Dietary Sweeteners Containing Fructose: Overview of a Workshop on the State of the Science

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Abstract
The occurrence and impact of fructose in the American food supply has garnered much recent attention in the popular press as well as the scientific community. This paper provides an overview of a workshop cosponsored by the International Life Sciences Institute North America and the USDA, Agricultural Research Service, titled "State of the Science on Dietary Sweeteners Containing Fructose." Papers in the workshop addressed the chemical composition and properties of dietary sweeteners that contain fructose, the sources and amount of fructose in the American diet, and the metabolism of fructose in the human body. Further, the authors of each paper assessed the strength of the existing data linking dietary fructose intake and risk for overweight, metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, and other disorders. The assessment considered factors in study design, including the amount fed, the food form, the length of the study, the characteristics of the subjects, the specific methodology, and other potential confounders including diet. In addition to papers assessing the basic science of fructose, some papers also addressed consumer concern about sugars and fructose in the diet, the way fructose and other sugars are presented in the media, and the resulting confusion of consumers about fructose and other sugars in the diet. The purpose of the papers in the aggregate was to clarify what data exist about fructose and what the gaps are in the data and to help both scientists and consumers understand issues surrounding fructose in the food supply. J. Nutr. 139: 1210S–1213S, 2009.

Introduction
The occurrence and impact of fructose in the American food supply have garnered much attention in recent years in both the popular press and the scientific community. Much of the popular attention has originated from concern about the shift toward the use of high-fructose corn syrup (HFCS) from sucrose and a lack of understanding that HFCS and sucrose are compositionally quite similar. Simultaneously, the available body of scientific literature has offered mixed results about the physiological effects of dietary fructose, further complicating popular messages and consumer perception. For example, whereas epidemiological studies linking fructose intake (1) and intervention trials using high levels of pure fructose (2,3) (which is rarely used as an ingredient) have suggested adverse health outcomes, other intervention trials with fructose have not demonstrated any negative effects (4,5). These contradictory outcomes suggested the need for a critical review of the available data to assess the potential health effects associated with current intake levels of sweeteners containing fructose and to inform us where more research is needed.

HFCS production became technologically practical on a large scale in the 1970s with the development of a process to enzymatically convert some of the low-sweetness glucose moieties, derived from corn starch hydrolysis to produce corn syrup, into the sweeter fructose. An immobilized isomerase enzyme is used to convert the glucose to fructose. An immobilized isomerase enzyme is used to convert the glucose to fructose. An immobilized isomerase enzyme is used to convert the glucose to fructose. An immobilized isomerase enzyme is used to convert the glucose to fructose. Because the parent corn syrup contains virtually no fructose, the new product was christened high-fructose corn syrup. The Journal of Nutrition

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3 Abbreviations used: E, percent of energy; HFCS, high-fructose corn syrup; ILSI, International Life Sciences Institute; TG, triglyceride.

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(HFCS-55) or 42% fructose and 58% glucose (HFCS-42). This makes HFCS’s sweetening intensity and overall composition only marginally different from the 50% fructose and 50% glucose composition of the sucrose it replaces.

In normal dietary situations, glucose and fructose are consumed together in nearly equal quantities. Diets comprised of normal foods do not contain extreme concentrations of either glucose alone or fructose alone. In fact only a few natural foods, such as agave syrup (85% fructose) or apple and pear juice (66% fructose), contain fructose at a ratio higher than glucose. In most fruits and vegetables, the ratio of glucose to fructose is nearly equal.

Nonetheless, many experiments are designed to feed fructose at levels that would not occur in a typical diet (6–8). These fructose feeding study data suggest that high consumption of fructose causes perturbations in glucose metabolism, glucose uptake pathways, and uric acid metabolism and leads to alterations in adipose deposition. The changes are thought to lead to a markedly enhanced rate of de novo lipogenesis and triglyceride (TG) synthesis driven by levels of glycerol and fatty acids produced by driving fructose metabolism. Increases in TG have been associated with elevated blood lipids, insulin resistance, and other precursors of the metabolic syndrome (9–11). In both human and animal experiments, fructose-induced insulin resistance is associated with hepatic and intestinal overproduction of potentially atherogenic lipoprotein particles and may lead to increased deposition of fat in tissues. In addition, feeding of extremely high levels of fructose is associated with changes in hormone levels (12–15).

