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Translational Medicine: Bench to Bedside

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Mechanisms Of Fructose Absorption

Fructose consumption has increased by one-third from 1978 to 2004 in the western diet.[1] It has been implicated in the epidemic of obesity, and associated with elevated fasting blood sugar levels and hypertension.[2] In addition, fructose consumption is thought to trigger functional abdominal pain and diarrhea in susceptible individuals via increased gas production from its fermentation by bacteria in the gut, and increased intraluminal osmotic load.[3] Recently, a diet low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols, which includes fructose restriction, has been demonstrated in adults and children to reduce a variety of symptoms of irritable bowel syndrome including abdominal discomfort, bloating, gas and diarrhea.[4] Although reduced fructose intake has been associated with improvement in symptoms, it remains uncertain whether this is due to an altered response to fructose in the gut lumen or impaired absorption of fructose. A better understanding of the mechanisms of fructose absorption may lead to an improved awareness of these issues and, ultimately, a decrease in the morbidity associated with fructose use.

It is widely accepted that fructose is absorbed via glucose transporters (GLUT) in the intestine, mainly GLUT-2 and GLUT-5. Recently, important research has focused on the GLUT-5 transporter itself and its regulation. In a series of recent elegant experiments, Patel and colleagues[5] demonstrated that GLUT-5 is the principal apical transporter of fructose in the small intestinal epithelia of mice and that its expression is increased by fructose intake. They showed that, GLUT-5 knockout (KO) mice were incapable of fructose uptake despite having normal levels of GLUT-2. There was no facilitated diffusion of fructose across the everted intestinal mucosa of GLUT-5-KO mice, while fructose diffusion was increased across the intestinal mucosa of wild type mice after gavage with fructose (compared with gavage with lysine and glucose). Furthermore, using western blot analysis of protein extracted from the mouse intestinal mucosa, they demonstrated that, after gavage with fructose, GLUT-5 expression increased sixfold in wild type mice, but only half as much in GLUT-5 heterozygous mice and not at all in GLUT-5-KO mice. Fructose is metabolized by the enzyme ketohexokinase (KHK) into fructose-1-phosphate. These investigators went on to show that GLUT-5 expression was increased in KHK-KO mice; however, the degree of increase was significantly less than in wild type mice and, in fact, was similar to the increase in GLUT-5 expression that was seen in wild type mice after gavage with glucose. Fructose uptake was increased in KHK-KO mice after gavage with glyceraldehyde, a product of fructose metabolism by KHK. In contrast, there was no increase in the expression of GLUT-2, 7, 8 or 12 after gavage with fructose in wild-type, KHK-KO or GLUT-5-KO mice. Finally, Rab11a is thought to play a role in endosomal protein trafficking of GLUT-5. After deletion of Rab11a, a decrease in glucose transporters in the apical membrane was found as was a decreased response to fructose gavage. In summary, this report suggests that GLUT-5 is the main apical transporter for fructose, is induced by increased fructose intake via transcriptional activation, and is dependent upon the presence of KHK- and Rab11a-mediated endosomal protein trafficking.

There appears to be more to the story of fructose absorption, however, than simply the presence of GLUT-5 and GLUT-2 transporters. This was demonstrated in a study involving 26 human subjects that included 11 patients with fructose malabsorption, as indicated by an abnormal fructose breath test and symptoms of intolerance during the test, and 15 control individuals, without food intolerances or functional gastrointestinal disorders, who had a normal breath test.[6] To date, most of the research in this area has been performed using rabbit or rat intestine or cell cultures. To our knowledge, this article is the first that uses human tissue in an attempt to explain the mechanism of fructose malabsorption in patients with functional gastrointestinal disorders. Using tissue from small bowel biopsy, GLUT-2 and GLUT-5 mRNA expression was measured via multiplex reverse-transcription quantitative polymerase chain reaction in reference to the beta-actin gene, and GLUT-2 and GLUT-5 proteins were quantified via Western immunoblotting relative to tubulin and total protein. The principal finding was that no significant difference was identified between either GLUT-2 or GLUT-5 mRNA expression or proteins. Although there was a small sample size and the subjects were fasting before the endoscopic biopsies, the findings suggest that either fructose malabsorption is not directly related to the quantity or density of GLUT-2 and GLUT-5 transporters, or gastrointestinal symptoms after ingestion of fructose are not solely secondary to its malabsorption.

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Inflammation also appears to play a role in the regulation of fructose absorption. Rodriquez-Yoldi and colleagues showed that IL-1β, an inflammatory cytokine, inhibits the transport of fructose.[7] After a 24 h fast, rabbits were injected with saline, IL-1β, or an inhibitor or activator of a kinase prior to IL-1β. Fructose transport was assessed using jejunal rings and purified brush border membrane vesicles, and uptake in both was measured. In the presence of PKC inhibitor, the effect of IL-1β on fructose uptake in intestinal tissue was reversed. In the presence of a PI3K inhibitor and activator, however, fructose uptake was not affected by IL-1β. Finally, a proteasome inhibitor decreased the effect of IL-1β, although it had no independent effect on fructose absorption, suggesting a role of NF-κB. To prove that the effects were independent of neuronal and hormonal effects, Caco-2 cells were cultured in a medium containing IL-1β and pre-incubated in solutions with kinase inhibitors or activators, and then incubated in a buffer with fructose. Fructose absorption was then measured. In the presence of a PI3K activator or PKC inhibitor, the effect of IL-1β on fructose absorption was reversed. In the presence of an inhibitor of NF-κB nuclear translocation, there was no inhibitory effect of IL-1β on fructose absorption. In summary, the results suggest that IL-1β could regulate the activation of PKCα 73, PI3K 55 and NF-kB proteins, and could exert an inhibitory effect on fructose intestinal absorption by a modification of GLUT5 insertion to brush-border membrane and/or the functional transporter activity. This article suggests a novel mechanism for fructose malabsorption, whereby the absorption of fructose is not entirely dependent on the abundance of transporters, but also on the inflammatory milieu of the intestinal epithelium.

Fructose is an important factor in the development of several metabolic disorders and has been implicated as a cause of a number of common functional gastrointestinal symptoms. A better understanding of the mechanisms of fructose absorption and its regulation may provide a key to discovering a means of preventing or improving these conditions. As described above, GLUT-5 appears to be a principal apical transporter of fructose in the small intestine, and its expression is upregulated by increased fructose intake via transcriptional activation, in the presence of ketohexokinase. However, other factors also appear to be necessary in fructose absorption. One such factor appears to involve the inflammatory milieu in the intestinal epithelium. Further investigation is needed to elucidate the mechanisms involved in fructose absorption and handling in humans, and better understand whether fructose consumption is actually the source of symptoms in patients with functional gastrointestinal disorders.

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