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Endocrine and metabolic effects of consuming beverages sweetened with fructose, glucose, sucrose, or high-fructose corn syrup¹⁻⁵

Kimber L Stanhope and Peter J Havel

ABSTRACT

Our laboratory has investigated 2 hypotheses regarding the effects of fructose consumption: 1) the endocrine effects of fructose consumption favor a positive energy balance, and 2) fructose consumption promotes the development of an atherogenic lipid profile. In previous short- and long-term studies, we showed that consumption of fructose-sweetened beverages with 3 meals results in lower 24-h plasma concentrations of glucose, insulin, and leptin in humans than does consumption of glucose-sweetened beverages. We have also tested whether prolonged consumption of high-fructose diets leads to increased caloric intake or decreased energy expenditure, thereby contributing to weight gain and obesity. Results from a study conducted in rhesus monkeys produced equivocal results. Carefully controlled and adequately powered long-term studies are needed to address these hypotheses. In both short- and long-term studies, we showed that consumption of fructose-sweetened beverages substantially increases postprandial triacylglycerol concentrations compared with glucose-sweetened beverages. In the long-term studies, apolipoprotein B concentrations were also increased in subjects consuming fructose, but not in those consuming glucose. Data from a short-term study comparing consumption of beverages sweetened with fructose, glucose, high-fructose corn syrup, and sucrose suggest that high-fructose corn syrup and sucrose increase postprandial triacylglycerol to an extent comparable with that induced by 100% fructose alone. Increased consumption of fructose-sweetened beverages along with increased prevalence of obesity, metabolic syndrome, and type 2 diabetes underscore the importance of investigating the metabolic consequences of fructose consumption in carefully controlled experiments. *Am J Clin Nutr* 2008;88(suppl):1733S-7S.

INTRODUCTION

Some investigators have proposed that increased fructose consumption may be related to the current epidemics of obesity and metabolic syndrome (1-4). The purpose of this article is to review some of our recent work investigating 2 hypotheses: 1) fructose consumption promotes a state of positive energy balance, and 2) fructose consumption favors the development of an atherogenic lipoprotein profile.

FRUCTOSE CONSUMPTION AND ENERGY BALANCE

Consumption of dietary fructose has increased in conjunction with rising intake of fructose-containing sugars, largely in the form of sugar-sweetened beverages. Malik et al (5) conducted a

systematic review of the relation between sugar-sweetened beverage consumption and risk of weight gain and concluded that the evidence indicates that increased consumption of sugar-sweetened beverages is associated with weight gain. We have hypothesized that fructose consumption could promote weight gain because it does not stimulate insulin secretion or leptin production by adipose tissue (2, 3). Because leptin production is regulated by insulin-mediated glucose metabolism (6-8) and ingestion of fructose does not result in meal-related increases of plasma glucose or insulin concentrations, we hypothesized that meals accompanied by fructose-sweetened beverages would result in reduced circulating leptin concentrations when compared with glucose-sweetened beverages. We compared leptin concentrations over 2 separate 24-h periods in 12 normal-weight young women who consumed fructose- or glucose-sweetened beverages with meals. Consumption of fructose-sweetened beverages at 30% of energy requirements with 3 meals resulted in lower 24-h circulating concentrations of glucose, insulin, and leptin and resulted in less postprandial suppression of ghrelin after each meal compared with consumption of glucose-sweetened beverages (9). In a second short-term study comparing fructose- and glucose-sweetened beverages (30% of energy requirements),

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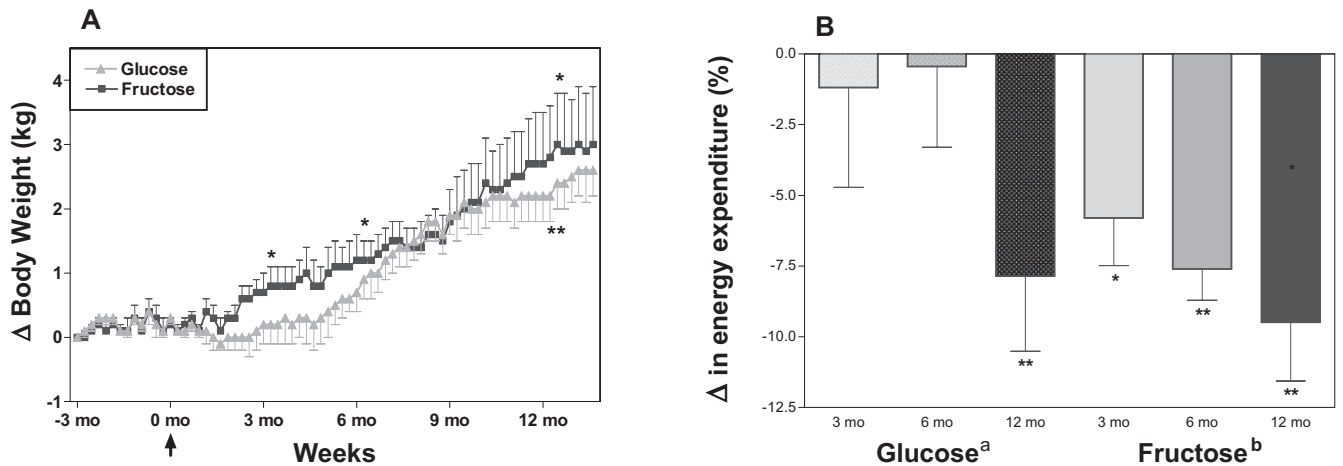


