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Supplement: The State of the Science on Dietary Sweeteners Containing Fructose

Fructose and Satiety[1,2]

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Abstract

A role for the increased intake of dietary fructose in general and high-fructose corn syrup (HFCS) in particular in the current obesity epidemic has been proposed. Consumed fructose and glucose have different rates of gastric emptying, are differentially absorbed from the gastrointestinal tract, result in different endocrine profiles, and have different metabolic fates, providing multiple opportunities for the 2 saccharides to differentially affect food intake. The consequences of fructose and glucose on eating have been studied under a variety of experimental situations in both model systems and man. The results have been inconsistent, and the particular findings appear to depend on the timing of saccharide administration or ingestion relative to a test meal situation, whether the saccharides are administered as pure sugars or as components of a dietary preload, and the overall volume of the preload. These factors rather than intrinsic differences in the saccharides' ability to induce satiety appear to carry many of the differential effects on food intake that have been found. On balance, the case for fructose being less satiating than glucose or HFCS being less satiating than sucrose is not compelling. J. Nutr. 139: 1253S–1256S, 2009.

Introduction

The role of high-fructose corn syrup (HFCS) in the current obesity epidemic is uncertain. The timing of the increase in the prevalence of obesity coincides with the increased use of HFCS in the diet and especially in soft drinks and with an overall increase in daily energy consumption, leading to suggestions that this dietary shift may be contributing to the obesity epidemic (1–3). Yet, HFCS has been primarily substituted for sucrose in such beverages, and HFCS and sucrose are not substantially different in monosaccharide content (4).

Increased ingestion of HFCS-sweetened beverages could result in overall higher energy intake because of poor compensation for the ingestion of such palatable high-energy liquids. In support of such an increase, a direct evaluation of the effects of HFCS-sweetened soda on overall energy intake indicated that scheduled HFCS ingestion resulted in increased overall energy intake and body weight over the 3-wk study period (5). However, in this study, it was not clear whether this was a function of the increased fructose consumed or simply an outcome of the ingestion of a relatively high-energy sweetened beverage.

Chronic access to saccharide solutions in general has been associated with increased food intake and body weight gain in rodent studies. Kanarek and Orthen-Gambill (6) reported that 50 d access to 32% glucose, sucrose, or fructose resulted in excess energy intake, weight gain, and increased fat deposition in rats. Rats with fructose access gained the most weight, and both the sucrose and fructose groups had decreased ability to clear a glucose load at the end of the study. In a more recent study, Jurgens et al. (7) demonstrated that mice with access to a 15% fructose solution gained significantly more weight and had significantly higher percentages of body fat than mice with access to a 10% sucrose solution or to an aspartame-sweetened water. Interpretations from these later data are complicated by the different concentrations of sucrose and fructose and the absence of a glucose-only condition.

Differential endocrine consequences of fructose *versus* glucose ingestion

Glucose and fructose ingestion can result in very different endocrine and metabolic states (8). Teff et al. (9) have provided the most complete data available on 24-h plasma profiles of a variety of endocrine parameters following meals in which 30% of the total energy intake was in the form of free glucose or free fructose. Consistent with the known effects of glucose and fructose on insulin secretion, the high-glucose diet elevated plasma glucose and insulin significantly more than did the high-fructose diet. High glucose also resulted in higher leptin levels, which were maintained throughout most of the day, a finding likely secondary to the difference in glucose and insulin secretions. High glucose also resulted in greater postprandial

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decreases in plasma ghrelin levels. This overall profile of decreased elevations in the adiposity signals insulin and leptin and smaller postprandial decreases in the orexigenic peptide ghrelin has been suggested to have the potential to result in decreased satiety and increased food intake during long-term fructose consumption.

Palatability and long-term preferences

Although both the fat deposition and endocrine profile data suggest the possibility that fructose may be less satiating than glucose or other saccharides, the issue is whether fructose is actually overconsumed or is less effective at reducing intake of other dietary energy sources. Comparisons between fructose and glucose ingestion have been made on many levels. In rats, brief access tests in which satiety influences are minimized have demonstrated a small but consistent increased rate of ingestion of fructose relative to glucose suggestive of increased fructose palatability or preferences (10). Such a finding is consistent with results from measures of perceived sweetness of the sugars dating back to 1925 (11). However, longer ingestion tests that compared the overall ingestion of saccharide solutions provided a different profile. In tests in which saccharide solutions were always available, although such availability tended to produce greater weight gain overall, rats consumed more glucose, maltose, and sucrose relative to fructose, suggesting that factors other than relative sweetness or palatability were ultimately controlling intake (12).

Fructose and glucose satiating potential: gastrointestinal differences

Short-term effects of glucose and fructose on subsequent ingestion have been evaluated in a variety of testing situations. The results have been mixed, with some data suggesting differences, but others have found similar satiating potential for the 2 saccharides. The differences may relate to differences in the testing protocol or experimental subjects.

