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Intestinal fructose transport and malabsorption in humans

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Jones HF, Butler RN, Brooks DA. Intestinal fructose transport and malabsorption in humans. *Am J Physiol Gastrointest Liver Physiol* 300: G202–G206, 2011. First published December 9, 2010; doi:10.1152/ajpgi.00457.2010.—Fructose is a hexose sugar that is being increasingly consumed in its monosaccharide form. Patients who exhibit fructose malabsorption can present with gastrointestinal symptoms that include chronic diarrhea and abdominal pain. However, with no clearly established gastrointestinal mechanism for fructose malabsorption, patient analysis by the proxy of a breath hydrogen test (BHT) is controversial. The major transporter for fructose in intestinal epithelial cells is thought to be the facilitative transporter GLUT5. Consistent with a facilitative transport system, we show here by analysis of past studies on healthy adults that there is a significant relationship between fructose malabsorption and fructose dose ($r = 0.86$, $P < 0.001$). Thus there is a dose-dependent and limited absorption capacity even in healthy individuals. Changes in fructose malabsorption with age have been observed in human infants, and this may parallel the developmental regulation of GLUT5 expression. Moreover, a GLUT5 knockout mouse has displayed the hallmarks associated with profound fructose malabsorption. Fructose malabsorption appears to be partially modulated by the amount of glucose ingested. Although solvent drag and passive diffusion have been proposed to explain the effect of glucose on fructose malabsorption, this could possibly be a result of the facilitative transporter GLUT2. GLUT5 and GLUT2 mRNA have been shown to be rapidly upregulated by the presence of fructose and GLUT2 mRNA is also upregulated by glucose, but in humans the distribution and role of GLUT2 in the brush border membrane are yet to be definitively decided. Understanding the relative roles of these transporters in humans will be crucial for establishing a mechanistic basis for fructose malabsorption in gastrointestinal patients.

fructose malabsorption; GLUT5 transport; GLUT2 transport; breath hydrogen test; gastrointestinal disease

FRUCTOSE IS A MONOSACCHARIDE increasingly found in the Western diet, both as an added sweetener and in more "natural" forms such as fruit juice (45, 63). Dietary fructose has been variously implicated in obesity (6), insulin resistance syndrome (19), and fructose malabsorption, the latter of which has been linked with irritable bowel syndrome (28), small intestinal bacterial overgrowth (26), and depression (42). This review will focus on the mechanism of fructose transport in the small intestine, particularly as a potential contributor to the gastrointestinal complaint of fructose malabsorption in humans.

With no clearly established mechanism for fructose malabsorption, its analysis, by the proxy of a breath hydrogen test (BHT), has become a source of debate (25, 34). Patients with fructose malabsorption present with symptoms that include chronic diarrhea and abdominal pain (9). Clinical confirmation can include dietary history, a BHT, and the relief of symptoms following the removal of fructose from the patient's diet. For a BHT, the patient consumes fructose, and fructose that is not absorbed in the small intestine reaches the large intestine, where it is metabolized by intestinal flora, resulting in hydrogen production. Detection of hydrogen in breath samples from the patient therefore indicates malabsorption of the sugar. The use of a BHT to detect lactose malabsorption has been well established (25, 53). Malabsorption of a disaccharide, such as lactose, has been characterized by a deficiency in the enzyme that cleaves the sugar. However, as a monosaccharide sugar, fructose does not require enzymatic cleavage and, therefore, absorption is most likely reliant on a transport mechanism.

Most of the understanding of fructose transport has been elucidated by animal studies (17). Recently, a GLUT5 knockout mouse model was shown to exhibit decreased absorption of dietary fructose, with consequent distension of the large intestine with fluid and gas. The model was described as having the hallmarks of profound fructose malabsorption (2). With this and other advances in the understanding of fructose transport, it may become possible to characterize a mechanism for fructose malabsorption in humans.

Transport of Fructose

Fructose is thought to be transported across the intestinal epithelium by facilitative transporters. In the conventional

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model of fructose transport, fructose is transported across the apical membrane of intestinal epithelial cells by the facilitative transporter GLUT5 (Fig. 1) (17). GLUT5 is a low-affinity, high-capacity fructose transporter that appears to be specific for fructose. Moreover, dietary fructose has been shown to upregulate GLUT5 mRNA expression (10, 12, 36, 47). Transport of fructose across the basolateral membrane of gastrointestinal epithelial cells has been reported to utilize the facilitative hexose transporter GLUT2 (8). GLUT2 is a facilitative transporter for the hexose sugars glucose and fructose that also operates with low affinity and high capacity (38). GLUT2 mRNA expression has been shown to be upregulated by both glucose and fructose (13). However, there have been questions raised about the distribution of these GLUT transporters, with GLUT5 found to be localized to the basolateral membrane in human jejunum (5). Additionally, GLUT2 has been found to be transiently upregulated in the brush border membrane of murine models (1, 27, 30, 31, 39). This has raised questions about the distribution of these two transporters and contributed to a debate about which of these sugar transporters has the greater role in fructose absorption.

