

Fructose: It's "Alcohol Without the Buzz"^{1–3}

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ABSTRACT

What do the Atkins Diet and the traditional Japanese diet have in common? The Atkins Diet is low in carbohydrate and usually high in fat; the Japanese diet is high in carbohydrate and usually low in fat. Yet both work to promote weight loss. One commonality of both diets is that they both eliminate the monosaccharide fructose. Sucrose (table sugar) and its synthetic sister high fructose corn syrup consist of 2 molecules, glucose and fructose. Glucose is the molecule that when polymerized forms starch, which has a high glycemic index, generates an insulin response, and is not particularly sweet. Fructose is found in fruit, does not generate an insulin response, and is very sweet. Fructose consumption has increased worldwide, paralleling the obesity and chronic metabolic disease pandemic. Sugar (i.e., fructose-containing mixtures) has been vilified by nutritionists for ages as a source of "empty calories," no different from any other empty calorie. However, fructose is unlike glucose. In the hypercaloric glycogen-replete state, intermediary metabolites from fructose metabolism overwhelm hepatic mitochondrial capacity, which promotes *de novo* lipogenesis and leads to hepatic insulin resistance, which drives chronic metabolic disease. Fructose also promotes reactive oxygen species formation, which leads to cellular dysfunction and aging, and promotes changes in the brain's reward system, which drives excessive consumption. Thus, fructose can exert detrimental health effects *beyond* its calories and in ways that mimic those of ethanol, its metabolic cousin. Indeed, the only distinction is that because fructose is not metabolized in the central nervous system, it does not exert the acute neuronal depression experienced by those imbibing ethanol. These metabolic and hedonic analogies argue that fructose should be thought of as "alcohol without the buzz." *Adv. Nutr.* 4: 226–235, 2013.

Introduction

We are in the midst of a global pandemic of chronic metabolic disease, 30 y in the making. The UN Secretary General in 2011 declared that metabolic syndrome (type 2 diabetes, hypertension, dyslipidemia, heart disease) and other non-communicable diseases (e.g., cancer, dementia) are now a greater threat to both the *developed* and *developing* worlds than is acute infectious disease, including HIV (1). Most people blame obesity as the driver of these other diseases; however, 20% of obese subjects are metabolically normal, whereas as many as 40% of normal-weight people manifest specific components of metabolic syndrome (2–4). Obesity is not the cause of metabolic syndrome; rather, it is a marker for the metabolic dysfunction that is occurring worldwide.

Furthermore, there are now >30% more obese people on the planet than those who are malnourished. Two decades ago, it was the opposite. Is it really possible, even in the most impoverished countries, that so many people became gluttons and sloths in such a short period of time? The ever-onward progression of these diseases in countries that also witness severe malnutrition is more reminiscent of an exposure than it is an alteration in behavior.

But, aside from caloric overconsumption, what kind of exposure could cause metabolic syndrome? One specific foodstuff that has increased in all countries during the pandemic and has the capacity to promote chronic metabolic disease is the monosaccharide fructose. Fructose is half of sucrose (cane or beet sugar) and 55% of high-fructose corn syrup (HFCS)⁴. In 1 century, Americans have increased fructose consumption from ~15 g/d (4% of total energy) to 75 g/d (12% of total energy) (5). Currently, per capita consumption of fructose or fructose-containing disaccharides is

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⁴ Abbreviations used: DNL, *de novo* lipogenesis; Foxo1, forkhead protein O1; HFCS, high-fructose corn syrup; IRS-1, insulin receptor substrate 1; JNK-1, *c-jun* N-terminal kinase 1; MKK7, MAP kinase kinase 7; MTP, microsomal transfer protein; NA, nucleus accumbens; NO, nitric oxide; ROS, reactive oxygen species; SREBP-1c, sterol regulatory element binding protein 1c; VTA, ventral tegmental area.

at ~130 lb/y (almost 60 kg/y) or 6.5 oz/d for the average American. Although America is the greatest sugar consumer, other countries are not far behind (6).

Although most people consider fructose, and sugar in general, as “empty calories,” there is nothing empty about these calories. First, there is not 1 human biochemical reaction that requires dietary fructose. The only place in the body that fructose is of physiologic import is in semen, and the fructose is manufactured *de novo* from glucose using the aldose reductase/sorbitol pathway (7). In other words, fructose is a vestigial nutrient for humans, held over from the differentiation between plants and animals. Indeed, patients with hereditary fructose intolerance, who are missing the enzyme fructose-1-phosphate aldolase B, and cannot consume fructose lest they become hypoglycemic, do not only have fewer dental caries (8), but they are quite healthy provided they continue to restrict their fructose exposure (9,10).

Second, fructose exerts 3 different negative impacts on human metabolism, each of which is exclusive of its calories. Most people compare fructose with its isomer glucose, which is so essential for life that your liver will produce it when it is in short supply via the process of gluconeogenesis. Although fructose is an energy source, the actions of fructose on the body more closely resemble those of ethanol (grain alcohol), another nonessential energy source. This paper compares the metabolic actions of fructose with those of glucose and ethanol to make the point that fructose is “alcohol without the buzz.”