Their differential intestinal absorption provided the basis for examinations of the relative effects of glucose and fructose on rates of gastric emptying and subsequent food consumption in nonhuman primates. Glucose is mainly absorbed from the gastrointestinal tract by the sodium-dependent glucose transporter-1, whereas fructose is absorbed by a facilitated diffusion via glucose transporter-5 (13). Glucose transporter-2, a low-affinity transporter, plays some role with both fructose and glucose via facilitative diffusion (13). These differential transport mechanisms result in different rates of gastric emptying for fructose and glucose.

The gastric emptying of glucose solutions is characterized by a 2-phase process with the initial rapid rate of emptying affected primarily by the gastric volume and rate of stomach filling (14). This is followed by a slower linear phase of emptying that is sensitive to the glucose concentration such that emptying is slower with more concentrated solutions, allowing an equivalent rate of glucose delivery from the stomach to the intestine over a wide range of glucose concentrations (14). The gastric emptying of fructose is more rapid and less linear. Emptying does slow with increasing fructose concentration, but the overall rate of delivery of fructose from the stomach to the intestine is almost twice as rapid as with glucose (15).

These differences in the dynamics of gastric emptying were verified in monkeys using a dye dilution method and were then used as a test for the relevance of potential preabsorptive and absorptive events in the production of satiety (15). Rhesus monkeys received gastric preloads of glucose or fructose immediately before daily 4-h access, and the effects on cumulative food intake were monitored. Although the overall effects on 4-h intake did not differ, the dynamics of feeding through the 4-h period were differentially affected. Despite a more rapid delivery from the stomach to the intestine, fructose had less effect on food intake at early time points. Monkeys receiving fructose preloads had more rapid rates of consumption during the first 60 min of the test, suggesting the possibility that fructose is less satiating than glucose. However, this period of more rapid ingestion was followed by a period in which the ingestion rate was reduced relative to that following the glucose preloads. Overall, these data suggest differences in the satiating ability of fructose and glucose, differences that are related to temporal effect rather than to their overall ability to affect intake.

Differential time courses of the effects of fructose and glucose preloads on subsequent intake have also been found by other investigators in rodent studies. Warwick and Weingarten (16) examined the effects of glucose and fructose preloads on scheduled food intake when the preloads were administered at various intervals before the meal. In their hands, glucose and fructose resulted in equivalent suppression in intake at short intervals, but fructose had a greater suppressive effect than glucose as the intervals between the preload and meal were extended. They suggested that responses to preloads were differentially affected by test condition and the state of the animal and that there was no overall tendency for one saccharide to be more or less satiating than the other.

Satiety comparisons in human subjects

Comparisons of the ability of fructose and glucose to reduce test meal intake have also been studied in experiments with human subjects. Rodin and her colleagues (17–19) carried out a series of experiments comparing the satiating effects of fructose and glucose preloads. Fifty-gram preloads of fructose and glucose had a differential effect on buffet test meal intake when administered 2 h before lunch. In these experiments, fructose reduced intake by 500 kcal (2092 kJ) more than did glucose and by 200 kcal (837 kJ) relative to a water preload, suggesting an overall appetite suppressive effect of fructose.

Follow-up studies demonstrated similar greater suppressive effects of fructose preloads in lean and obese subjects, and the authors suggested a role for plasma insulin in the differential effects: glucose loads elevated plasma glucose and insulin levels, whereas the fructose preload did not (18). Importantly, the difference in subsequent intake was lost when the fructose and glucose preloads were given as a part of a mixed breakfast meal rather than as single-nutrient constituents (20).

Guss et al. (21) examined the effects of glucose and fructose solutions on food intake and gastric emptying in nonobese women. In this study, the effects of 2 different concentrations of the saccharides (1% and 10%; total doses 5 and 50 g of sugar) were examined at 2 different intervals between the preload and the test meal. As in the nonhuman primate studies, fructose emptied from the stomach more rapidly than glucose as determined by the disappearance of a radioactive tracer from the stomach. In these studies, the effects of the preloads on subsequent intake were relatively small. In all cases the satiating efficiency (ratio of the drop in test meal intake to energy content of the preload) was <1. At the 30-min delay, both 10% fructose and 10% glucose significantly reduced intake relative to the more dilute solutions. At the 135-min interval, the 10% fructose but not the 10% glucose, significantly reduced intake relative to a water control, again suggesting differential effects of the 2 saccharides on the timing of satiating influences.

The idea of differential timing affecting the abilities of glucose and fructose to influence subsequent intake was directly assessed by Rodin in an experiment in which the preloads were given 38 min rather than 2 h before the test meal (17). The findings from the earlier experiments with a 2-h delay were replicated: fructose produced significantly greater reductions in test meal intake than did glucose. Guss et al. (21) have suggested that a remaining difference between the paradigms may explain the different results across studies. In the Rodin experiments, subjects were food deprived from the evening before, whereas in the Guss experiments, subjects consumed a standard breakfast.

The addition of glucose or fructose to a cereal preload produced a trend for differential timing of effects (22). Equicaloric cereal preloads containing either fructose or glucose resulted in equivalent effects on intake in a test meal scheduled 30 min following the preload, but there was a trend for a greater effect of the fructose on test meal intake 2 h later. The fructose preload resulted in 70.2% compensation, whereas the compensation in response to the glucose preload was only 42.5% at that time point.

