No differences in satiety or energy intake after high-fructose corn syrup, sucrose, or milk preloads

Stijn Soenen and Margriet S Westerterp-Plantenga

ABSTRACT

Background: It is unclear whether energy-containing drinks, especially those sweetened with high-fructose corn syrup (HFCS), promote positive energy balance and thereby play a role in the development of obesity.

Objective: The objective was to examine the satiating effects of HFCS and sucrose in comparison with milk and a diet drink.

Design: The effects of 4800-mL drinks containing no energy or 1.5 MJ from sucrose, HFCS, or milk on satiety were assessed, first in 15 men and 15 women with a mean (±SD) body mass index (BMI; in kg/m²) of 22.1 ± 1.9 according to visual analogue scales (VAS) and blood variables and second in 20 men and 20 women (BMI: 22.4 ± 2.1) according to ingestion of a standardized ad libitum meal (granola cereal + yogurt, 10.1 kJ/g).

Results: Fifty minutes after consumption of the 1.5-MJ preload drinks containing sucrose, HFCS, or milk, 170%-mm VAS changes in satiety were observed. Glucagon-like peptide 1 (GLP-1) (P < 0.001) and ghrelin (P < 0.05) concentrations changed accordingly. Compensatory energy intake did not differ significantly between the 3 preloads and ranged from 30% to 45%. Energy intake compensations were related to satiety (r = 0.35, P < 0.05). No differences were observed between the effects of the sucrose- and HFCS-containing drinks on changes in VAS and on insulin, glucose, GLP-1, and ghrelin concentrations. Changes in appetite VAS ratings were a function of changes in GLP-1, ghrelin, insulin, and glucose concentrations.

Conclusion: Energy balance consequences of HFCS-sweetened soft drinks are not different from those of other isoenergetic drinks, eg, a sucrose-drink or milk.

INTRODUCTION

Trends in overweight are consistent with increased energy intake over recent decades (1). The upward shift in energy intake may partly consist of the consumption of soft drinks (2–5). Increased soft drink consumption has coincided with the increase in prevalence of overweight and obesity (6, 7) over the past 3 decades in the United States (8–10). In the 1970s, the food industry in the United States introduced high-fructose corn syrup (HFCS) sweetener as a substitute for sucrose (11). It has been suggested that the obesity epidemic may have been aggravated by the increase in HFCS consumption (12).

Drinking HFCS-sweetened soda was reported to increase energy intake and body weight (13). However, several studies have reported that fructose, when consumed alone, reduced subsequent energy intake equally in some (14–16) or significantly more in other studies (17–19) compared with a monosaccharide glucose preload. Yet, it should be noted that the principal sweetener in soft drinks in the United States, HFCS, is not pure fructose but a mixture of fructose (55%) and glucose (45%). Factors that may account for the different effects of fructose alone or a mix of fructose and glucose are its gastrointestinal effects and absorption characteristics (20, 21).

In addition to the composition of ingested carbohydrates, the physical state of intake may be important in influencing subsequent energy intake compensation. Compensatory dietary responses to energy-containing beverages have been found to be less precise than those to isoenergetic solid loads (22, 23). Thus, fluid carbohydrates such as soft drinks could increase the risk of excess total energy intake. An effect of soft drink consumption, eg, of sucrose compared with artificial sweeteners, on weight gain and obesity has been found in children (24–26), adolescents (27), and adults (28, 29). On the basis of these studies, it is suggested that carbohydrates in liquid form promote a positive energy balance and therefore contribute to the development of obesity.

Compensation for energy intake from drinks by a change in energy intake at the subsequent meal depends on the moment in

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time of preload ingestion. Time delay between preload and test meal interferes with the outcome of preload studies (30–32).

The objective of the present study was to examine whether there is a difference in response between a HFCS-sweetened and a sucrose-sweetened isoenergetic, isovolumetric orange-flavored preload and a no-energy control. A milk preload was used to compare the soft drinks with another type of liquid preload. In the first study, the responses were measured as the appetitive profile using visual analogue scales (VAS) and as a possible change in the satiety hormones: glucagon-like peptide 1 (GLP-1), insulin, ghrelin, and glucose. Moreover, the latest time point after ingestion when relevant differences in satiety scores or satiety hormone concentrations were still present was determined as the moment in time for the subsequent test meal. In the second study, possible compensation in energy intake during an ad libitum subsequent meal was determined. The studies were conducted in Europe, so subjects had a negligible history of consuming HFCS-containing products.