Mixed messages about the entire topic of carbohydrate intake, including fructose and HFCS, leave most consumers confused about the health effects of different sugars. Astute consumers know that fructose has some unique properties. Some know that it does not initially require insulin to enter the cell. Others know that it causes a much lower rise in postprandial blood glucose. Some actually advocate its use for serum glucose control based on this precept. Many scientists and consumers erroneously equate the feeding of high levels of pure fructose with the feeding of HFCS. Amplifying this misunderstanding, the media and some researchers fail to distinguish clearly between HFCS and pure fructose when reporting study results. The lack of precision in conveying the message adds to this confusion.

Fervent beliefs especially around potential associations of HFCS and obesity have led legislatures, local governments, some parent groups, and schools to seek bans on products containing HFCS obtainable from school vending machines and other venues (16–18). Four arguments regarding fructose, especially as HFCS in beverages, were cited in such campaigns. First, they note the associational data linking increased HFCS intake with increases in obesity over the same time period. Second, they cite studies showing that the body does not compensate for energy from sweeteners in beverages the same way as it does from solid food (19–21). Third, they charge that changes in metabolism and satiety with HFCS result in overconsumption of energy. Fourth, they recount recommendations from a number of sources that call for the reduction of added sugars in foods and sweetened beverages.

An expert panel convened by the Center for Food, Nutrition and Agriculture Policy recently addressed the association between body weight and HFCS in sweetened beverages (22). The panel specifically examined the published scientific literature to determine the relationship between consumption of HFCS or “soft drinks” (proxy for HFCS) and weight gain. The panel concluded that evidence from ecological studies linking HFCS consumption with rising BMI rates is unreliable. Unlike some prominent epidemiologists, the expert panel concluded that the evidence from epidemiologic studies and randomized controlled trials is inconclusive. They also noted that there were inadequate data available that distinguish between HFCS consumption and sucrose consumption with respect to weight gain. Further, they acknowledged that while the sweetener level and type have changed over time, the fructose:glucose ratio in the U.S. food supply has remained the same for 50 y. Finally, the panel concluded that HFCS did not contribute to weight gain any differently than other energy sources.

The furor in the popular press highlighted by books such as Good Calories, Bad Calories by Gary Taubes (23), together with position pieces in well-recognized nutrition and medical journals that sport titles such as “Is High-Fructose Corn Syrup the New Trans Fat?” (24) or “How Bad is Fructose?” (25), suggested to members of the International Life Sciences Institute’s (ILSI) North America branch Technical Committee on Carbohydrates and to members of the National Program Staff at the USDA, Agricultural Research Service the need for 2 things. First, there needed to be an accurate and current assessment of fructose intake by the population especially looking at those sectors of the population that are consuming the highest levels of fructose (e.g. those at the 90th percentile of intake) regardless of source. Second, there needed to be a review of the scientific literature on all aspects of fructose metabolism. Thus, the USDA, Agricultural Research Service and ILSI North America branch sponsored a workshop that addressed issues surrounding the consumption of fructose. Authors not only assessed the role of fructose in body weight but also its effects on insulin and blood glucose, satiety and satiety hormone levels, metabolic changes, blood lipids, markers of inflammation, advanced glycation end products, and other concerns. This Supplement contains papers by the invited experts. The original paper was amended after critique, commentary, questions, and discussion by other panel experts and nearly 50 academicians, government representatives, industry scientists, and nutrition communicators in attendance at the workshop.

