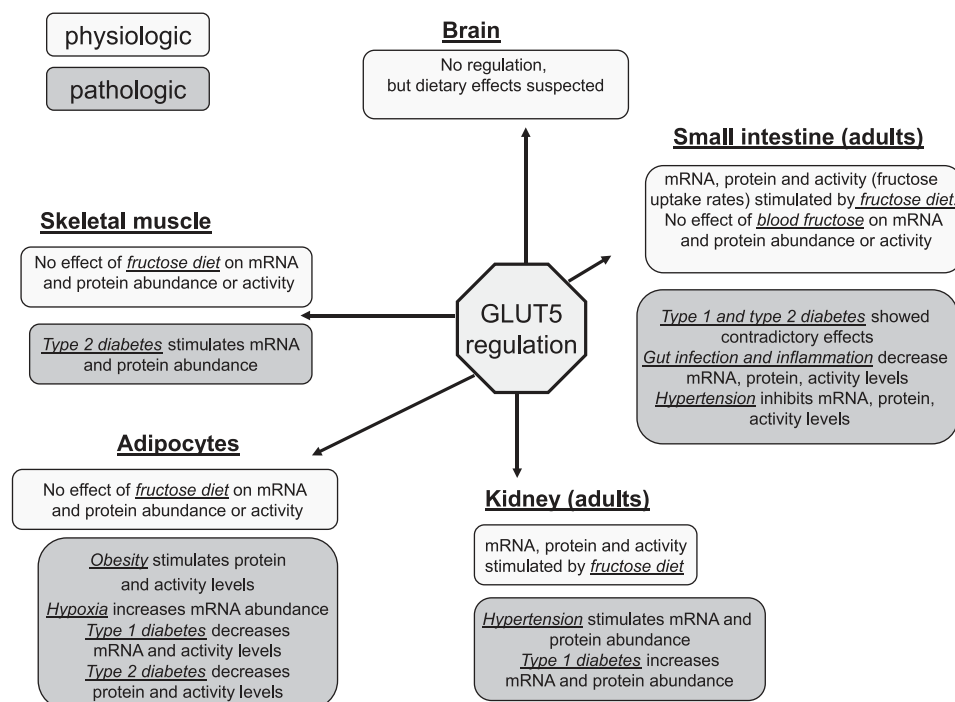

Fig. 2. Multiple regulatory parameters of GLUT5 expression and protein abundance and activity under physiological (light shading) and pathological (darker shading) conditions in small intestine, kidney, adipocytes, skeletal muscle, and brain.

Estimates of fructose concentrations in plasma, urine, and cerebrospinal and intracellular fluids, as well as kinetic properties of GLUT5 in other tissues, are needed to better understand the role of GLUT5 in fructose metabolism and the role of fructose in GLUT5 regulation.

GLUT5 is expressed in only a limited number of tissues seemingly capable of or preferentially metabolizing fructose, and there exist two major categories of transcriptional and/or posttranscriptional regulation of GLUT5. In the apical membrane of polarized cells (e.g., enterocytes and renal cells), GLUT5 is acutely and specifically regulated by its own substrate, whereas in the other tissues, like adipocytes, fructose seems to have no acute effect. The signaling cascade regulating this specific and acute regulation in epithelial cells of GLUT5 by fructose is not known and can be compared with signals regulating substrate-independent modulation of GLUT5 in other tissues. The subcellular redistribution of GLUT5 following different stimuli also merits attention.

In Caco2 cells and in highly proliferative cancer cells, GLUT5 expression is significant enough that it appears to be a good marker of malignancy or high proliferation rate. This suggests that cancerous cells lose the inhibitory factor(s) that blocks intensive GLUT5 expression in normal cells. The mechanisms underlying GLUT5 induction in cancer need to be identified.

Until now, the developmentally regulated biological factor(s) allowing luminal fructose to enhance GLUT5 expression after but not before 14 days of age has not been identified. Moreover, related factors that trigger diurnal rhythms of GLUT5 expression in adults are not known. The mechanisms underlying and the factors involved in the glucocorticoid-allowed, fructose-induced regulation of GLUT5 in suckling rats need further study.

Information about ontogenetic development of human intestinal GLUT5 is needed to increase our understanding not only of the role fructose plays in intestinal fructose malabsorption but also of the correlation between fructose malabsorption and infant colic.

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