SUBJECTS AND METHODS

Subjects

Subjects were recruited by means of an advertisement in local newspapers and on notice boards at Maastricht University. Subjects who were willing to participate in the study were subsequently screened by means of a detailed medical history and a physical examination. All subjects were in good health, were normotensive, were nonsmokers, were nonrestrained eaters, were regular breakfast consumers, were at most moderate alcohol users, had a stable body weight (a change of less than 2 kg over at least the past 2 mo) and did not use prescription medication. Excluded from the study were athletes, defined as those who trained ≥10 h/week. Thirty subjects (equal numbers of men and women) participated in the first study, 40 in the second study. Subject characteristics are given in Table 1. Subjects were requested to maintain their customary level of physical activity and normal dietary habits and not to gain or lose weight for the duration of the study. All subjects gave written informed consent, and the experimental protocol was approved by the local Medical Ethics Committee of the University of Maastricht, Maastricht, Netherlands.

Study design

A within-subjects design was used, with each subject returning for 4 separate test days ≥1 wk apart. The preloads were offered blindly and in randomized order to avoid the order-of-treatment effect. To analyze possible differences in the appetitive profile, VAS ratings and blood samples for the measurement of GLP-1, ghrelin, insulin, and glucose concentrations were collected before and after preload consumption in the first study. The last moment in time at which relevant differences in satiety were present was determined to decide on the timing of the test meal in the second study. The second study consisted of the same preload consumptions as in the first study, with VAS ratings of the appetitive profile before and after the preload and a test meal at the relevant moment in time, as defined by the first study.

TABLE 1

Subject characteristics


<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th></th>
<th>Study 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>(n = 15)</td>
<td>(n = 15)</td>
<td>(n = 20)</td>
<td>(n = 20)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>21.1 ± 1.5 (7)</td>
<td>21.5 ± 1.8 (8)</td>
<td>21.2 ± 2.2 (10)</td>
<td>22.3 ± 4.5 (20)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.7 ± 7.3 (12)</td>
<td>75.8 ± 9.5 (13)</td>
<td>65.0 ± 7.7 (12)</td>
<td>76.2 ± 6.0 (8)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.4 ± 5.6 (3)</td>
<td>183.3 ± 8.0 (4)</td>
<td>171.6 ± 4.6 (3)</td>
<td>183.0 ± 7.2 (4)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.6 ± 1.9 (9)</td>
<td>22.5 ± 1.8 (8)</td>
<td>22.0 ± 2.1 (10)</td>
<td>22.8 ± 2.0 (9)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>123 ± 14 (11)</td>
<td>131 ± 11 (8)</td>
<td>123 ± 11 (9)</td>
<td>130 ± 10 (8)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>73 ± 9 (12)</td>
<td>78 ± 10 (13)</td>
<td>74 ± 8 (11)</td>
<td>77 ± 7 (9)</td>
</tr>
<tr>
<td>F1, cognitive restraint</td>
<td>5.1 ± 2.9 (57)</td>
<td>3.3 ± 2.2 (67)</td>
<td>5.5 ± 3.0 (55)</td>
<td>3.3 ± 2.1 (64)</td>
</tr>
<tr>
<td>F2, disinhibition</td>
<td>4.9 ± 1.9 (39)</td>
<td>3.1 ± 1.1 (35)</td>
<td>5.0 ± 2.0 (40)</td>
<td>4.0 ± 2.0 (50)</td>
</tr>
<tr>
<td>F3, hunger</td>
<td>4.5 ± 2.9 (64)</td>
<td>3.3 ± 1.8 (55)</td>
<td>4.4 ± 2.9 (66)</td>
<td>5.1 ± 3.4 (67)</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>12.9 ± 4.1 (32)</td>
<td>12.7 ± 3.8 (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.9 ± 0.3 (6)</td>
<td>5.3 ± 0.4 (8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Represents differences between men and women; all subjects participated in either study 1 or 2 (n = 57; 13 subjects participated in both studies).
2 ± SD; CV in parentheses (all such values).
3 A measure of cognitive restraint with the Three-Factor Eating Questionnaire (TFEQ); minimum score = 0, maximum score = 21; cutoff point for the Dutch population was 9. Values >9 indicate cognitive restraint eating.
4 A measure of disinhibition or emotional eating with the TFEQ; minimum score = 0, maximum score = 14.
5 A general feeling of hunger with the TFEQ; minimum score = 0, maximum score = 10.
6 Average plasma concentrations over the 4 test days after the subjects fasted overnight.

