

Sugars and Health Controversies: What Does the Science Say?^{1–3}

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ABSTRACT

The consumption of sugar and its relation to various potential adverse health consequences are the subjects of considerable debate and controversy. This supplement to *Advances in Nutrition* provides an expanded summary of a symposium held on 26 April 2014 entitled “Sugars and Health Controversies: What Does the Science Say?” as part of the ASN Scientific Sessions and Annual Meeting at Experimental Biology 2014. The articles in the supplement discuss results of current systematic reviews and meta-analyses as well as randomized controlled trials and draw implications for public policy considerations. In addition, future research gaps are identified. Current research trials conducted with commonly consumed sugars [e.g., sucrose and high-fructose corn syrup (HFCS)] do not support a unique relation to obesity, metabolic syndrome, diabetes, risk factors for heart disease, or nonalcoholic fatty liver disease. Neurologic differences in response to studies that used pure fructose compared with pure glucose have not been confirmed using typical sugars that are consumed (i.e., sucrose and HFCS), which contain ~50% glucose and fructose. We conclude that added sugars consumed in the normal forms in which humans consume them, at amounts typical of the human diet and for the time period studied in randomized controlled trials, do not result in adverse health consequences. Although more research trials are needed in many areas of sugar consumption and health, there is little scientific justification for recommending restricting sugar consumption below the reasonable upper limit recommended by the Dietary Guidelines for Americans, 2010 of no more than 25% of calories. *Adv Nutr* 2015;6(Suppl):493S–503S.

Keywords: fructose, high-fructose corn sugar, sucrose, metabolism, added sugars, diabetes, the metabolic syndrome, non-alcoholic fatty liver disease

Introduction

Few topics in nutrition engender as much debate and controversy as the relation between sugar and various potential health consequences (1–14). The effects of the major added sugars in our diet, namely sucrose and high-fructose corn syrup (HFCS)⁸, have

been the subject of numerous research studies ranging from epidemiologic and cohort studies to randomized controlled trials (RCTs). In addition, numerous research studies have compared pure fructose and pure glucose with regard to their metabolism and health effects, although these 2 monosaccharides are rarely, if ever, consumed in isolation in the human diet.

Given the ongoing controversies related to sugar in the diet, a symposium was held on 26 April 2014 entitled “Sugars and Health Controversies: What Does the Science Say?” during the ASN Scientific Sessions and Annual Meeting at Experimental Biology 2014. Presenters at this symposium explored controversies related to the metabolism and health effects of sugar; reviewed the recent science related to these issues with particular reference to systematic reviews, meta-analyses, and RCTs; explored how scientific understandings of these issues interact with public policy; and finally, suggested further areas of needed research.

The symposium was framed around the following 6 key questions:

- Are there differences in metabolism and health effects between fructose, HFCS, and sucrose?

¹ Published in a supplement to *Advances in Nutrition*. Presented at the ASN Scientific Sessions and Annual Meeting at Experimental Biology 2014 held in San Diego, CA, 26–30 April 2014. The satellite program was sponsored by the ASN Medical Nutrition Council and supported in part by an educational grant from the Corn Refiners Association. Publication costs for this supplement were defrayed in part by the payment of page charges. This publication must therefore be hereby marked “advertisement” in accordance with 18 USC section 1734 solely to indicate this fact. The opinions expressed in this supplement are those of the authors and are not attributable to the sponsor or the publisher, Editor, or Editorial Board of *Advances in Nutrition*.

² The authors reported no funding received for writing this article.

³ Author disclosures: JM Rippe’s research laboratory has received unrestricted grants and JM Rippe has received consulting fees from ConAgra Foods, Kraft Foods, the Florida Department of Citrus, PepsiCo International, The Coca-Cola Company, the Corn Refiners Association, Weight Watchers International, Dr. Pepper Snapple Group, and various publishers. TJ Angelopoulos, no conflicts of interest.

⁸ Abbreviations used: CHD, coronary heart disease; HFCS, high-fructose corn syrup; MetS, metabolic syndrome; NAFLD; nonalcoholic fatty liver disease; RCT, randomized controlled trial; SSB, sugar-sweetened beverage.

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- Do fructose-containing sugars contribute substantially to conditions such as nonalcoholic fatty liver disease (NAFLD), obesity, metabolic syndrome (MetS), diabetes, cardiovascular disease, dyslipidemias, and/or elevated blood pressure?
- Do fructose-containing sugars react differently in the brain than glucose? If so, are those differences relevant to appetite, food consumption, weight gain, and obesity?
- What is the appropriate upper limit of consumption of sugars?
- Are public policy recommendations to limit consumption of sugars through such mechanisms as taxation or limiting portion sizes based on sound science and/or likely to succeed?
- What directions should future research take?