Satiety effect of saccharide combinations

Recent studies have concentrated on comparisons between HFCS and sucrose or varying glucose-to-fructose ratios. These studies have produced mixed results. Work from Andersen et al. has demonstrated that 300-kcal (1255 kJ, 75 g of sugar) oral preloads have different effects on subsequent food intake depending on the relative glucose:fructose concentrations (23,24). In these experiments, 1 kcal/mL (4.18 MJ/L) liquid preloads containing varying mixtures of glucose and fructose or HFCS were consumed 80 min before a test meal of pizza. Overall, the 80% glucose:20% fructose and sucrose preloads produced the greatest effects on subsequent intake. The 20% glucose:80% fructose and the 35% glucose:65% fructose preloads were less satiating, and the 50% glucose:50% fructose and HFCS preloads produced intermediate effects. Plasma glucose, insulin, and ghrelin were also measured in these experiments. Consistent with prior data, solutions with the higher glucose concentrations had the greatest effect on plasma glucose and insulin (25). In contrast to the results from the Teff experiment, all solutions lowered plasma ghrelin except for the 80% glucose:20% fructose solution, suggesting that reductions in plasma ghrelin were not mediating the greater inhibitory feeding actions of the solutions with the higher glucose concentrations.

Other investigators have not found differences between sucrose and HFCS on subsequent food intake. Soenen and Westerterp-Plantenga (26) report that although there were time course differences in appetite ratings in response to sucrose and HFCS preloads, there were no differences in test meal intake or in plasma profiles of glucose, ghrelin, insulin, or glucagon-like peptide-1. Similarly, Drewnowski et al. (27) report no differences between sucrose- and HFCS-sweetened soft drinks on hunger and satiety profiles or test meal intake.

The disparity among the experimental results suggests that aspects of method may have a significant impact on the degree to which different energy-containing sweeteners affect food intake. The differences in timing of the preload relative to the test meal have already been discussed. With a few exceptions, it appears to be the case that glucose and fructose affect food intake with different dynamics. The inhibitory actions of fructose appear to be more long lasting. Potential reasons for the more lasting effects of fructose could depend on differences in gastric emptying or the rapid rise in plasma glucose and insulin in response to glucose preloads playing a short-term inhibitory role. In addition, the prolonged effects with fructose could be secondary to metabolic factors or, as raised by some investigators, a negative influence on intake caused by gastrointestinal malaise from the tendency for concentrated fructose solutions to draw water into the GI tract (23,28,29). Fructose absorption from the GI tract is improved in the presence of glucose (28), providing a potential explanation for why fructose effects appear to disappear when the fructose:glucose mixtures are used or when fructose is given as part of a mixed meal.

Other factors that may have influenced results are the overall energy content of the preloads and the volumes in which they were administered. Energy loads in human experiments ranged from a low of 214 kcal (895 kJ) to a high of 500 kcal (2092 kJ). The greater the energy load, the more likely it seems that differences may be found, as smaller energy preloads have little effect on subsequent ingestion. Effects of saccharide concentration across the various sugars have not been systematically studied.

The original question was: is fructose or HFCS less satiating than glucose or sucrose? Any differences seem to arise from experiments in which fructose is given alone or in relative concentrations that are not normally found in sweetened beverages or other foods. Thus, the relevance of such results to the consequences of consuming HFCS is unclear. Another issue of importance to the impact of increased fructose or HFCS consumption is whether results from short-term studies demonstrating different satiating potentials predict long-term regulatory consequences. Alterations in intake at one meal can produce compensatory changes in subsequent food intake such that the long-term consequences are difficult to predict (30). Only studies of effects at individual meals over the longer term would provide such information. Given the overall lack of consistency across experimental designs (**Table 1**), the questionable relevance of data

TABLE 1 Summary of results from preload studies

Study (ref.)	Design	Mixed or Pure	Subjects	Result
Moran and McHugh (15)	Preload	Pure solutions	Nonhuman primates	Differential timing effects
Warwick and Weingarten (16)	Preload	Pure solutions	Rats	Differential timing effect
Rodin et al. (17–20)	Preload	Pure solutions	Humans	Fructose > glucose
Guss et al. (21)	Preload	Pure solutions	Humans	Differential timing effects
Stewart et al. (22)	Preload	Mixed in cereal	Humans	Differential timing effects
Anderson et al. (23–25)	Preload	Mixed fructose/ glucose concentrations	Humans	Glucose > fructose
Soenen and Westerterp-Plantenga (26)	Preload	Sucrose vs. HFCS	Humans	No differences
Monsivais et al. (27)	Preload	Sucrose vs. HFCS	Humans	No differences

using fructose at concentrations greater than normally consumed, and issues about generalization from individual assessments, the case for a lower satiating efficacy of fructose as a contributor to the current obesity epidemic is simply not compelling.

Other articles in this supplement include references (31–40).

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