Fructose metabolism and noncommunicable diseases: recent findings and new research perspectives

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Purpose of review
There is increasing concern that dietary fructose may contribute to the development of noncommunicable diseases. This review identifies major new findings related to fructose's physiological or adverse effects.

Recent findings
Fructose is mainly processed in splanchnic organs (gut, liver, kidneys) to glucose, lactate, and fatty acids, which can then be oxidized in extrasplanchnic organs and tissues. There is growing evidence that splanchnic lactate production, linked to extrasplanchnic lactate metabolism, represents a major fructose disposal pathway during and after exercise. Chronic excess fructose intake can be directly responsible for an increase in intrahepatic fat concentration and for the development of hepatic, but not muscle insulin resistance. Although it has long been thought that fructose was exclusively metabolized in splanchnic organs, several recent reports provide indirect that some fructose may also be metabolized in extrasplanchnic cells, such as adipocytes, muscle, or brain cells; the quantity of fructose directly metabolized in extrasplanchnic cells, and its physiological consequences, remain however unknown. There is also growing evidence that endogenous fructose production from glucose occurs in humans and may have important physiological functions, but may also be associated with adverse health effects.

Summary
Fructose is a physiological nutrient which, when consumed in excess, may have adverse metabolic effects, mainly in the liver (hepatic insulin resistance and fat storage). There is also concern that exogenous or endogenously produced fructose may be directly metabolized in extrasplanchnic cells in which it may exert adverse metabolic effects.

Keywords
cardiac failure, free sugars, hypoxia, insulin resistance, ketohexokinase, nonalcoholic fatty liver disease, placenta, polyol pathway

INTRODUCTION

A high consumption of fructose, whether as sucrose or fructose–glucose syrups, has been proposed almost 15 years ago to be a major driver of metabolic-related noncommunicable diseases such as obesity, type 2 diabetes mellitus, nonalcoholic fatty liver disease (NAFLD), and cardiovascular diseases. Since then, many national and international agencies have released recommendations to reduce 'added' or 'free' sugar intake to less than 10% [1,2] or even less than 5% [3] total energy intake. The average 'free' sugar consumption is unfortunately high in most Western countries, and these recommendations are currently met by only a small percentage of the population [4].

'Free sugar' corresponds to 'all monosaccharides and disaccharides added to foods by the manufacturer, cook, or consumer, and sugars naturally present in honey, syrups, and fruit juices [1,2]. Such a distinction is made by most agencies to differentiate the effects of refined sugars and those of sugars naturally present in fruits and vegetables. There is currently no universal definition of added or free sugars, however [5]. Recently, the French agency ANSES took another approach by setting an upper level of 100 g/day for

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KEY POINTS

- Dietary fructose is primarily metabolized in small bowel enterocytes, liver cells, and kidney proximal tubules, in which it is converted into lactate, glucose, or fatty acid.
- During exercise, splanchnic conversion of fructose into lactate followed by lactate oxidation in skeletal muscle is one major pathway for fructose disposal.
- Excess fructose intake is associated with hepatic insulin resistance, increased hepatic VLDL-TG secretion, increased blood triglyceride concentrations, and intrahepatic fat deposition.
- Some extrasplanchnic cells (adipose tissue, cardiac and skeletal muscle fibers, some brain cells) express specific fructose transporters.
- In many cells of the body, the ketohexokinase (KHK)/fructokinase gene gives rise by alternate splicing to an isoform of fructokinase, KHK-A. The amount of fructose directly metabolized by KHK-A remains unknown.
- Fructose can be produced endogenously from glucose in the polyol pathway. Endogenous fructose production may have important physiological roles in the male genital system and in the placenta. Endogenous fructose production may also be increased by hyperglycemia or by hypoxia in some cells.
- Hypoxic cardiac cells can switch from KHK-A to KHK-C during hypoxia. This may be associated with the development of cardiac failure.
- Hepatocarcinoma cell at the opposite appear to operate a switch from KHK-C to KHK-A, which may act as a kinase to activate the pentose–phosphate pathway and support nucleotide synthesis for cell proliferation.

total sugars (corresponding to about 20% total energy), with a strong recommendation to favor consumption of fresh fruits and vegetable products [6].

