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Narrative Review

Metabolism of sugars: A window to the regulation of glucose and lipid homeostasis by splanchnic organs

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SUMMARY

Background &aims: Dietary sugars are absorbed in the hepatic portal circulation as glucose, fructose, or galactose. The gut and liver are required to process fructose and galactose into glucose, lactate, and fatty acids. A high sugar intake may favor the development of cardio-metabolic diseases by inducing Insulin resistance and increased concentrations of triglyceride-rich lipoproteins.
Methods: A narrative review of the literature regarding the metabolic effects of fructose-containing sugars.
Results: Sugars' metabolic effects differ from those of starch mainly due to the fructose component of sucrose. Fructose is metabolized in a set of fructolytic cells, which comprise small bowel enterocytes, hepatocytes, and kidney proximal tubule cells. Compared to glucose, fructose is readily metabolized in an insulin-independent way, even in subjects with diabetes mellitus, and produces minor increases in glycemia. It can be efficiently used for energy production, including during exercise. Unlike commonly thought, fructose when ingested in small amounts is mainly metabolized to glucose and organic acids in the gut, and this organ may thus shield the liver from potentially deleterious effects.
Conclusions: The metabolic functions of splanchnic organs must be performed with homeostatic constraints to avoid exaggerated blood glucose and lipid concentrations, and thus to prevent cellular damages leading to non-communicable diseases. Excess fructose intake can impair insulin-induced suppression of glucose production, stimulate de novo lipogenesis, and increase intrahepatic and blood triglyceride concentrations. With chronically high fructose intake, enterocyte can switch to lipid synthesis and accumulation of triglyceride, possibly causing an enterocyte dysfunction.

1. Introduction: the coordination between splanchnic and peripheral organs for energy production

Our food contains a variety of energy-rich nutrients, i.e. carbohydrate, lipids, proteins, or alcohol which are digested and absorbed into the blood stream mainly as monosaccharides, triglycerides, fatty acids, amino-acids and alcohol, to be eventually oxidized to produce the energy required by the cells that compose our organism. Among energy-rich substrate, dietary fibers are polysaccharides which cannot be digested by human gut enzymes, but are nonetheless degraded by gut microbiota to lactic acid and short-chain fatty acids, which can be subsequently absorbed in the blood and be oxidized by our cells for energy production [1]. The digestive tract therefore makes an important contribution to whole body metabolism by controlling the digestion of macronutrients such as starch, sugars, dietary fibers and protein into smaller units and their rate of absorption in the blood stream. This results in the appearance in the blood, mainly in the hepatic portal circulation, of a large variety of compounds, the main ones being glucose, fructose, galactose, lactic acid, acetate, propionate, butyrate, alcohol, and twenty different amino acids! However, the human organism is constituted of many highly specialized organs and tissues, whose cell cannot afford to produce continuously all the enzymes required for the metabolism of so many different compounds and who rely almost exclusively on glucose, lactate or fatty acids for their energy production. We will try to illustrate here how the splanchnic organs, and more specifically the gut, liver, and kidneys contribute to process dietary sugars, who are mainly made up of the monosaccharides glucose, fructose and galactose in order to deliver their energy content to all cells of the organism.

Sugars have long been recognized as a key source of energy for the human organism, and as prime substrates to support physical exercise [2]. However, there has been growing concern, over the

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past 30 years or so, that a high sugar intake may favor the development of cardio-metabolic diseases, i.e. obesity, diabetes, and cardiovascular diseases (CVDs) [3]. These conditions not only are major causes of morbidity and mortality worldwide, but in addition represent risk factors for severe forms of COVID-19 [4]. We will therefore attempt to briefly summarize the main mechanisms by which sugars may favor the development of these diseases, and the potential contribution of splanchnic organs in this process.