Hepatic insulin resistance and metabolic syndrome

The pathogenesis of metabolic syndrome remains a puzzle (11,12). One reason for this puzzle is trying to explain the phenomenon of “selective hepatic insulin resistance” (13). Insulin normally exerts its effects on hepatic energy metabolism via 2 metabolic pathways. Insulin’s effects on maintaining euglycemia occurs through phosphorylation of the forkhead protein O1 (FoxO1), thus restricting it from entering the nucleus and preventing transcription of various gluconeogenic enzymes (14,15). Insulin also activates the lipogenic pathway by stimulating sterol regulatory element binding protein 1c (SREBP-1c), which activates the enzymes of *de novo* lipogenesis (DNL) to turn excess mitochondrial energy substrate into fatty acids, which are then linked to apolipoprotein B100 and packaged into VLDL for hepatic export.

However, metabolic syndrome does not result from complete hepatic insulin resistance (16) because this would result in hyperglycemia (lack of FoxO1 phosphorylation) and low serum VLDL (lack of SREBP-1c activation). Rather, metabolic syndrome results from “selective” hepatic insulin resistance in which FoxO1 is not phosphorylated yet SREBP-1c is still activated to promote triglyceride synthesis and dyslipidemia. If there is only 1 insulin receptor, how can it activate 1 pathway and not the other (17)? To parse this dichotomy, the hepatic metabolism of glucose, ethanol, and fructose are considered in turn.

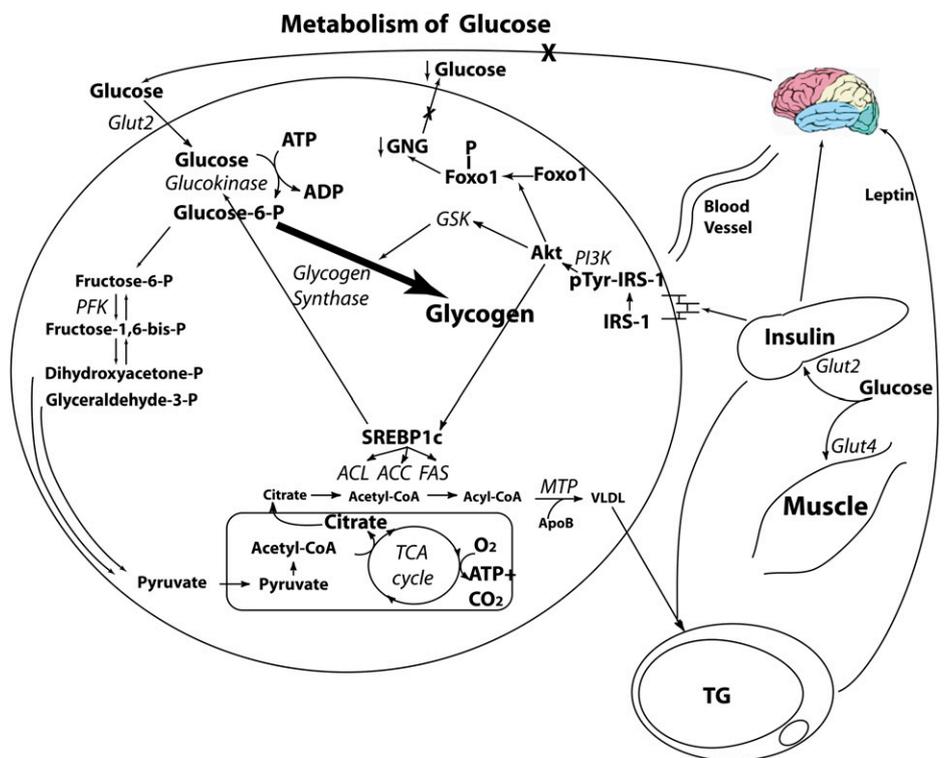
Hepatic glucose metabolism

Glucose is unique in that every prokaryotic and eukaryotic cell on the planet has the capacity to use glucose for energy. After oral consumption of glucose (Fig. 1), the bolus enters the portal circulation. Approximately 20% of the glucose bolus enters the liver via the Glut2 glucose transporter, which is insulin independent (18). The rest (80%) appears in the peripheral circulation plasma glucose levels increase, and insulin is released by the β -cells in response. Insulin binds to its liver receptor, which promotes the tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1), which increases the activity of phosphatidylinositol 3-kinase, inducing the transcription factor Akt responsible for insulin’s intracellular metabolic effects. 1) Akt phosphorylates FoxO1, downregulating gluconeogenesis, keeping blood glucose low (15). 2) Akt activates glycogen synthase kinase, which then activates glycogen synthase. This leads to the conversion of the majority of glucose molecules as hepatic glycogen for storage. The small amount that undergoes glycolysis reaches the mitochondria as pyruvate and is quickly esterified into acetyl-CoA. 3) Akt increases the activity of SREBP-1c. This allows any excess acetyl-CoA that cannot be β -oxidized for energy and exits the mitochondria to be rebuilt into FFAs, which then are packaged into VLDL for hepatic export and storage in adipocytes. This VLDL can promote atherogenesis and/or obesity, but only ~2% of ingested glucose will find its way into VLDL; thus, glucose contributes extremely slowly to cardiovascular disease and other aspects of metabolic syndrome.

