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1 **Symposium overview: Fructose in Physiology**

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6 One of the first uses of the term “fructose” was in 1857 by William Allen Miller FRS,
7 and it was already known then that fructose was a distinctive carbohydrate,
8 characterised by sweet taste (Miller, 1957). In most circumstances dietary free sugars
9 can also be classified as fructose-containing carbohydrates (e.g. sucrose, high-
10 fructose corn syrup), and the fructose component of these sugars is thought to be
11 primarily responsible for unique metabolic effects. The role of sugars in the diet could
12 be viewed as contentious, with many arguing that dietary sugar is the cause of type 2
13 diabetes and obesity (Bray & Popkin, 2014), whereas others posit that dietary sugars
14 are innocuous to healthy individuals (Archer, 2018). One reason for this confusion and
15 conflict is that much evidence presented is observational and/or based upon self-
16 report assessments of dietary intake or physical activity. This is a problem, because
17 observational data can never definitely establish cause-and-effect and can lead to
18 spurious, misleading correlations. Furthermore, self-report methods are subject to
19 observation and reporting biases. Herein lies the potential for a physiological approach
20 to solve some of this confusion and conflict.

21 By understanding mechanistic links, we can explain some apparent
22 discrepancies in observational data, and also take a step towards establishing
23 causality. Plausible physiological links can increase confidence in causality of a
24 behaviour when randomized controlled trials with hard endpoints would be considered
25 unethical or impossible to perform. For example, it might be deemed unethical to
26 randomise people to high *versus* low fructose intakes for decades to establish whether
27 fructose intake causes type 2 diabetes or cardiovascular disease. However, by
28 assessing the effects of fructose intake of physiological process that underlie disease
29 risk, shorter-term studies can be used to establish causal effects of fructose intake,
30 without necessarily affecting long-term health risk.

31 “Fructose in Physiology: Friend or Foe” was the title of a Symposium delivered
32 at Europhysiology 2018 in London (UK), and was supported by *The Journal of*
33 *Physiology*. The aim of this symposium was to bring together leading researchers
34 across various career stages to discuss the physiology of fructose metabolism in

1 health and disease. In doing so, this symposium highlighted the potential mechanisms
2 by which fructose may exert metabolic effects within specific populations, thereby
3 overcoming some of the confusion around fructose and health.

4 Pinnick and Hodson (2019) describe the potential tissue- and sex-specific
5 effects of fructose metabolism. Short-term (<7 days) high-fructose intake can increase
6 plasma triglyceride concentrations and intrahepatic fat content, which are implicated
7 in metabolic disease risk (Pinnick & Hodson, 2019). The mechanisms by which high
8 fructose intake increases plasma triglyceride concentrations includes hepatic *de novo*
9 lipogenesis (*DNL*) and fatty acid oxidation (Pinnick & Hodson, 2019). A novel focus
10 was the discussion of the potential effects of fructose on adipose tissue metabolism,
11 which could be direct or indirect (Pinnick & Hodson, 2019). The classical view is that
12 the splanchnic tissues are the primary site of fructose metabolism (Gonzalez & Betts,
13 2018), and therefore adipose tissue is unlikely to be directly affected by fructose
14 intake. Nevertheless, fructose could indirectly affect adipose tissue metabolism *via*
15 increased plasma lactate concentrations following fructose consumption (Liu *et al.*,
16 2009; Gonzalez *et al.*, 2015). Furthermore, there is potential for some direct effects of
17 fructose on adipose tissue, since it has been recently estimated that ~15% of a 30-g
18 oral fructose load can escape first-pass splanchnic metabolism and thereby be
19 exposed to peripheral tissues (Francey *et al.*, 2019). In addition to evidence that
20 adipose tissue expresses the fructose-specific transporter, GLUT5, it is plausible that
21 fructose could have some direct effects on adipose tissue, and this will be an important
22 avenue for future research (Pinnick & Hodson, 2019). With respect to sex-specific
23 responses, there is some evidence that males may display greater metabolic
24 perturbations to high fructose intake when compared to females, including increased
25 incorporation of fructose carbons into very low-density lipoprotein (VLDL)-TAG
26 palmitate (reflective of hepatic *DNL*), greater suppression of fat oxidation, and
27 increased basal endogenous glucose production (Pinnick & Hodson, 2019). However,
28 other work has shown that females displayed higher hepatic *DNL* than males, when
29 assessed using deuterium oxide (Low *et al.*, 2018). The discrepancies between
30 studies may be explained by doses of fructose ingested (absolute vs normalised to
31 fat-free mass), the method of assessing hepatic *DNL*, or participant characteristics
32 and background diet. Accordingly, fructose can clearly stimulate lipogenesis in
33 hepatocytes, but there is a need to further understand the sex-specific effects of
34 fructose intake on metabolism and health.

