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Fructose: Metabolic, Hedonic, and Societal Parallels with Ethanol

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ABSTRACT

Rates of fructose consumption continue to rise nationwide and have been linked to rising rates of obesity, type 2 diabetes, and metabolic syndrome. Because obesity has been equated with addiction, and because of their evolutionary commonalities, we chose to examine the metabolic, hedonic, and societal similarities between fructose and its fermentation byproduct ethanol. Elucidation of fructose metabolism in liver and fructose action in brain demonstrate three parallelisms with ethanol. First, hepatic fructose metabolism is similar to ethanol, as they both serve as substrates for de novo lipogenesis, and in the process both promote hepatic insulin resistance, dyslipidemia, and hepatic steatosis. Second, fructosylation of proteins with resultant superoxide formation can result in hepatic inflammation similar to acetaldehyde, an intermediary metabolite of ethanol. Lastly, by stimulating the "hedonic pathway" of the brain both directly and indirectly, fructose creates habituation, and possibly dependence; also paralleling ethanol. Thus, fructose induces alterations in both hepatic metabolism and central nervous system energy signaling, leading to a "vicious cycle" of excessive consumption and disease consistent with metabolic syndrome. On a societal level, the treatment of fructose as a commodity exhibits market similarities to ethanol. Analogous to ethanol, societal efforts to reduce fructose consumption will likely be necessary to combat the obesity epidemic.

J Am Diet Assoc. 2010;110:1307-1321.

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Manuscript accepted: March 15, 2010.

0002-8223/$36.00

doi: 10.1016/j.jada.2010.06.008

The last 30 years has witnessed an inexorable rise in obesity, diabetes, and metabolic syndrome coincident with a rise in daily calorie intake (1). Aside from quantitative overconsumption, various macronutrients have been postulated to contribute to the metabolic syndrome (2,3). Some suggest that specific dietary fats, such as saturated and *trans* fats, are the culprit (4-6), while others suggest that a deficiency of monounsaturated lipids, such as olive oil (oleic acid) (7) or linoleic acid (8), are implicated. However, our absolute consumption of dietary fat has not changed in these last 30 years (9), and high-fat, low-carbohydrate diets appear to be protective against the metabolic syndrome (10). Although epidemiologic studies associate light to moderate ethanol consumption with improved insulin sensitivity (11) and wine consumption with reduced cardiovascular risk (12), other cross-sectional (13,14) and prospective (15) studies implicate a dose-dependent effect of larger doses of ethanol in the pathogenesis of insulin resistance and the metabolic syndrome, especially in beer and shochu, which provide a large dose of carbohydrate in addition to ethanol (13,14).

Another likely culprit, and the focus of this review, is the monosaccharide fructose. An ever-increasing percentage of calories in the American diet are derived from fructose. Before 1900, Americans consumed approximately 15 g/day fructose (4% of total calories), mainly through fruits and vegetables. Before World War II, fructose intake had increased to 24 g/day; by 1977, 37 g/day (7% of total calories); by 1994, 55 g/day (10% of total calories); and current estimates put fructose consumption by adolescents at 73 g/day (12% of total calories) (16). Current fructose consumption has incrementally increased fivefold in the last century and doubled in the last 30 years. Disappearance data from the Economic Research Service of the US Department of Agriculture support this secular trend. These data document partial substitution for sucrose by high-fructose corn syrup; however, annual per capita total caloric sweetener usage increased from 73 to 95 lb in that interval (17). Although high-fructose corn syrup in soda has received most of the attention (18,19), high fruit juice intake (sucrose) is also associated with childhood obesity (20), although it is not captured in the Economic Research Service. Thus, after adjustment for juice intake, per capita consumption of fructose or fructose-containing disaccharides is at ap-

proximately 156 lb/year or 0.4 lb/day for the average American.

Although originally proposed as the ideal sweetener for people with diabetes because of its inability to raise serum glucose levels and its insulin-independent metabolism, many (21-28), although certainly not all (29), investigators have elaborated fructose's unique hepatic properties and have indirectly implicated fructose in the dual epidemics of obesity and type 2 diabetes and its primacy in the pathogenesis of the metabolic syndrome. The American Heart Association has recently called for a reduction in added sugars intake to help quell these epidemics (30).

The purpose of this work is to highlight, in both animal and human studies, the unique aspects of hepatic fructose metabolism, central nervous system fructose action, and their associations with obesity and the metabolic syndrome, and to draw parallels to the mechanisms of action of ethanol. Using PubMed and the substrate key terms *fructose* or *ethanol,* combined with the effector terms *de novo lipogenesis, hypertriglyceridemia, steatosis or fatty liver, insulin resistance, metabolic syndrome, reactive oxygen species,* and *addiction,* a review of the literature on the secular trends of fructose consumption, hepatic glucose, ethanol, and fructose metabolism, carbohydrate-protein adduct and reactive oxygen species formation, and of sugar as an addictive substance, between the years 1966 and 2009, was conducted. Mechanistic studies in animals that addressed directionality of effect, along with correlative or mechanistic data in humans that supported or detracted from such mechanisms were included. After syntheses of these data, consultations with experts in the field of fructose metabolism, hepatic lipid metabolism, and addiction were obtained to establish veracity of these findings (listed in Acknowledgments).

HEPATIC INSULIN RESISTANCE AND THE METABOLIC SYNDROME

The pathogenesis of the metabolic syndrome remains a conundrum; to the point where some have called into question its very existence (31). One reason for this puzzle is the phenomenon of "selective hepatic insulin resistance" seen in the metabolic syndrome (32). Insulin normally exerts its effects on liver metabolism through two primary metabolic pathways. In the first, phosphorylation of the forkhead protein Foxo1 occurs, excluding it from the nucleus of the hepatocyte, and thus reducing transcription of genes for enzymes involved in gluconeogenesis, thus maintaining euglycemia (33,34). The second pathway is the activation of sterol regulatory element binding protein-1c (SREBP-1c). This transcription factor activates de novo lipogenesis to turn excess energy from either fat or carbohydrate into triglyceride, which is then packaged into very low density lipoproteins (VLDL) for hepatic export and peripheral storage in adipocytes.

Complete hepatic insulin resistance, such as seen in the liver insulin receptor knockout mouse (35), results in both lack of Foxo1 phosphorylation (with resultant gluconeogenesis and hyperglycemia) and lack of SREBP-1c activation (with lack of triglyceride synthesis). In contrast, hepatic insulin resistance in metabolic syndrome is "selective." Foxo1 remains dephosphorylated (promoting gluconeogenesis, hepatic glucose output, and driving reflex hyperinsulinemia), but SREBP-1c is activated (promoting triglyceride synthesis, dyslipidemia, and other negative downstream effects, see "Hepatic Fructose Metabolism"). The reason for this uncoupling of insulin's two main hepatic signaling pathways remains unclear.

