Effects of Dietary Fermentable Fiber on Fatty Acid Synthesis and Triglyceride Secretion in Rats Fed Fructose-Based Diet: Studies with Sugar-Beet Fiber[1] (43367)

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Abstract. **In an attempt to elucidate the role of the dietary fermentable fiber in reduction of hyperlipidemia, we substituted 30% wheat starch with 30% sugar-beet fiber in rats fed a fructose-based (41% fructose), low-fat (2% corn oil) diet. Male Wistar rats ate the test diets for 3 weeks. Feeding the sugar-beet fiber (SBF) diet resulted in a significant enlargement of the cecum; it also increased the concentration of volatile fatty acids compared with rats fed a fiber-free (FF) diet. Feeding SBF decreased plasma triglyceride and cholesterol concentrations in the postprandial as well as the postabsorptive period. In the liver, triglyceride levels were depressed in concert with the decreased liver lipogenesis and the post-Triton triglyceride secretion. Liver cholesterol levels were unaffected by SBF diet feeding. SBF-fed animals were markedly less fat compared with fiber-free-diet-fed rats. Adipose tissue lipogenesis was depressed in the postprandial period in SBF-fed animals. In short, this study suggests that substitution of easily digested carbohydrates by certain fermentable fibers may play an interesting role in the reduction of hyperlipidemia and obesity.** [P.S.E.B.M. 1992, Vol 199]

Primary and secondary hypertriglyceridemia states are the most common form of lipid transport disorders in humans and are frequently related to enhancement of atherosclerosis (for reviews, see Refs. 1–3). It has been well documented that feeding high levels of sucrose or fructose causes an increase in plasma triglycerides in both humans and experimental animals (4–6). This hypertriglyceridemia has been frequently ascribed to an increase in liver lipogenesis and overproduction of very low density lipoprotein (VLDL) (7). Conversely, high-fiber diets may be effective in reducing elevated plasma triglyceride levels (8–11). Thus, they may be of great interest from a preventive and therapeutic point of view for the pathology related to hyperlipidemia.

Recent studies from this laboratory indicate that diets high in fermentable carbohydrates significantly decrease not only plasma cholesterol concentrations, but also plasma triglyceride concentrations in the rat (12, 13). In the present study, in order to determine whether dietary fermentable fiber affects liver lipogenesis and lipid secretion, we used rats fed a high-fructose, low-fat diet to maximize the proportion of endogenous plasma triglycerides. The results suggest that dietary fermentable fibers may play an important role in regulating plasma triglyceride levels affecting lipid synthesis and secretion.

Materials and Methods

Animals and Diets. Male Wistar rats weighing approximately 190 g were raised for 3 weeks on purified diets (Table I) containing (as w/w) 30% wheat starch (fiber-free [FF] diet) or 30% sugar-beet fiber (sugar-beet fiber [SBF] diet). Rats were housed in wire-bottomed

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cages in a temperature-controlled room (22°C) with the dark period from 2000 hr to 0800 hr. Food and water were allowed *ad libitum* during the dark period. Food was withdrawn at 0800 hr and the animals were restricted during the light period.

Blood and Tissue Sampling. At the end of the experimental period, rats were sampled at 0800 hr after maximal food consumption during the dark period (postprandial period) or at 1600 hr (postabsorptive period). The animals were anesthetized with sodium pentobarbital (40 mg/kg) and maintained at 37°C. After laparotomy, blood was withdrawn into syringes containing EDTA (1 mg/ml of blood) from the abdominal aorta and plasma was obtained by low-speed centrifugation. The liver was excised and portions from the right lobe were taken for lipid analysis. The digestive tract was removed and weighed; thereafter, about 1 g of cecal content was drawn into microfuge tubes. Liver or cecal content samples were immediately plunged into liquid nitrogen, then stored frozen at −20°C until the assays were performed.

Chemical Analysis. Cecal contents were centrifuged at 8000*g* for 5 min at 4°C, and the concentration of volatile fatty acids (VFA) present in the supernatant was measured directly by gas-liquid chromatography (14). Triglycerides and cholesterol were determined in plasma by enzymatic procedures (15, 16). Liver samples were homogenized and lipids were extracted with chloroform-methanol (2/1, v/v) according to the method described by Folch *et al.* (17). Triglyceride and cholesterol contents were measured in the lipid residue as described previously (12).

Lipogenesis. Fatty acid synthesis was measured *in vivo* using ^3H_2O (18, 19). On Day 21 of the experiment, the animals were injected intraperitoneally with 100 μCi of ^3H_2O (108 mCi/ml; Commissariat à l'Energie Atomique, Gif-sur-Yvette, France)/100 g body wt. Injection was made at 0800 hr or at 1600 hr and animals were sacrificed 1 hr later. A sample of blood was taken from the abdominal aorta for the determination of serum-specific radioactivity. Livers were perfused with 100 ml of cold saline, blotted on filter paper, weighed, and frozen in liquid nitrogen. About 1 g of retroperitoneal fat tissue was dissected out, weighed, and frozen. Tissues were saponified in ethanolic KOH and acidified with HCl, and fatty acids were extracted with petroleum ether. After evaporation of the petroleum ether, the radioactivity was determined by liquid scintillation spectrometry with a liquid scintillation counter (Beckman Instruments, Irvine, CA). Results were corrected for recovery of internal standard ([1-^{14}C]palmitic acid, 45–60 mCi/mmol; Commissariat à l'Energie Atomique).

