The Fructose Epidemic

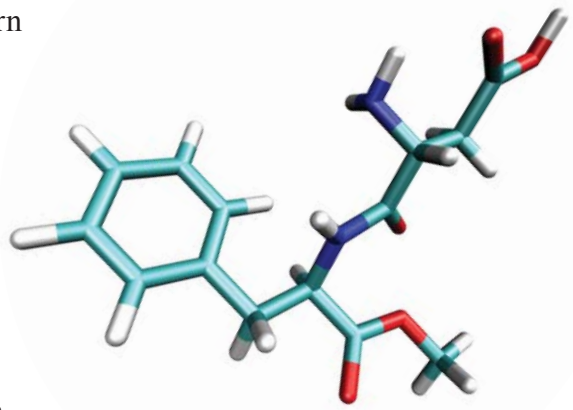
By Robert H. Lustig, MD

ABSTRACT

Fructose consumption (as both high fructose corn syrup and sucrose) has increased coincidentally with the worldwide epidemics of obesity and metabolic syndrome. Fructose is a primary contributor to human disease as it is metabolized in the liver differently to glucose, and is more akin to that of ethanol. When consumed in large amounts, fructose promotes the same dose-dependent toxic effects as ethanol, promoting hypertension, hepatic and skeletal muscle insulin resistance, dyslipidemia and fatty liver disease. Also similar to ethanol, through direct stimulation of the central nervous system "hedonic pathway" and indirect stimulation of the "starvation pathway," fructose induces alterations in central nervous system energy signaling that lead to a vicious cycle of excessive consumption, with resultant morbidity and mortality. Fructose from any source should be regarded as "alcohol without the buzz." Obesity prevention and treatment is ineffective in the face of the current "fructose glut" in our food supply. We must learn from our experiences with ethanol and nicotine that regulation of the food industry, along with individual and societal education, will be necessary to combat this fructose epidemic.

INTRODUCTION

As America's (and the world's) collective girth continues to increase, we ponder the answer to our dilemma: **Who or what are to blame for the obesity epidemic?** That depends upon who you ask. The Institute of Medicine says it is an interaction between genetics and environment. Well, our genetics have not changed in 30 years but our environment sure has, and in particular, our diet. The distribution curve for Body Mass Index (BMI) shows that all segments of the population are increasing in weight (1), so whatever is happening is clearly pervasive and insidious. Even developing countries that have adopted a Western diet for convenience and expense have paid for it by manifesting the same obesity prevalence, co-morbidity profiles and mortality (2).



SECULAR TRENDS IN FRUCTOSE CONSUMPTION

One of the striking features of the modern Western diet is its reliance on refined carbohydrate as the predominant energy source. Due to the "low-fat" admonition by the United States Department of Agriculture (USDA), American Medical Association and American Heart Association (AHA) in the early 1980's, the percentage of fat in the Western diet has reduced from 40% to 30% over the past 25 years; which has resulted in the percentage of carbohydrate rising from 40% to 55%; coinciding with the obesity epidemic. Of this, a sizeable and ever-increasing portion of the diet is attributable to monosaccharides and disaccharides used to sweeten foods and drinks. Furthermore, in response to the market for lower fat fare, food companies have chosen to substitute disaccharides to maintain palatability of processed foods. Until recently the most commonly used sugar in the U.S. diet was disaccharide sucrose (e.g. cane or beet sugar) which is composed of 50% fructose and 50% glucose. However, in North America and many other countries, due to its abundance, sweetness, and low price, high-fructose corn syrup (HFCS) which contains between 42% and 55% of the monosaccharide fructose, has overtaken sucrose as the most ubiquitous caloric sweetener. These factors have led to an inexorable rise in fructose consumption. Prior to 1900, Americans consumed approximately 15 gm/day of fructose, mainly through fruits and vegetables. Prior to World War II this amount had increased to 24 gm/day. By