Hundreds of publications addressing the metabolic effects of fructose-containing sweeteners are published every year. Many of them address the associations between 'free' sugar or sugar-sweetened beverages intake on one hand, and incidence of diseases or markers of cardiovascular and metabolic diseases on the other hand. A detailed evaluation of the evidence available was reported in the WHO and the Sub-advisory Committee for Nutrition, UK 2015 reports [1,3]. The systematic reviews and meta-analysis of prospective cohort studies and randomized controlled trials (RCTs) performed as part of their evaluation provided weak evidence a causal relationship between sugar consumption and noncommunicable diseases. Their recommendation to reduce free sugar intake was therefore mainly supported by data linking sugar intake and dental caries in children [1], and by associations between sugar-sweetened beverages intake and body weight in children and adults [3]. This indicates that many scientific gaps remain in this domain. This review will attempt to summarize major advances made regarding fructose effects in humans over the past 5 years, and to identify gaps and novel research perspective based on both human and animal research.

FRUCTOSE METABOLISM

Unlike glucose, fructose is assumed not to be directly metabolized by most cells of the human body, but to be first processed into ubiquitous substrate in three splanchnic organs, that is, the proximal small bowel, the liver, and the kidney. All three organs contain cells expressing fructose transporters (GLUT5, GLUT2) and fructolytic enzymes [fructokinase-C, also called ketohexokinase-C (KHK-C), aldolase B, triokinase]. These same cells also synthesize gluconeogenic enzymes and glucose-6-phosphatase, which enable them to release glucose into the blood stream, and enzymes allowing the de novo synthesis of fatty acids (FAs) from acetyl-CoA, that is, acetyl-CoA carboxylase and FA synthase, the elongation of palmitate into stearate, and the desaturation of palmitate and stearate, to palmitoleate and oleate, respectively [7]. As there is no physiological feedback on fructolytic enzymes, all intracellular fructose is quickly and entirely converted into trioses-phosphate (dihydroxyacetone phosphate and glyceraldehyde phosphate), which are then metabolized to pyruvate/lactate, glucose, glycogen, and FA. All these pathways can also be fueled by glucose, but fructose is markedly more efficient than glucose in stimulating de novo lipogenesis, and hence FA/TG synthesis and VLDL-TG secretion.

Pathways used for fructose metabolism in physiological conditions

The relative contributions of gluconeogenesis/glycogen synthesis/systemic glucose release and de novo lipogenesis/VLDL-TG secretion in healthy humans have been in part elucidated with the use of various labeled substrates. Over 5–6 h following ingestion of a ^{13}C-labeled fructose load, about 50% of labeled carbons are recovered in blood glucose, and about 50% are recovered in breath CO_2. In addition, about 20–35% of labeled carbons are recovered in blood lactate, whereas hepatic and muscle glycogen synthesis may account for about 15% fructose carbon disposal [8]. This suggests that fructose can be directly oxidized in fructolytic

organs, and indirectly oxidized as glucose and lactate in other organs and tissues, and that nonoxidized fructose is predominantly stored as hepatic or muscle glycogen. Labeled fructose carbons can also be recovered on the glycerol and FAs moieties of VLDL-triglyceride, indicating that glyceroneogenesis and de novo lipogenesis may contribute to overall fructose disposal. A quantitative estimate of lipid synthesis from fructose has not been possible so far, mainly as this would require a quantitative assessment of labeled VLDL-FA secretion, intrahepatic storage of de novo synthesized triglycerides, and extrasplanchnic (adipose, muscle) de novo lipogenesis. However, as gluconeogenesis, glycogen synthesis, and lactate production together account for 70–90% total fructose disposal, it appears likely that de novo lipogenesis represents a quantitatively minor pathway for fructose disposal [8].

The studies discussed in [8] mainly addressed the effects of large, pure fructose loads in healthy volunteers and in overweight or obese volunteers without or with type 2 diabetes mellitus. In 2012, an NIH conference on the future of fructose research however made the point that our usual diet contains fructose under the form of sucrose or glucose–fructose mixtures, and hence that studies should address the effects of coingestion of isocaloric amounts of fructose and glucose to be physiologically relevant [9]. Since then, one isotope study monitored the fate of fructose carbons after ingestion of mixed meals containing protein, fat, and either 25-g ^{13}C-labeled fructose or 25-g ^{13}C-labeled fructose + 25-g unlabeled glucose. Recovery of ^{13}C-labeled fructose carbons in blood glucose was somewhat lower that with a pure 50-g fructose load, but fructose oxidation and glucose production nonetheless accounted for the major portion of fructose disposal. Coingestion of glucose with fructose decreased fructose oxidation from 50 to 45%, and glucose synthesis from 36 to 24% of ingested fructose, but did not significantly enhance ^{13}C carbons recovery in VLDL-TG [10]. These results underline the need for further studies assessing the interactions between fructose and other dietary macronutrients.

