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REVIEW

Fructose-containing caloric sweeteners as a cause of obesity and metabolic disorders

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ABSTRACT

Compared with other carbohydrates, fructose-containing caloric sweeteners (sucrose, high-fructose corn syrup, pure fructose and fructose-glucose mixtures) are characterized by: a sweet taste generally associated with a positive hedonic tone; specific intestinal fructose transporters, i.e. GLUT5; a two-step fructose metabolism, consisting of the conversion of fructose carbones into ubiquitous energy substrates in splanchnic organs where fructolytic enzymes are expressed, and secondary delivery of these substrates to extrasplanchnic tissues. Fructose is a dispensable nutrient, yet its energy can be stored very efficiently owing to a rapid induction of intestinal fructose transporters and of splanchnic fructolytic and lipogenic enzymes by dietary fructose-containing caloric sweeteners. In addition, compared with fat or other dietary carbohydrates, fructose may be favored as an energy store because it uses different intestinal absorption mechanisms and different inter-organ trafficking pathways. These specific features make fructose an advantageous energy substrate in wild animals, mainly when consumed before periods of scarcity or high energy turnover such as migrations. These properties of fructose storage are also advantageous to humans who are involved in strenuous sport activities. In subjects with low physical activity, however, these same features of fructose metabolism may have the harmful effect of favoring energy overconsumption. Furthermore, a continuous exposure to high fructose intake associated with a low energy turnover leads to a chronic overproduction of intrahepatic trioses-phosphate production, which is secondarily responsible for the development of hepatic insulin resistance, intrahepatic fat accumulation, and increased blood triglyceride concentrations. In the long term, these effects may contribute to the development of metabolic and cardiovascular diseases.

KEY WORDS: Carbohydrate absorption, *De novo* lipogenesis, Fat storage, Lactate, Sugars, Insulin resistance

Introduction

Sugar is a generic name for soluble carbohydrates that elicit a sweet taste when present in the mouth. The granulated sugar most commonly used in food preparation is sucrose, a disaccharide made up of one molecule of glucose linked to one molecule of fructose, and refined mainly from sugar cane or sugar beets. Sucrose is also an early product of photosynthesis and is present, together with the monosaccharides glucose and fructose, in fruits and some vegetables, in honey, and in natural agave and maple syrups. Mixtures of glucose and fructose are also prepared industrially from starch and used as a sweetener in various industrial food products. In North America, these products are mainly manufactured from maize and known as high-fructose corn syrup (HFCS) (Hanover and White, 1993). Beside sucrose, glucose and fructose, other mono- and disaccharides such as galactose, lactose and maltose are also sugars, but these molecules have a lesser sweetening power than fructose-containing caloric sweeteners (FCCSs). Traditional European and North American diets were based on cereals, and hence on starch as a main carbohydrate source. Consumption of sugar has, however, undergone a marked increase from the nineteenth century onwards and now represents between 10% and 20% of our daily energy intake. Both starch and disaccharides are cleaved into monosaccharides by digestive enzymes. They are eventually absorbed into the blood stream as glucose and fructose, which can be metabolized to form starch, maltose or (when combined with equimolar amounts of fructose) sucrose. The unique effects of FCCs, which are absorbed as glucose and fructose, compared with starch, which is exclusively absorbed as glucose, are therefore closely linked to those of fructose.

Glucose and fructose share many physico-chemical and biochemical properties. Fructose is a keto-hexose whereas glucose is an aldo-hexose, but both have the same crude chemical formula ($C_6H_{12}O_6$) and energy density (3.75 kcal g^{-1}), have reducing properties, and spontaneously react with free amino groups, resulting in the non-enzymatic glycation of proteins. Both can be metabolized by some bacteria, resulting in the production of cariogenic acidic end-products in the oral cavity or of osmotically active end-products and gases when accidentally present in the large bowel. Given their structural similarity, it is not surprising that glucose and fructose share most of their metabolic pathways – the terminal part of glycolysis, pyruvate decarboxylation to acetyl-CoA, oxidation in the Kreb's cycle, and even temporary storage as glycogen. The presence of fructose in FCCSs nonetheless results in specific physiological events that are not normally elicited by the ingestion of glucose and starch. First, the fructose component of FCCSs is not a primary, ubiquitous energy substrate like glucose, and it is first processed into ubiquitous energy substrates in the splanchnic organs. In this two-step metabolism, the splanchnic organs act as a kind of buffer that regulates the delivery of fructose carbons and energy to systemic organs and tissues. Second, the presence of fructose and sucrose in the mouth elicits a sweet sensation, which is not the case with starch. The same sensation is also produced by free glucose, but in a normal human diet, glucose is always co-ingested with free fructose, either in fruits or fruit juices or in products sweetened with HFCS. It is therefore hardly an exaggeration to say that foods containing FCCSs have a sweet taste, whereas fructose-free foods do not. Both the specific, two-steps-metabolism of fructose and its unique sensorial properties mean that the ingestion of FCCSs has important functional consequences.

