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Fructose: Metabolic signal and modern hazard

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Abstract

There is much interest in the role of sweeteners like 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, that account for 15% of the Western diet. While 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

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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), have increased markedly in the last 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 United States 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 balance [5]. Another hypothesis is that the glucose component in sugar results in chronic stimulation of insulin that favors fat storage [5]. While both hypotheses carry merit, this review focuses on the metabolic effects of fructose, the other sugar present in sucrose and HFCS. Fructose has also been implicated in driving metabolic syndrome[6], and while a large exposure comes from added sugars, fructose can also be generated from glucose within the body. Despite the evidence for dietary fructose, and the potential importance of endogenous fructose production in metabolic disease, 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 disease [5].

The physiological effects of fructose metabolism are distinct from glucose (Table 1). Fructose catabolism bypasses the regulated steps of glycolysis, with high fructose doses triggering ATP depletion, lactate and glycerate production, and fat synthesis[7]. The metabolic effects of fructose appear to serve as a physiological signal to trigger storage of carbohydrate as fat, to enable survival during future times of limited food availability[8]. While 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 (like 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 (GLP-1).

Glucose is primarily catabolized to generate ATP through glycolysis and oxidative phosphorylation (Figure 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 ($F1,6P_2$) by phosphofructokinase-1 (PFK-1). This is cleaved into trioses that yield 2 ATP and 2 lactate (or pyruvate) per glucose. Subsequent oxidation of pyruvate through the TCA cycle and oxidative phosphorylation produces an additional 20–30 ATP per glucose molecule.

Glucose metabolism is tightly regulated via 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 AMP and ADP promoting the key regulated step of phosphofructokinase-1. Glycolysis is feedback inhibited by key downstream carbonaceous products including lactate and citrate (Figure 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. While in principle, fructose can be metabolized by hexokinase to generate fructose 6-phosphate (F6P) with further catabolism by the same glycolytic pathway as glucose, in practice fructose mainly follows an alternative pathway (Figure 2). This alternative pathway begins with fructokinase (also known as ketohexokinase, KHK), which has higher affinity for fructose than do standard hexokinases. Crucially, KHK phosphorylates fructose on carbon one, making fructose 1-phosphate (F1P), a distinctive metabolite with signaling effects. KHK has two major isoforms. KHK-C has high affinity (K_m = 0.5 mM) for fructose and is expressed in small intestine, liver, and kidney, as well as brain microglia and pancreatic islet cells[9,10]. KHK-A is lower affinity (K_m = 10 mM) and is ubiquitously expressed but at low levels. Thus, most fructose is metabolized by KHK-C [9].

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 PFK-1 (Figure 2). One of these three carbon units is a standard lower glycolytic intermediate (dihydroxyacetone phosphate) and the other is free phosphorylated glyceraldehyde, which has multiple potential fates: phosphorylation by triose kinase to enter lower glycolysis, reduction to glycerol, or oxidation to glycerate (see Figure 3). Consequences of the distinctive metabolic pathway for fructose include production of the pro-lipogenic signaling metabolite F1P; flow of fructose carbon into F1P, and inhibition of PFK-1 in the classic glycolytic pathway, and generation of lipogenic substrates without the positive and negative regulatory signals that normally tune glycolytic flux to energy status; and thus promotion of *de novo* lipogenesis (DNL). [11]

Fructose-associated signaling and non-caloric effects

1] 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 (Figure 4)[12,13]. While 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 subjects taking fructose orally (75 g) as measured by magnetic resonance spectroscopy [14], as well as intravenously using lower doses[15,16]. ATP typically recovers within one hour. This effect is most severe in pericentral hepatocytes and is not observed in mammals similarly administered glucose.[17]

The fall in ATP levels is accompanied by a rise in adenosine monophosphate (AMP) and fall in guanosine triphosphate (GTP) and inorganic phosphate (Pi) levels (see Figure 4). The low GTP and Pi levels activate liver and intestinal AMP deaminase-2 (AMPD2) 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 to 60 minutes—following fructose ingestion, coinciding with a drop in intracellular ATP levels[19]. While 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 long-term[20]. This is mediated by stimulation of urate synthesis[21].

2] Unregulated Fructolysis. F1P is cleaved by aldolase B to generate trioses that enter into glycolysis or gluconeogenesis but bypass PFK-1, which is the site where glycolysis is normally regulated [22]. This allows for the rapid and unregulated production of glycolytic end products (see Figure 3). Isotope studies document as much as 25% of fructose is converted to lactate; other major fructose fates are resynthesis into glucose/glycogen, glycerate generation, and oxidation in the liver[23].

3] F1P as a Signaling Molecule that Enhances 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 IMP[24]. In the setting of fructose consumption, the accumulated F1P functions as a nutrient-sensing signal. One of the signaling effects of F1P is activation of liver glucose catabolism via glucokinase, the low-affinity liver-specific hexokinase. F1P dissociates glucokinase from its regulatory protein (GCKR) in the hepatocyte nucleus. Glucokinase 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 due to PFK-1 inhibition (Figure 2).[25] The result is a buildup of these hexoses that activates the polyol pathway.

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 tracing.[26] The first enzyme of this pathway, aldose reductase (AR), has a similar affinity for glucose as GCK and hence this pathway may be substantial in the liver (Figure 2). Thus, in addition to directly being catabolized into pyruvate/lactate, fructose can also promote liver glucose catabolism.

4] ChREBP Orchestrates Fructose-mediated Events. Fructose rapidly activates the carbohydrate-sensing transcription factor (ChREBP) and induces expression of the ChREBP-β isoform in the intestine and liver[6,27,28]. In the liver, ChREBP may be activated by metabolites produced from fructose like glycerol 3-phosphate[29] or xylulose 5-phosphate[30]. It may also be triggered by fructose's induction of uric acid[31] and of glucose-derived metabolites whose levels rise in response to glucokinase activation by F1P[28]. ChREBP drives many fructose-dependent pathways, including glycolysis, fructolysis, gluconeogenesis, and *de novo* lipogenesis (DNL) (see Figures 3)[28]. DNL is stimulated by fructose to a greater extent than glucose[32-35] and this is mediated in part by ChREBP[28] and the sterol regulatory element-binding protein (SREBP1c)[32]. Activation of both transcriptional pathways is greater with fructose than glucose[32].

Cellular and Physiological role of Fructose signaling

1] Shift from Fatty Acid to Carbohydrate Oxidation. Fructose ingestion causes a remarkable shift from fatty-acid to carbohydrate oxidation as measured by an increase in the respiratory exchange ratio (RER) that is greater than that observed with glucose[36-38]. This occurs despite glucose more strongly inducing circulating insulin, a major effector of increased RER. The decrease in fatty-acid oxidation following fructose ingestion is distinct from glucose and is greatest in the postprandial period[36,37], and may be mediated, in part, by fructose's ability to increase hepatocellular malonyl CoA, which drives fatty acid synthesis and inhibits fat oxidation (see Figure 3)[25,38]. However, inhibition of hepatic fatty acid oxidation is likely insufficient to account for this acute, systemic shift to carbohydrate oxidation and reduced fatty acid oxidation in skeletal muscle is also likely required[36].

2] De Novo Lipogenesis (DNL). Several mechanisms have been identified for how fructose metabolism stimulates DNL in the liver. First, fructose metabolism is associated with citrate accumulation, perhaps by inhibition of mitochondrial aconitase. Citrate is a substrate for ATP citrate lyase (ACLY) and subsequent DNL (Figure 3)[39]. Excess fructose intake can also lead to passage of fructose to the colon, where it can be metabolized to acetate, that subsequently can reach the portal vein and liver, to be converted to acetyl CoA and fat[40]. Fructose metabolism in the intestine also causes local ATP depletion, F1P accumulation, and ChREBP activation[27,41], which may disrupt tight junctions and cause leaky gut[42]. This leakiness can produce endotoxemia that stimulates cytokine release by hepatic macrophages and Kupffer cells that can contribute to upregulation of enzymes involved in DNL[43]. Suppression of endotoxemia with antibiotics in fructose-fed mice reduces hepatic fat accumulation, as can blocking KHK metabolism specifically in the liver[44]. This suggests that the fatty liver induced by fructose is dependent on multiple mechanisms including substrate availability, enzymatic activity, and inflammation.

3] Increased Circulating Triglycerides. Fructose consumption elevates circulating triglycerides, which typically peak 4 to 6 hours 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[34,45] and in the long-term with increased visceral obesity[34]. These effects are not observed to the same extent with equivalent glucose consumption[34,45].

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 labeled fatty acids (palmitate) or fructose[37]. One isotope tracer study found that nearly 40 percent of the glycerol fraction of triacylglycerol contained fructose carbons (probably from the glycerol-3-phosphate generated during fructose catabolism, see Figure 2), while only a small amount of fructose carbon (<1%) were present in the fatty acids of the VLDL-triacylglycerol[37]. However, fructose carbons are incorporated into lysophosphatidyl-cholines, and these lipid species have not been the focus of prior isotopic tracing studies[46]. Thus, fructose contributes to DNL both through substrate provision and lipogenic signaling.

Other mechanisms for the increase in circulating triglycerides have been identified. First, fructose-containing SSBs increases intestinal absorption of fats in mice in part by lengthening villi[47]. Metabolism of fructose also results in impaired clearance of VLDL-triglycerides[48], possibly by altering lipolysis in adipose, or by decreased removal of VLDL-triglycerides by the liver[37] that is linked with a fructose-dependent rise of apolipoprotein CIII [49].

4] Hepatic and Systemic Insulin Resistance. While dietary fructose does not elicit an insulin response due to lack of the fructose transporter, GLUT5, on the islet cells, over time there is development of both hepatic and peripheral insulin resistance and associated hyperinsulinemia[32,34]. In contrast glucose-enriched diets induce hepatocellular insulin resistance to a lesser degree[32]. Hepatic insulin resistance is linked with fructose-induced steatosis and accumulation of specific lipid species like ceramides[50], a reduction in insulin signaling due to a reduction in insulin receptor and insulin-receptor substrate-2 (IRS2) expression, increased protein-tyrosine phosphatase 1B (PTP1b),[32] and inhibition of the PI3K/Akt signaling pathway[32]. In addition, fructose-induced glucose production is enhanced by ChREBP-mediated upregulation of G6P phosphatase (G6Pase), the final step in gluconeogenesis[28]. Hepatic insulin resistance in humans has been reported two to three weeks after ingestion of fructose-based beverages, but not glucose-based beverages[51,52].

Systemic insulin resistance has been documented with fructose feeding in rats, with impaired insulin signaling in skeletal muscle and adipocytes[53]. 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 (AGEs)[54,55]. Similarly impaired Akt phosphorylation also develops in adipose tissue of fructose-fed rats[53]. There is evidence that the peripheral insulin resistance may develop secondary to events downstream of KHK-mediated fructose metabolism in the liver.[56,57] Similarly, the administration of fructose to humans alters fat oxidation and mitochondrial function in skeletal muscle[58], and, similar to rats, hepatic insulin resistance occurs first followed by systemic insulin resistance[51,59].

Of interest, cerebral insulin resistance develops in response to dietary fructose manifesting as reduction in the signaling of the insulin receptor and IRS1[60]. The cerebral effects appear to be mediated by local fructose metabolism by microglia expressing KHK[10].

5] Biologic Effects from Nucleotide Degradation. Activation of the nucleotide-degradation pathway by fructose may lead to biological consequences beyond altered nucleotide levels. These may include the stimulation of intracellular and mitochondrial oxidative stress, which can occur via uric acid-mediated translocation of NADPH oxidase to the mitochondria[39]. Uric acid and associated oxidative stress may also impact the activity of other key metabolic enzymes and regulatory factors, including inhibiting aconitase in the TCA cycle[50,61] and enoyl CoA hydratase, an enzyme in β-oxidation[31]. A rise in intracellular uric acid can also activate ChREBP[31] and SREBP-1c[62], as well as stimulate expression and activation of KHK[31] and AR,[63] which can lead to further fructose generation (Figure 4). Uric acid also inhibits AMP-activated protein kinase (AMPK)[64], and stimulates proinflammatory and vasoconstrictive factors [65].

6] 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[26,50,66]. Mitochondrial oxidative stress due to translocation of NADPH oxidase to the mitochondria also occurs[10,39] associated with downregulation of nuclear factor erythroid 2-related factor-2 (NRF2) and antioxidant pathways[50]. Possibly as a consequence, long-term consumption in rats of high-fructose corn syrup has been reported to adversely affect liver mitochondrial function, with decreased mitochondrial numbers, disrupted cristae, reduced ATP production and decreased energy efficiency [61,67,68]. While studies in humans remain limited, there is some evidence that fructose impairs mitochondrial function in muscle[58]. Accordingly, reducing fructose intake could potentially enhance mitochondrial health [69].