Hepatic ethanol metabolism

The hepatic pathway of ethanol metabolism is different from that of glucose in its regulation and the disposition of intermediary metabolites (Fig. 2). Ethanol enters the hepatocyte through osmosis, it does not require insulin for its metabolism, and it does not stimulate insulin secretion. Ethanol does not undergo glycolysis. Instead, it is converted by alcohol dehydrogenase 1B to form acetaldehyde, which, due to its free aldehyde, can generate reactive oxygen species (ROS) formation and toxic damage (19) if not quenched by hepatic antioxidants such as glutathione and ascorbic acid (see ROS formation and aging section) (20). Acetaldehyde is then quickly metabolized by the enzyme aldehyde dehydrogenase 2 to the intermediary acetic acid. From there, acetic acid is metabolized by the enzyme acyl-CoA synthetase short-chain family member 2 to form acetyl-CoA, which can then enter the mitochondrial tricarboxylic acid cycle (as per glucose). However, in the event of consumption of a large dose of ethanol producing a large amount of acetyl-CoA or due to the presence of other caloric substrate (i.e., as in beer in which ethanol and glucose are consumed together), the ethanol will more likely be converted to FFAs through DNL (21). Furthermore, acetaldehyde stimulates SREBP-1c, activating the enzymes of DNL (22) to increase rate of formation of FFAs. Although the absolute rate of DNL of ethanol (i.e., that which is metabolized to VLDL) is relatively small, fractional DNL increases from 1% at baseline to 31% after an ethanol bolus

Figure 1 Hepatic glucose metabolism. Of an ingested glucose load, 20% is metabolized by the liver. Under the action of insulin, glycogen synthase is increased, and the majority of the glucose load is stored as glycogen. Although insulin activation of sterol response element binding protein 1c (SREBP-1c) activates the lipogenic pathway, there is little citrate formed to act as a substrate for lipogenesis. In addition, insulin action on the liver phosphorylates forkhead protein O1 (FoxO1), excluding it from the nucleus, and suppressing the enzymes involved in gluconeogenesis (GNG). ACC, acetyl CoA carboxylase; ACL, ATP citrate lyase; ACS2, acyl-CoA synthetase short-chain family member 2; ApoB, apolipoprotein B; ChREBP, carbohydrate response element binding protein; CPT-1, carnitine palmitoyl transferase 1; FAS, fatty acid synthase; Glut2, glucose transporter 2; Glut4, glucose transporter 4; Glut 5, glucose transporter 5; GSK, glycogen synthase kinase; IRS-1, insulin receptor substrate 1; MTP, microsomal transfer protein; PFK, phosphofructokinase; PI3K, phosphatidylinositol 3-kinase; SREBP-1c, sterol regulatory element binding protein 1c. Reproduced from (59) with permission.



(21); thus, the liver is primed to convert ethanol to FFAs. Normally, intrahepatic lipid is exported as VLDL. Ethanol suppression of MTP alters VLDL production and lipid export machinery (23) to increase VLDL production and contribute to hypertriglyceridemia (24–26). By increasing intrahepatic lipid formation, ethanol drives hepatic insulin resistance (27,28). Although the mechanism is still unclear, dyslipidemia and hepatic insulin resistance may be due to hepatic diacylglycerol and triglyceride accumulation seen in hepatic steatosis, with resultant activation of the enzyme *c-jun* N-terminal kinase 1 (JNK-1) (see the following) (29).

Hepatic fructose metabolism

Only the liver possesses the Glut5 transporter (30), and the liver has a very high fructose extraction rate (31); thus, virtually an entire ingested fructose load finds its way to the liver. In contrast to the majority of hepatic glucose being converted to glycogen in the liver under the influence of insulin, fructose does not get converted to glycogen directly [although in case of glycogen depletion due to starvation or exercise, it can be converted to fructose-6-phosphate, which is isomerized to glucose-6-phosphate, which can rebuild glycogen (32)]. Rather, fructose is phosphorylated independently of insulin to fructose-1-phosphate by the enzyme fructokinase (Fig. 3), which undergoes glycolysis, and is metabolized to pyruvate, with the resultant large volume of acetyl-CoA entering the mitochondrial tricarboxylic acid cycle. Any extra intermediary will be available for DNL, similar to ethanol. Alternatively, a proportion of early glycolytic intermediaries will recombine

to form fructose-1,6-bisphosphate, which then also combines with glyceraldehyde to form xylulose-5-phosphate (33). Xylulose-5-phosphate is a potent stimulator of protein phosphatase 2A (34), which activates carbohydrate response element binding protein (35), stimulating the activity of DNL. Furthermore, fructose also stimulates PPAR- γ coactivator 1 β , a transcriptional coactivator for SREBP-1c, which further accentuates DNL enzymatic activity (36). In other words, fructose drives “double DNL” because carbohydrate response element binding protein and PPAR- γ coactivator 1 β drive these enzymes additively. Human studies demonstrate a rate of fractional DNL of 2% with glucose, yet up to 10% after 6 d of high fructose feeding (37,38). A recent human study demonstrated that fructose feeding increased fractional DNL to 17% (39). More importantly, when the liver receives glucose and fructose simultaneously, the glucose occupies the glycogenic pathway, forcing the fructose down the lipogenic pathway, thus tripling the rate of DNL compared with fructose alone (40). The attachment of hepatic triglyceride to apolipoprotein B by MTP completes its conversion to VLDL, which is exported out of the liver to contribute to fructose-induced hypertriglyceridemia (39,41–43), along with the production of “small dense” LDL (44), which is particularly atherogenic because it can be oxidized rapidly and is small enough to get under the surface of vascular endothelial cells to start the foam cell process (39,45–47). Some of the fatty acyl-CoA products from DNL escape packaging into VLDL for export and instead accumulate as lipid droplets in the hepatocyte (48), driving hepatic steatosis, similar to ethanol. In

