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Twenty-four-hour endocrine and metabolic profiles following consumption of high-fructose corn syrup-, sucrose-, fructose-, and glucose-sweetened beverages with meals¹⁻³

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ABSTRACT

Background: We have reported that, compared with glucose-sweetened beverages, consuming fructose-sweetened beverages with meals results in lower 24-h circulating glucose, insulin, and leptin concentrations and elevated triacylglycerol (TG). However, pure fructose and glucose are not commonly used as sweeteners. High-fructose corn syrup (HFCS) has replaced sucrose as the predominant sweetener in beverages in the United States.

Objective: We compared the metabolic/endocrine effects of HFCS with sucrose and, in a subset of subjects, with pure fructose and glucose.

Design: Thirty-four men and women consumed 3 isocaloric meals with either sucrose- or HFCS-sweetened beverages, and blood samples were collected over 24 h. Eight of the male subjects were also studied when fructose- or glucose-sweetened beverages were consumed.

Results: In 34 subjects, 24-h glucose, insulin, leptin, ghrelin, and TG profiles were similar between days that sucrose or HFCS was consumed. Postprandial TG excursions after HFCS or sucrose were larger in men than in women. In the men in whom the effects of 4 sweeteners were compared, the 24-h glucose and insulin responses induced by HFCS and sucrose were intermediate between the lower responses during consumption of fructose and the higher responses during glucose. Unexpectedly, postprandial TG profiles after HFCS or sucrose were not intermediate but comparably high as after pure fructose.

Conclusions: Sucrose and HFCS do not have substantially different short-term endocrine/metabolic effects. In male subjects, short-term consumption of sucrose and HFCS resulted in postprandial TG responses comparable to those induced by fructose. *Am J Clin Nutr* 2008;87:1194–203.

INTRODUCTION

It has been suggested that the consumption of fructose, which is consumed mainly in the form of high-fructose corn syrup (HFCS) and sucrose, may be a contributing factor to the increased incidence of obesity and metabolic syndrome (1, 2). The current estimate for the mean intake of added sugars by Americans is 15.8% of energy. However, this value is based on consumption data from the 1994–1996 Continuing Survey of Food Intakes by Individuals (CSFII) (3), and recent reports suggest that energy intake from sugar-sweetened beverages alone approaches or exceeds 15% of calories in several population groups (4–8). The large standard deviations in several of these reports

suggest that at least 16% of the studied populations were consuming >2 times the mean intake and likely well over 25% of daily energy requirements from sugar-sweetened beverages (5, 7, 8). Based on these reports, it is reasonable to estimate that the percentage of energy consumed as sugar from both beverages and solid food is >20% in a significant portion of the US population.

We have reported that consuming fructose-sweetened beverages with meals results in lower 24-h circulating glucose, insulin, and leptin concentrations and decreased postprandial suppression of plasma ghrelin levels when compared with consumption of glucose-sweetened beverages (9). We and others have reported that consuming fructose-sweetened beverages increases postprandial triacylglycerol (TG) concentration compared with glucose-sweetened beverages (9–11). These responses are more pronounced in men compared with women (10, 11) and in overweight/obese subjects compared with normal-weight subjects (11). Because insulin, leptin, and possibly ghrelin function as key signals to the central nervous system in the long-term regulation of energy balance, prolonged consumption of diets high in energy from fructose could lead to increased caloric intake and contribute to weight gain and obesity (2). The sustained elevation of plasma TG concentrations after fructose ingestion suggests that chronic overconsumption of fructose could also contribute to atherogenesis and cardiovascular disease (12, 13). However, pure fructose and pure glucose are not commonly employed as sweeteners. Until a few decades ago, most foods and beverages in the United States were sweetened with the disaccharide

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sucrose, which is composed of 50% glucose and 50% fructose. In 1970 an enzymatic process to convert corn sugar (composed of glucose) into HFCS was developed. Since then, HFCS, mainly in the form containing 55% fructose and 45% glucose, has replaced sucrose as the predominant sweetener used in soft drinks and represents $\approx 40\%$ of sweeteners added to foods consumed in the United States (14).

Currently, there are few studies comparing the metabolic and endocrine effects of HFCS with sucrose (15, 16), and, to our knowledge, no studies comparing the effects of consuming HFCS with pure fructose or glucose. The objectives of this study, therefore, were to compare the metabolic and endocrine effects of consuming HFCS- and sucrose-sweetened beverages and to determine whether responses are affected by sex and adiposity. A third objective was to compare the effects of consuming HFCS- and sucrose-sweetened beverages with the consumption of beverages sweetened with fructose or glucose.

SUBJECTS AND METHODS

Design

Circulating glucose, insulin, leptin, ghrelin, triacylglycerol (TG), and free fatty acid (FFA) concentrations were measured in 34 subjects over a 24-h period on 2 separate days, during which they consumed 3 isocaloric, mixed nutrient meals accompanied by either sucrose-sweetened or HFCS-sweetened beverages. In a subset of 8 male subjects, these variables were also measured on 2 additional days, during which these subjects consumed the same isocaloric meals accompanied by beverages sweetened with 100% fructose or 100% glucose.

Subjects

Thirty-four subjects (18 men and 16 women) with an age range of 20–50 y (\bar{x} 34.7 \pm 1.7 y) participated in the study. Participants were recruited through newspaper advertisements and underwent a telephone interview, a complete blood count, and a serum biochemistry panel to assess eligibility. Respondents with anemia, hepatic or renal disease, diabetes mellitus, fasting serum TG levels > 400 mg/dL, hypertension, eating disorders, or who had surgery for weight loss were excluded from the study. Individuals who smoked; who took thyroid, lipid-lowering, glucose-lowering, antihypertensive, antidepressant, or weight-loss medications; or who were pregnant or lactating were also excluded. The Institutional Review Board of the University of California, Davis, CA approved the experimental protocol, and subjects provided informed consent to participate in the study.

Experimental protocol

Each subject participated in 2 experimental trials conducted in random order. The experimental days were spaced 1 mo apart, and each required an overnight stay in the University of California General Clinical Research Center (GCRC). During each experimental day the subjects consumed identical meals based on calculated energy requirements (as described below) that included beverages sweetened with either HFCS or sucrose. The 18 male subjects were invited to extend participation in the study,

and, of these, a subset of 8 men completed 2 additional study days during which they consumed the identical meals accompanied by beverages sweetened with either 100% fructose or glucose. Participation in the additional fructose and glucose trials was limited to male subjects because of budgetary constraints.