1977 fructose intake was 37 gm/day; by 1994 55 gm/day; and currently Vos et al. estimates that adolescents average 72.8 gm/day (3). Thus current fructose consumption has incrementally increased 5-fold compared to a century ago. Disappearance data over the past 25 years from Economic Research Service (ERS) of the USDA also supports this secular trend. The ERS documents partial substitution for sucrose by HFCS; however annual per capita total caloric sweetener usage has increased from 73 to 95 lbs in that interval. Although soda has received most of the attention (4, 5), high fruit juice intake (sucrose) is also associated with childhood obesity, especially by lower income families (6), although it is not captured in the ERS. Thus, after adjustment for juice intake, per capita consumption of mono- and disaccharides is at approximately 113 lbs/yr or 1/3 lb/day for all Americans.

HOW WE GOT HERE: POLITICAL, ECONOMIC, AND MEDICAL DRIVERS OF FRUCTOSE CONSUMPTION

The reader is referred to *The Omnivore's Dilemma* (7) for a complete discussion of the political and economic factors that led to the secular trend in fructose consumption. In brief, the 1966 industrialization of the discovery of the glucose oxidase process to convert glucose to fructose (8), combined with a directed policy by the USDA in the 1970's to reduce the price of food by advancing growth and production of corn as a dietary staple, provided the political and economic impetus for this trend. In addition, during this decade the medical establishment focused on dietary reduction of coronary heart disease. Two competing schools of thought dominated this discussion. John Yudkin, a British physiologist and nutritionist, championed the anti-sugar movement. His work "Pure, White, and Deadly" (9) espoused the primary role of sugar in human disease. Conversely, the anti-saturated fat movement was spearheaded by Minnesota epidemiologist Ancel Keys. His work, the *Seven Countries*: study (10), was one of the first multivariate linear regression analyses. A review of this document (P. 262) notes: "The fact that the incidence of coronary heart disease was significantly correlated with the average percentage of calories from sucrose in the diets is explained by the intercorrelation of sucrose with saturated fat. Partial correlation analysis demonstrates that with saturated fat constant there was no significant correlation between dietary sucrose and the incidence of coronary heart disease" (10). However, Keys neglected to perform the converse analysis demonstrating that the effect of saturated fat on cardiovascular disease (CVD) was independent of sucrose. In other words, sucrose and saturated fat co-migrated; it is impossible to tease out the relative contributions of sucrose vs. saturated fat on CVD from this study.

Furthermore, the medical establishment based their low-fat recommendations on the goal of LDL reduction; however, several studies have since demonstrated little to no effect of low-fat diets on weight gain or CVD events (11, 12). However, we now know that there are two LDL's. The large buoyant or Type A LDL is driven by dietary fat, but is neutral from a cardiovascular standpoint. The small dense or Type B LDL, which is driven by carbohydrate and fructose (13), is the species associated with CVD (14). Conversely, we have ample evidence that triglyceride (TG) is a major risk factor for CVD (15) and that fructose consumption is a primary contributor to TG accumulation (16, 17). A recent analysis has led the AHA Nutrition Committee to publish a policy statement on the negative role of sugars in the pathogenesis of CVD (18).