2. Insulin resistance and increased concentrations of triglyceride-rich lipoprotein particles as factors linking sugar consumption and cardiometabolic diseases

During the second part of the twentieth century, tremendous progress was made regarding the pathophysiology of type 2 diabetes mellitus and its complications. The availability of a radioimmunoassay for insulin allowed to document that subjects with type 2 diabetes still secreted insulin, and were even sometime hyperinsulinemic [5]. The presence of insulin resistance in patients with type 2 diabetes and in some obese patients was largely documented, mainly with the use of functional tests such as the hyperinsulinemic euglycemic clamp [6] or the frequently sampled iv glucose tolerance test-based minimal model [7]. Furthermore, with the use of glucose tracers to quantify whole body glucose fluxes, it was observed that type 2 diabetic patients had both muscle and liver insulin resistance, and that a relative insulin deficiency, an impaired insulin-mediated glucose uptake in insulin sensitive tissue, and an increased hepatic glucose production were all simultaneously at work to cause hyperglycemia [8]. Around the same time, it was also recognized that obesity and type 2 diabetes mellitus were tightly associated with alterations of blood lipids, and with coronary heart diseases and hypertension. This led to the recognition of a link between insulin resistance and several non-communicable diseases, which further proceeded to the identification of the metabolic syndrome [9]. One proposed mechanism responsible for this link was the presence of increased VLDL-TG secretion and postprandial hypertriglyceridemia, which developed because of insulin resistance and was in turn a cause of cardiovascular diseases. Research performed in the subsequent decades indicated that an increased visceral adipose tissue mass, due either to a preferential storage of excess energy in visceral adipose tissue [10] or to an impaired safe storage of fat in subcutaneous adipose tissue [11], was tightly associated with this, and that postprandial increases in triglyceride-rich lipoprotein particles (TRL) and of their remnants was directly associated with the pathogenesis of atherosclerosis [12]. We will therefore focus on attention of the effects of dietary sugars on insulin sensitivity and blood TRL subfractions as the more likely mediators toward cardiometabolic diseases.

3. Metabolism of an acute fructose or galactose load differs from that of glucose

In healthy human subjects, about 15–25% of ingested glucose is metabolized in the gut and liver, where it is mainly used to restore hepatic glycogen stores. In the liver, glucose is phosphorylated to glucose-6-phophate by the enzyme glucokinase, and then is degraded to pyruvate in the glycolytic pathway. The amount of glucose undergoing glycolysis is tightly regulated at the level of the enzyme phosphofructokinase, which is inhibited when intracellular ATP and citrate concentration increase. The amount of glucose escaping splanchnic metabolism reaches the systemic circulation, and arterial blood glucose can transiently increase from ca 5 mmol/l (fasting) to 8–10 mmol/l postprandial. This elicits a marked stimulation of insulin secretion, and arterial glucose will be taken up by peripheral organs, either independently of insulin (brain) or under the control of insulin (skeletal muscle, adipose tissue) [13].

In contrast, ingestion of a pure fructose meal does not increase glycemia to any great extent, nor does it trigger insulin secretion [14]. The concentration of fructose in the systemic blood transiently increases up to 0.5 mmol/l in the arterial blood, indicating that most of it is extracted by splanchnic organs. Fructose metabolism occurs primarily in the gut, liver, and kidney, where specific fructolytic enzymes: fructokinase (ketohexokinase C); aldolase B; triokinase, are expressed. Fructolysis is not dependent on the presence of insulin, and operates the conversion of fructose into dihydroxyacetone-phosphate and glyceraldehyde-3-P. It is remarkably like the initial steps of glycolysis, except that fructokinase and aldolase B are highly active constitutively and are inhibited neither by their products nor by signals arising from cellular energy status. As a consequence of this, trioses-phosphate metabolism in fructolytic cells is directly proportional to fructose uptake (Fig. 1) [14,15].