1 Von Holstein-Rathlou and Gillum (2019) discuss a key potential regulator of
2 fructose intake, fibroblast growth factor 21 (FGF21). FGF21 is a hepatically-derived
3 hormone that, in mice, can be produced in response to low-protein and ketogenic
4 diets, fructose feeding and ethanol (von Holstein-Rathlou & Gillum, 2019). It has also
5 been shown that FGF21 preferentially inhibits *ad libitum* consumption of sugars and
6 ethanol in mice, without affecting the intake of other dietary nutrients such as non-
7 sugar carbohydrates, fat and protein, thereby exerting negative-feedback (von
8 Holstein-Rathlou & Gillum, 2019). In humans, ingestion of sugars and ethanol can also
9 stimulate FGF21 secretion, and genetic variants in the FGF locus have been
10 associated with reported intakes of sweet foods (Søberg *et al.*, 2017). The potential
11 mechanisms by which FGF21 is thought to regulate feeding behaviours is thought to
12 involve the activation of the FGF21 receptor complex (comprising FGF receptor 1c
13 and beta-klotho) in the paraventricular nucleus of the hypothalamus (von Holstein-
14 Rathlou & Gillum, 2019). This opens up the intriguing possibility of reducing free-living
15 sugar (and ethanol) intakes by treatment with FGF21 or by making use of other
16 strategies that can increase endogenous FGF21 production.

17 Fuchs *et al.* (2019) describe how athletes can exploit some of the metabolic
18 effects of fructose to benefit endurance performance and recovery. Intestinal fructose
19 absorption primarily occurs via GLUT5. This contrasts with glucose, which is primarily
20 absorbed via the sodium-dependent glucose transporter, SGLT1 (Fuchs *et al.*, 2019).
21 Since SGLT1 is thought to be saturable at a rate of 1 g/min this can limit the amount
22 of exogenous carbohydrate that athletes can ingest and metabolise during exercise.
23 However, by combining fructose with glucose it is possible to make use of both of
24 these intestinal transport pathways and thereby deliver more exogenous carbohydrate
25 to the circulation, whilst also decreasing gastrointestinal discomfort associated with
26 ingestion of large amounts of carbohydrate during exercise (Gonzalez *et al.*, 2015;
27 Fuchs *et al.*, 2019). A higher availability of carbohydrates during exercise can have
28 performance benefits in many endurance sports, thereby highlighting a potential
29 beneficial role of fructose-containing carbohydrates. Furthermore, rapid restoration of
30 depleted glycogen stores is a key factor dictating recovery time in multi-stage
31 endurance events. Since fructose can potently stimulate hepatic glycogen synthesis
32 (Fuchs *et al.*, 2016) there is potential for fructose-containing carbohydrates to
33 accelerate recovery. Indeed, when the total amount of carbohydrate is matched, the
34 ingestion of fructose-glucose mixtures can double the rate of liver glycogen repletion

1 in recovery from exercise, when compared to glucose-based carbohydrates (Fuchs *et*
2 *al.*, 2019). Furthermore, ingestion of fructose-containing carbohydrates during
3 recovery from exercise can enhance subsequent endurance running capacity, when
4 compared to glucose-based carbohydrates (Maunder *et al.*, 2018). Therefore, at least
5 for specific scenarios, fructose-containing carbohydrate can be useful for athletic
6 performance.