The articles contained in this supplement issue contain expanded and updated summaries of information presented at this symposium.

Recent Scientific Studies

A wide variety of scientific studies have been published in the past decade related to sugars and their metabolism as well as their health effects. These studies are summarized in detail in the article by Sevenpiper et al. (15) in this supplement issue. In this article we will summarize some of the key studies that were published during this period of time. There are many position statements and review articles suggesting that sugar may have deleterious effects on health. Such statements and summaries occasionally stand on disputable or clinically irrelevant findings, which we will briefly discuss in this article.

Sugars and energy-regulating hormones. Some studies in both animals and humans compared high levels of consumption of pure fructose to pure glucose and their influence on energy-regulating hormones. It should be noted that these experiments, in addition to giving large doses of these 2 monosaccharides, also create a highly artificial environment because neither pure fructose nor pure glucose is consumed to any appreciable degree in the human diet.

Teff et al. (16) reported that consumption of fructose-sweetened beverages compared with glucose-sweetened beverages, both consumed at 25% of calories, resulted in lower 24-h concentrations of circulating insulin, glucose, and leptin and decreased postprandial suppression of plasma ghrelin concentrations. Using a similar model, other investigators reported that consuming fructose- compared with glucose-sweetened beverages resulted in increased postprandial TG concentrations and that these effects were more pronounced in overweight/obese subjects than in normal-weight subjects and more pronounced in men than in women (17, 18).

Given that insulin, leptin, and ghrelin interact with each other, these data have been extrapolated to suggest that prolonged consumption of energy from fructose could lead to increased caloric intake and contribute to weight gain and obesity. It should be noted, however, that meta-analyses published by Dolan et al. (19) of multiple studies in normal-weight, overweight, or obese individuals (20) consuming up to the 95th percentile of the adult population's intake of fructose did not report any metabolic abnormalities including weight gain.

Our laboratory compared the commonly consumed sugars HFCS and sucrose (each of which consists of ~50% fructose and 50% glucose) and determined that there were no differences with respect to energy-regulating hormone response, appetite, and/or ad libitum energy intake between these 2 sources of added sugar at the 90th percentile population consumption in acute experiments (21, 22) and up to the 90th percentile population consumption of added sugars over a free-living protocol lasting 10 wk (23). These findings were subsequently corroborated by Stanhope and Havel (24) and extended to obese individuals by Zuckley et al. (25).

A more recent study published by Yu et al. (26), also from our research group, compared 8% of calories from either HFCS or sucrose (25th percentile population consumption level), 18% of calories from these 2 sugars (50th percentile population consumption level), and 30% of calories from these 2 sugars (90th percentile population consumption level) and found no differences or adverse effects related to insulin, glucose, leptin, or ghrelin and no acute differences or differences after 10 wk of consumption among these 3 dose amounts. Thus, it appears that the dosage of these 2 added sugars also does not matter when energy-regulating hormones are assessed. Given that no differences in energy-regulating hormones exist between the commonly consumed sugars where fructose and glucose are consumed together, extrapolation from findings comparing pure fructose to pure glucose must be treated with extreme caution.

Sugars and obesity. In retrospect, the modern concern about a potential role for sugars as a unique cause of obesity can be traced back to a commentary in *The American Journal of Clinical Nutrition* in 2004 (6). In that commentary, Bray et al. argued that the use of HFCS in the United States was temporally associated with a rapid increase in obesity prevalence. These authors argued that the metabolism of fructose compared with glucose differed in ways that energy consumption could be increased after fructose consumption and result in the increased likelihood of obesity as well as cardiovascular disease, diabetes, and MetS.

Subsequent research trials, however, failed to support the hypothesized linkage between HFCS and obesity (5, 23, 27). Indeed, multiple studies have now demonstrated that HFCS and sucrose are virtually identical with regard to calories, sweetness, and absorption (20, 24). Studies from our research laboratory (21, 26), as well as others (27), concluded that HFCS and sucrose are virtually identical with regard to glucose, insulin, leptin, ghrelin, and appetite responses in normal-weight and obese individuals. The American Medical Association (28) and the Academy of Nutrition and Dietetics have both issued statements concluding that there are no differences between HFCS and sucrose with regard to the likelihood of causing obesity (29).