Compared to an isomolar glucose load, ingestion of fructose elicits only modest increases in blood glucose and insulin [16], but nonetheless stimulates total carbohydrate oxidation and energy expenditure to a larger extent in healthy lean volunteers, and in obese insulin-resistant subjects and subjects with type 2 diabetes [17,18]. It however produces larger postprandial increases in blood lactate concentration. Interestingly, studies using ^{13}C-labelled fructose indicated that about 40–50% of ingested fructose recirculated as labelled glucose over the 6 h following fructose ingestion [19]. This is consistent with fructose being converted into lactate and glucose in fructolytic splanchnic organs to be secondarily oxidized in peripheral tissues. Surprisingly, however, oral or iv fructose results in an increased glucose synthesis, or gluconeogenesis, but did not actually increase glycemia [20,21]. Further experiments using ^{13}C-labeled fructose and the combined use of indirect calorimetry and monitoring of ^{13}C glucose and $^{13}CO_2$ production suggested that increased fructose gluconeogenesis and hepatic glycogen synthesis while inhibiting glycogenolysis. These findings with fructose were similar to what had been observed by other investigators with administration of other gluconeogenic substrates: infusion of lactate, alanine, or glycerol increased gluconeogenesis at the substrate level, yet failed to increase net hepatic glucose output [22,23]. As a matter of fact, net hepatic glucose production increased after fructose only when hyperglucagonemia was simultaneously induced by exogenous glucagon infusion [21]. These findings were consistent with an autoregulation of hepatic glucose production. According to this concept, net glucose production is dependent on the balance between glucose-6-P synthesis from gluconeogenesis, glycogenolysis and glucose uptake followed by phosphorylation by glucokinase on one hand, and glucose 6-phosphate disposal into glycolysis and glycogen synthesis on the other hand. According to this scheme, variations in gluconeogenesis induced by gluconeogenic substrate availability is equilibrated by alterations of glycogen turnover, while net hepatic glucose release remains regulated at the glucokinase/glucose-6-phosphatase level (Fig. 2) This allows to maintain steady blood glucose concentrations, but is nonetheless associated with an slight increase in insulin need indicating the presence of hepatic insulin resistance [24].

Administration of fructose was also shown to impact some markers of other non-communicable diseases. Shortly after fructose became available for parenteral administration, it was observed that rapid IV fructose administration led to transient increases in uric acid [25]. This was attributed to fructose-induced degradation of ATP into AMP, a uric acid precursor. It was also observed that blood triglyceride concentrations increased more in response to a mixed meal containing fructose than glucose in

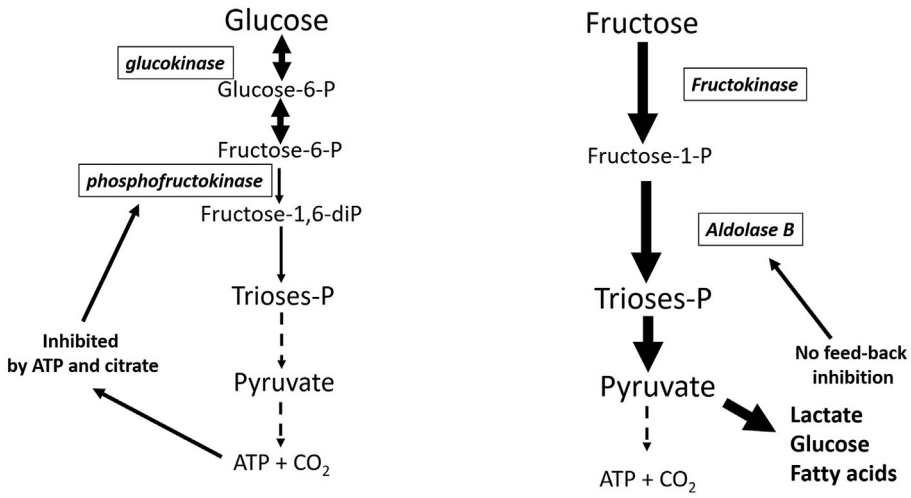

Fig. 1. Glycolysis and fructolysis in small bowel enterocytes, hepatocytes, and kidney proximal tubule cells. The initial steps for glucose and fructose degradation differ until the formation of trioses-phosphate. When the delivery of substrates, i.e. glucose and fructose for glycolysis and fructolysis respectively, is high, overall rate of glycolysis is limited by inhibition by ATP and citrate of phosphofructokinase, and the formation of trioses-phosphate does not exceeds cellular energy needs. In contrast fructolytic enzymes are not inhibited by fructose metabolites or ATP and trioses-phosphate formation is proportional to fructose uptake.