DIFFERENTIAL HEPATIC METABOLISM OF ENERGY SUBSTRATE

To explain the dichotomy of selective insulin resistance in the pathogenesis of metabolic syndrome, it is essential to delineate the hepatic metabolism of three energy substrates: glucose, ethanol, and fructose. As an illustration, in each case, we will follow a 120-kcal oral bolus of each substrate. However, it should be noted that the hepatic metabolism of each substrate delineated below is subject to numerous environmental and behavioral factors, such as ambient temperature, altitude, sleep debt, smoking, thyroid status, and, most importantly, physical activity. The following breakdown is meant to depict a sedentary American adult.

Hepatic Glucose Metabolism

Glucose is the preferred substrate for energy metabolism. Each cell in the body possesses a glucose transporter (Glut1 through Glut4 constitute the majority) to facilitate transport of glucose into the cell for energy utilization. Upon ingestion of 120 kcal of glucose (eg, two slices of white bread) (Figure 1), plasma glucose levels rise and insulin is released by the pancreas through glucose stimulation of β-cell depolarization via the Glut2 transporter. Ninety-six kilocalories (80%) of the glucose bolus are utilized by other organs immediately (36). Only 24 kcal (20%) enter the liver through the Glut2 transporter.

Insulin binds to the hepatic insulin receptor, activating its endogenous B-chain tyrosine kinase, which promotes the tyrosine phosphorylation of insulin receptor substrate-1, which increases the activity of phosphatidyl inositol-3 kinase, inducing the transcription factor Akt. Akt activates three distinct pathways of hepatic insulin action. The first is the phosphorylation of the forkhead protein Foxo1, downregulating gluconeogenesis to maintain euyglycemia (34). The second is the increase of SREBP-1c, which then activates the enzyme glucokinase, fixing glucose in the hepatocyte by forming glucose-6-phosphate. The third is activation of glycogen synthase kinase, which then activates glycogen synthase. The majority of glucose-6-phosphate (approximately 20 kcal, depending on the amplitude of the insulin signal) is deposited in the liver as glycogen, the storage carbohydrate. The liver can store large amounts of glycogen without experiencing dysfunction or damage, as demonstrated by the continued normal hepatic function into adulthood of patients with glycogen storage diseases (37).

Only a small amount of glucose-6-phosphate (the exact amount is dependent on quantity of other substrates, and magnitude of insulin action) is broken down by the Embden-Meyerhoff glycolytic pathway to pyruvate. Pyruvate enters the mitochondria, where it is converted to acetyl-CoA, which then participates in the Krebs tricarboxylic acid (TCA) cycle to generate adenosine triphosphate, the chemical storage form of energy, carbon dioxide, and wa-

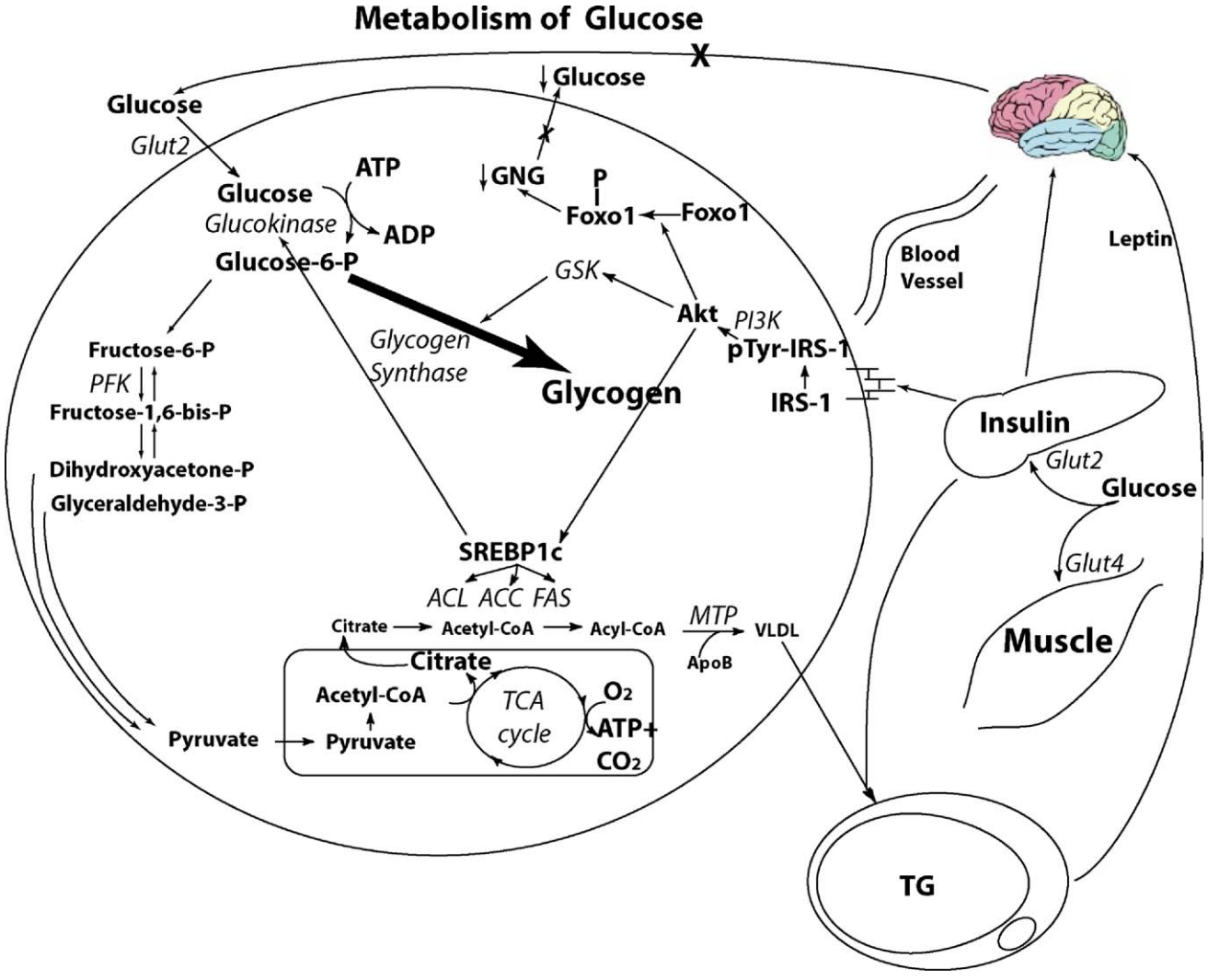

Figure 1. Hepatic glucose metabolism. Of an ingested glucose load, 20% is metabolized by the liver. Under the action of insulin, glycogen synthase is increased, and the majority of the glucose load is stored as glycogen. While insulin activation of sterol response element binding protein-1c (SREBP-1c) activates the lipogenic pathway, there is little citrate formed to act as substrate for lipogenesis. In addition, insulin action on the liver phosphorylates forkhead protein-1 (Foxo1), excluding it from the nucleus, and suppressing the enzymes involved in gluconeogenesis (gluconeogenesis). ADP=adenosine diphosphate. ATP=adenosine triphosphate. GNG=gluconeogenesis. IRS-1=insulin receptor substrate-1. TG=triglyceride.