Physiological role of lactate production after fructose ingestion

It has long been known that fructose ingestion increases blood lactate concentration, but the physiological role of lactate production from fructose has generally received relatively little attention. Studies performed in exercising subjects have now documented that this pathway may be quantitatively and functionally more important than previously thought. It has indeed been reported that, in exercising subjects, about 50% of ingested fructose carbons were transferred to muscle as lactate and about 50% as glucose [11]. Another report indicated that lactate produced from fructose ingested at rest was mainly metabolized through nonoxidative pathways (gluconeogenesis and glycogen storage), whereas lactate produced from fructose ingested during an exercise was mainly oxidized to CO_2 [12]. Finally, it was observed that lactate produced from fructose may be used to replenish muscle glycogen stores during the postexercise phase [13▪]. One recent review has nicely revisited this concept of a hepatic fructose–lactate shuttle for fructose [14▪▪].

Fructose consumption and body weight

Many narrative reviews and scientific position articles [15,16▪▪,17] rely on the postulates that fructose is obesogenic as it stimulates de novo lipogenesis and causes insulin resistance and hyperinsulinemia, and as it does not elicit satiety signals to the brain. These statements however rested on few, sometime controversial studies. As discussed above, the amount of fat newly synthetized from fructose had not been actually measured. In addition, no study had nonequivocally demonstrated that fructose, whether ingested in a solid food or consumed in a drink, failed to suppress food intake or caused muscle insulin resistance. What are the recent developments regarding these postulated effects of fructose?

Fructose and de novo lipogenesis

There is indeed overwhelming evidence that fructose promotes hepatic de novo lipogenesis to a larger extent than glucose or glucose polymers. Fructose-induced de novo lipogenesis has been robustly demonstrated with high-fructose, hypercaloric diet, but the respective roles played by fructose *per se* and excess energy intake remain disputed. Two studies reported that a chronic isocaloric substitution of dietary starch with fructose stimulated hepatic de novo lipogenesis and significantly increased blood triglyceride concentration. These effects could clearly not be attributed to excess energy intake, nor to total carbohydrate (starch + fructose) intake as both were experimentally maintained at the same level when subjects consumed the control, starch-based diet, and the high-fructose diet, and hence were to be attributed to fructose *per se*, independently of energy balance [18,19]. One of these studies however demonstrated that ingestion of an amount of fructose corresponding to 30% of 24-h energy expenditure over 4 days stimulated de novo

lipogenesis when subjects did not exercise, but not when subjects performed two daily 30-min cycling sessions. Total energy intake was adjusted to match energy expenditure with and without exercise, and both fructose intake and total energy expenditure were therefore higher when subjects exercised than in sedentary conditions. These observations indicate that fructose-induced hepatic de novo lipogenesis does not depend strictly on energy balance, but is strongly modulated by total daily energy output [18].

It appears however unlikely that stimulation of de novo lipogenesis is causal in the development of obesity. Obesity indeed results from a positive energy balance associated with body fat accretion, not from a mere stimulation of de novo lipogenesis! A meta-analysis clearly documented that body weight significantly increased in intervention studies with addition of fructose (and hence of calories) to a control diet, but did not change in studies in which fructose isocalorically replaced other macronutrients [20]. A review also documented that basal and postprandial energy expenditure did not change significantly during a high-fructose diet [21]. This seemingly banal observation however demonstrates that fructose does not decrease energy expenditure, and by the same token invalidates the hypothesis that dietary fructose may cause obesity independently of increased energy intake. The latter review also recalled that storing fat from fructose is energetically far less efficient than storing dietary fat [21].