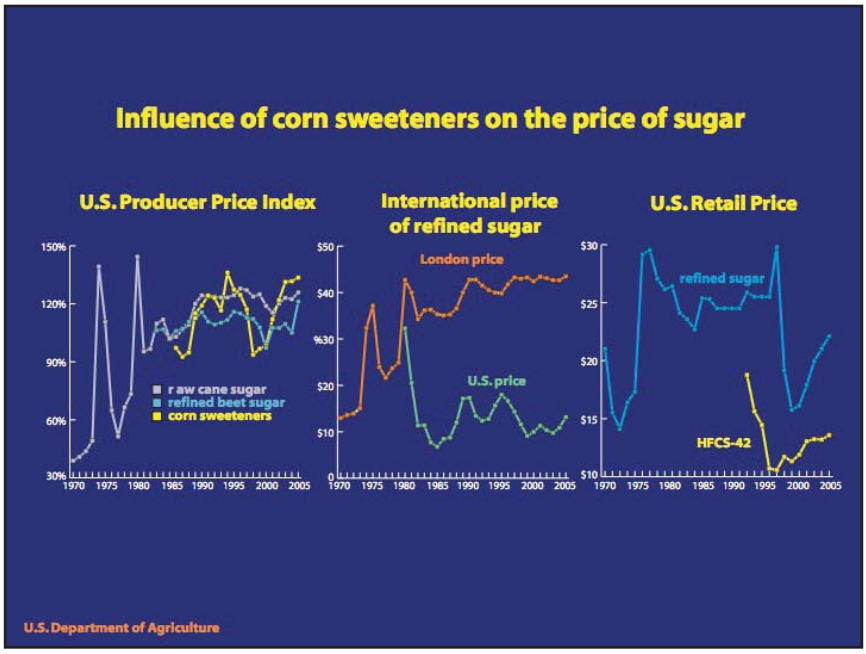


Figure 1: Effects of introduction of corn sweeteners (HFCS) to the American diet in 1975 on: a) the U.S. Producer Price Index for sugar; b) the U.S. and international (London) price of sugar; and c) the U.S. retail price of sugar and on HFCS. Data document stabilization or lowering of sugar prices.

HIGH FRUCTOSE CORN SYRUP (HFCS) VS. SUCROSE

Although many consumer activist groups have specifically vilified HFCS as the cause of obesity and CVD, scientific studies of acute satiety vs. energy intake support the notion that HFCS is not metabolically different from sucrose (19-27). This has led to a vociferous campaign by the Corn Refiners Association to influence the debate on fructose consumption by equating HFCS with sucrose, suggesting that it is no different, "natural," and it is safe (see www.sweetsurprise.com). Indeed, the distinction between HFCS and sucrose is not metabolic (as they are essentially equivalent), but rather economic. The introduction of HFCS to the Western diet in 1975 resulted in stability of the U.S. Producer Price Index for sugar, and sizeable reductions in the U.S. and international price of sugar (**Fig. 1**). HFCS on average costs about one third that of sucrose. This, along with changes in the Farm Bill and food policy, promoted the addition of fructose to our collective diets; not just in soft drinks and juice, but in salad dressing, condiments, baked goods and virtually every processed food, which raised our total consumption 5-fold in the last 100 years. Below, it becomes clear that it is not the specific vehicle (sucrose vs. HFCS) that makes it unsafe, but rather the total dose of fructose.

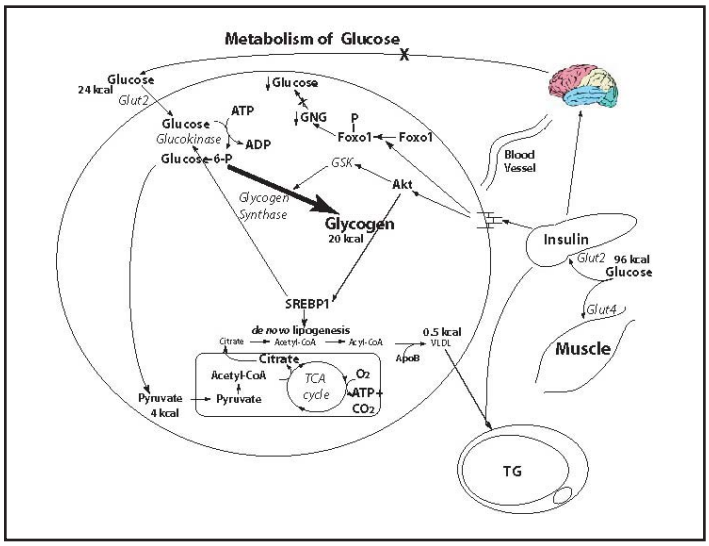


Figure 2: Hepatic metabolism of 120 kcal carbohydrate: a) glucose; b) ethanol; and c) sucrose (fructose). Similarities in hepatic metabolism between ethanol and fructose are highlighted.