The review papers from diverse perspectives and disciplines were presented to develop an understanding of the following: the chemical composition and properties of dietary sweeteners that contain fructose; the food supply availability of dietary sweeteners that contain fructose; the sources and amount of fructose in the American diet; the metabolism of fructose in the human body; the extent and nature of human research on dietary fructose intake and risk for overweight, metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, and other disorders; and the factors in study design that are critical in evaluating the effects of fructose and for conducting systematic reviews. These include aspects such as the amount fed, the form of the food (e.g. liquid vs. solid vs. semisolid), the length of the study, the characteristics of the subjects, the specific methodology, and the dietary and other confounding factors to control.

The workshop papers

John White reviewed the history, chemistry, and some commonly held myths about fructose (26). The review documented that fructose occurs in over 50 fruits and vegetables, sugar cane, and honey in similar glucose:fructose ratios that are present in HFCS and that the glucose:fructose ratio in the food supply has remained the same since the 1960s before HFCS was introduced. Contrary to popular misconception, fructose occurs alone only in pure crystalline fructose (or in very-high fructose corn syrup, which is 90% fructose but is very rarely used as an ingredient).
He noted that some consumers seek HFCS alternates such as agave or concentrated fruit juices as potentially “healthier” choices even though these contain more fructose than HFCS. One principal argument of this paper is that experimental diets comprised of pure fructose, while academically interesting, have little bearing on human diets as eaten or on HFCS as used in the diet. Although there are correlations between HFCS intake and body weight increases in some countries, there are data from many countries in which body weight is increasing but there is no HFCS consumption. This paper cited data from countries where obesity rates are high and increasing at faster rates than in the US. Finally, accusations that HFCS consumption produces reactive dicarboxyls are not borne. Fewer dicarboxyls result with HFCS than occur with many common foods such as coffee, bread, beer, or cheese.

Bernadette Marriott (27) compared the intakes and food sources of fructose from NHANES 1999–2004 with data from the 1977–1978 dietary survey, which was summarized in the 1993 benchmark paper of Park and Yetley (28). Intake data from the more recent assessment are critically important, because sweeteners providing fructose in the diet have changed since 1970 with the introduction of HFCS. In 1970 the primary source of fructose in the diet was sucrose, which comprised 85% of sweetener consumption, with other sweeteners comprising 14% and HFCS <1%. In 2005 sucrose comprised 44%, HFCS 42%, and others sweeteners 14% (29).

According to this more recent analysis, fructose intakes for all age and sex groups, expressed as g/d, have increased since 1977–1978. When expressed as percent of energy (E), dietary intakes of fructose have remained relatively constant. As with the Park and Yetley assessment, teenaged and young adult males and females have the mean highest fructose intakes at 10–12% of E. At the 90th percentile of intake, fructose contributed from 11 to 16% of E depending on age-sex group. Similar to Park and Yetley’s assessment, nonalcoholic beverages and grain products are the major food sources of fructose.

Peter Havel (30) summarized seminal work on feeding with very high levels of fructose. In these studies, overweight and obese men and women were fed diets with fructose- or glucose-sweetened beverages contributing 25% of E to the diet. Fructose in these situations caused an increase in postprandial TG concentrations in blood serum compared with glucose despite equal effects on body weight. The studies also point to potential adverse effects of these high levels of fructose with respect to insulin sensitivity and intra-abdominal fat deposition. The studies showed the expected relation between postprandial glucose and insulin excursions and the glycemic index of the sweeteners tested. These studies with humans fed high levels of fructose are important to understand the effects of these extremes in dietary consumption, but studies that reflect what is commonly consumed are needed to understand the impact of its use.

James Rippe (31) assessed the effects of fructose on mediators of energy balance and other potentially adverse outcomes. This review noted that fructose causes less insulin release than glucose and as such may alter leptin production in response to insulin. The downregulation of the satiety hormone leptin could be associated with weight gain if it can be shown that fructose feeding is actually less satiating. His work has focused on short-term effects by comparing HFCS with sucrose at levels commonly consumed.