7] 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 hormone[70]. 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 glucose[70]. Studies in mice show that the release is dependent on fructose metabolism by KHK[71]. SSBs also increase vasopressin (as reflected by an increase in plasma copeptin, a stable cleavage product of the vasopressin pro-protein)[72], and circulating copeptin levels both predict and are elevated in subjects with metabolic syndrome and diabetes[73].

The arginine vasopressin receptor 1a (V1a) receptor is responsible for the increased systemic blood pressure triggered by vasopressin. In contrast, the V1b receptor mediates vasopressin-induced production of adrenocorticotropic hormone (ACTH). ACTH stimulates the release of cortisol and glucagon, powerful glucose-elevating hormones. Mice lacking vasopressin V1b receptor (but not V1a receptor) have lower cortisol, glucagon, and liver KHK and are protected from fructose-induced metabolic syndrome[71]. 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 mice[71]. 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 high fructose corn syrup (HFCS) is most commonly a 55:45% mixture of fructose and glucose. The major source of dietary fructose comes from SSBs and ultra-processed foods with abundant sucrose or HFCS, but fructose is also high 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 HFCS[74]. 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 venous system through the GLUT2 transporter.

Once in the enterocyte, fructose is metabolized by KHK-C, generating primarily glucose and organic acids (Figure 5).[75] 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 fructose.[75] 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 understood[76]. Expression of GLUT5, the essential luminal fructose transporter, is low in infancy, but expression increases in response to dietary fructose and sugar[77]. This increase is dependent on ChREBP[27]. Higher GLUT5 expression is associated with a higher risk for obesity in children[78].

Fructose-based drinks are also more effective than fructose-based foods to induce KHK-dependent metabolism and downstream events in the liver[79]. Not only is this due to the amount ingested, but the speed of ingestion[72], likely because rapid intake leads to saturation of intestinal fructose clearance and higher fructose concentrations in the liver. The presence of fiber can also slow absorption, and, along with 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 effects[8,80]. 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 liver[81]. However, other fructans (such as levans that form net-like structures of fructose) can be degraded by bacteria such as *Streptococcus* that releases fructose, and may induce metabolic syndrome, at least in horses[42].

Of the dietary fructose that reaches the liver, the majority is metabolized on 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 obesity[57]. Only 10 to 20 percent of the ingested fructose enters the systemic circulation[6,75,82], where it is metabolized by other tissues (with contributions from the kidney, muscle, heart, adipose tissue, lung, brain, and circulating monocytes[9,10,83-85]) 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 F1,6P_2, F6P, G6P and then to glucose (see Figure 3). Conversely, glucose can be transformed to fructose via the *polyol pathway:* glucose is first converted to sorbitol by aldose reductase (AR) followed by conversion to fructose by sorbitol dehydrogenase (SDH) (see Figure 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 fluid[86] and in the prostate gland and seminal vesicles where fructose concentrates in semen[87]. Sperm use hexokinase and not KHK to metabolize fructose[87], and both mice and humans lacking KHK are fertile.

AR, the committal enzyme, is not normally expressed in non-reproductive tissues, except for the renal medulla where it generates sorbitol as an intracellular osmolyte that protects kidney epithelial cells from osmotic stress. Importantly however, AR can be induced in other tissues by stimuli including hyperglycemia, hyperosmolarity, hypoxia, ischemia, heat, trauma, hyperuricemia, and glucokinase activation (Figure 5 and Table 2) [88-97].

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 AR with accumulation of fructose and sorbitol in the liver[98]. Importantly, mice lacking either AR or KHK were protected from developing fatty liver or insulin resistance[98].

Endogenous fructose production is increased with high salt[88] or alcohol intake[99] 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, ischemic or heat-stressed kidneys, ischemic heart, and the brains of animals with diabetes, head trauma, dehydration, or intake of high salt or high sugar diets[84,92,100-102]. Systemic hypoxia can also increase serum fructose levels in the naked mole rat, and this facilitates survival in hypoxic burrows, nominally by promoting glycolysis[103].

Evidence for endogenous fructose production in humans is also emerging. Francey et al documented a tripling of the endogenous fructose production rate following administration

of an oral glucose-fructose beverage in healthy people[82]. 'Clamping' blood glucose at hyperglycemic levels in healthy individuals induced fructose production in human brain[104]. Interestingly, fructose and sorbitol levels are elevated in brain tissue or cerebral spinal fluid in multiple sclerosis, cranial hypertension, Alzheimer's disease, bipolar disease, pregnancy, and individuals with brain tumors [105-111]. Various cancers have also been shown to have AR expression associated with fructose production[112]. Diabetes, obstructive sleep apnea, 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 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. Indeed, it is the unique aspects related to F1P signaling, ATP depletion, uric acid generation, and stimulation of glycolytic and lipogenic pathways that drive 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 foods[117]. 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 sugars[118]. Indeed, mice lacking taste still seek sugar (or fructose), and, although they drink less than normal mice, they still develop metabolic syndrome[119].

KHK knockout mice no longer prefer fructose, although they continue to prefer glucose. Mice lacking KHK only in the intestine show reduced preference for fructose, but demonstrate enhanced delivery of fructose to the liver that leads to increased propensity for metabolic syndrome [57,75]. 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 intake[57]. Mice with liver-specific KHK knockout continue to show marked preference for and excessive intake of fructose, but are protected from weight gain or metabolic syndrome[57]. These studies show that while the taste and palatability of fructose encourages intake, it is the metabolism of fructose in the liver that drives metabolic disease.

Central orexigenic and other pathways are also likely important for how fructose induces hunger and food intake[120]. For example, glucose injected into the cerebral ventricles of mice causes a rise in brain ATP levels, induces satiety and curtails food intake[121]. In contrast, injection of fructose lowers ATP, stimulates hunger, and increases food intake[121]. Fructose ingestion also causes in humans a reduction in cerebral cortical blood flow to

brain areas involved in self-control while stimulating occipital visual centers to identify appealing foods[122,123], consistent with the stimulation of foraging-like activity[124,125]. In contrast, glucose acutely increases cortical blood flow and satiety. The liver ATP depletion that occurs with fructose also stimulates hunger[126].

Nevertheless, mice provided fructose in drinking water initially compensate for the fructose caloric intake by lowering their intake of chow to maintain overall caloric balance[127]. 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 favor fructose metabolism in driving hunger and weight gain, fructose (and sucrose) stimulates hepatic fibroblast growth factor 21 (FGF21) that acts to reduce sugar intake and sweet preference in human. Ingestion of glucose is less potent than fructose in stimulating FGF21[130]. Studies in laboratory mice suggest the stimulation of FGF21 is dependent on fructose metabolism by hepatic KHK[57]. 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 SSBs[131]. Studies in mice have found that the metabolic syndrome can be prevented if KHK-C is knocked out or inhibited [32,127,132]. While this could be attributed to that fact that KHK KO mice drink less fructose than wild type controls, the protection persists when fructose consumption is matched[127].

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, overweight or have borderline insulin resistance[133]. One study in healthy, physically active and lean young adults found minimal effects when given packets of high dose (150 g/d) crystalline fructose daily for 8 weeks[134], while another study in overweight men found that high doses of fructose in the drinking water (200g/d) resulted in increases in blood pressure, fasting insulin and serum triglycerides within 2 weeks [135].

In a prospective clinical trial, fructose-sweetened or glucose-sweetened beverages were administered as 25 percent of the energy requirement to overweight or obese individuals 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, LDL cholesterol, plasminogen activator inhibitor-1 (PAI-1), and monocyte chemotactic protein-2 (MCP-1) compared to the group receiving glucose[20,36,136].

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 production.[57] This can potentially confound studies that attempt to distinguish effects of these two sugars.

Another confounding issue is the common cooccurrence of excess calorie intake and fructose consumption. If caloric intake is controlled, fructose consumption has a minimal effect on body weight in both experimental[77,137] and human[138] studies. Any observed modest weight increases are likely attributable to higher expression of transporters (GLUT5) for fructose [78,139] or greater intestinal villous area that allows more efficient absorption of fat[47].

As evidenced by pair-feeding studies, however, sugar, HFCS, glucose, or fructose can produce metabolic disease even if weight does not increase[77,98,140,141]. For example, one study found that rats can develop diabetes, fatty liver and hypertension on a high sugar diet despite caloric restriction[77]. Consistent with this observation, men consuming a weight-maintaining diet that included fructose-sweetened beverage for 9 days (versus a weight-maintaining diet with the fructose beverage) showed decreased fat oxidation and increased DNL, liver fat, postprandial triglyceride and hepatic insulin resistance[59]. In another study, isocaloric restriction of fructose in obese adolescents improved features of metabolic syndrome[142]. Thus, even in the absence of excessive caloric intake, sugar can drive metabolic disease.

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Alcoholic Liver Disease

SSBs are strongly linked with the development and severity of MASLD, likely due to the effect of fructose to stimulate DNL and to inhibit fatty-acid oxidation [143]. Subjects with MASLD have been found to have elevations of KHK mRNA in the liver biopsies[144]. Administration of SSBs has also been found to increase liver fat [74,145] while 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[57,148]. Fatty liver from high glycemic or high salt diets are also associated with endogenous fructose production and are prevented in mice lacking KHK[88,98]. 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 development of liver disease[99]. More recently it has been shown that alcohol-induced liver disease also involves endogenous fructose, likely resulting from induced AR due to alcohol's osmotic effects.[99,149,150]. AR is also induced in the liver of patients with alcoholic liver disease. Mice lacking AR or KHK are largely protected from alcohol-induced liver disease. Of interest, mice lacking KHK or given KHK inhibitors also drink less ethanol[99].

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 gut[151] and sodium reabsorption in the kidney tubules[151,152], and high salt intake raises osmolality and induces endogenous fructose production[88]. Perhaps most strikingly, mice lacking KHK are protected from salt-induced blood pressure elevation and cardiac hypertrophy[88,153].

Systemic inflammation can potentially also be induced by fructose, by effects on circulating monocytes[83,85] and the release of chemokines into the circulation[136]. Local inflammation can also be induced, such as the release of inflammatory mediators by kidney epithelial cells[154], or by the activation of local macrophage-like cells including Kupffer cells [155] and microglia[10].

Acute and chronic kidney disease may also be dependent on endogenous fructose production, including in experimental models of acute ischemic tubular injury, contrast nephropathy, heat stress induced chronic kidney disease, and diabetic nephropathy[92,100,102]. In mouse models of these conditions, endogenous fructose production was shown to occur in the kidney, and mice lacking the ability to metabolize the fructose (i.e., KHK KO 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 show enhanced risk for hypertension, kidney disease and metabolic syndrome and also a relatively greater metabolic response to fructose (reviewed in [156]).

One of the more interesting findings involved the process of aging. Mice and rats are known to develop aging-associated kidney disease, similar to humans. However, a study of aging KHK knockout mice on a high carbohydrate but sugar-free chow found that they were protected from age-associated kidney disease and hypertension[157]. Since the dietary carbohydrates were corn, soybean and wheat, all with minimal fructose content, it is likely that the aging-associated changes in the wild-type mice resulted from endogenous fructose.

Cancer

Fructose metabolism has emerged as tumor promoter, supporting both tumor-intrinsic and systemic processes that promote disease progression. In multiple cancers, including breast, gastric, lung, hepatic, pancreatic, and prostate, fructose metabolism has been implicated in cancer growth, proliferation, and metastasis.[158-162] In several instances, fructose is produced endogenously by tumor cells via the polyol pathway, which facilitates cancer cell metabolism, migration, and resistance to apoptosis[112]. In cases where tumors 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 due to the expression of KHK-A instead of KHK-C, may contribute to expression of the oncogenic antioxidant transcription factor Nrf2[165,166]. Dietary fructose can also promote tumor growth in organs without direct access to dietary nutrients via fructose-derived metabolites, like lactate and lipids, which are produced by the liver following first-pass metabolism[46]. Within cancer cells, fructose

fuels glycolysis and DNL to support macromolecule synthesis and proliferation[46,163,167]. Moreover, the major product of fructolysis, F1P, functions as a survival signal by increasing HIF1α transactivation, thereby promoting adaptation to hypoxic conditions[163]. Furthermore, fructose metabolism may shape the tumor microenvironment by influencing the activity of immunosuppressive cell populations[168,169]. In sum, through multiple mechanisms that merit further investigation, fructose likely promotes cancer.

Brain Disorders

The human brain makes endogenous fructose (such as from hyperglycemia)[104] and also responds to dietary fructose. Ingestion of fructose stimulates foraging-like behavior with activation of occipital centers involved in food cues while suppressing blood flow to areas associated with self-control (cortex) and recent memory (hippocampus), while 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 behavioral disorders and dementia[124,125]. High fructose and sorbitol levels in the brain occur in both bipolar disease[106,171] and dementia[111]. Microglia contain KHK-C and are activated by fructose [10], and when this occurs in pregnant mice, the progeny display anxiety disorders[172].

