High-fructose corn syrup, energy intake, and appetite regulation

Kathleen J Melanson, Theodore J Angelopoulos, Von Nguyen, Linda Zukley, Joshua Lowndes, and James M Rippe

ABSTRACT
High-fructose corn syrup (HFCS) has been implicated in excess weight gain through mechanisms seen in some acute feeding studies and by virtue of its abundance in the food supply during years of increasing obesity. Compared with pure glucose, fructose is thought to be associated with insufficient secretion of insulin and leptin and suppression of ghrelin. However, when HFCS is compared with sucrose, the more commonly consumed sweetener, such differences are not apparent, and appetite and energy intake do not differ in the short-term. Longer-term studies on connections between HFCS, potential mechanisms, and body weight have not been conducted. The main objective of this review was to examine collective data on associations between consumption of HFCS and energy balance, with particular focus on energy intake and its regulation. Am J Clin Nutr 2008;88(suppl):1738S–44S.

INTRODUCTION
The effect of caloric sweeteners on body weight remains unclear (1–5). Some studies show inverse relations between intake of sugars and body weight (6–8), whereas others show positive correlations (9–11). Different outcomes may arise from differences in study designs, subjects, liquid versus solid sources of sweeteners, types of sugars studied, and other factors (12). The World Health Organization (13), the US Dietary Guidelines (14), and the American Dietetic Association (15) all recommend moderate intakes of total added sugars. However, questions have arisen as to whether certain types of sugars should be limited more than others.

In particular, some experts have implicated high-fructose corn syrup (HFCS) as a possible contributing factor to energy overconsumption, weight gain, and, thus, the rise in the prevalence of obesity over the past decades (9, 16, 17). The purpose of this review was to examine current scientific evidence on HFCS and energy intake regulation in humans to discern whether there may be something inherent about this sweetener that would warrant moderation beyond that of other sweeteners to curb obesity. This review is not intended to refute recommendations by the World Health Organization, the US Dietary Guidelines, or the American Dietetic Association regarding moderation of total added sugars in the diet.

HFCS is produced from the isomerization of some of the glucose in corn syrup to fructose. HFCS-55, consisting of 55% fructose and 42% glucose, is used in many sweetened beverages, whereas HFCS-42 (42% fructose; 53% glucose) is used to sweeten other products (e.g., confections). Before the mid-1960s, sucrose (50% glucose and 50% fructose) was the predominant sweetener, but food industry developments in the following decades led to increased production of HFCS to replace much of the sucrose (12, 18, 19). HFCS is now estimated to be a major source of fructose in the US diet (3). Although fructose is present in fruit, honey, and some other carbohydrate sources, the quantities consumed from these sources are not as large as is found in foods and beverages sweetened by HFCS.

RELEVANT MECHANISMS OF SUGARS IN THE REGULATION OF APPETITE AND BODY WEIGHT
Postprandial glycemia influences appetite responses to nutrient ingestion either directly or indirectly (20). The glycemic index (GI) values reported for fructose, glucose, and sucrose are considerably different: 19 ± 2, 99 ± 3, and 68 ± 5, respectively (21). The GI of HFCS has not been published, but the GI of cola sweetened with HFCS is 63 ± 5 (21), a figure close to that of sucrose, which might be expected because of the similarities between the sweeteners. Past data have indicated that fructose is more satiating than glucose (22–26). This may have been due, in part, to its low GI; low-GI foods have been associated with greater satiety than high-GI foods (20). Low-GI foods may prolong satiety between meals, whereas high-GI foods may signal immediate satiety (1). Fructose is passively absorbed further down the small intestine than is glucose (27), which may allow prolonged exposure to gastrointestinal satiety signals than higher GI sugars (28). It also imparts high postprandial thermogenic responses and hepatic oxidation (29–33), which may be associated with satiety (34–36).

More recently, fructose’s unique metabolism, mainly through energy balance regulatory hormones, has been suggested as a possible mechanism to explain temporal trends in HFCS consumption and obesity (16). Fructose, unlike glucose, does not stimulate insulin secretion from pancreatic β-cells (25). Insulin

1 From Rippe Lifestyle Institute, Shrewsbury, MA, and Celebration Health, FL (TJA, VN, LZ, and JMR); the Center for Lifestyle Medicine, University of Central Florida, Orlando, FL (TJA, JL, and JMR); and the Department of Nutrition & Food Sciences, University of Rhode Island, Kingston, RI (KJM).
3 Supported by PepsiCo North America.
4 Address reprint requests to TJ Angelopoulos, Rippe Lifestyle Institute, 21 North Quinsigamond Avenue, Shrewsbury, MA 01545. E-mail: tangelop@mail.ucf.edu. doi: 10.3945/ajcn.2008.25825E.
may be a key element in the chain of events that leads to increased satiety with the ingestion of most carbohydrates (37). As a result of high blood glucose, increased circulating insulin can amplify satiety through actions within the central nervous system (37–41) or by stimulating leptin secretion (42). Whereas insulin is secreted in acute response to meals, leptin stimulation is delayed for several hours (43, 44).

