

Fructose: metabolic signal and modern hazard

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There is much interest in the role of sweeteners such as table sugar (sucrose) and high-fructose corn syrup in obesity and metabolic disease. Both sweeteners consist of glucose and fructose, two six-carbon isomeric sugars. Whereas glucose ingestion may promote obesity through its effects to stimulate insulin secretion, fructose has unique metabolic effects that promote triglyceride synthesis and fat accumulation. These effects arise from fructose's well-known role as a signal of metabolic plenty. Under modern conditions of overnutrition, chronic excess fructose drives features of metabolic syndrome. Emerging evidence further links fructose to cancer and dementia. Here we review the biochemical, molecular and physiological distinctions between fructose and glucose, as well as the endogenous fructose pathway that makes fructose from glucose. Through this Review, we highlight the role of fructose not only as a caloric source, but also as a regulator of metabolic health and disease.

Intake of added sugars, such as table sugar (sucrose) and high-fructose corn syrup (HFCS), has increased markedly in the past few centuries in parallel with the rise in obesity and diabetes, with the strongest association being with sugar-sweetened beverages (SSBs)¹. The World Health Organization recommends a total daily energy intake from 'free' sugars of <10%². In the USA and many high-income countries, SSB intake is dropping but overall free sugar consumption still exceeds 10%. In low and middle-income countries, SSB and overall free sugar consumption continue to rise^{3,4}.

One hypothesis for how added sugars might cause obesity is that the sweet and highly palatable characteristics of sugar encourage excessive caloric intake that leads to positive energy balance⁵. Another hypothesis is that the glucose component in sugar results in chronic stimulation of insulin that favours fat storage⁵. Although both

hypotheses carry merit, this Review focuses on the metabolic effects of fructose, the other sugar present in sucrose and HFCS. Fructose has been implicated in driving metabolic syndrome⁶, and while a large exposure comes from added sugars, fructose can also be generated from glucose within the body. Although fructose, especially in the form of SSBs, is a clear contributor to metabolic syndrome, the role of fructose is often less emphasized than the energy balance or glucose–insulin models in reviews discussing the pathogenesis of obesity and metabolic disease⁵.

The physiological effects of fructose metabolism are distinct from those of glucose (Table 1). Fructose catabolism bypasses the regulated steps of glycolysis, with high fructose doses triggering ATP depletion, lactate and glycerate production, and fat synthesis⁷. The metabolic effects of fructose appear to serve as a physiological signal to trigger

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Table 1 | Differences in fructose and glucose actions

| Glucose effects substantially greater than those of fructose |
|---|
| Insulin secretion |
| Satiety |
| Fructose effects substantially greater than those of glucose |
| Carbohydrate oxidation ³⁸ |
| Suppressed fatty acid oxidation ²⁵ |
| De novo lipogenesis ^{25,33} |
| Circulating triglycerides (VLDL triglycerides) ^{25,29} |
| Lactate production (hepatic and intestinal) ²⁵ |
| Acute ATP depletion ¹²¹ |
| Uric acid generation ¹⁸⁷ |
| Hyperinsulinaemia and insulin resistance ^{29,33} |
| Gluconeogenesis (increase G6P phosphatase) ²⁹ |
| Increased intestinal surface (villi) area to enhance fat absorption ⁴⁸ |
| Leptin resistance ¹²⁸ |
| GCK activation ²⁹ |
| ChREBP activation |
| Vasopressin release ⁷¹ |
| FGF21 release ¹³⁰ |
| Increased systemic blood pressure ¹⁸⁸ |
| Increased glomerular hydrostatic pressure ¹⁸⁹ |
| Leaky gut and endotoxaemia ⁴⁴ |
| Reduced satiety |

storage of carbohydrate as fat, to enable survival during future times of limited food availability⁸. Although these effects were evolutionarily beneficial, the excessive intake of fructose today makes it a hazardous nutrient that contributes to obesity and metabolic disease.

Differences in glucose and fructose metabolism

Glucose metabolism

Starches are polysaccharides composed of long chains of glucose molecules, serving as the primary storage form of carbohydrate in plants (such as grains, potatoes and legumes) and the major source of dietary calories worldwide. Starch is broken down into glucose in the intestinal lumen. Some of the glucose is metabolized as it passes through the intestinal wall and liver with the rest entering the systemic circulation where it is the most abundant circulating carbon source (5–10 mM). The rise in blood glucose stimulates a release in insulin that is further enhanced by the gut stimulation of incretins such as glucagon-like peptide 1 (GLP1).

Glucose is primarily catabolized to generate ATP through glycolysis and oxidative phosphorylation (Fig. 1). After entering cells via glucose transporters, glucose is phosphorylated to glucose 6-phosphate (G6P), converted to fructose 6-phosphate (F6P), and then to fructose 1,6-bisphosphate (F1,6P₂) by phosphofruktokinase 1 (PFK1). This is cleaved into trioses that yield two ATP and two lactate (or pyruvate) molecules per glucose. Subsequent oxidation of pyruvate through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation produces an additional 20–30 ATP molecules per glucose molecule.

Glucose metabolism is tightly regulated via the actions of insulin, which promotes both glucose catabolism and glucose storage as glycogen and lipids. Glycolysis is further regulated by energy balance, with ATP inhibiting and adenosine monophosphate (AMP) and adenosine diphosphate (ADP) promoting the key regulated step of PFK1. Glycolysis is feedback inhibited by key downstream carbonaceous products

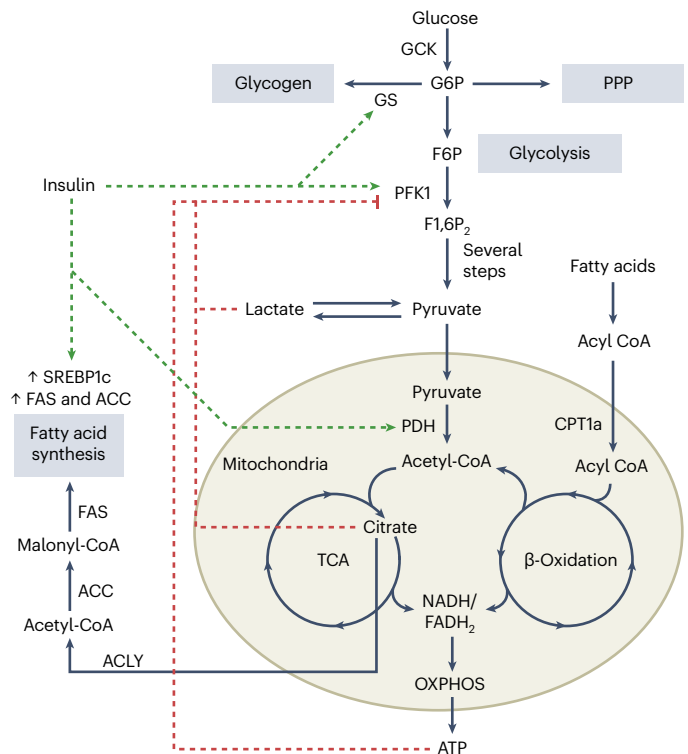


Fig. 1 | Hepatocyte glucose metabolism. The schematic highlights insulin-stimulated (green dashed arrows) hepatic metabolic flux in the fed state that promotes energy storage. This is balanced by inhibition of glucose usage when ATP is high (red dashed arrows). Several key pathways are denoted with grey boxes. ACC, acetyl-CoA carboxylase; ACLY, ATP citrate lyase; CoA, coenzyme-A; CPT1a, carnitine palmitoyltransferase 1a; FAS, fatty acid synthase; FADH₂, flavin adenine dinucleotide (reduced); GS, glycogen synthase; NADH, nicotinamide adenine dinucleotide (reduced); OXPHOS, oxidative phosphorylation pathway; PDH, pyruvate dehydrogenase complex; PPP, pentose phosphate pathway.

including lactate and citrate (Fig. 1). The balance between positive and negative regulation of glucose catabolism helps maintain energy and metabolite homeostasis. Yet glucose can still have pernicious metabolic effects beyond its calories. Specifically, insulin drives fat and glycogen storage, providing an argument for the glucose–insulin model of obesity. So how is fructose different?