Fructose metabolism in the brain may have a role in Alzheimer's disease[125]. Rats ingesting fructose chronically develop cognitive dysfunction, with cerebral insulin resistance, mitochondrial dysfunction, neuroinflammation, and eventually amyloid plaques and tau protein aggregates[60,173-175]. Diabetic mice also have increased endogenous fructose production with cognitive dysfunction that is improved by targeted knockout of KHK-C in the hippocampus[10]. Intake of sugar and high glycemic foods are also risk factors for Alzheimer's disease, and this disease is associated with 5 to 6-fold higher levels of fructose and sorbitol in the brain in autopsy studies. [111]

Genetic Disorders

Two rare genetic disorders of fructose metabolism are *essential fructosuria* (KHK deficiency) and hereditary *fructose intolerance* (HFI, aldolase B deficiency). The former is asymptomatic, while the latter results in a pathological reaction to fructose, characterized by hypoglycemia and lactic acidosis acutely and MASLD chronically (Box 1)[176-178]. Both experimental and pilot clinical studies suggest that inhibition of KHK could be a promising therapy for subjects 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 Lanaspa and D Tolan, unpublished data).

CONCLUSIONS AND FUTURE DIRECTIONS

Open questions

The role of endogenously produced fructose in metabolic disease remains controversial. While 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 last two decades failed, prior to the common use of GLP-1 agonists, to slow the obesity and diabetes epidemic? Historically, there has been a 10–20 year lag between sugar exposure and metabolic outcomes[180], and changes in incidence often precede changes in prevalence. Indeed, while the prevalence of diabetes has not decreased, the incidence of diabetes began to fall soon after sugar reduction[181], while obesity prevalence plateaued around 2020 and began decreasing by 2023[182]. Importantly, while recent changes in obesity prevalence are impacted by widespread GLP-1 therapy, the decrease in diabetes incidence predates this.

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 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 effects[156].

Finally, whether targeting fructose metabolism through KHK inhibition offers therapeutic benefit remains uncertain. Two pharmaceutical companies abandoned KHK inhibitor programs after phase 2 studies yielded modest outcomes[183,184]. Pfizer's PF-06835919 initial studies 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, the need to use it in a more select population (such as those with high dietary intake of fructose), and also the possibility that KHK inhibition is more effective for disease prevention than treatment[185]. As mentioned earlier, there is some clinical evidence that KHK inhibition may benefit subjects with HFI [179]. Given KHK's broad metabolic role, its inhibition may still hold future 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 program intended to prepare for periods of food scarcity (Figure 6). Fructose's induction of vasopressin may similarly reflect preparation for water scarcity, with fat storage also supplying metabolic water[186]. In modern society, however, this ancient signaling role can backfire. In the context of consistently abundant food, fructose intake is a hazard, promoting insulin resistance, hypertriglyceridemia, fatty liver, and elevated blood pressure[8].

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References

1. Malik VS & Hu FB The role of sugar-sweetened beverages in the global epidemics of obesity and chronic diseases. Nat Rev Endocrinol (2022). 10.1038/s41574-021-00627-6
2. Organization, W. H. 1–59 (World Health Organization, Geneva, Switzerland, 2015).
3. Yang Q. et al. Added Sugar Intake and Cardiovascular Diseases Mortality Among US Adults. JAMA Intern Med (2014).
4. Russell C, Baker P, Grimes C, Lindberg R & Lawrence MA Global trends in added sugars and non-nutritive sweetener use in the packaged food supply: drivers and implications for public health. Public Health Nutr 26, 952–964 (2023). 10.1017/S1368980022001598 [PubMed: 35899782]
5. Magkos F. et al. On the pathogenesis of obesity: causal models and missing pieces of the puzzle. Nat Metab (2024). 10.1038/s42255-024-01106-8
6. Herman MA & Birnbaum MJ Molecular aspects of fructose metabolism and metabolic disease. Cell Metab 33, 2329–2354 (2021). 10.1016/j.cmet.2021.09.010 [PubMed: 34619074]
7. Woods HF & Krebs HA Lactate production in the perfused rat liver. Biochem J 125, 129–139 (1971). 10.1042/bj1250129 [PubMed: 5158899]
8. Johnson RJ et al. The Fructose Survival Hypothesis for Obesity. Philos Trans R Soc Lond B Biol Sci 378 (2023). 10.1098/rstb.2022.0230
9. Diggle CP et al. Ketohexokinase: expression and localization of the principal fructose-metabolizing enzyme. J Histochem Cytochem 57, 763–774 (2009). jhc.2009.953190 [pii] 10.1369/jhc.2009.953190 [PubMed: 19365088]
10. Li Y. et al. Ketohexokinase-dependent metabolism of cerebral endogenous fructose in microglia drives diabetes-associated cognitive dysfunction. Exp Mol Med (2023). 10.1038/s12276-023-01112-y
11. Helsley RN et al. Tissue-Specific Fructose Metabolism in Obesity and Diabetes. Curr Diab Rep 20, 64 (2020). 10.1007/s11892-020-01342-8 [PubMed: 33057854]
12. Maenpaa PH, Raivio KO & Kekomaki MP Liver adenine nucleotides: fructose-induced depletion and its effect on protein synthesis. Science 161, 1253–1254 (1968). [PubMed: 5673437]
13. van den Berghe G, Bronfman M, Vanneste R & Hers HG The mechanism of adenosine triphosphate depletion in the liver after a load of fructose. A kinetic study of liver adenylate deaminase. Biochem J 162, 601–609 (1977). [PubMed: 869906]
14. Bawden SJ et al. Investigating the effects of an oral fructose challenge on hepatic ATP reserves in healthy volunteers: A (31)P MRS study. Clin Nutr 35, 645–649 (2016). 10.1016/j.clnu.2015.04.001 [PubMed: 25935852]
15. Abdelmalek MF et al. Higher dietary fructose is associated with impaired hepatic adenosine triphosphate homeostasis in obese individuals with type 2 diabetes. Hepatology 56, 952–960 (2012). 10.1002/hep.25741 [PubMed: 22467259]
16. Bode JC, Zelder O, Rumpelt HJ & Wittkamp U Depletion of liver adenosine phosphates and metabolic effects of intravenous infusion of fructose or sorbitol in man and in the rat. Eur J Clin Invest 3, 436–441 (1973). [PubMed: 4772339]
17. Samarah LZ et al. Spatial metabolic gradients in the liver and small intestine. Nature (2025). 10.1038/s41586-025-09616-5
18. Van den Berghe G. Fructose: metabolism and short-term effects on carbohydrate and purine metabolic pathways. Prog Biochem Pharmacol 21, 1–32 (1986).
19. Petrie JL et al. The rate of production of uric acid by hepatocytes is a sensitive index of compromised cell ATP homeostasis. Am J Physiol Endocrinol Metab 305, E1255–1265 (2013). 10.1152/ajpendo.00214.2013 [PubMed: 24045866]
20. Cox CL et al. Consumption of fructose- but not glucose-sweetened beverages for 10 weeks increases circulating concentrations of uric acid, retinol binding protein-4, and gamma-glutamyl transferase activity in overweight/obese humans. Nutr Metab (Lond) 9, 68 (2012). 10.1186/1743-7075-9-68 [PubMed: 22828276]

21. Zhang P. et al. Dietary intake of fructose increases purine de novo synthesis: A crucial mechanism for hyperuricemia. Front Nutr 9, 1045805 (2022). 10.3389/fnut.2022.1045805 [PubMed: 36601078]
22. Evans PR, Farrants GW & Hudson PJ Phosphofructokinase: structure and control. Philos Trans R Soc Lond B Biol Sci 293, 53–62 (1981). 10.1098/rstb.1981.0059 [PubMed: 6115424]
23. Sun SZ & Empie MW Fructose metabolism in humans - what isotopic tracer studies tell us. Nutr Metab (Lond) 9, 89 (2012). 10.1186/1743-7075-9-89 [PubMed: 23031075]
24. Woods HF, Eggleston LV & Krebs HA The cause of hepatic accumulation of fructose 1-phosphate on fructose loading. Biochem J 119, 501–510 (1970). 10.1042/bj1190501 [PubMed: 5500310]
25. Topping DL & Mayes PA Comparative effects of fructose and glucose on the lipid and carbohydrate metabolism of perfused rat liver. Br J Nutr 36, 113–126 (1976). 10.1079/bjn19760062 [PubMed: 181044]
26. Liu L. et al. Triose Kinase Controls the Lipogenic Potential of Fructose and Dietary Tolerance. Cell Metab 32, 605–618 e607 (2020). 10.1016/j.cmet.2020.07.018 [PubMed: 32818435]
27. Kim M. et al. Intestinal, but not hepatic, ChREBP is required for fructose tolerance. JCI Insight 2 (2017). 10.1172/jci.insight.96703
28. Kim MS et al. ChREBP regulates fructose-induced glucose production independently of insulin signaling. J Clin Invest 126, 4372–4386 (2016). 10.1172/JCI81993 [PubMed: 27669460]
29. An J. et al. Integration of metabolomic and transcriptomic analyses reveals regulatory functions of the ChREBP transcription factor in energy metabolism. Cell Rep 44, 115278 (2025). 10.1016/j.celrep.2025.115278 [PubMed: 39921857]
30. Kabashima T, Kawaguchi T, Wadzinski BE & Uyeda K Xylulose 5-phosphate mediates glucose-induced lipogenesis by xylulose 5-phosphate-activated protein phosphatase in rat liver. Proc Natl Acad Sci U S A 100, 5107–5112 (2003). 10.1073/pnas.0730817100 [PubMed: 12684532]
31. Lanaspa MA et al. Uric acid stimulates fructokinase and accelerates fructose metabolism in the development of fatty liver. PLoS One 7, e47948 (2012). 10.1371/journal.pone.0047948 [PubMed: 23112875]
32. Softic S. et al. Divergent effects of glucose and fructose on hepatic lipogenesis and insulin signaling. J Clin Invest 127, 4059–4074 (2017). 10.1172/JCI94585 [PubMed: 28972537]
33. Beysen C. et al. Dose-dependent quantitative effects of acute fructose administration on hepatic de novo lipogenesis in healthy humans. Am J Physiol Endocrinol Metab 315, E126–E132 (2018). 10.1152/ajpendo.00470.2017 [PubMed: 29558206]
34. Stanhope KL et al. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. J Clin Invest 119, 1322–1334 (2009). https://doi.org/37385 [pii] 10.1172/JCI37385 [PubMed: 19381015]
35. Taskinen MR et al. Adverse effects of fructose on cardiometabolic risk factors and hepatic lipid metabolism in subjects with abdominal obesity. J Intern Med 282, 187–201 (2017). 10.1111/joim.12632 [PubMed: 28548281]
36. Cox CL et al. Consumption of fructose-sweetened beverages for 10 weeks reduces net fat oxidation and energy expenditure in overweight/obese men and women. Eur J Clin Nutr 66, 201–208 (2012). https://doi.org/ejcn2011159 [pii] 10.1038/ejcn.2011.159 [PubMed: 21952692]
37. Chong MF, Fielding BA & Frayn KN Mechanisms for the acute effect of fructose on postprandial lipemia. Am J Clin Nutr 85, 1511–1520 (2007). https://doi.org/85/6/1511 [pii] [PubMed: 17556686]
38. Softic S. et al. Dietary Sugars Alter Hepatic Fatty Acid Oxidation via Transcriptional and Post-translational Modifications of Mitochondrial Proteins. Cell Metab 30, 735–753 e734 (2019). 10.1016/j.cmet.2019.09.003 [PubMed: 31577934]
39. Lanaspa MA et al. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: potential role in fructose-dependent and - independent fatty liver. J Biol Chem 287, 40732–40744 (2012). [PubMed: 23035112]
40. Zhao S. et al. Dietary fructose feeds hepatic lipogenesis via microbiota-derived acetate. Nature 579, 586–591 (2020). 10.1038/s41586-020-2101-7 [PubMed: 32214246]

