Novel insights in intestinal and hepatic fructose metabolism

Novel insights in intestinal and hepatic fructose metabolism: from mice to men

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Purpose of review
The rise in fructose consumption in parallel with the current epidemic of obesity and related cardiometabolic disease requires a better understanding of the pathophysiological pathways that are involved.

Recent findings
Animal studies have shown that fructose has various effects on the intestines that subsequently affect intrahepatic lipid accumulation and inflammation. Fructose adversely affects the gut microbiome – as a producer of endotoxins and intermediates of de novo lipogenesis – and intestinal barrier function. Furthermore, intestinal fructose metabolism shields fructose away from the liver. Finally, fructose 1-phosphate (F1-P) serves as a signal molecule that promotes intestinal cell survival and, consequently, intestinal absorption capacity. Intervention and epidemiological studies have convincingly shown that fructose, particularly derived from sugar-sweetened beverages, stimulates de novo lipogenesis and intrahepatic lipid accumulation in humans. Of interest, individuals with aldolase B deficiency, who accumulate F1-P, are characterized by a greater intrahepatic lipid content. First phase II clinical trials have recently shown that reduction of F1-P, by inhibition of ketohexokinase, reduces intrahepatic lipid content.

Summary
Experimental evidence supports current measures to reduce fructose intake, for example by the implementation of a tax on sugar-sweetened beverages, and pharmacological inhibition of fructose metabolism to reduce the global burden of cardiometabolic disease.

Keywords
aldolase B, colorectal cancer, fructose, ketohexokinase, nonalcoholic fatty liver disease

INTRODUCTION

The consumption of fructose, as a sweetener in processed foods, has drastically increased over the past decades [1]. High intakes of added sugars have been associated with a greater weight gain, an increased risk of type 2 diabetes, and cardiovascular mortality [2,3].

To date, it has been commonly accepted that fructose is primarily metabolized in the liver, where it is phosphorylated by ketohexokinase (KHK) and subsequently converted to the trioses glyceraldehyde and dihydroxyacetone phosphate by aldolase B (ALDOB). These trioses subsequently enter the glycolytic pathway where they can serve as a substrate for, among others, de novo lipogenesis, resulting in the accumulation of intrahepatic lipids. Nonalcoholic fatty liver disease (NAFLD), a histological spectrum ranging from intrahepatic lipid accumulation, steatohepatitis and fibrosis, has not only been associated with hepatic complications, such as liver failure and hepatocellular carcinoma, but also with a greater risk of type 2 diabetes and coronary artery disease [4,5].

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KEY POINTS

- Animal studies have identified a prominent role for the intestines in fructose-mediated metabolic derangements, which deserve translation to humans.
- Intestinal fructose metabolism reduces the flux of fructose towards the liver, thereby protecting the liver from lipid accumulation.
- F1-P is a signal molecule that promotes intestinal absorption capacity and intrahepatic lipid storage.
- Intervention and epidemiological studies have convincingly shown that fructose per se, particularly fructose derived from sugar-sweetened beverages, drives de novo lipogenesis and intrahepatic lipid accumulation in humans.
- Reduction of F1-P levels, by inhibition of ketohexokinase, may be a new pharmaceutical option to treat nonalcoholic fatty liver disease.

Recent studies have identified the intestines, which also express KHK and ALDOB, as another major player in the pathogenesis of fructose-mediated metabolic derangements. In this review, we give an overview of these recent advances by focusing on intestinal and hepatic fructose metabolism in both animal models and human studies. We specifically aimed to identify translational alignments and inconsistencies, on which we based our conclusions with suggestions for further research.

INTESTINAL FRUCTOSE METABOLISM

Animal studies

Recent studies have demonstrated that, prior to intestinal absorption, dietary fructose already exerts adverse health effects by affecting the intestinal environment. Fructose-fed rodents and piglets were found to have an altered gut microbiome composition and reduced tight junction expression resulting in an impaired intestinal barrier function [6–8]. Several mechanisms for the decreased tight junction expression have been proposed, including intestinal endoplasmic reticulum and nitroxidative stress [7,8]. A disturbed barrier function drives endotoxemia, which was shown to trigger tumour necrosis factor production by liver macrophages stimulating hepatic de novo lipogenesis [8].

Zhao *et al.* [9] assigned another function to the gut microbiome. They found that fructose-derived acetyl-CoA, a precursor of de novo lipogenesis, was not synthesized in the liver. Instead, the gut microbiome appeared to be a major source of the acetyl-CoA pool that reached the liver [9].