As a result of this expanding literature, the emphasis has shifted to a consideration of whether or not fructose-containing sugars in general (e.g., sucrose, HFCS, concentrated fruit juices, etc.) may be uniquely linked to obesity. Several meta-analyses suggested that sugar-containing soft

drinks are associated with weight gain and obesity in both children and adults. Malik et al. (30) reviewed 30 publications (15 cross-sectional, 10 prospective, and 5 experimental) that met the criteria for their meta-analysis and showed a positive association between greater intake of sugar-sweetened soft drinks and weight gain. Another meta-analysis by Olsen and Heitmann (31) including 14 prospective and 5 experimental studies concluded that the consumption of soft drinks was a determinant of obesity.

There have been 3 recent systematic reviews and meta-analyses of RCTs of sugar consumption or sugar-sweetened beverage (SSB) consumption and body weight (32–34). Taken together, these meta-analyses of RCTs demonstrate that replacing sugar with other energy-equivalent macronutrients has no effect on body weight. There is suggestive evidence that increasing energy consumption by increasing sugar intake in adults may lead to modest weight gain. The weight gain, however, appears to be due not to sugar per se, but to an increase in energy consumed, because participants in these hypercaloric RCTs were told to increase their sugar consumption on a background of their typical caloric intake.

Prospective cohort trials have yielded similar results (32–34). These cohort studies, both in adults and children, provided inconsistent results and typically did not adjust for total energy intake. When this adjustment was performed in one meta-analysis, the results showed no relation between sugar consumption and body weight. Thus, both cohort studies and RCTs are consistent in failing to demonstrate a unique relation between sugar consumption and obesity.

Several recent summary articles reached the same conclusion that there is a lack of evidence linking sugars to obesity (3, 35). Moreover, RCTs performed in our research laboratory demonstrated that the consumption of average amounts of fructose-containing sugars did not result in increased body weight during a 10-wk free-living trial where they were added isocalorically (36). In a separate study in our laboratory, average amounts of fructose-containing sugars were used as part of a hypocaloric diet and did not impede weight loss (37). These studies add further evidence against a unique linkage between added sugars and obesity or weight gain.

Thus, evidence from a variety of sources does not suggest that sugars per se make a unique contribution to obesity. Moreover, in a condition as complicated as obesity it is highly unlikely that one single nutrient would uniquely cause this condition. It is more likely that the totality of the diet, including increased caloric consumption from all sources, exerts a significant impact on the likelihood of obesity. This view is consistent with the recent scientific statement from the ASN, which emphasized the complexity of energy regulation and weight and cautioned against isolating one component of the diet as a primary cause of weight gain and/or obesity (38).

Sugars and Risk Factors for Cardiovascular Disease

Lipids. Some studies have explored the potential linkage between the consumption of added sugars and dyslipidemia

(39, 40). The American Heart Association (AHA) recommended restricting the consumption of fructose-containing sugars as a mechanism for controlling TGs (41). The data to support this, however, are inconclusive as reported in several recent systematic reviews and meta-analyses (42–44). Fructose, when substituted in an isocaloric fashion or other sources of carbohydrate in individuals both with and without diabetes, did not show adverse effects on fasting lipid profiles (42, 43) or postprandial TGs (44). It should be noted, however, that a recent trial conducted by Egli et al. (45) demonstrated that an isocaloric high-fructose diet significantly increased blood TGs. These investigators also reported that exercise prevented increases in TGs in this acute study in healthy young subjects. Moreover, a recent meta-analysis by Te Morenga et al. (46) reported that the most marked relation between sugar intake and TGs occurred in studies that measured energy, and no weight change was reported. Thus, the effects of fructose-containing sugars on blood lipids remain inconclusive and will require further research to resolve.

A key issue appears to be whether or not studies have been designed to match energy intake. In isocaloric trials, even large doses of fructose-containing sugars did not result in lipid abnormalities, even at doses above the 95th percentile population consumption level for fructose. Livesey et al. (47) did not find an overall adverse effect on lipids and suggested a dose threshold for TG-elevating effects of fructose in isocaloric substitution for other carbohydrates at 100 g/d for fasting and 50 g/d for postprandial TGs. Sievenpiper et al. (48) proposed a threshold of <50 g/d of fructose-containing sugars for fasting TGs in people with diabetes.

In contrast, in hypercaloric trials in which fructose was supplemented to background diets, thereby creating excess energy, increases in LDL cholesterol and TGs were reported (42–44). Research in an RCT in our laboratory, however, showed that individuals who consumed either sucrose or HFCS at 10% or 20% of total calories (25th or 50th percentile population intake levels of fructose) in an isocaloric diet in a free-living environment showed no changes in total cholesterol, TGs, LDL cholesterol, or apoB (36). In a mildly hypercaloric trial, however, a 10% increase in TGs occurred (49, 50). Thus, it appears that adverse effects of sugars related to lipids are more likely to be a result of excess energy than to sugar per se.