Fructose metabolism

In contrast with glucose, fructose metabolism is not tightly regulated by insulin or feedback signals. Whereas in principle, fructose can be metabolized by hexokinase to generate F6P with further catabolism by the same glycolytic pathway as glucose, in practice fructose mainly follows an alternative pathway (Fig. 2). This alternative pathway begins with fructokinase (also known as ketohexokinase or KHK), which has higher affinity for fructose than do standard hexokinases. Crucially, KHK phosphorylates fructose on the first carbon, making fructose 1-phosphate (F1P), a distinctive metabolite with signalling effects. KHK has two major isoforms. KHK-C has high affinity ($K_m = 0.5$ mM) for fructose and is expressed in the small intestine, liver and kidney, as well as in brain microglia and pancreatic islet cells^{9,10}. KHK-A has a lower affinity ($K_m = 10$ mM) and is ubiquitously expressed but at low levels. Thus, most fructose is metabolized by KHK-C⁹.

The resulting F1P, in addition to serving as a signal, can be broken down by the enzyme F1P aldolase (also known as aldolase B) without further phosphorylation into three carbon units, bypassing the heavily regulated glycolytic enzyme PFK1 (Fig. 2). One of these three carbon units is a standard lower glycolytic intermediate (dihydroxyacetone phosphate) and the other is unphosphorylated glyceraldehyde, which

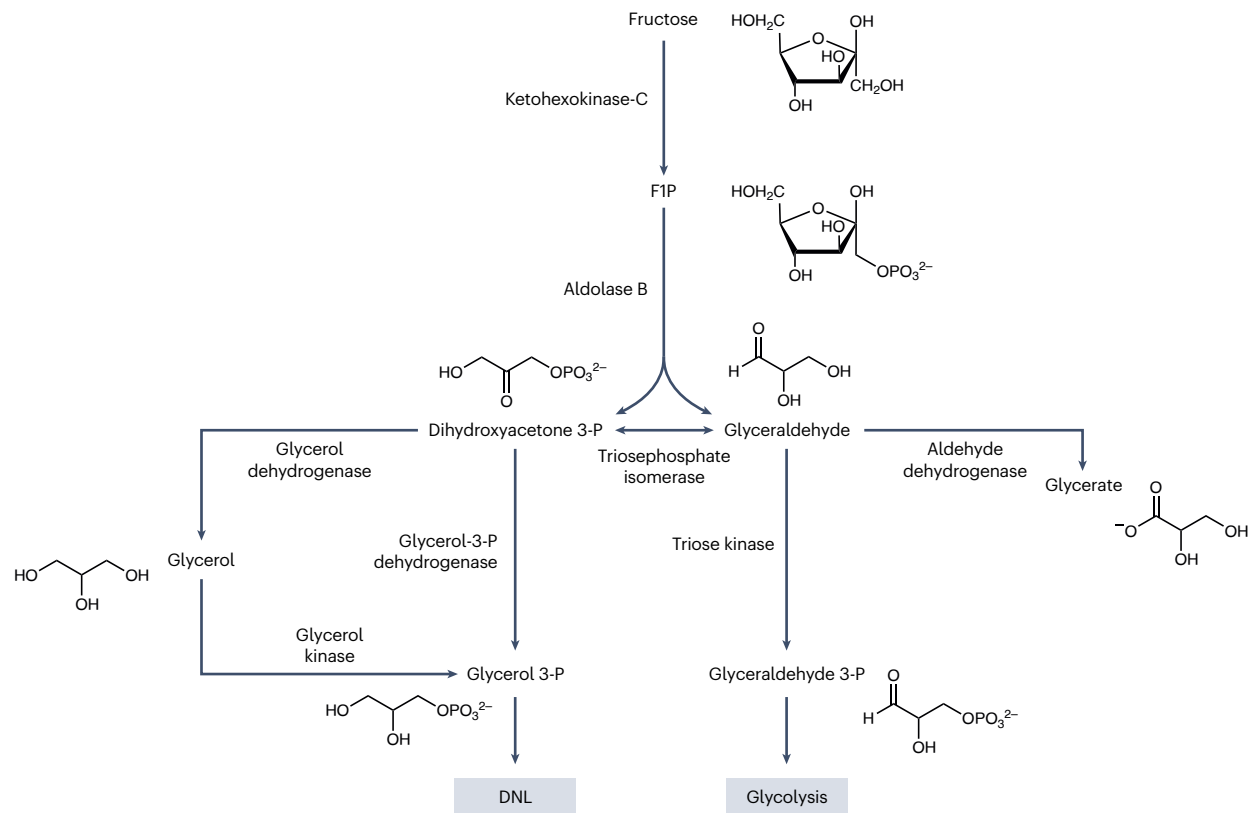


Fig. 2 | Fructose metabolism. The chemical pathway from fructose to triose phosphates is shown with known end-products from fructose. The structures of metabolic intermediates are shown. The structures of the hexoses are in the β -anameric forms utilized by the enzymes. Glycerate enters glycolysis as

2-phosphoglycerate via glycerate kinase (not shown). The major pathways, glycolysis and DNL, to which these triose phosphates enter (thick arrows) are noted by grey boxes. P, phosphate.

has multiple potential fates: phosphorylation by triose kinase to enter glycolysis distal to the PFK1 step, reduction to glycerol, or oxidation to glycerate (Fig. 3). Consequences of the distinctive metabolic pathway for fructose include production of the pro-lipogenic signalling metabolite F1P and promotion of de novo lipogenesis (DNL)¹¹.

Fructose-associated signalling and direct metabolic effects.

Rapid ATP consumption, nucleotide degradation and uric acid generation. The phosphorylation of fructose to F1P by KHK-C is rapid and results in a transient drop in ATP concentration in the liver^{12,13} (Fig. 4). Although seemingly paradoxical—an energy substrate depleting ATP—this reflects initial ATP-consuming steps outpacing downstream ATP generation. This occurs because of the rapidity of the reaction and because there is no regulatory feedback to slow the reaction to preserve ATP levels.

Fructose-induced ATP depletion has been demonstrated in the livers of individuals taking fructose orally (75 g) as measured by magnetic resonance spectroscopy¹⁴, as well as intravenously using lower doses^{15,16}. ATP typically recovers within 1 h. This effect is most severe in pericentral hepatocytes and is not observed in mammals similarly administered glucose¹⁷.

The fall in ATP levels is accompanied by a rise in AMP and fall in guanosine triphosphate (GTP) and inorganic phosphate levels (Fig. 4). The low GTP and inorganic phosphate levels activate liver and intestinal AMP deaminase 2 to convert the AMP to inosine monophosphate (IMP)^{13,18}. The IMP is further degraded, generating uric acid. Both intracellular and serum uric acid levels rise rapidly—within 15 min to 60 min—following fructose ingestion, coinciding with a drop in intracellular ATP levels¹⁹. Whereas the acute postprandial rise in serum uric acid lasts only a few hours, both fasting and postprandial serum uric

acid levels rise when fructose is administered in the long term²⁰. This is mediated by stimulation of urate synthesis²¹.

Unregulated fructolysis. F1P is cleaved by aldolase B to generate trioses that enter into glycolysis or gluconeogenesis but bypass PFK1, which is the site where glycolysis is normally regulated²². This allows for the rapid and unregulated production of glycolytic end-products (Fig. 3). Isotope studies document that as much as 25% of fructose is converted to lactate; other major fructose fates are resynthesis into glucose and glycogen, glycerate generation and oxidation in the liver²³.

F1P as a signalling molecule that enhances hepatic glucose metabolism.

F1P accumulates when KHK makes F1P faster than F1P is cleaved by aldolase B. Such accumulation is augmented by an inhibition of aldolase B by the IMP²⁴. In the setting of fructose consumption, the accumulated F1P functions as a nutrient-sensing signal. One of the signalling effects of F1P is activation of liver glucose catabolism via glucokinase (GCK), the low-affinity liver-specific hexokinase. F1P dissociates GCK from its regulatory protein (GCKR) in the hepatocyte nucleus. GCK then translocates to the cytosol where it stimulates liver glucose uptake and production of G6P that can feed glycogen synthesis or the pentose phosphate pathway; however, glycolysis is attenuated owing to PFK1 inhibition²⁵ (Fig. 2). The accumulation of G6P and NADPH (from the pentose phosphate pathway) can activate aldose reductase and the generation of fructose from glucose via the polyol pathway²⁶.