Percentage of body fat was determined by measurement of bioelectrical impedance (Tanita 310GS Body Composition Analyzer; Tanita Corporation, Tokyo, Japan). Bioelectrical impedance measurements of body fat in healthy adults has been shown to correlate well with body fat measurements by dual-energy X-ray absorptiometry (17, 18). As there is no consensus on the percentage of body fat standards for overweight and obesity (19), we used a statistical approach of dividing subjects of each sex into 2 equal groups based on ranking by percentage of body fat. Therefore, the men and women were divided into 2 groups with lower and higher body adiposity based on a percentage of body fat less than or greater than 22% and 32%, respectively.

The subjects were instructed to maintain their normal dietary intake and level of physical activity during the interval between the GCRC studies. Following a 12-h overnight fast, the subjects checked into the GCRC at 0700. A physical examination was conducted by the study physician, and an intravenous catheter was inserted and kept patent with a slow saline infusion. Blood sampling commenced at 0800 and continued for 24 h. Thirty-six blood samples were collected for substrate and hormone measurements over the 24-h sampling period during which the subjects consumed 3 standardized meals. Each meal was accompanied by a sucrose-, HFCS-, glucose-, or fructose-sweetened beverage.

Meals

The meals consisted of whole foods and were designed by a registered dietitian. The nutrient composition of the diets was determined using the FOOD PROCESSOR SQL, (ESHA Research Inc, Salem, OR). Each subject ingested 3 meals per day. Breakfast consisted of scrambled eggs, ham, potatoes, and asparagus. Lunch consisted of chicken/tortilla soup with corn chips and cheese. Dinner consisted of lasagna with beef and a salad with lettuce, tomato, cucumber, celery, cheese, and vinaigrette dressing. The energy content of the meals was based on each subject's daily energy requirement as estimated by the Mifflin equation with an activity factor of 1.3 (20). The activity factor was low because the subjects remained relatively sedentary while at the GCRC. Twenty percent of the energy requirement was consumed at breakfast, 35% at lunch, and 45% at dinner. The meals contained 30% energy from fat, 15% from protein, 30% from complex carbohydrate, and 25% from sugar. The 25% sugar consisted of sucrose, HFCS, glucose, or fructose in the form of a beverage. It is important to study the effects of sugars at the 25% of energy intake level. The Institute of Medicine of the National Academies, in the 2002 Dietary References Intakes, concluded that there was insufficient evidence to set an upper-intake level for added sugars because there were no specific adverse health outcomes associated with excessive intake (21). Therefore, they suggested a maximal intake level of 25% of energy intake from added sugars. The sucrose and HFCS beverages were provided by the sponsor (PepsiCo Inc, Purchase, NY) as 11% w:w sugar in noncaffeinated carbonated sodas. The fructose and glucose were prepared as 11% w:w solutions in carbonated soda water, fla-



vored with a commercial unsweetened drink mix. The subjects and GCRC study staff were blinded to the sweetener contained in the beverages. The beverages were not matched for sweetness, but, because the trials were spaced approximately 1 mo apart, it is unlikely the subjects would have noticed a difference in the sweetness of the beverages. The only other beverage served during the 24-h study period was water. Breakfast was consumed at 0900, lunch at 1300, and dinner at 1800. The subjects were required to ingest all of the provided food and beverage within 20 min and were observed to ensure compliance.

Blood sampling

Blood samples were drawn from the catheters at 30-min intervals around periods of meal ingestion and during the predicted nocturnal rise of plasma leptin concentrations (ie, 5 h after the evening meal) and at hourly intervals at other times (22). After the 3 baseline samples, which were collected at 0800, 0830, and 0900 before ingestion of the first meal, a total of 33 additional samples were collected 30–60 min apart. Each sample collection involved the removal of 1 mL of blood to clear the catheter tubing, followed by a 5 mL collection into blood-collection tubes containing EDTA. Samples were then centrifuged, divided into aliquots, and stored at -80°C until assayed.

Assays and data analysis

Plasma glucose and lactate concentrations were measured with an automatic analyzer (YSI 2300 StatPlus Glucose Analyzer; Yellow Springs Instruments, Yellow Springs, OH). Insulin and leptin concentrations were measured by radioimmunoassay (Linco Research Inc, St Charles, MO). Total ghrelin concentrations were measured in unextracted plasma with radioimmunoassay (Phoenix Peptide, Phoenix, AZ). TG concentrations were measured with an automatic analyzer using manufacturer's reagents (PolyChem Analyzer; PolyMedCo Inc, Cortlandt Manor, NY). FFAs were measured with enzymatic colorimetric reagents (Wako Chemicals, Richmond, VA). Fasting lipid concentrations were measured at baseline and at 0800 the following morning, and apolipoprotein B100 (ApoB) concentrations were measured at baseline and at 2200 with an automatic analyzer (PolyChem Analyzer).

The area under the curve (AUC) was calculated for glucose, insulin, ghrelin, FFA, and TG with a data spreadsheet program (Microsoft EXCEL; Microsoft, Redmond, WA) using the trapezoidal method. The mean of the 3 baseline values was determined, and net AUC was calculated by subtracting the areas below baseline from AUC values above baseline. AUCs for glucose, insulin, ghrelin, FFA, and TG are expressed as units per

23 h above each subject's fasting baseline levels because the 3 samples taken during the first hour determined the baseline levels. The nadirs for plasma leptin were determined as the 2 lowest consecutive morning values before 1200 h, as described previously (22). The AUCs for leptin are therefore expressed as units above each subject's nadir over 24 h. Data from the 34 subjects were analyzed with the statistical software program SPSS (version 15.0; SPSS Inc, Chicago, IL) by using the general linear model for repeated measures that included a sugar \times adiposity group \times sex interaction. Age was also included in the analysis, with subjects grouped by 20–29, 30–39, and 40–50 y. Time was included as a within-subject factor to assess change from fasting levels in lipid concentrations. When the general linear model results indicated the presence of a significant sugar effect or sex or body adiposity interaction, paired and unpaired *t* tests were performed within group, between men and women, or between adiposity groups, respectively. Differences between the responses to the 4 sugars in the subset of 8 male subjects were assessed with GRAPHPAD PRISM (version 4.03; San Diego, CA, USA) using repeated-measures, one-factor ANOVA, and posttests were performed using Tukey's test for multiple comparisons.