ter. The hepatic TCA cycle has a relatively fixed maximum velocity, modulated only by thyroid status, cold exposure, altitude, and exercise (38,39). Thus, whatever tiny fraction of pyruvate is not metabolized by the mitochondria exits back into the cytoplasm as citrate through the "citrate shuttle" (40). This small amount of cytoplasmic citrate can serve as substrate for the process of de novo lipogenesis (DNL). In DNL, the enzyme adenosine triphosphate citrate lyase cleaves citrate to acetyl-CoA, the enzyme acetyl-CoA carboxylase carboxylates acetyl-CoA to form malonyl-CoA, and the enzyme fatty acid synthase adds serial acetyl-CoAs to the carbon backbone. These enzymes are activated serially under the transcriptional regulation of SREBP-1c to metabolize citrate into fatty acyl-CoA (41), which is then esterified with glycerol to form triglyceride. From there, triglyceride binds to apolipoprotein B (apoB) to form VLDL (measured peripherally in the triglyceride fraction), which are transported out of the liver for storage in adipocytes, and can serve as substrate for peripheral energy metabolism, but in excess will promote atherogenesis and/or obesity. Thus, only a tiny fraction of glucose can be hepatically metabolized to VLDL, which could contribute slowly to cardiovascular disease during a lifetime.

Hepatic Ethanol Metabolism

Ethanol is a naturally occurring energy substrate and, in small doses, may confer health benefits, but it is also recognized in acute large quantities as a central nervous

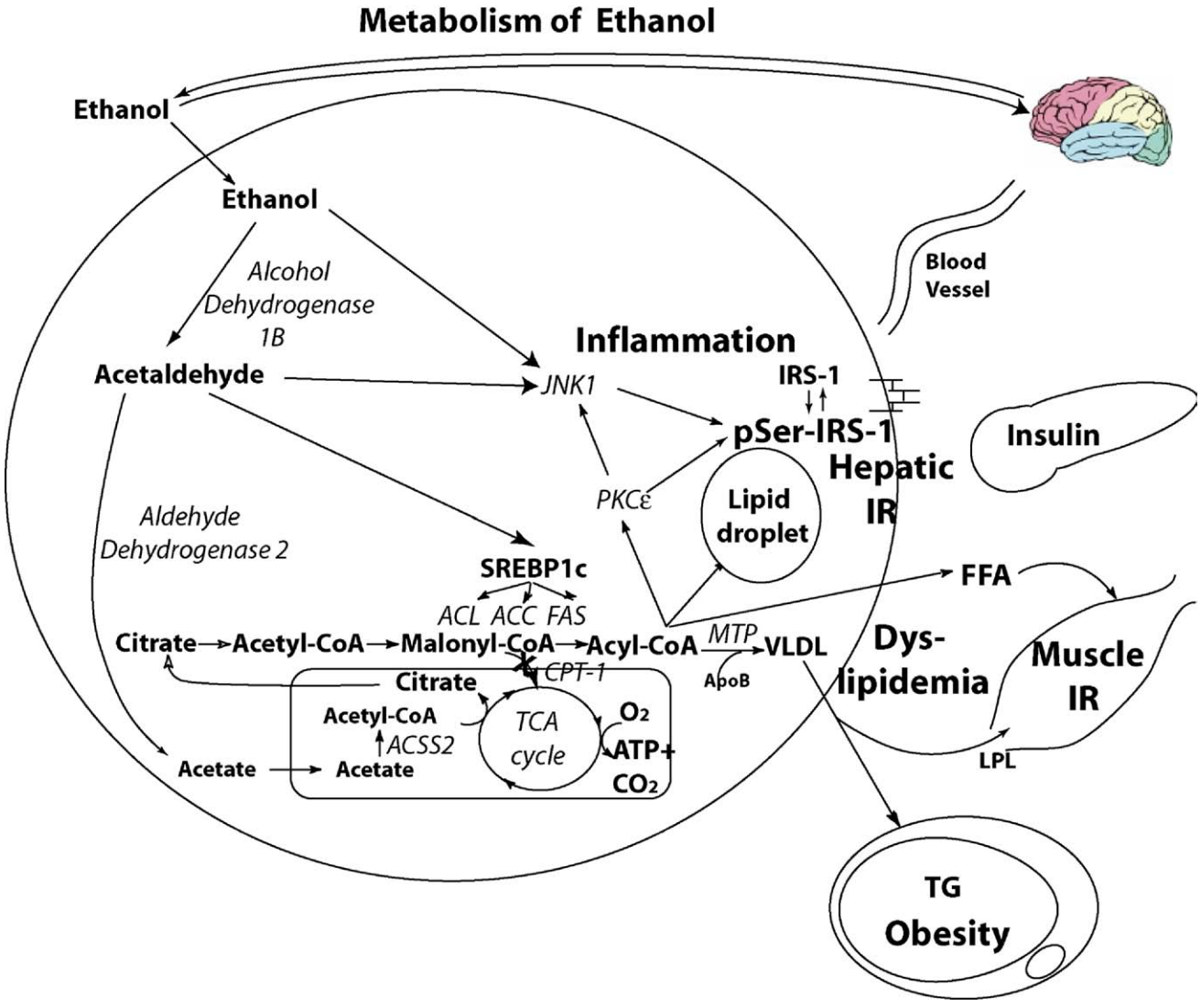

Figure 2. Hepatic ethanol metabolism. Of an ingested load, 80% reaches the liver. Ethanol induces: de novo lipogenesis and dyslipidemia; c-jun N-terminal kinase (JNK-1) activation, which serine phosphorylates hepatic insulin receptor substrate-1 (IRS-1), rendering it inactive, and contributing to hepatic insulin resistance, which promotes hyperinsulinemia and influences substrate deposition into fat; hepatic lipid droplet formation, leading to steatosis; and stimulation of the reward pathway, promoting continuous consumption. ACC=acetyl CoA carboxylase. ACL=adenosine triphosphate citrate lyase. CPT-1=carnitine palmitoyl transferase-1. FAS=fatty acid synthase. FFA=free fatty acids. IR=insulin resistance. IRS-1=insulin receptor substrate-1. JNK-1=c-jun N-terminal kinase 1. LPL=lipoprotein lipase. MTP=microsomal transfer protein. PKCε=protein kinase C$-\varepsilon$. SREBP-1c=sterol regulatory element binding protein-1c. TCA=tricarboxylic acid. TG=triglyceride.

system toxin and in chronically large quantities as a hepatotoxin. Although epidemiologic studies associate light to moderate ethanol consumption with improved insulin sensitivity (11) and wine consumption with reduced cardiovascular risk (12), other cross-sectional (13,14) and prospective (15) studies implicate a dose-dependent effect of the chronic consumption of larger doses of ethanol, especially in beer, shochu, and spirits (13,14), in the genesis of insulin resistance and metabolic syndrome.

