Effects of glucose-to-fructose ratios in solutions on subjective satiety, food intake, and satiety hormones in young men[1–3]

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ABSTRACT

Background: The greater prevalence of obesity and the metabolic syndrome in the past 35 y has been attributed to the replacement of sucrose in the food supply with high-fructose corn syrup (HFCS).

Objective: Two experiments were conducted to determine the effect of solutions containing sucrose, HFCS, or various ratios of glucose to fructose (G:F) on food intake (FI), average appetite (AA), blood glucose (BG), plasma insulin, ghrelin, and uric acid (UA) in men.

Design: Sugar solutions (300 kcal/300 mL) were (in %) G20:F80, HFCS 55 (G45:F55), sucrose, and G80:F20 (experiment 1, $n = 12$) and G20:F80, G35:F65, G50:F50, sucrose, and G80:F20 (experiment 2, $n = 19$). The controls were a sweet energy-free control (experiment 1) and water (both experiments). Solutions were provided in a repeated-measures design. AA, BG, and FI were measured in all subjects. Hormonal responses and UA were measured in 7 subjects in experiment 2. Measurements were taken from baseline to 75 min. FI was measured at 80 min.

Results: Sucrose and HFCS (experiment 1) and sucrose and G50:F50 (experiment 2) had similar effects on all dependent measures. All sugar solutions similarly reduced the AA area under the curve (AUC). FI and plasma UA concentrations were significantly ($P < 0.05$) lower after high-glucose solutions than after low-glucose solutions. The lower FI was associated with a greater BG AUC ($P < 0.05$) and smaller AA and ghrelin AUCs ($P < 0.01$). Insulin and BG AUCs were positively associated ($P < 0.001$).

Conclusion: Sucrose, HFCS, and G50:F50 solutions do not differ significantly in their short-term effects on subjective and physiologic measures of satiety, UA, and FI at a subsequent meal. *Am J Clin Nutr* 2007;86:1354–63.

KEY WORDS Fructose, glucose, sucrose, high-fructose corn syrup, blood glucose, insulin, ghrelin, uric acid, appetite, food intake

INTRODUCTION

The increase in the prevalence of obesity in the past 35 y has occurred concurrently with the increased availability of added sugars in the food supply and the increased replacement of sucrose with high-fructose corn syrup (HFCS). Thus, it has been hypothesized that HFCS has contributed to overeating and obesity (1, 2).

However, the role of increased availability of sugars—and specifically of HFCS—in the national food supply, as a significant independent contributor to the current epidemic of obesity, is uncertain for several reasons. First, the availability of sugars has not increased disproportionately to the increased availability of total fat, protein, and energy per capita (3). Second, sugars suppress short-term food intake (FI) in children (4, 5) and adults (6–9), and the magnitude of this effect is inversely related to the glycemic response that those sugars elicit (10, 11). Third, HFCS is a nutritive sweetener containing an unbound form of the same monosaccharides as sucrose (sugar). Sucrose is composed of 50% fructose and 50% glucose linked together by α-1–4 glycosidic bonds. The most common forms of HFCS are HFCS 55% and 42%. HFCS 55%, used primarily in beverages, is composed of 45% glucose and 55% fructose, and HFCS 42%, used primarily in foods, is composed of 58% glucose and 42% fructose (2).

Nevertheless, it is biologically plausible that the ratio of glucose to fructose (G:F) in solutions is a determinant of FI. Fructose does not increase the satiety signals of blood glucose (BG) and insulin to the same extent as does sucrose or glucose do (12–14). Short-term FI is inversely related to the glycemic (10, 11) and insulin (15) responses to sugars, and it has been proposed that fructose does not suppress ghrelin, a gastric appetite hormone (2). Therefore, we hypothesized that high G:F consumed in solutions would lead to a greater response in satiety hormones, subjective satiety, and FI at a later meal than would low G:F, but that there would be no differences among equicaloric solutions containing sucrose, its monosaccaride components, and HFCS.

SUBJECTS AND METHODS

Subjects

Nonsmoking males aged 18–35 y with a body mass index (BMI; in kg/m^2) between 20 and 26 were recruited by postings around the St George campus of the University of Toronto. Subjects who had diabetes (fasting glucose ≥ 7.0 mmol/L) or liver or kidney disease, who had undergone a major medical or surgical event within the past 6 mo, or who were breakfast skippers,

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dieters, or under medication were excluded from all sessions. Restrained eaters were also excluded on their identification by a score of ≥11 on an eating habits questionnaire (16).

Written informed consent was obtained from all subjects. The study protocol was approved by the Human Subjects Review Committee, Ethics Review Office, University of Toronto.

Study design and treatments

Two experiments with a randomized repeated-measures design were conducted. Health young men were randomly assigned to receive 1 of 6 sugar solutions at weekly intervals. In experiment 1, the 4 sugar solutions were HFCS (G45:F55, 75% concentrate; Cargill Sweeteners Company, Wayzata, MN), sucrose (Redpath Sugar; Tate and Lyle North American Sugars, Toronto, Canada), G20:F80, and G80:F20. Two control solutions were used. One was a sweet energy-free control that contained water sweetened with sucralose (McNeil Specialty Products Company, New Brunswick, NJ), and one was water alone (Crystal Springs, Quebec City, Canada). Sweetness was equalized for all treatments except the water control by the addition of 54, 52, 27, and 480 g sucralose to the F20:G80, sucrose, HFCS, and sweetened control solutions, respectively. Sucralose was chosen as a noncaloric sweetener because it has no interaction with carbohydrate metabolism, BG, blood fructose, or insulin secretion and has no effect on the central nervous system (17, 18). To reduce sweetness and improve palatability, lemon juice (Equality; The Great Atlantic and Pacific Company of Canada Ltd, Toronto, Canada) was added. These test solutions were rated equally sweet and equally palatable by a test panel of 8 subjects. In experiment 2, subjects received solutions of G20:F80, G35:F65, G50:F50, sucrose, and G80:F20 as test treatments and water as a control. Treatments were not equalized for sweetness and palatability because no associations and interactions were found in experiment 1 between the sweetness or palatability of treatments and subjective appetite or FI.

Twelve subjects were used in experiment 1, which is consistent with the sample size used in many previous studies in which greater suppression of FI was found after a 75-g preload of sucrose or glucose (6, 10) or a preload of 50 g protein (19) than with the energy-free control. Because the sample size may have been too small to show differences among solutions in experiment 1, we calculated that a sample size of 18 (α error = 0.05; β error = 0.20) was needed for identification of a 120-kcal difference in response between the sugar (G20:F80 and G80:F20) solutions. Therefore, in experiment 2, 19 subjects completed the study sessions.