Fructose and food intake

Postprandial plasma glucose, insulin, GLP-1, and leptin concentrations increase less after ingestion of sucrose or fructose than after ingestion of isocaloric amounts of glucose or starch. This supports the hypothesis that fructose and sucrose may elicit less satiety than starch. Along the same line, one study confirmed that, in healthy volunteers, ingestion of pure fructose elicited less insulin and GLP-1 responses than glucose, and that this was associated with a distinct pattern of activity in brain areas involved in food intake control [22]. Another study reported that ghrelin suppression by fructose was blunted in obese insulin resistant compared with obese insulin-sensitive adolescents [23]. Finally, a study reported that the brain responses normally elicited by fructose ingestion in the prefrontal cortex of lean subjects were significantly decreased in obese subjects. As the prefrontal cortex is involved in executive control (such as voluntary limitation of food), this finding is consistent with higher food intake in obese subjects consuming fructose [24▪▪]. To date, there are still few human studies which addressed the effects of fructose on brain centers involved in food intake control. Furthermore, the interpretation of such brain imaging studies remains difficult as recordings of activity in discrete brain areas may not always correspond to unequivocal physiological effects. This is a fast-growing field, however, and we may expect to have more information available in the forthcoming years.

Fructose and insulin resistance

It is commonly accepted that dietary fructose is responsible for the development of insulin resistance. This was mainly supported by animal models of obesity, in which selected strains of rats developed visceral obesity, decreased insulin-mediated muscle glucose transport, and hyperglycemia when fed a high-fructose or high-sucrose diet. A link between dietary fructose and insulin resistance in humans was also supported by a meta-analysis showing an association between sugar-sweetened beverages intake and the risk of developing type 2 diabetes in adults. The association between sugar intake and diabetes risk was in part related to adiposity, however [25]. Another meta-analysis reported a significant association between fructose consumption and biomarkers for the metabolic syndrome [26]. The mechanisms by which fructose would be responsible for the development of insulin resistance and diabetes remains an unsolved riddle, however, as muscle insulin resistance is a hallmark of type 2 diabetes, whereas fructose is supposedly not directly metabolized in skeletal muscle.

Many studies, performed between 1980 and now, have specifically assessed the effects of pure fructose supplementation on insulin sensitivity in humans. Some of them differentially assessed hepatic insulin sensitivity (i.e., suppression of hepatic glucose production at moderately elevated insulin concentrations) and muscle insulin sensitivity (i.e., whole body insulin-mediated glucose disposal at high insulin concentrations). A meta-analysis of these studies recently documented that ingestion of a high-fructose diet, consumed over periods ranging from 4 to 80 days, significantly reduced hepatic insulin sensitivity, but had no effect on muscle insulin sensitivity [27▪▪]. In contrast, two studies showed that a high-fructose diet downregulated glucose transporters in muscle and adipose tissue [28,29], suggesting that it may impair insulin-mediated glucose transport in these tissues. Whether these effects are mediated directly by the low-systemic fructose concentrations observed after fructose ingestion, by a fructose metabolite such as lactate, or by still other mediators, remains currently

unknown. It was also proposed that fructose-induced hyperuricemia may cause muscle insulin resistance by impairing insulin-mediated vasodilation [30].

EFFECT OF FRUCTOSE ON NONALCOHOLIC FATTY LIVER DISEASE

Several small-sized RCTs indicated that addition of fructose to a weight-maintenance diet dose-dependently increased intrahepatic fat content in normal-weight and overweight subjects. A mismatch between hepatic de novo lipogenesis and hepatic FA disposal through oxidation and/or VLDL-TG secretion are thought to be responsible, but the relative contribution of each of these processes to overall fat deposition has not yet been accurately evaluated [31]. Several recent studies further assessed the short-term effects of a high-fructose diet on intrahepatic fat content. One study compared the effects of isocaloric amounts of glucose and fructose in overweight subjects. It reported that glucose or fructose increased intrahepatic fat content to the same extent when they were added to a normal, weight maintenance diet; in contrast, no change in intrahepatic fat concentration was observed when glucose or fructose isocalorically replaced starch in a weight maintenance diet. The authors of this study concluded that excess calories from carbohydrates, not fructose *per se*, was responsible for an increase in hepatic fat [32]. Another study involved overweight subjects with NAFLD who received supplementary fructose drinks during 12 weeks. These subjects consumed an ad-libitum diet during intervention, but had a detailed assessment of their dietary intake. Significantly, they reduced significantly their carbohydrate, fat, and protein intake from solid foods during the intervention. Fructose produced significant, but relatively modest increases in average intrahepatic fat concentrations. There was much interindividual variability, however, and some subjects even decreased their intrahepatic fat with fructose [33▪▪]. Surprisingly, all other markers of metabolic risk, such as plasma triglyceride concentration, or indexes of insulin sensitivity, were not changed with fructose supplementation [34]. Another study compared the effects of high-sugar vs. low-sugar weight maintenance diet in overweight subjects with and without NAFLD. It reported that intrahepatic fat content was significantly higher with the high-sugar diet. This sugar-induced increase in intrahepatic fat was, in absolute value, larger in subjects with NAFLD than in subjects without NAFLD. In addition, fructose differentially altered the kinetics of VLDL-TG subclasses according to the presence or not of NAFLD [35▪▪].