CORRELATION OF FRUCTOSE CONSUMPTION WITH DISEASE

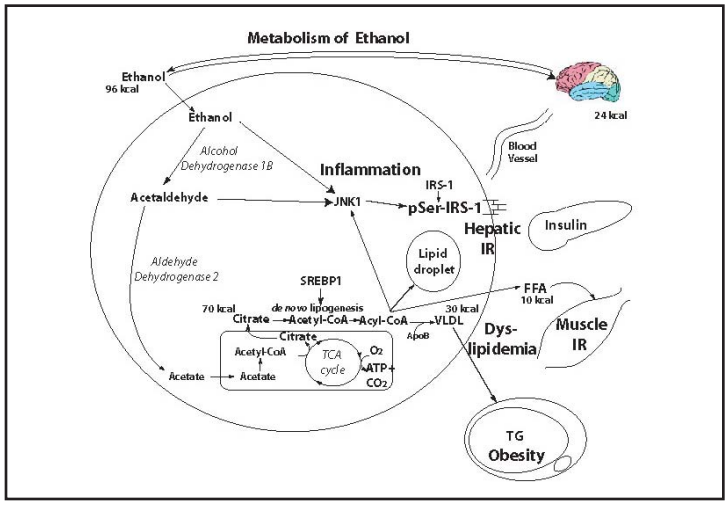
Numerous reviews have indirectly implicated fructose consumption in the current epidemics of obesity and Type 2 Diabetes Mellitus (T2DM) (28-30). Correlative studies in humans link soft drink consumption with energy overconsumption, body weight, poor nutrition (31) and T2DM (32). Similarly, juice consumption also correlates with risk for T2DM (33), suggesting that excessive fructose consumption is playing a role in the epidemics of insulin resistance, obesity, hypertension, dyslipidemia, and T2DM in humans (28, 34-38). Collectively, this constellation of findings is referred to as the Metabolic Syndrome (MetS). Conversely, early short-term prospective studies limiting soft drink ingestion in children have met with some success in stabilization of weight and CVD parameters (39, 40).

MECHANISMS OF FRUCTOSE TOXICITY

Although others have already pointed out the unique metabolic effects of fructose (28-30, 34, 36, 38), this review was written to outline the unique, pernicious, and dose-dependent toxic effects of fructose in the pathogenesis of both metabolic disease and excessive consumption. Fructose is similar in its metabolism to a more familiar toxin, ethanol. Therefore, it is necessary to delineate the hepatic outcomes of metabolism of glucose and ethanol first. In each case, we will follow a 120 kcal oral bolus of each carbohydrate.

Hepatic Glucose Metabolism

Glucose is the body's preferred carbohydrate substrate for energy metabolism. Each cell in the body can utilize glucose for energy. Upon ingestion of 120 kcal of glucose (e.g. two slices of white bread) (**Fig. 2a**), 24 kcal (20%) enter the liver; the remaining 96 kcal (80%) of the glucose bolus are utilized by other organs (41). Plasma glucose levels rise, insulin is released by the pancreas which binds to its receptor on the liver, generating two metabolic signals (42). The first is the phosphorylation of the forkhead protein Foxo1; which reduces the expression of the enzymes of gluconeogenesis (GNG), to keep blood sugar levels from rising (43). The second is an increase in the expression of the transcription factor Akt, which causes the majority of G6P (about 20 kcal) to be deposited as the non-toxic storage carbohydrate glycogen. Only a small amount of G6P is broken down by the Embden-Meyerhoff glycolytic pathway to pyruvate (approx 4 kcal). Pyruvate enters the mitochondria where it is converted to acetyl-CoA, which then participates in the Krebs tricarboxylic acid (TCA) cycle, which generates adenosine triphosphate (ATP), the chemical storage form of energy, and carbon dioxide. Any pyruvate not metabolized in the