Fructose was shown to be absorbed entirely by the GLUT5 transporter in the intestine of both wild-type and GLUT2 knockout mice, which had been previously fed a low-carbohydrate diet (27). However, isolated brush border membrane vesicles from mice previously fed a high-fructose diet showed a 5.7-fold higher fructose uptake than low-carbohydrate diet mice, and it was estimated that GLUT2 was responsible for around 60% of the intestinal fructose uptake. Additionally, mice previously fed a high-glucose diet showed a 2.1-fold higher fructose uptake than the low-carbohydrate-fed mice. This was consistent with dietary upregulation of the GLUT transporters and suggested that GLUT5 is primarily responsible for fructose absorption, but that GLUT2 recruitment to the brush border membrane could be an important adaptation when the intestine is challenged with a large dose of fructose (27). Although GLUT2 has not been confirmed in the brush border membrane for humans, the biopsy samples were obtained from patients who were fasted (18) or deceased (5). These findings suggest that GLUT2 is not constitutively located on the brush border membrane of the human small intestine, but it could be transiently upregulated by glucose, as observed in a murine model. In humans, individuals with glucose/galactose malabsorption have a mutation in the active glucose transporter SGLT1 and do not absorb glucose, despite the presence of functional GLUT2 (56, 62), implying that this transporter is not effectively expressed on the brush border membrane. If the murine model of transient apical GLUT2 operates in humans, this apparent anomaly may be explained by the demonstration that inhibition of SGLT1 results in inhibition of GLUT2 translocation to the brush border membrane (29, 39, 46). Another genetic disorder of glucose transport, Fanconi-Bickel syndrome, involves individuals who have a mutation in the GLUT2 gene yet are reportedly able to tolerate fructose in their diet (55). These observations imply that there may be a possible role for GLUT2 in high-load situations, but definitive evidence for this supposition is yet to be established in humans.

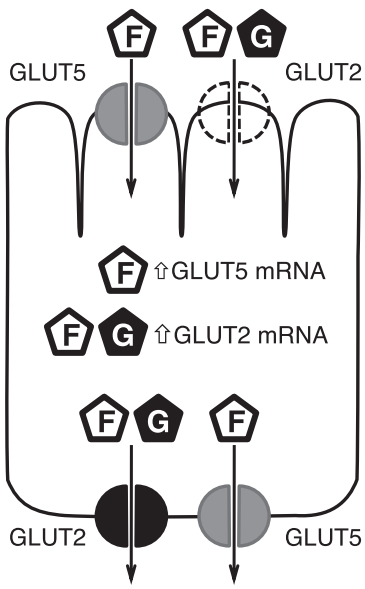

Fig. 1. Fructose transport across the intestinal epithelium. The established transporters, on the left of the diagram, are fructose (F) transporter GLUT5 across the apical membrane and fructose and glucose (G) transporter GLUT2 across the basolateral membrane. The transient upregulation of GLUT2 at the apical membrane in response to luminal sugar has been shown in murine models but has not yet been demonstrated in humans (indicated by dotted lines). GLUT5 has been identified in the basolateral membrane from human small intestine (5). Upregulation of GLUT5 and GLUT2 mRNA by these sugars is indicated.

The importance of GLUT5 in fructose absorption has been investigated further in a GLUT5 knockout mouse model (2). In these GLUT5 knockout mice fructose absorption was decreased by 75% in the jejunum and the concentration of serum fructose was decreased by 90%, compared with wild-type mice. In knockout mice on a high-fructose diet, the cecum and proximal colon became distended with significantly more cecal contents, including fluid and gas. This was only witnessed in mice fed a high-fructose diet and not in those having a normal or high-glucose diet. The GLUT5 knockout mice had GLUT2 protein detected on the apical and basolateral membrane, but the presence of GLUT2 did not compensate for the GLUT5 deletion. These studies would appear to support a primary role for GLUT5 in fructose absorption. GLUT7 has been identified as another transporter of glucose and fructose (43), but it was only shown to be expressed in the ileum, the distal region of the small intestine, making it an unlikely candidate for the majority of fructose and glucose transport. It has been hypothesized that GLUT7 may be responsible for the uptake of sugar that has not been absorbed in the proximal small intestine and reaches the ileum. Thus GLUT7 would not appear to impact on the major role of GLUT5 in fructose transport.