Metabolism of fructose through specific fructolytic enzymes

All mitochondria-containing cells of the human body are equipped with membrane glucose transporter proteins and glycolytic

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enzymes, Kreb's cycle enzymes, and proteins of the respiratory mitochondrial chain, which allow these cells to use glucose efficiently as a direct source of energy. Nearly all cells have also evolved to use fatty acids as an alternate source of energy when glucose is scarce. In contrast, many of the glucose transporters expressed in human cells, such as GLUT1, GLUT3 and GLUT4, as well as the initial glycolytic enzymes, the hexokinases, have low affinity for fructose. Hence, these cells cannot metabolize the intact fructose molecule as a direct source of energy. Interestingly, most highly specialized cells within the human body are unable to metabolize not only fructose but also many other dietary energy-containing substrates, such as galactose, alcohol and many amino-acids. Instead, the human liver, and that of many other animal species, has developed the capacity to process these substrates into glucose and fatty acids, which can subsequently be released into the systemic circulation. Lactate and acetate, as direct precursors of pyruvate and acetyl-CoA, respectively, can also be released as a ubiquitous energy substrate in this process (Campos and Tappy, 2016).

In humans, fructose is generally held as being metabolized almost completely in the liver, which synthesizes both fructose-specific (GLUT5) and glucose–fructose (GLUT2) membrane transporter proteins as well as a set of three specific fructose metabolizing enzymes. The first of these enzymes, ketohexokinase C (or fructokinase), catalyzes the phosphorylation of fructose to fructose-1-phosphate. The second, aldolase B, converts fructose-1-phosphate into one dihydroxyacetone phosphate (DHAP) and one glyceraldehyde. The third, triokinase, phosphorylates glyceraldehyde to yield glyceraldehyde-3-phosphate (GAP). Fructose's initial degradation into DHAP and GAP, also called fructolysis, is a close counterpart of the initial steps of glycolysis for glucose. Indeed, DHAP and GAP are involved in the final steps of glycolysis leading to the formation of pyruvate and acetyl-CoA, which feed into the Kreb's cycle and gluconeogenesis. However, glycolysis is closely regulated by a potent inhibition of phosphofructokinase by ATP and citrate, whereas fructokinase and aldolase B are essentially unregulated, with the consequence that all of the fructose that is transported into liver cells is almost immediately degraded, irrespective of cellular energy need. As a consequence, ingestion of large amounts of fructose as a single meal produces an excess fructose degradation into DHAP and GAP which, in the absence of a need for ADP regeneration, cannot enter the Kreb's cycle and are instead converted into lactate, glucose, and fatty acids.

Systemic blood fructose concentration increase only slightly after ingestion of fructose-containing foods, which is generally held to reflect a nearly complete first-pass fructose hepatic extraction. Liver is not the sole organ involved in fructose uptake: GLUT5 fructose transporters and fructose-metabolizing enzymes are also synthesized in small bowel enterocytes (Patel et al., 2015) and in renal proximal tubular cells (Diggle et al., 2009). Enterocytes and renal cells also synthesize: gluconeogenic enzymes, such as glucose-6 phosphatase, that enable them to release glucose into the bloodstream; lactate dehydrogenases and monocarboxylate transporters, which allow them to release lactate into the blood stream; and acetyl-CoA carboxylase and fatty acid synthase, which allow them to convert fructose-derived acetyl-CoA into fatty acids (Hao et al., 2011; Haidari et al., 2002). Fructose metabolism by enterocytes contributes to first-pass splanchnic fructose extraction, but the relative contributions of the human gut and liver in this process are not yet known.

The physiological functions of fructolytic intestinal and renal cells remain largely putative. In enterocytes, fructolysis may contribute to gut fructose absorption by decreasing the intracellular fructose concentration and generating an intraluminal–enterocyte concentration gradient that allows the facilitated diffusion of fructose. In renal proximal cells, fructolysis may merely contribute to the clearance of fructose that has escaped first-pass splanchnic metabolism. The functional significance of renal fructose metabolism, and more widely of overall extrahepatic fructose metabolism, remains largely unexplored. Interestingly, specific GLUT5 glucose transporters are present in several extrahepatic cell types, including adipocytes, skeletal muscle cells (Hajduch et al., 1998; Darakhshan et al., 1998) and some neurons and glial cells in discrete regions of the brain (Kojo et al., 2016). Many extrasplanchnic tissues also express low levels of a ketohexokinase A, an isoform of ketohexokinase C or fructokinase. How much fructose is metabolized in extrasplanchnic tissues and the functional consequences of this metabolism remain largely unknown. It has been reported that ketohexokinase A deficiency enhances fructose-induced adverse metabolic effects in mice, possibly by increasing the rate of splanchnic fructose metabolism relative to that of extrasplanchnic fructose metabolism (Ishimoto et al., 2012). It has also been reported that a switch from ketohexokinase C to ketohexokinase A in liver cells may be involved in the development of hepatocellular carcinoma (Li et al., 2016).

Sensorial effects of fructose-containing caloric sweeteners

The presence of some nutrients in our mouth activates taste receptors, the function of which is to produce a sensorial perception that provides cognitive clues to the nutritional values of foods. Five basic tastes are recognized: bitterness, which mainly conveys aversive responses and may prevent the consumption of potentially toxic foods; saltiness, which modulates the intake of sodium and hence contribute to hydro-mineral homeostasis; umami, which signals the presence of (presumably beneficial) proteins in foods; sourness, which essentially signal these presence of acidic compounds and may protect against excessive ingestion of potentially damaging dietary acids; and finally sweetness. Sugars and natural or artificial (industrial) sweeteners specifically activate G-coupled activated proteins that are expressed by taste bud cells. All sweeteners, whether natural (glucose, fructose and sucrose) or industrial (aspartame, saccharin and other 'artificial' sweeteners) interact with the same taste receptor, a heterodimeric G-protein-coupled receptor (GCPR) comprising Tas1R2 and Tas1R3. Sweet taste is often proposed to reinforce the consumption of energy-dense foods, but this explanation is disputable as most naturally occurring foods that contain sugars (i.e. fruits) are much less energy dense than starchy or lipid-rich foods.