The hepatic metabolism of ethanol is quite dichotomous from that of glucose (Figure 2). Upon oral ingestion of 120 kcal of ethanol (eg, 1.5 oz hard spirits at 80 proof, or 40%), approximately 10% is metabolized by the stomach and stomach and intestine in a "first-pass" effect before entry into the portal circulation (42). Another 10% are metabolized by muscle and kidney. So approximately 96 calories reach the liver, accounting for four times the substrate as for glucose. Ethanol enters the hepatocyte through osmosis and does not stimulate insulin secretion. Once inside the liver, ethanol bypasses glycolysis and is converted by alcohol dehydrogenase 1B to form acetaldehyde, which, because of its free aldehyde, can generate reactive oxygen species (ROS) formation and toxic damage (43) if not quenched by hepatic antioxidants such as glutathione or ascorbic acid (see "ROS Formation") (44).

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 substrate-dependent phosphate depletion, which increases uric acid and contributes to hypertension through inhibition of endothelial nitric oxide synthase and reduction of nitric oxide (NO); de novo lipogenesis (DNL) and dyslipidemia; hepatic lipid droplet formation and steatosis; muscle insulin resistance; c-jun N-terminal kinase (JNK-1) activation, contributing to hepatic insulin resistance, which promotes hyperinsulinemia and influences substrate deposition into fat; increased forkhead protein-1 (Foxo1), promoting gluconeogenesis and hyperglycemia; and central nervous system (CNS) hyperinsulinemia, which antagonizes central leptin signaling and promotes continued energy intake. ACC=acetyl CoA carboxylase. ACL=adenosine triphosphate citrate lyase. ACSS2=acyl-CoA synthetase short-chain family member 2. AMP=adenosine monophosphate. ApoB=apolipoprotein B. ChREBP=carbohydrate response element binding protein. CPT-1=carnitine palmitoyl transferase-1. FAS=fatty acid synthase. FFA=free fatty acids. Glut 5=glucose transporter 5. Glut2=glucose transporter 2. Glut4=glucose transporter 4. GNG=gluconeogenesis. GSK=glycogen synthase kinase. IR=insulin resistance. IRS-1=insulin receptor substrate-1. LPL=lipoprotein lipase. MKK7=mitogen activated protein kinase kinase 7. MTP=microsomal transfer protein. PFK=phosphofructokinase. PGC-1β=peroxisome proliferator-activated receptor-γ coactivator-1β. PI3K=phosphatidyl inositol-3-kinase. PKCε=protein kinase C$-\varepsilon$. PP2A=protein phosphatase 2a. SREBP-1c=sterol regulatory element binding protein-1c. VLDL=very-low-density lipoprotein.

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 TCA cycle (as per glucose, see "Hepatic Glucose Metabolism"); or, in the presence of other caloric substrate, it is more likely to participate in synthesis of fatty acids through DNL (as per fructose, see "Hepatic Fructose Metabolism"). Furthermore, acetaldehyde stimulates SREBP-1c, activating the enzymes of DNL (45). Although the absolute rate of DNL of ethanol (ie, that which is metabolized to VLDL) is relatively small, fractional DNL increases from 1% at baseline to 31% after an ethanol bolus (46); thus, the liver is primed to convert convert ethanol to lipid.

In the process of DNL, the intermediary malonyl-CoA is formed in excess. However, malonyl-CoA is a steric inhibitor of the mitochondrial enzyme carnitine palmitoyl transferase-1 (47). Carnitine palmitoyl transferase-1 is the key rate-limiting and regulatory step in mitochondrial β-oxidation; the fatty acid transporter carnitine must be regenerated for transesterification and import of fatty acids into the mitochondrial matrix to generate two-carbon fragments for ketone formation (48). Furthermore, ethanol blocks fatty acid β-oxidation through inhibition of both peroxisome proliferation-activated receptor$-\alpha$ and adenosine monophosphate–activated protein kinase, which leads to decreased phosphorylation and resultant increased activity of acetyl-CoA carboxylase, increased levels of malonyl-CoA, and decreased activity of carnitine palmitoyl transferase-1 (49). Thus, increased DNL inhibits intrahepatic lipid β-oxidation, resulting in further intrahepatic lipid buildup (45,50).

The principal exit strategy for intrahepatic lipid is the export of VLDL; its synthesis depends on microsomal triglyceride transfer protein (MTP) for correct apoB100 protein folding prior to export. Reduction of hepatic peroxisome proliferation-activated receptor$-\alpha$ by ethanol downregulates MTP activity (51). Hepatic triglyceride availability is the major determinant of the VLDL secretion rate, but MTP activity seems to determine VLDL size and subsequent rates of clearance in the plasma (52). Similarly, ethanol suppression of MTP alters VLDL production and lipid export machinery (48) to increase VLDL production and contribute to hypertriglyceridemia (53-55).

Lastly, ethanol is a known contributor to hepatic insulin resistance (56,57). Although the mechanism is still unclear, dyslipidemia and hepatic insulin resistance may be due to hepatic diacylglycerol (DAG) and triglyceride accumulation seen in hepatic steatosis, with resultant activation of the enzyme c-jun N-terminal kinase 1 (JNK-1; see "Hepatic Fructose Metabolism") (58).

Hepatic Fructose Metabolism

Although the intestine and kidney possess the Glut5 transporter to resorb fructose into the bloodstream, only the liver possesses the Glut5 fructose transporter in order to metabolize fructose. Upon ingestion of 120 kcal of sucrose (eg, 8 oz of orange juice; composed of 60 kcal fructose and 60 kcal glucose) (Figure 3), the overwhelming majority of the 60-kcal fructose bolus reaches the liver, along with 20% of the glucose bolus (12 kcal), for a total of 72 kcal; thus, the liver must handle triple the substrate as it did for glucose alone (36).

Phosphate Depletion and Hypertension

In the liver, fructose is converted to fructose-1-phosphate by the enzyme fructokinase. This is an adenosine triphosphate–requiring reaction (59), depleting available intracellular phosphate. Phosphorylation of this large substrate load leads to activation of the scavenger enzyme adenosine monophosphate deaminase-1, which recoups intracellular phosphate by converting the adenosine phosphate breakdown products (adenosine diphosphate, adenosine monophosphate, and inosine monophosphate) to the cellular waste product uric acid (60). Buildup of urate in the circulation inhibits endothelial nitric oxide synthase, resulting in decreased nitric oxide in the vasculature. Nitric oxide is an endogenous vascular smooth muscle relaxant; its depletion by urate results in hypertension (61,62).