FIGURE 1. (A) Changes (Δ) in body weight from baseline in male rhesus monkeys consuming 380 kcal/d of fructose- or glucose-sweetened beverage for 1 y ($n = 8$ /group). Baseline body weights were not significantly different. Data are mean \pm SEM (analysis described in Figure 2). Responses to each sugar over time were analyzed by repeated-measures ANOVA (SAS version 9.1; SAS Institute Inc, Cary, NC) with contrasts comparing weights at 3, 6, and 12 mo to baseline weights ($^*P < 0.05$, $^{**}P < 0.01$). Comparison of fructose and glucose response analyzed by 2-factor repeated measures ANOVA: sugar \times time interaction = NS. (B) Percentage change in energy expenditure (measured by indirect calorimetry) from baseline in rhesus monkeys after 3, 6, and 12 mo of consuming 380 kcal/d of fructose- or glucose-sweetened beverages. Baseline energy expenditure was not significantly different between groups. Data are mean \pm SEM. Responses to each sugar over time were analyzed by repeated-measures, one-factor ANOVA ($^*P < 0.05$; $^bP < 0.01$ with Greenhouse-Geisser Epsilon correction with contrasts comparing energy expenditure at 3, 6, and 12 mo to baseline energy expenditure ($^*P < 0.05$, $^{**}P < 0.01$). Comparison of fructose and glucose response analyzed by two-factor repeated measure ANOVA: sugar \times time interaction = NS. $n = 6$ /group.

meal-induced insulin secretion was attenuated and 24-h circulating leptin profiles were reduced in both overweight and obese men and overweight and obese women (10). Fructose-sweetened beverage consumption also reduced the percent (proportional) change of leptin concentrations between the morning nadir and the late night peak (9, 10). Results from a clinical study investigating weight and body fat loss during an ad libitum, low-fat, high-carbohydrate diet suggest an association between the amplitude of the diurnal leptin pattern and long-term energy balance (11).

In long-term comparisons of fructose- and glucose-sweetened beverages (25% of energy requirements consumed with meals), fructose consumption resulted in significant reductions in the 24-h areas under the curve for glucose, insulin, and leptin (12), whereas consumption of glucose did not. These results indicate that reductions of insulin secretion and attenuated 24-h leptin profiles observed in the short-term studies are not transient, but are maintained during long-term fructose consumption.

Insulin and leptin function as key endocrine signals to the central nervous system in the long-term regulation of energy balance (13, 14). Therefore, prolonged consumption of diets high in energy from fructose could lead to increased caloric intake or decreased caloric expenditure, contributing to weight gain and obesity as a result of reduced insulin and leptin signaling in the brain (3). However, obtaining definitive evidence in support of this hypothesis in human subjects would be extremely difficult. It would require that subjects be provided and restricted to ad libitum consumption of a high-fructose or high-glucose diet that has been designed to achieve a comparable and controlled macronutrient distribution in all subjects, regardless of quantities consumed. It would also require that the intervention last ≥ 12 mo, because a difference in body weight change as small as 0.5 kg/y between groups would be a clinically relevant finding. The costs, as well as the compliance and retention issues, involved in conducting such a study would likely prove to be prohibitive.

FRUCTOSE AND LONG-TERM ENERGY BALANCE IN RHESUS MONKEYS

We conducted a 12-mo study in 16 adult male rhesus monkeys (*Macaca mulatta*) to determine whether prolonged consumption of a diet high in energy from fructose would lead to greater weight gain via increased caloric intake, decreased energy expenditure, or both compared with a diet high in glucose. Monkeys ($n = 8$ /group) were fed an ad libitum standard chow diet supplemented with either glucose- or fructose-sweetened beverages (100 g sugar/d). The 2 groups of monkeys consumed an average of $43.8 \pm 4.1\%$ and $41.5 \pm 2.7\%$ of total energy as glucose and fructose, respectively, during the 12-mo intervention period. Monkeys fed fructose beverages gained significant amounts of weight at 3 and 6 mo compared with their baseline weights, whereas the animals consuming glucose did not. However, weight gain was not significantly different between the 2 groups by the end of the study at 12 mo (Figure 1A).