As a counterpoint to these intervention studies involving increased dietary fructose intake, several studies at the opposite assessed whether intervention involving a reduction of fructose or sugar intake in overweight or obese subjects would revert NAFLD or decrease intrahepatic fat concentration. One randomized controlled study involved adult overweight subjects who were high-SSBs' consumers and observed a significant 25% reduction in intrahepatic fat after subjects replaced SSBs by artificially sweetened beverages during 12 weeks [36]. Another intervention study involved obese children and also reported *c.* 25% reduction in intrahepatic fat after subjects had their usual sugar intake substituted with isocaloric amounts of complex carbohydrate for 9 days [37▪]. Finally, a third study involved overweight children and reported that the severity of NAFLD, as staged from abdominal echography and biochemical parameters, decreased after 6 weeks of a reduction to less than 20 g/day fructose intake [38▪]. Participants lost weight in all three studies, however.

NOVEL EMERGING RESEARCH PERSPECTIVES

Is fructose metabolized directly by extrasplanchnic tissues?

It is generally assumed that fructose is exclusively metabolized in the liver and the kidney. Over the past decade, the role of the enterocytes in fructose metabolism has been however robustly demonstrated in animal and human studies (reviewed in [39]). The generally accepted scheme for oral fructose disposal is that a major portion is taken up by the enterocytes and the liver, and that whatever fructose escapes first-pass gut/liver extraction is mainly metabolized in the kidney. Although this scheme is supported by the fact that blood fructose concentrations increases only slightly and transiently after fructose ingestion, the actual systemic delivery of intact fructose remains currently unknown.

The concept that nonsplanchnic tissues do not metabolize fructose to any significant extent was however challenged by observations that brain cells, adipocytes, muscles, and many other cells, expressed specific fructose transporters [40]. The gene coding for KHK is expressed in most tissues, but, due to alternate splicing, is associated with the synthesis of KHK-C or fructokinase-C in fructolytic organs only, and of KHK-A, an isoform with much lower affinity for fructose in other tissues [41,42] (Fig. 1). The physiological role of KHK-A remains largely unknown. Mice with invalidation of both

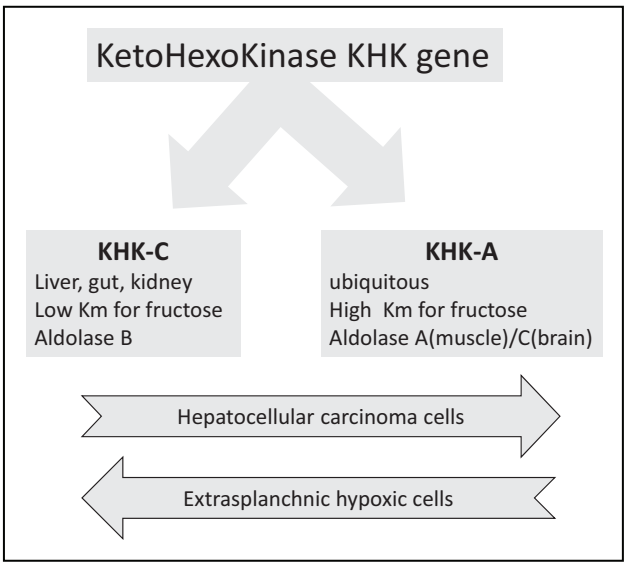

FIGURE 1. The fructokinase/ketohexokinase gene can give rise to two isoforms of the enzyme. Ketohexokinase-C is expressed in liver cells, small bowel enterocytes, and kidney proximal tubules. It has a high affinity for fructose and confer high fructose metabolizing capacity to these cells. The same cells usually express aldolase B, gluconeogenic enzymes, glucose-6-phosphatase enabling them to release glucose into the blood, and lipogenic enzymes. Ketohexokinase-A is more ubiquitously expressed, in cells usually expressing also aldolase A or C. It has a low affinity for fructose, and is functional role remains unknown. There is evidence that some cells can switch from ketohexokinase-A to ketohexokinase-C in response to hypoxia; there is also evidence that hepatocellular carcinoma cells operate the reverse switch, from ketohexokinase-C to ketohexokinase-A.

isoforms or with isolated invalidation of KHK-A had a normal phenotype and remained fertile when fed a standard diet [43]. Invalidation of KHK-A was associated with increased sensitivity to the adverse metabolic effects of a high-fructose diet, however, suggesting that KHK-A activity may to some extent protects the liver through mechanisms which remain to be elucidated [44].

