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Effects of Fructose and Other Dietary Carbohydrates on Plasma Glucose, Insulin, and Lipids in Genetically Obese (Ob/Ob) Mice (39569)

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While there is no general agreement about the effects of various dietary carbohydrates on lipid metabolism and cardiovascular disease in humans, some experimental studies have shown that hyperlipidemia can be produced in both man and in experimental animals, such as the rat, when fructose or sucrose is fed in comparison to feeding glucose or starch (1–3). A metabolic explanation for this effect has been that absorbed fructose is preferentially transported into the liver where it increases lipogenesis (4). In addition, fructose feeding can result in lower plasma glucose, a reduced insulin response, and a decreased lipoprotein lipase stimulation. However, the reported results are not consistent and vary with experimental conditions.

Because genetically obese mice show increased lipogenesis, hyperlipidemia, and abnormalities in carbohydrate metabolism even when fed usual laboratory diets (5), this animal model was used to investigate any additional effects of dietary fructose in comparison to other carbohydrates on these parameters.

Materials and methods. Male weanling mice of the mutant strain, C57BL/6J ob (Jackson Laboratories, Bar Harbor, Me.), were distributed into groups of 12 obese (genotype, ob/ob) and 12 nonobese (genotype, +/?) mice, caged separately and fed one of four experimental diets and water *ad libitum* for 24 weeks. Body weight and food intake data were recorded weekly.

The experimental diets contained either fructose, cornstarch, sucrose, or glucose as the carbohydrate source and had the following composition (grams per kilogram of diet): carbohydrate, 643; casein, 200; hydrogenated vegetable oil (Spry, Lever Brothers, New York, N.Y.), 100; salt mix (6), 50; vitamin mix, 5.0; and choline chloride, 2.0. The vitamin mix in glucose contained the following (per gram of mix): thiamin·HCl, 0.8 mg; riboflavin, 1.6 mg; pyridoxine·HCl, 0.8 mg; calcium pantothenate, 5.0 mg; nicotinamide, 8.0 mg; folic acid, 1.0 mg; biotin, 40 μg; cyanocobalamin, 20 μg; menaquinone, 20 μg; retinyl acetate, 6500 IU; ergocalciferol, 650 USP units; *dl*-α-tocopheryl acetate, 10 IU.

Fasting blood samples were taken from the orbital sinus biweekly during the 24-week experimental period. Because it was only possible to obtain about 200 μl of blood from these mice each time, determinations of plasma glucose (7) and immunoreactive insulin (Phadebus insulin test, Pharmacia, Piscataway, N.J.) were made in alternate samples starting after the mice had been fed the experimental diets 2 weeks, and plasma triglycerides (enzymatic method, Dow Diagnostics, Indianapolis, Ind.) and total cholesterol (8) were determined in alternate samples starting at 4 weeks. Statistical analyses were performed using Scheffe's method for *a posteriori* comparisons between groups (9).

Results. Dietary fructose reduced body weight gain in the obese but not in the nonobese mice in comparison to the other dietary carbohydrates (Fig. 1). After the obese mice had been fed the experimental diets for 4 weeks, the fructose-fed group gained significantly ($P < 0.01$) less, 6.8 ± 1.4 g (mean ± SE), in comparison to 12.5 ± 1.3 g, 13.6 ± 0.9 g, or 13.1 ± 1.3 g for the starch-, sucrose-, or glucose-fed groups, respectively. However, there were no longer any significant differences in body weight or weight gain after 16 weeks. There were no significant differences in food intake between obese and nonobese mice fed any of the carbohydrates or between different time periods, although there was a trend toward lower intakes as growth rate decreased. The mean daily food intake was 3.56 ± 0.05 g for obese mice and 3.49 ± 0.08 g for nonobese mice for the entire experimental period.

Because our collected data showed no

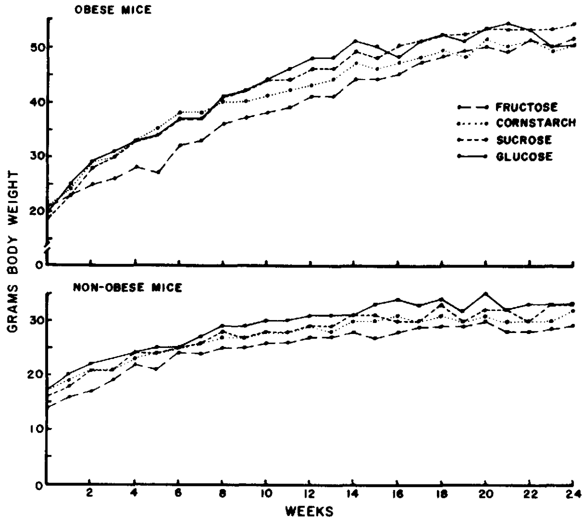

FIG. 1. The effect on body weight of feeding diets containing 64.3% fructose, cornstarch, sucrose, or glucose in obese and nonobese mice.