Activation of sweet-taste receptors is generally associated with a high hedonic tone, which is perceived as a pleasant sensation. Animal studies have further shown that sugar consumption activates the mesolimbic, or dopaminergic, "reward" pathway in the brain. Activation of this pathway may play a role in the feeling of pleasure, and increases the motivation to obtain repeated exposure to the rewarding stimulus (Yamamoto, 2008). As such, sweet products may have an addictive potential, and several models of addiction to sugar have been described in laboratory rodents (Ahmed et al., 2013). The relevance of this for human obesity, and the existence of sugar addictions in humans, remain controversial (Westwater et al., 2016). Nonetheless, it is clear that sweet snacks and sugar-sweetened beverages make an important contribution to the daily energy intake of many of us, and that the pleasure associated with the consumption of sweet foods is a factor that is potentially responsible for overfeeding.

Interestingly, ingestion of either sucrose or sucralose (a calorie-free artificial sweetener) activates brain regions (anterior insula,

frontal operculum, striatum and anterior cingulate) that are involved in sweet taste perception, but only sucrose simultaneously activates the dopaminergic reward pathways in healthy women (Frank et al., 2008). Stimulation by sucrose of dopamine release was observed even in mice lacking sweet taste receptors (de Araujo et al., 2008). It is therefore likely that activation of sweet taste receptors and simultaneous signaling of meal energy content exert complex effects on hedonic tone. This has led some authors (Swithers, 2013) to express concern regarding the effects of non-nutritive sweeteners on food intake control and overall energy balance.

Gut fructose absorption

Intestinal fructose absorption is only partly elucidated. It is known to involve GLUT5 transporters at the luminal pole and GLUT2 transporters at the basolateral pole of enterocytes. The role of other glucose transporters (GLUT2 and SGLT1) at the luminal pole remain the subject of debate. Furthermore, the additional fructose transporters GLUT8 and GLUT12 are expressed in enterocytes and may be involved in the regulation of fructose absorption by dietary fructose itself (DeBosch et al., 2012).

In many healthy subjects, the acute administration of oral fructose causes abdominal discomfort, meteorism, or osmotic diarrhea. This is due to a relatively low capacity for gut fructose absorption compared with that for glucose absorption. Chronic fructose consumption stimulates the synthesis of GLUT5, GLUT2 (Jones et al., 2011b) and fructokinase (Roncal-Jimenez et al., 2011) in enterocytes and enhances the capacity for gut fructose absorption. Co-ingestion of glucose also facilitates fructose absorption (Douard and Ferraris, 2013). Interestingly, fructose absorption is particularly low in small children and tends to increase progressively with age. This is mainly explained by the induction of fructose transporters by dietary fructose itself. Very few GLUT5 fructose transporters are present at the luminal pole of the enterocytes of weaning rats, but these transporters increase in number progressively when fructose is added to the diet (Douard and Ferraris, 2013; Jones et al., 2011a,b).

Endogenous fructose production

Fructose can be synthesized endogenously from glucose through the polyol pathway (also called the “aldose reductase pathway”) in many tissues and organs, including testis and seminal vesicles, placenta, liver, muscle, and brain. This pathway involves the reduction of glucose to form sorbitol, which is associated with the consumption of one molecule of NADPH, followed by the oxidation of sorbitol to fructose, with production of one mole of NADH (Tang et al., 2012). This pathway is responsible for the provision of fructose as an energy substrate to spermatozoids in the seminal vesicles (Kobayashi et al., 2002). In the placenta, the same pathway is responsible for the higher fructose concentration in the umbilical cord than in maternal blood. This has been observed mainly in ungulates (Steinhauser et al., 2016), but placental fructose synthesis has been well documented in humans too (Maragoudakis et al., 1984; Trindade et al., 2011). The functional significance of this observation remains unknown, although some authors propose that fructose may act as a growth factor during normal fetal development (Bazer et al., 2012; Wang et al., 2016). In other tissues, endogenous fructose synthesis is mainly active when blood glucose concentrations exceed 7 mmol l^{-1} (Tang et al., 2012), and its physiological role remains largely unknown (Wang et al., 2016; Kim et al., 2012). It has nonetheless been suggested that endogenous fructose production may be associated with adverse metabolic effects (Lanaspa et al., 2013).

Acute metabolic effects of fructose compared with glucose

Many research reports indicate that adding FCCSs to the diets of various animal species causes profound metabolic disturbances. Experimental research protocols generally consist of either incorporating FCCSs into solid food or providing FCCS-containing drinking water, while leaving food and fluid intake unlimited. Such procedures causes a spectrum of metabolic disorders, ranging from mild, microvacuolar hepatic steatosis to the development of a full metabolic syndrome, i.e. visceral obesity, insulin resistance, diabetes mellitus, dyslipidemia, or high blood pressure (Bizeau and Pagliassotti, 2005; Bremer et al., 2011; Martinez et al., 1994).