Unexpectedly, it was also observed that some cells may switch from the synthesis of one to the other KHK isoform in response to external signals. Thus, cardiomyocytes exposed to hypoxia switched to the synthesis of KHK-C instead of KHK-A, and thus increased their fructose metabolism. This has been proposed as a potential pathogenic mechanism leading to cardiac failure [45] (Fig. 2). At the opposite, a switch from KHK-C to KHK-A was observed in hepatocarcinoma cell. Although the mechanism responsible for this switch remains unknown, it was observed that KHK-A in hepatocarcinoma cells promoted nucleotide synthesis by acting as a protein kinase, phosphorylating and activating phosphoribosyl pyrophosphate synthetase 1, and increasing the pentose phosphate pathway activity [46▪▪].

One original article reported how fructose directly altered glucose metabolism in adipocytes *in vitro*. It nicely documented, with the use of ^{13}C-labeled tracers, that fructose dose-dependently decreased glucose carbon disposal in the Krebs cycle and classical mitochondrial ATP synthesis, but increased the ATP synthesis from the one carbon pathway [47]. In this pathway, serine is converted into glycine to allow for the synthesis of purines. Significantly, this pathway may also be directly fueled with fructose and produces anaerobic ATP while at the same time, reducing NADH/NADPH to NAD/NADP [48].

Is there a significant endogenous fructose production, and what may be its physiological role?

The 'polyol pathway' is a two-step metabolic pathway in which glucose is reduced to sorbitol by the enzyme aldose reductase, and sorbitol is converted to fructose by the enzyme sorbitol dehydrogenase. Increased polyol synthesis secondary to hyperglycemia has long been recognized as a potential contributor to long-term diabetic complications [49]. This pathway is active in male genital organs and is responsible for the high fructose concentration of sperm [50]. Significantly, during pregnancy, fructose concentration is also increased in the cord blood and fetal circulation relative to maternal blood in several species, including humans [51–53]. This is thought to involve an increased polyol pathway activity, together with enhanced expression of fructose and sorbitol transporters. The role of this placental fructose production remains largely unknown. It has been proposed that fructose may play a role of growth factor or growth modulator in the fetal circulation [54▪▪].

Apart from these two special organs, it is believed that the polyol pathway has little activity at physiological glucose concentrations, but that hyperglycemia above 7 mmol/l dose-dependently stimulates fructose synthesis. In humans, it was observed by magnetic resonance spectroscopy that brain fructose concentration increased during hyperglycemia in the absence of any fructose ingestion [55▪▪]. Such an endogenous fructose production may be associated with physiological effects, as fructose can be directly metabolized actively in specific brain regions [56▪,57▪]. What these effects may actually be remains to be elucidated, however. It was also reported that hyperglycemia in rodents caused an increase in their liver fructose concentration, and