Anthropometric measures

Body weight was determined during screening and on each test day with a digital balance (weighing accuracy of 0.02 kg; Chyo-MW-150K; Chyo, Japan) while the subjects were wearing undergarments and in a fasted state and after they had emptied their bladders. Height was measured to the nearest 0.1 cm with a wall-mounted stadiometer (model 220; Seca, Hamburg, Germany). Body mass index (BMI) was calculated by dividing body weight (kg) by height squared (m²). Systolic and diastolic blood pressures were recorded during screening with an automatic blood pressure monitor (OSZ 5 easy; Spreidel & Keller GmBH and Co, KG, Jungingen, Germany).
Preloads

The 4 beverages were as follows: a beverage containing sucrose, one containing HFCS, one containing milk, and a diet drink. The energy content and macronutrient composition of the 4 beverages are specified in Table 2. All 4 drinks were isovolumetric and had a volume of 800 mL. The energy drinks were isonitrogenous and provided 1.5 MJ. The diet drink had an energy content of 0.2 MJ. The drinks containing sucrose or HFCS and the diet drink were orange-flavored custom-made beverages and were equally sweet. The sucrose-containing preload had the same consistency as a commercially available sucrose-sweetened drink containing 450 g sucrose and 236 g glucose syrup (91% glucose and 9% fructose). The HFCS-containing preload had the consistency of a commercially available HFCS-sweetened drink containing 55% fructose and 45% glucose syrup (91% glucose and 9% fructose). The diet preload consisted of the sweeteners aspartame, acesulfame-K, and sodium cyclamate. Additionally, all 3 preloads contained water, citric acid, orange flavoring, coloring E160, preservative E202, and antioxidant E300. Drinks were prepared by diluting 133 mL syrup with 667 mL water. All 4 beverages were served chilled at 8 °C.

Test meal

The test meal that was served in the second study consisted of a granola cereal and yogurt; values are expressed per 100 g.

Attitude toward eating

The subjects’ attitude toward eating was determined during screening with the use of a validated Dutch translation of the Three-Factor Eating Questionnaire (TFEQ) (33, 34). The scores on cognitive restrained and unrestrained eating behavior (F1), emotional eating and disinhibition of control (F2), and subjective feeling of hunger (F3) are shown in Table 1.

Appetite profile

The subjects’ feelings of hunger, satiety, fullness, prospective food and drink consumption, and desire to eat and drink were scored on anchored 100-mm VAS at 6 different 0.5-h time points in study 1 and at 7 time points in study 2. The scale ranged from “not at all” on the left to “extremely” on the right. Subjects were instructed to mark, with a single vertical line, a point where the length of the line matched their subjective sensation. All VASs were collected immediately after they had been completed.

Taste perception and hedonics

Subjects rated their taste perception and hedonics for the 4 test drinks on anchored 100-mm VAS during screening and at the first and last sip of the beverage consumed during each test day (Table 3). The following scales had to be completed: how sweet, sour, bitter, or salty the drink was; how rich, creamy, and fresh the flavor of the drink was; and how pleasant the drink was in the mouth.

Blood samples

Venous blood samples were taken at 5 time points: one fasting sample at baseline before and 4 samples 15, 30, 60, and 120 min after preload consumption. After each blood collection, the intravenous cannula was rinsed with 0.9% sterile sodium chloride solution containing 1% heparin. Blood samples were taken to determine concentrations of plasma GLP-1, ghrelin, insulin, and glucose.