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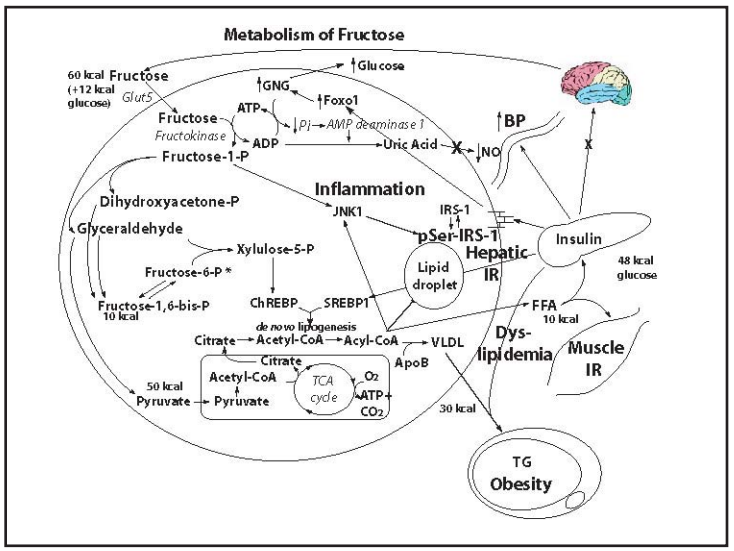
mitochondrial TCA cycle exits back into the cytoplasm as citrate through the "citrate shuttle" (44). This small amount of citrate (perhaps 0.5 kcal) can serve as substrate for the process of *de novo* lipogenesis, which turns excess citrate into free fatty acids (FFA). These can then be packaged with apolipoprotein B (apoB) to form very low density lipoproteins (VLDL; measured in the triglyceride fraction), which are transported out of the liver, and can serve as a substrate for atherogenesis or obesity. Thus, in response to a 120 kcal glucose bolus, only a tiny fraction (less than 1 kcal) contributes to adverse metabolic outcomes.

Hepatic Ethanol Metabolism

Ethanol is a naturally occurring carbohydrate, but is also recognized as both an acute central nervous system (CNS) toxin and chronic hepatotoxin, due to its unique dose-dependent hepatic metabolism (**Fig. 2b**). Upon ingestion of 120 kcal of ethanol (e.g. 1.5 oz. of 80 Proof hard spirits), approximately 10% (12 kcal) is metabolized within the stomach and intestine as a first-pass effect, and 10% is metabolized by the brain and other organs (41). Thus approximately 96 calories reach the hepatocyte (4 times more than with glucose). Ethanol enters the liver and is converted by alcohol dehydrogenase 1B to form the toxic substrate acetaldehyde, which in high dosage can promote free radical formation and toxic damage. Acetaldehyde is then quickly metabolized by the enzyme aldehyde dehydrogenase 2 to acetic acid, which can then enter the mitochondrial TCA cycle (as per glucose, above); but now, a large amount of excess citrate is formed (perhaps 70 kcal), which exits into the cytosol and then participates in synthesis of fatty acids through *de novo* lipogenesis. Thus, the metabolism of an ethanol bolus is likely to cause the liver to increase FFA and VLDL production, and contribute to dyslipidemia. Intrahepatic lipid and ethanol are both able to induce the transcription of the enzyme *c-jun* N-terminal kinase-1 (JNK-1) (45). This enzyme is the bridge between hepatic energy metabolism and inflammation; and once induced, begins the inflammatory cascade (46). As part of its inflammatory action, JNK-1 activation induces serine phosphorylation of insulin receptor substrate-1 (IRS-1) in the liver (47), leading to hepatic insulin resistance, hepatic triglyceride accumulation in lipid droplets, with resultant inflammation (48); eventually leading to alcoholic steatohepatitis, and ultimately to cirrhosis. Lastly, FFA can exit the liver, which can contribute to skeletal muscle insulin resistance. The VLDL produced (perhaps 30 kcal) can be transported to the adipocyte to serve as a substrate for obesity, or participate in atherogenic plaque formation. Thus, in response to a 120 kcal ethanol bolus, a large fraction (perhaps 40 kcal) can contribute to disease.