The metabolic effects of FCCSs in humans remain the subject of debate, however, possibly due to limitations in the duration of intervention studies inherent to clinical research. The administration of pure fructose loads produces much smaller postprandial increases in plasma glucose and in insulin concentrations than does an isocaloric, pure glucose load, but larger increases in plasma lactate concentration (Swanson et al., 1992; Bantle et al., 1992). Both fructose and glucose nonetheless produce a large increase in net carbohydrate oxidation, together with a suppression of net lipid oxidation and an important drop in plasma free fatty acid concentrations (Delarue et al., 1993). The latter may possibly be explained by the slight increase in insulin observed after fructose ingestion, as adipose tissue lipolysis is extremely sensitive to insulin (Tappy et al., 1986). Hyperlactatemia may also directly inhibit adipose tissue lipolysis (Abdel-Sayed et al., 2008). The same pattern of response is observed when fructose is incorporated in a mixed meal also containing protein, fat and glucose (Theytaz et al., 2014).

The low glycemic response associated with pure fructose ingestion is mainly explained by the fact that fructose is initially metabolized in gut and liver cells independently of insulin, and then secondarily released as lactate and glucose. In this process, fructose ingestion dose-dependently increases fructose conversion into glucose (Delarue et al., 1993) while total glucose production remains under the regulation of insulin and glucagon, and hence fails to increase unless glucagon:insulin ratio increases (Surmely et al., 1999; Paquot et al., 1996; Tounian et al., 1994). This explains the low postprandial glucose response to fructose in non-diabetic subjects. In patients who have Type 2 diabetes, blood glucose increases substantially after fructose, but still remains lower than after isomolar amounts of glucose (Bantle et al., 2000; Simonson et al., 1988).

Short-term effects of high-FCCS diets on lipid metabolism

Several randomized controlled trials have assessed the short-term (a few days to a few weeks) metabolic effects of high-FCCS diets in healthy normal-weight and overweight subjects. Results differ according to study designs (i.e. addition of pure fructose or FCCSs to weight-maintenance diet, addition of FCCSs versus addition of glucose, or isocaloric substitution of fructose or FCCSs for other dietary components) (Rosset et al., 2016; Stanhope et al., 2013; Madero et al., 2011; Lowndes et al., 2014; Teff et al., 2009). Although the general interpretation and clinical relevance of these studies varies widely, their results concord in showing increases of both fasting and postprandial blood lipid concentrations in those on high-FCCS diets. This increase is highly statistically significant, but quantitatively small, and absolute blood triglyceride concentration remains within the normal range for most normal-weight subjects, even with very high dietary fructose content (Lecoultre et al., 2014). It may, however, increase to concentrations associated with increased cardiovascular risk in overweight and insulin-resistant subjects (Teff et al., 2009).

FCCS-induced dyslipidemia appears to be multifactorial: an increased hepatic *de novo* lipogenesis (Faeh et al., 2005; Stanhope et al., 2009), an increased rate of very low density lipoprotein (VLDL)-triglyceride secretion (Theytaz et al., 2012) and a decreased extrahepatic clearance of blood triglyceride (Jeppesen et al., 1995; Teff et al., 2004) have all been observed. Some of the circulating triglyceride-rich lipoproteins have a low density similar to that of chylomicrons (Theytaz et al., 2014) and may correspond to the fats produced from fructose in small bowel enterocytes, as has been documented in rodents (Haidari et al., 2002). Increased blood triglyceride concentrations are consistently observed when FCCSs are consumed together with an excess total energy intake, but not with weight-maintenance diets (Chiavaroli et al., 2015; David Wang et al., 2014). Some studies have nonetheless reported that isocaloric replacement of starch with FCCSs also increases blood triglyceride concentration and hepatic *de novo* lipogenesis (Schwarz et al., 2015; Egli et al., 2013).

Dietary FCCSs affect not only blood lipids but also intrahepatic fat content. Intrahepatocellular lipid concentration, as measured by *in vivo* ^{1}H magnetic resonance spectroscopy, increases rapidly and dose-dependently after FCCSs are added to the diet of healthy volunteers, although this effect is observed only when a large amount of fructose is added to the diet (Lecoultre et al., 2013). Furthermore, similar effects were reported after glucose was added to the diet (Ngo Sock et al., 2010; Johnston et al., 2013). As is the case for blood triglycerides, the observed increases are statistically significant but absolute amounts of intrahepatic fat remain within the normal range for most subjects. Addition of 3 g fructose per kg body weight per day increased intrahepatic fat concentration within 6–7 days, whereas addition of 1.5 g fructose per kg per day had no significant effect even after 4 weeks (Lê et al., 2006; Lê et al., 2009). Interestingly, blood triglyceride concentrations were significantly increased after one week on a 1.5 g kg^{-1} day^{-1} fructose diet, but then did not further increase when the same diet was continued for 4 weeks. This suggests that switching from a low- to a high-FCCS diet is associated with early adaptive changes in splanchnic carbohydrate metabolism. Longer studies are unfortunately lacking to assess whether dietary FCCSs produce additional metabolic changes in the very long term. Nonetheless, two studies have reported that intrahepatic fat concentrations decreased significantly in overweight adults when the sugar-sweetened beverages that they consumed were replaced by artificially sweetened beverages (Campos et al., 2015), or in obese children when dietary fructose was isocalorically substituted by starch (Schwarz et al., 2017).

Importantly, a small number of clinical trials have observed that subjects fed a high-energy, high-fructose diet store significantly more fat in visceral adipose depots than do control subjects fed isocaloric high-glucose diets (Stanhope et al., 2009; Maersk et al., 2012). The mechanisms by which fructose may specifically favor visceral fat storage remain unknown. Such an effect, if confirmed by larger studies, would be highly concerning, given the close association between visceral obesity and the risk of developing metabolic and cardiovascular diseases.