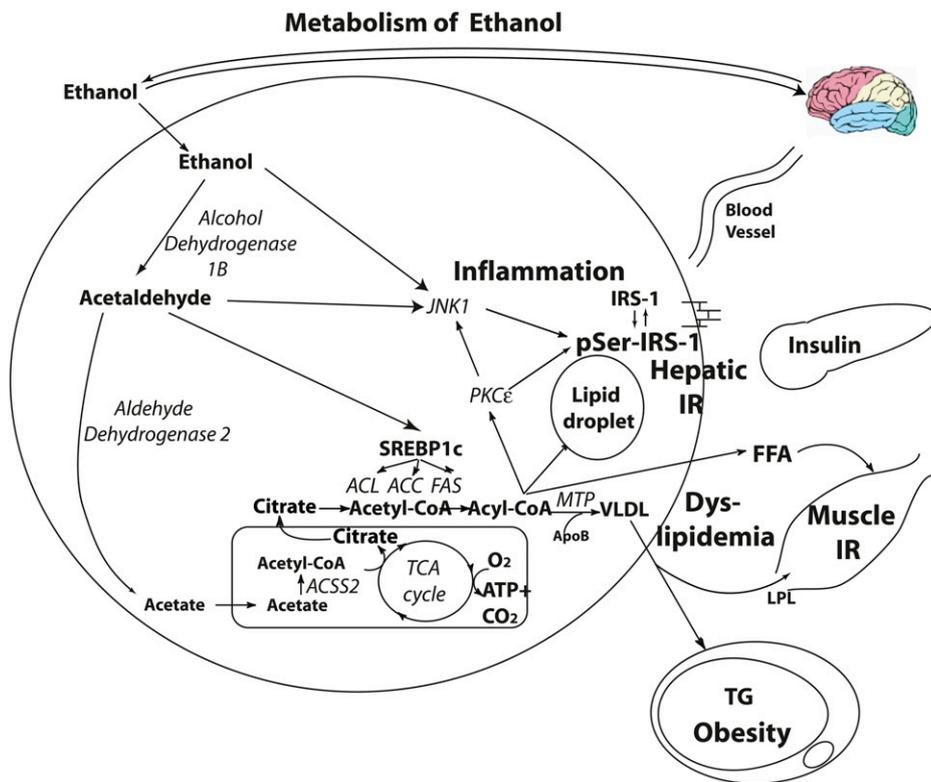


Figure 2 Hepatic ethanol metabolism. Of an ingested load, 80% reaches the liver. Ethanol induces the following: 1) de novo lipogenesis and dyslipidemia; 2) *c-jun* N-terminal kinase (JNK1) activation, which serine phosphorylates hepatic insulin receptor substrate 1 (IRS-1), rendering it inactive and contributing to hepatic insulin resistance, which promotes hyperinsulinemia and influences substrate deposition into fat; 3) hepatic lipid droplet formation, leading to steatosis; and 4) stimulation of the reward pathway, promoting continuous consumption. ACC, acetyl CoA carboxylase; ACL, ATP citrate lyase; ACS2, acyl-CoA synthetase short-chain family member 2; ApoB, apolipoprotein B; FAS, fatty acid synthase; IR, insulin resistance; IRS-1, insulin receptor substrate 1; LPL, lipoprotein lipase; MTP, microsomal transfer protein; PKC-

PI3K, phosphatidylinositol 3-kinase; PKCε, protein kinase C-ε; SREBP1c, sterol regulatory element binding protein 1c. Reproduced from (59) with permission.

doing so, the enzyme JNK-1 (49) is activated, which induces serine phosphorylation of IRS-1 in the liver (50), thereby preventing normal insulin-mediated tyrosine phosphorylation of IRS-1 and promoting hepatic insulin resistance. This drives hyperinsulinemia (51), with resultant obesity causing worsening insulin resistance. Furthermore, fructose increases the expression of FoxO1 (52). In the face of hepatic insulin resistance, FoxO1 is not phosphorylated to maintain its exclusion from the nucleus, with resultant transcription of gluconeogenic enzymes and hyperglycemia, requiring an even greater β-cell insulin response. Eventually, in response to the hepatic insulin resistance, gluconeogenesis, and the phenomena of glucotoxicity, lipotoxicity, endoplasmic reticulum stress (53–56), and the unfolded protein response (57) at the β-cell, this leads to inadequate insulin secretion in relation to the degree of peripheral insulin resistance and type 2 diabetes (58).