Sugar solutions contained 300 kcal in 300 mL. In both experiments, treatment formulations used D-glucose monohydrate (Grain Process Enterprises Ltd, Scarborough, Canada) and pure fructose (Now Natural Foods, Bloomingdale, IL). Fructose was not added in proportions of >80% of the sugars in solutions because, when fructose is used alone, even small amounts (eg, 26 g) have resulted in symptoms of nausea and diarrhea in 50% of the population (20, 21). In a pilot study in our laboratory, male subjects reported gastrointestinal discomfort after they consumed 75 g (300 mL) of a G10:F90 solution.

The prepared solutions were stored in the refrigerator overnight and served chilled. An additional 100 mL of water was served after the solutions were consumed to reduce aftertaste.

Protocol

The protocol and procedures are similar to those reported in previous studies (6, 10, 19). Subjects chose a time between 1100 and 1400 at which to participate in the sessions, and they were asked to arrive at the same time and on the same day of the week for all sessions. They were required to fast for 10–12 h and then to consume a standard breakfast 4 h before arrival at the testing facilities of the Department of Nutritional Sciences, University of Toronto. The standard breakfast consisted of a single serving of a ready-to-eat cereal (Honey Nut Cheerios; General Mills, Mississauga, Canada), a 250-mL box of 2%-fat milk (Sealtest Skim Milk; Sealtest, Markham, Canada), a 250-mL box of orange juice (Tropicana Products Inc, Bradenton, FL), and tea or coffee without sugar or sweetener. The subjects were asked not to eat or drink anything between their breakfast and the study session except water, which was allowed up to 1 h before the session. They were also instructed to refrain from alcohol consumption and any unusual exercise and activity the night before a study session.

On arrival, subjects completed questionnaires assessing their sleep habits and stress factors and their compliance with fasting and their pattern of activity on the preceding day. If they reported significant deviations from their usual patterns, they were asked to reschedule. Before subjects consumed the test solutions, they completed visual analogue scale (VAS) questionnaires measuring motivation to eat (7, 22) and physical comfort (7), and a blood sample was obtained. If BG was >6 mmol/L, which suggested that the subject had eaten recently or may be insulin resistant, he or she was rescheduled. Participants were moved to another room (feeding room) where they received one of the test solutions. They were instructed to consume the treatment within 3 min and to return to the experiment room to complete questionnaires assessing the sweetness and palatability of the treatments (6). At 15, 30, 45, 60, and 75 min after consumption of the drinks, the VAS scales were completed and blood samples collected. Subjects remained seated throughout the experimental session and were allowed to read or listen to music.

Pizza (McCain Foods Ltd, Florenceville, NB) and water (Crystal Springs) intakes were measured at an ad libitum lunch 80 min after the subjects consumed the preload solutions. In addition, in experiment 2, to measure thirst before eating, subjects received a bottle of water (500 mL) at 75 min. The bottle was removed and replaced by another before the subjects received the pizza tray.

Three varieties of pizza (Deluxe, Pepperoni, and Three Cheese Deep 'N Delicious pizza; McCain Foods Ltd) were purchased from local retailers. All 3 varieties were similar in contents—averaging 10.0 g protein, 7.6 g fat, 26.6 g carbohydrate, and 226 kcal/100 g energy—and in size (5-in diameter). Because of the lack of a thick outer crust, the pizzas have a uniform energy content that eliminates the possibility that participants would eat the energy-dense filling and leave the outside crust of the pizza. Participants ranked the pizzas according to their preference at screening, and their same choices were provided at each of the 6 sessions. Each pizza (cooked for 8 min at 430 °F and cut in 4 slices) was weighed before serving. Subjects were provided 3 varieties of pizzas to reduce the effect of sensory-specific satiety on test meal intake. The pizzas were served to the subjects on trays at 10-min intervals; in each case, the previous tray was removed and the remaining pizza weighed, until the subjects

declined further trays. Each tray contained 2 pizzas of their first choice and 1 pizza each of their second and third choices. Subjects were instructed to eat until they were comfortably full.

The energy intake from the pizza was calculated from the weight consumed and the compositional information provided by the manufacturer. Water intake was measured by weight. Cumulative energy intakes were calculated by adding the energy consumed from the sugar solution to the energy consumed at the test meal. Caloric compensation at the test meal for that consumed in the preloads was calculated by the formula [(kcal consumed at the test meal after the water control – kcal consumed at the test meal after the sugar solution)/300 kcal (in sugar solution)] × 100. A 100% caloric compensation indicates that, at sessions when he was given the 300-kcal treatment, a subject had a lunch intake 300 kcal lower than that at sessions when he was given the control preload. Caloric compensation of <100% indicated that the subject had low compensation for the preload energy at the test meal, whereas scores > 100% indicated overcompensation for preload energy at the test meal.

In each experiment, BG was measured in 12 subjects by finger-prick with the use of a glucometer (Accu-Chek Compact; Roche Diagnostics Canada, Laval, Canada). The same glucometer was used for the same subject for all 6 sessions. Subjects cleaned their fingers before and after each finger-prick with an alcohol swab (Ingram and Bell Medical, Don Mills, Canada). The first drop of blood was wiped off, and the next drop was placed on glucometer strip for measurement of the BG.

To obtain sufficient blood for the measurement of insulin, ghrelin, and uric acid (UA) concentrations in experiment 2, an indwelling intravenous catheter was inserted by a registered nurse into the antecubital fossa vein in the arm of 7 different subjects upon their arrival. The blood samples were drawn into chilled heparinized tubes (Vacutainer; Becton Dickinson, Rutherford, NJ). Two lavender-capped Vacutainer tubes, coated with potassium oxalate–sodium fluoride anticoagulant (EDTA; at 1 mg/mL blood), were used at baseline and 15, 30, 45, 60, and 75 min. For analysis of BG, insulin, and UA, a blood sample was collected in 1 tube (5 mL). For analysis of ghrelin, a separate sample was obtained in a 4-mL Vacutainer tube, and 400 μL aprotinin was added to the tube immediately (<30 s) after blood collection. The tubes were centrifuged at 4 °C for 10–15 min at 2000 × g, and the plasma was stored at −80 °C for analysis. Plasma glucose was measured by using a glucose analyzer (Cobas Integra 800; Roche Diagnostics GmbH, Mannheim, Germany), insulin was measured by using an electrochemiluminescence immunoassay (Roche Diagnostics GmbH), total ghrelin was measured by using a radioimmunoassay (GHRT-89HK; Linco Research Inc, St Charles, MO), and UA was measured by using an enzymatic colorimetric test (11875426 216; Roche Automated Modular Systems, Basel, Switzerland).