Rodent models demonstrate that a high-fructose diet leads to hypertension and renovascular damage (63). Recently, sugar consumption has been correlated with uric acid concentrations in American adults (64). Similarly, soft drink consumption in adolescents in the recent National Health and Nutrition Examination Survey evaluation demonstrates a positive relationship with uric acid levels and with systolic hypertension (65). Lastly, soft drink consumption correlates with blood pressure elevation in adolescents, although concurrent caffeine ingestion may be a complicating variable (66). Furthermore, inhibition of uric acid synthesis by allopurinol reduces blood pressure in obese adolescents (67).

DNL

In contrast to glucose's conversion to glycogen, the fructose-1-phosphate load enters the Embden-Meyerhoff glycolytic cascade. The majority of fructose-1-phosphate is metabolized directly to pyruvate, with the resultant large volume of acetyl-CoA entering the mitochondrial TCA cycle. The liver mitochondria cannot metabolize the entire fructose-derived pyruvate/acetyl-CoA substrate excess; any extra will exit the mitochondria into the cytoplasm as citrate via the "citrate shuttle" (40). 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 (68). Xylulose-5-phosphate is a potent stimulator of protein phosphatase 2A (69), which activates carbohydrate response element binding protein (70), stimulating the activity of all three DNL enzymes adenosine triphosphate citrate lyase, acetyl-CoA carboxylase, and fatty acid synthase, which then rebuild the excess cytoplasmic citrate into fatty acyl-CoA and free fatty acids (FFA). Furthermore, fructose also stimulates peroxisomal proliferator-activated receptor-γ coactivator-1β, a transcriptional coactivator for SREBP-1c, which further accentuates DNL enzymatic activity (71).

Excess accumulation of metabolites of DNL is seen in both human and rat models of steatosis (72,73). For instance, tracer studies in obese subjects with steatosis show that 26.1% of the intrahepatic lipid pool occurs through the process of DNL (74). On a typical high-fat diet, lean subjects exhibited $<3\%$ (1 to 2 g/day) of carbohydrate (CHO) converted to FFA by DNL (75,76). However, obese insulin-resistant subjects show markedly increased fractional DNL $>10\%$ (77). DNL is markedly increased by excess dietary CHO, rather than excess dietary fat (78). For example, if total CHO energy intake exceeds total energy expenditure, hepatic DNL is incremented 10-fold (79). Similarly, on a high-CHO diet, DNL synthesis is 27 times increased in the fasting state as compared with a low-CHO diet, and 4 times increased in the fed state (80). Fructose is a primary driver of DNL. Human studies demonstrate a rate of fractional DNL of 2% with glucose and 10% after 6 days of high-fructose feeding (81,82) A recent human study demonstrated that fructose feeding increased fractional DNL to 17% (83).

Dyslipidemia

The attachment of hepatic triglyceride to apoB by MTP completes its conversion to VLDL, which is exported out of the liver to contribute to fructose-induced hypertriglyceridemia (84). Elevated circulating VLDL in animal models of high-fructose feeding may be a result of overproduction (85) driven by insulin resistance; increased triglyceride flux and hepatic inflammation (86); and decreased clearance (87,88).

In rodents, fructose feeding reduces hepatic peroxisome proliferation-activated receptor-α (89); inducing hepatic inflammation (90), and also inducing apoB100 overproduction (85,91), resulting in rapid development of hypertriglyceridemia (92). Similarly, laboratory studies of fructose feeding in humans result in marked increases in serum triglycerides, VLDL, and serum FFA (83,93-95). In children, fructose consumption correlates with the development of "small dense" LDL (96), a lipid particle thought to be particularly atherogenic. These data implicate fructose ingestion as a primary cause of dyslipidemia (77,83,97,98).

Hepatic Lipid Deposition and Steatosis

Some of the fatty acyl-CoA products from DNL escape packaging into VLDL for export, but instead accumulate as lipid droplets in the hepatocyte (3). Similarly, diets that increase carbohydrate response element binding protein activity lead to hepatic lipid deposition by increasing DNL (99) while genetically reducing this pathway reduces hepatic lipid deposition (70).

Animal studies demonstrate increased hepatic lipid deposition in response to high-fructose feeding (92,100). In human studies, eucaloric replacement of glucose with fructose increased intrahepatic lipid levels by 38% within 8 days, as measured by magnetic resonance spectroscopy (81). Although this effect can occur in other states of increased FFA production, eg, type 2 diabetes (101,102), correlative data in obese children between soft drink ingestion and alanine aminotransferase levels (103) suggest a similar pathogenesis. Our group also has also found a correlation between soft drink consumption and alanine aminotransferase levels in obese children (104).

Inflammation, JNK-1, and Hepatic Insulin Resistance

Fructose is able to induce the transcription of the enzyme JNK-1 (105) via activation of mitogen-activated protein kinase kinase 7 (106). In addition, the DNL product DAG can also induce JNK-1 via activation of protein kinase C$-\varepsilon$ (22). JNK-1 is the bridge between hepatic energy metabolism and inflammation and, once induced, begins the inflammatory cascade (107). As part of its inflammatory action, JNK-1 activation induces serine phosphorylation of insulin receptor substrate-1 (IRS-1) in the liver (108), thereby preventing normal insulin-mediated tyrosine phosphorylation of IRS-1 and promoting hepatic insulin resistance. Alternatively, DAG-induced protein kinase C$-\varepsilon$ may phosphorylate IRS-1 on a serine moiety directly (109), worsening hepatic insulin resistance.

Animal studies of fructose ingestion demonstrate increases in serine phosphorylation at position 307 of hepatic IRS-1 (110,111) and resultant insulin resistance (112-116). Numerous human studies demonstrate the induction of hepatic insulin resistance in response to increased fructose feeding (82,83,94) and, in particular, peripheral markers of inflammation (117), although some studies have failed to show induction of insulin resistance (118).

Skeletal Muscle Insulin Resistance

Excessive FFA exported from the liver leads to increased uptake into skeletal muscle. There, DAG reassembled from FFA, reduces glucose transport, resulting in skeletal muscle insulin resistance (119). FFA, liberated from circulating VLDL by insulin stimulation of lipoprotein lipase, also contributes to increased storage of intramyocellular lipid, which perpetuates the insulin resistant state in skeletal muscle (120).

In rodent models, high-fructose feeding increases skeletal muscle lipid deposition and oxidative stress (121) and reduces IRS-1 phosphorylation and PI3-kinase activation in skeletal muscle (112). Similarly, in obese children, intramyocellular lipid correlates with insulin resistance (122); although the primacy of intramyocellular lipid in the genesis of the metabolic syndrome remains controversial (123).

