Markedly Blunted Metabolic Effects of Fructose in Healthy Young Female Subjects Compared With Male Subjects

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OBJECTIVE — To compare the metabolic effects of fructose in healthy male and female subjects.

RESEARCH DESIGN AND METHODS — Fasting metabolic profile and hepatic insulin sensitivity were assessed by means of a hyperglycemic clamp in 16 healthy young male and female subjects after a 6-day fructose overfeeding.

RESULTS — Fructose overfeeding increased fasting triglyceride concentrations by 71 vs. 16% in male vs. female subjects, respectively ($P < 0.05$). Endogenous glucose production was increased by 12%, alanine aminotransferase concentration was increased by 38%, and fasting insulin concentrations were increased by 14% after fructose overfeeding in male subjects (all $P < 0.05$) but were not significantly altered in female subjects. Fasting plasma free fatty acids and lipid oxidation were inhibited by fructose in male but not in female subjects.

CONCLUSIONS — Short-term fructose overfeeding produces hypertriglyceridemia and hepatic insulin resistance in men, but these effects are markedly blunted in healthy young women.

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High fructose intake has been associated with adverse metabolic effects (1). Few studies have addressed whether the metabolic effects of fructose are sex dependent, however. In rats, several reports show that fructose has more pronounced adverse metabolic effects in males than in females (2,3); similarly, in humans, only men showed fructose-induced hypertriglyceridemia (4,5). The aim of this study was to further assess whether the effects of short-term fructose overfeeding on fasting lipid metabolism and insulin sensitivity differ between men and women.

RESEARCH DESIGN AND METHODS

— Healthy, nonsmoking, Caucasian male ($n = 8$, mean ± SD age 22.5 ± 0.93 years, BMI 22.5 ± 1.4, and percent fat mass 14.2 ± 3.1%) and female ($n = 8$, age 22.9 ± 0.62 years, BMI 21.0 ± 1.4, and percent fat mass 24.6 ± 2.5%) volunteers took part in the study. All subjects were in good health, and none were taking medications (except oral contraception for women).

Each subject was studied on two occasions. On one occasion (control test), they were placed on a balanced, isoenergetic diet (100% energy requirements: 15% proteins, 35% lipids, 40% starch, and 10% mono- and disaccharides) for 6 days. On the other occasion, they were placed on the same isoenergetic diet supplemented with 3.5 g fructose · kg fat-free mass^{-1} · day^{-1} for 6 days (130% energy requirements: 11% proteins, 26% lipids, 30% starch, 8% glucose and disaccharides, and 25% fructose). The two dietary conditions were applied in a randomized order with a 4-week washout period. On the seventh day, subjects underwent a metabolic assessment including basal hormone and substrate concentrations, fasting endogenous glucose, and glucose metabolism during a two-step hyperglycemic clamp (6). Women who were not on oral contraceptive ($n = 2$) were studied during the first 10 days of their menstrual cycle.

Statistical analysis

Data are expressed as means ± SEM. Comparisons between control diet and fructose supplementation were performed using the paired Wilcoxon's signed-rank test. Comparison between male and female subjects was done using Wilcoxon's rank-sum test.

RESULTS

— Basal metabolic parameters were comparable in female and male subjects, except for a higher glucose production ($P < 0.05$) and a trend toward higher plasma insulin ($P = 0.12$), triglycerides ($P = 0.06$), and β-hydroxybutyrate ($P = 0.17$) in female subjects.

Body weight was increased by 1.1% in male and 0.7% in female subjects after fructose supplementation. In male subjects, fructose supplementation caused significant ($P < 0.05$) increases in fasting glucose (5% increase), insulin (14% increase), triglyceride (71% increase), alanine aminotransferase (38% increase), and lactate (44% increase) and decreases in free fatty acids (−43%), β-hydroxybutyrate (−87%), and glucagon (−10%). It also significantly ($P < 0.05$) increased fasting endogenous glucose production (12% increase) and basal carbohydrate oxidation (43% increase) and decreased basal lipid oxidation (−48%) (Table 1).

The metabolic effects of fructose supplementation were markedly attenuated in female subjects, in whom it caused only significant increases in fasting glucose (4%) and triglyceride (16%) and decreases in β-hydroxybutyrate (−55%) and glucagon (−9%) while all other parameters showed no significant changes (Table 1). The increment in en-

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Table 1—*Hormone and substrate concentrations and metabolic parameters observed in male (n = 8) and female (n = 8) subjects after a 6-day isocaloric diet (control) and a 6-day isocaloric diet supplemented with 3.5 g · kg fat-free mass^{-1} · day^{-1} (high fructose)*