Blood pressure. Several RCTs examined whether fructose itself or fructose-containing sugars contribute to increased blood pressure. Raben et al. (51) randomly assigned 21 overweight subjects to supplements of either sucrose (in solid or beverage form; mean 152 g/d) or artificial sweeteners. After 10 wk, blood pressure in the sucrose group was significantly higher than in controls. However, these data are confounded by the fact that these individuals also gained, on average, 2.6 kg more than did controls. Brown et al. (52) in a non-blinded, randomized crossover trial administered to 15 subjects an acute load (60 g in 500 mL of water) of fructose, glucose, or pure water and found a significant increase (~3 mm Hg) over the 120 min of the study when fructose

was consumed compared with either glucose or water. As already indicated, fructose and glucose are invariably consumed together in the diet such as in sucrose or HFCS. Grasser et al. (53) compared blood pressure responses with sucrose with those with fructose with the amount of fructose equalized (30 g of fructose in 500 mL tap water). These investigators found that fructose increased blood pressure, whereas sucrose did not—suggesting that the glucose component of sucrose may abrogate increases in blood pressure that may occur when consuming fructose alone.

Other studies did not find increases in blood pressure related to fructose administration. Lê et al. (54) provided fructose (1.5 g/kg body weight) to 7 subjects in an isocaloric diet. Blood pressure did not change over the 4-wk study. Maersk et al. (55) randomly assigned 47 subjects to 4 different test drinks. After 4 wk, subjects given SSBs had significantly greater systolic blood pressure than did those given diet cola or isocaloric milk. However, there were no significant blood pressure differences between the SSB group and those given water. Ha et al. (56) performed a meta-analysis of 13 randomized and nonrandomized controlled feeding trials in which subjects were given an isocaloric exchange of fructose for other carbohydrates. The studies in this meta-analysis did not show any effect on systolic blood pressure, but there was high interstudy heterogeneity.

Prospective cohort studies have shown conflicting results related to blood pressure and sugar consumption. Several studies have shown an association between SSB consumption and incident hypertension (40, 57–59). Other studies have not corroborated these findings. Results from several RCTs from our research laboratory did not show elevations in blood pressure at amounts up to the 90th percentile population consumption level for fructose-containing sugars (49, 50). Thus, there is little evidence to support that sugar consumption per se is a significant risk factor for elevated blood pressure.

Coronary heart disease. There are no reported RCTs, to our knowledge, that examined the effect of sugar consumption on coronary heart disease (CHD) itself. Three prospective cohort studies explored the association between SSB consumption and incident CHD. de Koning et al. (60) explored data from the all-male Health Professionals Follow-Up Study and found a significant association between CHD events and the highest quintile of SSB consumption compared with the lowest. Fung et al. (61) explored data from the Nurses' Health Study and found a significant elevated risk associated with CHD with ≥ 2 servings (355 mL) of SSBs/d compared with < 1 serving/mo. Eshak et al. (62) in a large prospective cohort study found no association between SSBs and myocardial infarction. These studies, however, were subject to all of the limitations of prospective cohort studies, particularly given that RCTs have not persuasively linked sugar consumption to risk factors for CHD.

The AHA has, nonetheless, issued a Scientific Statement recommending that American women consume no more than 100 kcal/d and American men no more than 150 kcal/d from added sugars (63). The AHA acknowledged that these recommendations are far lower than those recommended by

the Dietary Guidelines for Americans, 2010 (64) and the Institute of Medicine (65) and also recognized that these recommendations are largely based on epidemiologic studies or animal data. Clearly, a need for RCTs exists to clarify issues of whether or not sugar consumption in fact increases CHD events.

Sugars and Diabetes

Diabetes is rapidly emerging as a major worldwide health concern in the 21st century. It is estimated that the prevalence of diabetes will double by 2035 (3). The increase in diabetes has paralleled the dramatic increase in worldwide obesity and insulin resistance (66–68). This has prompted investigators to explore nutritional links to diabetes. One of the factors that has been suggested as a unique link to diabetes is the consumption of fructose-containing sugars.