Statistical analysis

We used SAS software (version 8.2; SAS Institute Inc, Cary, NC) to conduct the statistical analyses. To test for the effect of the treatments on the outcome variables, one-factor repeated-measures analysis of variance (ANOVA) using the general linear model (PROC GLM procedure) was performed on data for food and water intakes at 80 min, perceived sweetness, palatability of treatments and pizza, physical comfort, and net areas under the curve (AUCs) for average appetite (AA), BG, UA, insulin, and ghrelin. The net AUCs were calculated by applying the trapezoid rule (23), and they included areas over and under the baseline values.

In both experiments, 2-factor repeated-measures ANOVA (GLM) was applied to test for the effects of treatment and time and for treatment × time interaction for AA scores, for the individual VAS used in calculating AA scores, and for BG, insulin, ghrelin, and UA concentrations over 75 min. When an interaction was statistically significant, a one-factor ANOVA using a GLM procedure was followed by Tukey's post hoc test to identify mean differences among treatments at each time of measurement.

In experiment 2, a 2-factor ANOVA (PROC GLM) was performed to determine the effect of the route of blood sampling (finger-prick, $n = 12$; intravenous catheter, $n = 7$) and of treatment on BG, AA, and FI. When venous blood was collected through the indwelling catheter, subjects had significantly lower BG AUC, AA AUC, and FI ($P < 0.01$ for all) than did subjects from whom capillary blood was collected by finger-prick. However, because no significant interaction ($P > 0.05$) was found between treatment and the method of blood sampling, the effect of treatment was consistent across both sampling methods. Therefore, the data for the dependent measures are reported for the pooled sample.

A composite score of the 4 motivation-to-eat VASs was calculated, as described previously by us (6, 10) and others (22), to obtain the AA score. The AA score was reflective of the individual scores on the motivation-to-eat questions and was used here as a summary measure of subjective appetite for analyses.

Correlation analyses of dependent measures were made by using Pearson's correlation coefficients. Significance was set at $P < 0.05$. Data are presented as means ± SEMs.

RESULTS

Subjects

In experiment 1 ($n = 12$) and experiment 2 ($n = 19$), subjects had BMIs of 22.8 ± 0.52 and 24.0 ± 0.37, ages of 29.0 ± 1.33 and 23.6 ± 1.05 y, and weights of 67.6 ± 2.5 and 73.3 ± 1.6 kg, respectively.

Food intake

In both experiments, treatments affected FI. In experiment 1, all sugar solutions except G20:F80 suppressed FI at the test meal significantly ($P = 0.0001$) more than did the water control, but only the G80:F20 and sucrose solutions suppressed FI significantly ($P = 0.0001$) more than did the sweet control (**Table 1**). There were no significant differences in FI among HFCS and the other sugar solutions.

In experiment 2, all sugar solutions except the G20:F80 and G35:F65 solutions suppressed FI at the test meal significantly ($P = 0.0001$) more than did the water control (**Table 2**). Subjects had significantly ($P = 0.0001$) lower FIs after consuming the G80:F20 and sucrose solutions than after consuming the G20:F80 and G35:F65 solutions. However, there were no significant differences in FI between the G50:F50 solution and sucrose or between the G20:F80 and G35:F65 solutions.

Cumulative energy intake

In both experiments, treatments affected cumulative energy intake. In experiment 1, G20:F80 led to the highest cumulative energy intake, although it did not differ significantly from that

TABLE 1
Experiment 1: energy intake, cumulative energy intake, caloric compensation, and water intake after sugar solutions[1]

Solution	Energy intake at test meal[2]	Cumulative energy intake[3]	Caloric compensation[4]	Water intake at test meal
	kcal	*kcal*	*%*	*g*
G20:F80	1207.4 ± 73.4^{a,b}	1507.4 ± 73.4^{a}	44.5 ± 17.2^{b}	416.5 ± 55.6^{a,b}
HFCS	1131.9 ± 89.1^{b,c}	1431.9 ± 89.0^{a,b}	62.7 ± 13.7^{a,b}	434.3 ± 54.9^{a}
Sucrose	1052.4 ± 75.3^{c}	1352.4 ± 75.3^{b}	89.2 ± 11.7^{a}	348.8 ± 33.4^{a,b}
G80:F20	1045.5 ± 83.1^{c}	1343.4 ± 83.1^{b,c}	92.2 ± 15.5^{a}	339.7 ± 27.6^{a,b}
Sucralose	1220.0 ± 73.3^{a,b}	1220.0 ± 73.3^{c}		275.5 ± 40.2^{b}
Water	1320.1 ± 83.2^{a}	1320.1 ± 83.2^{b,c}		327.2 ± 41.3^{a,b}
P	0.0001	0.0001	0.05	0.02

[1] All values are $\bar{x}$ ± SEM; $n = 12$. G, glucose; F, fructose; HFCS, high-fructose corn syrup. Solution ratios are by percentage—eg, G20:F80 = 20% glucose:80% fructose. Means in the same column with different superscript letters are significantly different. $P < 0.05$ [one-factor ANOVA (general linear model) for treatment effect, Tukey's post hoc].

[2] Energy (kcal) consumed in a test meal 80 min after treatments.

[3] Energy in solution (kcal) + energy from test meal (kcal).

[4] Calculated by using the formula [(kcal consumed at the test meal after water control − kcal consumed at the test meal after sugar solution)/300 kcal (in sugar solution)] × 100.

with HFCS (Table 1). The HFCS and sucrose solutions did not differ significantly from each other or the water control, but they resulted in significantly ($P = 0.0001$) higher cumulative energy intakes than did the noncaloric sweet control (sucralose). Cumulative intakes did not differ significantly after water or the G80:F20, HFCS, and sucrose solutions.

In experiment 2, the G20:F80 and G35:F65 solutions resulted in significantly ($P = 0.0001$) higher cumulative energy intakes than did the sucrose and G80:F20 solutions, but the energy intakes did not differ significantly from those with the water control or the G50:F50 solution (Table 2). No statistically significant differences in cumulative energy intakes were observed among sucrose, G50:F50, and the water control.

Caloric compensation

In experiment 1, caloric compensation of 92% and 89% for the G80:F20 and sucrose solutions, respectively, was significantly ($P < 0.05$) greater than that of 45% for G20:F80. At 63%, HFCS did not differ significantly from the other sugar solutions (Table 1). In experiment 2, G80:F20 resulted in a caloric compensation (155%) that was significantly ($P = 0.0001$) greater than that of 46%, 41%, and 56% seen for G20:F80, G35:F65 and, G50:F50, respectively (Table 2). Sucrose at 118% did not differ significantly from the other sugar solutions.