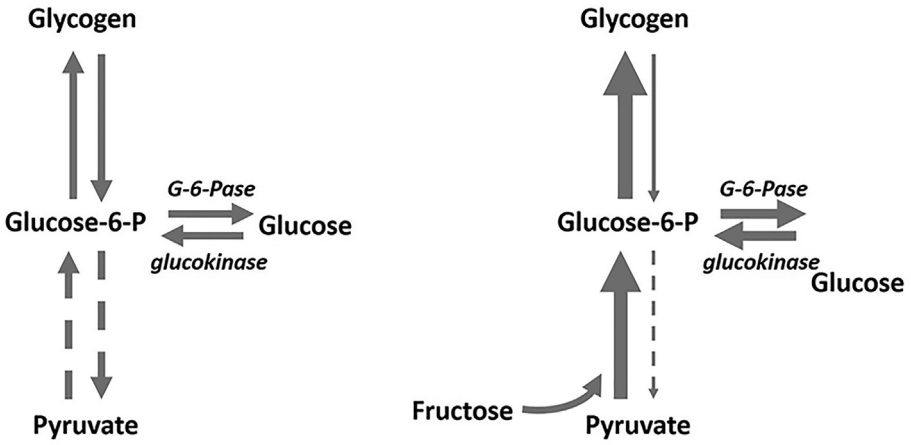

Fig. 2. Glucose release from hepatocytes (and gut enterocytes) is represented by the balance between intracellular glucose-6-P synthesis from glycogenolysis, gluconeogenesis and glucose phosphorylation on one hand, and glucose-6-phosphate disposal into glycogen synthesis and glycolysis on the other hand. A stimulation of gluconeogenesis at the substrate level, (e.g. fructose administration is associated with increased glycogen synthesis and decreased glycogenolysis, allowing to maintain net glucose output and glycemia constant.

isocaloric amounts [25]. Tracer experiments using ^{13}C-fructose showed that part of the ^{13}C-tracer was recovered on plasma VLDL-TG, indicating that de novo lipogenesis contributed to this effect. In addition, it was observed that VLDL-TG secretion was higher, while extrahepatic VLDL-TG clearance was lower with fructose than glucose [26].

Like for fructose, ingestion of a pure galactose load does not increase blood glucose and insulin concentration to any great extent. The concentration of galactose in arterial blood hardly increases, indicating that the near totality is extracted by splanchnic organs. Galactose is metabolized predominantly in the liver in the Leloir pathway: β-D galactose is converted into α-D galactose by the enzyme galactose mutarotase and is then phosphorylated to galactose-1-phosphate by the enzyme galactokinase. Galactose-1-phopsphate uridyltransferase then catalyzes the transfer of a uridine monophosphate group from uridine-diphospho(UDP)-glucose to galactose-1-phosphate, resulting in the formation of one molecule of glucose-1-phosphate and of one molecule of UDP-galactose. UDP-galactose finally is reconverted into UDP-glucose by the enzyme UDP-galactose epimerase [27]. Glucose-1-phosphate can then either enter the glycogen synthesis pathway or be converted into glucose-6-phophate to enter the glycolytic pathway or be released into the blood stream as free glucose. Tracer experiment with ^{13}C-labelled galactose indicated that ca 10 g was thus released from the liver over the 8 h following ingestion of a 50g galactose load [28].

4. Metabolic effects of chronically increased fructose intake

Several small scales clinical trials, reviewed in an elegant meta-analysis, indeed confirmed that replacing sucrose by fructose in the diet of healthy subjects and of patients with type 2 diabetes decreased average 24-h blood glucose concentration [29]. At the opposite, many animal studies reported that consumption of a high sucrose diet led to the development of obesity, hyperinsulinemia and insulin resistance or overt diabetes mellitus [30], and suggested that this was due to the fructose component of sucrose. This raised the concern that fructose may alter insulin sensitivity. In short term experiments in humans, administration of a high fructose diet for several days to weeks was not associated with

impaired insulin-mediated glucose uptake [31], but consistently impaired hepatic insulin sensitivity [32].