Short-term effects of high-FCCS diets on glucose homeostasis

Many clinical trials have assessed short-term effects of high-FCCS diets on glucose homeostasis in normal-weight and overweight or obese subjects. Here again, the results of these studies are consistent. Fasting blood glucose and insulin may increase slightly with FCCSs and excess energy intake, mainly in overweight subjects (Stanhope et al., 2009). These changes may be related to a small but significant increase in fasting hepatic glucose production (Lecoultre et al., 2014; Faeh et al., 2005). Similarly, addition of FCCSs to the usual diet enhanced blood-glucose concentrations after an oral glucose-tolerance test (Stanhope et al., 2009) and blunted insulin-induced suppression of glucose production, indicating that the addition of FCCSs decreased hepatic insulin sensitivity (Faeh et al., 2005; Aeberli et al., 2013). By contrast, insulin-mediated whole-body (presumably mainly muscle) glucose disposal was not altered in the vast majority of studies that measured it directly with hyperinsulinemic euglycemic clamps (reviewed by Ter Horst et al., 2016; Tappy and Le, 2015). It therefore appears that, in the short term, a high-fructose diet may cause a mild glucose intolerance, essentially by producing mild hepatic insulin resistance, but it does not reproduce the severe hepatic insulin resistance or induce the muscle insulin resistance that are both observed in Type 2 diabetes mellitus. These conclusions rest on short-term interventions however, and the effects of exposure to FCCSs over several years or decades, as occurs in real life, remain speculative. One may nonetheless speculate, on the basis of the consistent positive associations between FCCS consumption and obesity and between FCCS consumption and the risk of developing diabetes and cardiovascular diseases (Lean and Te Morenga, 2016; Te Morenga et al., 2012; Huang et al., 2014), that deleterious effects of FCCSs may be closely dependent on excess body-fat mass and visceral obesity.

Metabolism of fructose ingested during exercise

It is well documented that glucose is a key energy substrate for the exercising muscle, mainly when working at high power output. It is also recognized that the whole-body carbohydrate reserve is limited to a few hundred grams of glycogen stored in the liver and skeletal muscle. Glucose or dietary compounds that release glucose in the gut (maltose and maltodextrins) are, of course, prime dietary substrates for exercising athletes as, unlike fructose, these substrates can be used directly for muscle energy production. The ingestion of exogenous glucose and maltodextrins during exercise does indeed increase whole-body carbohydrate oxidation dose-dependently, until this process reaches a maximum at an ingestion rate of about 1 g min^{-1} of glucose or maltodextrin. Surprisingly, when this maximum is reached, any further increase in glucose ingestion rate is ineffective but ingestion of fructose in addition to glucose further increases total exogenous carbohydrate oxidation (Hulston et al., 2009). Furthermore, ingestion of glucose-fructose drinks at rates allowing maximal carbohydrate oxidation was also shown to improve exercise performance (Currell and Jeukendrup, 2008).

The mechanisms underlying the putative ergogenic effects of fructose remain only partially elucidated. Glucose absorption is limited by, among other factors, the number of SGLT1 transporters on the luminal side of enterocytes. As a consequence, high glucose ingestion rate fails to increase systemic glucose delivery and total carbohydrate oxidation when intestinal glucose transport has reached its maximum. In contrast, the addition of fructose, which uses different transporters, results in a net increase in the intestinal absorption of hexoses (Jeukendrup, 2010).

Metabolism of fructose ingested with glucose during and after exercise

It has been reported on many occasions that ^{13}C-label in fructose that is ingested during exercise is quickly eliminated as breath $^{13}CO_2$, indicating that fructose can provide energy to the working muscle (Jandrain et al., 1993). Interpretation of ^{13}C-labeled fructose studies is difficult, however, as $^{13}CO_2$ can eventually be produced

from direct fructose oxidation, or from the oxidation of lactate, glucose, or fatty acids synthesized from fructose (Sun and Empie, 2012). Simultaneous monitoring of all these pathways with the use of labeled metabolites is complex and requires major assumptions. Such studies provide a fair picture of fructose metabolism, but nonetheless fall short of providing accurate figures for each metabolic pathway used for fructose carbon disposal.

One recent study provided important novel information about how fructose is metabolized in exercising humans (Lecoultre et al., 2010). In this study, participants were studied on two occasions during exercise. On one occasion, they ingested 2 g min^{-1} unlabeled glucose, together with tracer infusions of ^{2}H-labeled glucose and ^{13}C-labeled lactate to allow calculation of their systemic glucose appearance, lactate kinetics, and lactate oxidation. On a second occasion, the same experiment was repeated but the participants ingested 1.2 g min^{-1} unlabeled glucose plus 0.8 g min^{-1} unlabeled fructose. Finally, the same exercise protocol was performed a third time with administration of 1.2 g unlabeled glucose and 0.8 g ^{13}C-labeled fructose, and to allow calculation of the contribution of fructose to systemic lactate and glucose production. The overall results indicated that total carbohydrate oxidation was higher when subjects ingested 2 g min^{-1} of a glucose-fructose mixture than 2 g min^{-1} pure glucose. It was further observed that this was due to both a higher systemic rate of glucose appearance and a higher systemic rate of lactate appearance and lactate oxidation when fructose was in the mixture. These results are certainly consistent with the hypothesis that total hexose absorption is higher with the fructose-glucose mixture than with pure fructose because of the use of different intestinal transporters for glucose and fructose. It further indicates that some of the absorbed fructose is converted into glucose in splanchnic organs and hence increases glucose delivery to exercising muscle. The results also indicate that fructose conversion into lactate (presumably in splanchnic tissues) increases total lactate production (presumably in splanchnic fructolytic organs) and total lactate oxidation (presumably in exercising muscle). This clearly indicates that fructose provides additional energy substrate to the muscle through a splanchnic tissue to muscle lactate shuttle.