	Male subjects		Female subjects	
	Control	High fructose	Control	High fructose
Fasting metabolic parameters				
Glucose (mmol/l)	5.0 ± 0.2	5.3 ± 0.03*	4.7 ± 0.3	4.9 ± 0.2*
Lactate (mmol/l)	0.9 ± 0.2	1.3 ± 0.3*	0.8 ± 0.2	1.0 ± 0.3
Insulin (pmol/l)	44 ± 8.5	50 ± 5.6*	52 ± 5.6	59 ± 8.5
Glucagon (ng/l)	51.5 ± 12.1	46.2 ± 7.9*	52.3 ± 11.6	47.8 ± 9.6*
Triglycerides (mmol/l)	0.79 ± 0.17	1.35 ± 0.31*	1.10 ± 0.31†	1.28 ± 0.28*†
Free fatty acids (g/l)	0.14 ± 0.03	0.08 ± 0.02*	0.17 ± 0.03	0.17 ± 0.06†
β-hydroxybutyrate (μmol/l)	165 ± 85	21 ± 8.5*	252 ± 74	114 ± 62*†
ALT (U/l)	7.88 ± 3.08	10.88 ± 4.63*	5.38 ± 1.83	4.50 ± 1.72
EGP (μmol · kg^{-1} · min^{-1})	11.1 ± 0.8	12.4 ± 0.56*	12.2 ± 0.3†	12.2 ± 0.56†
Carbohydrate oxidation (μmol · kg^{-1} · min^{-1})	8.3 ± 1.7	11.9 ± 2.26*	8.8 ± 1.2	9.6 ± 1.69
Lipid oxidation (mg · kg^{-1} · min^{-1})	0.54 ± 0.11	0.28 ± 0.11*	0.49 ± 0.08	0.54 ± 0.17
Energy expenditure (cal · kg^{-1} · min^{-1})	13.1 ± 0.84	13.0 ± 0.56	13.2 ± 0.8	13.6 ± 0.85
Hyperglycemic clamp				
1st-phase insulin	298 ± 124	318 ± 90	327 ± 113	287 ± 79
2nd-phase insulin (glycemia 7.5 mmol/l)	109 ± 28	116 ± 31	169 ± 45	166 ± 54
2nd-phase insulin (glycemia 10 mmol/l)	225 ± 48	279 ± 62*	318 ± 88	294 ± 71
EGP (glycemia 7.5 mmol/l)	2.3 ± 2.5	4.4 ± 1.13*	3.6 ± 2.54	3.7 ± 1.41
EGP (glycemia 10 mmol/l)	1.2 ± 1.1	2.5 ± 0.9	3.1 ± 4.0	2.1 ± 2.26

Data are means ± SD.*Significantly different for high-fructose diet vs. control diet ($P < 0.05$, by Wilcoxon's signed-ranks test); †significantly different for female vs. male subjects. ALT, alanine aminotransferase; EGP, endogenous glucose production.

dogenous glucose production and plasma triglyceride and the decrement in β-hydroxybutyrate were all significantly lower in female than in male subjects ($P < 0.05$).

During the clamp, endogenous glucose production during the first step was significantly higher (13%, $P < 0.05$) after fructose supplementation in male subjects but not in female subjects. The first-phase insulin secretion and the plasma insulin concentration at the first plateau of glycemia were not altered after fructose overfeeding in male and female subjects. During the second plateau of glycemia, plasma insulin concentration was increased by 26% ($P < 0.05$) after fructose supplementation in male but not female subjects (Table 1).

CONCLUSIONS — The female subjects participating in this study had, at baseline, slightly higher plasma triglycerides and endogenous glucose production than the male subjects, suggesting a lower metabolic fitness. In spite of this, they showed a markedly blunted increase in plasma triglycerides in response to fructose. Several explanations can be proposed for this lesser effect of fructose: first, the effect of fructose on metabolism may be modulated by sex hormones. In support of this hypothesis, studies done in rats showed that intact, but not oophorectomized, female rats were protected against the deleterious metabolic effects of fructose (3). It was also reported that fructose increased plasma triglyceride in postmenopausal but not premenopausal women (7). Fatty acid synthase gene expression is also lower in hepatocytes of female or estrogen-treated male rats than in untreated male rats, which suggests that fructose-induced hepatic de novo lipogenesis may be attenuated in women (8). Second, women have a larger fat mass than men at comparable BMI and may have a more efficient removal of triglyceride-rich particles from circulation (9).

This study was done in small groups of healthy male and female subjects with different baseline metabolic characteristics and needs to be replicated by larger-scale studies. It nonetheless calls for attention to sex-related factors in future studies. It is possible that the vascular risk associated with high fructose intake is reduced in young women due to their lower plasma triglycerides. In addition to this differential effect on plasma triglycerides, fructose inhibited lipolysis and lipid oxidation in male subjects, presumably secondary to a slight increase in insulin secretion (10), but failed to do so in female subjects. Furthermore, it increased basal glucose production and fasting insulin concentrations, which indicates hepatic insulin resistance, in male subjects, whereas these effects were totally abolished in female subjects. It also failed to increase alanine aminotransferase in female subjects as it did in male subjects. Given the importance attributed to lipotoxicity and to ectopic fat deposition in skeletal muscle and the liver (11) in the development of insulin resistance, it can be speculated that an enhanced triglyceride removal in subcutaneous adipose tissue and a lesser inhibition of fat oxidation may offer some protection against fructose-induced insulin resistance in young women by reducing fructose-induced lipotoxicity.

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