Several ecological analyses suggested that as sugar consumption has increased in countries so has the prevalence of diabetes (69, 70). Ecological analyses, however, are considered a weak form of evidence. It is also important to note that not all ecological studies showed a positive correlation between sugar intake and diabetes rate. For example, in the United States, total sugar consumption decreased substantially between 1980 and 2003 as it did both in Australia and the United Kingdom (71). In Australia, there was a 10% decrease in the contribution of sugar from SSBs despite increases in obesity and diabetes. This has been called the “Australian paradox.” Similar “paradoxes” have been seen in the United States, where prevalences of both obesity and diabetes have increased in the past decade whereas sugar consumption has declined.

Just as with obesity, the etiology in type 2 diabetes is certainly complicated and not entirely resolved. However, the most likely primary pathologic event is excess energy intake leading to overweight and obesity (66–68). The central question of whether or not sugar is a unique cause of diabetes has not been addressed in any RCT. Thus, most of the data come from cohort studies and RCTs looking at risk factors for diabetes rather than diabetes per se.

Prospective cohort studies provided mixed evidence concerning sugar consumption and diabetes (72, 73). Malik et al. (72) reported a meta-analysis of cohort studies related to SSBs and incident diabetes. Of the 8 studies reported, 4 did not find a significant effect of SSBs on the incidence of diabetes and 5 did not adjust findings for energy intake and body weight. Another study published by the same group did not show a relation between sugar consumption and risk of diabetes (73). Another large cohort study (Health Professionals Follow-Up Study) reported no association between diabetes risk and SSB consumption once data were adjusted for total energy intake (74). Other prospective cohort studies also failed to find significant associations between total sugar intake and diabetes (75, 76). In fact, one study found a significant negative association (77).

With regard to RCTs and meta-analyses, once again, few data are available to support an association between sugar intake and diabetes. Cozma et al. (78) reported a systematic review and meta-analysis of RCTs and nonrandomized controlled trials of fructose and diabetes. Of the 18 feeding

studies they identified, fructose had no adverse impact on glycemic control, including fasting insulin, glucose, or glycated blood proteins (including glycated hemoglobin). Most, but not all, randomized controlled studies in nondiabetic subjects that used the substitution of sucrose or fructose with a controlled diet did not show adverse effects on multiple risk factors for diabetes, including insulin, postprandial glucose, and fasting blood insulin (79–83).

A recent RCT conducted in our laboratory studied 123 individuals who consumed 18% of calories from either sucrose or HFCS or 9% of calories from fructose or glucose (84). This study did not yield any increase in fasting glucose, insulin, or insulin resistance via HOMA. Another RCT conducted in our laboratory compared sucrose or HFCS at 8%, 18%, or 30% of calories in a large sample size of 267 individuals and also found no increases in glucose, insulin, or insulin resistance (49). In addition, an RCT from our research group looked at total body insulin sensitivity and hepatic insulin sensitivity using the Matsuda index and found no increases in either variable after 10 wk of consumption of average amounts (50th percentile) of fructose-containing sugars (85). Taken together, there is little direct evidence that sugar consumption increases the risk of diabetes.

Fructose-Containing Sugars and Risk of MetS

MetS represents a constellation of factors, including abnormal glucose handling, dyslipidemia, and high blood pressure (86). The prevalence of MetS has increased considerably in the United States in the past 20 y. Reports using NHANES data have suggested a prevalence of MetS of up to 39% of adults (87).

It has been argued that the consumption of fructose-containing sugars may increase the risk of developing MetS. Johnson et al. (88) proposed a model in which fructose metabolism in the liver may lead to ATP depletion and ultimately increases in uric acid through ATP degradation to AMP, which, in turn, may lead to endothelial dysfunction and create an increased risk of MetS due to increased blood pressure, insulin resistance, and inflammation.

Excess accumulation of abdominal fat is strongly associated with MetS (89). Several investigators reported increases in abdominal fat in response to the consumption of various sugars. Stanhope et al. (90) compared the consumption of fructose and glucose at 25% of calories and reported an increase in visceral abdominal fat in the fructose-consuming group. It should be noted that this increase occurred only in comparison to baseline in the fructose group and did not achieve significance when compared with the glucose group. Maersk et al. (55) conducted a 6-mo trial comparing 1 L/d of sucrose-sweetened cola, diet cola, milk, or water. They reported that the sucrose-sweetened cola group showed an increase in abdominal fat and other risk factors for MetS. There was, however, no significant difference in visceral adiposity when comparing the regular cola, diet cola, and water groups.