41. Tharabenjasin P. et al. Acute interactions between intestinal sugar and calcium transport in vitro. Am J Physiol Gastrointest Liver Physiol 306, G1–12 (2014). 10.1152/ajpgi.00263.2013 [PubMed: 24177030]
42. Johnson RJ et al. Fructokinase, Fructans, Intestinal Permeability, and Metabolic Syndrome: An Equine Connection? J Equine Vet Science 33, 120–126 (2013). 10.1016/j.jevs.2012.05.004
43. Todoric J. et al. Fructose stimulated de novo lipogenesis is promoted by inflammation. Nat Metab 2, 1034–1045 (2020). 10.1038/s42255-020-0261-2 [PubMed: 32839596]
44. Bergheim I. et al. Antibiotics protect against fructose-induced hepatic lipid accumulation in mice: role of endotoxin. J Hepatol 48, 983–992 (2008). https://doi.org/S0168-8278(08)00132-3 [pii] 10.1016/j.jhep.2008.01.035 [PubMed: 18395289]
45. Stanhope KL et al. Consumption of fructose and high fructose corn syrup increase postprandial triglycerides, LDL-cholesterol, and apolipoprotein-B in young men and women. J Clin Endocrinol Metab 96, E1596–1605 (2011). https://doi.org/jc.2011-1251 [pii] 10.1210/jc.2011-1251 [PubMed: 21849529]
46. Fowle-Grider R. et al. Dietary fructose enhances tumour growth indirectly via interorgan lipid transfer. Nature (2024). 10.1038/s41586-024-08258-3
47. Taylor SR et al. Dietary fructose improves intestinal cell survival and nutrient absorption. Nature 597, 263–267 (2021). 10.1038/s41586-021-03827-2 [PubMed: 34408323]
48. Hirano T, Mamo J, Poapst M & Steiner G Very-low-density lipoprotein triglyceride kinetics in acute and chronic carbohydrate-fed rats. Am J Physiol 255, E236–240 (1988). 10.1152/ajpendo.1988.255.3.E236 [PubMed: 3421324]
49. Hieronimus B & Stanhope KL Dietary fructose and dyslipidemia: new mechanisms involving apolipoprotein CIII. Curr Opin Lipidol 31, 20–26 (2020). 10.1097/MOL.0000000000000653 [PubMed: 31789670]
50. Crescenzo R. et al. Increased hepatic de novo lipogenesis and mitochondrial efficiency in a model of obesity induced by diets rich in fructose. Eur J Nutr 52, 537–545 (2013). 10.1007/s00394-012-0356-y [PubMed: 22543624]
51. Hieronimus B. et al. Effects of Consuming Beverages Sweetened with Fructose, Glucose, High-Fructose Corn Syrup, Sucrose, or Aspartame on OGTT-Derived Indices of Insulin Sensitivity in Young Adults. Nutrients 16 (2024). 10.3390/nu16010151
52. Aeberli I. et al. Moderate amounts of fructose consumption impair insulin sensitivity in healthy young men: a randomized controlled trial. Diabetes Care 36, 150–156 (2013). https://doi.org/dc12-0540 [pii] 10.2337/dc12-0540 [PubMed: 22933433]
53. Baena M. et al. Fructose, but not glucose, impairs insulin signaling in the three major insulin-sensitive tissues. Sci Rep 6, 26149 (2016). 10.1038/srep26149 [PubMed: 27194405]
54. Li P. et al. A high-fructose diet impairs Akt and PKCzeta phosphorylation and GLUT4 translocation in rat skeletal muscle. Horm Metab Res 40, 528–532 (2008). 10.1055/s-2008-1073162 [PubMed: 18500676]
55. Rai AK et al. Fructose-induced AGEs-RAGE signaling in skeletal muscle contributes to impairment of glucose homeostasis. J Nutr Biochem 71, 35–44 (2019). 10.1016/j.jnutbio.2019.05.016 [PubMed: 31272030]
56. Marek G. et al. Adiponectin resistance and proinflammatory changes in the visceral adipose tissue induced by fructose consumption via ketohexokinase-dependent pathway. Diabetes 64, 508–518 (2015). 10.2337/db14-0411 [PubMed: 25187370]
57. Andres-Hernando A. et al. Deletion of Fructokinase in the Liver or in the Intestine Reveals Differential Effects on Sugar-Induced Metabolic Dysfunction. Cell Metab 32, 117–127 e113 (2020). 10.1016/j.cmet.2020.05.012 [PubMed: 32502381]
58. Seyssel K. et al. Fructose overfeeding in first-degree relatives of type 2 diabetic patients impacts energy metabolism and mitochondrial functions in skeletal muscle. Mol Nutr Food Res 60, 2691–2699 (2016). 10.1002/mnfr.201600407 [PubMed: 27468128]
59. Schwarz JM et al. Effect of a High-Fructose Weight-Maintaining Diet on Lipogenesis and Liver Fat. J Clin Endocrinol Metab 100, 2434–2442 (2015). 10.1210/jc.2014-3678 [PubMed: 25825943]

60. Agrawal R. et al. Dietary fructose aggravates the pathobiology of traumatic brain injury by influencing energy homeostasis and plasticity. J Cereb Blood Flow Metab 36, 941–953 (2016). 10.1177/0271678X15606719 [PubMed: 26661172]
61. Garcia-Arroyo FE et al. Allopurinol Prevents the Lipogenic Response Induced by an Acute Oral Fructose Challenge in Short-Term Fructose Fed Rats. Biomolecules 9 (2019). 10.3390/biom9100601
62. Choi YJ et al. Uric acid induces fat accumulation via generation of endoplasmic reticulum stress and SREBP-1c activation in hepatocytes. Lab Invest 94, 1114–1125 (2014). 10.1038/labinvest.2014.98 [PubMed: 25111690]
63. Sanchez-Lozada LG et al. Uric acid activates aldose reductase and the polyol pathway for endogenous fructose and fat production causing development of fatty liver in rats. J Biol Chem 294, 4272–4281 (2019). 10.1074/jbc.RA118.006158 [PubMed: 30651350]
64. Cicerchi C. et al. Uric acid-dependent inhibition of AMP kinase induces hepatic glucose production in diabetes and starvation: evolutionary implications of the uricase loss in hominids. FASEB J 28, 3339–3350 (2014). 10.1096/fj.13-243634 [PubMed: 24755741]
65. Kang DH, Park SK, Lee IK & Johnson RJ Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. J Am Soc Nephrol 16, 3553–3562 (2005). [PubMed: 16251237]
66. Crescenzo R. et al. Increased skeletal muscle mitochondrial efficiency in rats with fructose-induced alteration in glucose tolerance. Br J Nutr 110, 1996–2003 (2013). 10.1017/S0007114513001566 [PubMed: 23693085]
67. Garcia-Berumen CI et al. The severity of rat liver injury by fructose and high fat depends on the degree of respiratory dysfunction and oxidative stress induced in mitochondria. Lipids Health Dis 18, 78 (2019). 10.1186/s12944-019-1024-5 [PubMed: 30927921]
68. Cioffi F. et al. Fructose-Rich Diet Affects Mitochondrial DNA Damage and Repair in Rats. Nutrients 9 (2017). 10.3390/nu9040323
69. Hernandez-Rios R. et al. Low fructose and low salt diets increase mitochondrial DNA in white blood cells of overweight subjects. Exp Clin Endocrinol Diabetes 121, 535–538 (2013). 10.1055/s-0033-1349144 [PubMed: 23934680]
70. Wolf JP, Nguyen NU, Dumoulin G & Berthelay S Influence of hypertonic monosaccharide infusions on the release of plasma arginine vasopressin in normal humans. Horm Metab Res 24, 379–383 (1992). 10.1055/s-2007-1003340 [PubMed: 1526626]
71. Andres-Hernando A et al. Vasopressin mediates fructose-induced metabolic syndrome by activating the V1b receptor. JCI Insight 6 (2021). 10.1172/jci.insight.140848
72. Kanbay M. et al. The Speed of Ingestion of a Sugary Beverage Has an Effect on the Acute Metabolic Response to Fructose. Nutrients 13 (2021). 10.3390/nu13061916
73. Enhorning S. et al. Plasma copeptin, a unifying factor behind the metabolic syndrome. J Clin Endocrinol Metab 96, E1065–1072 (2011). https://doi.org/jc.2010-2981 [pii] 10.1210/jc.2010-2981 [PubMed: 21490073]
74. Sigala DM et al. Consuming Sucrose- or HFCS-sweetened Beverages Increases Hepatic Lipid and Decreases Insulin Sensitivity in Adults. J Clin Endocrinol Metab 106, 3248–3264 (2021). 10.1210/clinem/dgab508 [PubMed: 34265055]
75. Jang C. et al. The Small Intestine Converts Dietary Fructose into Glucose and Organic Acids. Cell Metab 27, 351–361 e353 (2018). 10.1016/j.cmet.2017.12.016 [PubMed: 29414685]
76. Ushijima K, Riby JE, Fujisawa T & Kretchmer N Absorption of fructose by isolated small intestine of rats is via a specific saturable carrier in the absence of glucose and by the disaccharidase-related transport system in the presence of glucose. J Nutr 125, 2156–2164 (1995). [PubMed: 7643250]
77. Roncal-Jimenez CA et al. Sucrose induces fatty liver and pancreatic inflammation in male breeder rats independent of excess energy intake. Metabolism 60, 1259–1270 (2011). https://doi.org/S0026-0495(11)00020-5 [pii] 10.1016/j.metabol.2011.01.008 [PubMed: 21489572]
78. Socha-Banasiak A. et al. Intestinal fructose transporters GLUT5 and GLUT2 in children and adolescents with obesity and metabolic disorders. Adv Med Sci 69, 349–355 (2024). 10.1016/j.advms.2024.07.008 [PubMed: 39059468]

79. Sundborn G. et al. Are Liquid Sugars Different from Solid Sugar in Their Ability to Cause Metabolic Syndrome? Obesity (Silver Spring) 27, 879–887 (2019). 10.1002/oby.22472 [PubMed: 31054268]
80. Gonzalez JT Are all sugars equal? Role of the food source in physiological responses to sugars with an emphasis on fruit and fruit juice. Eur J Nutr 63, 1435–1451 (2024). 10.1007/s00394-024-03365-3 [PubMed: 38492022]
81. Jung S. et al. Dietary fibre-adapted gut microbiome clears dietary fructose and reverses hepatic steatosis. Nat Metab 7, 1801–1818 (2025). 10.1038/s42255-025-01356-0 [PubMed: 40954286]
82. Francey C. et al. The extra-splanchnic fructose escape after ingestion of a fructose-glucose drink: An exploratory study in healthy humans using a dual fructose isotope method. Clin Nutr ESPEN 29, 125–132 (2019). 10.1016/j.clnesp.2018.11.008 [PubMed: 30661675]
83. Jones N. et al. Fructose reprogrammes glutamine-dependent oxidative metabolism to support LPS-induced inflammation. Nat Commun 12, 1209 (2021). 10.1038/s41467-021-21461-4 [PubMed: 33619282]
84. Song Z. et al. Role of fructose and fructokinase in acute dehydration-induced vasopressin gene expression and secretion in mice. J Neurophysiol 117, 646–654 (2017). 10.1152/jn.00781.2016 [PubMed: 27852737]
85. Staltner R. et al. Fructose intake enhances lipoteichoic acid-mediated immune response in monocytes of healthy humans. Redox Biol 85, 103729 (2025). 10.1016/j.redox.2025.103729 [PubMed: 40517600]
86. Nakagawa T. et al. Fructose might be a clue to the origin of preeclampsia insights from nature and evolution. Hypertens Res 46, 646–653 (2023). 10.1038/s41440-022-01121-w [PubMed: 36539464]
87. Jones AR & Connor DE Fructose metabolism by mature boar spermatozoa. Reprod Fertil Dev 12, 355–359 (2000). 10.1071/rd00116 [PubMed: 11545174]
88. Lanaspa MA et al. High salt intake causes leptin resistance and obesity in mice by stimulating endogenous fructose production and metabolism. Proc Natl Acad Sci U S A (2018). 10.1073/pnas.1713837115
89. Wang M. et al. Elevated Fructose and Uric Acid Through Aldose Reductase Contribute to Experimental and Human Alcoholic Liver Disease. Hepatology 72, 1617–1637 (2020). 10.1002/hep.31197 [PubMed: 32086945]
90. Mirtschink P & Krek W Hypoxia-driven glycolytic and fructolytic metabolic programs: Pivotal to hypertrophic heart disease. Biochim Biophys Acta 1863, 1822–1828 (2016). 10.1016/j.bbamcr.2016.02.011 [PubMed: 26896647]
91. Kanbay M. et al. Responses to Hypoxia: How Fructose Metabolism and Hypoxia-Inducible Factor-1a Pathways Converge in Health and Disease. Curr Nutr Rep (2023). 10.1007/s13668-023-00452-5
92. Andres-Hernando A. et al. Protective role of fructokinase blockade in the pathogenesis of acute kidney injury in mice. Nat Commun 8, 14181 (2017). 10.1038/ncomms14181 [PubMed: 28194018]
93. Mirtschink P. et al. HIF-driven SF3B1 induces KHK-C to enforce fructolysis and heart disease. Nature 522, 444–449 (2015). 10.1038/nature14508 [PubMed: 26083752]
94. Shepherd EL et al. Ketohexokinase inhibition improves NASH by reducing fructose-induced steatosis and fibrogenesis. JHEP Rep 3, 100217 (2021). 10.1016/j.jhepr.2020.100217 [PubMed: 33490936]
95. Wang S. et al. Acute heat stress upregulates Akr1b3 through Nrf-2 to increase endogenous fructose leading to kidney injury. J Biol Chem 301, 108121 (2025). 10.1016/j.jbc.2024.108121 [PubMed: 39710324]
96. van Zuylen ML et al. Perioperative cerebrospinal fluid sorbitol and fructose concentrations in patients undergoing thoracic aortic surgery. Br J Anaesth 129, e73–e76 (2022). 10.1016/j.bja.2022.06.012 [PubMed: 35843747]
97. Hwang JJ et al. Fructose levels are markedly elevated in cerebrospinal fluid compared to plasma in pregnant women. PLoS One 10, e0128582 (2015). 10.1371/journal.pone.0128582 [PubMed: 26035307]

98. Lanaspa MA et al. Endogenous fructose production and metabolism in the liver contributes to the development of metabolic syndrome. Nat Commun 4, 2434 (2013). 10.1038/ncomms3434 [PubMed: 24022321]

99. Andres-Hernando A. et al. Identification of a common ketohexokinase-dependent link driving alcohol intake and alcohol-associated liver disease in mice. . Nature Metabolism in press (2025).