Hepatic metabolic profile and substrate burden: fructose vs. ethanol

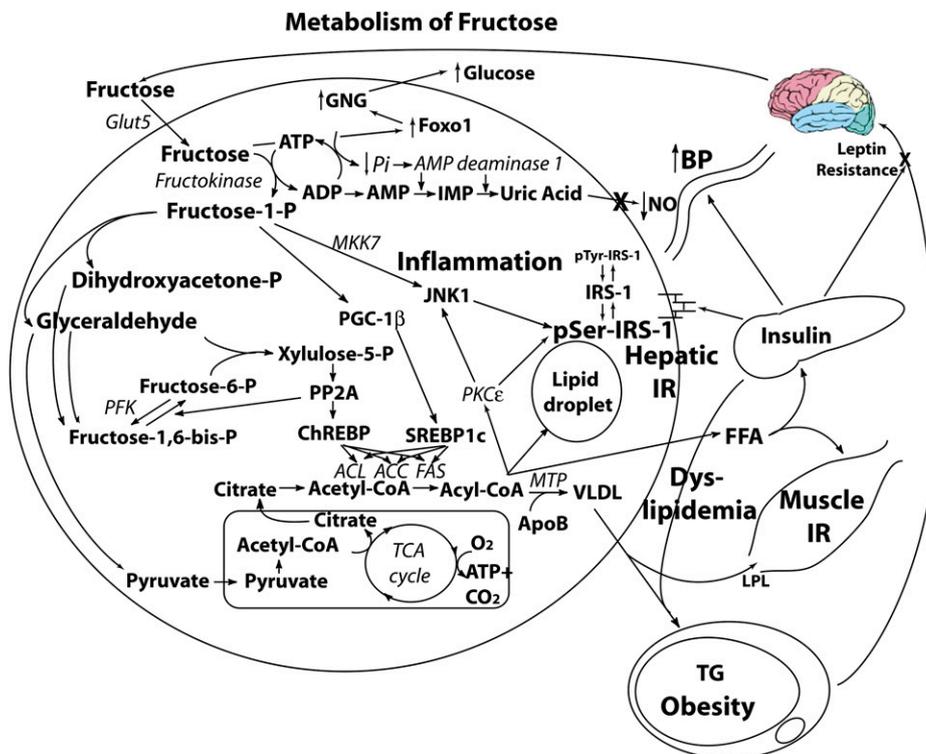
Thus, fructose and ethanol are analogous qualitatively in terms of hepatic metabolism. In small doses, neither will overwhelm hepatic mitochondrial capacity. However, as Paracelsus stated, “The dose determines the poison.” In a substrate overload/hypercaloric paradigm, excess energy substrate conversion to acetyl-CoA without any insulin regulation and with limited diversion to nontoxic intermediaries such as glycogen will occur. Both fructose and ethanol uniquely drive DNL, generating intrahepatic lipid, inflammation, and insulin resistance. Through the phenomena of enhanced DNL, JNK-1

activation, and hepatic insulin resistance, the hepatic metabolic profile of fructose is analogous to that of ethanol. Furthermore, fructose and ethanol are also analogous quantitatively. **Table 1** demonstrates the hepatic burden of a can of beer vs. a can of soda. Both contain 150 kcal per 12-oz (355-mL) can (59). Both contain a concomitant glucose load combined with either the ethanol load (beer) or the fructose load (soda). The first-pass effect of ethanol in the stomach and intestine removes 10% of the ethanol. In the case of beer (3.6% ethanol and 6.6% maltose, a glucose disaccharide), ~92 kcal reach the liver, whereas for soda, 90 kcal reach the liver. Indeed, the quantitative metabolic demand on the liver from beer and soda are analogous as well (59).

ROS formation and aging

Any nutritional substrate with a free reactive aldehyde or ketone can induce ROS formation when that reactive moiety binds to an ε-amino group of lysine found in proteins or DNA bases or with a free hydroxyl group found in lipids. In the case of carbohydrate, that reactive moiety may be available in the linear form or hidden in the ring form. Because glucose forms a 6-member glucopyranose ring with only 1 hydroxymethyl group, the ring form is stable, thereby reducing the availability of the free aldehyde. However, fructose forms a 5-member fructofuranose ring with 2 axial hydroxymethyl groups, which forces fructose at greater frequency into its linear form with the free ketone moiety (60).

Figure 3 Hepatic fructose metabolism. Of an ingested sucrose load, 20% of the glucose and 100% of the fructose is metabolized by the liver. Fructose induces the following: 1) substrate-dependent phosphate depletion, which increases uric acid and contributes to hypertension via inhibition of endothelial nitric oxide synthase and reduction of nitric oxide (NO); 2) de novo lipogenesis and dyslipidemia; 3) hepatic lipid droplet formation and steatosis; 4) muscle insulin resistance; 5) *c-jun* N-terminal kinase (JNK1) activation, contributing to hepatic insulin resistance, which promotes hyperinsulinemia and influences substrate deposition into fat; 6) increased forkhead protein O1 (FoxO1), promoting gluconeogenesis (GNG) and hyperglycemia; and 7) central nervous system hyperinsulinemia, which antagonizes central leptin signaling and promotes continued energy intake. ACC, acetyl CoA carboxylase; ACL, ATP citrate lyase; ACS2, acyl-CoA synthetase short-chain family member 2; ApoB, apolipoprotein B; ChREBP, carbohydrate response element binding protein; CPT-1, carnitine palmitoyl transferase 1; FAS, fatty acid synthase; Glut2, glucose transporter 2; Glut4, glucose transporter 4; Glut 5, glucose transporter 5; GSK, glycogen synthase kinase; IR, insulin resistance; IRS-1, insulin receptor substrate 1; LPL, lipoprotein lipase; MKK7, MAP kinase kinase 7; MTP, microsomal transfer protein; PFK, phosphofructokinase; PGC-1 β , PPAR- γ coactivator-1 β ; PI3K, phosphatidylinositol 3-kinase; PKC ϵ , protein kinase C- ϵ ; PP2A, protein phosphatase 2a; SREBP-1c, sterol regulatory element binding protein 1c. Reproduced from (59) with permission.



Effects of glucose

The aldehyde form of glucose can react with free amino groups on proteins in a nonenzymatic exothermic reaction, leading to nonenzymatic protein glycation (61), termed the Maillard or “browning” reaction (e.g., hemoglobin A_{1c}). Each glycation generates 1 superoxide radical that must be quenched by an antioxidant or cellular damage will occur (62). However, at 37°C and pH 7.4, the majority of glucose molecules are found in the stable 6-member glucopyranose ring form, limiting aldehyde exposure and reducing ROS generation.