RESULTS

Baseline measures

The age, body weight, percentage of body fat, and body mass index of the subjects are presented in **Table 1**. Body weight and baseline fasting plasma concentrations of glucose, hormones, and lipids are shown in **Table 2** for the sucrose and HFCS study days. Fasting TG and apoB concentrations were lower in women (-14.1 ± 6.5 and -12.1 ± 4.2 mg/dL, respectively; $P < 0.05$, paired *t* test) and higher in men (12.0 ± 5.1 and 6.9 ± 3.4 mg/dL, respectively; $P < 0.05$, paired *t* test) on the day of the sucrose feeding compared with the day of the HFCS feeding. There were no differences in baseline concentrations of the other measured parameters on the 2 study days.

Effects of HFCS and sucrose with 24-h profiles

Twenty-four-hour plasma profiles of glucose, leptin, ghrelin, TG, and FFA concentrations, as assessed by AUC, were not different on the days that HFCS-sweetened beverages were consumed with meals compared with when sucrose-sweetened beverages were consumed (**Figure 1, Table 3**). The insulin AUC was slightly but significantly increased by consumption of sucrose-sweetened beverages compared with HFCS-sweetened

TABLE 1
Age, body weight, and adiposity of study participants¹

	Women <32 %BF (n = 8)	Women >32 %BF (n = 8)	Men <22 %BF (n = 9)	Men >22 %BF (n = 9)	Men 4-Sugar Subset (n = 7)
Age (y)	29.1 \pm 3.6	39 \pm 3	38 \pm 4	31 \pm 3	37.1 \pm 4.3
BW (kg) ²	60.2 \pm 1.7	76.4 \pm 4.0 ³	73.7 \pm 3.0	88.5 \pm 3.6 ³	82.0 \pm 5.2
Body fat (%) ²	25.7 \pm 1.4	39.2 \pm 1.7 ⁴	18.3 \pm 1.1	25.1 \pm 1.1 ⁴	21.0 \pm 2.5
BMI (kg/m ²) ²	21.9 \pm 0.6	28.9 \pm 1.6 ⁴	24.3 \pm 0.5	28.0 \pm 0.7 ⁴	26.1 \pm 1.0

¹ All values are $\bar{x} \pm \text{SEM}$. Within gender groups, subjects were ranked by %BF (body fat) and divided into 2 equal groups. General linear model–Univariate with gender and adiposity group as fixed factors.

² $P < 0.0001$ for differences among the 4 gender/weight groups.

^{3,4} Within gender unpaired *t* tests for adiposity group differences: ³ $P < 0.01$, ⁴ $P < 0.001$.

TABLE 2

Baseline body weight and fasting plasma concentrations of glucose, hormones, and lipids on each study day¹

	All (n = 34)	Women <32 %BF (n = 8)	Women >32 %BF (n = 8)	Men <22 %BF (n = 9)	Men >22 %BF (n = 9)
Body Weight (kg)					
Sucrose	75.2 ± 2.4	60.1 ± 1.7	76.1 ± 4.2	74.0 ± 3.0	89.0 ± 3.5
HFCS	74.9 ± 2.3	60.2 ± 1.7	76.6 ± 3.8	73.4 ± 2.9	88.0 ± 3.6
Glucose (mg/dL)					
Sucrose	88.0 ± 1.4	82.5 ± 1.4	86.4 ± 2.3	89.5 ± 2.3	92.9 ± 3.7
HFCS	86.8 ± 1.4	81.5 ± 1.8	84.6 ± 2.8	87.7 ± 1.2	92.6 ± 3.3
Insulin (μU/mL)					
Sucrose	11.6 ± 1.2	9.5 ± 0.6	14.9 ± 2.7	7.6 ± 1.2	14.4 ± 3.4
HFCS	11.4 ± 1.3	9.2 ± 0.7	14.8 ± 2.9	7.3 ± 0.9	14.5 ± 3.6
Leptin (ng/mL)					
Sucrose	10.8 ± 1.6	8.5 ± 1.4	23.7 ± 3.9	3.6 ± 0.4	8.6 ± 1.3
HFCS	10.1 ± 1.4	8.3 ± 1.1	20.9 ± 2.9	3.5 ± 0.5	8.5 ± 1.5
Ghrelin (pg/mL)					
Sucrose	441.0 ± 36.4	613.2 ± 111.3	414.9 ± 60.6	396.7 ± 50.9	355.6 ± 31.9
HFCS	435.4 ± 30.6	590.0 ± 75.2	398.9 ± 66.5	399.8 ± 47.7	365.9 ± 29.9
TG (mg/dL) ²					
Sucrose	107.7 ± 10.4	78.2 ± 9.7	94.5 ± 16.0	106.1 ± 20.9	147.1 ± 25.9
HFCS	109.2 ± 9.1	98.9 ± 12.2	102.9 ± 10.2 ³	92.0 ± 17.5	135.5 ± 23.6 ³
FFA (mEq/L)					
Sucrose	0.34 ± 0.02	0.39 ± 0.06	0.39 ± 0.04	0.30 ± 0.05	0.30 ± 0.03
HFCS	0.37 ± 0.02	0.41 ± 0.05	0.43 ± 0.04	0.32 ± 0.04	0.32 ± 0.03
Cholesterol (mg/dL) ⁴					
Sucrose	176.1 ± 5.5	153.4 ± 6.0	181.8 ± 14.5	186.4 ± 9.0	180.9 ± 11.0
HFCS	176.8 ± 5.7	156.9 ± 4.2	199.4 ± 13.9 ⁵	175.8 ± 11.0	175.6 ± 10.7 ⁵
LDL (mg/dL)					
Sucrose	107.7 ± 4.4	86.1 ± 5.9	106.6 ± 8.8	120.9 ± 7.8	114.7 ± 8.9
HFCS	108.0 ± 5.1	85.9 ± 5.7	120.0 ± 12.8	113.8 ± 10.4	111.3 ± 8.0
HDL (mg/dL)					
Sucrose	47.0 ± 1.8	51.6 ± 3.9	56.1 ± 3.2	44.3 ± 2.2	37.3 ± 1.2
HFCS	47.4 ± 1.9	52.0 ± 3.7	58.4 ± 3.8	44.0 ± 1.7	37.1 ± 1.6
ApoB (mg/dL) ⁶					
Sucrose	76.4 ± 4.4	56.3 ± 4.9	72.3 ± 8.9	95.1 ± 6.2	79.4 ± 9.6
HFCS	77.6 ± 4.3	60.6 ± 5.3	88.5 ± 9.3 ³	87.0 ± 8.5	73.7 ± 8.6 ³

¹ All values are $\bar{x} \pm \text{SEM}$. General linear model for repeated measures for the interaction of sugar and gender, adiposity and age group.