100. Lanaspa MA et al. Endogenous fructose production and fructokinase activation mediate renal injury in diabetic nephropathy. J Am Soc Nephrol 25, 2526–2538 (2014). 10.1681/ASN.2013080901 [PubMed: 24876114]

101. Mirtschink P. et al. HIF-driven SF3B1 induces KHK-C to enforce fructolysis and heart disease. Nature 522, 444–449 (2015). 10.1038/nature14508 [PubMed: 26083752]

102. Roncal Jimenez CA et al. Fructokinase activity mediates dehydration-induced renal injury. Kidney Int 86, 294–302 (2014). 10.1038/ki.2013.492 [PubMed: 24336030]

103. Park TJ et al. Fructose-driven glycolysis supports anoxia resistance in the naked mole-rat. Science 356, 307–311 (2017). 10.1126/science.aab3896 [PubMed: 28428423]

104. Hwang JJ et al. The human brain produces fructose from glucose. JCI Insight 2, e90508 (2017). 10.1172/jci.insight.90508 [PubMed: 28239653]

105. Prockop LD Hyperglycemia, polyol accumulation, and increased intracranial pressure. Arch Neurol 25, 126–140 (1971). 10.1001/archneur.1971.00490020044005 [PubMed: 4998960]

106. Regenold WT et al. Relationship of cerebrospinal fluid glucose metabolites to MRI deep white matter hyperintensities and treatment resistance in bipolar disorder patients. Bipolar Disord 10, 753–764 (2008). 10.1111/j.1399-5618.2008.00626.x [PubMed: 19032707]

107. Regenold WT, Phatak P, Makley MJ, Stone RD & Kling MA Cerebrospinal fluid evidence of increased extra-mitochondrial glucose metabolism implicates mitochondrial dysfunction in multiple sclerosis disease progression. J Neurol Sci 275, 106–112 (2008). 10.1016/j.jns.2008.07.032 [PubMed: 18783801]

108. Smith SL, Novotny M & Karmen A Elevation of certain polyols in the cerebrospinal fluid of patients with multiple sclerosis. J Chromatogr 336, 351–355 (1984). 10.1016/s0378-4347(00)85159-2 [PubMed: 6530467]

109. Tigchelaar C. et al. Elevated cerebrospinal fluid glucose levels and diabetes mellitus are associated with activation of the neurotoxic polyol pathway. Diabetologia 65, 1098–1107 (2022). 10.1007/s00125-022-05693-7 [PubMed: 35380232]

110. Watanabe S, Kamiyama J, Chigasaki H & Yoshioka S Polyol content of cerebrospinal fluid in brain-tumor patients. J Neurosurg 70, 183–189 (1989). 10.3171/jns.1989.70.2.0183 [PubMed: 2913216]

111. Xu J. et al. Elevation of brain glucose and polyol-pathway intermediates with accompanying brain-copper deficiency in patients with Alzheimer's disease: metabolic basis for dementia. Sci Rep 6, 27524 (2016). 10.1038/srep27524 [PubMed: 27276998]

112. Zhao Q. et al. AKR1B1-dependent fructose metabolism enhances malignancy of cancer cells. Cell Death Differ 31, 1611–1624 (2024). 10.1038/s41418-024-01393-4 [PubMed: 39406918]

113. Aloia JF Monosaccharides and polyols in diabetes mellitus and uremia. J Lab Clin Med 82, 809–817 (1973). [PubMed: 4746819]

114. Daniels LJ et al. Elevated myocardial fructose and sorbitol levels are associated with diastolic dysfunction in diabetic patients, and cardiomyocyte lipid inclusions in vitro. Nutr Diabetes 11, 8 (2021). 10.1038/s41387-021-00150-7 [PubMed: 33558456]

115. Heaf DJ & Galton DJ Sorbitol and other polyols in lens, adipose tissue and urine in diabetes mellitus. Clin Chim Acta 63, 41–47 (1975). 10.1016/0009-8981(75)90376-9 [PubMed: 1181073]

116. Nakatsuka Y. et al. Hyperfructosemia in sleep disordered breathing: metabolome analysis of Nagahama study. Sci Rep 13, 12735 (2023). 10.1038/s41598-023-40002-1 [PubMed: 37543666]

117. Canovas JA, Wang L, Mohamed AAM, Abbott LF & Zuker CS A brain center that controls consummatory responses. Cell (2025). 10.1016/j.cell.2025.08.021

118. de Araujo IE et al. Food reward in the absence of taste receptor signaling. Neuron 57, 930–941 (2008). https://doi.org/S0896-6273(08)00119-0 [pii] 10.1016/j.neuron.2008.01.032 [PubMed: 18367093]

119. Andres-Hernando A. et al. Sugar causes obesity and metabolic syndrome in mice independently of sweet taste. Am J Physiol Endocrinol Metab (2020). 10.1152/ajpendo.00529.2019

120. Payant MA & Chee MJ Neural mechanisms underlying the role of fructose in overfeeding. Neurosci Biobehav Rev 128, 346–357 (2021). 10.1016/j.neubiorev.2021.06.034 [PubMed: 34182019]

121. Cha SH, Wolfgang M, Tokutake Y, Chohnan S & Lane MD Differential effects of central fructose and glucose on hypothalamic malonyl-CoA and food intake. Proc Natl Acad Sci U S A 105, 16871–16875 (2008). 10.1073/pnas.0809255105 [PubMed: 18971329]

122. Luo S, Monterosso JR, Sarpelleh K & Page KA Differential effects of fructose versus glucose on brain and appetitive responses to food cues and decisions for food rewards. Proc Natl Acad Sci U S A 112, 6509–6514 (2015). 10.1073/pnas.1503358112 [PubMed: 25941364]

123. Purnell JQ et al. Brain functional magnetic resonance imaging response to glucose and fructose infusions in humans. Diabetes Obes Metab 13, 229–234 (2011). 10.1111/j.1463-1326.2010.01340.x [PubMed: 21205113]

124. Johnson RJ, Wilson WL, Bland ST & Lanaspa MA Fructose and Uric Acid as Drivers of a Hyperactive Foraging Response: A Clue to Behavioral Disorders Associated with Impulsivity or Mania? Evol Hum Behav 42, 194–203 (2021). 10.1016/j.evolhumbehav.2020.09.006 [PubMed: 33994772]

125. Johnson RJ et al. Could Alzheimer's disease be a maladaptation of an evolutionary survival pathway mediated by intracerebral fructose and uric acid metabolism? Am J Clin Nutr (2023). 10.1016/j.ajcnut.2023.01.002

126. Friedman MI, Harris RB, Ji H, Ramirez I & Tordoff MG Fatty acid oxidation affects food intake by altering hepatic energy status. Am J Physiol 276, R1046–1053 (1999). [PubMed: 10198384]

127. Ishimoto T. et al. Opposing effects of fructokinase C and A isoforms on fructose-induced metabolic syndrome in mice. Proc Natl Acad Sci U S A 109, 4320–4325 (2012). https://doi.org/1119908109 [pii] 10.1073/pnas.1119908109 [PubMed: 22371574]

128. Shapiro A. et al. Fructose-induced leptin resistance exacerbates weight gain in response to subsequent high-fat feeding. Am J Physiol Regul Integr Comp Physiol 295, R1370–1375 (2008). https://doi.org/00195.2008 [pii] 10.1152/ajpregu.00195.2008 [PubMed: 18703413]

129. Shapiro A, Tumer N, Gao Y, Cheng KY & Scarpace PJ Prevention and reversal of diet-induced leptin resistance with a sugar-free diet despite high fat content. Br J Nutr 106, 390–397 (2011). 10.1017/S000711451100033X [PubMed: 21418711]

130. Dushay JR et al. Fructose ingestion acutely stimulates circulating FGF21 levels in humans. Mol Metab 4, 51–57 (2015). 10.1016/j.molmet.2014.09.008 [PubMed: 25685689]

131. Togo J, Hu S, Li M, Niu C & Speakman JR Impact of dietary sucrose on adiposity and glucose homeostasis in C57BL/6J mice depends on mode of ingestion: liquid or solid. Mol Metab (2019). 10.1016/j.molmet.2019.05.010

132. Miller CO et al. Ketohexokinase knockout mice, a model for essential fructosuria, exhibit altered fructose metabolism and are protected from diet-induced metabolic defects. Am J Physiol Endocrinol Metab 315, E386–E393 (2018). 10.1152/ajpendo.00027.2018 [PubMed: 29870677]

133. Hallfrisch J. et al. Effects of dietary fructose on plasma glucose and hormone responses in normal and hyperinsulinemic men. J Nutr 113, 1819–1826 (1983). [PubMed: 6350544]

134. Smajis S. et al. Metabolic effects of a prolonged, very-high-dose dietary fructose challenge in healthy subjects. Am J Clin Nutr 111, 369–377 (2020). 10.1093/ajcn/nqz271 [PubMed: 31796953]

135. Perez-Pozo SE et al. Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response. Int J Obes (Lond) 34, 454–461 (2010). https://doi.org/ijo2009259 [pii] 10.1038/ijo.2009.259 [PubMed: 20029377]

136. Cox CL et al. Circulating concentrations of monocyte chemoattractant protein-1, plasminogen activator inhibitor-1, and soluble leukocyte adhesion molecule-1 in overweight/obese men and women consuming fructose- or glucose-sweetened beverages for 10 weeks. J Clin Endocrinol Metab 96, E2034–2038 (2011). https://doi.org/jc.2011-1050 [pii] 10.1210/jc.2011-1050 [PubMed: 21956423]