TABLE I. EFFECTS OF DIETARY CARBOHYDRATE ON PLASMA GLUCOSE, INSULIN, TRIGLYCERIDES, AND TOTAL CHOLESTEROL IN GENETICALLY OBESE AND NONOBESE MICE.[a]

	Glucose (mg/100 ml)		Insulin (μU/ml)		Triglycerides (mg/100 ml)		Cholesterol (mg/100 ml)	
Dietary carbohydrate	Obese	Nonobese	Obese	Nonobese	Obese	Nonobese	Obese	Nonobese
Fructose	88±8[b, c] (44)	70±6[b, d] (58)	62±9 (43)	14±2 (42)	108±11 (26)	86±9[b] (41)	293±14 (33)	194±7 (37)
Cornstarch	128±8[c] (42)	110±9[d] (52)	80±13 (46)	15±1 (47)	139±17 (30)	147±18[b] (36)	265±19 (26)	186±8 (41)
Sucrose	108±9 (47)	89±7[c] (56)	62±9 (45)	14±2 (44)	113±14 (32)	124±12 (43)	333±17 (35)	212±8 (52)
Glucose	114±11[b] (37)	123±8[b, c] (61)	43±4 (40)	15±3 (49)	113±14 (27)	119±9 (48)	289±18 (23)	201±6 (53)

[a] Each value represents the mean ± SE. Numbers of samples are in parentheses.

[b, c, d] For each column, the significant differences between groups are noted by the same superscripts: [b] $P < 0.01$; [c] $P < 0.05$; [d] $P < 0.01$.

change with time for any plasma parameter measured, the data were grouped for analyses as shown in Table I. The number of samples analyzed is indicated for each mean value; these numbers vary because some determinations were not possible due to inadequate blood volumes and early death of a few mice caused by the stress of repeated bleedings.

When comparing obese to nonobese mice, there were highly significant ($P < 0.001$) differences in plasma insulin and total cholesterol concentrations. While the kind of dietary carbohydrate had no significant effect on fasting insulin concentration, plasma glucose concentrations were affected by feeding different carbohydrates to both obese and nonobese mice. Fructose-fed mice had the lowest plasma glucose concentrations. In obese mice, plasma glucose concentration was significantly lower in comparison to the starch- ($P < 0.05$) and the glucose-fed ($P < 0.01$) groups, but not the sucrose-fed group. In nonobese mice, the fructose diet produced significantly lower plasma glucose concentrations when compared to the means for the starch- ($P < 0.01$) and glucose-fed ($P < 0.01$) groups. Sucrose feeding also significantly ($P < 0.05$) reduced plasma glucose concentration in comparison to glucose feeding. Although the effect of the fructose diet was greater than that of the sucrose diet in lowering plasma glucose, the difference was not significant.

Total cholesterol concentrations in plasma were similar for all carbohydrate-fed groups, and plasma triglyceride concentrations were also not affected by the type of carbohydrate fed, with one exception. Nonobese mice fed the fructose diet had a significantly ($P < 0.01$) lower plasma triglyceride concentration in comparison to starch-fed mice.

Discussion. Apparently, when fructose was fed to genetically obese mice as the only dietary carbohydrate, weight gain was not as great during the early postweaning period of rapid fat deposition, but the fructose-fed mice attained the same body weight as those mice fed starch, sucrose, and glucose as the growth rate slowed. Waterman *et al.* (10) have noted a similar depression in body weight gain as well as decreased food intake in rats fed fructose, in comparison to those fed glucose or sucrose. Our data did not show significantly lower food intake for the obese mice at the time when body weight gain was depressed. However, the food intake measurements were probably not accurate enough to detect the small difference in food intake which could account for the lower body weight.

The hyperglycemia usually observed in the genetically obese mouse was not observed in this study. This has been noted before in our laboratory in fasting obese mice fed semisynthetic, high-carbohydrate diets. The observation that sucrose feeding produced plasma glucose values between those of fructose and glucose or starch can be explained by the fructose part of the sucrose molecule. Since the genetically obese mouse can represent one model for human adult-onset diabetes, i.e., obesity associated with hyperinsulinemia, reduced glucose tolerance, and hyperglycemia, it is noteworthy that dietary fructose was beneficial in lowering plasma glucose under our conditions. However, if fructose is introduced into diets for diabetic humans, the amount would probably represent only a minor fraction of the total carbohydrate in the diet, and for this reason, may not have any effect on plasma glucose. While plasma fructose concentration reportedly rises when rats are fed fructose (10), it is doubtful that any small increment in fructose concentration would affect total plasma hexose concentration in the fasting state. The fact that the fructose or sucrose diet did not raise plasma triglycerides in obese and nonobese mice is in contrast to that observed in man and the rat (1). Other investigators have shown that, at least in the rat, the sucrose or fructose effect on plasma triglycerides occurred either throughout life (11) or only in mature rats (12). Therefore, it is unlikely that we missed this effect in our study, and we must conclude that these mice reacted quite differently to dietary fructose by showing either no elevation or a reduction in plasma triglycerides when fed fructose in comparison to the other carbohydrates. Both the mouse and rat show high lipogenic activity in the liver (5) in comparison to peripheral tissues. Therefore, it is possible that either plasma clearance of triglycerides is more efficient in these mice or that lipogenic activity is not increased as much in the the rat fed fructose diets. Our finding that the hyperlipidemia in the obese mice was due to hypercholesterolemia rather than to hypertriglyceridemia under our conditions demonstrates that this is a poor animal model for studying the effects of dietary fructose or sucrose in hypertriglyceridemia.

Summary. Genetically obese mice initially gained less body weight when fed diets containing fructose in comparison to mice fed starch, sucrose, or glucose diets. Plasma glucose concentrations were significantly lowered by fructose diets in both obese and nonobese mice in comparison to starch and glucose but not sucrose diets. Fructose or sucrose feeding did not induce hypertriglyceridemia in obese or nonobese mice as has been shown in the rat. In fact, the fructose diet significantly lowered plasma triglyceride concentrations in nonobese mice.

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