² Sugar, $P = 0.37$; Sugar \times Gender, $P < 0.001$; Sugar \times Age, $P = 0.012$; Sugar \times Gender \times weight \times Age, $P = 0.019$.

^{3,5} Significant Sugar \times Gender differences tested for within gender group difference by paired t test: ³ $P < 0.05$, ⁵ NS.

⁴ Sugar, $P = 0.83$; Sugar \times Gender, $P = 0.038$.

⁶ Sugar, $P = 0.76$; Sugar \times Gender, $P = 0.0034$.

beverages. This difference was significant in subjects younger than 35 y ($n = 17$; $P < 0.01$) but not significant in subjects older than 35 y ($n = 17$; $P = 0.5$).

Effects of HFCS and sucrose on changes of fasting lipid concentrations

There were no differences between the effects of consuming sucrose- or HFCS-sweetened beverages with 3 meals on changes in fasting lipid concentrations from baseline to the following morning (0800 h) for plasma TG, cholesterol, LDL, or HDL concentrations, and on changes between baseline and postprandial concentrations of ApoB at 2200 h (Table 4). Consumption of both sucrose and HFCS significantly increased fasting TG concentrations the following morning (sucrose: $+28.3 \pm 5.4$ mg/dL, $P < 0.001$; HFCS: $+18.9 \pm 4.5$ mg/dL, $P < 0.001$) and decreased postprandial ApoB concentrations at 2200 (sucrose: -5.8 ± 1.3 mg/dL, $P < 0.001$; HFCS: -6.0 ± 1.9 mg/dL, $P < 0.01$).

Effects of HFCS- and sucrose-sweetened beverages in men and women and in adiposity groups

The 24-h AUCs of glucose, insulin, leptin, ghrelin, TG, or FFA were not significantly different between the lower and higher adiposity groups. The 24-h leptin AUC in women was ≈ 3 times higher than in men ($P < 0.01$, unpaired t test) during consumption of both HFCS and sucrose (Table 3, Figure 2A). There was a marked sex difference in 24-h TG AUC, with a mean AUC during sucrose consumption 3 times higher ($P < 0.01$) and during HFCS consumption 7 times higher ($P < 0.001$, unpaired t test) in men than in women (Table 3, Figure 2B). The AUC for FFA was less suppressed (ie, less negative) in men compared with women (Table 3), with the effect being statistically significant during HFCS consumption (men: -2.6 ± 0.3 mmol/L \cdot 23 h; women: -4.5 ± 0.6 mmol/L \cdot 23 h; $P < 0.05$) but not during sucrose consumption (men: -2.3 ± 0.3 mmol/L \cdot 23 h; women: -3.7 ± 0.7 mmol/L \cdot 23 h; NS, unpaired t test).

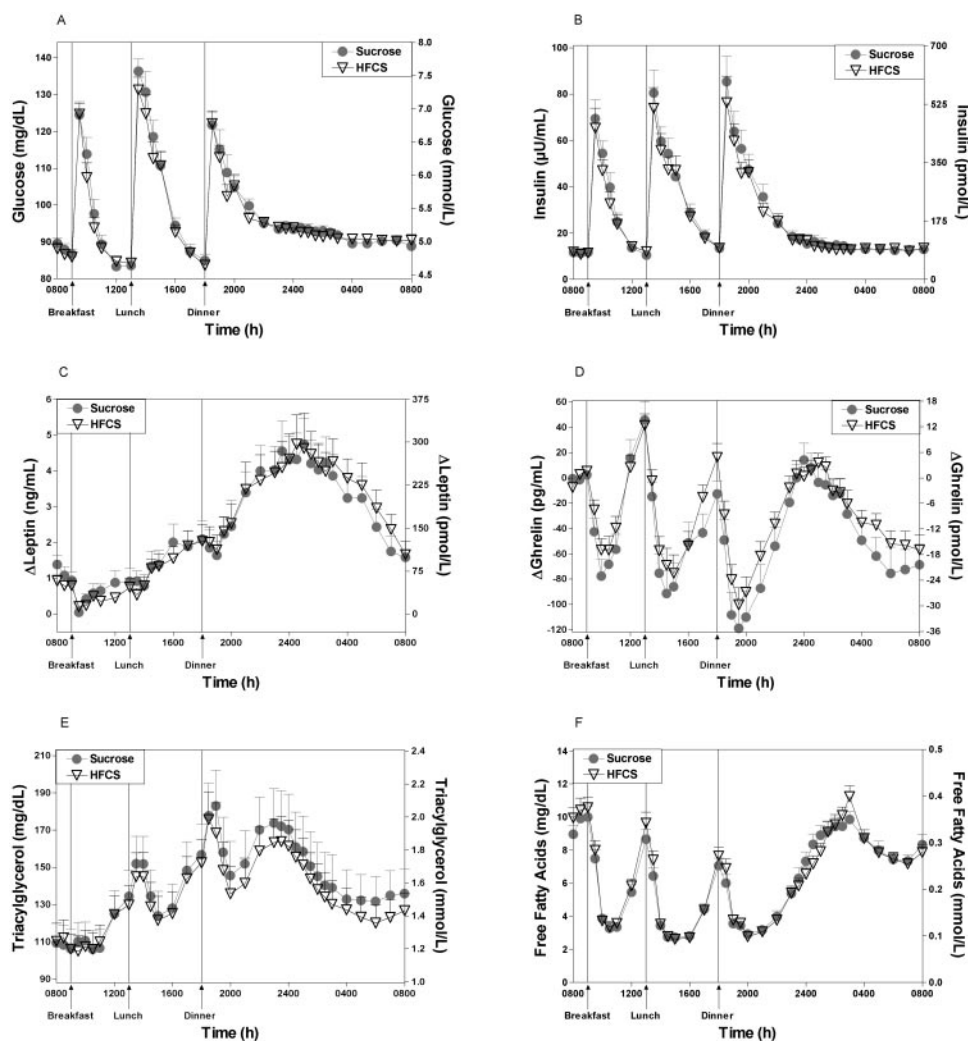


FIGURE 1. Plasma glucose (A), insulin (B), triacylglycerol (E), and free fatty acid (F) concentrations during a 24-h period (0800–0800) in 34 women and men consuming HFCS- or sucrose-sweetened beverages with each meal. Change (Δ) in plasma leptin (C) over the morning nadir and ghrelin concentrations (D) from mean baseline levels (0800–0900) during a 24-h period (0800–0800) in 34 women and men consuming HFCS- or sucrose-sweetened beverages with each meal. Data shown as mean \pm SEM.