Water intake

In experiment 1, subjects had the highest and lowest water intakes at the test meal after HFCS and the sweet control (sucralose), respectively (Table 1). Water intakes after all other solutions were intermediate and not significantly different from either the HFCS or sucralose solution. In experiment 2, neither cumulative water intakes nor water consumed before or within the test meal differed significantly among the treatments (Table 2).

Average appetite score

All sugar solutions except G20:F80 and HFCS (experiment 1) and G50:F50 (experiment 2) lowered subjective AA AUCs significantly ($P < 0.01$) more than did the water control. However,

TABLE 2
Experiment 2: energy intake, cumulative energy intake, caloric compensation, and water intake after sugar solutions[1]

Solution	Energy intake at test meal[2]	Cumulative energy intake[3]	Caloric compensation[4]	Water intake		
				Before meal	Within meal	Total
	kcal	*kcal*	*%*		*g*	
G20:F80	1466.8 ± 80.3^{a,b}	1766.9 ± 80.3^{a}	45.7 ± 22.0^{c}	138.5 ± 42.6	379.9 ± 42.1	518.4 ± 54.8
G35:F65	1414.2 ± 85.2^{a,b}	1714.2 ± 85.2^{a}	41.3 ± 20.9^{c}	84.7 ± 27.2	337.2 ± 41.7	421.9 ± 51.1
G50:F50	1375.1 ± 85.9^{b,c}	1675.1 ± 85.9^{a,b}	55.8 ± 22.7^{b,c}	102.4 ± 38.4	374.2 ± 41.8	476.7 ± 52.5
Sucrose	1183.2 ± 60.9^{c,d}	1483.2 ± 60.9^{b,c}	118.2 ± 11.8^{a,b}	20.7 ± 13.6	355.9 ± 50.4	376.6 ± 49.4
G80:F20	1140.5 ± 70.0^{d}	1440.5 ± 70.0^{c}	154.5 ± 19.4^{a}	67.1 ± 33.4	353.2 ± 44.6	420.4 ± 47.1
Water	1603.9 ± 91.9^{a}	1603.9 ± 91.9^{a,b,c}		40.1 ± 27.3	357.9 ± 36.2	398.0 ± 34.5
P	0.0001	0.0001	0.0001	0.12	0.97	0.15

[1] All values are $\bar{x}$ ± SEM; $n = 19$. G, glucose; F, fructose. Solution ratios are by percentage—eg, G20:F80 = 20% glucose:80% fructose. Means in the same column with different superscript letters are significantly different, $P < 0.05$ [one-factor ANOVA (general linear model) for treatment effect, Tukey's post hoc].

[2] Energy consumed in a test meal 80 min after treatments.

[3] Energy in solution + energy from test meal.

[4] Calculated by using the formula [(kcal consumed at the test meal after water control − kcal consumed at the test meal after sugar solution)/300 kcal (in sugar solution)] × 100.

TABLE 3
Experiments 1 and 2: average appetite area under the curve (AUC) and blood glucose AUC[1]

Solution	Average appetite AUC[2]	Blood glucose AUC[3]
	mm · min	*mmol · min/L*
Experiment 1		
G20:F80	−319.5 ± 322.4[a,b]	109.1 ± 8.6[c]
HFCS	−96.7 ± 319.4[a,b]	154.4 ± 13.0[b]
Sucrose	−397.3 ± 230.3[b]	156.6 ± 12.5[b]
G80:F20	−421.3 ± 254.6[b]	218.8 ± 19.9[a]
Sucralose	332.7 ± 259.3[a,b]	4.8 ± 6.0[d]
Water	463.4 ± 301.4[a]	7.4 ± 4.3[d]
P	0.005	0.0001
Experiment 2		
G20:F80	−521.2 ± 331.2[b]	70.0 ± 10.3[c]
G35:F65	−526.8 ± 303.8[b]	106.8 ± 14.4[b,c]
G50:F50	−112.6 ± 292.4[a,b]	137.1 ± 13.9[b]
Sucrose	−661.3 ± 247.7[b]	142.2 ± 15.5[b]
G80:F20	−802.5 ± 297.5[b]	189.7 ± 17.5[a]
Water	427.0 ± 197.0[a]	2.1 ± 6.9[d]
P	0.0004	0.0001

[1] All values are $\bar{x}$ ± SEM. G, glucose; F, fructose; HFCS, high-fructose corn syrup. Solution ratios are by percentage—eg, G20:F80 = 20% glucose:80% fructose. Means in the same column with different superscript letters are significantly different, $P < 0.05$ [one-factor ANOVA (general linear model) for treatment effect, Tukey's post hoc].

[2] Average appetite net AUC to 75 min after solution consumption (experiment 1, $n = 12$; experiment 2, $n = 19$).

[3] Blood glucose net AUC to 75 min after solution consumption (experiment 1, $n = 12$; experiment 2, $n = 19$).

AA AUCs did not differ significantly among the sugar solutions in either experiment (**Table 3**).

The AA score was significantly ($P < 0.05$) affected by treatment, time, and treatment × time interaction (**Table 4**). The interaction is explained by the significantly ($P < 0.05$) greater and earlier increase in AA score with time after the controls than after the sugar solutions. The decrease from baseline in AA score after the sugar solutions was the greatest at 15 and 30 min; the AA score then returned to baseline or rose above it at 75 min. In both experiments, AA scores at each time did not differ significantly among the sugar solutions over the 75-min span.

Of the individual VASs used in calculating AA scores, only the fullness scale showed a treatment effect in experiment 1, and this was at 75 min (data not shown). The fullness score was significantly ($P < 0.05$) higher after the G20:F80 and sucrose solutions than after the water control, which is consistent with the overall lower AA score (at 75 min) and FI (at 80 min). In experiment 2, fullness, desire to eat, and hunger all showed a significant ($P < 0.05$) effect of treatment. Sucrose, G80:F20, and G35:F65 led to significantly ($P < 0.05$) lower hunger and higher fullness scores than those seen with the water control. Subjects had less desire to eat after sucrose than after water at 75 min (data not shown).

Blood glucose

In both experiments, all sugar solutions resulted in significantly ($P < 0.0001$) higher BG AUC than did the controls (Table 3). In experiment 1, of the sugar solutions, G80:F20 and G20:F80 resulted in the highest and lowest BG AUCs, respectively; sucrose and HFCS were intermediate and did not differ significantly from each other (Table 3). In experiment 2, the highest and lowest BG AUCs were seen after the G80:F20 and G20:F80 solutions, respectively. The BG AUCs for sucrose, G50:F50, and G35:F65 solutions did not differ significantly (Table 3).