Insulin-mediated glucose uptake and metabolism in adipose tissues play a key regulatory role in leptin concentrations (41, 45). Leptin, the diurnal patterns of which have been shown to be regulated by insulin (46), is recognized as a medium- to long-term regulator of energy balance through its effects on reducing energy intake and stimulating energy expenditure (47). Leptin acts via the hypothalamus, blocking the drive to eat caused by energy expenditure from basal metabolism (47) and potentially inhibiting the effects of the orexigenic hormone ghrelin (48–50).

It has been suggested that in the case of fructose, which does not stimulate insulin secretion, this chain of satiety-producing events does not occur (16).

Data suggest that the satiating effects of carbohydrates may be mediated through changes in blood glucose, insulin, and carbohydrate utilization (20, 51–57). Secretion of leptin and suppression of ghrelin offer additional potential mechanistic explanations for the satiating effects of carbohydrates (58–60). For example, consumption of high-carbohydrate, low-fat meals results in higher 24-h circulating leptin concentrations in normal-weight women compared with low-carbohydrate, high-fat meals (61). A 12-wk weight reduction study in obese persons showed that a high-carbohydrate (65%), low-fat (15%) diet did not result in the expected weight-loss-induced increases in ghrelin or appetite. This suggests that isocaloric substitution of dietary carbohydrate for fat may lower ghrelin and, thus, hunger (62). Such data may also indicate a role of carbohydrate in ghrelin suppression.

Studies show that both oral and intravenous glucose administration lower plasma ghrelin (63, 64). However, fructose consumption does not result in such increases in insulin and leptin secretion or in ghrelin suppression (65). Melanson et al (66) showed that although pure fructose does not increase plasma glucose or insulin, HFCS results in increased plasma glucose and insulin, most likely as a result of the glucose moiety. As discussed below, HFCS and sucrose consumption also produce similar leptin responses and ghrelin suppression (66), as has been seen in other studies in which mixed carbohydrates were fed (67).

Intravenous infusion of glucose does not decrease food intake or visual analogue scale appetite ratings, whereas glucose administered orally or by tube leads to decreased hunger (28). These findings suggest that gastrointestinal factors may mediate carbohydrate-induced satiety. Furthermore, glucose decreases ghrelin secretion and leads to increased glucagon-like peptide-1 (GLP-1) secretion, more so than fructose (68). GLP-1, which is inversely related to ghrelin (69), has an inhibitory effect on food intake through increased satiety (70, 71) and satiation (72).

FRUCTOSE, ENERGY INTAKE, AND ENERGY BALANCE REGULATION

Discrepancies exist between the effects of pure glucose and pure fructose on satiety and energy intake. Some studies show that a glucose preload decreases hunger and inhibits future food intake more than does fructose (73, 74). Others show that fructose inhibits food intake more than does glucose (22–26). Still yet other studies have found no significant differences between the sugars (33, 68, 75–77). A study in 14 healthy men compared 75-g loads of an 80% fructose, 20% glucose mixture (glucose was added to reduce fructose malabsorption), glucose, sucrose and polycose (a branched polymer of glucose often used as a bulking agent), and a sucralose (a calorie-free sweetener) control (78). No significant differences were found in subjective appetite ratings. Ad libitum energy intake at 1 h was suppressed by glucose relative to the sucralose control. Blood glucose correlated with satiety ratings in this study. Intake after the fructose-glucose mixture did not differ significantly from any of the other conditions, including the sucralose condition. Energy intake compensation at the meal 1 h after fructose-glucose consumption was only 11.5% compared with 36–48% from the other beverages. Although this was not statistically significant, it suggests incomplete energy intake compensation.