It was also rapidly recognized that very fructose intake was often associated with high blood triglyceride and LDL-cholesterol concentrations [33]. This raised the concern that any beneficial effect of fructose on blood glucose control may be offset by alterations of blood lipids associated with a high risk of cardiovascular diseases. It had been known for a long time that fructose was a lipogenic substrate and indeed stimulated hepatic triglyceride concentrations in rodents [14]. Until the 1990s, however, de novo lipogenesis in humans was mainly assessed by indirect calorimetry, based on the principle that it is the main metabolic pathways proceeding with a respiratory exchange ratio superior to 1.0. By using this method, it was indeed observed that dietary carbohydrate could stimulate de novo lipogenesis in humans, but that this required the use of massive carbohydrate feeding protocols over >3 days periods [34]. Indirect calorimetry however assessed only net, but not actual de novo lipogenesis, and hence studies showing that fructose intake did not increase RQ above 1.0 could not exclude the hypothesis that fructose-induced de novo fat synthesis occurred in the liver at the same time as fat oxidation proceeded in extrahepatic tissues. The development of the mass isotopomer distribution analysis method in the 1990s [35] was instrumental in documenting that hepatic de novo lipogenesis actually occurred in carbohydrate fed subjects even when respiratory exchange ratio was <1.0, and completely changed our view of this process [36]. It was indeed observed that a high carbohydrate intake increased hepatic de novo lipogenesis, and that fructose was more lipogenic than glucose or starch. Acetyl-CoA formed from intrahepatic fructolysis can be directly used as lipogenic substrate. It has also been recently demonstrated in mice that a portion of ingested fructose remains unabsorbed and gets fermented by colonic bacteria, and that the generated acetate is absorbed into the blood stream and makes a major contribution to hepatic de novo lipogenesis [37]. It was also observed that fructose-induced de novo lipogenesis came along with increased VLDL-TG secretion from the liver [38–40], thus explaining the development of hypertriglyceridemia. In addition, other conventional tracer methods also showed that the extrahepatic clearance of secreted VLDL-TG was lower after ingestion of a fructose than a glucose meal [26], further enhancing postprandial hypertriglyceridemia.

Another consequence of carbohydrate-induced de novo lipogenesis relates to non-alcoholic fatty liver disease. Until the 1990es, the major portion of hepatic cirrhosis was attributed to alcohol abuse. In 1980, however, clinicians from the Mayo clinics described the occurrence of a form of obesity-associated hepatopathy indistinguishable from alcohol hepatopathy in subjects not consuming alcohol [41]. Over the next decades, it became rapidly apparent that non-alcoholic fatty liver diseases, which start with a deposition of intrahepatic fat within hepatocytes, and then proceeds to hepatic steatosis, non-alcoholic steatohepatitis, cirrhosis, and eventually hepatocarcinoma, were highly prevalent in the population [42]. It was also observed, using magnetic resonance spectroscopy to non-invasively assess intrahepatic fat concentrations, that consumption of a high fructose diet was associated within a few days to significant increases in intrahepatic fat content in healthy subjects [32]. This effect was subsequently shown not to be restricted to fructose, however, since it was equally observed with fructose and glucose when energy intake exceeded actual energy needs [43].

5. Enterocytes' role in fructose metabolism

It is often considered that fructose is exclusively metabolized in the liver. It has however been known for decades that kidney proximal tubule cells express fructolytic enzymes, and that a substantial portion of intravenously infused fructose is metabolized in the kidney [44,45]. In addition, small bowel enterocytes have been known for a long time to express fructolytic enzymes and to synthesize labelled lactate, glucose and fatty acids from labelled fructose [46,47]. Interestingly, small bowel enterocytes, like hepatocytes, express, not only fructose-metabolizing enzymes, but also glucose-6-phosphatase, lipogenic enzymes, and the enzymatic machinery to secrete TRL particles. The role of enterocytes in overall metabolic control has remained however ignored until relatively recently. It has however been observed in rodents that, at low levels of intake, the near totality of fructose was metabolized in enterocytes to be released into the hepatic portal circulation as glycerate, glucose, or other fructose metabolites [48]. It has also been observed, in both rodents [46] and humans [49], that a high fructose diet stimulated de novo lipogenesis in enterocytes, and that, at high levels of intake, a portion of ingested fructose was released in the systemic circulation as triglycerides associated with chylomicrons. Furthermore, it was recently reported that deletion of fructokinase in enterocytes increased de novo lipogenesis from fructose in the liver, while overexpression of this enzyme in enterocytes shielded the liver against deleterious effects of fructose linked to de novo lipogenesis [50]. The authors of these studies concluded that "fructose induces lipogenesis when its dietary intake rate exceeds the intestinal clearance capacity" and that "the resulting fructose spill over drives metabolic syndrome".