Besides the involvement of the gut microbiota, two experimental studies independently unveiled an important role for intestinal fructose metabolism in protecting the liver from intrahepatic lipid accumulation [10,11▪]. Intestine-specific deletion of the KHK C isoform (KHK-C) caused an increased flux of fructose towards the liver resulting in de novo lipogenesis and intrahepatic lipid accumulation [10,11▪], whereas intestine-specific KHK-C overexpression stimulated intestinal fructose metabolism and, consequently, decreased hepatic de novo lipogenesis [11▪]. Furthermore, fructose administered as either one large bolus or in liquid form (as solution), overwhelmed intestinal fructose metabolism, resulting in increased spillover to the liver and de novo lipogenesis, in contrast to similar amounts of fructose administered as multiple small boluses or in a solid phase [11▪].

Finally, Taylor *et al.* [12▪▪] recently demonstrated that intermediates of fructose metabolism, that is fructose 1-phosphate (F1-P), promote intestinal cell survival, resulting in an increase in intestinal villus length and, consequently, increased absorption capacity. They showed that – while fructose 1,6-bisphosphate, a product of glycolysis, stimulates pyruvate kinase M2 (PKM2) activity by forming active tetramers – F1-P inhibits PKM2 by forming inactive monomers. Inactive PKM2 drives hypoxic cell survival allowing villus elongation (Fig. 1a) [12▪▪]. Furthermore, the same process led to the development of intestinal tumours in susceptible mice [12▪▪]. Of interest, a recent study in neonatal calves fed fructose (in addition to milk replacer) showed an increase in small intestinal mass [13]. On the contrary, it was not investigated whether this increase was explained by fructose-mediated villus hypertrophy, nor was this study controlled for energy intake, which tended to be higher in fructose-fed calves compared with controls receiving milk replacer only [13].

Human studies

The translation of the observations obtained from animal studies to humans is currently not straightforward. Fructose-rich diets (100 g/day) resulted in a change in faecal microbiome composition – with divergent effects for fructose derived from fruits and sugar-sweetened beverages (SSBs) [14] – and short-term, very-high fructose feeding (~180 g/day) was associated with an increase in plasma endotoxin levels [15]. In contrast, however, a recent double-blind, cross-over trial did not show an effect of added fructose (75 g/day) on the faecal microbiome,