RCTs conducted in our research laboratory compared effects of either sucrose or HFCS on body weight and abdominal fat in 116 individuals who consumed these sugars at the 25th, 50th, and 90th percentile population consumption level of

fructose. Despite a 0.9-kg increase in body mass over the entire cohort, there was no increase in abdominal fat as evaluated by DXA. A subsequent RCT in 123 individuals comparing HFCS and sucrose at 18% of calories with glucose and fructose at 9% of calories showed similar findings. A slight decrease in HDL cholesterol (~1 mg/dL) and an increase in TGs (10–14% increase) occurred in these studies (91), although the values remained within normal limits. These increases may be attributable to the fact that the trial was mildly hypercaloric, resulting in an approximate 2-pound average weight gain in participants.

As already indicated, multiple other research trials have not yielded an association between sugar and elevated blood pressure, TGs, or postprandial TGs when fructose-containing sugars were substituted isocalorically for other carbohydrates. Thus, the effects of fructose-containing sugars on risk factors for MetS would appear to be very small if present.

Sugar and Liver Fat Accumulation

Fatty infiltration of the liver leading to NAFLD has been steadily increasing worldwide over the past 20 y. Worldwide (92), NAFLD represents the leading cause for chronic liver failure and the need for liver transplantation.

Concern about the potential interaction between the consumption of fructose-containing sugars and NAFLD has been evaluated by a number of investigators (93–95). The theoretical basis for concern relates to the well-known differential metabolism of fructose and glucose in the liver (96). This process is illustrated in **Figure 1**. As depicted in the figure, fructose can be metabolized in the liver to ultimately create FFAs. However, it should be pointed out that the pathways between fructose and glucose metabolism are interactive. Thus, the quantity of fat produced by this mechanism in humans is extremely small. When fructose-containing sugars are consumed, it has been estimated that >50% of the fructose is

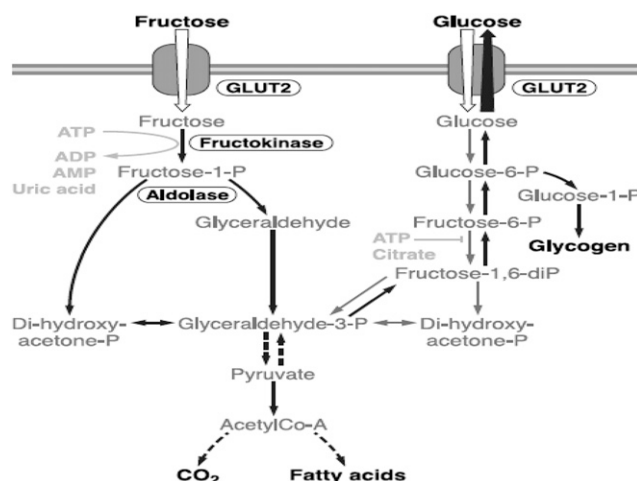


FIGURE 1 Metabolism of fructose and glucose in the liver: The metabolic pathways, although different, are interactive. diP, diphosphate; P, phosphate. Reproduced from reference 96 with permission.

metabolized in the liver to glucose, another 25% to lactate, 15% to glycogen, and another few percent into carbon dioxide (90). The issue of intestinal lipogenesis and its possible interactions between fructose and glucose has been explored by several investigators. Lewis et al. (97) using an animal model of Syrian golden hamsters demonstrated intestinal lipoprotein overproduction when hamsters were fed a diet of 60% fructose. This intestinal lipoprotein overproduction was demonstrated to be ameliorated with the insulin sensitizer Rosiglitazone (Avandia by GlaxoSmithKline). Theytaz et al. (98) showed that amino acid supplementation blunted the fructose-induced increase in intrahepatic lipid concentration, and interactions between fructose and other components of the diet must be taken into consideration when considering the potential for increasing liver fat. Two recent studies reported that hypercaloric glucose and fructose consumption similarly increased intrahepatic fat, whereas isocaloric fructose did not (99, 100). These studies suggest that increases in liver fat appear to be an energy-mediated rather than a specific macronutrient-mediated effect.

Various investigators reported that only 1–5% of the fructose consumed will be converted to TGs through the process of de novo lipogenesis (90, 101). The amount of fat generated in this process is estimated to be ~1% of that typically consumed in the human diet (96, 101). Nonetheless, some investigators speculated that de novo lipogenesis may contribute to substantially increased fat in the liver. Multiple RCTs in humans, however, have not demonstrated the effect of fructose-containing sugars leading to increased fat in the liver. Lê et al. (102) gave individuals 1 mg fructose/kg of lean body mass and did not demonstrate increased liver fat. Silbernagel et al. (103) reported similar findings from a 4-wk trial. Our research group conducted an RCT in which individuals were given up to 30% of calories from either HFCS or sucrose during a 10-wk free-living period and did not demonstrate increased fat accumulation in the liver (104). Two recent systematic reviews and meta-analyses also failed to find a linkage between fructose consumption and NAFLD (105, 106). In contrast, Stanhope et al. (90) provided individuals with 25% of energy as glucose or fructose and found increased liver fat after fructose consumption. Lê et al. (54) gave descendants of diabetics doses of 3.5 mg/kg of lean body mass and found some increase in the accumulation of liver fat. It should be pointed out that both of these studies used doses far in excess of normal amounts of consumption and used fructose by itself, which is normally not consumed in isolation in the human diet. Thus, there seems to be little evidence for fructose-containing sugars causing NAFLD at typical amounts of human consumption.