137. Reungjui S. et al. Thiazide-induced subtle renal injury not observed in states of equivalent hypokalemia. Kidney Int 72, 1483–1492 (2007). [PubMed: 17928827]
138. Sievenpiper JL et al. Effect of fructose on body weight in controlled feeding trials: a systematic review and meta-analysis. Ann Intern Med 156, 291–304 (2012). https://doi.org/156/4/291 [pii] 10.1059/0003-4819-156-4-201202210-00007 [PubMed: 22351714]
139. Sullivan JS et al. Oral fructose absorption in obese children with non-alcoholic fatty liver disease. Pediatr Obes 10, 188–195 (2015). 10.1111/ijpo.238 [PubMed: 24961681]
140. Nakagawa T. et al. A causal role for uric acid in fructose-induced metabolic syndrome. Am J Physiol Renal Physiol 290, F625–631 (2006). [PubMed: 16234313]
141. Reungjui S. et al. Thiazide diuretics exacerbate fructose-induced metabolic syndrome. J Am Soc Nephrol 18, 2724–2731 (2007). [PubMed: 17855639]
142. Erkin-Cakmak A. et al. Isocaloric Fructose Restriction Reduces Serum D-Lactate Concentration in Children With Obesity and Metabolic Syndrome. J Clin Endocrinol Metab (2019). 10.1210/jc.2018-02772
143. Jensen T. et al. Fructose and sugar: A major mediator of non-alcoholic fatty liver disease. J Hepatol 68, 1063–1075 (2018). 10.1016/j.jhep.2018.01.019 [PubMed: 29408694]
144. Ouyang X. et al. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. J Hepatol 48, 993–999 (2008). [PubMed: 18395287]
145. Maersk M. et al. Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study. Am J Clin Nutr 95, 283–289 (2012). https://doi.org/ajcn.111.022533 [pii] 10.3945/ajcn.111.022533 [PubMed: 22205311]
146. Schwimmer JB et al. Effect of a Low Free Sugar Diet vs Usual Diet on Nonalcoholic Fatty Liver Disease in Adolescent Boys: A Randomized Clinical Trial. JAMA 321, 256–265 (2019). 10.1001/jama.2018.20579 [PubMed: 30667502]
147. Schwarz JM et al. Effects of Dietary Fructose Restriction on Liver Fat, De Novo Lipogenesis, and Insulin Kinetics in Children with Obesity. Gastroenterology (2017). 10.1053/j.gastro.2017.05.043
148. Ishimoto T. et al. High-fat and high-sucrose (western) diet induces steatohepatitis that is dependent on fructokinase. Hepatology 58, 1632–1643 (2013). 10.1002/hep.26594 [PubMed: 23813872]
149. Wang M. et al. Elevated fructose and uric acid via aldose reductase contribute to experimental and human alcoholic liver disease. Hepatology (2020). 10.1002/hep.31197
150. Shi C. et al. Inhibition of aldose reductase ameliorates alcoholic liver disease by activating AMPK and modulating oxidative stress and inflammatory cytokines. Mol Med Rep 16, 2767–2772 (2017). 10.3892/mmr.2017.6895 [PubMed: 28677809]
151. Singh AK et al. Fructose-induced hypertension: essential role of chloride and fructose absorbing transporters PAT1 and Glut5. Kidney Int 74, 438–447 (2008). [PubMed: 18496516]
152. Zhang R. et al. Abnormal activation of the mineralocorticoid receptor in the aldosterone-sensitive distal nephron contributes to fructose-induced salt-sensitive hypertension. bioRxiv (2024). 10.1101/2024.08.19.608663
153. Sanchez-Lozada LG et al. Sugar, salt, immunity and the cause of primary hypertension. Clin Kidney J 16, 1239–1248 (2023). 10.1093/ckj/sfad058 [PubMed: 37529651]
154. Cirillo P. et al. Ketohexokinase-dependent metabolism of fructose induces proinflammatory mediators in proximal tubular cells. J Am Soc Nephrol 20, 545–553 (2009). https://doi.org/ASN.2008060576 [pii] 10.1681/ASN.2008060576 [PubMed: 19158351]
155. Lodge M. et al. Fructose regulates the pentose phosphate pathway and induces an inflammatory and resolution phenotype in Kupffer cells. Sci Rep 14, 4020 (2024). 10.1038/s41598-024-54272-w [PubMed: 38369593]
156. Johnson RJ et al. Do thrifty genes exist? Revisiting uricase. Obesity (Silver Spring) in press, 1–10 (2022).
157. Roncal-Jimenez CA et al. Aging-associated renal disease in mice is fructokinase dependent. Am J Physiol Renal Physiol 311, F722–F730 (2016). 10.1152/ajprenal.00306.2016 [PubMed: 27465991]

158. Chen WL et al. GLUT5-mediated fructose utilization drives lung cancer growth by stimulating fatty acid synthesis and AMPK/mTORC1 signaling. JCI Insight 5 (2020). 10.1172/jci.insight.131596

159. Carreno DV et al. Dietary Fructose Promotes Prostate Cancer Growth. Cancer Res 81, 2824–2832 (2021). 10.1158/0008-5472.CAN-19-0456 [PubMed: 33762358]

160. Liu H. et al. Fructose induces transketolase flux to promote pancreatic cancer growth. Cancer Res 70, 6368–6376 (2010). 10.1158/0008-5472.CAN-09-4615 [PubMed: 20647326]

161. Kang YL et al. The polyol pathway and nuclear ketohexokinase A signaling drive hyperglycemia-induced metastasis of gastric cancer. Exp Mol Med 56, 220–234 (2024). 10.1038/s12276-023-01153-3 [PubMed: 38200154]

162. Kim J. et al. Ketohexokinase-A acts as a nuclear protein kinase that mediates fructose-induced metastasis in breast cancer. Nat Commun 11, 5436 (2020). 10.1038/s41467-020-19263-1 [PubMed: 33116123]

163. Goncalves MD et al. High-fructose corn syrup enhances intestinal tumor growth in mice. Science 363, 1345–1349 (2019). 10.1126/science.aat8515 [PubMed: 30898933]

164. Bu P. et al. Aldolase B-Mediated Fructose Metabolism Drives Metabolic Reprogramming of Colon Cancer Liver Metastasis. Cell Metab 27, 1249–1262 e1244 (2018). 10.1016/j.cmet.2018.04.003 [PubMed: 29706565]

165. Xu D. et al. The protein kinase activity of fructokinase A specifies the antioxidant responses of tumor cells by phosphorylating p62. Sci Adv 5, eaav4570 (2019). 10.1126/sciadv.aav4570 [PubMed: 31032410]

166. Tee SS et al. Ketohexokinase-mediated fructose metabolism is lost in hepatocellular carcinoma and can be leveraged for metabolic imaging. Sci Adv 8, eabm7985 (2022). 10.1126/sciadv.abm7985 [PubMed: 35385296]

167. Jeong S. et al. High Fructose Drives the Serine Synthesis Pathway in Acute Myeloid Leukemic Cells. Cell Metab 33, 145–159 e146 (2021). 10.1016/j.cmet.2020.12.005 [PubMed: 33357456]

168. Yan H. et al. Hexokinase 2 senses fructose in tumor-associated macrophages to promote colorectal cancer growth. Cell Metab 36, 2449–2467 e2446 (2024). 10.1016/j.cmet.2024.10.002 [PubMed: 39471815]

169. Schild T. et al. Metabolic engineering to facilitate anti-tumor immunity. Cancer Cell 43, 552–562 e559 (2025). 10.1016/j.ccell.2025.02.004 [PubMed: 40020672]

170. Page KA et al. Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways. JAMA 309, 63–70 (2013). 10.1001/jama.2012.116975 [PubMed: 23280226]

171. Regenold WT, Phatak P, Kling MA & Hauser P Post-mortem evidence from human brain tissue of disturbed glucose metabolism in mood and psychotic disorders. Mol Psychiatry 9, 731–733 (2004). 10.1038/sj.mp.4001517 [PubMed: 15098005]

172. Wang Z. et al. Early life high fructose impairs microglial phagocytosis and neurodevelopment. Nature (2025). 10.1038/s41586-025-09098-5

173. Cisternas P. et al. Fructose consumption reduces hippocampal synaptic plasticity underlying cognitive performance. Biochim Biophys Acta 1852, 2379–2390 (2015). 10.1016/j.bbadis.2015.08.016 [PubMed: 26300486]

174. Mohamed HE, Asker ME, Shaheen MA, Eissa RG & Younis NN Alleviation of fructose-induced Alzheimer's disease in rats by pioglitazone and decaffeinated green coffee bean extract. J Food Biochem 45, e13715 (2021). 10.1111/jfbc.13715 [PubMed: 33782984]

175. Mohamed HE, Asker ME, Younis NN, Shaheen MA & Eissa RG Modulation of brain insulin signaling in Alzheimer's disease: New insight on the protective role of green coffee bean extract. Nutr Neurosci 23, 27–36 (2020). 10.1080/1028415X.2018.1468535 [PubMed: 29712510]

176. Steinmann B, Gitzelmann R & Van den Berghe G in The Metabolic and Molecular Basis of Inherited Disease (eds Scriver C, Beaudet A, Sly W, & Valle D) 1489–1520 (McGraw-Hill, 2001).

177. Lanaspa MA et al. Ketohexokinase C blockade ameliorates fructose-induced metabolic dysfunction in fructose-sensitive mice. J Clin Invest 128, 2226–2238 (2018). 10.1172/JCI94427 [PubMed: 29533924]

178. Andres-Hernando A. et al. Endogenous Fructose Production and Metabolism Drive Metabolic Dysregulation and Liver Disease in Mice with Hereditary Fructose Intolerance. Nutrients 15 (2023). 10.3390/nu15204376

179. Koene EJ et al. Safety and efficacy of pharmacological inhibition of ketohexokinase in hereditary fructose intolerance. J Clin Invest 135 (2025). 10.1172/JCI187376

180. Cleave TL & Campbell GD The saccharine disease. Am J Proctol 18, 202–210 (1967). [PubMed: 6046370]

181. (ed US Dept of Health and Human Services; 2018.) (Centers for Disease Control and Prevention, , Atlanta, GA).

182. Rader B, Hazan R & Brownstein JS Changes in Adult Obesity Trends in the US. JAMA Health Forum 5, e243685 (2024). 10.1001/jamahealthforum.2024.3685 [PubMed: 39671205]

183. Korsmo HW, Ekperikpe US & Daehn IS Emerging Roles of Xanthine Oxidoreductase in Chronic Kidney Disease. Antioxidants (Basel) 13 (2024). 10.3390/antiox13060712

184. Saxena AR et al. A phase 2a, randomized, double-blind, placebo-controlled, three-arm, parallel-group study to assess the efficacy, safety, tolerability and pharmacodynamics of PF-06835919 in patients with non-alcoholic fatty liver disease and type 2 diabetes. Diabetes Obes Metab 25, 992–1001 (2023). 10.1111/dom.14946 [PubMed: 36515213]

185. Park SH et al. Knockdown of ketohexokinase versus inhibition of its kinase activity exert divergent effects on fructose metabolism. JCI Insight 9 (2024). 10.1172/jci.insight.184396

186. Johnson RJ et al. Water scarcity and conservation and their role in obesity in nature and in humans. J Intern Med (2025). 10.1111/joim.70003

187. Perheentupa J & Raivio K Fructose-induced hyperuricaemia. Lancet 2, 528–531 (1967). [PubMed: 4166890]

188. Brown CM, Dulloo AG, Yepuri G & Montani JP Fructose ingestion acutely elevates blood pressure in healthy young humans. Am J Physiol Regul Integr Comp Physiol 294, R730–737 (2008). [PubMed: 18199590]

189. Sanchez-Lozada LG et al. Fructose-induced metabolic syndrome is associated with glomerular hypertension and renal microvascular damage in rats. Am J Physiol Renal Physiol 292, F423–429 (2007). [PubMed: 16940562]

Box 1

Genetic Disorders of Fructose Metabolism

Essential Fructosuria

- Fructokinase (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 of type 2 diabetes in affected individuals)
- Excrete 10 percent of ingested fructose load in urine. Most ingested fructose is metabolized in adipose and other tissues via other hexokinases.

Hereditary Fructose Intolerance

- Aldolase B deficiency; Autosomal recessive (1:22,000).
- Manifests after weaning with exposure to fructose.
- Presents with acute hypoglycemia upon fructose intake, due to impaired hepatic glucogenesis.
- Biochemically, F1P accumulates pathologically, ATP is depleted.
- Causes chronic liver disease and kidney disease (Fanconi syndrome).
- Rescued by inhibition or knocking out KHK.
- Management consists of dietary fructose and sorbitol avoidance.
- Associated with fructose, sorbitol and ethanol aversion.
- Restriction of high glycemic carbohydrate to reduce endogenous fructose generation may also be helpful.

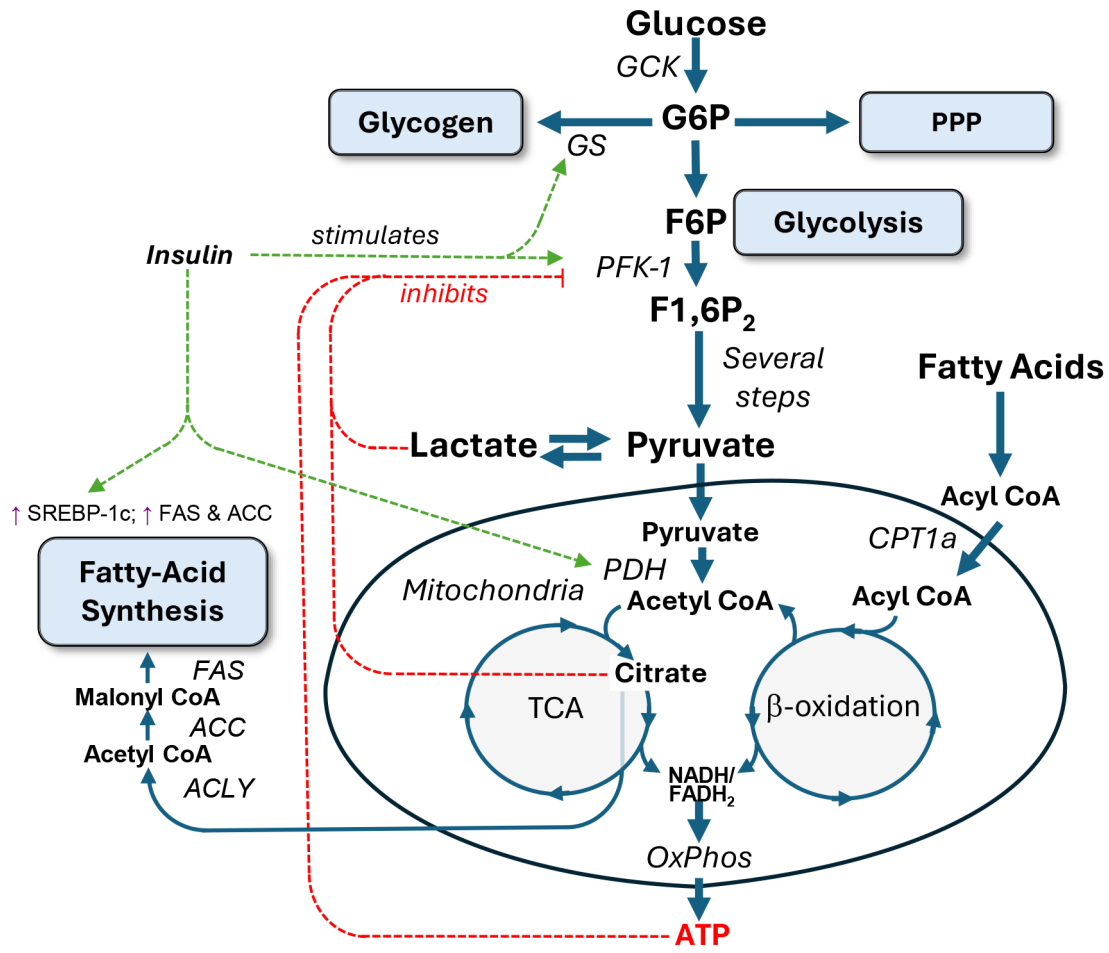

Figure 1. Hepatocyte Glucose Metabolism.