Thus, in addition to being made from dietary fructose, F1P may also arise from an alternative pathway of glucose catabolism, in which glucose is first converted to fructose before being broken down. Hepatic flux from glucose to F1P has been demonstrated by isotope tracing²⁷. The first enzyme of this pathway, aldose reductase, has a

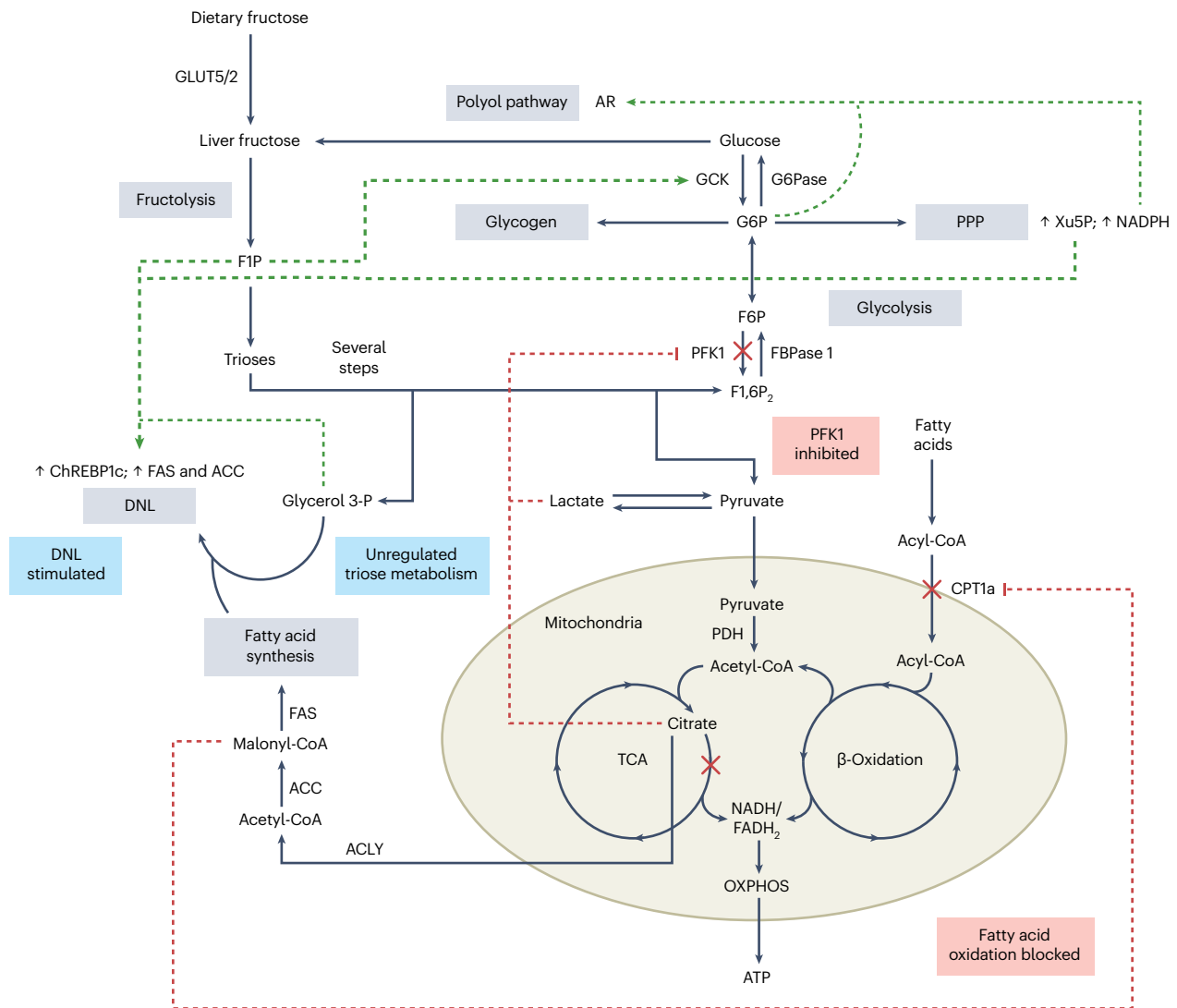


Fig. 3 | Hepatocyte fructose metabolism. The major differences with glucose metabolism are highlighted in the shaded boxes, which are consequences of regulatory effects that activate (green dashed arrows) or inhibit (red dashed arrows) key enzymes or transcription factors as indicated. The stimulation of GCK facilitates glucose uptake and might further enhance

fructose generation via the polyol pathway. AR, aldose reductase; FBpase 1, fructose 1,6-bisphosphatase 1; G6Pase, glucose 6-phosphatase; GLUT, glucose transporter; NADPH, nicotinamide adenine dinucleotide phosphate (reduced); Xu5P, xylulose 5-phosphate.

similar affinity for glucose as GCK; hence, this pathway may be substantial in the liver (Fig. 2). Thus, in addition to directly being catabolized into pyruvate and lactate, fructose can also promote liver glucose catabolism.

ChREBP orchestrates fructose-mediated events. Fructose rapidly activates the carbohydrate-sensing transcription factor (carbohydrate-response element-binding protein or ChREBP) and induces expression of the ChREBP- β isoform in the intestine and liver^{6,28,29}. In the liver, ChREBP may be activated by metabolites produced from fructose such as glycerol 3-phosphate³⁰ or xylulose 5-phosphate³¹. It may also be triggered by fructose's induction of uric acid³² and of glucose-derived metabolites whose levels rise in response to GCK activation by F1P²⁹. ChREBP drives many fructose-dependent pathways, including glycolysis, fructolysis, gluconeogenesis and DNL²⁹ (Fig. 3). DNL is stimulated by fructose to a greater extent than glucose^{33–36} and this is mediated in part by ChREBP²⁹ and the sterol regulatory element-binding protein 1c (SREBP1c)³³. Activation of both transcriptional pathways is greater with fructose than with glucose³³.

Downstream physiological and pathological effects. *Shift from fatty acid to carbohydrate oxidation.* As measured by the respiratory exchange ratio, fructose ingestion shifts metabolism from fatty acid to carbohydrate oxidation to a yet greater extent than that observed with glucose^{37–39}. This occurs despite glucose more strongly inducing circulating insulin, a major effector of increased respiratory exchange ratio. The decrease in fatty acid oxidation following fructose ingestion is distinct from glucose and is greatest in the postprandial period^{37,38}, and may be mediated, in part, by fructose's ability to increase hepatocellular malonyl-CoA, which drives fatty acid synthesis and inhibits fat oxidation^{25,39} (Fig. 3). However, additional mechanisms are probably required to account for this systemic shift to carbohydrate oxidation³⁷.

DNL. The stimulation of hepatic ChREBP during fructose metabolism is a primary mechanism driving DNL. However, several additional mechanisms have been identified. First, fructose metabolism is associated with citrate accumulation, perhaps by inhibition of mitochondrial aconitase. Citrate is a substrate for ATP citrate lyase and subsequent

DNL⁴⁰ (Fig. 3). Excess fructose intake can also lead to passage of fructose to the colon, where it can be metabolized to acetate, which subsequently can reach the portal vein and liver, to be converted to acetyl-CoA and fat⁴¹. Fructose metabolism in the intestine also causes local ATP depletion, F1P accumulation and ChREBP activation^{28,42}, which may disrupt tight junctions and cause leaky gut⁴³. This leakiness can produce endotoxaemia that stimulates cytokine release by hepatic macrophages and Kupffer cells that can contribute to upregulation of enzymes involved in DNL⁴⁴. Suppression of endotoxaemia with antibiotics in fructose-fed mice reduces hepatic fat accumulation, as can blocking KHK metabolism specifically in the liver⁴⁵. This suggests that the fatty liver induced by fructose is dependent on multiple mechanisms including substrate availability, enzymatic activity and inflammation.

Increased circulating triglycerides. Fructose consumption elevates circulating triglycerides, which typically peak 4 h to 6 h after ingestion. The magnitude of triglyceride increase depends on the dose and duration of fructose exposure and is associated with elevated postprandial serum apolipoprotein B^{35,46} and in the long term with increased visceral obesity³⁵. These effects are not observed to the same extent with equivalent glucose consumption^{35,46}.

Whether or not fructose carbons are incorporated into the circulating triglycerides is a matter of debate. Fructose increases the synthesis of triglycerides as noted by studies using labelled fatty acids (palmitate) or fructose³⁸. One isotope tracer study found that nearly 40% of the glycerol fraction of triacylglycerol contained fructose carbons (probably from the glycerol 3-phosphate generated during fructose catabolism; Fig. 2), whereas only a small amount of fructose carbon (<1%) was present in the fatty acids of very low-density lipoprotein (VLDL) triacylglycerol³⁸. However, fructose carbons are incorporated into lysophosphatidylcholines that have not been the focus of previous isotopic tracing studies⁴⁷. Thus, fructose contributes to DNL both through substrate provision and lipogenic signalling.