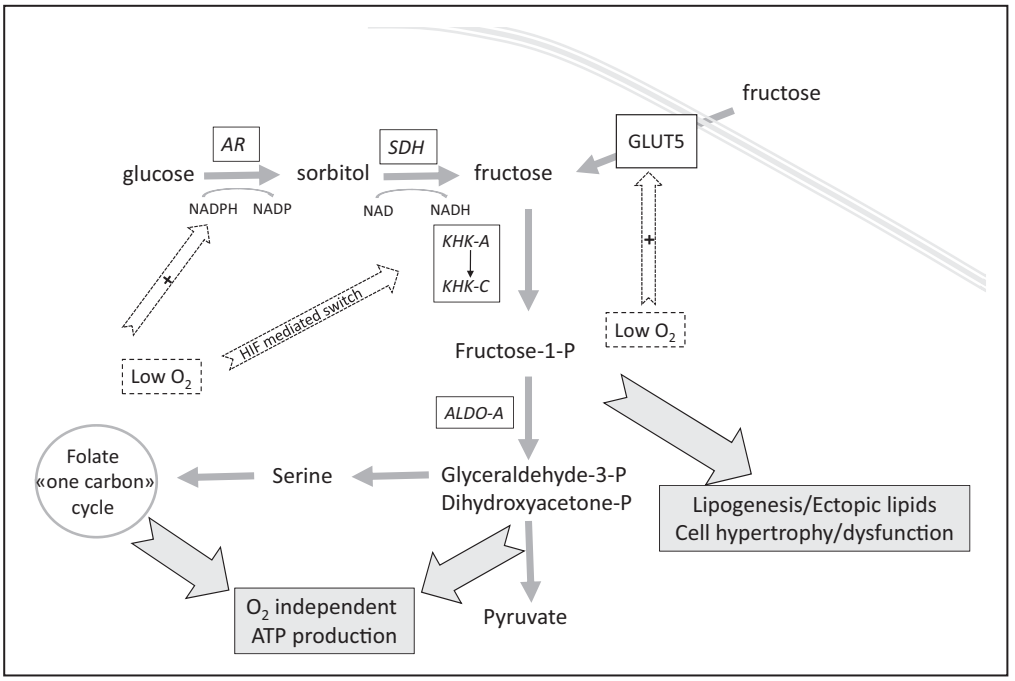

FIGURE 2. Fructose can be synthesized from glucose in many cells by the polyol pathway, which involves the enzyme aldose reductase and sorbitol dehydrogenase. This pathway is active in male seminal vesicles, in placenta, and in many other tissues during hyperglycemia. Recent evidence suggests that it may be stimulated during hypoxia, at least in specific animal models. In hypoxic cells, increased endogenous fructose production, associated with increased expression of fructose transporters GLUT5, and with a switch from ketohexokinase-A to ketohexokinase-C may favor ATP production from unregulated fructolysis. Whether nonoxidative ATP synthesis from serine-one carbon cycle-purine synthesis may contribute to anaerobic ATP production remains unknown. Stimulation of fructolysis may confer some benefit regarding energy provision, but may also come along with adverse effects resulting in metabolic dysregulation and cellular damage.

it was proposed that this endogenous fructose may contribute to the development of hepatic insulin resistance, dyslipidemia, and ectopic fat deposition [58]. It was further shown that enzymes of the polyol pathway were upregulated, and that fructose production from glucose was increased in streptozotocin-induced diabetic rats. Furthermore, the development of glomerular and tubular injury was significantly reduced in streptozotocin-diabetic KHK-C deficient rats compared with rats with normal KHK-C expression [59]. This raises the hypothesis that endogenous fructose may be involved in the development of diabetic nephropathy, or of other kidney diseases related to obesity and insulin resistance.

In contrast with these reports proposing that endogenous fructose production may be linked to metabolic diseases, a very surprising study reported a beneficial, life-saving effect of fructose production in the naked mole-rat [60▪▪]. This rodent lives in deep holes, sometime several meters under the earth surface, and is known to be exceptionally resistant to hypoxia and acidosis. Its blood concentration of fructose (and surprisingly, sucrose) was shown to increase several fold during hypoxia, suggesting that hypoxia increased polyol pathway activity and endogenous fructose synthesis. The ensuing fructose metabolism in the hypoxic mole rat turned out to be advantageous in replacing anaerobic ATP production from glycolysis, which is potently inhibited by downstream substrates accumulation and acidosis, by unregulated fructolysis (Fig. 2).

CONCLUSION

There is no doubt that sugar nowadays makes a major contribution to our total energy intake, and as such contributes to the pathogenesis of obesity. Ingestion of large amounts of fructose causes an overflow of energy substrates which results in increased gluconeogenesis and de novo lipogenesis in the liver. This is associated with mild hepatic insulin resistance, increased VLDL-TG secretion, and increased hepatic triglyceride storage. These effects of fructose may be instrumental in the development of diabetes, NAFLD, and cardiovascular diseases in the long term.

Significantly, some recent observations challenge prevalent dogmas related to fructose metabolism. The presence of fructose transporters and

fructose metabolizing enzymes has now been demonstrated in many cells which were not presumed to metabolize fructose, such as adipocytes, skeletal muscle, cardiomyocytes, and some brain cells. There is also growing evidence that endogenous fructose production may be stimulated by specific physiological signals or in pathological conditions and may exert previously unrecognized functions. The role of exogenous and endogenous fructose in the pathogenesis of cancer and metabolic diseases opens important novel research perspectives.

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Conflicts of interest

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