The role of enterocytes in postprandial metabolic homeostasis may even be more complex than this. It has indeed been observed that dietary lipids can remain as lipid droplets in the enterocytes for several hours after absorption of a meal, and that the ingestion of glucose in a subsequent meal acutely drives chylomicrons secretion from the enterocyte [51]. It has also been observed that the secretion of previously synthesized chylomicrons after ingestion of a mixed meal made a major contribution to fasting and postprandial hyperlipidemia in overweight subjects. Furthermore, this was totally corrected after Roux-en-Y-gastric bypass [52], suggesting the presence of a reversible enterocyte dysfunction in obese patients with the metabolic syndrome. The links which may exists between enterocytes' carbohydrate and sugar metabolism and lipogenesis remains to be further explored, but clearly represent important future research topics.

6. Adverse metabolic effects of fructose: in any physiological condition?

Several controlled intervention studies thus showed that administration of a fructose enriched diet, whether from pure fructose or from sucrose or high fructose corn syrup, sometimes induces alterations of hepatic insulin sensitivity and of blood lipid profile which may be associated with a long term risk of type 2 diabetes, cardiovascular diseases, and non-alcoholic fatty liver disease [53]. These effects were however dose dependent, and were observed at fructose intake >50/day for postprandial TG, > 100 g/day for fasting TG, and >150 g/d for intrahepatic lipid concentrations [54]. Furthermore, they were generally observed in hypercaloric conditions: it was indeed shown that consumption of a 30% fructose diet calculated to match the participants' energy expenditure did alter neither blood lipids nor intrahepatic triglyceride concentrations of overweight subjects. In contrast, administration of diets containing either 30% fructose or 30% glucose in excess of participants' energy requirements significantly increased blood triglyceride and intrahepatic fat concentrations within 2 weeks [43].

One can also note that participants invariably had restrained physical activity during these studies. Physical activity, as a major determinant of total energy expenditure, is however a key factor in

nutritional sciences. It was thus observed that the metabolic effects of dietary carbohydrates, and more specifically those of fructose, were tightly dependent on the level of physical activity, and that exercise prevented the increase in TRL particles and of their remnants induced by a high carbohydrate diet [55,56].

How can we account for this protection of exercise against the adverse metabolic effects of fructose? Glucose and fatty acids are the prime substrates for working skeletal muscles, but fructose cannot be directly used by muscle, which lacks fructolytic enzymes. It has however been well documented that co-administration of oral fructose and glucose during exercise can increase total carbohydrate oxidation to a larger extent than glucose alone [57]. This has been attributed to the fact that fructose and glucose use two distinct gut transporters, and hence that maximal hexoses absorption is higher with glucose-fructose mixtures than with glucose alone [58]. Fructose is not directly metabolized by skeletal muscle, however, but is primarily converted by the liver into lactate and glucose, and these two substrates are then released into the circulation as energy fuels for muscle [59]. Exercise thus directs fructose metabolism toward energy production in skeletal muscle, thus preventing the accumulation of fructose metabolites in splanchnic organs. This clearly points to a role, not of fructose per se, but of excess non-oxidative fructose metabolism in splanchnic organs at the origin of fructose-induced adverse effects.

7. Does fructose have more adverse metabolic effects in specific population subgroups?

We just discussed the fact that people with low habitual physical activity may be at increased risk of developing hypertriglyceridemia and hepatic steatosis in response to a high fructose diet than people with high physical activity. Our next question is: are adverse metabolic effects of fructose enhanced in specific subgroups of the population?

There is indeed evidence that obese subjects with insulin resistance may have enhanced blood triglyceride responses to fructose [60]. It has also been reported that genetic variations of patatin-like phospholipase domain containing protein 3 (PNPLA3) may affect fructose effects. PNPLA3 is a lipase associated with lipid droplets in the liver. It has been observed that hispanic children with gene variant rs7384of PNPLA3 show a correlation between carbohydrate intake and intrahepatic fat concentration [61]. A similar correlation between intrahepatic fat and sugar-sweetened beverage intake was made in Italian adolescents with the same variant [62].