Hyperinsulinemia, Obesity, and Type 2 Diabetes

Hepatic and skeletal muscle insulin resistance, through increases in FFA levels, promotes reciprocal hyperinsulinemia (124). Furthermore, cytokines released from visceral fat into the portal circulation also promotes hepatic insulin resistance, also exacerbating hyperinsulinemia (125). The excess insulin can act peripherally to promote increased adipocyte lipoprotein lipase, which cleaves FFA off circulating VLDL, which is then stored in adipocytes. The resulting obesity causes worsening of the peripheral insulin resistance. Furthermore, fructose increases expression of Foxo1 (126); in the face of hepatic insulin resistance, this Foxo1 cannot all be phosphorylated to maintain its exclusion from the nucleus, and hepatic gluconeogenesis results, raising serum glucose and requiring an even greater β-cell insulin response. Eventually, in response to the hepatic insulin resistance, gluconeogenesis, and the phenomena of glucotoxicity, lipotoxicity, and endoplasmic reticulum stress at the level of the β-cell (127-130), inadequate insulin secretion in relation to the degree of peripheral insulin resistance leads to hyperglycemia and type 2 diabetes (131).

In some animal models, fructose administration leads to insulin resistance and dyslipidemia (92), while in others, full-fledged type 2 diabetes can ensue (132). In humans, sugar-sweetened beverage consumption correlates with prevalence of type 2 diabetes in adults (133-135), while soft drink consumption correlates with obesity and insulin resistance in children (18).

Thus, fructose's action on the liver is unique among carbohydrates and appears independent of insulin. Fructose metabolism gives rise to the phenotype of "selective hepatic insulin resistance" typical of metabolic syndrome by uncoupling effects on gluconeogenesis and DNL. Fructose increases the synthesis of Foxo1 (126), not all of which can be phosphorylated (especially in the face of burgeoning hepatic insulin resistance), allowing gluconeogenesis to drive further insulin need, with resultant hyperglycemia. Fructose also directly increases the syn-

Table. Similarities between soda and beer with respect to hepatic handling

	Soda (12-oz can)	Beer (12-oz can)
Calories	150	150
Percent carbohydrate (%)	10.5 (sucrose)	3.6 (alcohol) 5.3 (other carbohydrates)
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

thesis of peroxisomal proliferator-activated receptor-γ coactivator-1β (71), which activates SREBP-1c independently of insulin, promoting DNL to foment dyslipidemia, hepatic steatosis, and further insulin resistance.

Hepatic Metabolic Profile and Substrate Burden: Fructose vs Ethanol

Thus, hepatic metabolism of either fructose or ethanol results in energy substrate conversion to acetyl-CoA, without any insulin regulation and with limited diversion to nontoxic intermediaries such as glycogen. The overwhelming majority of the acetyl-CoA produced will find its way into 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 metabolism parallels that of ethanol.

The hepatic substrate burden between fructose and ethanol are also similar. The Table demonstrates the hepatic burden of a can of beer vs a can of soda. Both contain 150 kcal per 12 oz can. Both contain a glucose load combined with either an ethanol load (beer) or 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), about 92 calories reach the liver, while for soda, 90 calories reach the liver. Indeed, the metabolic demand on the liver from beer and soda are congruent.

ROS FORMATION

Any carbohydrate can induce ROS formation through actions of its free aldehyde or ketone. The aldehyde form of glucose is reactive with free amino groups on proteins in a nonenzymatic exothermic reaction, leading to nonenzymatic protein glycation (136), termed the *Maillard* or *browning* reaction (eg, hemoglobin A1c). Each glycation generates one superoxide radical, which must be quenched by an antioxidant or cellular damage will occur (137). However, at 37°C and pH 7.4, the majority of glucose molecules are found in the stable six-membered glucopyranose ring form, limiting ROS formation.

Effects of Ethanol

Ethanol induces hepatocellular damage through several different mechanisms (44), including mitochondrial damage, membrane effects, hypoxia, cytokine production, and iron mobilization. In addition, ethanol is thought to exert toxicity through its metabolism by alcohol dehydrogenase 1B to the intermediary acetaldehyde, which, because of its free aldehyde moiety engages rapidly in ROS formation (138). In the absence of antioxidant quenching, these ROS may lead to lipid peroxidation, fibrogenesis, and, ultimately, cirrhosis (Figure 4).

Effects of Fructose

Because the ring form of fructose is a five-membered ring with steric hindrance from the two axial (abutting) hydroxymethyl groups, the linear form is preferred, and the reactive ketone moiety is available for reaction with proteins. In vitro studies demonstrate that fructosylation of proteins with fructose occurs seven times more rapidly than glycation with glucose (139,140). Thus, fructose-generated ROS species are abundant (141,142), which, if not quenched by an antioxidant, can promote hepatocellular damage (Figure 4).

The hepatotoxic effects of fructose via ROS formation have been demonstrated in both cultured hepatocytes (143) and in animal models (144). Although mechanistic data remain lacking in humans, case-controlled studies demonstrate that fructose consumption correlates with development of hepatic steatosis and nonalcoholic steatohepatits (145,146).

THE HEDONIC PATHWAY OF FOOD REWARD

The limbic structures central to the hedonic pathway that motivates the "reward" of food intake are the ventral tegmental area (VTA) and nucleus accumbens (NA), with inputs from various components of the limbic system, including the striatum, amygdala, hypothalamus, and hippocampus. The NA is also referred to as the "pleasure center" of the brain, as this is the brain area responsive to morphine, nicotine, and ethanol. 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 (147). Dopamine neurotransmission from the VTA to the NA mediate the reward properties of food (148), while obesity results in decreased density of dopamine D_2 receptors as measured by positron emission tomography scanning (149).

Effects of Ethanol

Ethanol is a known substance of abuse through its effects on fostering reward through the hedonic pathway (150). By altering γ-amino-butryic acid and opioid transmission within the VTA and central area of the amygdala, acute ethanol exposure activates dopamine neurotransmission (151). However, following repeated exposure to ethanol, increases in basal dopamine are apparent, but peak effects relative to baseline are decreased, indicating downregulation (152), a postulated mechanism of tolerance. Human genetic studies demonstrate that downregulation of dopamine transport (and resultant inadequate neuro-