Other mechanisms for the increase in circulating triglycerides have been identified. First, fructose-containing SSBs increase intestinal absorption of fats in mice in part by lengthening villi⁴⁸. Metabolism of fructose also results in impaired clearance of VLDL triglycerides⁴⁹, possibly by altering lipolysis in adipose, or by decreased removal of VLDL triglycerides by the liver³⁸, which is linked with a fructose-dependent rise of apolipoprotein CIII⁵⁰.

Hepatic and systemic insulin resistance. Although dietary fructose does not elicit an insulin response due to lack of the fructose transporter GLUT5 on islet cells, over time there is development of both hepatic and peripheral insulin resistance and associated hyperinsulinaemia^{33,35}. By contrast, glucose-enriched diets induce hepatocellular insulin resistance to a lesser degree³³. Hepatic insulin resistance is linked with fructose-induced steatosis and accumulation of specific lipid species such as ceramides⁵¹, a reduction in insulin signalling due to a reduction in insulin receptor and insulin-receptor substrate 2 (IRS2) expression, increased protein-tyrosine phosphatase 1B (PTP1b)³³ and inhibition of the PI3K–Akt signalling pathway³³. In addition, fructose-induced glucose production is enhanced by ChREBP-mediated upregulation of G6P phosphatase, the final step in gluconeogenesis²⁹. Hepatic insulin resistance in humans has been reported 2 to 3 weeks after ingestion of fructose-based beverages, but not glucose-based beverages^{52,53}.

Systemic insulin resistance has been documented with fructose feeding in rats, with impaired insulin signalling in skeletal muscle and adipocytes⁵⁴. In skeletal muscle there is impaired translocation of the glucose transporter GLUT4 to the plasma membrane, and some reports of impaired insulin-mediated Akt phosphorylation, possibly related to skeletal muscle accumulation of advanced glycation end-products^{55,56}. Similarly, impaired Akt phosphorylation also develops in adipose tissue of fructose-fed rats⁵⁴. There is evidence that

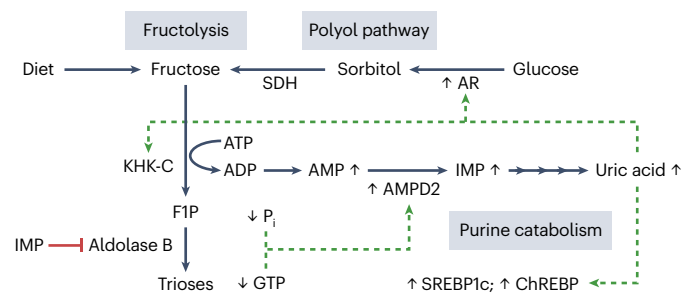


Fig. 4 | Fructose induced ATP depletion and uric acid generation. The schematic highlights the relationship among the fructolytic, polyol and purine degradation pathways (grey boxes). Activation (green dashed arrows) and inhibition (red lines) of key enzymes or transcription factors are indicated. The rapid consumption of ATP by KHK-C and resulting sequestration of phosphate in F1P results in transient ATP depletion and activation of AMP deaminase 2 (AMPD2) to eventually generate uric acid. Uric acid stimulates AR, KHK-C and the transcription factors SREBP1c and ChREBP. IMP inhibits aldolase B, perhaps enhancing the amplification of F1P sequestration. Because humans lack uricase, which converts uric acid to allantoin, the uric acid response is greater in humans than in most mammals. P_i, inorganic phosphate; SDH, sorbitol dehydrogenase.

the peripheral insulin resistance may develop secondary to events downstream of KHK-mediated fructose metabolism in the liver^{57,58}. Similarly, the administration of fructose to humans alters fat oxidation and mitochondrial function in skeletal muscle⁵⁹, and, similarly to rats, hepatic insulin resistance occurs first, followed by systemic insulin resistance^{52,60}.

Of interest, cerebral insulin resistance develops in response to dietary fructose manifesting as a reduction in the signalling of the insulin receptor and IRS1 (ref. 61). The cerebral effects appear to be mediated by local fructose metabolism by microglia expressing KHK¹⁰.

Downstream effects of nucleotide degradation. Activation of the nucleotide-degradation pathway by fructose produces IMP, inosine and eventually uric acid. Uric acid may stimulate intracellular and mitochondrial oxidative stress by driving translocation of NADPH oxidase to mitochondria⁴⁰. Uric acid and associated oxidative stress may also inhibit metabolic enzymes including aconitase in the TCA cycle^{51,62} and enoyl CoA hydratase in β -oxidation³². Uric acid can further activate ChREBP³² and SREBP1c⁶³ and stimulate expression and activation of KHK³² and aldose reductase⁶⁴, which can lead to further fructose generation (Fig. 4). Uric acid also inhibits AMP-activated protein kinase⁶⁵ and stimulates pro-inflammatory and vasoconstrictive factors⁶⁶.

Effects of fructose on mitochondrial function. Studies in fructose-fed animals document that fructose-induced ATP consumption is commonly associated with a compensatory stimulation of the TCA cycle and enhanced mitochondrial respiration and coupling^{27,51,67}. Mitochondrial oxidative stress due to translocation of NADPH oxidase to the mitochondria also occurs^{10,40}, associated with downregulation of nuclear factor erythroid 2-related factor 2 (NRF2) and antioxidant pathways⁵¹. Possibly as a consequence, long-term consumption in rats of HFCS has been reported to adversely affect liver mitochondrial function, with decreased mitochondrial numbers, disrupted cristae, reduced ATP production and decreased energy efficiency^{62,68,69}. Although studies in humans remain limited, there is some evidence that fructose impairs mitochondrial function in muscle⁵⁹. Accordingly, reducing fructose intake could potentially enhance mitochondrial health⁷⁰.

Vasopressin regulation. Much like glucose stimulates a hormonal response in the form of insulin, fructose stimulates production and release of the hormone vasopressin, also known as antidiuretic hormone⁷¹. Vasopressin is synthesized in the hypothalamus and released

by the pituitary to increase water retention and blood pressure. The rise in plasma vasopressin levels in humans in response to fructose does not occur with equimolar glucose⁷¹. Studies in mice show that the release is dependent on fructose metabolism by KHK⁷². SSBs also increase vasopressin (as reflected by an increase in plasma copeptin, a stable cleavage product of the vasopressin pro-protein)⁷³, and circulating copeptin levels both predict and are elevated in individuals with metabolic syndrome and diabetes⁷⁴.

The arginine vasopressin receptor 1a (V1a) is responsible for the increased systemic blood pressure triggered by vasopressin, whereas the V2 receptor mediates urinary concentration. By contrast, the V1b receptor mediates vasopressin-induced production of adrenocorticotropic hormone (ACTH) and the release of cortisol, and also stimulates the release of glucagon, which are powerful glucose-elevating hormones. Mice lacking vasopressin V1b (but not V1a) have lower cortisol, glucagon and liver KHK, and are protected from fructose-induced metabolic syndrome⁷². This metabolic improvement may not be specific to fructose, as mice lacking V1b show reduced ACTH and corticosterone responses in response to other stressors such as forced swimming. The role of vasopressin suggests that better hydration, which lowers vasopressin, could potentially mitigate metabolic syndrome, with proof of concept shown in mice⁷². Thus, vasopressin is a fructose-induced hormone with strong connections to blood pressure and metabolic syndrome. Both the ancient reasons for evolution of the fructose–vasopressin circuit and the clinical potential of its targeting to treat modern metabolic problems merit further investigation.

Dietary fructose absorption and metabolism

Table sugar (sucrose) is a disaccharide containing equimolar fructose and glucose, whereas HFCS is most commonly a mixture comprising 55% fructose and 45% glucose. The major source of dietary fructose comes from SSBs and ultra-processed foods with abundant sucrose or HFCS, but high levels of fructose are also found in fruits, fruit juices and honey. Small amounts of fructose are also present in certain vegetables (such as sweet potatoes and carrots).