Food and beverage intake was measured daily, and differences in energy intake did not account for the weight gain in monkeys fed fructose-sweetened beverages during the first 6 mo of the study. Differences in energy expenditure between the 2 groups of animals may have explained the early differences in body weight gain (Figure 1B). Energy expenditure was measured by indirect calorimetry at baseline and at 3, 6, and 12 mo. We monitored the monkeys for three 24-h periods at each time point, calculated postprandial energy expenditure (from 1700 h to 0100 h), and averaged the results from the 2 closest measurements.

The energy expenditure profiles at baseline were comparable for both groups (glucose: 0.205 ± 0.004 ; fructose: 0.202 ± 0.007 $\text{kJ} \cdot \text{min}^{-1} \cdot \text{kg BW}^{-0.75}$). At 3 and 6 mo, energy expenditure during the postprandial period in the fructose-fed monkeys was significantly decreased when compared with baseline, whereas energy expenditure in monkeys consuming glucose was unchanged (Figure 1B). However, at 12 mo, the energy expenditure

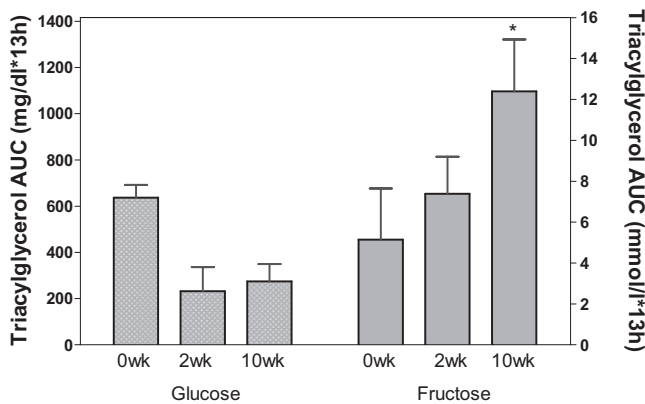


FIGURE 2. Fourteen hour area under the curve (AUC) for plasma triacylglycerol at baseline and at 2 and 10 wk of dietary intervention in women consuming 25% of energy as glucose-sweetened beverages ($n = 3$) or fructose-sweetened beverages ($n = 5$). Comparison of fructose and glucose response was analyzed by two-factor repeated-measures ANOVA by using GraphPad Prism (version 4.03; San Diego, CA) with Bonferroni post-tests. Sugar \times time interaction: $P = 0.017$; * $P < 0.05$ versus 10 wk glucose. Data are mean \pm SEM.

of the monkeys consuming glucose was significantly reduced compared with the earlier time points, and more comparable to the profiles of the monkeys consuming fructose. Thus, the timing of changes in body weight of both the animals consuming fructose and those consuming glucose appear to have been more closely related to changes in energy expenditure than to changes in energy intake. These equivocal results from a year-long study in nonhuman primates indicate that additional carefully controlled studies will be required to determine whether fructose consumption preferentially promotes positive energy balance compared with consumption of glucose.

FRUCTOSE AND LIPID METABOLISM

Other important differences in the metabolic consequences of fructose and glucose consumption warrant investigation. Both of our short-term studies (in normal-weight women and overweight men and women) showed that consumption of fructose-sweetened beverages with meals increased 24-h circulating plasma triacylglycerol concentrations compared with consumption of glucose-sweetened beverages (9, 10). Results from a long-term study indicate that consuming fructose-sweetened beverages at 25% of energy requirements for 10 wk increased 24-h triacylglycerol exposure by 140% in overweight women (12). In contrast, in subjects consuming the same amount of glucose-sweetened beverages for 10 wk, the 24-h triacylglycerol area under the curve tended to decrease (Figure 2; 15). These findings are consistent with our current long-term study in a larger number of overweight and obese men and women (16).

Previous studies indicated that hepatic de novo lipogenesis increases during fructose ingestion (17, 18). Fructose consumption may promote hepatic lipogenesis via several mechanisms: the liver is the main site of fructose metabolism (19); fructose enters glycolysis via fructose-1-phosphate, bypassing the main rate-controlling step of glucose metabolism through glycolysis catalyzed by phosphofructokinase, thus providing unregulated amounts of the lipogenic substrates acetyl-CoA and glycerol-3-phosphate (19); fructose upregulates sterol receptor element binding protein-1c (SREBP-1c) independently of insulin, thus

activating genes involved in de novo lipogenesis, eg, fatty acid synthase and acetyl coA carboxylase (20, 21).

