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Title

Dietary fructose metabolism by splanchnic organs: size matters.

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Abstract

The initial metabolism of fructose is thought to primarily take place in the liver. Using stable isotope labelling and tissue/arterio-venous sampling, Jang et al. demonstrate that in mice, the small intestine is the primary site of fructose metabolism, raising important questions about fructose handling in humans.

Main body

Global health guidelines are calling for reductions in consumption of dietary sugars due to concerns over their potential role in disease. Prominent dietary sugars include sucrose, lactose and their constituent monomers, glucose, fructose and galactose. Of these, fructose has been identified as a primary candidate responsible for poor health outcomes resulting from high sugar intake. A high fructose intake can stimulate endogenous glucose production and lipid synthesis which can increase fasted and postprandial glucose and triglyceride concentrations. While the primary site of oral fructose metabolism was thought to be the liver, Jang *et al*. employ a sophisticated combination of stable isotopes, isotopomers and tissue/arterio-venous sampling to reveal that most ingested fructose is in fact, initially metabolised by the small intestine in mice (Jang *et al.*, 2018).

In humans, plasma fructose concentrations remain relatively low (<0.5 $mmol \cdot L^{-1}$), even when ingesting large fructose doses. Since peripheral tissues such as skeletal muscle have a low capacity for fructose metabolism, fructose is first heavily metabolised prior to entering the systemic circulation. The liver is one such organ with capacity for this initial phosphorylation due to a high abundance of ketohexokinase (Gonzalez *et al.*, 2017). Direct assessment of hepatic and intestinal metabolism *in vivo* is notoriously difficult due to (in)accessibility of these organs, and current knowledge

in this area could therefore be considered a black box. However, these new data from Jang *et al.* (2018) demonstrate that ~90% of fructose phosphorylation occurs in the jejunum, duodenum or ileum of mice following low fructose doses (<0.5 g·kgBM^{-1}). These findings therefore advance our fundamental understanding of mammalian fructose metabolism from an integrative perspective.

Orally ingested fructose is primarily converted into other substrates which circulate in plasma for oxidation by tissues (Tappy & Le, 2010). Major pathways of fructose metabolism include conversion to glucose and lactate. By sampling blood from the portal vein, Jang *et al.* (2018) demonstrate that low-dose fructose ingestion results in the majority of fructose appearing in the portal blood as glucose and lactate (~60%), with less than 20% appearing as fructose . This suggests that low fructose doses expose the liver to a similar metabolic milieu as does glucose ingestion. This then raises some important questions in relation to observations in humans, such as why fructose ingestion would therefore accelerate liver glycogen synthesis, stimulate hepatic *de novo* lipogenesis and exacerbate postprandial lipaemia (Tran *et al.*, 2010; Fuchs *et al.*, 2016; Gonzalez *et al.*, 2016).

The answers to these questions may lie in the interaction between the fructose dose and relative organ sizes. As highlighted by Jang *et al.* (2018), the role of the small intestine in fructose metabolism may not be conserved across species. Humans are renowned for having a relatively small gut; thought to be an evolutionary adaptation to energy dense food, thereby allowing greater brain size. Indeed, relative to body mass, humans have a smaller intestinal surface area compared to rodents (Casteleyn *et al.*, 2010). This may have consequences for the relative importance of the gut and the liver with respect to fructose metabolism. For example, in mice, the incremental dose of fructose from 0.5 to 1.0 g·kgBM^{-1} dramatically shifts whole-body

fructose metabolism; the capacity of the small intestine is saturated, exposing the liver to more fructose. Under these conditions, the murine liver would be expected to exhibit alterations in glycogen and lipid metabolism had glucose only been ingested (Gonzalez *et al.*, 2016; Jang *et al.*, 2018). In contrast, the human small intestine and liver are relatively smaller, which may explain why fructose doses as low as ~0.1 $g \cdot kgBM^{-1}$ can elicit detectable increases in circulating fructose concentrations (Moore *et al.*, 2000) and 0.33 $g \cdot kgBM^{-1}$ is sufficient to stimulate *de novo* lipogenesis (Tran *et al.*, 2010).