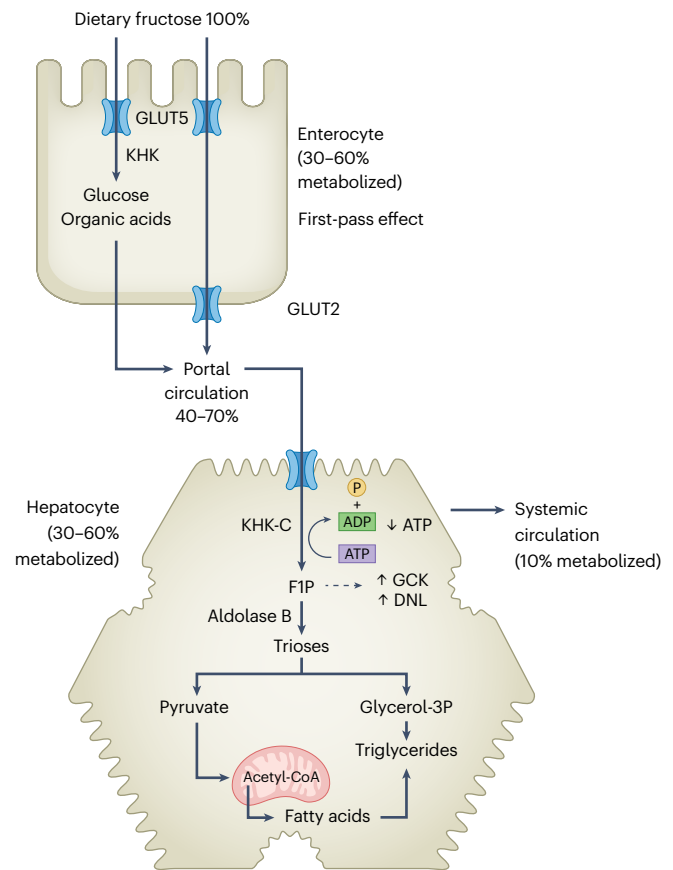
Whereas HFCS sugars are ingested as monosaccharides, the sucrose disaccharide is cleaved into glucose and fructose in the small intestine by sucrase-isomaltase. Despite this extra enzymatic step, there appears to be minimal difference in the physiological effects of sucrose and HFCS⁷⁵. Glucose is absorbed by enterocytes in the small intestine by the sodium-dependent transporter SGLT1, while fructose is taken up by GLUT5, and both exit into the portal system through the GLUT2 transporter.

Once in the enterocyte, fructose is metabolized by KHK-C, generating primarily glucose and organic acids⁷⁶ (Fig. 5). With low intake, most fructose is metabolized in the intestine, but higher intakes can saturate intestinal metabolism and lead to greater fructose delivery to the liver. Thus, intestinal metabolism functions to shield the liver from small quantities of ingested fructose⁷⁶. The fructose clearance rate of the human intestine is uncertain. Fructose metabolism in the gut also enlarges intestinal villi, increases absorption of high-fat foods and may induce leaky gut by disrupting tight junctions.

Fructose absorption is affected by many factors. For example, it is enhanced by the presence of glucose via mechanisms still not fully understood⁷⁷. Expression of GLUT5, the essential luminal fructose transporter, is low in infancy, but expression increases in response to dietary fructose and sugar⁷⁸. This increase is dependent on ChREBP²⁸. Higher GLUT5 expression is associated with a higher risk for obesity in children⁷⁹.

Fructose-based drinks are also more effective than fructose-based foods to induce KHK-dependent metabolism and downstream events in the liver⁸⁰. Not only is this due to the amount ingested, but the speed of ingestion⁷³, probably because rapid intake leads to saturation of intestinal fructose clearance and higher fructose concentrations in the liver. The presence of fibre can also slow absorption and, along with

a Dietary fructose



b Endogenous fructose

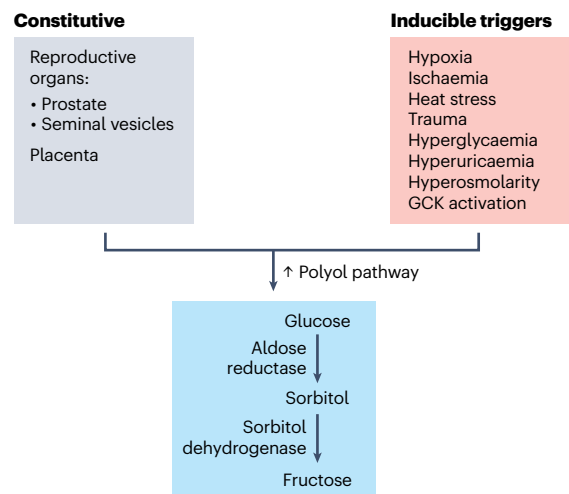


Fig. 5 | Sites of fructose metabolism. **a**, Dietary fructose is absorbed by enterocytes of the small intestine, exported to the portal circulation and then enters the liver and systemic circulation. Percentages shown may vary according to species and condition. **b**, Fructose can also be produced endogenously from glucose through the polyol pathway (blue box). Fructose production is regulated by aldose reductase. Those tissues with constitutive expression are listed in the grey box. Other tissues require induced expression by various stresses listed in the red box. Image originally created in BioRender. Sánchez-Lozada, L. <https://biorender.com/trgqhiw> (2025).

ascorbate, potassium and flavanols, slow or inhibit fructose metabolism. This may help explain why ingestion of fruit, the main source of natural fructose, does not typically result in adverse metabolic

Table 2 | Factors that activate endogenous fructose production

| Type of stress | Examples |
|---|---|
| Hyperosmolarity | Water deprivation ¹⁰² |
| | Salt intake ⁸⁹ |
| | Alcohol intake ¹⁴⁹ |
| Hyperglycaemia | Hyperglycaemia and diabetes ¹⁰¹ |
| | High-glycaemic diet ⁹⁹ |
| Low oxygen | Hypoxia (sleep apnoea) ¹¹⁶ |
| Ischaemia | Myocardial infarction, acute kidney injury ^{93,94} |
| Fructose metabolism by KHK (such as GCK activation) | Western diet-induced steatosis ¹⁴⁸ |
| Heat stress | Heat stress-induced kidney injury ⁹⁶ |
| Physical or emotional stress | Following major surgery ⁹⁷ |
| Pregnancy | Brain production ⁹⁸ |
| Uric acid | Hyperuricaemia ⁶⁴ |

effects^{8,51}. Ingestion of inulin (a fructan polymer consisting of a linear chain of fructose molecules) can stimulate the growth of bacteria that will degrade fructose in the gut and protect mice from fructose-induced fatty liver⁸². However, other fructans (such as levans that form net-like structures of fructose) can be degraded by bacteria such as *Streptococcus* that release fructose, and may induce metabolic syndrome, at least in horses⁴³.

Of the dietary fructose that reaches the liver, the majority is metabolized on the first pass. Many of the detrimental metabolic effects of fructose are mediated by its metabolism in the liver, and liver-specific KHK knockout mice are protected from fructose-induced fatty liver, insulin resistance and obesity⁵⁸. Only 10% to 20% of the ingested fructose enters the systemic circulation^{6,76,83}, where it is metabolized by other tissues (with contributions from the kidney, muscle, heart, adipose tissue, lung, brain and circulating monocytes^{9,10,84–86}) or excreted in the urine. Overall, the first-pass metabolism of fructose aligns with its role as an ancient signal to store carbohydrate as fat, with intestinal clearance ensuring that the liver ‘fat switch’ is turned on only when fructose is sufficiently abundant.

Endogenous fructose production and metabolism

Fructose can be converted to glucose via gluconeogenesis where fructolytic products are diverted to F1,6P₂, F6P, G6P and then to glucose (Fig. 3). Conversely, glucose can be transformed to fructose via the polyol pathway: glucose is first converted to sorbitol by aldose reductase, followed by conversion to fructose by sorbitol dehydrogenase (Fig. 4).

Constitutive production of fructose has been documented in human reproductive organs including in the placenta in early pregnancy where fructose is present in amniotic fluid¹⁸⁷ and in the prostate gland and seminal vesicles where fructose concentrates in semen⁸⁸. Sperm use hexokinase and not KHK to metabolize fructose⁸⁸, and both mice and humans lacking KHK are fertile.

Aldose reductase, the committal enzyme, is not normally expressed in non-reproductive tissues, except for in the renal medulla where it generates sorbitol as an intracellular osmolyte that protects kidney epithelial cells from osmotic stress. Importantly, however, aldose reductase can be induced in other tissues by stimuli including hyperglycaemia, hyperosmolarity, hypoxia, ischaemia, heat, trauma, hyperuricaemia and GCK activation^{89–98} (Fig. 5 and Table 2).