Absorption Capacity and Diagnosis

Fructose absorption in humans appears to be limited at high concentrations of fructose, and this is consistent with the limited absorption capacity of a facilitative transport system (11). The proportion of adults tested who show fructose malabsorption by a BHT has been shown to be dependent on the fructose dose given (Fig. 2) (4, 15, 41, 50, 54). Functionally, fructose malabsorption may therefore arise when dietary intake is greater than absorption capacity (taking into account the form of fructose and whether there is glucose present to enhance the absorption; see discussion below). If fructose malabsorption does occur as a result of a reduced absorption

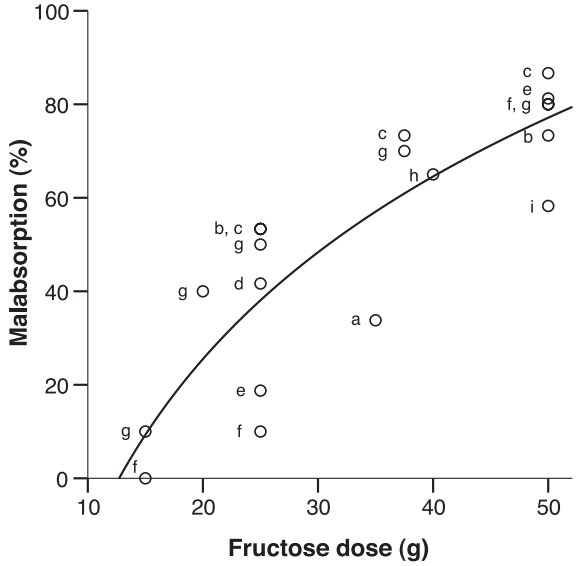

Fig. 2. Relationship between the dose of fructose (grams) and percent positive for malabsorption on the fructose breath hydrogen test in healthy adults ($r = 0.86$, $P < 0.001$, $n = 19$, logarithmic regression, SPSS 18.0 for Windows) from 9 studies (reference numbers in parentheses) incorporating 455 breath hydrogen tests: a (3), b (4), c (15), d (20), e (41), f (50), g (54), h (59), i (61).

threshold, potentially corresponding to reduced transport capacity, there is not going to be a clear dichotomous diagnostic answer to the question of malabsorption. Rather there will be, among both healthy people and those symptomatic for malabsorption, a range of fructose absorptive capacities, which are balanced against dietary fructose consumption. To define fructose malabsorption as an unusually low level of fructose absorption would require a dose of sugar for the BHT that most healthy people can tolerate; from previous studies, this threshold appears to be ~15 g of fructose (Fig. 2) (50, 54). The BHT shows a direct relationship between dose of fructose and malabsorption and demonstrates that there is a dose-dependent limited absorption capacity present even in healthy individuals.

Glucose Effect on Fructose Absorption in Humans

Glucose has been shown to significantly improve the threshold for fructose malabsorption (23, 40, 51, 54, 61). The glucose effect on fructose absorption may be reduced in the modern Western diet by the decrease in the consumption of fructose in the form of the disaccharide sucrose, with a concomitant rise in consumption of fructose (49). The enhancing effect of glucose led to an early hypothesis that fructose was absorbed through a disaccharidase-related transport system which simultaneously transported glucose and fructose (52), but fructose is now considered to be transported by facilitated diffusion, primarily using the GLUT5 transporter, as discussed above (17). Without a disaccharidase-related simultaneous transport mechanism to explain the effect of glucose on fructose absorption, alternative hypotheses have been proposed to explain this effect.

It has been hypothesized that the glucose effect on fructose absorption is a result of nonspecific movement of fructose across the intestinal epithelium by solvent drag or passive diffusion (11, 22, 52). Thus, when healthy children were given amino acids with fructose, this reduced the hydrogen response on the BHT to the same extent as when glucose was given with fructose (33). It was hypothesized that the active transport of glucose would result in glucose-induced water streaming across the mucosa, causing increased solvent drag and passive diffusion of fructose (11). However, a study in rats found that although glucose and galactose ameliorated the response to the fructose BHT, the same effect was not observed when 3-*O*-methylglucose or sorbitol were added (24), leading to the conclusion that the effect was caused by direct stimulation of fructose transport. A case study in one child also found that galactose ameliorated the fructose BHT to a similar extent to glucose, but found no effect on the BHT when urea was added (40). If the glucose effect on fructose absorption is a result of transport, and not a result of solvent drag or a concentration gradient (32, 33), then GLUT2 may be the best candidate for this effect (8, 26). The effect whereby galactose, but not 3-*O*-methylglucose, improved fructose malabsorption was not anomalous with a role for GLUT2, given that although GLUT2 was shown to transport both galactose and 3-*O*-methylglucose, GLUT2 mRNA has been shown to be upregulated by glucose and galactose, but not by 3-*O*-methylglucose (40, 47). Similarly, paracellular drag was invoked to explain glucose diffusion across the intestinal membrane beyond the capacity of the active glucose transporter SGLT1, which was saturated at 30–50 mM glucose. However, this component of glucose absorption is now considered to be explained by facilitated diffusion due to rapid trafficking of GLUT2 to the brush border membrane (39). GLUT2 upregulation has also been shown to be an adaptation to a high-fructose diet, which increased fructose transport in mice, as discussed above (27). Since GLUT2 can transport fructose and glucose and is upregulated by the presence of glucose, it is a potential candidate for the effect of increased fructose transport in the presence of glucose.