Hepatic Fructose Metabolism and the MetS

The liver is the only organ possessing the Glut5 fructose transporter and is solely responsible for fructose metabolism (49). Upon ingestion of 120 kcal of sucrose (e.g. 8 oz. of orange juice; composed of 60 kcal glucose and 60 kcal fructose) (**Fig. 2c**), the entire 60 kcal fructose bolus reaches the liver, along with 20% of the glucose bolus (12 kcal), for a total of 72 kcal; in other words, the liver must handle triple the substrate as it did for glucose alone



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(50). The fructose is immediately converted to fructose-1-phosphate (F1P) by the enzyme fructokinase (51), depleting the hepatocyte of intracellular phosphate. This leads to activation of the enzyme adenosine monophosphate (AMP) deaminase-1, which converts the adenosine phosphate breakdown products into the cellular waste product uric acid (52, 53). Buildup of urate in the circulation inhibits endothelial nitric oxide synthase (eNOS), resulting in decreased nitric oxide (NO) and contributing to hypertension (54-56). Almost the entire F1P load (50 kcal) is metabolized directly to pyruvate, entering the mitochondrial TCA cycle; again, excess citrate (perhaps 40 kcal) will be exported to the cytosol, to participate in de novo lipogenesis, with resultant dyslipidemia from FFA and VLDL formation. Alternatively, a proportion (10 kcal) of early glycolytic intermediaries will recombine to form fructose-1,6-bisphosphate, which then also combines with glyceraldehyde to form xylulose-5-phosphate (X5P) (57, 58), which activates carbohydrate response element binding protein (ChREBP), also stimulating *de novo* lipogenesis and contributing to fructose-induced dyslipidemia (13, 17, 59-62). FFA export from the liver leads to uptake into skeletal muscle, resulting in skeletal muscle insulin resistance (63, 64). Some of the FFA will precipitate in the hepatocyte, leading to lipid droplet accumulation (65). Intrahepatic lipid and FIP are both able to induce the transcription of JNK-1 (45), which induces serine phosphorylation of insulin receptor substrate-1 (IRS-1) in the liver (47), thereby preventing normal insulin-stimulated tyrosine phosphorylation of IRS-1, and promoting hepatic insulin resistance. This will prevent Foxo1 from becoming phosphorylated; Foxo1 enters the nucleus and gluconeogenesis ensues, raising blood sugar and furthering the hyperinsulinemia (43). Thus, in response to a 120 kcal sucrose bolus, a large fraction (perhaps 40 kcal) can contribute to disease.

Comparison of Hepatic Metabolic Detriments of Fructose vs. Ethanol

As the brain does not possess the Glut5 transporter, fructose does not lead to the acute CNS toxic effects like those of ethanol. However, its hepatic metabolic profile strongly resembles that of ethanol. **Table 1** demonstrates the hepatic burden of a can of beer vs. a can of soda. Both contain 150 kcal per 12 oz. can. 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% other carbohydrate (e.g. maltose, which is a glucose disaccharide), this amounts to 92 calories reaching the liver, while for soda this amounts to 90 calories reaching the liver. Thus, hepatic metabolism of either fructose or ethanol results in the majority of energy substrate being converted to lipid, without any insulin regulation or ability to be diverted to non-toxic intermediaries such as glycogen. Intrahepatic lipid generation promotes inflammation and insulin resistance (66). Indeed, the hepatic metabolic strain of beer and soda are congruous; such that beer or sugar sweetened beverage consumption similarly led to visceral adiposity, insulin resistance, and the metabolic syndrome.