Geoffrey Livesey (32) reviewed studies on the dose effects of fructose. His work suggests that outcomes with consumption of very high levels (>100 g/d) can be very different from those with usual dietary levels of fructose. In fact, his analysis suggests that low (<50 g/d) or moderate (50 to 100 g/d) intake levels of fructose may have effects that are diametrically opposite to those exerted at high intake levels.

Timothy Moran (33) reviewed the effects of fructose feeding with respect to satiety and obesity. He reviewed rodent experiments where high levels of sugars were fed. These experiments indicated that animals receiving the fructose diets gained more weight and had increased adiposity. He pointed out that interpretation of the results is difficult due to aspects such as the lack of certain controls such as a glucose-only control and differences in the concentrations tested. Both the human and animal studies reviewed suggest that the timing of satiety measurements and test conditions affect the results. Under different conditions and with different time intervals between feeding and measurement, fructose both showed and failed to show a satiating effect. Moran’s analysis showed that glucose caused a higher insulin release than fructose in diets containing 30% of E coming from either glucose or fructose. Higher glucose intakes also resulted in higher plasma leptin, a hormone that is associated with satiety, and lower plasma ghrelin, a hormone that promotes feeding. Despite these metabolic differences, he concluded that the overall body of literature investigating differences in the satiety effects of fructose compared with other sugars shows great variability and is “simply not compelling.”

Ernst Schaefer (34) compared the research on the effects of fructose to effects of other sugars and carbohydrates on lipid metabolism. In his comprehensive review, many of the studies showed no difference in lipid metabolism in either diabetic or normal subjects when comparing glucose or sucrose to fructose. However, some studies comparing diets with fructose to diets with resistant starch did show mild increases in TG levels resulting from high fructose levels, particularly in diabetic subjects. Also, Schaefer noted that in human studies where subjects consumed fructose at levels exceeding those of the highest fructose consumers, subjects did have abnormalities of blood lipids, particularly TG. Despite the fact that the fructose intakes were high, the adverse effects occurring at high levels flag the need for more research with fructose in the diet at customary levels to ensure that these effects are not seen over the long term.

John Bantle (35) reviewed the research on fructose and metabolic syndrome and diabetes. He reviewed evidence from studies in healthy and diabetic subjects (both type 1 and type 2) that demonstrates that fructose produced a smaller postprandial rise in plasma glucose and serum insulin than other common carbohydrates. In fact, dietary fructose intakes in diabetics are inversely associated with glycosylated proteins (e.g. glycosylated hemoglobin A1c and glycosylated albumin).

Susan Borra (36) characterized consumer understanding of sugars and carbohydrates. She reviewed the changes in wording of the Dietary Guidelines for Americans in recommendations regarding sugars intake that have occurred since 1980 and in the recommendations found in the Institute of Medicine’s macro-nutrient report suggesting a maximum added sugars intake of 25% of E and in the WHO/FAO expert consultation recommendation to keep “free sugars” to <10% of E intake. Additionally, her review noted that sugars have been addressed differently in various policies and programs related to school nutrition, in a plethora of nutrient profiling systems, as well as in the ways they are presented to consumers and the media. Surveys indicate that consumers are concerned about sugars, but her International Food Information Council’s data suggest that sugars terminology may not always be understood by consumers. In fact, the International Food Information Council’s consumer taped interviews dramatically show that consumers...
are confused about most sugars. Fructose provides just one more carbohydrate issue that consumers find perplexing.

**Summary of the papers**

Suzanne Murphy (37) synthesized the results presented at the workshop. Her paper rounded out the symposium on fructose by listing points of agreement and gaps in the data where further research is needed. All agreed that studies should be conducted that: 1) reflect current consumption data of both the total amount of fructose and its usual food sources; 2) measure the appropriate biochemical indices and health-related endpoints; 3) compare fructose, glucose, sucrose, starch, and HFCS; and 4) test the effects within a variety of populations, including those who are physically active and sedentary, are lean and overweight or obese, and who have diabetes, insulin resistance, and/or hyperlipidemia.

**Literature Cited**

16. Havel PJ. Fructose state of the science 1213S. Fructose: state of the science 1213S.