Growing evidence links postprandial lipemia with proatherogenic conditions (22–25). The relation between triacylglycerol-rich lipoproteins and atherogenesis is most likely mediated by the effects of postprandial hypertriacylglycerolemia, which promotes lipoprotein remodeling to a more atherogenic lipid profile consisting of increased concentrations of triacylglycerol-rich lipoprotein remnants and small, dense LDL cholesterol (25–27). This mechanism is consistent with our long-term results showing increased concentrations of fasting and postprandial apolipoprotein B-100 (apo B), (12, 16) with fructose consumption. Apo B concentrations were increased in the absence of comparable increases in LDL cholesterol, which suggests that fructose consumption increased the number of total LDL cholesterol particles (28) while decreasing particle size (29). As LDL cholesterol particles become smaller, conformational changes occur in apo B that increase its affinity for arterial wall proteoglycans (30). Thus, apo B is a clinically important apolipoprotein that assembles atherogenic lipoproteins and promotes the development of atherosclerosis (30). Therefore, long-term consumption of diets containing 25% of energy from fructose produces a lipoprotein profile that has been associated with the development of atherosclerosis.

In these studies, we have compared the metabolic effects of beverages sweetened with fructose and glucose alone; however, pure fructose and pure glucose are not commonly used as sweeteners. Until a few decades ago, most foods and beverages in the United States were sweetened with the disaccharide sucrose, which is composed of 50% glucose and 50% fructose. In 1970, the enzymatic process to convert corn sugar (composed of glucose) into high-fructose corn syrup (HFCS) was developed. Since then, HFCS, primarily 55% fructose and 45% glucose (HFCS-55), has replaced sucrose as the predominant sweetener in soft drinks and represents $\approx 40\%$ of the sweeteners added to foods consumed in the United States (31).

It is reasonable to hypothesize that the endocrine and metabolic effects of HFCS and sucrose would be similar to each other and that both would produce responses intermediate between those of pure fructose and glucose, and we have investigated this hypothesis (32). In a short-term study comparing the effects of consuming beverages sweetened with HFCS, sucrose, fructose, and glucose (25% of energy) with meals in male subjects, consumption of either HFCS- or sucrose-sweetened beverages produced postprandial glucose, insulin, and leptin profiles that were intermediate to responses induced by pure fructose and pure glucose. However, unexpectedly, postprandial triacylglycerol responses to consumption of sucrose and HFCS were comparable to 100% fructose in both peak concentrations and integrated 24-h areas under the curve (Figure 3; 32). Long-term studies are needed to confirm these results, and we are currently initiating a dose-response study to compare the effects of consuming diets containing 3 different levels of HFCS or fructose.

FRUCTOSE AND ADDED SUGAR CONSUMPTION

If prolonged consumption of 25% of energy from HFCS or sucrose increases postprandial triacylglycerol, apo B, and small, dense LDL to a comparable degree as fructose alone, this finding is likely to have important public health implications. The Institute of Medicine of the National Academies in the 2002 Dietary

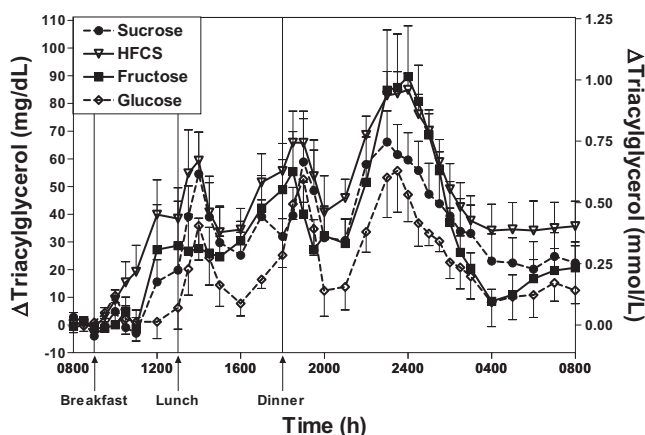


FIGURE 3. Change (Δ) in plasma triacylglycerol concentrations from mean baseline levels (0800–0900 h) during 4 separate 24-h periods (0800–0800 h) in 7 men consuming high-fructose corn syrup (HFCS-), sucrose-, fructose-, and glucose-sweetened beverages at 25% of calculated energy requirements with each meal. Baseline triacylglycerol concentrations were not significantly different on the 4 study days. The effects of the 4 sugars on 24-h triacylglycerol area under the curve (AUC) were significantly different, $P = 0.007$ (repeated-measures one-factor ANOVA) and the 24-h AUC during HFCS was significantly higher than during glucose consumption, $P < 0.01$ (Tukey's post-test). Data are mean \pm SEM.