Effects of ethanol

After ethanol is metabolized by alcohol dehydrogenase 1B to the intermediary acetaldehyde, its free aldehyde moiety

engages rapidly in ROS formation (63). Acetaldehyde induces hepatocellular damage through several different mechanisms (20), including mitochondrial damage, membrane effects, hypoxia, cytokine production, and iron mobilization. In the absence of antioxidant quenching (due to micronutrient malnutrition often seen in alcoholics), ROS formation may lead to lipid peroxidation, fibrogenesis, and ultimately cirrhosis (Fig. 4).

Effects of fructose

Because fructose forms a 5-member fructofuranose ring with steric hindrance from the 2 axial (abutting) hydroxymethyl groups, more molecules find themselves in the linear form, which exposes their reactive keto group and leads to fructation of proteins 7 times more rapidly than with glucose

Table 1. Similarities between soda and beer with respect to hepatic handling¹

	Soda (12 oz can)	Beer (12 oz can)
Calories	150	150
Percentage of carbohydrate	10.5% (sucrose)	3.6% (alcohol), 5.3% (other carbs)
Calories from		
Fructose	75 (4.1 kcal/g)	
Alcohol		90 (7 kcal/g)
Other carbohydrate	75 (glucose)	60 (maltose)
First-pass stomach-intestine metabolism	0%	10%
Calories reaching liver	90	92

¹ Reproduced with permission from (59).

(64,65). Thus, fructose-generated ROS species are abundant (66,67) and require quenching by a hepatic antioxidant (e.g., glutathione) or hepatocellular damage will result (Fig. 4). The hepatotoxic effects of fructose via ROS formation have been demonstrated in both cultured hepatocytes (68) and animal models (69). Although mechanistic data in humans are difficult to obtain, case-control studies demonstrate that fructose consumption correlates with the development of hepatic steatosis and nonalcoholic steatohepatitis (70–72).

Central nervous system effects to increase consumption

The hedonic pathway that motivates the “reward” of food intake consists of the ventral tegmental area (VTA) (the home of the dopamine perikarya) and the nucleus accumbens (NA) (the destination of the dopamine axons, also referred to as the “pleasure center” of the brain). Food intake is a “readout” of the reward pathway; for example, administration of morphine to the NA increases food intake in a dose-dependent fashion (73). Dopamine neurotransmission from the VTA to the NA mediates the reward properties of food (74), whereas

obesity results in decreased density of dopamine D₂ receptors as measured by positron emission tomography scanning (75). Indeed, any process that reduces dopamine receptor density or occupancy can drive increased food intake and weight gain (76).

Effects of glucose

In a rat model, 30-d ad libitum administration of 25% glucose solution did not result in significantly altered dopaminergic or opioidergic tone versus chow-fed animals (77). However, when the glucose was instead administered in a cyclic food deprivation/supply paradigm designed to create dependency, reductions in dopamine neurotransmission in the NA, which were also exacerbated by naloxone administration, mimicked withdrawal. These data suggest that glucose by itself does not routinely alter dopamine neurotransmission in the NA, but can exert some degree of dependency in a susceptible animal.

Effects of ethanol

Ethanol is a known substance of abuse via its effects on fostering reward (78). By altering γ -aminobutyric acid and opioid