TABLE 2

<table>
<thead>
<tr>
<th>Preload</th>
<th>Sucrose-containing preload</th>
<th>HFCS-containing preload</th>
<th>Milk preload</th>
<th>Diet preload</th>
<th>Meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate [kJ (%)]</td>
<td>1500</td>
<td>1500</td>
<td>632</td>
<td>0</td>
<td>554 (55)</td>
</tr>
<tr>
<td>Glucose [kJ (%)]</td>
<td>960 (64)</td>
<td>615 (41)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fructose [kJ (%)]</td>
<td>540 (36)</td>
<td>885 (59)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Lactose [kJ (%)]</td>
<td>0</td>
<td>0</td>
<td>632 (42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein [kJ (%)]</td>
<td>0</td>
<td>0</td>
<td>442 (30)</td>
<td>2</td>
<td>80 (8)</td>
</tr>
<tr>
<td>Fat [kJ (%)]</td>
<td>0</td>
<td>0</td>
<td>426 (28)</td>
<td>0</td>
<td>378 (37)</td>
</tr>
<tr>
<td>Energy (kJ)</td>
<td>1500</td>
<td>1500</td>
<td>1500</td>
<td>2</td>
<td>1012</td>
</tr>
<tr>
<td>Volume (mL)</td>
<td>800</td>
<td>800</td>
<td>800</td>
<td>800</td>
<td>100</td>
</tr>
<tr>
<td>Energy density (kJ/g)</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>0</td>
<td>10.1</td>
</tr>
</tbody>
</table>

1 HFCS, high-fructose corn syrup. Values reported as percentages represent the percentage of energy of the energy-containing macronutrients.
2 66% sucrose and 34% glucose syrup (91% glucose and 9% fructose).
3 55% fructose and 45% glucose syrup (91% glucose and 9% fructose).
4 The test meal consisted of a granola cereal and yogurt; values are expressed per 100 g.
blood samples were collected in tubes containing EDTA to prevent clotting. Blood samples for GLP-1 analysis were collected in ice-chilled syringes containing 20 μL dipeptidyl peptidase-IV (DPP-IV) inhibitor (Linco Research Inc, St Charles, MO) to prevent degradation. Plasma was obtained by centrifugation (1500 × g, 10 min, 4 °C), frozen in liquid nitrogen, and stored at −80 °C until analyzed. Plasma ghrelin samples were mixed with hydrochloric acid, methanol, and phenylmethanesulfonyl fluoride (Sigma-Aldrich, Zwijndrecht, Netherlands). Plasma concentrations of active ghrelin were measured by radioimmunoassay (Linco Research Inc) and those of active GLP-1 by enzyme-linked immunosorbent assay (ELISA) (35K, Linco Research Inc). Insulin samples were analyzed with a radioimmunoassay kit (Linco Research Inc), and glucose samples were measured by using a hexokinase method (ABX Diagnostics, Montpellier, France).

Test day procedure

After fasting overnight, the subjects arrived at the laboratory at 0815. The subjects were asked to consume their habitual evening meals, to refrain from alcohol or strenuous exercise, and to refrain from eating and drinking after 2300 on the day before each test. Body weight was measured, and an intravenous Venflon cannula (Baxter BV, Utrecht, Netherlands) was inserted in the antecubital vein to enable blood sampling (study 1). The subjects remained seated in comfortable chairs separated by large room dividers with minimal disturbance from the investigators throughout the experimental session. During each test day, the subjects were isolated from time cues to eliminate as much as possible habitual (time-determined) meal patterns; no watches, clocks, or radios were present in the test room, and the research refrained from making time-related statements. The subjects were allowed to stretch their legs, use the bathroom, read, listen to music, or watch movies, but not while drinking the preload or eating the meal (study 2). At 0900, after collection of the baseline appetite profile and blood sample, the subjects received 1 of the 4 liquid preloads. The preloads had to be consumed entirely within 10 min. The preloads were accompanied by a VAS of taste perception and hedonics at the first and last sips of the beverage. Blood sampling in study 1 was repeated 15, 30, 60, and 120 min after preload consumption and the appetite profile 20, 50, 80, 110, and 140 (last time point only in study 2) min after preload consumption. The catheter was removed after the last blood sample had been taken. The meal in study 2 was served 50 min after preload consumption based on the VAS ratings or differences in increases of satiety hormones in the first study.