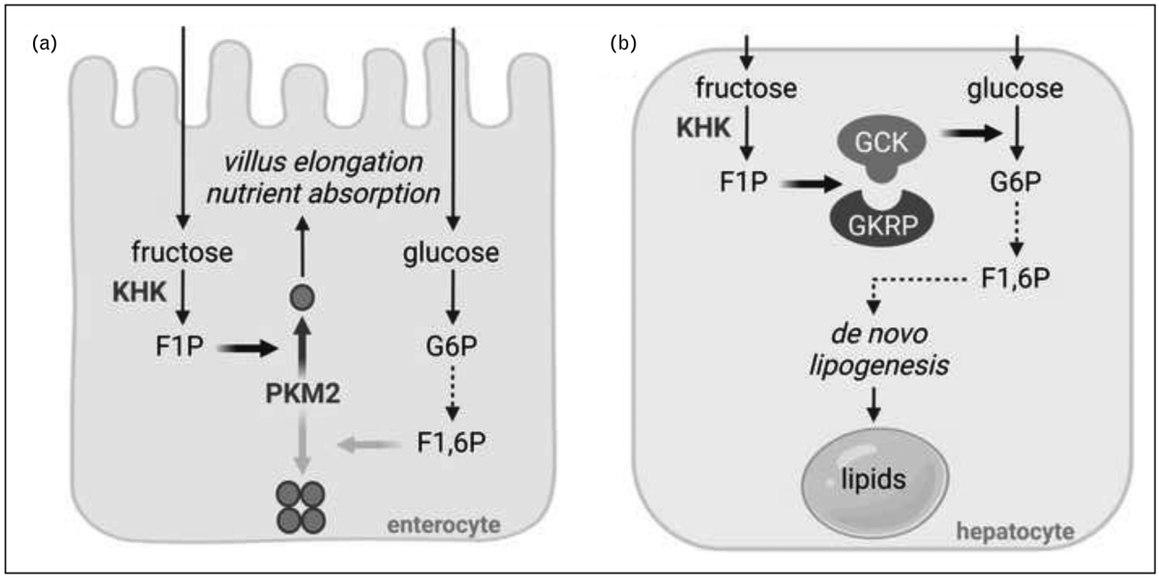

FIGURE 1. Fructose 1-phosphate as a signal molecule. In the gut, fructose 1-phosphate stimulates the formation of the inactive monomer of pyruvate kinase M2 (in contrast to the active tetramer), which drives enterocyte survival and, consequently, villus elongation and nutrient absorption (a). In the liver, fructose 1-phosphate dissociates glucokinase from glucokinase regulatory protein, which facilitates glucose phosphorylation thereby stimulating hepatic glucose disposal and *de novo* lipogenesis (b). Figure created with BioRender.com.

gut permeability and plasma endotoxins in comparison with added glucose (75 g/day) [16▪].

To date, the role of the intestines as a fructose scavenger has not been studied in humans, which is – at least in part – explained by the poor accessibility to portal blood. Although invasive portal vein sampling studies have been performed in the sixties of the last century (as summarized in Ref. [17]), they did not quantify the net intestinal fructose extraction. More recently, Francey *et al.* [18] used stable isotopes to show that approximately 15% of the ingested fructose after a high oral fructose load (30 g) escapes clearance by both the intestines *and* the liver. It would be interesting to know whether lower fructose loads show disproportionally lower escapes, which would be indicative of relatively more scavenging by the intestines (and liver) in these situations, in line with previous animal studies [10,11▪].

Finally, in corroboration with the experimental evidence provided by Taylor *et al.* [12▪▪], showing that F1-P drives intestinal tumour growth in mice, recent epidemiological studies have demonstrated an association between a high intake of SSB during adolescence (and in adulthood) and risk of colorectal adenomas and cancer [19,20▪]. Further studies are required to elucidate whether specifically F1-P is responsible for the observed associations.

HEPATIC FRUCTOSE METABOLISM

Animal studies

Although previous animal studies have shown that fructose favours hepatic de novo lipogenesis more than glucose [21], Bouwman *et al.* [22] recently failed to replicate these findings. They did not observe a difference in hepatic triglyceride accumulation nor in the expression of lipogenic genes in mice fed either glucose or fructose. One striking difference between both studies is the mode of monosaccharide administration, that is dissolved in drinking water in the former study and as part of the pelletized diet in the latter study [21,22], which, as outlined above, may have differential effects on intestinal fructose metabolism.

The role of F1-P as a signal molecule has not only been unveiled in the intestines, but also in the liver. Lanaspa *et al.* [23] showed that *ALDOB* knockout mice – which cannot convert F1-P to trioses – were characterized by higher intrahepatic F1-P and triglycerides levels in comparison with wild-type mice, which were mitigated after knockdown of KHK-*C*. Detailed phenotyping of *ALDOB* knockout mice showed a greater expression of lipogenic genes and a higher cytosolic to nuclear ratio of glucokinase, indicative of increased dissociation of glucokinase from glucokinase regulatory protein (GKRP). GKRP is a liver-specific protein that resides in the

nucleus where it binds and inactivates glucokinase. Experimental studies have shown that catalytic amounts of F1-P dissociate glucokinase from GKRP, allowing migration of glucokinase to the cytosolic space favouring hepatic glucose uptake, glycolysis, de novo lipogenesis and intrahepatic lipid accumulation (Fig. 1b) [24,25]. This mechanism may explain the F1-P-mediated increase in intrahepatic lipid content in *ALDOB* knockout mice.

Human studies

To what extent specifically fructose contributes to NAFLD in humans is still highly debated. Geidl-Flueck *et al.* recently reported the results from a double-blind randomized controlled trial in which 94 healthy men were allocated to daily consumption of SSBs containing either fructose, sucrose or glucose (80 g/day). After 7 weeks, the rate of de novo lipogenesis, assessed by stable isotopes, was increased after consumption of fructose-containing and sucrose-containing SSBs, but not after glucose-containing SSBs [26]. Consistently, rates of de novo lipogenesis and intrahepatic lipid content were decreased in an uncontrolled study in obese children who were treated with a fructose-restricted diet for 9 days [27], as well as in a randomized controlled trial that compared a 8-week diet low in free sugars versus usual diet in adolescents with NAFLD [28▪]. Although these studies provided consistent results on the effects of a fructose-restricted diet, it cannot be distinguished whether the observed effects are the results of fructose restriction per se or the fructose-restricted diet as a whole, which differs from a usual diet not only in fructose content but also in other macro/micronutrients. To address this issue, Simons and colleagues conducted the 'Effects of fructose restriction on liver steatosis' (FRUITLESS) study, in which 44 adult, overweight individuals with a high fatty liver index were randomized to either fructose or glucose supplementation on a background of a 6-week fructose-restricted diet (<10 g/day). As such, both diets were identical and the only difference was the amount of fructose (and glucose) that was supplemented. It was demonstrated that intrahepatic lipid content showed a small but more pronounced decrease in the group allocated to glucose supplementation, that is complete fructose restriction [29▪]. These findings show that fructose per se affects intrahepatic lipid content more than glucose.