Fructose-Containing Sugars and Neurologic Responses

Animal experiments have suggested differences in brain responses with fructose compared with glucose (107, 108). However, these experiments must be treated with great caution because animal brains (particularly rodents, which were

used in many of these studies) differ in very significant ways from the human brain.

Over the past 2 decades, an increasing number of human studies have used fMRI to explore potential differential neurologic responses to various sugars in human beings (109, 110). Smeets et al. (109) compared fMRI responses to aspartame, maltodextrin, and water. These investigators reported that both calories and sweetness must be present in order to stimulate brain reward pathways. Page et al. (111) compared a 75-g oral bolus of fructose with a 75-g oral bolus of glucose in 20 healthy, young volunteers in a randomized blinded fashion. They reported differences in hypothalamic blood flow, with glucose suppressing hypothalamic blood flow assessed by arterial spin labeling. These investigators also reported differences between fructose and glucose in brain connectivity. Purnell et al. (112) explored the neurologic response to 25 g of either fructose or glucose delivered as an intravenous bolus. These investigators reported no changes in blood flow to the hypothalamus but differences between fructose and glucose in blood flow to the cerebral cortex.

It should be noted that in both of these experiments, large doses of pure fructose were compared with pure glucose. As already indicated, neither of these sugars is consumed to any appreciable degree in the human diet. Moreover, the Purnell experiment gave these conditions through an atypical route (intravenously). Findings from these studies have led to speculation that fructose may lead to stimulation in reward pathways, thereby leading to a form of sugar “addiction,” contributing to overeating and obesity. It must be pointed out, however, that the entire concept of sugar “addiction” has been challenged on multiple grounds (113–115).

A recent study by Stice et al. (116), which used a model with various amounts of sugar compared with various amounts of fat in isocaloric milkshakes, reported that sugar activates reward, gustatory, and somatosensory pathways more than does fat. These investigators speculated that their results could provide an impetus to regulate sugar rather than fat in the diet. These results, however, should be viewed with great caution because there are other studies that showed exactly the opposite (117, 118). Moreover, the acute nature of this experiment does not demonstrate whether or not differences in stimulation of reward pathways results in either overeating or weight gain.

A pilot study conducted in our research laboratory examined HFCS or sucrose given as 18% of calories compared with 9% of calories from either fructose or glucose in the context of mixed-nutrient meals (119). Preliminary data from this study suggest that these sugars appear to behave similarly in this acute setting and are not different from an unsweetened control condition with regard to either hypothalamic blood flow or brain connectivity. Clearly, there is a need for larger RCTs to sort out whether or not neurologic differences exist in response to various sugars. Such a trial is currently underway in our research laboratory.

Future Research Directions

The ongoing controversies with clear public health implications related to the metabolism and health effects of fructose-containing sugars have stimulated several organizations to explore and offer guidance for future research priorities. In November 2012, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Heart, Lung, and Blood Institute, and the USDA sponsored a workshop entitled “Clinical Research Strategies for Fructose Metabolism” (120). This 2-d conference explored various issues related to both short-term mechanistic studies and longer-term studies with health implications. The conference concluded that mechanistic studies designed to elucidate pathways of fructose metabolism could reasonably compare pure monosaccharides, glucose, and fructose. However, “health outcomes research meant to inform public policy should use large, long term studies using combinations of sugar found in a typical American diet rather than pure fructose or glucose.”

An initiative has also been launched by the International Life Sciences Institute to explore research gaps remaining in the area of sugar consumption and health. To date in this initiative, a process has been identified for evaluating the current literature and research gaps. Fourteen different areas of particularly high priority for future research were identified (121). Importantly, this initiative also recommended that future studies should routinely have a physical activity component and should emphasize the study of sugars normally consumed in the human diet, such as sucrose and HFCS.