Historically, the role of endogenous fructose was considered minimal. However, a study in mice found that chronic glucose ingestion led to obesity and metabolic syndrome accompanied by induction

of aldose reductase with accumulation of fructose and sorbitol in the liver⁹⁹. Importantly, mice lacking either aldose reductase or KHK were protected from developing fatty liver or insulin resistance⁹⁹.

Endogenous fructose production is increased with high salt⁸⁹ or alcohol intake¹⁰⁰ and this endogenously produced fructose may contribute to metabolic syndrome and fatty liver in these contexts. Experimental studies have now identified increased endogenous fructose production in many contexts, including diabetes, ischaemic or heat-stressed kidneys, ischaemic heart and the brains of animals with diabetes, head trauma, dehydration or intake of high-salt or high-sugar diets^{85,93,94,101,102}. Systemic hypoxia can also increase serum fructose levels in the naked mole rat, and this facilitates survival in hypoxic burrows, nominally by promoting glycolysis¹⁰³.

Evidence for endogenous fructose production in humans is also emerging. Francey et al.⁸³ documented a tripling of the endogenous fructose production rate following administration of an oral glucose–fructose beverage in healthy people. ‘Clamping’ blood glucose at hyperglycaemic levels in healthy individuals induced fructose production in the human brain¹⁰⁴. Interestingly, fructose and sorbitol levels are elevated in brain tissue or cerebrospinal fluid in multiple sclerosis, cranial hypertension, Alzheimer’s disease, bipolar disease, pregnancy and individuals with brain tumours^{105–111}. Various cancers have also been shown to have aldose reductase expression associated with fructose production¹¹². Diabetes, obstructive sleep apnoea and chronic kidney disease are all associated with increased fasting circulating fructose levels in human populations, suggestive of increased endogenous fructose production in these conditions^{113–116}.

These studies suggest that the potential exposure to fructose is high in Western societies, not only from added sugars in the diet, but also due to the high dietary content of carbohydrate that can provide substrate for fructose production, a process amplified by intake of salty foods and alcohol.

Biological consequences of fructose metabolism

An important question is how fructose metabolism translates into its biological effects. Sweet taste, F1P signalling, ATP depletion, uric acid generation and stimulation of glycolytic and lipogenic pathways are all involved in driving the biological effects of fructose metabolism.

Taste, hunger and food intake

Sugar (sucrose) and HFCS are sweet and palatable, and the sweet signals activate orexigenic pathways, including an amygdala-to-hypothalamic circuit that stimulates consumption of sweet foods¹¹⁷. However, the increase in food intake cannot fully explain the effects of fructose on systemic metabolism. For example, mice lacking sweet taste receptors still develop a dopamine response to sucrose, whereas this does not occur with artificial sugars¹¹⁸. Indeed, mice lacking taste still seek sugar (or fructose), and, although they drink less than normal mice, they still develop metabolic syndrome¹¹⁹.

KHK knockout mice no longer prefer fructose, although they continue to prefer glucose. Mice lacking KHK only in the intestine show a reduced preference for fructose, but demonstrate enhanced delivery of fructose to the liver that leads to increased propensity for metabolic syndrome^{58,76}. It is possible that mice lacking intestinal KHK may have some impaired absorption of fructose that could cause subclinical gastrointestinal side effects that lead to less intake⁵⁸. Mice with liver-specific KHK knockout continue to show a marked preference for and excessive intake of fructose but are protected from weight gain or metabolic syndrome⁵⁸. These studies show that while the taste and palatability of fructose encourage intake, it is the metabolism of fructose in the liver that drives metabolic disease.

Central orexigenic and other pathways are also likely to be important for how fructose induces hunger and food intake¹²⁰. For example, glucose injected into the cerebral ventricles of mice causes a rise in

brain ATP levels, induces satiety and curtails food intake¹²¹. By contrast, injection of fructose lowers ATP, stimulates hunger and increases food intake¹²¹. In humans, fructose ingestion also causes a reduction in cerebral cortical blood flow to brain areas involved in self-control while stimulating occipital visual centres to identify appealing foods^{122,123}, consistent with the stimulation of foraging-like activity^{124,125}. By contrast, glucose acutely increases cortical blood flow and satiety. The liver ATP depletion that occurs with fructose also stimulates hunger¹²⁶.

Nevertheless, mice provided fructose in drinking water initially compensate for the fructose caloric intake by lowering their intake of chow to maintain overall caloric balance¹²⁷. This can last for several weeks, but then food intake gradually increases with an increase in weight. Experimentally, this is associated with the development of central leptin resistance^{128,129}.

While experimental studies favour fructose metabolism in driving hunger and weight gain, fructose (and sucrose) stimulates hepatic fibroblast growth factor 21 (FGF21), which acts to reduce sugar intake and sweet preference in humans. Ingestion of glucose is less potent than fructose in stimulating FGF21 (ref. 130). Studies in laboratory mice suggest the stimulation of FGF21 is dependent on fructose metabolism by hepatic KHK⁵⁸. These studies suggest fructose metabolism may also have a negative feedback system to limit excessive sugar intake.

Metabolic syndrome and obesity

The administration of fructose to mice and rats is commonly used to induce obesity, metabolic syndrome, diabetes and fatty liver. However, large doses are often required when incorporated into food (50% to 60%) and the most effective method is to provide fructose in the drinking water as HFCS at concentrations similar to SSBs¹³¹. Studies in mice have found that metabolic syndrome can be prevented if KHK-C is knocked out or inhibited^{33,127,132}. Although this could be attributed to the fact that KHK knockout mice drink less fructose than wild-type controls, the protection persists when fructose consumption is matched¹²⁷.

In humans, the metabolic effects of fructose are also best observed with administration of fructose in drinks rather than in food, and especially in individuals who are older, have overweight or have borderline insulin resistance¹³³. One study in healthy, physically active and lean young adults found minimal effects when given packets of high dose (150 g) crystalline fructose daily for 8 weeks¹³⁴, whereas another study in men with overweight found that high doses of fructose in the drinking water (200 g per day) resulted in increases in blood pressure, fasting insulin and serum triglycerides within 2 weeks¹³⁵.

In a prospective clinical trial, fructose-sweetened or glucose-sweetened beverages were administered as 25% of the energy requirement to individuals with overweight or obesity for 10 weeks. Fructose supplementation promoted features of metabolic syndrome including decreased fat oxidation and insulin sensitivity and increased visceral obesity, DNL, postprandial plasma triglycerides and uric acid, and fasting apolipoprotein B, low-density lipoprotein cholesterol, plasminogen activator inhibitor 1 and monocyte chemoattractant protein 1 compared to the group receiving glucose^{20,37,136}.

While fructose induces worse metabolic effects than glucose in humans, most SSBs include both fructose and glucose. Moreover, and as mentioned earlier, experimental studies suggest that over time, glucose-sweetened beverages may increase endogenous fructose production⁵⁸. This can potentially confound studies that attempt to distinguish effects of these two sugars.

Another confounding issue is the common co-occurrence of excess calorie intake and fructose consumption. If caloric intake is controlled, fructose consumption has a minimal effect on body weight in both experimental^{78,137} and human¹³⁸ studies. Any observed modest weight increases are probably attributable to higher expression of transporters (GLUT5) for fructose^{79,139} or greater intestinal villous area that allows more efficient absorption of fat⁴⁸.

As evidenced by pair-feeding studies, however, sugar, HFCS, glucose or fructose can produce metabolic disease even if weight does not increase^{78,99,140,141}. For example, one study found that rats can develop diabetes, fatty liver and hypertension on a high-sugar diet despite caloric restriction⁷⁸. Consistent with this observation, men consuming a weight-maintaining diet that included a fructose-sweetened beverage for 9 days (versus a weight-maintaining diet with glucose beverage) showed decreased fat oxidation and increased DNL, liver fat, postprandial triglyceride and hepatic insulin resistance⁶⁰. In another study, isocaloric restriction of fructose in adolescents with obesity improved features of metabolic syndrome¹⁴². Thus, even in the absence of excessive caloric intake, sugar can drive metabolic disease.