Hereditary Fructose Intolerance (HFI) is an inherited metabolic disease in which both alleles of aldolase B are mutated. In affected subjects, fructose ingestion leads to accumulation of fructose-1-P in fructolytic cells due to complete aldolase B deficiency. ATP consumption for fructose-1-phosphate synthesis causes acute ATP deficiency in hepatocytes and renal proximal tubule kidney cells, leading to hypoglycemia and acute renal tubular acidosis. Another consequence of fructose ingestion in HFI patients is an increased degradation of ADP into IMP and uric acid synthesis, leading to hyperuricemia. HFI is a severe, life-threatening condition when fructose or sorbitol are present in the diet of affected subjects, but is otherwise a benign, asymptomatic condition when subjects abstain from fructose consumption. Its prevalence is estimated to be about 1/70,000, but many affected subjects develop early fructose aversion, spontaneously consume a fructose-devoid diet, and remain undiagnosed. Heterozygous mutations of aldolase B are predicted to be present in 1:55 to 1:122 in the general population, and subjects with heterozygous mutations have been considered to have unaltered fructose metabolism due to sufficient synthesis of aldolase B from the unmuted allele. It has however been observed that they have increased plasma uric acid concentration after ingestion of fructose, and may even be more prone to develop a mild insulin resistance when consuming a high fructose diet [63,64]. It is possible that increased uric acid production may be responsible for this, since this metabolite has been shown to impair endothelial -dependent vasodilation and cause pre-receptor insulin resistance in rodents [65].

8. Role of splanchnic organs in the metabolism of non-ubiquitous substrates

What can we conclude from the various aspects of fructose metabolism that we have just reviewed? On one hand, fructose is a nutritional compound naturally present in our diet. The expression of specific fructose-metabolizing enzymes, not only in humans, but in most mammals, suggests that the ability to metabolize this substrate has offered some selection advantage over evolution [66]. Interestingly, fructose cannot be directly metabolized by all cells of the human organism. The same is true for several other dietary substrates, such as galactose [67], alcohol [68], or most amino-acids (except branched-chain amino acids) [69], which cannot be directly oxidized to any great extent in peripheral cells such as muscle or brain neurons. These substrates are instead primarily metabolized in splanchnic organs, mainly in the gut and liver, where they are converted into other, ubiquitous energy substrate: glucose, lactate, fatty acids, or acetate. As such the splanchnic organs make a major contribution to overall metabolism by processing nutrients into energy sources readily available to any cell of the human organism. They are specifically involved in several key metabolic processes: first, the digestion of food and the complete or near complete absorption of a variety of energy-rich molecules from the gut through the use of distinct membrane transporters; second, the metabolism of these various molecules, each requiring specific enzymes, into ubiquitous energy substrates readily metabolized by all cells of the human organism, namely acetate, lactate, glucose and fatty acids; and third, the temporary storage of energy within splanchnic organs in the immediate postprandial period.

All these metabolic functions must be performed with homeostatic constraints to avoid exaggerated blood glucose and lipid concentrations, and thus to prevent cellular damages leading to non-communicable diseases. Maintenance of glucose and lipid homeostasis in turn depends on two requisites: first, there must be a match between the amount of energy obtained from alternate energy substrate as fructose in the diet on one hand, and the energy needed by peripheral cells on the other hand; second, normal glucoregulatory mechanisms must be operative. Figure 3 illustrate this concept for fructose: at low levels of fructose intake, this substrate is initially metabolized in the gut, and only a minor portion of it actually reaches the hepatic portal circulation to be metabolized by the liver. A small amount may escape gut and hepatic metabolism and reach the systemic circulation to be eventually metabolized in the kidney. At high levels of fructose intake, hepatic metabolism becomes preponderant and the metabolic pathways used for fructose disposal depend on whole body energy expenditure. If peripheral energy output is high, as for instance during exercise, fructose carbons will be mainly released as glucose and lactate by splanchnic tissues, to be used as energy substrate in peripheral cells. During exercise, both splanchnic glucose production and muscle glucose uptake are high, and large amounts of glucose can be transferred to the muscle without adverse effects on blood glucose [70]. It can be postulated that the same limitations apply to interorgan lactate exchange, i.e. high splanchnic lactate production and muscle lactate uptake during exercise, preventing the development of undue hyperlactatemia. At the opposite, if peripheral energy output is low, splanchnic glucose release is