One recent study further documented the relationship between the ingestion of FCCSs and lactate metabolism at rest and during exercise (Rosset et al., 2017c). In this study, healthy volunteers had their lactate production and oxidation measured with intravenous tracer infusion of ^{13}C-labeled lactate while receiving oral sucrose drinks, first at rest then during exercise. At rest, blood lactate concentration increased significantly after sucrose infusion. Systemic lactate production was not measured under fasting conditions, but the values measured after sucrose were 2–3 times higher than the fasting values reported in the literature. About 20% of the lactate that was produced was oxidized, whereas 80% was disposed of non-oxidatively. During exercise, the production of lactate increased about threefold, and 80% of it was oxidized.

Interestingly, another recent study compared the effects of liquid meals containing fat, protein, and either glucose or fructose on muscle energy repletion after a strenuous bout of exercise in healthy trained volunteers (Rosset et al., 2017b). Unexpectedly, fructose drinks were as effective as glucose drinks in replenishing muscle glycogen stores. Compared with glucose drinks, fructose drinks were associated with lower blood glucose and insulin levels but higher blood-lactate concentrations.

Altogether, these results are consistent with the hypothesis of a splanchnic to muscle fructose lactate shuttle (Tappy and Rosset, 2017; Rosset et al., 2017a). They suggest that a relatively small amount of fructose carbons are released as lactate by splanchnic organs under resting conditions, and that the lactate that is released under these conditions is mainly metabolized non-oxidatively. Splanchnic lactate production increases dramatically in fructose-fed subjects during exercise, and the lactate thus produced is essentially oxidized for energy production. Finally, splanchnic conversion of fructose into lactate may possibly play a role in the post-exercise replenishment of muscle glycogen stores.

Overview of fructose metabolism with a functional perspective

There is a large body of evidence to show that the ingestion of pure fructose, or of FCCSs, acutely stimulates gluconeogenesis and *de novo* lipogenesis in the splanchnic tissues of healthy individuals, and that a high-FCCS diet can cause potentially adverse effects on blood glucose and lipid levels, and on the levels of intrahepatic lipids in sedentary subjects. There is also strong evidence that athletes can consume large daily doses of FCCSs without apparent adverse effects. There is also emerging evidence that FCCSs may confer some energetic advantage during exercise. These apparently contradictory observations may be explained by the two-step metabolism of fructose, which involves an initial processing of fructose carbons into lactate, glucose, and fatty acids in splanchnic cells expressing fructokinase and aldolase B. For any given amount of fructose ingested, the fate of the fructose's carbon varies according to other environmental factors. One may therefore propose the following model (Tappy and Rosset, 2017) to account for the effects of dietary fructose on lipid and glucose homeostasis. (1) Fructose uptake and conversion to trioses-phosphate is directly proportional to dietary fructose absorption from the gut. The higher the fructose intake, the higher the rate and amount of triose-phosphate generated in fructose-metabolizing splanchnic organs. One can postulate that the triose-phosphate generated in this way will be preferentially metabolized in pathways that require less energy in order to use energy as efficiently as possible. According to this scheme, the triose-phosphate would be preferentially oxidized *in situ*, and/or converted into lactate as these metabolic processes will occur with minimal energy loss to heat. Gluconeogenesis and *de novo* lipogenesis would be used as a second choice, once the preferred pathways are saturated, as both processes consume substantial amounts of ATP (Tappy et al., 2013). Any adverse metabolic effects of fructose would therefore be observed mainly under conditions where fructose disposal through lactate is quantitatively small. (2) The maximal rate of lactate synthesis from fructose and its limiting factors remain largely speculative at this time (Fig. 1). One may postulate, however, that splanchnic lactate production depends on splanchnic ATP turnover, on splanchnic redox conditions, and on the concentration gradient between the intracellular lactate in the splanchnic tissues and blood lactate; the amount and functional activities of key enzymes, such as lactate dehydrogenase, and of lactate transporters will also be involved. Splanchnic lactate production will, however, also depend on extra-splanchnic lactate metabolism, which will impact on blood lactate concentrations. During exercise, increased ATP turnover markedly stimulates tricarboxylic cycle activity and oxidative phosphorylation in oxidative muscle fibers, and may therefore favor the uptake of lactate by muscle and its oxidative degradation to CO_2. (3) During periods of physical inactivity, whole-body ATP turnover is low, and splanchnic lactate production may be quickly inhibited by increasing blood lactate concentration. Under these