In both experiments, BG was significantly ($P < 0.0001$) affected by treatment, time, and treatment × time interaction. In experiment 1, the increase in BG was significantly ($P < 0.0001$) higher after all sugar solutions than after the water and sucralose controls at 15, 30, and 45 min; G80:F20 and G20:F80 resulted in the

TABLE 4
Experiments 1 and 2: baseline and change from baseline average appetite scores after treatments[1]

		Change from baseline				
Solution	Baseline	15 min	30 min	45 min	60 min	75 min
				mm		
Experiment 1						
G20:F80	64.5 ± 3.8	−10.9 ± 4.8	−9.1 ± 5.0[b]	−3.4 ± 5.0[a,b]	−0.8 ± 5.5[b]	4.5 ± 5.8
HFCS	57.3 ± 6.7	−8.1 ± 4.6	−6.8 ± 5.2[a,b]	−2.7 ± 5.4[a,b]	5.3 ± 5.6[b]	10.9 ± 6.2
Sucrose	66.1 ± 4.6	−10.7 ± 3.5	−9.0 ± 3.3[b]	−6.3 ± 3.9[b]	−1.9 ± 4.2[b]	2.2 ± 4.5
G80:F20	62.0 ± 4.5	−11.1 ± 3.5	−9.8 ± 4.0[b]	−7.0 ± 4.4[b]	−2.7 ± 4.3[b]	4.9 ± 5.4
Sucralose	59.1 ± 6.8	−3.4 ± 4.8	2.8 ± 3.8[a,b]	5.6 ± 4.2[a,b]	10.1 ± 4.1[a]	13.2 ± 4.4
Water	66.2 ± 4.5	−0.2 ± 2.8	4.8 ± 4.0[a]	10.4 ± 5.3[a]	8.8 ± 5.9[a,b]	13.6 ± 6.1
P	0.38	0.14	<0.01	<0.01	<0.02	0.07
Experiment 2						
G20:F80	68.9 ± 4.4	−16.2 ± 5.1[b]	−12.9 ± 5.4[b]	−5.9 ± 5.5[a,b]	−1.4 ± 5.1[b]	2.4 ± 5.2[b]
G35:F65	71.3 ± 3.0	−11.1 ± 4.9[b]	−9.9 ± 4.9[b]	−8.9 ± 4.9[b]	−5.9 ± 4.8[b]	0.8 ± 4.4[b]
G50:F50	62.5 ± 4.4	−10.5 ± 4.2[a,b]	−8.4 ± 4.2[a,b]	−3.9 ± 4.6[a,b]	−0.1 ± 4.8[a,b]	5.7 ± 4.9[a,b]
Sucrose	69.6 ± 3.3	−12.3 ± 3.2[b]	−12.0 ± 3.8[b]	−11.6 ± 4.2[b]	−8.0 ± 4.6[b]	−1.6 ± 4.2[b]
G80:F20	65.5 ± 3.9	−16.1 ± 4.5[b]	−17.3 ± 4.5[b]	−13.1 ± 4.8[b]	−6.9 ± 5.0[b]	−1.1 ± 4.3[b]
Water	65.8 ± 4.0	0.1 ± 2.2[a]	1.8 ± 2.8[a]	6.6 ± 3.3[a]	12.3 ± 3.8[a]	15.3 ± 3.7[a]
P	0.34	<0.001	<0.001	<0.001	<0.001	<0.001

[1] All values are $\bar{x}$ ± SEM. Experiment 1, $n = 12$; experiment 2, $n = 19$. G, glucose; F, fructose; HFCS, high-fructose corn syrup. Solution ratios are by percentage—eg, G20:F80 = 20% glucose:80% fructose. Treatment, time, and treatment × time interaction were significant, $P < 0.05$ for all [2-factor ANOVA (general linear model)]. Means within a column with different superscript letters are significantly different, $P < 0.05$ [one-way ANOVA (general linear model), Tukey's post hoc].

TABLE 5
Experiments 1 and 2: baseline and change from baseline blood glucose concentration[1]

Solution	Baseline	Change from baseline				
		15 min	30 min	45 min	60 min	75 min
				mmol/L		
Experiment 1						
G20:F80	5.1 ± 0.1	2.8 ± 0.2^{b}	2.8 ± 0.3^{b}	1.4 ± 0.3^{b}	0.2 ± 0.1^{b,c}	0.1 ± 0.1^{b}
HFCS	5.0 ± 0.2	3.6 ± 0.3^{a,b}	3.9 ± 0.3^{a}	2.3 ± 0.3^{a,b}	0.6 ± 0.3^{b,c}	−0.2 ± 0.3^{b}
Sucrose	5.2 ± 0.1	3.2 ± 0.2^{a,b}	3.7 ± 0.3^{a}	2.4 ± 0.4^{a,b}	1.2 ± 0.4^{b}	0.2 ± 0.3^{b}
G80:F20	5.1 ± 0.1	3.7 ± 0.3^{a}	4.4 ± 0.3^{a}	3.3 ± 0.5^{a}	2.5 ± 0.5^{a}	1.4 ± 0.4^{a}
Sucralose	5.1 ± 0.1	0.2 ± 0.1^{c}	0.0 ± 0.1^{c}	0.1 ± 0.1^{c}	0.1 ± 0.1^{c}	0.0 ± 0.1^{b}
Water	5.0 ± 0.1	0.2 ± 0.1^{c}	0.1 ± 0.1^{c}	0.1 ± 0.1^{c}	0.1 ± 0.1^{b,c}	0.0 ± 0.1^{b}
P	0.7	<0.0001	<0.001	<0.0001	<0.0001	<0.001
Experiment 2						
G20:F80	4.8 ± 0.2	1.6 ± 0.2^{b}	1.7 ± 0.3^{c}	1.0 ± 0.2^{c,d}	0.4 ± 0.2^{c,d}	0.0 ± 0.2^{b}
G35:F65	4.8 ± 0.2	2.3 ± 0.3^{a,b}	2.7 ± 0.3^{b,c}	1.6 ± 0.4^{b,c}	0.5 ± 0.3^{b,c,d}	0.1 ± 0.1^{b}
G50:F50	4.7 ± 0.2	2.5 ± 0.3^{a,b}	3.5 ± 0.3^{a,b}	2.2 ± 0.3^{b}	0.9 ± 0.2^{b,c}	0.1 ± 0.2^{b}
Sucrose	4.9 ± 0.1	2.5 ± 0.3^{a,b}	3.1 ± 0.4^{a,b}	2.2 ± 0.4^{b}	1.4 ± 0.3^{a,b}	0.7 ± 0.2^{a,b}
G80:F20	4.8 ± 0.2	2.6 ± 0.4^{a}	3.9 ± 0.3^{a}	3.4 ± 0.4^{a}	2.1 ± 0.3^{a}	1.3 ± 0.3^{a}
Water	4.8 ± 0.2	0.0 ± 0.1^{c}	0.0 ± 0.1^{d}	0.1 ± 0.1^{d}	0.0 ± 0.1^{d}	0.1 ± 0.1^{b}
P	0.6	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