MASLD and alcoholic liver disease

SSBs are strongly linked with the development and severity of metabolic dysfunction-associated steatotic liver disease (MASLD), probably due to the effect of fructose to stimulate DNL and to inhibit fatty acid oxidation¹⁴³. Individuals with MASLD have been found to have elevated KHK mRNA in liver biopsy samples¹⁴⁴. Administration of SSBs has also been found to increase liver fat^{75,145}, whereas reducing fructose intake can decrease liver fat^{146,147}. Experimental studies have also found that knocking out KHK can substantially reduce fatty liver in mice given a high-fat, high-sugar diet as well as a diet supplemented with HFCS^{58,148}. Fatty liver from high-glycaemic or high-salt diets is also associated with endogenous fructose production and is prevented in mice lacking KHK^{89,99}. These studies provide strong support for fructose as a key driver of MASLD.

Alcohol intake can also lead to fatty liver and cirrhosis with histological and biochemical similarities to MASLD. Indeed, the combination of fructose with alcohol can markedly accelerate the development of liver disease¹⁰⁰. More recently it has been shown that alcohol-induced liver disease also involves endogenous fructose, probably resulting from induced aldose reductase due to alcohol's osmotic effects^{100,149,150}. Aldose reductase is also induced in the liver of individuals with alcoholic liver disease. Mice lacking aldose reductase or KHK are largely protected from alcohol-induced liver disease. Of interest, mice lacking KHK or given KHK inhibitors also drink less ethanol¹⁰⁰.

Hypertension, kidney disease and other conditions

A variety of other conditions have been linked with fructose metabolism. Primary hypertension, for example, is strongly linked with intake of SSBs. There is also an interesting interaction, as fructose enhances sodium absorption in the gut¹⁵¹ and sodium reabsorption in the kidney tubules^{151,152}, and high salt intake raises osmolality and induces endogenous fructose production⁸⁹. Perhaps most strikingly, mice lacking KHK are protected from salt-induced blood pressure elevation and cardiac hypertrophy^{89,153}.

Systemic inflammation can potentially also be induced by fructose, by effects on circulating monocytes^{84,86} and by the release of chemokines into the circulation¹³⁶. Local inflammation can also be induced, such as the release of inflammatory mediators by kidney epithelial cells¹⁵⁴, or by the activation of local macrophage-like cells including Kupffer cells¹⁵⁵ and microglia¹⁰.

Acute and chronic kidney disease may also depend on endogenous fructose production. This is suggested by data from mouse models of acute ischaemic tubular injury, contrast nephropathy, heat stress-induced chronic kidney disease and diabetic nephropathy^{93,101,102}. In such models, endogenous fructose production has been shown to occur in the kidney, and mice lacking the ability to metabolize the fructose (that is, KHK knockout mice) were protected from kidney damage.

Ingestion of SSBs also increases the risk of gout. Humans and great apes are much more susceptible to gout from fructose as they lack the hepatic enzyme, uricase, that helps regulate uric acid by degrading it to allantoin. Indeed, mice or rats that have uricase knocked out or inhibited not only have higher uric acid levels but also show enhanced risk

for hypertension, kidney disease and metabolic syndrome, as well as a relatively greater metabolic response to fructose (reviewed in ref. 156).

One of the more interesting findings involves the process of ageing. Mice and rats are known to develop ageing-associated kidney disease, similarly to humans. However, a study of ageing KHK knockout mice on a high-carbohydrate but sugar-free chow found that they were protected from age-associated kidney disease and hypertension¹⁵⁷. Because the dietary carbohydrates were corn, soybean and wheat, all with minimal fructose content, it is likely that the ageing-associated changes in the wild-type mice resulted from endogenous fructose.

Cancer

Fructose metabolism has emerged as a tumour promoter, supporting both tumour-intrinsic and systemic processes that promote disease progression. In multiple cancers, including breast, gastric, lung, hepatic, pancreatic, brain (glioblastoma) and prostate, fructose metabolism has been implicated in cancer growth, proliferation and metastasis^{158–162}. In several instances, fructose is produced endogenously by tumour cells via the polyol pathway, which facilitates cancer cell metabolism, migration and resistance to apoptosis¹¹². In cases where tumours have access to fructose-rich environments, such as the intestine and liver, fructose can be directly obtained and utilized from dietary sources^{163,164}. That said, hepatocellular carcinoma loses fructolytic capacity compared to healthy liver and, owing to the expression of KHK-A instead of KHK-C, stimulates the transcription factor NRF2 that reduces oxidative stress and facilitates cancer growth^{165,166}. Dietary fructose can also promote tumour growth in organs without direct access to dietary nutrients via fructose-derived metabolites, such as lactate and lipids, which are produced by the liver following first-pass metabolism⁴⁷. Within cancer cells, fructose fuels glycolysis and DNL to support macromolecule synthesis and proliferation^{47,163,167}. Moreover, the major product of fructolysis, FIP, functions as a survival signal by increasing HIF1 α transactivation, thereby promoting adaptation to hypoxic conditions¹⁶³. Furthermore, fructose metabolism may shape the tumour microenvironment by influencing the activity of immunosuppressive cell populations^{168,169}. In sum, through multiple mechanisms that merit further investigation, fructose probably promotes cancer.

Brain disorders

The human brain both makes endogenous fructose (such as from hyperglycaemia)¹⁰⁴ and responds to dietary fructose. Ingestion of fructose stimulates foraging-like behaviour with activation of occipital centres involved in food cues while suppressing blood flow to areas associated with self-control (cortex) and recent memory (hippocampus), whereas glucose has opposing effects^{122,123,170}. Chronic inhibition of cortical and hippocampal function from excessive ingestion or production of fructose has been postulated to increase the risk of behavioural disorders and dementia^{124,125}. High fructose and sorbitol levels in the brain occur in both bipolar disease^{106,171} and dementia¹¹¹. Microglia contain KHK-C and are activated by fructose¹⁰, and when this occurs in pregnant mice, the progeny display anxiety disorders¹⁷².

Fructose metabolism in the brain may have a role in Alzheimer's disease¹²⁵. Rats ingesting fructose chronically develop cognitive dysfunction, with cerebral insulin resistance, mitochondrial dysfunction, neuroinflammation and, eventually, amyloid plaques and tau protein aggregates^{61,173–175}. Diabetic mice also have increased endogenous fructose production with cognitive dysfunction that is improved by targeted knockout of KHK-C in the hippocampus¹⁰. Intake of sugar and high-glycaemic foods are also risk factors for Alzheimer's disease, and this disease is associated with fivefold to sixfold higher levels of fructose and sorbitol in the brain in autopsy studies¹¹¹.

Genetic disorders

Two rare genetic disorders of fructose metabolism are essential fructosuria (KHK deficiency) and hereditary fructose intolerance

BOX 1

Genetic disorders of fructose metabolism

Essential fructosuria

- KHK deficiency; autosomal recessive (<1 per 130,000)
- Normal lifespan; asymptomatic
- Prefer salty over sweet foods
- May be protective against obesity or type 2 diabetes (no reports of obesity or type 2 diabetes in affected individuals)
- Excrete 10% of ingested fructose load in urine. Most ingested fructose is metabolized in adipose and other tissues via other hexokinases

HFI

- Aldolase B deficiency; autosomal recessive (1 per 22,000)
- Manifests after weaning with exposure to fructose
- Presents with acute hypoglycaemia after fructose intake, due to impaired hepatic gluconeogenesis
- Biochemically, FIP accumulates pathologically, ATP is depleted
- Causes chronic liver disease and kidney disease (Fanconi syndrome)
- Rescued by inhibition or knock-out of KHK
- Management consists of dietary fructose and sorbitol avoidance
- Associated with fructose, sorbitol and ethanol aversion
- Restriction of high-glycaemic carbohydrate to reduce endogenous fructose generation may also be helpful

(HFI, aldolase B deficiency). The former is asymptomatic, whereas the latter results in a pathological reaction to fructose, characterized by hypoglycaemia and lactic acidosis acutely and MASLD chronically^{176–178} (Box 1). Both experimental and pilot clinical studies suggest that inhibition of KHK could be a promising therapy for individuals with HFI^{177,179}. There are also ongoing experimental studies to genetically edit some of the common mutations that cause HFI in the hope of a permanent cure (M. Lanaspá and D. Tolan, unpublished data).

Conclusions and future directions

Open questions

The role of endogenously produced fructose in metabolic disease remains controversial. Whereas the risk of SSBs on metabolic health is robust, there is less evidence that fructose from other sources carries risk. Interpretation of epidemiological studies is confounded by fruits, which are rich in fructose but carry countering substances. There are also only limited studies in humans to determine the contribution of endogenous fructose.