Effects of HFCS-, sucrose-, fructose- and glucose-sweetened beverages

One of the male subjects who participated in 4 of the 24-h blood collections while consuming sucrose, HFCS, fructose, or glucose had mild hypertriacylglycerolmia (fasting [TG] = 196 mg/dL); therefore, this subject's results were not included in the final analyses. See Figure S1 under "Supplemental Data" in the current online issue for the 24-h profile graphs from this subject. The characteristics of the 7 male subjects with normal fasting TG concentrations (<150 mg/dL, US National Cholesterol Education Program Guideline) are presented in Table 1. There were no significant differences in body weight or baseline concentrations of any of the measured parameters across the 4 study days (Table 5).

The effects of the 4 sugars on 24-h AUC were significantly different for glucose ($P = 0.010$), insulin ($P < 0.0001$), and TG ($P = 0.007$) by repeated-measure, one-factor ANOVA, while there were no differences in the AUCs for leptin, ghrelin, or FFA (Figure 3, Table 6).

Consumption of fructose-sweetened beverages resulted in glucose and insulin AUCs that were significantly lower than the

AUCs induced by glucose consumption ($P < 0.01$, $P < 0.001$ glucose and insulin, respectively, Tukey's posttest). As expected, consumption of the HFCS- and sucrose-sweetened beverages resulted in glucose and insulin AUCs that tended to be intermediate between the higher AUCs induced by glucose consumption and the lower AUCs induced by fructose. However, the glucose AUCs were lower during consumption of sucrose and HFCS than would be expected based on the relative glucose concentrations of the 4 beverages. The 24-h AUCs for plasma glucose concentrations averaged 76% of the expected AUC (\bar{x} of the glucose AUCs during fructose and glucose consumption) during sucrose consumption, and 81% of the expected AUC ($0.55 \times \text{fructose } \bar{x} + 0.45 \times \text{glucose } \bar{x}$) during HFCS consumption. Accordingly, the insulin AUCs during sucrose and HFCS consumption were also lower than expected (84% of the expected value for sucrose; 83% of expected value for HFCS). The 24-h postprandial TG profiles on the days the subjects consumed HFCS or sucrose were not intermediate between those of glucose and fructose as expected but were comparable to the magnitude of the profile following consumption of 100% fructose beverages

TABLE 3

24-h AUC of endocrine/metabolic variables during consumption of sucrose- and HFCS-sweetened beverages with meals¹

	All (n = 34)	Women <32 %BF (n = 8)	Women >32 %BF (n = 8)	Men <22 %BF (n = 9)	Men >22 %BF (n = 9)
Glucose (mg/dL, ×23hr)					
Sucrose	222.2 ± 27.2	278.7 ± 41.1	243.0 ± 55.6	209.6 ± 41.7	166.2 ± 72.6
HFCS	226.8 ± 25.2	299.6 ± 40.4	276.0 ± 46.5	210.5 ± 52.4	134.6 ± 47.0
Insulin (μU/mL, ×23hr) ²					
Sucrose	381.1 ± 48.9	321.2 ± 64.5	544.3 ± 164.4	237.7 ± 31.6	432.6 ± 75.7
HFCS	344.4 ± 43.3	255.0 ± 42.9	515.9 ± 148.9	221.1 ± 25.3	394.8 ± 59.5
Leptin (ng/mL, ×24hr) ⁴					
Sucrose	57.0 ± 10.4	56.4 ± 18.0	120.1 ± 28.2	19.2 ± 3.9	39.3 ± 11.3 ⁶
HFCS	57.2 ± 9.5	61.3 ± 13.8	117.6 ± 24.4	18.6 ± 5.0	38.5 ± 11.2 ⁷
Ghrelin (pg/mL, ×23hr)					
Sucrose	-933.6 ± 234.8	-1,677.9 ± 786.1	-841.1 ± 294.2	-685.9 ± 350.1	-602.0 ± 323.9
HFCS	-897.2 ± 188.1	-1,331.7 ± 358.4	-547.2 ± 496.6	-946.2 ± 341.2	-773.2 ± 326.7
TG (mg/dL, ×23hr) ⁵					
Sucrose	793.3 ± 135.8	359.5 ± 153.1	398.7 ± 145.3	1,017.3 ± 344.5	1,305.8 ± 238.4 ⁶
HFCS	611.1 ± 132.1	-29.2 ± 184.2	315.2 ± 257.2	978.2 ± 177.4	1,076.2 ± 251.8 ⁷
FFA (mEq/L, ×23hr) ⁴					
Sucrose	-3.0 ± 0.4	-3.7 ± 1.1	-3.8 ± 0.9	-2.4 ± 0.6	-2.2 ± 0.3 ⁸
HFCS	-3.5 ± 0.4	-4.3 ± 1.1	-4.7 ± 0.8	-2.3 ± 0.5	-2.8 ± 0.3 ⁶

¹ All values are $\bar{x} \pm$ SEM. General linear model for repeated measures for the interaction of sugar and gender, adiposity and age group.

² Sugar, $P = 0.016$; Sugar × Age, $P < 0.001$. Sugar × Age interaction for insulin tested for within age group difference by paired t test (cutoff 35 y; $n = 17$ /group). Subjects < 35 y: Mean insulin AUC = $398.5 \pm 53.4 \mu\text{U/mL} \times 23\text{hr}$ sucrose, $310.6 \pm 39.4 \mu\text{U/mL} \times 23\text{hr}$ HFCS, $P = 0.0011$. Subjects > 35 y: Mean insulin AUC = $363.6 \pm 83.5 \mu\text{U/mL} \times 23\text{hr}$ sucrose, $378.2 \pm 77.7 \mu\text{U/mL} \times 23\text{hr}$ HFCS, $P = 0.51$. All other Sugar × between subject factors, $P > 0.05$.

^{4,5} Gender difference by general linear model (⁴ $P < 0.05$, ⁵ $P < 0.01$).

^{6,7,8} Variables with significant gender differences tested for between gender group differences by paired t test (Female, $n = 16$; Male, $n = 18$; ⁶ $P < 0.01$, ⁷ $P < 0.001$, ⁸NS). All other between subject factors and 2- and 3-way interactions, $P > 0.05$.