[1] All values are $\bar{x}$ ± SEM. Experiment 1, $n = 12$; experiment 2, $n = 19$. G, glucose; F, fructose. Solution ratios are given by percentage—eg, G20:F80 = 20% glucose:80% fructose. Treatment, time, and treatment × time interaction were significant, $P < 0.0001$ for all [2-factor ANOVA (general linear model)]. Means within a column with different superscript letters are significantly different, $P < 0.05$ ([one-factor ANOVA (general linear model), Tukey's post hoc].

highest and lowest BG responses, respectively (**Table 5**). At 60 and 75 min, BG remained significantly ($P < 0.0001$) higher than the water control only after the G80:F20 solution. Sucrose and HFCS resulted in an intermediate and identical significant ($P < 0.0001$) increase in BG. In experiment 2, BG was significantly ($P < 0.0001$) higher after all of the sugar solutions—except the G20:F80 (at 45 and 60 min) and G35:F65 (60 min) solutions—than after the water control at 60 min (Table 5). However, at 75 min, BG was significantly ($P < 0.0001$) higher than the water control only after the G80:F20 solution. There was no significant difference between G50:F50 or sucrose at any time.

Uric acid

Except for the G80:F20 solution, all sugar solutions increased the UA AUC significantly ($P < 0.0001$) more than did the water control (**Table 6**). Of the sugar solutions, G80:F20 and G20:F80 had the lowest and highest UA AUCs, respectively. UA AUCs did not differ significantly after the G35:F65, G50:G50, and sucrose solutions.

UA concentrations were significantly ($P < 0.05$) affected by treatment, time, and treatment × time interaction. The solutions containing G20:F80 (at all times) and G35:F65 (at 30, 45, and 75 min) resulted in significantly ($P < 0.05$) greater increases in UA concentrations than did the solutions containing G80:F20 (**Figure 1**). At 75 min, UA concentrations were highest after G20:F80. The sucrose and F50:G50 solutions each resulted in significantly ($P < 0.05$) lower UA concentrations than did the G20:F80 solution, but they did not differ significantly from any other solutions.

Insulin

Of the sugar solutions, G80:F20 solution had the highest and G20:F80 and G35:F65 solutions had the lowest insulin AUCs (Table 6). The G50:F50 and sucrose solutions did not differ significantly from each other or from any other sugar solution.

Insulin concentrations were significantly ($P < 0.05$) affected by treatment, time, and treatment × time interaction. All sugar

TABLE 6
Experiment 2: effect of sugar solutions on the area under the curve (AUC) for uric acid, insulin, and ghrelin[1]

Solution	Uric acid AUC	Insulin AUC	Ghrelin AUC
	μmol · min/L	*pmol · min/L*	*pg · min/m/L*
G20:F80	3350 ± 389^{a,}[2]	10460 ± 1250^{b}	−11383 ± 3457^{b}
G35:F65	2354 ± 581^{a,b}	12638 ± 2218^{b}	−12063 ± 2695^{b}
G50:F50	1550 ± 525^{b,c}	15208 ± 2494^{a,b}	−14808 ± 3727^{b}
Sucrose	1668 ± 300^{a,b,c}	16593 ± 1796^{a,b}	−10093 ± 2828^{b}
G80:F20	334 ± 186^{c,d}	20583 ± 3093^{a}	−8753 ± 2034^{b}
Water	−474 ± 352^{d}	−218 ± 369^{c}	1848 ± 1199^{a}
P	0.0001	0.0001	<0.001

[1] Experiment 2, $n = 7$. G, glucose; F, fructose. Solution ratios are given by percentage—eg, G20:F80 = 20% glucose:80% fructose. Means in the same column with different superscript letters are significantly different, $P < 0.05$ [one-factor ANOVA (general linear model), Tukey's post hoc].

[2] $\bar{x}$ ± SEM (all such values).

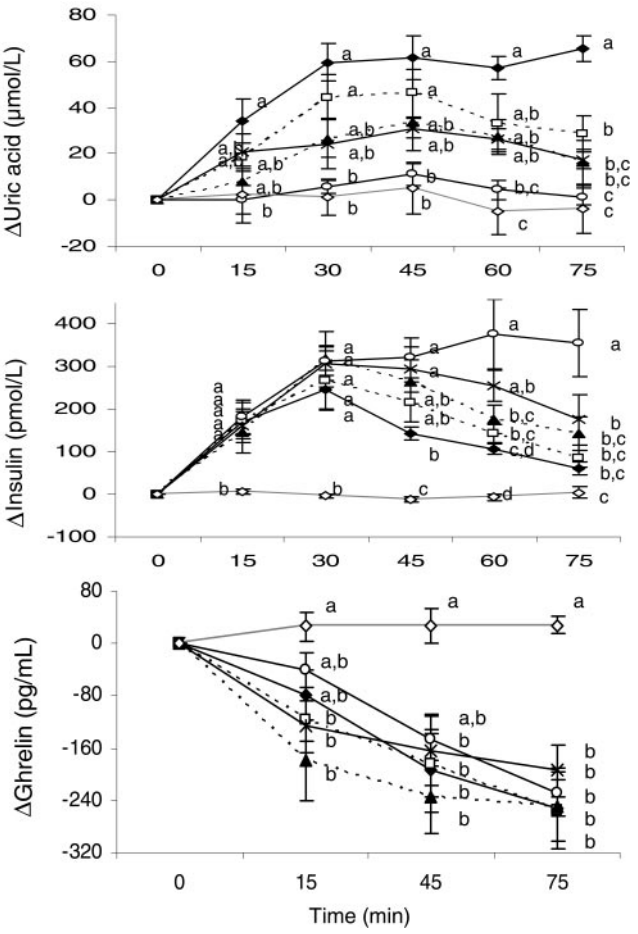

FIGURE 1. Effect of sugar solutions on plasma uric acid, insulin, and ghrelin in experiment 2. Solutions were glucose (G) and fructose (F) at ratios of G20:F80 (♦), G35:F65 (□), G50:F50 (▲), sucrose (*), G80:F20 (○), and water (◇). Δ, change. Mean plasma uric acid, insulin, and total ghrelin at baseline were 295.9 ± 8.5 μmol/L, 45.3 ± 3.8 pmol/L, and 733.4 ± 40.7 pg/mL, respectively. Significant treatment, time, and treatment × time interaction effects ($P < 0.05$ for all) were found by 2-factor ANOVA (general linear model, GLM). One-factor ANOVA (GLM) followed by Tukey's post hoc was used to differentiate the effect of treatment at each measured time. Means at the same time with different superscript letters were significantly different, $P < 0.05$ ($n = 7$).

solutions increased insulin concentrations at 15, 30, and 45 min significantly ($P < 0.05$) more than did the water control. The G20:F80 solution resulted in significantly ($P < 0.05$) lower insulin concentrations than did the sucrose and G80:F20 solutions at 45 min (Figure 1). At 60 min, insulin concentrations after the G20:F80 solution did not different from those after the control. At 75 min, insulin concentrations remained significantly ($P < 0.05$) higher than those after the control only after the G80:F20 and sucrose solutions, but there were no significant differences among G20:F80, G35:F65, sucrose, and G50:F50.