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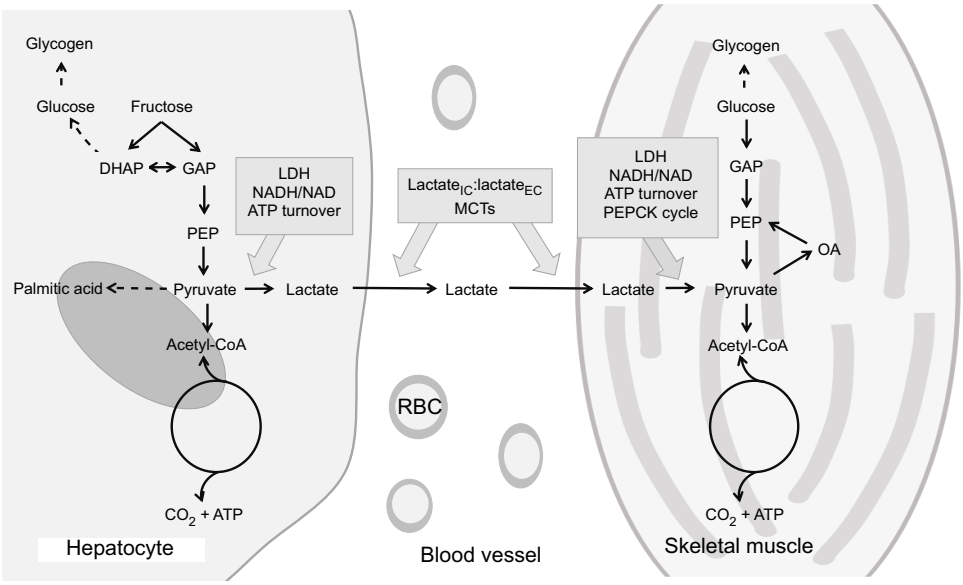

Fig. 1. Proposed regulatory steps for lactate synthesis and release in the liver. LDH-catalysed pyruvate conversion into lactate in the liver is activated when hepatic fructose uptake and conversion into pyruvate exceeds liver energy needs and NADH:NAD ratio is high. At high fructose intake in resting conditions, lactate production linked to a low muscle lactate uptake increases blood lactate concentration. One can hypothesize that this inhibits lactate efflux as a result of a low intracellular to extracellular lactate gradient. During exercise, a high muscle ATP turnover will favor muscle lactate oxidation. This will decrease intramuscular lactate concentration, increase transport of blood lactate into muscle, and decrease blood lactate concentration. As a consequence of this higher blood lactate turnover, transfer of fructose carbons as lactate to skeletal muscle will be enhanced. DHAP, dihydroxyacetone phosphate; EC, extracellular; GAP, glyceraldehyde 3-phosphate; IC, intracellular; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter; NADH, reduced nicotinamide-adenine dinucleotide; OA, oleic acid; PEP, phosphoenolpyruvate; PEPCK, phosphoenolpyruvate carboxykinase; RBC, red blood cell.

conditions, fructose disposal may initially switch to gluconeogenesis because this process is associated with a significant, yet relatively modest, energy cost when compared with *de novo* lipogenesis. As for lactate production, splanchnic glucose output is closely regulated by both insulin and blood glucose itself, and hence is quantitatively limited in resting conditions. *De novo* lipogenesis is highly energy inefficient, and therefore may be activated mainly when triose-phosphate generation and splanchnic lactate production have reached their maximal rates relative to overall energy turnover. This process can be increased to some extent with a single administration of fructose, but will really become quantitatively important when fructose intake remains high over several days and the expression of lipogenic enzymes increases.

This model, attempting to describe how fructose metabolism varies according to total energy turnover, is hypothetical at this stage and rests on many assumptions that remain to be addressed. The rapid advances in non-invasive methods allowing to assess organ-specific metabolism will hopefully bring important novel information allowing us to fill gaps in the near future.

Overview

Fructose and sucrose, as end-products of plant photosynthesis, have always been present in the human diet and in that of many animals, including insects, reptiles, birds, and mammals. Evolution has favored glucose as a prime energy substrate and fatty acids as a prime energy-storage molecule, and hence fatty acids are the second most metabolized (after glucose) and a nearly ubiquitous energy substrate. Metabolism of fructose, like that of galactose, the other non-glucose hexose present in substantial amounts in the diets of mammals, has evolved to involve an initial processing step that takes place in splanchnic organs such as the gut, liver, and kidney (Mayes, 1993). These specialized organs synthesize a set of fructose-metabolizing enzymes and process fructose carbons into ubiquitous energy substrates such as lactate, glucose, and fatty acids. In a second step, these energy substrates are transported to extrasplanchnic tissues where they are metabolized to release their energy. This two-step metabolism uses fructose's energy while avoiding the need to synthesize specific fructose-metabolizing enzymes in all cells of the organism. Overall, however, it is energetically inefficient because fructose conversion into glucose and fat is associated with energy loss as heat.

Interestingly, all mammals consume carbohydrates in their diet and use glucose as an energy substrate. Mammalian herbivores absorb and use most of their dietary carbohydrates after they have been converted into short-chain fatty acids by gut bacteria, yet they can absorb glucose and fructose and they synthesize fructolytic enzymes (Buddington et al., 1991). Although sucrose and fructose represent a minor portion of the energy intake of mammalian herbivores, the majority being in the form of complex polysaccharides, these animals also express sweet taste receptors in their oral cavity, presumably signaling that FCCSs can be valuable energy sources for them. Most other mammals, including humans, eat both plants and other animals or animal products. Their diet therefore contains less carbohydrate and more fat and protein than that of herbivores. Unlike herbivores, non-herbivorous mammals have lost the ability to digest complex plant polysaccharides in order to spare the cost of maintaining a large fermentative gut. The FCCSs that are present in plants and fruits usually represent a small proportion of the daily energy intake of such mammals, although this proportion will vary greatly from season to season. Interestingly, non-herbivorous mammals have developed the ability to adapt the absorptive ability of their gut by increasing the amount of glucose and fructose transporters in proportion to the amount of free sugar present in their diet. Like herbivores, they synthesize fructolytic enzymes in the gut, liver and kidney, and