Public Policy Implications

Issues related to added sugars do not take place in a vacuum. Considerations related to the metabolism and health consequences of consuming sugars carry important public policy implications. For example, there are at least 3 different recommendations for appropriate upper limits for sugar consumption in the diet. The Dietary Guidelines for Americans, 2010 concluded that up to 25% of calories could be consumed as added sugars without adverse health consequences (64). These recommendations were based on the Institute of Medicine’s report on carbohydrates and health (65). The AHA offered more restrictive guidelines, suggesting that the average adult woman consume no more than 100 kcal/d and the average adult man no more than 150 kcal/d in added sugars (63). These guidelines represent ~5–6% of calories in the typical 2000-kilocalorie diet and are currently exceeded by >90% of the American population.

Recently, the WHO recommended an upper limit of added sugars of no more than 10% of calories with a goal of ultimately reducing the recommended upper limit to no more than 5% of calories (122). The WHO report acknowledged that evidence related to sugars and weight change in adults was “moderate” to “low” and based their recommendation largely on the well-established relation between added sugars and dental caries.

The subject of different amounts of added sugars and their relation to health variables has been the focus of several RCTs

in our research laboratory. In one RCT in 352 men and women between the ages of 20 and 60 y who consumed either HFCS or sucrose at 8% of calories (i.e., 4% of calories from fructose, which represents the 25th percentile population consumption level in the United States and approximately the upper limit recommended by the AHA and WHO), 18% of calories (i.e., 9% of calories from fructose, which represents approximately the 50th percentile of fructose consumption in the United States), or 30% of calories [i.e., 15% of calories from fructose, which represents approximately the 90th percentile of fructose consumption in the United States and is slightly higher than the upper limit of sugar calories recommended in the Dietary Guidelines for Americans, 2010; (64)]. Individuals who consumed these amounts of added sugars did not show any differences in blood pressure or blood lipids (2). Subsets of these individuals were studied in our metabolic units before and after a 10-wk free-living period and demonstrated no differences between these 3 amounts of sugar consumption with regard to insulin, leptin, ghrelin, glucose, postprandial TGs, or the TG AUC (26). A further subset of these individuals underwent computed tomographic scanning of the liver and MRI of the gluteus maximus and vastus lateralis muscles, which showed no changes over a 10-wk period and no differences between these 3 doses with regard to liver and ectopic muscle fat accumulation (104). Thus, our data support the recommendation by the Institute of Medicine and the Dietary Guidelines for Americans, 2010 that no adverse health consequences appear to occur at amounts of added sugar consumption up to 25% of calories. We wish to clearly state that we are not advocating this amount of added sugar consumption in the typical diet. We are simply reporting our findings that no adverse health consequences appear to occur at this amount of sugar consumption.

Various countries and organizations have struggled with how to interpret data with regard to sugar consumption and health policy. As Clemens et al. point out (123), the danger in this area is to make public policy on the basis of incomplete data supported by emotion, politics, or revenue needs rather than high-level science such as that available from RCTs.

Summary and Conclusions

Recent systematic reviews and meta-analyses as well as multiple RCTs have suggested that there is nothing unique with regard to sugar consumption and its health consequences, provided that sugar is substituted isocalorically for other carbohydrates and consumed within the normal range of human consumption (15). Some questions still remain from research trials in which fructose-containing sugars were substituted in a hypercaloric fashion (added to an already eucaloric diet). Further research trials will be necessary to settle issues in the area of hypercaloric consumption of sugars. For now, it appears safe to state that the current literature does not support a unique relation between fructose-containing sugar consumption and risk factors for cardiovascular disease, diabetes, MetS, or NAFLD at normally consumed amounts in the normal fashion (i.e., in the presence of glucose such as

in sucrose or HFCS). Neurologic responses to sugars remain an active area of interest, although great care must be exhibited when considering such concepts as sugar “addiction,” which does not appear to be currently supported by research trials or expert opinion (113–115).

The isolation of sugar with the suggestion that it somehow uniquely causes multiple health problems is a direction consistent with other previous attempts to isolate components of the diet and link them to metabolic diseases, which have universally failed. As Slavin (124) wrote in a recent editorial in the *American Journal of Clinical Nutrition*, “Nutritional nit-picking has been unsuccessful in improving public health. Nutrient-based interventions are generally ineffective, as are bans on sugar-sweetened beverages. Dietary pattern recommendations are more likely to show success in improving cardiovascular health.”

The debate on added sugar and its health consequences has provided useful and important information over the past decade. It is hoped that continued work in this area will lead to a science-based approach based on high levels of evidence from RCTs and meta-analyses. This can only improve public health and guide wise public policy as well as inform individual nutritional decisions.

Acknowledgments

Both authors read and approved the final manuscript.

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