Inconsistencies in the scientific literature about fructose and energy intake may be related to subjects or the experimental design, eg, the time at which satiety was measured, the amount of carbohydrate given, whether the carbohydrate was as an isolated monosaccharide or was part of a meal, and the route of administration. Lack of difference in energy intake is particularly consistent when fructose is consumed in combination with other carbohydrates (33, 65, 78), which is the case for HFCS and sucrose (Table 1). This may be because other carbohydrates influence the speed or completeness of fructose absorption (27) or because energy balance regulatory signals are influenced by the combination of the carbohydrates (66).

Longer-term studies designed specifically to test the effects of pure fructose on energy intake and body weight are extremely limited. An early study in which 14 men with type 2 diabetes supplemented a high-carbohydrate diet with 40–50 g of fructose for 24 wk showed significant weight gain (85). Because total energy intake increased with the fructose supplementation, it is difficult to discern whether the weight gain was specifically related to the fructose. Furthermore, because this study was conducted in persons with diabetes, and there was no control group, applicability to the general population is questionable.

More recently, an outpatient trial was conducted in 7 healthy-weight young males who underwent a 2-wk isocaloric diet that was then supplemented with 1.5 g fructose per kg body wt daily for 4 wk. With each of 3 daily meals, volunteers consumed a 20%–fructose solution. This supplementation resulted in a prescribed excess daily energy intake of 18% from fructose (86). Although total energy intake was not measured, body weight did not change over the 4 wk, suggesting a neutral energy balance despite the added fructose. This could have been due to energy intake compensation or to increased energy expenditure (EE), although 5-h EE, as measured by ventilated hood indirect calorimetry, did not differ significantly throughout the intervention. However, limitations of this study included a lack of a control group, a small sample size, and a short duration.

In terms of fructose and hormonal regulators of energy, fructose tends to blunt insulin responses compared with glucose; these findings are very consistent (33, 65, 68, 77). Although lower GLP-1 responses to fructose have been reported (68), this is not always the case (26, 65, 77). A randomized controlled study in 12 healthy-weight women compared fructose and glucose served in beverages with meals as 30% of total energy intake during two 2-d laboratory visits. On the first day, when the test beverages were included, total energy intake was controlled and...
subjective appetite was rated. On the second day, the test beverages were not served, and food intake was ad libitum. Results showed that with this large fructose dose, circulating insulin and leptin were lower and postprandial ghrelin suppression was attenuated compared with glucose (65).

After breakfasts served with fructose beverages, ghrelin decreased by ≈50 pg/mL compared with ≈100 pg/mL after glucose. Although postprandial peaks in the active form of GLP-1 were similar after meals served with fructose-sweetened versus glucose-sweetened beverages, active GLP-1 remained higher after lunch and dinner during the fructose trials compared with the glucose trials. Despite hormonal differences, subjective appetite and ad libitum energy intake did not differ between fructose and glucose conditions in this study. However, in the 5 women with high scores for dietary restraint (measured by the Three-Factor Eating Questionnaire), higher hunger and fat intake were seen in the fructose condition. Although these women did not have different hormonal responses, potential susceptibility to fructose according to subject characteristics should be followed up in larger groups of persons. This study would need to be followed up over longer periods to determine whether these differences in hormonal, but not overall appetitive responses, persist with time.

### HIGH-FRUCTOSE CORN SYRUP, ENERGY INTAKE, AND BODY WEIGHT: SHORT-TERM STUDIES

The study noted above (65), compared beverages sweetened with pure fructose and glucose, but as described earlier, HFCS is more similar to sucrose than it is to fructose. Thus, although the above study provides evidence that excess fructose consumption can be detrimental to metabolism, it did not address the issue of whether the replacement of sucrose in the American diet with HFCS may be problematic. Therefore, Melanson et al (66) conducted a similar study design with two 2-d visits in 30 healthy-weight young women to compare hormonal and appetitive responses to beverages sweetened by HFCS or sucrose. The beverages were served with 3 meals during the day and provided 30% of energy intake. As with the previous study, energy intake was controlled on the first day when the test beverages were served and appetite was rated, and food intake was ad libitum on the second day of each visit.