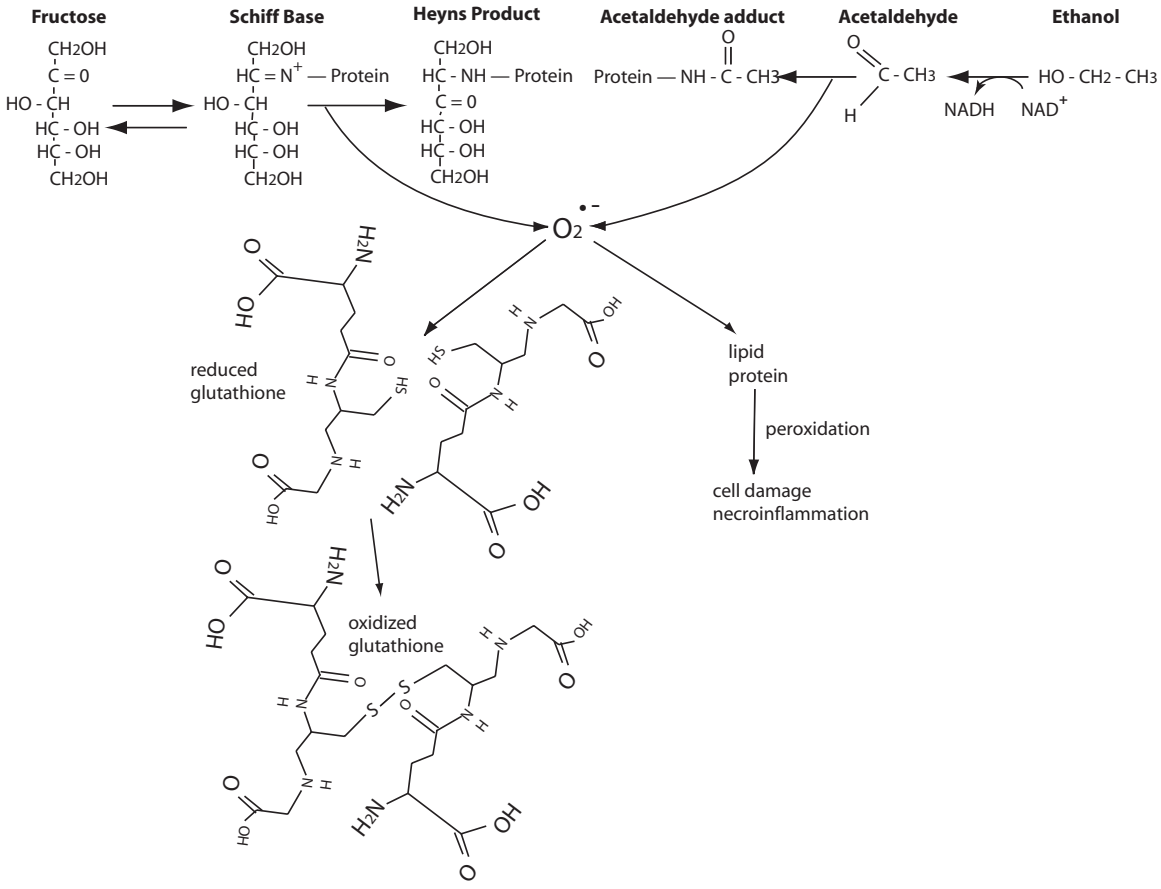

Figure 4. Generation of reactive oxygen species (ROS) by fructose or ethanol. Fructose first forms an intermediate Schiff base with the ε-amino group of lysine, which then spontaneously hydrogenates to form an irreversible Heyns product (hydroxyamide linkage or fructose adduct), termed the *Maillard reaction*. The heat of formation of this reaction is −19 kcal/mol, and is therefore exothermically favorable. Each protein fructosylation generates one 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, generating NADH, to acetaldehyde, which then participates in the same Maillard reaction to form acetaldehyde adducts, with generation of superoxide radicals which must also be quenched by antioxidants. In the absence of adequate antioxidant capacity, ROS production leads to peroxidation, hepatocellular damage, necroinflammation (non-alcoholic steatohepatitis [NASH]), fibrosis, and ultimately cirrhosis. From reference (194): Lim JS, Mietus-Snyder ML, Valente A, Schwarz JM, Lustig RH. Role of fructose in the pathogenesis of NAFLD and the metabolic syndrome. *Nat Rev Gastroenterol Hepatol.* 2010;7:251-264, reprinted with permission.

transmission) results in increased ethanol consumptive behavior (153), and human imaging studies show that dysfunction of dopamine neurotransmission is associated with withdrawal and relapse (154). Such downregulation of dopamine neurotransmission with chronic substrate exposure is a hallmark of the addictive state (155).

Effects of Fructose

Indirect Effects on Reward and Food Intake. Studies in diet-induced obesity document defects in both leptin transport across the blood-brain barrier and in central leptin signaling (156), termed *leptin resistance*. Both leptin and insulin receptors are colocalized in VTA neurons (157), and both hormones have been implicated in modulating rewarding responses to food and other pleasurable stimuli. Leptin decreases VTA-NA activity and extinguishes reward for food (158,159). In the acute situation, insulin increases expression and activity of the dopamine transporter, which clears and removes dopamine from the synapse (160); thus, acute insulin exposure blunts the reward of food in rats (157). D_2-receptor antagonists and insulin act additively to acutely decrease the rewarding response to a palatable sucrose solution; furthermore, insulin appears to inhibit the ability of VTA-agonists (eg, opioids) to increase intake of sucrose (161). Finally, acute insulin blocks the ability of rats to form a conditioned place-preference association to a palatable food (157).

However, chronic hyperinsulinemia, due to insulin resistance of the sort generated by chronic fructose consumption, may do the opposite; that is, contribute to increased caloric intake by preventing dopamine clearance from the NA, thus fostering pleasure derived from food in situations where energy stores are replete (162). Chronic hyperinsulinemia appears to prevent central leptin signaling (163,164), resulting in leptin resistance and

promotion of further food intake (165,166). Central nervous system insulin resistance sets the stage for unchecked caloric intake in the face of positive energy balance, as evidenced experimentally by the brain-specific insulin receptor knockout mice (167). Thus, by promoting hepatic and muscle insulin resistance, fructose ingestion may alter VTA-NA dopamine neurotransmission, the hedonic response to food, and may drive excessive energy intake. Leptin resistance also results from defective leptin transport across the blood-brain barrier. Recently, one cause of impaired leptin transport has been shown to be hypertriglyceridemia (168), possibly as an adaptation to increase food intake in the face of anorexia and starvation, but maladaptive in the face of fructose-induced dyslipidemia.

Ghrelin, an octanoylated 28-amino acid peptide produced by cells in the stomach, signals the hypothalamus to interpret hunger and increase food intake (169) and fat deposition (170,171). Ghrelin also increases the respiratory quotient in rats, suggesting a reduction of fat oxidation and promotion of fat storage. In humans, ghrelin levels rise with increasing subjective hunger and peak at the time of voluntary food consumption and decrease after meal (172). However, fructose feeding does not decrease ghrelin (93) and, therefore, caloric intake is not suppressed. Indeed, fructose consumption in the form of soft drinks does not reduce the volume of solid food and, therefore, increases the total calories consumed during the meal (24).

Fructose feeding also blunts blood levels of the satiety signal Peptide $YY_{3\text{-}36}$ and yields higher levels of hypothalamic endocannabinoid receptor messenger RNA, consistent with increased caloric intake (173). Lastly, fructose reduces hypothalamic malonyl-CoA levels, thought to represent the "fuel gauge" of the neuron, indicating energy inadequacy and promoting increased intake (174,175).