The elegant dose-response data provided by Jang *et al*. (2018) indicate that at the above doses, none of the ingested fructose would appear in the portal blood as fructose in mice. Humans may therefore saturate the small intestine's capacity for fructose metabolism at lower relative doses than mice. Supporting this, when doses are scaled to body surface area (more appropriate for comparing mice and human oral dosing) the saturation of intestinal fructose metabolism would occur at only ~5 g sugar intake (e.g. ¼ of a banana). Whilst data in humans are needed to support or refute this hypothesis, the saturation of intestinal fructose metabolism at low fructose doses may thereby make differences in small intestine metabolism redundant with typical sugar intakes, shifting the focus back to the liver. In humans, high-dose fructose-glucose co-ingestion (1 to 3 $g \cdot kgBM^{-1}$) dramatically enhances liver glycogen synthesis compared to glucose only (Gonzalez *et al.*, 2017). Unfortunately, there is no available evidence to infer the liver glycogen responses to lower fructose doses in humans. A better understanding of the ability to generalise the dose-response of fructose ingestion from mice to humans should therefore be a research priority.

Defining a dose of fructose whereby metabolism is affected in such a way that health is impaired is not easy. Even when considering only humans, there may be sex

differences and/or effects dependent on absolute (g) *versus* relative ($g \cdot kgBM^{-1}$) quantities (Tran *et al.*, 2010), and the metabolic consequences of fructose also depend upon whole-body energy status. High fructose diets may only negatively affect metabolism during positive energy balance and when relatively sedentary (**Figure 1**). In fact, only very modest amounts of exercise seem to be required to obliterate many effects of fructose overfeeding, independent of energy balance (Egli *et al.*, 2013). Perhaps a high energy flux is why Tour de France cyclists display exquisite metabolic health even though it has been reported they consume up to 6.7 $g \cdot kgBM^{-1}$ sugar per day (Saris *et al.*, 1989).

Whilst there is clearly further work needed understand the precise metabolic fate of fructose ingestion in humans, the work by Jang *et al.* provides an important step forward in our current understanding of mammalian fructose metabolism. The potential for intestine-liver interactions in human fructose metabolism should not be neglected, as this may provide important links between diet and disease.

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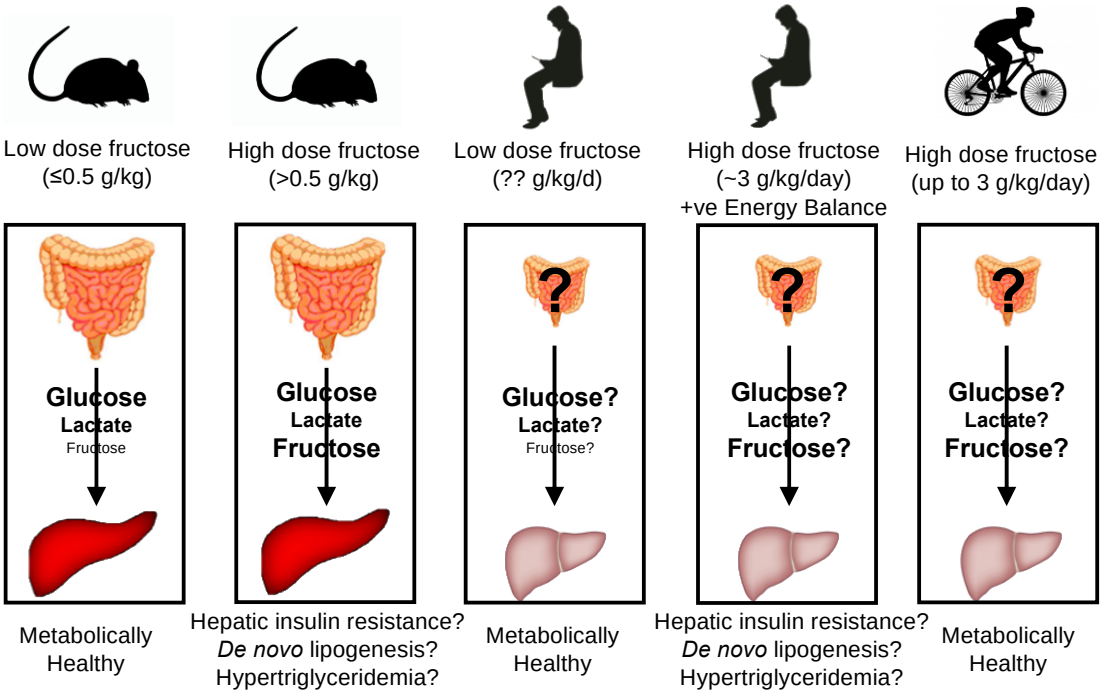