(Figure 3D). The TG 24-h AUC during HFCS consumption was significantly higher than the AUC during glucose consumption ($P < 0.01$, Tukey's posttests) (Table 6).

Consumption of all 4 sugar-sweetened beverages with meals also resulted in significant increases in the fasting TG concentrations the

following morning (0800 h), but there were no differences among the effects of the 4 sugars. Similarly, all 4 sugars decreased postprandial ApoB concentrations (2200 h); however, the sugar × time interaction was not statistically significant (Table 7).

TABLE 4

Absolute change from baseline lipid concentrations after consumption of sucrose- and HFCS-sweetened beverages with meals¹

	All Subjects (n = 34)	Women <32 %BF (n = 8)	Women >32 %BF (n = 8)	Men <22 %BF (n = 9)	Men >22 %BF (n = 9)
TG (mg/dL) ^{2,4}					
Sucrose	28.3 ± 5.4	15.2 ± 4.1	29.5 ± 9.5	19.0 ± 9.6	48.3 ± 14.1
HFCS	18.9 ± 4.5	-2.8 ± 7.1	16.8 ± 6.6	36.6 ± 9.5	22.3 ± 8.1
Cholesterol (mg/dL)					
Sucrose	2.4 ± 2.8	-5.3 ± 6.0	2.9 ± 4.5	-1.1 ± 6.3	12.1 ± 4.7
HFCS	1.1 ± 2.5	-7.5 ± 7.1	5.8 ± 5.3	3.2 ± 3.2	2.3 ± 3.9
LDL (mg/dL)					
Sucrose	-2.9 ± 1.9	-5.1 ± 4.1	-4.0 ± 3.1	-3.6 ± 5.0	0.9 ± 2.7
HFCS	-2.5 ± 1.7	-4.4 ± 4.0	0.8 ± 3.7	-3.7 ± 2.8	-2.4 ± 3.2
HDL (mg/dL)					
Sucrose	-0.4 ± 0.8	-3.1 ± 2.3	1.3 ± 1.6	-1.4 ± 1.1	1.4 ± 1.0
HFCS	-0.6 ± 0.8	-3.3 ± 2.2	1.6 ± 1.7	-0.9 ± 1.2	0.1 ± 1.3
ApoB (mg/dL) ^{3,4}					
Sucrose	-5.8 ± 1.3	-5.9 ± 1.1	-3.75	-10.7 ± 3.7	-2.8 ± 2.2
HFCS	-6.0 ± 1.9	-10.5 ± 4.4	-5.25	-5.9 ± 2.6	-2.8 ± 3.5

¹ All values are $\bar{x} \pm$ SEM. General linear model for repeated measures for the interaction of sugar and gender, adiposity and age group. TG, Cholesterol, LDL, HDL: Concentration at 0800h the following day minus baseline concentration. ApoB: Concentration at 2200h (4 h after dinner) minus baseline concentration.

² Sugar, $P = 0.43$; Time, $P < 0.0001$; Sugar × Time, $P = 0.23$.

³ Sugar, $P = 0.81$; Time, $P < 0.0001$; Sugar × Time, $P = 0.89$.

⁴ All Sugar × Time × Between Subject Factors, $P > 0.05$.

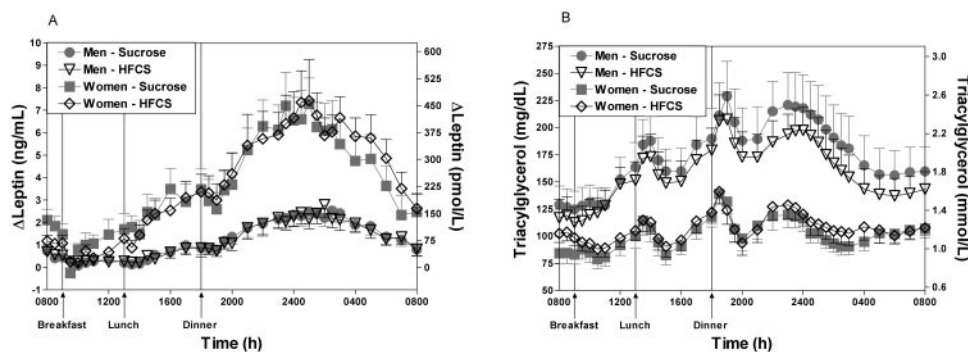


FIGURE 2. Change (Δ) in plasma leptin concentrations (A) over the morning nadir during a 24-h period (0800–0800) in 16 women and 18 men consuming HFCS- or sucrose-sweetened beverages with each meal. Plasma triacylglycerol concentrations (B) during a 24-h period (0800–0800 h) in 16 women and 18 men consuming HFCS- or sucrose-sweetened beverages with each meal. Data shown as mean \pm SEM.

DISCUSSION

Effects of HFCS and sucrose

The 24-h postprandial glucose, leptin, and ghrelin profiles during the consumption of HFCS-sweetened beverages were not significantly different from those when sucrose-sweetened beverages were consumed. These results are similar to those of Melanson et al (16), who investigated sucrose and HFCS consumption at 30% of energy by 30 normal-weight women. Our results extend their findings to men and to overweight and obese subjects. The insulin AUC was slightly but significantly increased during consumption of sucrose- compared with HFCS-sweetened beverages. This increase was not unexpected given that sucrose contains 10% more glucose than HFCS; however, Melanson et al (16) did not report a similar increase in their study. Consumption of HFCS and sucrose also resulted in similar 24-h TG and FFA AUCs, variables that were not examined in that study.

Fasting plasma TG concentrations at 0800 h the following morning were increased compared with baseline levels after both sucrose and HFCS consumption. In the subset of 7 men, consumption of all 4 sugars resulted in significant increases of fasting TG the following morning. These increases in fasting TG induced by 24-h exposure to sugar-sweetened beverages may be transitory. We and other investigators have reported that long-term consumption (≥ 2 wk) of fructose at 20–25% of energy did not increase fasting TG concentrations in healthy subjects (23), in older overweight and obese subjects (24, 25), in hyperinsulinemic female subjects (26), and in patients with type 2 diabetes

(27, 28) or hypertriacylglycerolemia (29). However, in other studies, 2 or more weeks of fructose consumption at 15–20% of energy increased fasting TG concentrations in healthy subjects (10, 30–32), in hyperinsulinemic male subjects (32, 33), and in subjects with type 2 diabetes (34). The reasons underlying these conflicting results are not clear. Interestingly, postprandial concentrations of ApoB, measured 4 h after dinner, were significantly decreased compared with baseline levels following consumption of HFCS or sucrose in the 34 subjects and following consumption of all 4 sugars in the subset of 8 male subjects. These data also contrast with results from our 2 long-term studies in which consumption of fructose-sweetened beverages for 10 wk increased both fasting and postprandial ApoB concentrations, whereas consuming glucose-sweetened beverages did not (24, 25). These differences in the effects of short-term and long-term sugar exposure on ApoB and fasting TG concentrations demonstrate the need for long-term studies with both fasting and postprandial measurements to determine the metabolic effects of prolonged daily consumption of sugar-sweetened beverages.