sweet taste receptors in their oral cavity. They also express sweet taste receptors in some gut endocrine cells, which may contribute to the enhancement of gut hexose transporters in response to a high-FCCS diet. Among mammals, only carnivores, such as cats and dolphins, no longer express sweet taste receptors (Jiang et al., 2012). These animals do not seek sweet foods but can tolerate carbohydrate, including fructose in moderate amounts [although they are prone to develop hyperglycemia owing to a lack of hepatic glucokinase (Schermerhorn, 2013)]. They can even use fructose's energy, as they synthesize fructolytic enzymes in their liver (Springer et al., 2009). However, dietary sugars fail to enhance the gut hexose absorptive capacity of these animals as they do for other mammals (Buddington et al., 1991).

The remarkable conservation of specific metabolic pathways in so many different animal species indicates that the ability to use dietary FCCSs as an energy substrate has conferred significant advantages during evolution. Fructose metabolism appears mainly suited to allow the use of as much dietary energy as possible whenever it is available. Compared with most other dietary energy substrate, fructose presents three key features that make it particularly well suited for rapid energy assimilation and storage. (1) First, key transporters and enzymes, which are involved in intestinal absorption of FCCSs and in fructose uptake and conversion to glucose, lactate and fatty acids in splanchnic organs, are expressed at low levels when animals consume a low-FCCS diet. They are upregulated within a few days when animals switch to a high-FCCS diet. In addition, FCCSs (mainly sucrose in wild foods, refined sucrose, HFCSs and honey) almost invariably contain almost equal amounts of fructose and glucose. These two hexoses mutually enhance each other's metabolism: glucose by increasing gut fructose transport, and fructose by indirectly activating liver glucokinase and hepatic glucose storage. (2) Second, fructose is initially metabolized into ubiquitous substrates in splanchnic organs. FCCSs therefore provide an ample supply of glucose and lactate that can be readily oxidized to support ATP synthesis in working muscles or that can rapidly replenish hepatic and muscle glycogen stores after exercise. Furthermore, the fructose component of these metabolites can be rapidly converted into fat, allowing efficient energy storage with minimal body-mass gain. (3) Trafficking of lactate, glucose and fat synthesized from fructose uses pathways that are distinct from those used for dietary starch or fat (Fig. 2). Fructose is absorbed through distinct intestinal transporters (separate from those used to transport glucose, including starch-derived glucose), and can therefore further enhance the total absorption of hexoses when SGLT1 glucose transporters are saturated. Some of the fructose carbons are made available to extrahepatic tissue as lactate, thus providing additional energy substrate when glucose production and intracellular transport may be limited. Fructose, unlike dietary fat, does not rely on classical pathways for dietary fat digestion and intestinal absorption, nor entirely on the secretion of chylomicrons in lymph. Instead it is mainly converted into fat in the liver, and then directly secreted into the blood as VLDL-triglycerides.

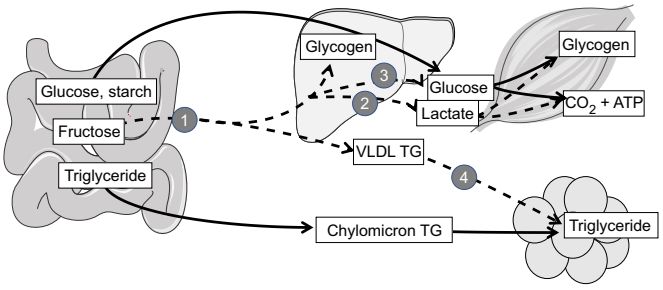

Fig. 2. Overview of processes involved in fructose metabolism. (1) Gut fructose extraction and metabolism to lactate, glucose or fat. (2) Fructolysis leading to lactate release in hepatocytes. (3) Hepatic gluconeogenesis. (4) *De novo* lipogenesis and very low density lipoprotein (VLDL)-triglyceride (TG) secretion. Solid arrows represent the (mainly extra-hepatic) metabolism of glucose and triglyceride absorbed from the gut. Dotted arrows indicate the two steps in the metabolism of fructose absorbed from the gut lumen: fructolysis linked to lactate production/gluconeogenesis/de novo lipogenesis in the enterocytes, liver and kidney, followed by metabolism of lactate, glucose and triglyceride in extra-splanchnic cells.

The use of distinct intestinal absorptive systems and inter-organ trafficking pathways for fructose may account for the unique energy assimilation capacity provided by FCCS diets. These special features were most probably advantageous for early humans in providing them with the ability to accumulate body energy when food was available and thus to optimize survival during periods of food scarcity. They are still essential for the rapid accumulation of energy reserves by some birds during the period immediately preceding migration, and in hibernating animals before the start of winter (Johnson and Murray, 2010). Unfortunately, these features have become a burden to many modern humans who consume FCCSs in their diet continuously rather than seasonally, for whom cheap, energy-dense foods are widely available, and who experience the decreased level of physical activity that results from urbanization and the development of sedentary work.

Competing interests
The author declares no competing or financial interests.

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