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**Table 1**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Test sweetener</th>
<th>Comparative sweetener</th>
<th>Time frame</th>
<th>VAS</th>
<th>EI</th>
<th>Metabolic responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holt et al, 2000 (79)</td>
<td>11 Lean men, 14 Healthy-weight men</td>
<td>Sugared cola (80% Fructose, 20% glucose)</td>
<td>Sugar-free cola, sucrose, polycose</td>
<td>1 d, 60 min</td>
<td>NS</td>
<td>NS</td>
<td>Not measured</td>
</tr>
<tr>
<td>Anderson et al, 2002 (78)</td>
<td>32 Normal-weight adults</td>
<td>HFCS</td>
<td>Orange juice, 1%-fat milk</td>
<td>2 h, 15 min</td>
<td>NS</td>
<td>NS</td>
<td>Not measured</td>
</tr>
<tr>
<td>Teff et al, 2004 (65)</td>
<td>12 Normal-weight women, 75 min (EI @ 80 min)</td>
<td>Fructose beverages with meals</td>
<td>Glucose beverages with meals</td>
<td>2 d</td>
<td>NS</td>
<td>NS</td>
<td>Lower blood glucose, insulin, and leptin, and less ghrelin suppression after fructose</td>
</tr>
<tr>
<td>Wei and Melanson, 2006 (33)</td>
<td>12 Obese men</td>
<td>Fructose milk shakes</td>
<td>Glucose milk shakes</td>
<td>3 h</td>
<td>NS</td>
<td>NS</td>
<td>Lower blood glucose after fructose; higher EE and RQ</td>
</tr>
<tr>
<td>Perrigue et al, 2006 (81)</td>
<td>37 Young adults, 140 min</td>
<td>HFCS-55, HFCS-42</td>
<td>Sucrose, 1%-fat milk</td>
<td>2 d</td>
<td>NS</td>
<td>NS</td>
<td>No significant difference in blood glucose, insulin, leptin, or ghrelin suppression after fructose</td>
</tr>
<tr>
<td>Melanson et al, 2007 (66)</td>
<td>30 Normal-weight women</td>
<td>HFCS beverages with meals</td>
<td>Sucrose beverages with meals</td>
<td>2 d</td>
<td>NS</td>
<td>NS</td>
<td>No significant difference in blood glucose, insulin, leptin, or ghrelin suppression after fructose</td>
</tr>
<tr>
<td>Zackley et al, 2007 (82)</td>
<td>29 Obese women</td>
<td>HFCS beverages with meals</td>
<td>Sucrose beverages with meals</td>
<td>2 d</td>
<td>NS</td>
<td>NS</td>
<td>No significant difference in blood glucose, insulin, leptin, or ghrelin suppression after fructose</td>
</tr>
<tr>
<td>Akhavan and Anderson, 2007 (83)</td>
<td>31 Healthy men</td>
<td>HFCS</td>
<td>Sucrose, varied fructose: glucose</td>
<td>75 min (EI @ 80 min)</td>
<td>NS</td>
<td>NS</td>
<td>No significant difference in blood glucose, uric acid, insulin, or ghrelin suppression after fructose</td>
</tr>
<tr>
<td>Soenen and Westerterp-Plantenga, 2007 (84)</td>
<td>70 Healthy men and women</td>
<td>HFCS</td>
<td>Sucrose (and milk)</td>
<td>120–140 min</td>
<td>NS</td>
<td>NS</td>
<td>No significant difference in blood glucose, GLP-1, insulin, or ghrelin suppression after fructose</td>
</tr>
</tbody>
</table>
Blood glucose, insulin, leptin, and ghrelin did not differ significantly between the 2 sweeteners. HFCS- and sucrose-sweetened beverages produced similar ghrelin suppression after each meal of ≈200 pg/mL after both sucrose and HFCS trials. As was seen in the fructose-glucose study described above (65), no significant differences were seen between HFCS and sucrose in ad libitum energy or macronutrient intakes. Appetite ratings were also similar (the one exception was a slightly greater desire to eat after sucrose consumption). Lack of differences between HFCS and sucrose in energy intake and appetite ratings are not surprising because of similar responses in plasma glucose, insulin, leptin, and ghrelin (66), all of which have been postulated as biomarkers of energy intake regulation (36).

Zuckley et al (82) recently repeated the same study design to compare hormonal and appetitive responses to HFCS and sucrose in obese and overweight women. As with the previous study, preliminary findings showed that these responses to HFCS and sucrose do not differ significantly in persons carrying excess body weight. Similar blood glucose and hormones, as well as appetite ratings and ad libitum energy intake, were seen with consumption of HFCS and sucrose. Such results should be explored in other populations, eg, obese men and older, and younger persons. Additionally, total dietary HFCS should be differentiated from beverage sources of HFCS, and outcomes beyond these 3 hormones and appetite should be measured.