	Soda (12 oz can)	Beer (12 oz can)
Calories	150	150
Percent Carbohydrate	10.5% (sucrose)	3.6% (alcohol) 5.3% (other carbs)
Calories From:		
Fructose	75 (4.1 kcal/gm)	
Alcohol		90 (7 kcal/gm)
Other carbs	75 (glucose)	60 (maltose)
1st pass stomach-intestine metabolism		
Calories Reaching Liver	**90**	**92**

Table 1: Similarities between soda and beer with respect to hepatic handling

FRUCTOSE EFFECTS ON THE CNS LEAD TO EXCESSIVE CONSUMPTION

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). The NA is also referred to as the "pleasure center" of the brain (67) and is the seat of goal-oriented behavior. This is also the brain area responsive to nicotine, morphine, cannabinoids, amphetamine, nicotine, and ethanol (68). Food intake is a result of activation of the reward pathway; for example, administration of morphine to the NA increases food intake in a dose-dependent fashion (69). Dopamine neurotransmission from the VTA to the NA mediate the reward properties of food (70). Leptin and insulin receptors are co-localized in VTA neurons (71), 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 (72, 73).

However, increasing the palatability of food by addition of fructose undermines normal satiety signals, and as a result increases total caloric consumption both in direct and indirect ways. Direct effects of fructose include motivation of food intake independent of energy need (74-79). Indeed, in animal models, sugar consumption can lead to dependence (80). There are four indirect effects of fructose on excessive food consumption. First, fructose does not stimulate a leptin rise, thus contributing acutely to a diminished sense of satiety (81). Secondly, fructose induces hypertriglyceridemia, which reduces leptin transport across the blood-brain barrier (82). The third is chronic hyperinsulinemia, which interferes with leptin signal transduction at the second messenger level (83). By reducing leptin's ability to extinguish hunger at the hypothalamus, and likely leptin's ability to extinguish the dopamine reward signal at the NA (84, 85), chronic hyperinsulinemia fosters a sense of starvation and need for reward, leading to increased caloric intake (86). Lastly, fructose has been shown to decrease the production in hypothalamic neurons of malonyl-CoA, which may help promote a sense of energy inadequacy (87). Together with promoting hepatic and muscle insulin resistance, fructose ingestion may alter the hedonic response to food to drive excessive energy intake, setting up a positive feedback cycle of hepatic and CNS dysfunction, leading to persistent overconsumption. Whether this CNS "vicious cycle" is tantamount to true addiction or merely psychological dependence is not yet clear. What is clear is that obesity, depression, and sugar craving and consumption are linked epidemiologically and mechanistically (88).

SUMMARY

The hepatic metabolic pathways outlined above demonstrate that fructose is a dose-dependent chronic hepatotoxin. Fructose is capable of promoting hepatic and skeletal muscle insulin resistance, hyperinsulinemia, dyslipidemia, hepatic lipid deposition, and inflammation; similar to the dose-dependent toxic effects of ethanol. Furthermore, the central pathways outlined above demonstrate that fructose is capable of promoting hypothalamic leptin resistance and activation of the reward pathway, resulting in an abnormal drive to continuous consumption, also similar to ethanol. Indeed, fructose may be described as "alcohol without the 'buzz'".

The metabolic and central similarities between fructose and ethanol are striking. Other stimulators of the nucleus accumbens have led to disease and societal deterioration, and thus have required education, regulation, and in some instances, interdiction. America attempted ethanol interdiction (prohibition) in the 1930's, but was unsuccessful; it will be even harder to restrict fructose consumption. Furthermore, the Food and Drug Administration has given fructose GRAS (generally regarded as safe) status, thus declining to regulate its use. While many obesity programs counsel voluntary reductions in personal fructose consumption, recidivism is frequent; thus, a major effort in public health education seems daunting. Nonetheless, we have made significant progress with ethanol reduction, mostly through regulation. Soda taxes have recently been proposed both in New York and California, and legislation for the removal of soft drinks from schools has been enacted in several states. However, until Yudkin's prophecies of 1972 are taken seriously and the public is made aware of the specific dangers of the fructose fraction of our current Western diet, our current vicious cycle of consumption and disease will continue.

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