Statistical analysis

Data are presented as means ± SDs or SEs. VAS ratings were measured in millimeters from the left end of the scale. The changes in concentrations of the hormones from baseline and changes from baseline in VAS ratings of the appetite profile were compared by analysis of variance (ANOVA), repeated-measures ANOVA (analysis of change score), and analysis of covariance (ANCOVA) with the baseline values as covariates. Because the experiment was fully randomized with a washout period between preloads containing sucrose and HFCS was statistically significant. This moment appeared to be 50 min after the preload consumption. This moment in time was underscored by the following. Although preloads containing sucrose or HFCS did not differ in satiety and hunger ratings in the total group (Figure 1), the reduction in hunger relative to baseline after a preload differed significantly between men and women (P < 0.05). Men had a significantly greater reduction in hunger after the preload containing HFCS than after the preload containing sucrose at the 50-min time point (−8 ± 14 compared with −17 ± 15 mm VAS, respectively; P < 0.05), whereas women showed the opposite. Women had a significantly greater reduction in hunger ratings at the 50-, 80-, and 110-min time points, with the maximal difference occurring 50 min (−24 ± 18 compared with −7 ± 19 mm VAS; P < 0.05) after consumption of...
The preload containing sucrose compared with the preload containing HFCS. Thus, the adequate moment in time to serve the test meal in study 2 was 50 min, as underscored by the significant treatment-by-sex interaction at 50 min (P < 0.05). Differences in VAS ratings between treatments differed by sex. This moment in time was not supported by differences in concentrations in GLP-1, ghrelin, insulin, or glucose relative to baseline, as illustrated in Figure 2. However, changes in VAS ratings relative to baseline were a function of changes in concentrations of the hormones GLP-1, ghrelin, and insulin relative to baseline values (Table 4). Stepwise multiple linear regression analysis of VAS appetite ratings showed that change in GLP-1 (r = −0.242, P = 0.014) and insulin (r = −0.239, P = 0.029) independently predicted changes in satiety. Moreover, glucose and insulin concentrations were related after preload consumption, as expected, and GLP-1 and ghrelin concentrations were related to insulin concentrations. GLP-1 and ghrelin concentrations were not related to each other (Table 4). Furthermore, the determination of the adequate moment in time to serve the meal in study 2 was underscored by the decrease in glucose concentrations (Figure 2).

**Energy-containing preloads compared with the diet preload**

Meal size and energy intake were significantly lower after consumption of preloads containing sucrose or HFCS or the milk preload than after the diet preload (Table 5). This finding was supported by the significantly higher GLP-1 and insulin concentrations (Figure 2; P < 0.001) and the significantly lower ghrelin concentrations (Figure 2; P < 0.05) and hunger (Figure 1; P < 0.05) after the energy-containing preloads than after the diet preload. Thus, less energy was consumed after consumption of an energy drink than after a drink designed to not deliver energy. Total energy intake (preload + meal) with the energy-containing preloads was significantly higher than total energy intake with the diet preload (Table 5). Therefore, during the meal, energy intake was only partly compensated for. Compensation for energy intake from the preloads containing sucrose, HFCS, or milk did not differ significantly (Table 5) and ranged from 30% to 45%. Energy consumed after preloads, compensation, and overconsumption differed significantly between men and women (P < 0.01). This sex difference was supported by the significant time-by-sex interactions for glucose and GLP-1 concentrations (P < 0.01). Compared with women, men had lower GLP-1 concentrations at baseline (P < 0.05) and a smaller change in GLP-1 concentration from baseline after preload consumption (P < 0.01). Appetite ratings after drink consumption decreased significantly more in women than in men (P < 0.05). Decreases in hunger scores were not different between the 4 conditions after ingestion of the meals.

Compensation after the energy-containing preloads was a function of the magnitude of change in satiety scores from baseline (r = 0.350, P = 0.023). In the men, overconsumption after the preload containing sucrose (r = −0.934, P = 0.020) or milk (r = −0.999, P < 0.001) was a function of the magnitude of change in satiety scores from baseline; after the preload containing HFCS, this relation was not observed. Hunger ratings were significantly more suppressed at each time point after the milk preload than after the diet preload (P < 0.05). The change from baseline in GLP-1 concentrations was significantly larger (P < 0.05) 30 min after the milk preload (3.6 ± 3.4 pmol/L) than after the preloads containing sucrose (2.1 ± 2.3 pmol/L) or HFCS (2.1 ± 3.3 pmol/L). In men, this difference was observed at each time point (P < 0.05).