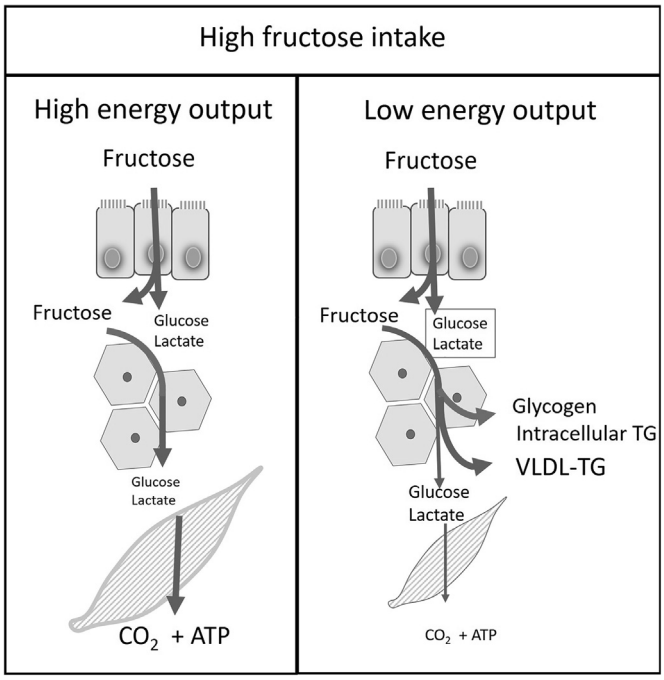

Fig. 3. At high levels of fructose intake, the metabolic pathways used for fructose disposal in hepatocytes depend on whole body energy expenditure. If peripheral energy output is high, as for instance during exercise (left panel), fructose carbons will be mainly released as glucose and lactate by splanchnic tissues, to be used as energy substrate in peripheral cells. At the opposite, if peripheral energy output is low (right panel), splanchnic glucose release is limited by glucoregulatory factors to prevent hyperglycemia, and lactate release may be limited by hyperlactatemia. Under such conditions, fructose carbons which cannot exit the liver are first diverted toward hepatic glycogen, and later, when glycogen stores become saturated, into de novo lipogenesis and increased secretion of VLDL-TG.

limited by glucoregulatory factors to prevent hyperglycemia, and lactate release may be limited by hyperlactatemia. Under such conditions, fructose carbons which cannot exit the liver are first diverted toward hepatic glycogen, and later, when glycogen stores become saturated, into de novo lipogenesis and increased secretion of VLDL-TG. Stimulation of de novo lipogenesis also occurs in small bowel enterocytes and results in an increased secretion of triglyceride-loaded chylomicrons. This may be associated with chronic elevation of TRL and of their remnants in the blood, which may in turn be responsible for initiating atherosclerosis. In addition, chronic imbalance between fructose intake and energy output may cause progressive hepatic fat accumulation, leading in the long term to non-alcoholic fatty liver disease. One can hypothesize that the same process occurs in gut enterocytes, leading to enterocytes lipotoxicity, the consequences of which remain to be assessed.

The consequences of high fructose diets in humans have been extensively studied. However, whether the same concepts apply to other alternate metabolic substrates such as alcohol or amino-acids, or combination of them, remain largely unexplored. Interestingly, a recent report indicates that ingestion of galactose with a mixed meal causes a similar postprandial increase in blood triglyceride than fructose [71].

9. Conclusions and perspectives

The efficient absorption of as much energy as possible, from many different energy-rich substrate present in our diet, and the processing of these substrate into substrate useable for energy production by all cells of the human organism are obviously key functions of the gut and liver. The capacity to use energy substrates such as fructose has most likely be important to allow survival in the past when energy sources were scarce. In our present world, the wide availability of energy-dense foods is associated with a well-known risk of obesity and of its cardiometabolic complications. In addition, excess consumption of fructose (or of other substrates dependent on a first-step hepatic metabolism) may expose the gut and liver to an overload of glucose, glycogen and triglycerides, which may lead to gut and hepatic dysfunction and be associated with a further risk of cardiometabolic diseases.

I would also mention that several areas of fructose metabolism remain underexplored. There is indeed evidence that fructose is present in the systemic circulation, as a result both of an incomplete splanchnic extraction of dietary fructose and of an endogenous fructose production [72]. There is also evidence that many cell types, such as adipocytes and skeletal muscle, express specific fructose transporters as well as alternate forms of fructose-metabolizing enzyme [73]. The importance and functional significance of this extra-splanchnic fructose metabolism remains to be determined.

Conflict of interest

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