Developmental Regulation

Fructose absorption may be highly dependent on age, and significantly reduced absorption of fructose has been reported in toddlers (34, 37) and infants (37). The evidence for significantly less absorption in infants consuming fruit juice is less well established, with findings characterized by levels of hydrogen excretion rather than malabsorption. Higher levels of hydrogen production after fruit juice challenge were found in toddlers (48, 60), and in infants in one study (48), but not in another investigation (60). Our laboratory (37) has recently shown that age has a significant effect on testing positive for fructose malabsorption on a BHT, with the odds of testing positive decreasing by a factor of 0.82 per year from infancy to 15 years old. Mammals receive nutrition prior to weaning from milk, which contains the sugars glucose and galactose, which are transported by SGLT1 and GLUT2. Mammals do not appear to transport fructose until such time as it would naturally arise in their diet (7), and the expression of GLUT5 has been shown to be developmentally regulated (17, 21). The capacity for fructose uptake in neonatal rats was paralleled by GLUT5 expression, with GLUT5 expressed at a low level through the suckling (0–14 days of age) and weaning (14–28 days) stages, but increasing dramatically after 28 days (57). Expression and activity of GLUT5 was enhanced, from 14 days of age at the earliest, by the introduction of fructose into

the diet (16, 35, 58). An increase in GLUT5 mRNA abundance has been shown to occur within a few hours of fructose consumption in differentiated cells lining the intestinal villi of 20-day-old rat pups (35). This upregulation of GLUT5 mRNA may involve cross talk between nutrient signals from dietary fructose and hormonal signals involved in intestinal maturation, such as from glucocorticoids (16). Developmental regulation of GLUT5 has been established in these animal models, but this is yet to be definitively confirmed in humans.

Expression of GLUT5 in humans was examined in two studies, which compared the expression of GLUT5 in the small intestine of fetuses (from the first and second trimester) with that in adults. One study found GLUT5 protein by immunofluorescence in both adult and fetal samples (44). The other found lower levels of GLUT5 mRNA expression in the fetal samples compared with adults (14). This difference was not seen for GLUT2 and the active glucose transporter SGLT1. This suggested that the developmentally regulated expression of GLUT5 mRNA seen in murine models may be present in human infants, but further investigation would be required for this to be confirmed.

A Definitive Role for GLUT5 in Human Fructose Malabsorption?

It has been investigated whether there are mutations in the protein coding region of the GLUT5 gene in patients with fructose malabsorption, but none have been detected thus far (64). This absence of a mutation in the coding region of the GLUT5 gene does not necessarily preclude a role for GLUT5 in fructose malabsorption. It is possible that reduced transport could result from changes in gene expression, response to the presence fructose in the small intestine, or activity of GLUT5. Additionally, in a mouse model, the intestine showed long-term adaptation to dietary glucose and fructose, resulting in higher fructose uptake (27). The rapid GLUT2 and GLUT5 upregulation in response to dietary sugars means that if a link is to be investigated between malabsorption and hexose transporter expression in humans, fasted patients would likely show different levels of transporter expression compared with those whose intestine has been exposed to a sugar (27). It may be that in a human malabsorption scenario there are differences in basal expression of the GLUT transporters, or in their short-term upregulation/localization or long-term adaption to dietary fructose, that need to be considered.

Conclusion

Significant advances have been made in our understanding of intestinal fructose transport, but this has not yet been clearly linked with the gastrointestinal problem of fructose malabsorption. Without this mechanistic link, the validity of the fructose BHT and its relationship with fructose malabsorption will continue to be debated. It appears that younger children have a reduced capacity to absorb fructose, particularly even small quantities of high-fructose fruit juices. Establishing the developmental regulation at a biochemical level, rather than reliance on the contentious proxy of measuring malabsorption by BHT will be important. This may help facilitate improvement in diagnostic accuracy in patients with fructose malabsorption and have a direct influence on dietary guidelines for fructose consumption, especially in infants and toddlers. Finally, the capacity to absorb fructose may have a significant impact on an individual's ability to utilize this energy substrate, and therefore its putative contribution to the obesity epidemic. Understanding the role of fructose transporters in humans will be crucial for establishing a mechanistic basis for fructose malabsorption.

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