Furthermore, compensation and satiety (r = 0.412, P < 0.05) were positively related to change in pleasantness of taste after the preload containing sucrose (the greater the suppression in pleasantness of taste, the larger the satiety and compensation), as shown in Figure 3. Accordingly, plasma glucose concentrations were significantly higher over time after the drinks containing sucrose or HFCS than after the milk or diet preloads (P < 0.001). Moreover, plasma glucose concentrations were linearly related to the content of glucose of the preloads (r = 0.581, P < 0.001).

**DISCUSSION**

Do the satiation effects of isocaloric isovolumetric sucrose- or HFCS-containing preloads differ from those of milk as measured on the basis of VAS (in mm) or GLP-1 or ghrelin responses? The increase in satiety from baseline as AUC did not differ significantly between the sucrose, HFCS, or milk preload. Furthermore, satiety was expressed as compensation or overconsumption during the next meal; no significant differences between the different preloads were observed. From these observations we concluded that there are no differences in the satiety or energy balance effects of isovolumetric sucrose- or HFCS-containing preloads or milk.

Subsequently the mechanisms underscoring the increases in satiety were revealed. Although no differences in satiety were observed, the mechanisms underlying satiety due to sucrose- or HFCS-containing drinks or milk were different and were related to evoking different increases in satiety hormone concentrations.

No significant differences in energy intakes or in total energy consumed were observed 50 min after consumption of the 1.5-MJ (800 mL) drinks containing sucrose or HFCS. Also, energy intake after the isonenergetic isovolumetric milk preload did not differ from that after the sucrose or HFCS drinks. Similarly
to our observations, a previous study found no significant differences between the effects of cola or chocolate milk consumption (0.9 MJ, 500 mL) with ad libitum intake 30 min later, despite significantly greater satiety 30 min after the chocolate milk (36) or in subsequent meal compensation 135 min after preloads (1.036 MJ, 590 mL) of cola, orange juice, and milk relative to sparkling water (37). As usual, energy intake including the energy-containing preloads was higher than total energy intake including the diet preload, despite the smaller consumption during the subsequent meal. Thus, subsequent energy intake only partly compensated for the energy delivered by the preloads; ie, for 45% with the sucrose-containing preload, for 42% with the HFCS-containing preload, and for 30% with the milk preload, all compared with energy intake after the diet preload. So, consumption of an energy-containing preload followed by a meal at 50 min led to overconsumption compared with a diet preload and subsequent meal. Previously, consumption of a 1.26-MJ high-fructose-glucose mixture (80–20%) was compensated with 12% of the meal consumed 60 min after preload, which was not different from that of an equisweet sucrose drink with 42% compensation (38). In conclusion, on the basis of these studies, subsequent energy intake did not differ significantly 30–135 min after a 0.9–1.5-MJ preload containing sucrose or HFCS or a milk preload. Therefore, in general, the effects of energy balance are positive, yet not different between different energy containing drinks.

A sex effect was observed in VAS ratings, energy intake, and energy compensation and overconsumption. A possible explanation for these sex differences was the different responses in GLP-1 and glucose when preloads of the same size were offered. Previous studies support these higher concentrations in women.
Milk

Energy intake from the meal and from the meal

TABLE 5

<table>
<thead>
<tr>
<th>Preload</th>
<th>GLP-1</th>
<th></th>
<th>Ghrelin</th>
<th></th>
<th>Insulin</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>All²</td>
<td>0.253</td>
<td>&lt;0.01</td>
<td>—</td>
<td>—</td>
<td>0.241</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Satiety</td>
<td>0.382</td>
<td>&lt;0.05</td>
<td>—</td>
<td>—</td>
<td>0.370</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Sucrose¹</td>
<td>0.429</td>
<td>&lt;0.05</td>
<td>-0.407</td>
<td>&lt;0.05</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HFCS¹</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Milk²</td>
<td>—</td>
<td>—</td>
<td>0.423</td>
<td>&lt;0.05</td>
<td>—</td>
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<tr>
<td>Diet¹</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<td>Ghrelin</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.36</td>
<td>&lt;0.001</td>
<td>-0.19</td>
<td>&lt;0.05</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Glucose</td>
<td>—</td>
<td>—</td>
<td>-0.22</td>
<td>&lt;0.05</td>
<td>0.49</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

¹ HFCS, high-fructose corn syrup.
² n for all preloads was 120.
³ n for each preload was 30.