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 flux is high (red dashed arrows). The available pathways are denoted with light-blue boxes, the important enzymes in italics, and metabolic intermediates in bold. Abbreviations in alphabetical order are as follows: ACC, acetyl-CoA carboxylase; ACLY, ATP-citrate lyase; CoA, Coenzyme-A; CPT1a, carnitine palmitoyltransferase-1a; FAS, fatty acid synthase; F6P, fructose 6-phosphate; F1,6P2, fructose 1,6-bisphosphate; FADH2, flavin adenine dinucleotide (reduced); G6P, glucose 6-phosphate; GCK, glucokinase (hexokinase IV); GS, glycogen synthase; NADH, nicotinamide adenine dinucleotide (reduced); OxPhos, oxidative phosphorylation pathway; PDH, pyruvate dehydrogenase complex; PFK-1, phosphofructokinase-1; PPP, pentose phosphate pathway; SREBP-1c, sterol regulatory element binding protein-1c; TCA, tricarboxylic acid cycle.

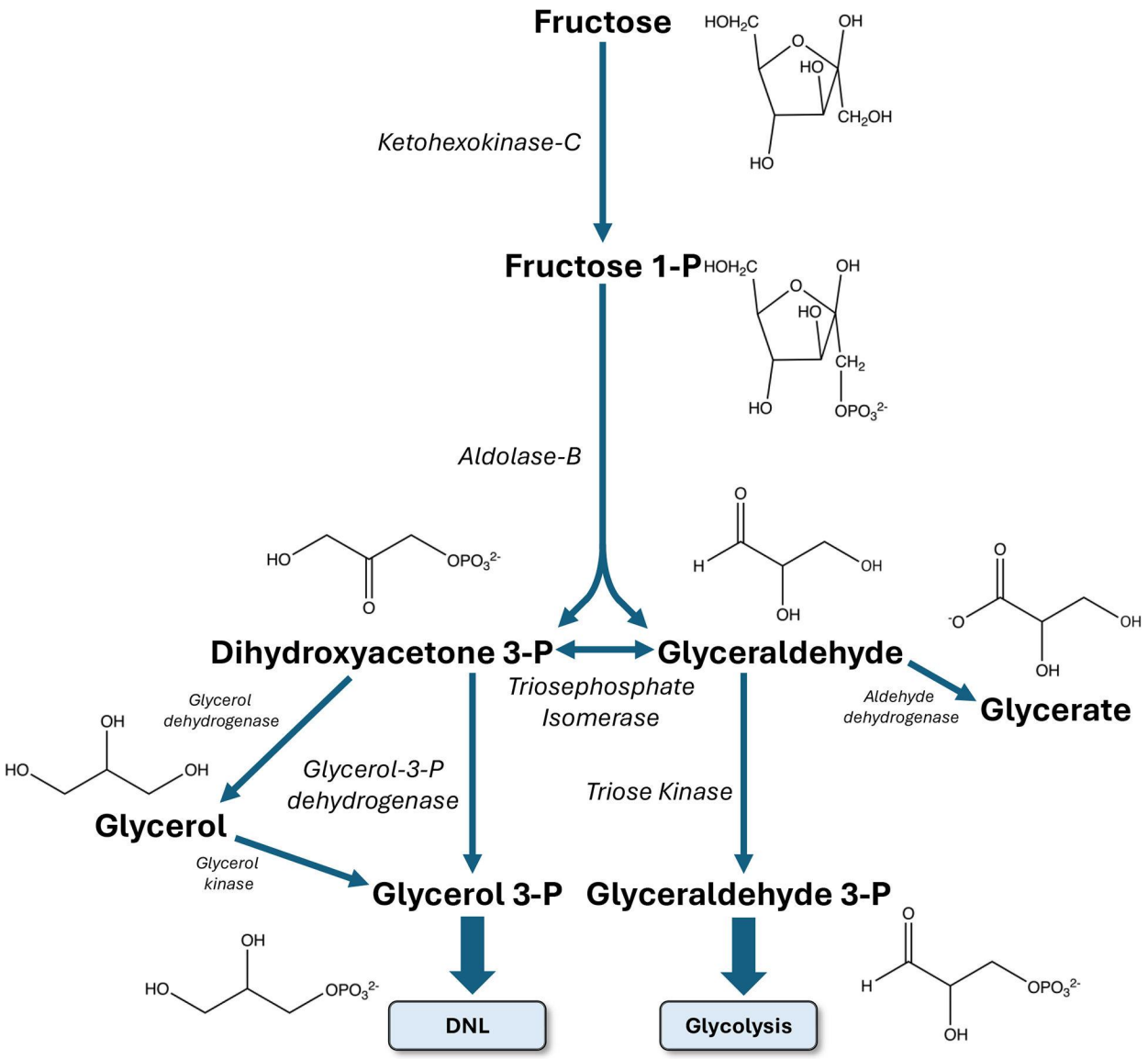

Figure 2. Fructose Metabolism.

The chemical pathway from fructose to triose phosphates is diagramed with all known end products from fructose. The structures of metabolic intermediates are shown with names in bold. The structures of the hexoses are in the b-anomeric forms utilized by the enzymes, which are noted in italics. Glycerate enters glycolysis as 2-phosphoglycerate via glycerate kinase (not shown). The major pathways, glycolysis and *de* novo lipogenesis (DNL) to which these triose phosphates enter (thick arrows) are noted by gray boxes.

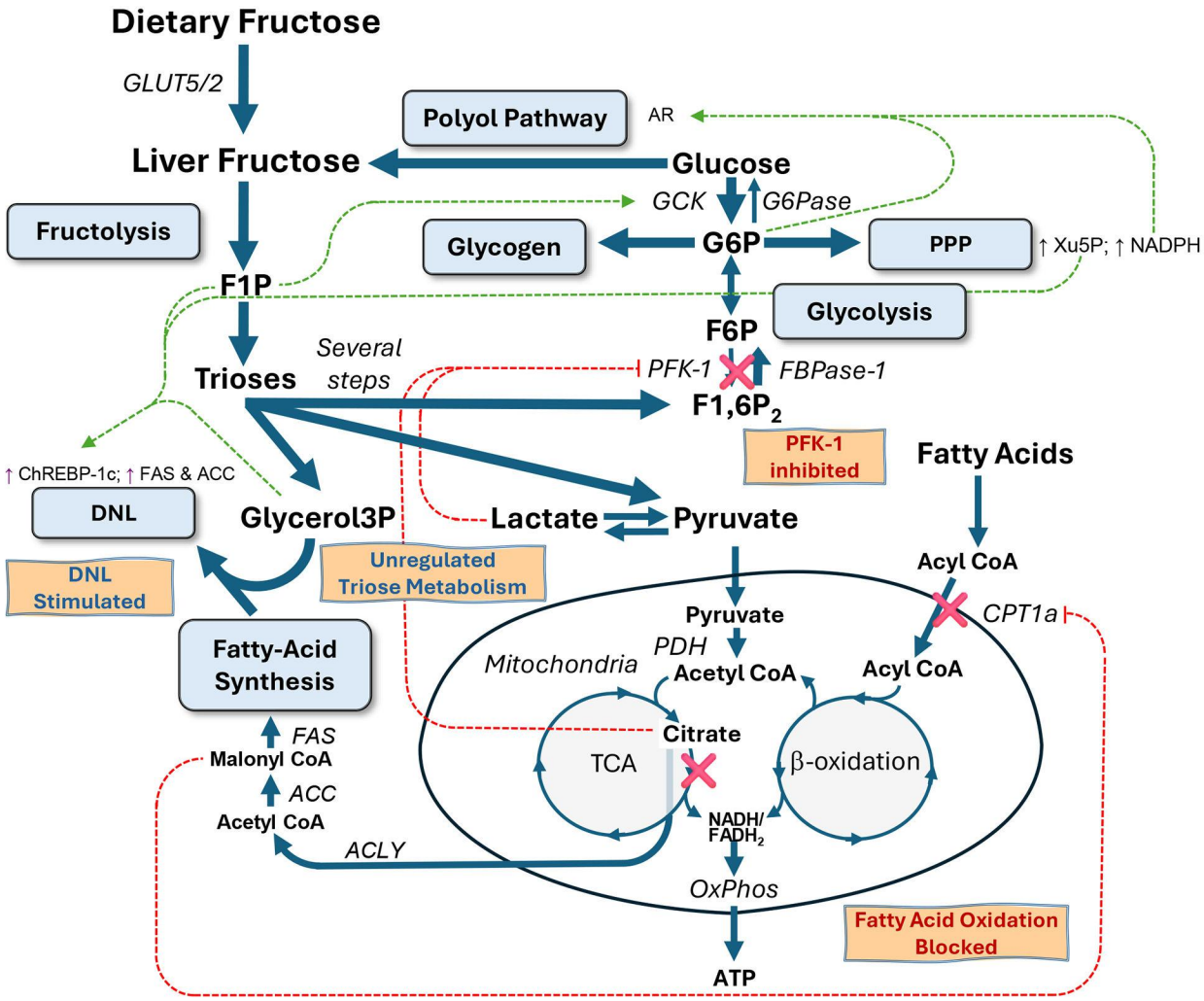

Figure 3. Hepatocyte Fructose Metabolism.

The major differences with glucose metabolism are highlighted in the colored boxes, which are consequences of regulatory effects that activate (green dashed arrows) or inhibit (red dashed arrows) key enzymes or transcription factors as indicated. This regulation leads to inhibition of these pathways as indicated with red X's. The stimulation of glucokinase (GCK) facilitates enhances glucose uptake and might further enhance fructose generation via the polyol pathway. The impacted pathways are denoted with gray boxes, the important enzymes in italics, and metabolic intermediates in bold. Other abbreviations in alphabetical order are as follows: ACC, acetyl-CoA carboxylase; ACLY, ATP-citrate lyase; AR, aldose reductase; ChREBP, carbohydrate-response element binding protein; CoA, Coenzyme-A; CPT1a, carnitine palmitoyltransferase-1a; DNL, *de novo* lipogenesis; FAS, fatty acid synthase; F1P, fructose 1-phosphate; F6P, fructose 6-phosphate; $F1,6P_2$, fructose 1,6-bisphosphate; $FADH_2$, flavin adenine dinucleotide (reduced); FBPase-1, fructose 1,6-bisphosphatase-1; GCK, glucokinase (hexokinase IV); G6Pase, glucose 6-phosphase; G6P, glucose 6-phosphate; GLUT, solute carrier family or glucose transporter; NADH, nicotinamide adenine dinucleotide (reduced); NADPH, nicotinamide adenine dinucleotide phosphate (reduced); OxPhos, oxidative phosphorylation pathway; PDH,

pyruvate dehydrogenase complex; PFK-1, phosphofructokinase-1; PPP, pentose phosphate pathway; SREBP-1c, sterol regulatory element binding protein-1c; TCA, tricarboxylic acid cycle; Xu5P, xyulose 5-phosphate.