The temporal relationship between sugar intake and metabolic disease trends remains debated. If fructose and sugar are important drivers of metabolic syndrome, then why has decreased intake of added sugars during the past two decades failed, before the common use of GLP1 agonists, to slow the obesity and diabetes epidemic? One potential reason is that there is generally a 10–20-year lag between sugar exposure and metabolic outcomes¹⁸⁰, and changes in incidence often precede changes in prevalence. Indeed, although the prevalence of diabetes has not decreased, the incidence of diabetes began to fall soon after sugar reduction¹⁸¹, whereas obesity prevalence plateaued around 2020 and began decreasing by 2023 (ref. 182). Importantly, although recent changes in obesity prevalence are affected by widespread GLP1 therapy, the decrease in diabetes incidence predates this.

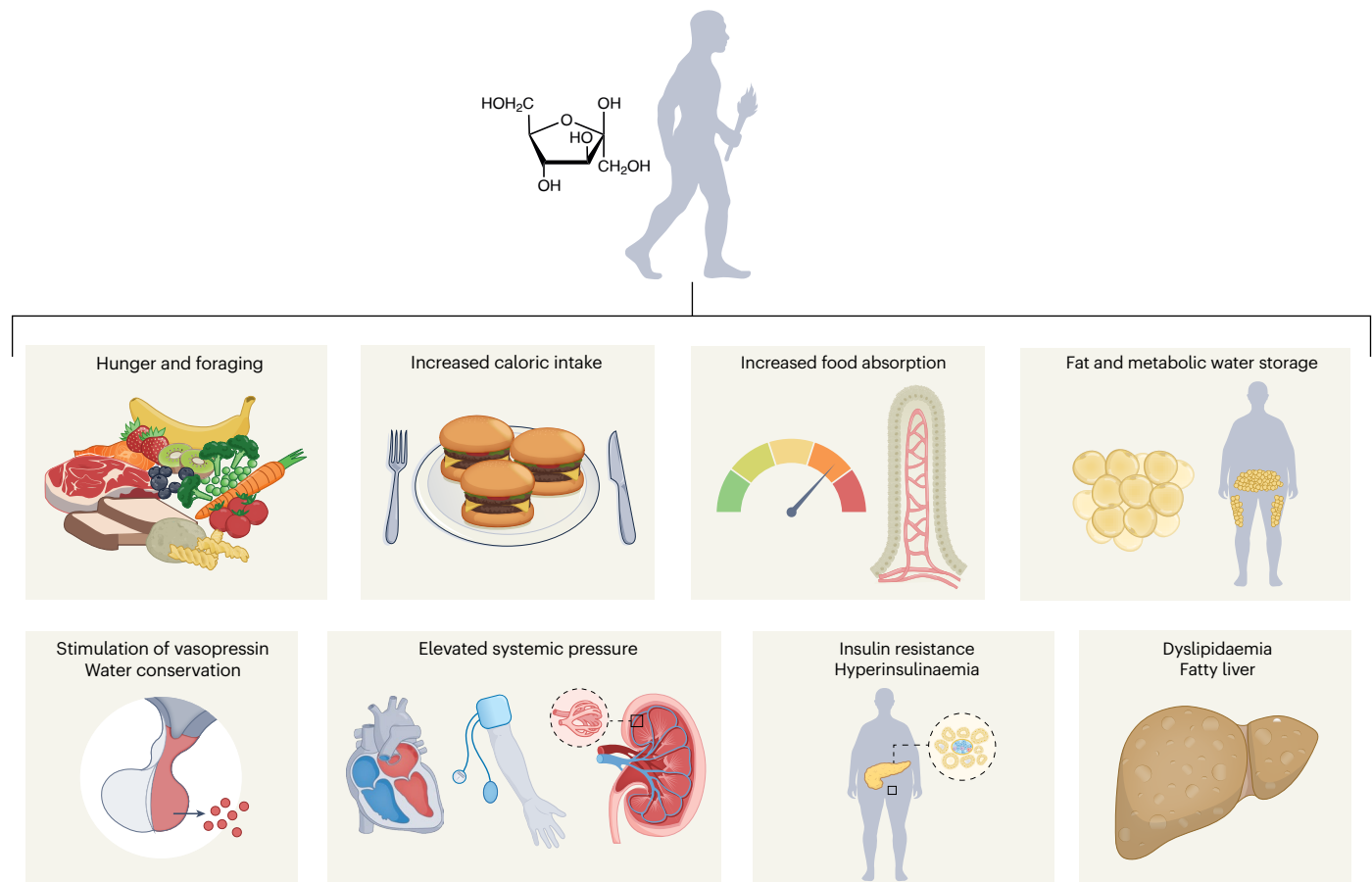


Fig. 6 | The fructose survival hypothesis. Fructose probably provided an evolutionary advantage by activating a ‘survival pathway’ that increased hunger, stimulated foraging and promoted efficient fat storage—traits that helped early hominids endure periods of famine. In modern environments with constant food availability, this once-beneficial mechanism can contribute to metabolic

disease^{8,125}. Six boxes show fructose effects that were probably evolutionarily beneficial but are now problematic (for example, increased caloric intake, elevated systemic pressure). The final two boxes show overtly pathological modern consequences. Image originally created in BioRender. Lanasp, M. <https://biorender.com/4tbwh9h> (2025).

The role of uric acid as a mediator of fructose’s metabolic effects is contentious. Experimental studies link fructose metabolism to increased uric acid and metabolic dysfunction, but Mendelian randomization and large clinical trials generally do not support uric acid as a causal mediator of cardiovascular or renal disease. These discrepancies may stem from genetic studies measuring serum rather than tissue uric acid, and from trial designs that inadequately capture tissue-specific effects¹⁵⁶.

Finally, whether targeting fructose metabolism through KHK inhibition offers therapeutic benefit remains uncertain. Two pharmaceutical companies abandoned KHK inhibitor programmes after phase II studies yielded modest outcomes^{183,184}. Initial studies using Pfizer’s PF-06835919 produced only mild reductions in liver fat (~20%) without significant improvements in insulin, uric acid, inflammation or weight. These limited benefits may reflect a short duration of treatment, suboptimal dosing, off-target effects, or the need to use it in a more select population (such as those with high dietary intake of fructose). It is also possible that KHK inhibition is more effective for disease prevention than treatment¹⁸⁵. As mentioned earlier, there is some clinical evidence that KHK inhibition may benefit individuals with HF1¹⁷⁹. Given KHK’s broad metabolic role, its inhibition still holds promise for improving metabolic health.

Conclusion

In conclusion, fructose has multiple distinctive metabolic effects beyond standard carbohydrate metabolism. It produces signals that promote hepatic glycolysis and lipogenesis. This pro-lipogenic

response presumably reflects an ancient evolutionary adaptive programme intended to prepare for periods of food scarcity (Fig. 6). Fructose’s induction of vasopressin may similarly reflect preparation for water scarcity, with fat storage providing a source of metabolic water¹⁸⁶. In modern society, however, this ancient signalling role can backfire. In the context of consistently abundant food, fructose intake is a hazard, promoting insulin resistance, hypertriglyceridaemia, fatty liver and elevated blood pressure⁸.

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Author contributions

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Competing interests

R.J.J., M.A.L., D.R.T. and J.D.R. have equity with Colorado Research Partners, which is developing KHK inhibitors. R.J.J. also consults for Amgen, Dynamicure, Soba Pharmaceuticals and Kibow and is on the Scientific Board of Blue Oak Nutraceuticals, Santa Barbara Nutrients and RxSugar. M.D.G. holds equity in Faeth Therapeutics and Skye Biosciences; reports consulting or advisory roles with Almac Discovery, Genentech, Faeth Therapeutics, Scorpion Therapeutics and Skye Biosciences; patents, royalties and other intellectual property with Weill Cornell Medicine and Faeth Therapeutics. J.D.R. is a member of the Rutgers Cancer Institute (RCI) and the University of Pennsylvania Diabetes Research Center (U Penn DRC); director of the U Penn DRC-Princeton inter-institutional metabolomics core and RCI metabolomics core; advisor and stockholder in Bantam Pharmaceuticals, Rafael Pharmaceuticals and Empress Therapeutics; a founder, director and stockholder of Farber Partners and Raze Therapeutics; a founder, advisor and stockholder in Marea Therapeutics and Fargo Biotechnologies; and inventor of patents held by Princeton University. S.S., K.L.S., L.G.S.-L. and M.A.H. declare no competing interests.

Additional information

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