(39, 40). Obviously, the preloads that were consumed by the men represented a smaller part of energy requirement than the preloads consumed by the women. Moreover, sex differences in water turnover may play a role (41) because it has been suggested that the increased energy intake after drinks may have been derived from physiologic mechanisms giving priority to quenching thirst (42). The preloads suppressed thirst equally, significantly more in women than in men however.

Are different mechanisms responsible for the satiety achieved after sucrose- or HFCS-containing preloads or a milk preload? Consumption of the preloads containing sucrose or HFCS caused similar changes in plasma concentrations of the hormones GLP-1, ghrelin, and insulin and of glucose. Also, leptin concentrations did not differ after consumption of either sucrose or HFCS (43). The increase in satiety was underscored by the increase in GLP-1 with the sucrose- or HFCS-containing preloads, but not with the milk preload. Because satiety did not differ between energy-containing preloads, it may well be that other satiety hormones such as peptide YY3-36 and cholecystokinin, which were not measured, supported the milk-induced satiety. Satiety after the sucrose-containing preload was also underscored by the increase in insulin and satiety after the HFCS-containing preload by the decrease in ghrelin. The changes in VAS ratings of the appetite profile were supported by the changes in the concentrations of the hormones GLP-1, ghrelin, and insulin and glucose. Stepwise regression showed that satiety was primarily related to increases in GLP-1 concentrations and secondarily to insulin concentrations. Thus, sucrose and HFCS likely trigger GLP-1 release, which may have triggered insulin release and a related increase in satiety.

TABLE 5

<table>
<thead>
<tr>
<th>Meal size</th>
<th>Total energy intake (preload + meal)</th>
<th>Compensation</th>
<th>Overconsumption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>kJ</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Sucrose-containing preload</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1742 ± 730⁶</td>
<td>3215 ± 730⁶</td>
<td>37 ± 37⁶</td>
</tr>
<tr>
<td>Men</td>
<td>2372 ± 794</td>
<td>3845 ± 794</td>
<td>53 ± 47</td>
</tr>
<tr>
<td>HFCS-containing preload</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1873 ± 868⁶</td>
<td>3347 ± 868⁶</td>
<td>28 ± 42⁶</td>
</tr>
<tr>
<td>Men</td>
<td>2335 ± 786</td>
<td>3808 ± 786</td>
<td>55 ± 54</td>
</tr>
<tr>
<td>Milk preload</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1945 ± 756⁶</td>
<td>3441 ± 756⁶</td>
<td>24 ± 42⁶</td>
</tr>
<tr>
<td>Men</td>
<td>2626 ± 880</td>
<td>4122 ± 880</td>
<td>36 ± 55</td>
</tr>
<tr>
<td>Diet preload</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>2290 ± 773⁶</td>
<td>2292 ± 773⁶</td>
<td>—</td>
</tr>
<tr>
<td>Men</td>
<td>3148 ± 984</td>
<td>3150 ± 984</td>
<td>—</td>
</tr>
</tbody>
</table>