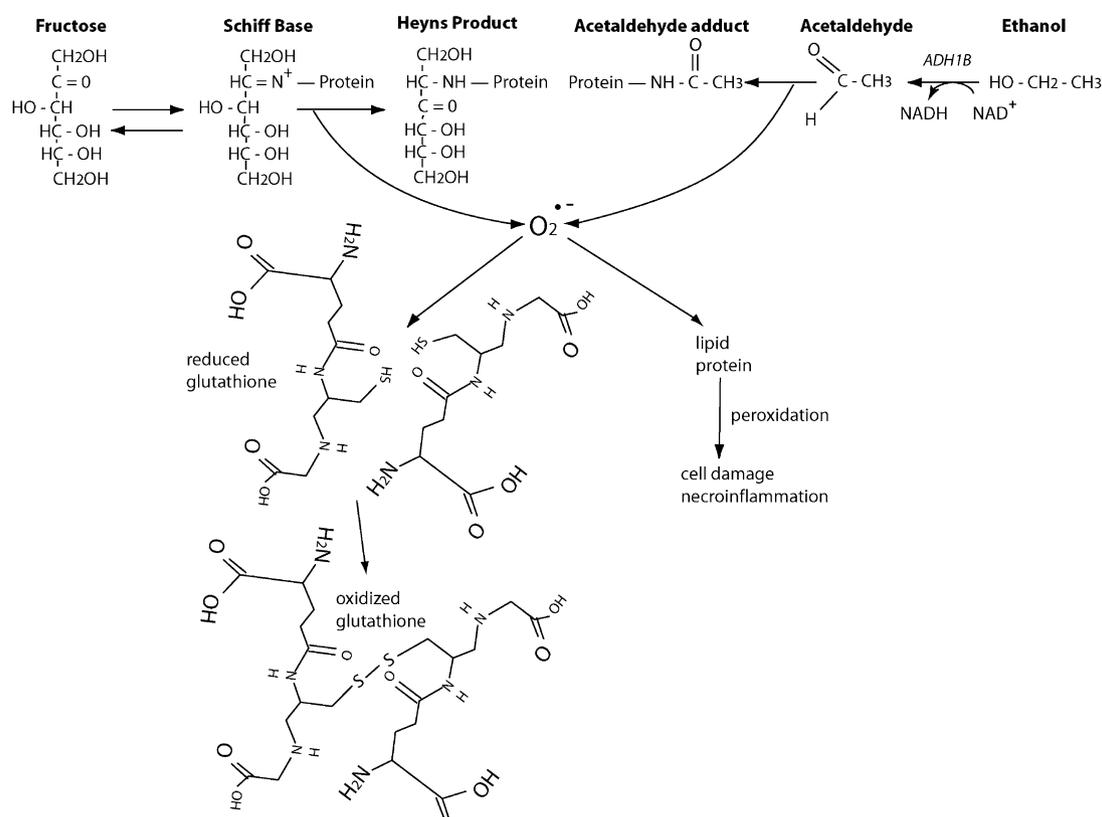


Figure 4 Generation of reactive oxygen species (ROS) by fructose or ethanol. Fructose first forms an intermediate Schiff base with the ϵ -amino group of lysine, which then spontaneously hydrogenates to form an irreversible Heyns product (hydroxyamide linkage or fructose adduct), termed the Maillard reaction. The heat of formation of this reaction is -19 kcal/mol and is therefore exothermically favorable. Each protein fructation generates 1 superoxide radical ($O_2^{\bullet-}$), which must be quenched by an antioxidant (such as glutathione with its reduced sulfhydryl groups). Conversely, ethanol is metabolized by alcohol dehydrogenase 1B (ADH1B), generating NADH, to acetaldehyde, which then participates in the same Maillard reaction to form acetaldehyde adducts, with generation of superoxide radicals that must also be quenched by antioxidants. In the absence of adequate antioxidant capacity, ROS production leads to peroxidation, hepatocellular damage, necroinflammation (nonalcoholic steatohepatitis), fibrosis, and ultimately cirrhosis. Reproduced from (59) with permission.

transmission within the VTA and central area of the amygdala, acute ethanol exposure activates dopamine neurotransmission (79). However, after repeated exposure to ethanol, dopamine increases, but dopamine receptor levels are decreased due to downregulation, and peak effects relative to baseline are attenuated (80), leading to tolerance. Human genetic studies demonstrate that downregulation of dopamine transport (and the resultant inadequate neurotransmission) results in increased ethanol consumptive behavior (81), and human imaging studies show that dysfunction of dopamine neurotransmission is associated with withdrawal and relapse (82). Such downregulation of dopamine neurotransmission with long-term substrate exposure is a hallmark of the addictive state (83).

Effects of fructose

Fructose has direct effects on increasing caloric consumption. Increasing the palatability of food by the addition of sucrose undermines normal satiety signals and motivates energy intake independent of energy need (84,85). For instance, sucrose infusion directly into the NA reduces D_2 receptors and μ -opioid receptors similar to that of morphine (86). Both sweet and high-fat foods mobilize both opioids and dopamine within the NA and establish hard-wired pathways for craving in these areas that can be identified by functional magnetic resonance imaging (73,87). Furthermore, animal models of intermittent sugar administration, over a 3-wk interval, can induce behavioral alterations consistent with dependence, i.e., bingeing, withdrawal and anxiety, craving, and cross-sensitization to other drugs of abuse (88). Neuropharmacologic analyses demonstrate a reduction in D_2 receptors in the NA, consistent with the fostering of reward and behavioral changes seen in addiction.

There is also evidence that sugar may be addictive in humans. Anecdotal reports from self-identified food addicts describe withdrawal as feeling “irritable,” “shaky,” “anxious,” and “depressed” (89). Other studies show that subjects will use sugar to treat psychological symptoms. Although dysphoria is a psychological manifestation of withdrawal, the directionality of this relationship is unclear. It is not known whether the negative effect is purely a symptom of withdrawal or that these subjects more likely had some degree of dysphoria that preceded the dependence on sugar to medicate it. Other areas that warrant study of potential sugar addiction in humans are craving and tolerance. Benton (90) points out that sugar craving can vary widely by age, menstrual cycle, and time of day. We have examined the content of the “fast food” meal as it relates to addiction; of the various components, fat and salt increase the salience of the food, but only sugar and caffeine exhibit true dependence (91). Although anecdotal reports abound supporting human “sugar addiction,” whether this “vicious cycle” of fructose consumption is merely habituation or full-fledged dependence is not yet clear (92).

Response of the sugar industry

It should be pointed out that all of these physiological similarities are just that — similarities. True quantitative and

mechanistic studies have not proved this qualitative analogy. It is also necessary to highlight that the food industry vehemently argues that HFCS is no different from sucrose (93) and that fructose is natural, benign, and certainly not a long-term dose-dependent hepatotoxin. However, a discussion of these points is clearly in order.

Animals are not humans

The food industry is quick to point out that most fructose studies are done in rodents with large doses over a short period of time. However, studies done in primates demonstrate similar detrimental effects (94). Furthermore, human studies are consistent with the analogies stated previously (39,43).