Additional evidence for the role of fructose in the pathogenesis of intrahepatic lipid accumulation was recently provided in a population-based study ($n \sim 4000$). After adjustment for potential confounders, including total energy intake and physical activity, fructose intake from SSBs and fruit juice, but not from fruit, was associated with a greater intrahepatic lipid content, as quantified by MRI [30▪]. The differential associations of these different sources of fructose with intrahepatic lipid content may be explained by residual confounding, that is fruit consumption is associated with a healthy lifestyle, despite statistical correction for lifestyle factors. Alternatively, other constituents of the food product, that is the food matrix, may counteract the adverse effects of fructose. For example, the presence of fibres in fruits may slow down intestinal transit, resulting in a more gradual intestinal exposure to fructose and, consequently, a lower fraction of fructose that escapes intestinal metabolism and reaches the liver.

Together, these interventional and observational studies provide robust evidence that fructose per se drives de novo lipogenesis resulting in intrahepatic lipid accumulation in humans. They also suggest that measures to reduce the intake of fructose – particularly rapidly absorbable fructose derived from SSBs – can have beneficial effects on the liver. One way to achieve this may be the implementation of a sugar tax on SSBs, which indeed was recently shown to reduce sugar intake from SSBs in the United Kingdom and several cities in the USA [31–33]. More importantly, a similar approach has led to beneficial weight changes in adolescent girls in Mexico [34▪▪]. Although these changes are modest at the individual level, they can have substantial health effects at the population level.

The central role for F1-P, as demonstrated in ALDOB knockout mice [23], has also been shown in humans with rare homozygous mutations in *ALDOB*, that is hereditary fructose intolerance. Despite the lifelong fructose-restricted diet to avoid acute symptoms and chronic complications [35], these patients were characterized by a greater intrahepatic lipid content [36], even when compared with healthy individuals matched for age, sex and BMI [37]. Furthermore, hypoglycosylated transferrin levels, a serum biomarker of hepatic F1-P levels [38], were more abundant in these patients [37].

These studies support the pharmacological inhibition of F1-P formation – by inhibition of KHK – as a means to reduce intrahepatic lipid content and its associated complications, including liver failure, hepatocellular carcinoma, type 2 diabetes and cardiovascular disease. Of interest, the results of the first phase I and II clinical trials in humans showed that PF-06835919, a KHK inhibitor, was well tolerated and reduced intrahepatic lipid content in individuals with nonalcoholic fatty liver disease [39,40▪▪]. Furthermore, this compound

reduced de novo lipogenesis in perfused human liver wedges [41].

CONCLUSION

Recent animal studies have identified the intestines as an important organ where fructose may exert disadvantageous effects on microbiome composition, barrier function and endotoxemia, which directly drive de novo lipogenesis. Furthermore, intestinal fructose metabolism shields fructose from the liver, thereby preventing intrahepatic lipid accumulation. This latter process particularly deserves confirmation in humans, as it may explain why some fructose-containing food products, such as SSBs, are associated with intrahepatic lipid content, whereas other products, such as fruits, are not.

In addition, animal studies have revealed that F1-P functions as a signal molecule that stimulates intestinal absorption capacity as well as intrahepatic lipid storage (Fig. 1). The latter has also been demonstrated in humans who accumulate F1-P due to an inborn error of metabolism.

These data, combined with convincing, recent reports on the causal relationship between fructose consumption and intrahepatic lipid accumulation in humans, justify the development of KHK inhibitors in order to reduce F1-P and, consequently, to treat NAFLD. Future studies are warranted to demonstrate whether these compounds will also be beneficial in reducing the risk of cardiometabolic complications of NAFLD, as well as colorectal cancer.

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Conflicts of interest

There are no conflicts of interest.

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