7 Whilst fructose ingestion may provide a benefit to certain athletic events, a
8 reasonable question to ask is whether such fructose intake is detrimental to the health
9 of athletes. Tappy and Rosset (2019) describe the potential for physical activity to
10 protect against the negative metabolic effects of high-fructose intake, independent
11 from total energy balance (i.e. when controlling for negative energy balance induced
12 by exercise). Whilst high-fructose intake can increase hepatic DNL, intrahepatic fat
13 content, hepatic insulin resistance and plasma triglyceride concentrations in sedentary
14 individuals, all these responses can be prevented under conditions of high physical
15 activity (Tappy & Rosset, 2019). Fructose ingested during conditions of high energy
16 output is thought to be directed more to lactate and glucose for utilisation as a fuel by
17 skeletal muscle, and less to triglycerides *via* DNL. The authors therefore speculate
18 that the negative metabolic health consequences of high-fructose intake occur when
19 fructose intake exceeds the capacity of the liver to release lactate and glucose for
20 skeletal muscle to utilise (Tappy & Rosset, 2019). This may be more likely to occur
21 under conditions of low energy output, where skeletal muscle utilisation of circulating
22 glucose and lactate is low. The authors propose that this could contribute to regulating
23 hepatic fructose metabolism *via* a feedback mechanism that is yet to be definitely
24 established.

25 Hengist *et al.* (2019) discuss a further potential mechanism that could explain
26 the protection against fructose-induced metabolic impairments conferred by high
27 levels of physical activity. Hepatic glycogen content plays a key role in regulating
28 hepatic lipid metabolism by acting on both DNL and on hepatic fatty acid oxidation
29 (Hengist *et al.*, 2019). Hengist *et al.* (2019) discuss the evidence that suggests
30 “pushing” glucose into the liver and saturating liver glycogen concentrations increases
31 DNL and hypertriglyceridaemia, whereas increasing the inherent capacity for liver
32 glycogen storage does not detrimentally alter plasma triglyceride concentrations. This
33 is consistent with the notion that net lipid synthesis is exacerbated when glycogen
34 stores are saturated. Therefore, under conditions where hepatic glycogen stores are

1 low, or are undergoing an increased rate of turnover, there is likely to be lower rates
2 of hepatic *DNL* and increased rates of hepatic fatty acid oxidation. The net result is
3 less lipid synthesis. Furthermore, this may contribute to the mechanisms explaining
4 why fructose can stimulate lipid synthesis to a greater extent than glucose, since
5 fructose potently stimulates hepatic glycogen synthesis at rest and post-exercise
6 (Petersen *et al.*, 2001; Fuchs *et al.*, 2016). Hepatic glycogen status may thereby
7 provide a key link between the energy status of an individual and the metabolic
8 responses to fructose intake.

9 In summary, this collection of review articles illuminates several key aspects of
10 fructose metabolism. It is clear that excessive fructose intakes in sedentary individuals
11 can induce a number of metabolic effects that may be detrimental to health. Whether
12 males or females are more sensitive to the effects of fructose intake remains to be
13 established. The hormone FGF21 could hold promise in reducing the levels of fructose
14 intake when a high-fructose intake is undesirable and could therefore contribute to
15 improvements in metabolic health. The metabolic effects of fructose ingestion can be
16 utilised to benefit endurance performance and recovery in athletes, and these athletes
17 seem to be protected against the negative metabolic effects of high-fructose intake.
18 The mechanisms underlying exercise-induced protection against these metabolic
19 effects remains to be established but may involve the greater conversion of fructose
20 into glucose and lactate for oxidation rather than conversion into lipid, and these
21 processes could be regulated by hepatic glycogen content. These physiological
22 mechanisms provide a better understanding of why specific populations seem to be
23 more or less vulnerable to high-fructose intakes and can be targeted for improving
24 metabolic health.

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