Ghrelin

All sugar solutions resulted in significantly ($P < 0.05$) lower ghrelin concentrations than did the water control. Thus, the ghrelin AUC was negative and significantly ($P < 0.05$) larger after all sugar solutions than after the water control (Table 6).

Ghrelin concentrations were significantly ($P < 0.05$) affected by treatment, time, and treatment × time interaction (Figure 1). The interaction appears to be explained by a significantly ($P < 0.05$) greater and earlier suppression in ghrelin by sucrose and G50:F50 than by G80:F20 and G20:F80, but no sugar solutions resulted in a significant difference in ghrelin concentrations at 30 min. All sugar solutions except G80:F20 (at 15 and 45 min) and G20:F80 (at 15 min) resulted in significantly ($P < 0.05$) lower ghrelin concentrations than did the water control.

Relations among dependent measures

FIs were positively correlated with AA score at 75 min (experiment 1: $r = 0.42$, $P < 0.001$; experiment 2: $r = 0.27$, $P < 0.005$), and inversely correlated with BG (experiment 2: $r = -0.41$, $P < 0.01$) and insulin (experiment 2: $r = -0.39$, $P < 0.05$) concentrations at 45 min. FIs were inversely correlated with BG AUC (experiment 1: $r = -0.30$, $P < 0.01$; experiment 2: $r = -0.38$, $P < 0.0001$) (**Figure 2**). The lower AA as reported by AUC was correlated with lower FIs (experiment 1: $r = 0.41$, $P < 0.001$; experiment 2: $r = 0.18$, $P = 0.06$) and higher BG AUCs (experiment 1: $r = -0.29$, $P < 0.05$; experiment 2: $r = -0.31$, $P < 0.001$) (Figure 2).

In the subsample ($n = 7$) in experiment 2, insulin AUC was positively correlated with BG AUC ($r = 0.51$, $P < 0.001$). At 15 min, insulin concentrations were correlated with BG ($r = 0.60$, $P < 0.001$) and UA ($r = 0.32$, $P < 0.05$) concentrations. At 45 min, insulin concentrations were positively correlated with BG concentrations ($r = 0.48$, $P < 0.01$) and inversely correlated with FIs at the test meal ($r = -0.39$, $P < 0.05$). At 75 min, insulin concentrations were significantly correlated with BG ($r = 0.73$, $P < 0.0001$). The magnitude of the decrease in ghrelin as measured by AUC was positively correlated with the reductions in AA AUCs ($r = 0.60$, $P = 0.0001$) and FIs ($r = 0.40$, $P < 0.01$). At 45 min, plasma ghrelin concentrations were inversely correlated with BG concentrations ($r = -0.30$, $P = 0.05$) and positively correlated with FIs at the test meal ($r = 0.42$, $P < 0.01$).

DISCUSSION

These studies do not support the hypothesis that the replacement of sucrose with HFCS as a caloric sweetener has contributed to overeating and obesity because of differences in their short-term physiologic affects (2). The equicaloric solutions of HFCS, F50:G50, and sucrose were similar in their effects on subjective measures of satiety, blood concentrations of physiologic signals of satiety and of UA, and short-term FIs. However, high G:F in isocaloric sugar solutions resulted in higher BG and insulin concentrations and lower UA concentrations and FIs than did low G:F.

Sucrose, HFCS, and G50:F50 solutions induced similar BG and hormonal responses and decreases in subjective satiety and FIs at the test meal. Sucrose and HFCS were similar to each other in their effects on BG in experiment 1, and it would be expected that the insulin responses were similar because it was previously shown that sucrose and HFCS have similar effects on postprandial BG and insulin concentrations (24). Furthermore, when sucrose or HFCS beverages were served at meals to make up ≈17% of the energy, no differences were found in BG, insulin, leptin, and ghrelin concentrations measured at frequent intervals over 24 h (25). In experiment 2, a solution of G50:F50 was compared with sucrose because, when sucrose is added to acidic solutions, as in soft drinks or fruit-flavored drinks, that sucrose is primarily hydrolyzed before consumption (26). Again, the disaccharide

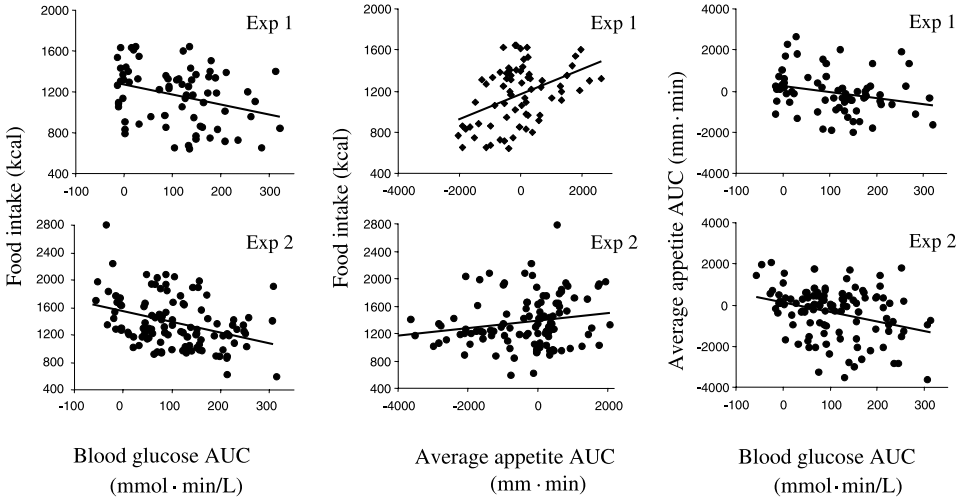

FIGURE 2. Associations between the blood glucose (BG) area under the curve (AUC; mmol · min/L) and food intake (FI; kcal): Experiment 1 (Exp 1): $n = 12$ ($r = -0.30$, $P < 0.01$); experiment 2 (Exp 2): $n = 19$ ($r = -0.38$, $P < 0.001$). Associations between average appetite (AA) AUC (mm · min) and FI (kcal): Exp 1: $n = 12$ ($r = 0.41$, $P < 0.001$); Exp 2: $n = 19$ ($r = 0.18$, $P = 0.06$)]. Associations between BG AUC (mmol · min/L) and AA AUC (mm · min): Exp 1: $n = 12$ ($r = -0.29$, $P < 0.05$); Exp 2: $n = 19$ ($r = -0.31$, $P < 0.001$). Associations were calculated by using Pearson's correlation coefficients.

and the monosaccharide mixtures led to the same results in all dependent measures.