Fructose does not increase blood glucose or hemoglobin A_{1c}

The industry argues that fructose does not increase the blood glucose. It has a very low glycemic index of 19 (glucose is the index at 100), which is a measure of a food's generation of an insulin response and used as a method for quantifying a food's potential for weight gain. Indeed, fructose alone does not increase the blood glucose nor does it generate an insulin response, nor does alcohol (in fact, alcohol lowers the blood glucose). But adding alcohol to foods is not a rational way to make foods healthier. There is no fructose alone in nature; it is always found paired with glucose (either as sucrose or HFCS), and the glucose contribution generates quite a hefty insulin response. So the glucose is metabolized by the liver's glycogenic pathway and drives up insulin, whereas the fructose is metabolized by the liver's lipogenic pathway and causes liver insulin resistance.

The industry also argues that as fructose does not increase the serum glucose and also does not increase hemoglobin A_{1c} levels (95). In the blood, fructose does not bind to the amino moiety at position 1 of hemoglobin to generate hemoglobin A_{1c} (leading the food industry to wrongly assume that fructose is benign); rather, fructation occurs at positions 7, 66, and 127 of the hemoglobin molecule instead (67).

Fructose for glucose exchange studies show no detrimental effects

Meta-analyses of controlled isocaloric “fructose for glucose” exchange studies demonstrate no effects of weight gain or other morbidities (96). Perhaps 1 reason for this is because crystalline fructose is incompletely absorbed, and thus its effects on glucose and HbA_{1c} may be minimal. If so, then the gastrointestinal symptoms of the residual fructose in the intestine are maximal, generating pain, bloating, and diarrhea (97). Furthermore, those meta-analyses in which fructose was supplied in excess showed weight gain, dyslipidemia, and insulin resistance (96). Thus, the dose determines the poison.

The food industry is fond of referring to a 1999 study showing that DNL of oral fructose occurs at a very low rate (<5%) (98). That is true if you are thin, insulin sensitive, fasting (and therefore glycogen depleted), and given just fructose alone (which is poorly absorbed). Conversely, if you are

Table 2. Phenotypes of long-term energy substrate exposure¹

Long-term ethanol exposure	Long-term fructose exposure
Hematologic disorders	
Electrolyte abnormalities	
Hypertension	Hypertension (uric acid)
Cardiac dilation	
Cardiomyopathy	Myocardial infarction (dyslipidemia, insulin resistance)
Dyslipidemia	Dyslipidemia (de novo lipogenesis)
Pancreatitis	Pancreatitis (hypertriglyceridemia)
Obesity (insulin resistance)	Obesity (insulin resistance)
Malnutrition	Malnutrition (obesity)
Hepatic dysfunction (ASH)	Hepatic dysfunction (NASH)
Fetal alcohol syndrome	
Addiction	Habituation, if not addiction

¹ Reproduced with permission from (59).

obese, insulin resistant, fed, and getting both fructose and glucose together (a sizable percentage of the population), then fructose gets converted to fat at a much higher rate, ~30% (40). In other words, the toxicity of fructose depends on the context. If you are an elite athlete and glycogen depleted, fructose is not an issue. But for the rest of us, our current excess fructose consumption drives chronic metabolic disease.

A little fructose improves insulin secretion

Studies of ethanol use show that small doses are healthy because ethanol increases HDL and improves insulin sensitivity and longevity (99). Like alcohol, a small dose of fructose has been shown in some studies to have a beneficial effect on insulin secretion (100). The negative effects of fructose, just like alcohol, are dose dependent. For alcohol, we have empirical evidence that in most people, a maximum dose of 50 g/d is the threshold for toxicity. By analogy, that is likely the threshold for fructose as well. **The problem is that the current average adult fructose consumption is 51 g/d (101). So the levels of half of all adults are likely above the threshold for fructose toxicity, and adolescents currently average 75 g/d.**

Conclusions

Most people consider sugar (i.e., fructose-containing compounds) to be just “empty calories.” However, this paper reports 3 separate ways that fructose exerts negative effects beyond its caloric equivalent. First, in the hypercaloric state, fructose drives DNL, resulting in dyslipidemia, hepatic steatosis, and insulin resistance, akin to that seen with ethanol. This should not be surprising because fructose and ethanol are congruent evolutionarily and biochemically. Ethanol is manufactured by the fermentation of fructose — the big difference is that for ethanol, the yeast performs the glycolysis, whereas for fructose, we humans perform our own glycolysis. Second, through production of reactive carbonyl moieties, both fructose and ethanol generate excess ROS, which increases the risk of hepatocellular damage if not quenched by antioxidants. Last, by downregulation of D₂ receptors in the reward pathway, chronic fructose exposure contributes

to a paradigm of continuous food intake independent of energy need and exerts symptoms of tolerance and withdrawal, similar to chronic ethanol abuse. Therefore, it should not be surprising that the disease profile of fructose and ethanol overconsumption would also be similar (**Table 2**).

Fructose also exhibits notable social and market similarities with ethanol. Both have been “fetishized” by various cultures in times past. Of course, today both sugar and alcohol are legal commodities and are traded freely. The problems of overuse and related health harm tend to occur in lower socioeconomic groups. Those who overconsume either substance are stigmatized. Finally, within public health circles, alcohol clearly evinces the 4 criteria of unavailability, toxicity, abuse, and negative impact on society, which warrant consideration for personal intervention (e.g., “rehab”) and societal intervention (e.g., “laws”). Sucrose/HFCS satisfies those same 4 criteria as well (6).

Although fructose does not exhibit the same acute toxic effects of ethanol (i.e., central nervous system depression and resultant auto accidents), it recapitulates all the chronic toxic effects on long-term health. It is time for a paradigm shift in our societal treatment of fructose, recognizing that fructose is “alcohol without the buzz.”

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