Two recent publications, each reporting 2 short-term experiments, have corroborated data showing a lack of differential hormonal and appetite responses to HFCS and sucrose in obese and overweight women. As with the previous study, preliminary findings showed that these responses to HFCS and sucrose do not differ significantly in persons carrying excess body weight. Similar blood glucose and hormones, as well as appetite ratings and ad libitum energy intake, were seen with consumption of HFCS and sucrose. Such results should be explored in other populations, eg, obese men and older, and younger persons. Additionally, total dietary HFCS should be differentiated from beverage sources of HFCS, and outcomes beyond these 3 hormones and appetite should be measured.

Eleven healthy young males participated in a randomized study to compare appetite after consumption of isovolumetric preloads of sugar-rich cola, sugar-free cola, and mineral water on separate days (79). The sweetener of the sugar-rich cola was not clarified in this study, but because it took place in Australia, it is possible that the sweetener was sucrose rather than HFCS. However, the results showed that satiety immediately after the preloads was more dependent on volume than on energy content or sweetness. Lunch intake after the preloads suggested insufficient energy intake compensation for the energy in the sugar-rich cola, although this was not statistically significant. Total energy intake over the full day did not differ among the preloads, which suggests that, with time, energy intake evened out.

HIGH-FRUCTOSE CORN SYRUP, ENERGY INTAKE, AND BODY WEIGHT: LONGER-TERM STUDIES

On the basis of studies focused specifically on fluids, high consumption of sugar-sweetened beverages, in general, may be associated with excess body weight (88). Drinking soda sweetened with HFCS has been associated with increased ad libitum energy intake and body weight compared with the same amount of soda sweetened with the noncaloric sweetener aspartame (10). Studies have also shown increases in energy intake and body weight over 10 wk when subjects incorporated sucrose, as compared with nonnutritive sweeteners, into their diets (11). In children, Ludwig et al (9) found that the overall quantity of sugar-sweetened beverages ingested was predictive of initial and follow-up body mass index. Prospective epidemiologic data in adults have associated increases in sugar-sweetened beverages with weight gain (89). Together, these studies imply that increased energy intake by sweetened beverages is not compensated for in subsequent intake, which may lead to overconsumption. However, these studies do not determine whether HFCS may be more of a factor in weight gain than other caloric sweeteners, nor do they specifically address the implications of total dietary HFCS from all sources on energy intake and body weight. Overall, longer-term studies have mainly compared HFCS with noncaloric sweeteners; prospective studies comparing HFCS with other caloric sweeteners are needed.

Most studies of HFCS, energy intake, and body weight have specifically focused on beverage consumption rather than total dietary HFCS. Some research has shown that energy intake compensation is less precise when caloric beverages are consumed versus solid food (1, 90, 91). For example, a study that compared weight gain after 4 wk of consumption of a sweetened soda versus the same carbohydrate load in the form of jelly beans found more weight gain after the beverage (91). However, a recent review (92) provided evidence that questions the plausibly of claims that liquid energy sources, in particular, may increase weight gain. For example, because liquid meal replacements can promote weight loss when used appropriately, appropriate use of caloric beverages (ie, replacing calories versus adding calories) may be more of a concern.

CONCLUSIONS

Collectively, scientific evidence suggests that high consumption of pure fructose may be problematic to energy intake regulation. However, HFCS is more similar to sucrose than it is to fructose in terms of its content, appetitive responses, and aspects
of its metabolism that have been measured to date. Thus, existing theoretical and empirical evidence suggests that fructose-induced problems are not more related to HFCS than sucrose consumption.

The potential hormonal and physiologic responses to HFCS have not yet been connected to longer-term appetite or metabolism, and, thus, to body weight regulation. Longer-term studies have mainly compared HFCS beverages with noncaloric beverages, and, therefore, are relevant more to the issue of increased caloric intake from sweeteners than to the effects of specific sweeteners relative to each other. Research is needed in this area, especially considering the significant use of sweeteners in the United States and other developed countries (3, 12, 18, 19). It is important to determine whether any sweetener needs to be limited more than others. Mechanistic approaches, as well as outcome-oriented approaches focused on energy intake and body weight, should be included in this research agenda.

As shown in Table 1, insufficient scientific evidence currently exists to indicate that HFCS disrupts short-term energy balance signals or increases short-term appetite and energy intake more than do other tested sweeteners. The metabolic and endocrine responses that have been measured to date are similar between HFCS and sucrose, the sweetener HFCS has largely replaced in the US diet. Additional work should be performed to see whether these results extend to other metabolic and endocrine responses. In addition, longer-term investigations of the effect of HFCS on energy balance regulatory systems are needed to further understand the role of this sweetener in body weight regulation. (Other articles in this supplement to the Journal include references 93–96.)

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