Figure 1. In mice, low doses of dietary fructose are primarily metabolized by the small intestine, exposing the liver primarily to glucose and lactate. High doses of fructose saturate the intestinal capacity to metabolize fructose, exposing the liver to higher fructose concentrations. Assuming this intestinal metabolism is conserved in humans, due to a relatively small gut it is unknown at what point intestinal fructose metabolism is saturated in humans. In humans, the metabolic fate of fructose depends not only on organ and body size, but also whole-body energy flux.

Selected Reading

Casteleyn C, Rekecki A, Van der Aa A, Simoens P & Van den Broeck W. (2010). Surface area assessment of the murine intestinal tract as a prerequisite for oral dose translation from mouse to man. *Lab Anim* **44,** 176-183.

Egli L, Lecoultre V, Theytaz F, Campos V, Hodson L, Schneiter P, Mittendorfer B, Patterson BW, Fielding BA, Gerber PA, Giusti V, Berneis K & Tappy L. (2013). Exercise prevents fructose-induced hypertriglyceridemia in healthy young subjects. *Diabetes* **62,** 2259-2265.

Fuchs CJ, Gonzalez JT, Beelen M, Cermak NM, Smith FE, Thelwall PE, Taylor R, Trenell MI, Stevenson EJ & van Loon LJ. (2016). Sucrose ingestion after exhaustive exercise accelerates liver, but not muscle glycogen repletion when compared to glucose ingestion in trained athletes. *J Appl Physiol* **120,** 1328-1334.

Gonzalez JT, Fuchs CJ, Betts JA & van Loon LJ. (2016). Liver glycogen metabolism during and after prolonged endurance-type exercise. *Am J Physiol Endocrinol Metab* **311,** E543-553.

Gonzalez JT, Fuchs CJ, Betts JA & van Loon LJ. (2017). Glucose Plus Fructose Ingestion for Post-Exercise Recovery-Greater than the Sum of Its Parts? *Nutrients* **9**.

Jang C, Hui S, Lu W, Cowan AJ, Morscher RJ, Lee GR, Liu W, Tesz GJ, Birnbaum MJ & Rabinowitz JD. (2018). The small intestine converts dietary fructose into glucose and organic acids. *Cell metabolism* **27,** 351-361.

Moore MC, Cherrington AD, Mann SL & Davis SN. (2000). Acute fructose administration decreases the glycemic response to an oral glucose tolerance test in normal adults. *J Clin Endocrinol Metab* **85,** 4515-4519.

Saris WH, van Erp-Baart MA, Brouns F, Westerterp KR & ten Hoor F. (1989). Study on food intake and energy expenditure during extreme sustained exercise: the Tour de France. *International journal of sports medicine* **10 Suppl 1,** S26-31.

Tappy L & Le KA. (2010). Metabolic effects of fructose and the worldwide increase in obesity. *Physiol Rev* **90,** 23-46.

Tran C, Jacot-Descombes D, Lecoultre V, Fielding BA, Carrel G, Le KA, Schneiter P, Bortolotti M, Frayn KN & Tappy L. (2010). Sex differences in lipid and glucose kinetics after ingestion of an acute oral fructose load. *Br J Nutr* **104,** 1139-1147.