Effects of sex-specific differences

The higher leptin AUC in women compared with men was not unexpected, as sex-specific differences in leptin are well established (35, 36). Men had higher postprandial TG responses than women, and this difference has been demonstrated previously by us (11) in a 24-h study of overweight and obese men and premenopausal women. Bantle et al (10) reported that men had increased postprandial TG levels during consumption of a 6-week, 17%-of-energy fructose diet, but this was not observed

TABLE 5

Baseline body weight and plasma concentrations of glucose, hormones, and lipids on each study day in 7 men¹

Beverage	Body weight	Glucose	Insulin	Leptin	Ghrelin	TG	FFA
	kg	mg/dL	μ U/mL	ng/mL	pg/mL	mg/dL	mEq/L
Glucose	82.4 \pm 5.5 ²	92.0 \pm 1.5	9.2 \pm 1.3	5.4 \pm 1.1	316.6 \pm 76.3	91.4 \pm 11.0	0.32 \pm 0.04
Fructose	81.3 \pm 5.8	93.7 \pm 2.1	10.2 \pm 2.1	5.5 \pm 1.3	316.9 \pm 73.3	102.0 \pm 13.6	0.34 \pm 0.04
Sucrose	82.0 \pm 5.6	93.5 \pm 2.4	10.5 \pm 1.5	4.8 \pm 1.0	312.6 \pm 53.6	96.7 \pm 9.0	0.26 \pm 0.04
HFCS	81.5 \pm 5.6	90.3 \pm 2.4	9.0 \pm 1.7	4.8 \pm 1.3	306.3 \pm 52.4	87.4 \pm 9.0	0.29 \pm 0.04
Repeated-measures							
1-factor ANOVA							
P	0.50	0.39	0.56	0.56	0.98	0.47	0.10

¹ There were no significant differences in baseline body weight and plasma concentrations of glucose, hormones, and lipids on the 4 study days.

² $\bar{x} \pm$ SEM (all such values).

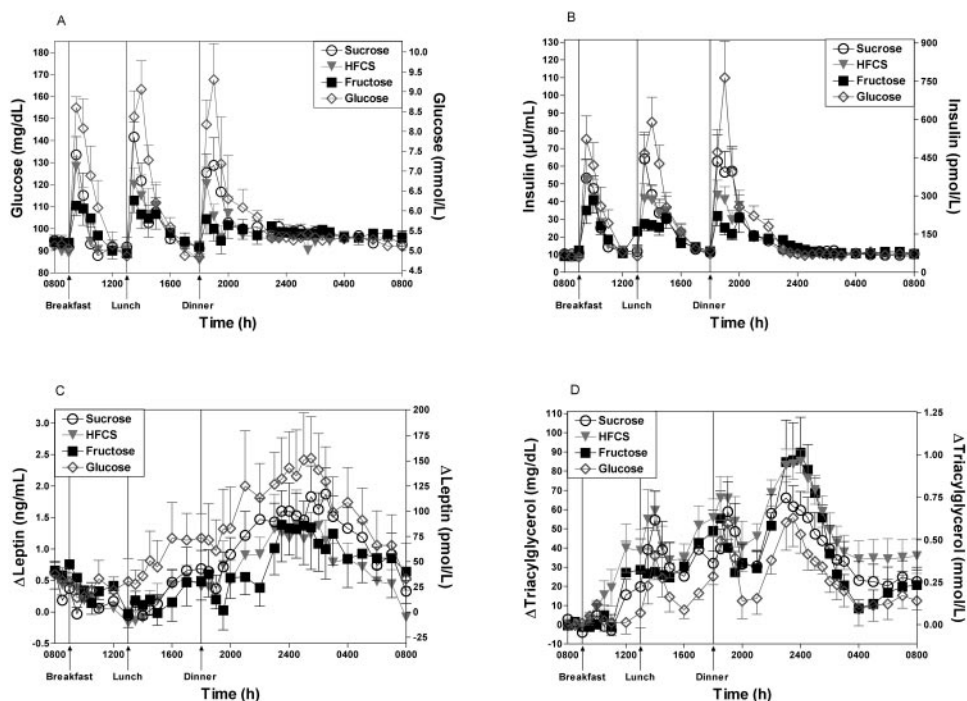


FIGURE 3. Plasma glucose (A) and insulin (B) concentrations during a 24-h period (0800–0800 h) in 7 men consuming HFCS-, sucrose-, fructose-, and glucose-sweetened beverages with each meal. Change (Δ) in plasma leptin concentration (C) over the morning nadir and plasma triacylglycerol (D) concentrations from mean baseline levels (0800–0900) during a 24-h period (0800–0800) in 7 men consuming HFCS-, sucrose-, fructose-, and glucose-sweetened beverages with each meal. Data shown as mean \pm SEM.

in women. Thus, available data suggest that men are more susceptible than women to the effects of sugars containing fructose to increase plasma TG concentrations. Whether this sex-specific difference exists in older males compared with postmenopausal female subjects remains to be determined.

Effects of fructose, glucose, sucrose, and HFCS

As expected, the responses of circulating glucose and insulin induced by consumption of sucrose and HFCS were relative to their glucose and fructose contents, thus intermediate to the larger responses induced by glucose and the lower responses after fructose. We had expected that the TG profiles would be directly related to the fructose content of the beverages consumed. We and Bantle et al (9–11, 25) have demonstrated previously that fructose consumption increases postprandial TG compared with glucose consumption. A likely mechanism is increased hepatic de novo lipogenesis (DNL), which has been

reported to increase markedly during fructose ingestion compared with glucose ingestion (37).

In the 7 male subjects who participated in the comparison of all 4 sugars, the 24-h postprandial TG responses to HFCS and sucrose were not intermediate between those induced by fructose and glucose. Sucrose and HFCS resulted in postprandial TG responses that were comparable to pure fructose alone, and consumption of HFCS-sweetened beverages significantly increased 24-h TG AUCs compared with glucose.