⁷ All values are x ± SD; n = 40. HFCS, high-fructose corn syrup. The treatment-by-sex interaction was not significant (multivariate ANOVA).
²,³ Significant difference between the diet preload and the other 3 preloads (ANOVA): ² P < 0.05, ³ P < 0.001.
⁴ Compensation = energy intake from the diet — energy intake after any preload as a percentage of the preload.
⁵ Overconsumption = total energy intake from the diet — total energy intake after any preload as a percentage of the preload.
⁶ Significantly different from men, P < 0.05 (ANOVA).
On the other hand, satiety and compensation after the preload containing sucrose correlated with change in pleasantness of taste. Individuals who did not eat solely based on hunger, taste is another reason for eating a specific food, and a decrease in pleasantness of taste is often given as a reason for terminating or reducing food intake. Therefore, the less sweet, refreshing, and pleasant milk preload may have contributed to incomplete compensation at the subsequent meal. Furthermore, high glycemic carbohydrates have been shown to be associated with a reduced appetite and food intake in the very short term (eg, 1 h), whereas lower glycemic carbohydrates showed a more delayed effect on the perception of satiety (eg, 2–3 h) (44, 45). We found a linear relation between the glucose content of the preloads and AUC plasma glucose concentrations. The glycemic indexes (GIs) of the monosaccharides glucose, fructose, and lactose are 99, 19, and 46, respectively (46). The GI of sucrose is 68 (46) and of HFCS is 73 (47) and 68 (48). The glucose concentrations peaked at 30 min and dropped below baseline at 60 min after the carbohydrate preloads and remained low until the end of the experiment. The same pattern of an initial steep increase in plasma glucose and insulin concentrations followed by a rebound effect, which stimulates hunger and food intake, has been found in several studies (16, 17, 32, 49–56). Thus, a rapid rise in blood glucose and a large insulin response stimulates peripheral glucose uptake to such an extent that the blood glucose concentration falls below the fasting concentration. Therefore, the lower GI of milk, full-fat milk (GI: 27), and skim milk (GI: 32) (46), may have contributed to its satiety effect.

Is satiety after sucrose- or HFCS-containing preloads influenced by its biochemical properties? The carbohydrate sucrose is a disaccharide and consists of one molecule of glucose and one molecule of fructose, which are not available for absorption until sucrose is hydrolyzed by intestinal brush-border enzymes. HFCS, on the other hand, contains glucose and fructose in their monosaccharide forms, which gives the solution a higher osmotic pressure. In soft drinks, however, a proportion of the sucrose is hydrolyzed into glucose and fructose by the acidic pH before the drinks are consumed. Fructose is passively absorbed in the duodenum and jejunum by a GLUT 5 transporter, which has a smaller absorption capacity than does the actively sodium-dependent hexose transporter, which absorbs glucose in the duodenum (57–59). However, there is a more complete and faster transport accompanied by a decrease in malabsorption when fructose is consumed in combination with other carbohydrates (20, 21). Both the differences in duration in the intestines and in the osmotic pressure of glucose and fructose could influence satiety differently. Furthermore, glucose triggers glucose sensors in the central nervous system involved in the regulation of food intake (60). Fructose, however, does not cross the blood-brain barrier (61). Fructose could trigger satiety by its oxidation (62), greater thermogenic response (63–65), and rapid metabolism in the liver (61). The liver is sensitive to its own metabolism and signals to the brain via the vagus nerve to inhibit the central control for meal initiation (61). Thus, glucose and fructose in sucrose- or HFCS-sweetened drinks contribute to satiety through different biochemical mechanisms.

In summary, a 1.5-MJ preload containing sucrose or HFCS or a milk preload did not affect energy intake differently 50 min later. Differences in satiety were absent despite different mechanisms underlying satiety due to sucrose- or HFCS-containing drinks or milk. Sucrose and HFCS triggered GLP-1 release, which triggered insulin release and a related increase in satiety. The different responses in GLP-1, glucose, and thirst when preloads of the same sizes were offered could explain the sex effect that was observed in VAS ratings, energy intake, and energy compensation and overconsumption. Obviously, the preloads that were consumed represented a smaller part of the energy requirement in men than in women.

On the basis of partial compensation for and overconsumption due to the energy-containing preloads, a long-term study to assess the effect on body weight regulation would be a necessary follow-up. The question remains whether, in the long-term, this partial overconsumption of ≈40–50% of the meal, amounting to 1 MJ, will accumulate. If no other long-term compensating mechanisms occurred, an increase in body weight over time of ≈1 kg over 1 mo would occur. Here, an additional 30 MJ accounts for a gain in body weight of 1 kg (66). To confirm this hypothetical approach or to find long-term compensating mechanisms, a well-controlled long-term study would be necessary.

In conclusion, despite differences in the biochemical properties of preloads containing sucrose, HFCS, or milk and differences in the mechanisms underlying satiety in relation to GLP-1 release and ghrelin release, no differences in satiety, compensation, or overconsumption were observed.

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SS designed the experiment, collected the data, analyzed the data, and wrote the manuscript. MSW-P designed the experiment, helped analyze the data, and supervised the project. None of the authors had any financial or personal interest in any company or organization sponsoring the research.

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