Both experiments showed greater suppression of FI and increased caloric compensation associated with higher G:F ratios in solutions. All sugar solutions except the low-glucose-containing sugar solutions (G20:F80 and G35:F65) led to lower FIs at 80 min than did the water control. These results are consistent with previous reports that 75-g sucrose and glucose solutions, but not a G20:F80 solution, suppressed FIs 60 min later (6, 10) and that FI shortly after the consumption of sugar solutions is inversely related to the effect of sugar solutions on BG (11). The results contrast with reports that solutions containing fructose alone suppress FI at a later meal more than do glucose solutions (12). However, in these comparisons, this effect of fructose was due to its slow absorption when consumed in the absence of glucose, which resulted in gastrointestinal distress (19). For this reason, a solution of fructose alone was not included in the present studies

All sugar solutions increased BG and insulin and reduced ghrelin more than did the control. Although BG may contribute directly to satiety (7, 8), it is clearly not the only reason for the more favorable effects of the high-glucose solutions than of the high-fructose solutions on FI. High-glucose treatments and the higher BG responses derived from them also were associated with greater responses in the satiety hormone insulin and a decrease in the orexigenic hormone ghrelin. However, the role of BG and insulin in the suppression of ghrelin remains uncertain for several reasons. Although a previous study reports that glucose at 15% of the energy in meals (27) leads to lower postprandial ghrelin than does fructose at 15% of the energy in meals, this association does not define the mechanism controlling the suppression of ghrelin secretion. In the present study, insulin and ghrelin responses were not found to be inversely related, and this observation is consistent with more recent data showing that, whereas the presence of insulin is required, a postprandial insulin response is not required, and nutrient sensing by ghrelin-producing cells is an important regulator of ghrelin secretion (28). For example, fat ingestion leads to ghrelin suppression but does not increase postprandial insulin (29). Our data support the proposed role of ghrelin-producing cells in nutrient sensing, because all sugar solutions suppressed ghrelin similarly, even though BG and insulin were higher in the high-glucose than in the low-glucose solutions.

Plasma UA was measured because replacement of sucrose with HFCS has been suggested to play a causal role in the metabolic syndrome (30). Fructose consumption increases plasma UA by increasing purine biosynthesis and decreases renal clearance of UA by increasing plasma lactate concentrations (31). In the present study, all sugar solutions except the G80:F20 solution significantly increased UA above control values and the fructose content of the solutions associated positively with UA AUC ($r = 0.69$, $P < 0.0001$) and inversely with insulin AUC ($r = -0.54$, $P < 0.001$). However, the G50:F50 and sucrose solutions increased UA AUC equally, which suggests that a significant difference between HFCS and sucrose is unlikely. Therefore, whereas greater intakes of fructose may elevate plasma UA, as reported previously (31), the substitution of HFCS for sucrose is an unlikely contributor to the metabolic syndrome by this mechanism.

The differing G:F in solutions did not affect water consumption. The observation that subjects in experiment 1 drank more water at their meal after the HFCS than after the sweet control was pursued in experiment 2 because it was possible that fructose, because of its slower absorption compared with that of glucose (32), created a hyperosmolar environment in the small intestine and thus caused the retention of fluid, feelings of thirst, and gastrointestinal discomfort (19). Because all sugar solutions resulted in similar water intake before and during the test meal in experiment 2, the differences found between HFCS and the sucralose solution in experiment 1 were attributed to reduced thirst after the sucralose solution and not to increased thirst due to fructose in the sugar solutions. Although there is no mechanism to account for this effect of sucralose, it does not appear to be unique because, when consumed during a meal, aspartame-sweetened drinks reduced thirst more than did sucrose-sweetened drinks (33).

Sweetness was not equalized among solutions in experiment 2 because it was proposed that the greater sweetness of fructose would also be an independent factor affecting FI (2). However, no significant relation was found between the sweetness ($r = -0.06$) and palatability ($r = 0.13$) of treatments and FI at the test meal, as expected if the time interval between treatment and FI is >1 h (34). In experiment 1, whereas the sweetness of all solutions except the water control was equalized with the sweetest solution (G20:F80), sweetness was reduced by adding lemon juice. The subjects judged the palatability of the test solutions to be equal to the water control.

High FIs by young men given test meals after an overnight fast and a light breakfast have been reported in many studies, but this has not been found to compromise treatment effects (6–8, 10–11). The higher FIs in experiment 1 than in experiment 2 may be due to several reasons. First, experiment 1 was conducted in the summer, and experiment 2 was conducted in the winter. Higher ambient temperatures are associated with lower FIs than are low ambient temperatures (35). Second, on average, subjects came in 2 h later in experiment 2. Therefore, the test meal later in the day would also contribute to greater hunger and FI. Third, subjects in experiment 2 were on average 5.4 y younger ($P < 0.004$) and 5.7 kg heavier ($P < 0.06$) and had a BMI 1.2 greater ($P < 0.06$) than did subjects in experiment 1. Appetite and FI are reduced by age (36) and are increased in association with body weight and the duration of fasting (37). The overall treatment effects in the 2 experiments were similar, however, which suggests that these differences in characteristics and FIs between the 2 samples did not affect the outcomes.

In conclusion, solutions of HFCS, F50:G50, and sucrose were similar in their effects on subjective measures and physiologic signals of satiety, plasma UA concentrations, and FIs in young men. However high G:F in isocaloric sugar solutions result in higher BG and insulin concentrations and lower UA concentrations and FIs than did low G:F.

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The authors' responsibilities were as follows—GHA: conceiving the hypothesis, designing the experiment, and writing the manuscript; and TA: conducting the experiments, collecting and analyzing the data, and writing the manuscript. GHA serves as the chair of the board of the International Life Sciences Institute and as a science advisor to the Canadian Sugar Institute and to Archer Daniels Midland (a producer of HFCS); he has no equity or other financial interests in either industry. GHA also has received unrestricted research grant funding from the US Sugar Association and the Canadian Sugar Institute. TA had no personal or financial conflict of interest.

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