References Intakes (DRIs) concluded that there was insufficient evidence to set an upper intake level for added sugars because there were not specific adverse health outcomes associated with excessive intake (33). Therefore, they suggested a maximum intake level of 25% of energy from added sugars.

The estimated mean intake of added sugars by Americans is 15.8%; however, this value is based on consumption data from the 1994–1996 Continuing Survey of Food Intakes by Individuals (34). Recent data suggest that these intake rates may significantly underestimate actual sugar and sugar-sweetened beverage consumption by children and young adults. It was reported that the mean energy intake from sugar-sweetened beverages by 265 college students was 543 kcal/d (35), representing >20% of energy in a 2500-kcal/d diet and >25% of a 2000-kcal/d diet. The mean intakes of sugar-sweetened beverages in 172 boys and 211 girls (age 13 y) were 809 and 674 mL/d, respectively (36). Assuming energy intakes of 2500 and 2000 kcal/d for the boys and girls, respectively, these adolescents consumed \approx 15% of energy as sugar-sweetened beverages. Mundt et al (37) followed 208 boys and girls (aged 8–19 y) for an average of 5 y and found that sugar-sweetened beverage consumption increased with age, whereas physical activity declined. By the final year of the study, both males and females were consuming >16% of energy as sugar-sweetened beverages. Similar results were reported for 2371 girls followed from ages 9 to 15 y (38). Sugar-sweetened beverage consumption increased with age and averaged 14–16% of total energy intake during the final study year. A recent analysis of energy consumed as beverages in the US population (using 1999–2002 National Health and Nutrition Examination Survey data; 39) reported that the percentage of energy consumed from soft drinks, fruit drinks, and juices averaged 18.5% for males and 13.5% for females (20–39 y of age). These data suggest that the proportion of energy intake consumed from sugar-sweetened beverages by adolescents, college students, and adults up to 39 y of age approaches or exceeds 15.8% (the current

estimate for the mean intake of total added sugar), without accounting for any other dietary sources of sugars. The large standard deviations in several of these reports (35–37) suggest that \geq 16% of the studied populations were consuming >2 times the mean intake, and therefore well over 25% of daily energy requirements from sugar-sweetened beverages. On the basis of these more recent intake data (35–39) and the current DRI guideline for maximal added sugar intake (33), as well as our short-term results suggesting that 25% of energy as HFCS or sucrose increases postprandial triacylglycerol concentrations comparably to fructose alone (32), long-term dose-response studies investigating the metabolic effects of consuming HFCS or sucrose up to the level of 25% of energy are needed.

CONCLUSIONS

Results from both short-term and long-term studies show that fructose consumption results in decreased circulating levels of insulin and leptin when compared with glucose. Because insulin and leptin 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 or decreased caloric expenditure, thereby contributing to weight gain and obesity. Results from a 1-y study in nonhuman primates were equivocal, and testing this hypothesis in human subjects is likely to be difficult and costly.

In both short- and long-term studies, we have shown that fructose consumption substantially increases postprandial triacylglycerol concentrations (9, 10, 12, 16). In long-term studies, plasma apo B concentrations and small, dense LDL are increased in subjects who consumed fructose-sweetened, but not glucose-sweetened, beverages for 10 wk (12, 16). Results from a short-term study suggest that consuming HFCS- and sucrose-sweetened beverages increases postprandial triacylglycerol concentrations to the same degree as fructose alone (32). Further long-term studies are needed to investigate the effects of fructose, sucrose, and HFCS not only on lipid metabolism, but also on glucose tolerance, insulin sensitivity, visceral adiposity, and hepatic triacylglycerol content. These studies should include populations that differ in age, sex, and metabolic status, as well as dose-response studies to determine the amounts of dietary fructose, HFCS, and sucrose that result in potentially adverse effects on lipid and carbohydrate metabolism. (Other articles in this supplement to the Journal include references 40–43).

We thank and acknowledge James Graham for his essential technical support of the studies presented in the manuscript. The contributions of the authors were as follows—KLS: implementing the studies presented in the article, organizing and analyzing the data, and preparing the manuscript; PJH: conceiving and designing the studies, obtaining funding, and preparing the manuscript. Both authors read and approved the final submitted manuscript. The authors had no conflicts of interest.

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