Direct Effects of Fructose on Reward and Food Intake. Fructose also has direct effects on increasing caloric consumption. Increasing the palatability of food by addition of sucrose undermines normal satiety signals and motivates energy intake independent of energy need (176,177). For instance, sucrose infusion directly into the NA reduces D_2 receptors and μ-opioid receptors similar to that of morphine (178). 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 (147,179). Furthermore, animal models of intermittent sugar administration, over a 3-week interval, can induce behavioral alterations consistent with dependence; ie, bingeing, withdrawal and anxiety, craving, and cross-sensitization to other drugs of abuse (180). Neuropharmacologic analyses demonstrate reduction in D_2 receptors in the NA, consistent with the fostering of reward and behavioral changes seen in addiction. 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.

SOCIETAL PARALLELS BETWEEN FRUCTOSE AND ETHANOL

Fructose also has notable societal parallels with ethanol. Both sugar and alcohol are legal and abundantly available substances. Both are treated as "ordinary commodities" in trade policy (181,182). Problems of overuse and related health harms are more prevalent in lower socioeconomic groups (183,184). Those who overconsume either substance are stigmatized (185,186). Finally, within policy debates, sugar and alcohol involve a parallel set of stakeholders, including industrial producers and distributors, nongovernmental advocacy groups, scientists, clinicians, and two types of government agencies: those charged with promoting economic development and production through trade (eg, US Department of Agriculture) vs those charged with protecting public health (eg, Health and Human Services, Bureau of Alcohol, Tobacco, and Firearms).

SUMMARY AND CONCLUSIONS

Most people consider sugar (ie, fructose-containing compounds) to be just "empty" calories. Although the hepatic metabolic pathways outlined here have been worked out primarily in animal models, the human phenotypes are quite similar. These data indicate that fructose exerts specific biochemical effects beyond its caloric equivalent. In the hypocaloric (eg, starvation) state, fructose is as beneficial as glucose in promoting glycogen repletion (187); but in the hypercaloric state, fructose drives DNL, resulting in dyslipidemia steatosis and insulin resistance akin to that seen with ethanol. The excess acetyl-CoA generated by both substrates overwhelm the mitochondrial TCA cycle, resulting in DNL with resultant dyslipidemia, hepatic lipid deposition, and inflammation. Furthermore, the hepatic insulin resistance results in gluconeogenesis, contributing to hyperglycemia and increasing β-cell insulin strain. In particular, fructose recapitulates the pentad of the metabolic syndrome and has been shown to contribute to cardiovascular disease (30,188). This should not be surprising, as fructose and ethanol are congruent evolutionarily and biochemically. Ethanol is manufactured by fermentation of fructose; the only difference is that for fructose, humans perform the glycolysis, while for ethanol, yeast have already performed the glycolysis. Secondly, through their free reactive carbonyl moieties, both fructose and ethanol produce ROS, which increases risk for hepatocellular damage. Lastly, the neuroendocrine mechanisms outlined here demonstrate that by blocking leptin signaling, promoting sensations of hunger, and activation of the reward pathway, fructose contributes to a positive feedback pathway of continuous ingestion of food independent of energy need, a phenomenon paralleling that of ethanol. Figure 5 lists the overlap in phenotypic phenomena exhibited by fructose and ethanol in a chronic state of overconsumption.

Aside from restriction of intake, there are two "antidotes" to the hepatic effects of fructose. Exercise enacts two benefits. By increasing hepatic TCA cycle maximal velocity (38), less acetyl-CoA will be converted to citrate, providing less substrate for DNL and reducing fructose's toxic downstream effects. Also, exercise has beneficial effects on both Foxo1 and peroxisomal proliferator-activated receptor-γ coactivator-1β, thus improving insulin action at the liver (189). Fiber also enjoys two benefits. By reducing glycemic load and rate of carbohydrate absorption, fiber reduces the bolus of energy substrate the liver has to metabolize acutely, thereby reducing the rate of DNL and improving insulin sensitivity (190). Fiber also increases satiety, reducing further consumption (191,

Chronic ethanol exposure	Chronic fructose exposure
• Hematologic disorders	
• Electrolyte abnormalities	
• Hypertension	• Hypertension (uric acid)
• Cardiac dilatation	
• 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

Figure 5. Phenotypes of chronic energy substrate exposure. ASH=alcoholic steatohepatitis. NASH=non-alcoholic steatohepatitis.

192). Unfortunately, both of these are currently in short supply in the Western lifestyle.

In order to reduce the cardiovascular sequelae associated with obesity and metabolic syndrome, the American Heart Association has recommended reduction of dietary sugar intake by more than half (30). Enacting such recommendations requires that food and nutrition practitioners reassess their current recommendations. In the process of dispensing "low-fat" dietary directives, an unstated implication is that replacement of fat with carbohydrate is a rational approach. Health care providers must recognize the differences between glucose and fructose and that despite fructose's classification as a carbohydrate, it is metabolized more like fat. It is this author's opinion that a low-fat diet in America is tantamount to a high-fat diet, as increased fructose ingestion because of substitution of fructose for fat to improve palatability causes the same metabolic perturbations as does a high-fat diet. Such a formulation also makes it important for the food and nutrition practitioner to assess a patient's sugar and ethanol consumption separately from their carbohydrate and fat consumption. It is also this author's opinion that in assessing a patient's risk for metabolic syndrome, instead of quantifying three macronutrient groups, clinical food and nutrition practitioners should evaluate five, ie, fat, protein, complex carbohydrate, fiber, and sugar/ethanol.

It should be noted that successful efforts to reduce consumption of other stimuli of the hedonic pathway, ie, amphetamine, cocaine, nicotine, cannabis, and ethanol, combine both individual education with some sort of public policy measure, such as taxation, restriction, or interdiction (193). The political, economic, and societal barriers in applying such lessons to reduce fructose consumption are substantial, but not insurmountable. Such policies to curtail fructose consumption, eg, through soda taxation, are currently being debated in New York and California and nationally. Indeed, it seems likely that individual behavioral counseling, combined with sound public health measures, will be necessary to combat this epidemic.

STATEMENT OF POTENTIAL CONFLICT OF INTEREST: No potential conflict of interest was reported by the author.

FUNDING/SUPPORT: The author states categorically that there were no external funding sources relevant to this project or manuscript.

ACKNOWLEDGEMENTS: The author would like to thank Jean-Marc Schwarz, PhD; Kathleen Mulligan, MD; Elissa Epel, PhD; Stanton Glantz, PhD; Neil Benowitz, MD; Laura Schmidt, PhD, MPH; Ronald Krauss, MD; Michele Mietus-Snyder, MD; Kristine Madsen, MD, MPH; Patrika Tsai, MD, MPH; Nathan Bass, MD; Philip Rosenthal, MD; Raphael Merriman, MD; Andrea Garber, PhD, RD; Stephanie Nguyen, MD, MAS; Jung Sub Lim, MD, PhD; and Young Eun Choi, MD, PhD; for their input to this analysis.

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