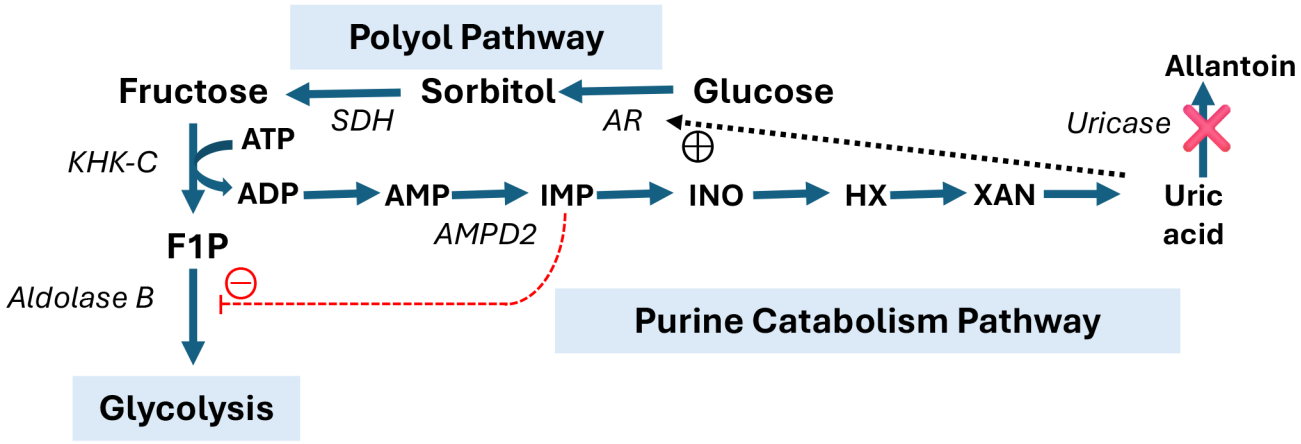

Figure 4. Fructose Induced ATP Depletion and Uric Acid Generation.

The schematic highlights the relationship among the fructolytic, polyol, and purine degradation pathways (gray boxes). The relative fluxes are indicated by thickness of arrows with the results on metabolites indicated with up or down arrows. Activation (green dotted arrows) and inhibition (red lines) of key enzymes or transcription factors are indicated. The rapid consumption of ATP by ketohexokinase-C (KHK-C) and resulting sequestration of phosphate in fructose 1-phosphate (F1P) results in transient ATP depletion and activation of AMP deaminase-2 (AMPD2) to eventually generate uric acid. Uric acid stimulates aldose reductase (AR), KHK-C, and the transcription factors sterol regulatory element binding protein-1c (SREBP-1c) and carbohydrate-response element binding protein (ChREBP). Inosine monophosphate (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 most mammals. Other abbreviations in alphabetic order: ADP, adenosine diphosphate; AMP, adenosine monophosphate; GTP, guanidylate triphosphate; P_i, inorganic phosphate; SDH, sorbitol dehydrogenase.

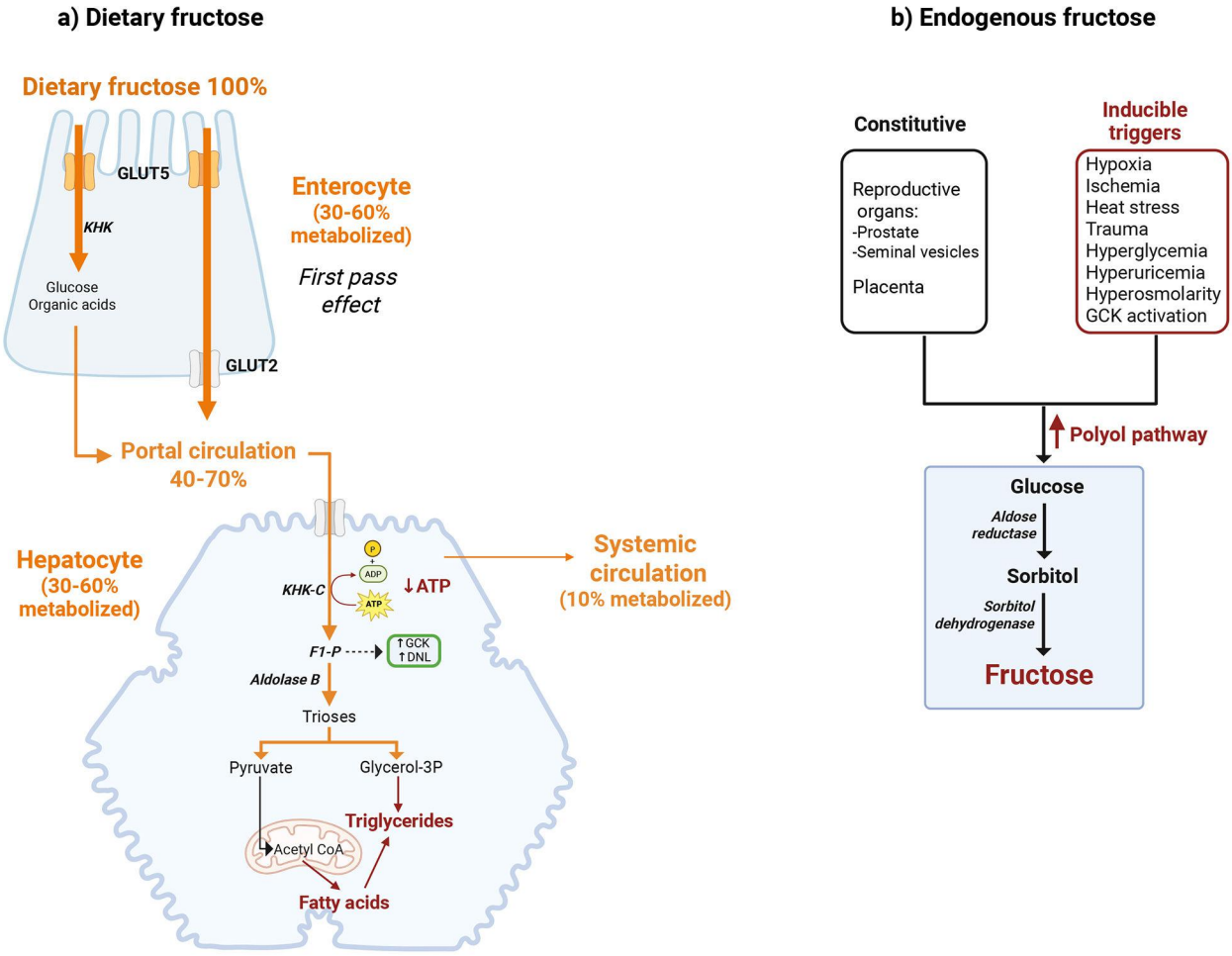

Figure 5. Sites of Metabolism for Fructose.

A) Dietary Fructose: Fructose metabolism begins with absorption by enterocytes of the small intestine, gets exported to the portal circulation, and picked up by the liver and systemic circulation. *B) Endogenous Fructose*: 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 black in box on the left. Other tissues require induced expression by various stresses listed in brown in middle box. Created in BioRender. Sánchez-Lozada, L.G. (2025)

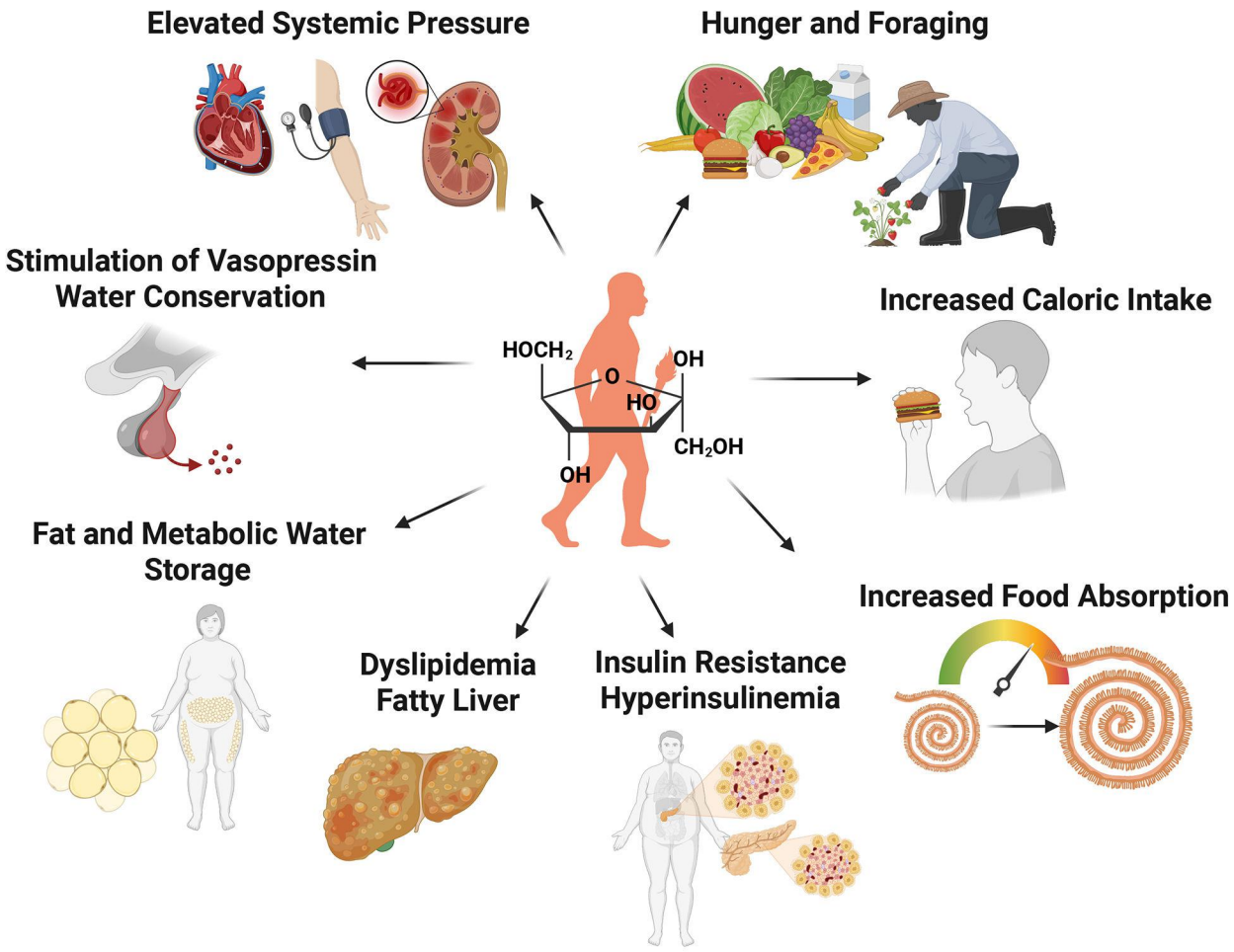

Figure 6. The Fructose Survival Hypothesis.

Fructose likely 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. This concept is described extensively in the literature[8,125] and has been proposed as the "fructose survival hypothesis Created in BioRender. Lanaspa, M. (2025) https://BioRender.com/7oh5q9r.

Table 1

Differences in Fructose and Glucose Actions

Glucose Effects Substantially Greater than Fructose
Insulin Secretion
Stimulate satiety
Fructose Effects Substantially Greater than Glucose
Increased Carbohydrate Oxidation[37]
Impaired Fatty Acid Oxidation[25]
Increased De novo Lipogenesis[25,32]
Increased Circulating Triglycerides (VLDL-triglycerides) [25,28]
Increased Lactate production[25]
Acute ATP depletion[121]
Rapid Uric Acid Generation[187]
Induce Hyperinsulinemia and Insulin Resistance[28,32]
Stimulate Gluconeogenesis (Increase G6P phosphatase) [28]
Increase Intestinal Surface (Villi) Area to Enhance Fat Absorption[47]
Induce Leptin Resistance[128]
GCK Activation[28]
Vasopressin Release[70]
FGF21 Release[130]
Increased Systemic Blood Pressure[188]
Increase Glomerular Hydrostatic Pressure[189]
Leaky Gut and Endotoxemia[43]
Reduce Satiety

Table 2

Factors that Activate Endogenous Fructose Production

Type of Stress	Examples
Hyperosmolarity	Water Deprivation[102]
	Salt intake[88]
	Alcohol intake[149]
Hyperglycemia	Hyperglycemia and Diabetes[100]
	High glycemic diet[98]
Low Oxygen	Hypoxia (Sleep apnea)[116]
Ischemia	Myocardial Infarction, Acute Kidney Injury [92,101]
Fructose Metabolism by KHK (such as GCK activation)	Western diet-induced steatosis[148]
Heat Stress	Heat Stress-induced kidney injury [95]
Physical or Emotional Stress	Following major surgery[96]
Pregnancy	Brain production[97]
Uric acid	Hyperuricemia[63]