It is possible the mechanism by which sucrose and HFCS increase postprandial TG comparably to pure fructose may involve fructose-stimulated hepatic glucose uptake. Low-dose IV infusion of fructose has been reported to increase portal uptake of glucose in dogs (38), and oral fructose has been shown to lower peripheral plasma glucose responses to oral glucose ingestion in humans (39). Data from the present study suggest that additional glucose, when consumed concurrently with fructose, may have

TABLE 6
24-h AUC of endocrine/metabolic variables during consumption of sucrose-, HFCS-, fructose-, and glucose-sweetened beverages with meals in 7 men

Beverage	Glucose	Insulin	Leptin	Ghrelin	TG	FFA
	$mg \cdot dL^{-1} \cdot 23h^{-1}$	$\mu U \cdot mL^{-1} \cdot 23h^{-1}$	$ng \cdot mL^{-1} \cdot 24h^{-1}$	$pg \cdot mL^{-1} \cdot 23h^{-1}$	$mg \cdot dL^{-1} \cdot 23h^{-1}$	$mEq \cdot L^{-1} \cdot 23h^{-1}$
Glucose	344.6 \pm 73.7 ¹	399.6 \pm 58.5	29.7 \pm 10.1	-874.1 \pm 614.1	458.3 \pm 89.1	-1.8 \pm 0.6
Fructose	113.8 \pm 53.7 ²	181.8 \pm 20.0 ³	14.9 \pm 6.7	-1,120.8 \pm 634.1	751.2 \pm 150.2	-2.7 \pm 0.5
Sucrose	175.1 \pm 48.9	242.7 \pm 33.2 ³	19.2 \pm 5.2	-570.0 \pm 311.4	738.7 \pm 170.7	-1.6 \pm 0.5
HFCS	177.7 \pm 79.0	230.6 \pm 42.9 ³	13.5 \pm 3.7	-640.2 \pm 422.2	1,043.5 \pm 132.0 ²	-2.0 \pm 0.4
Repeated-measures						
1-factor ANOVA						
P	0.010	<0.0001	0.081	0.27	0.0065	0.31

¹ $\bar{x} \pm SEM$ (all such values).

² $P < 0.01$, ³ $P < 0.001$ compared to glucose (reference) using the Tukey's Multiple Comparison Test.

TABLE 7

Absolute change from baseline lipid concentrations after consumption of glucose-, fructose-, sucrose-, and HFCS-sweetened beverages ($n = 7$) with meals¹

	TG ²	ApoB ³
	mg/dL	mg/dL
Glucose	12.7 ± 4.5	-3.3 ± 1.3
Fructose	20.9 ± 7.4	-7.6 ± 2.7
Sucrose	22.4 ± 7.0	-6.4 ± 2.7
HFCS	35.7 ± 8.4	-12.6 ± 4.0

¹ All values are $\bar{x} \pm \text{SEM}$. General linear model for repeated measures. TG: Concentration at 0800h the following day minus baseline concentration. ApoB: Concentration at 2200h (4 hours after dinner) minus baseline concentration.

² Sugar, $P = 0.87$; Time, $P < 0.0001$; Sugar \times Time, $P = 0.21$.

³ Sugar, $P = 0.95$; Time, $P < 0.0001$; Sugar \times Time, $P = 0.22$.

been taken up and metabolized in the liver. The consumption of sucrose and HFCS resulted in 24-h glucose and insulin AUCs that were less than would be expected relative to their glucose and fructose content and the AUCs measured during consumption of the beverages sweetened with 100% glucose or fructose.

Activation of sterol receptor element binding protein-1c (SREBP-1c), the major transcriptional regulator of fatty acid synthesis, may also contribute to the larger-than-expected postprandial TG responses during sucrose and HFCS consumption. Matsuzaka et al (40) have reported that glucose, fructose, and sucrose increased hepatic SREBP-1c mRNA expression independently of insulin in streptozotocin-diabetic mice. Interestingly, they found that the timing of the SREBP-1c up-regulation varied following sugar feeding. Glucose and sucrose feeding induced maximal expression of SREBP-1c within 6 h (4- to 7-fold increase), while maximal expression following fructose feeding occurred at 12 h (5-fold increase) (40).

Results from our 2 studies comparing the long-term (10 wk) effects of fructose and glucose consumption demonstrate that the marked postprandial hypertriglycerolemia induced by fructose consumption is not a transitory response (24, 25). Similar studies are needed to determine whether the postprandial hypertriglycerolemia induced by HFCS and sucrose consumption is also maintained with more prolonged exposure. There is growing evidence to link postprandial lipemia with proatherogenic conditions (12, 13, 41–44). Two recent articles provide clinical evidence to support the association between elevated concentrations of postprandial TG and increased risk of cardiovascular disease. In a prospective cohort study of 7587 women and 6394 men followed for 26 y, elevated nonfasting TG levels were associated with increased risk of myocardial infarction, ischemic heart disease, and death (13). In the Women's Health Study, 26 509 women were followed for 11 y (12). Nonfasting TG levels, but not fasting levels, were associated with incident cardiovascular events independent of traditional cardiac risk factors, levels of other lipids, and markers of insulin resistance (12). In both of these studies there was a significant linear relation between increased nonfasting TG and increased hazard ratio for all outcomes (12, 13).

Conclusions

While consumption of sucrose compared with HFCS-sweetened beverages induced a small increase in the 24-h insulin

AUC in 34 subjects, the effects of sucrose and HFCS on 24-h circulating glucose, leptin, and ghrelin concentrations were not otherwise different. Thus, it appears that sucrose and HFCS do not have substantially different short-term effects on endocrine signals involved in body-weight regulation. Consumption of HFCS beverages also did not increase postprandial TG levels to a greater extent than those observed during consumption of sucrose-sweetened beverages.

Comparison of the effects of glucose, fructose, sucrose, and HFCS beverages within the same male subjects demonstrated that postprandial glucose and insulin responses were intermediate between the lower responses induced by pure fructose and the larger responses induced by pure glucose. Unexpectedly, the effects of short-term consumption of HFCS and sucrose on postprandial TG levels were not intermediate to those of fructose and glucose but comparable to fructose alone. Studies to determine whether these high postprandial TG levels are sustained during long-term consumption of sucrose and HFCS are needed. Additional studies in women and in subjects with and without components of the metabolic syndrome, as well as dose-response studies, are needed to more fully understand the metabolic effects of fructose-containing sugars.

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