Triglyceride Secretion. The triglyceride secretion rate was determined by measuring the increase in plasma triglyceride concentration after an intravenous injection of Triton WR 1339, an inhibitor of plasma triglyceride hydrolysis (19, 20). One milliliter of 10% v/v solution of Triton (Tyloxapol; Sigma Chemical Co., St. Louis, MO) in saline was injected into rats at 0800 hr or at 1600 hr under light diethyl ether anesthesia. Blood samples (0.2 ml) were taken immediately before Triton WR 1339 injection and thereafter at 15, 30, and 60 min. Triglycerides were determined enzymatically (15). The linearity of the post-Triton secretion was verified for each rat. The slope of the change of triglyceride concentration as a function of time was calculated by linear regression analysis. The triglyceride secretion rate was calculated from the increment in triglyceride concentration per minute multiplied by the plasma volume (assumed to be 4% of body weight) and expressed as nmol per min per 100 g body wt.

Statistics. Student's *t* test was used to assess differences between groups. *P*-values lower than 0.05 were considered to be significant.

Table I. Composition of Diets (g/100 g)

Diet	Fiber-free	Sugar-beet fiber
Fructose	41	41
Casein	20	20
Corn oil	2	2
Mineral/vitamin mix	7	7
Wheat starch	30	—
Sugar-beet fiber[a]	—	30

[a] Sugar-beet fiber preparation contains 75% dietary fiber (21% cellulose, 33% hemicellulose, 19% pectin, and 2% lignin), 10% moisture, 7% protein, 4% sugar, and 4% ash.

Results

Effects of Diets on Animals and Their Digestive Tracts. As shown in Table II, rat body weight was not significantly influenced by the diets; however, differences in body weight could have been masked by the increased content of material in the digestive tract of SBF-fed rats (Table III). The replacement of wheat starch by SBF caused a reduction in the liver weight and a dramatic drop in retroperitoneal fat pad weight (Table II). Compared with rats fed the FF diet, rats fed the SBF diet presented lower pH in cecal content. The cecal concentrations of acetate, propionate, and butyrate were markedly increased (Table III).

Plasma and Liver Lipids. SBF diet feeding resulted in significantly lower plasma triglyceride and cholesterol concentrations than those in FF diet-fed rats both in postprandial and postabsorptive periods (Table IV). The liver triglyceride content of SBF-fed rats was reduced in both periods studied compared with FF diet-fed rats. The liver cholesterol level was unaffected by SBF diet feeding.

Lipogenesis and Triglyceride Secretion. Liver and adipose tissue fatty acid synthesis were markedly

Table II. Final Body Weight, Food Consumption, and Liver and Retroperitoneal Fat Pad Weights in Rats Fed Fiber-Free or Sugar-Beet Fiber Diets[a]

Diet	Total body wt (g)	Food/day[b] (g)	Liver wt (g)	Fat pad wt (g)
Fiber-free	295 ± 7	26.3 ± 1.0	15.9 ± 0.6	10.4 ± 0.4
Sugar-beet fiber	280 ± 8	25.8 ± 1.1	14.0 ± 0.6[c]	4.3 ± 0.3[d]

[a] Values are means ± SE of 12 determinations. Results were compared using a Student's *t* test to determine the effect of adding fiber to fructose-based diet.
[b] Food per day was measured during the last week of experiment.
[c] $P < 0.05$.
[d] $P < 0.001$.

Table III. Digestive Tract Weight and Parameters of Cecal Digestion in Rats Fed Fiber-Free or Sugar-Beet Fiber Diets[a]

Diet	Digestive tract wt[b] (g)	Cecum wt[b] (g)	Cecal pH	VFA concentration		
				Acetate (m*M*)	Propionate (m*M*)	Butyrate (m*M*)
Fiber-free	26.7 ± 1.1	3.1 ± 0.2	7.3 ± 0.1	62 ± 5	19 ± 2	6 ± 1
Sugar-beet fiber	40.8 ± 0.9[c]	10.5 ± 0.7[c]	6.0 ± 0.1[c]	89 ± 6[d]	37 ± 3[c]	14 ± 2[d]

[a] Obtained from rats sampled at 0800 hr. Values are means ± SE of six determinations. Results were compared using a Student's *t* test to determine the effect of adding fiber to fructose-based diet.
[b] weight with content.
[c] $P < 0.001$.
[d] $P < 0.01$.

Table IV. Plasma and Liver Lipids in Rats Fed Fiber-Free or Sugar-Beet Fiber Diets[a]

Diet	Plasma		Liver[b]	
	Triglycerides (m*M*)	Total cholesterol (m*M*)	Triglycerides (μmol/g)	Total cholesterol (μmol/g)
0800 hr				
Fiber-free	2.83 ± 0.32	1.60 ± 0.08	21.5 ± 1.4	14.7 ± 0.5
Sugar-beet fiber	1.81 ± 0.20[c]	1.14 ± 0.05[d]	14.1 ± 1.0[e]	13.2 ± 0.5
1600 hr				
Fiber-free	1.94 ± 0.23	1.68 ± 0.08	16.6 ± 1.8	15.5 ± 0.8
Sugar-beet fiber	1.02 ± 0.12[e]	1.14 ± 0.05[d]	11.5 ± 0.5[c]	14.0 ± 0.5

[a] Values are means ± SE of six determinations. Results were compared using a Student's *t* test to determine the effect of adding fiber to fructose-based diet.
[b] Wet liver weight.
[c] $P < 0.05$.
[d] $P < 0.001$.
[e] $P < 0.01$.

reduced in SBF-fed rats compared with FF diet-fed rats during the postprandial period (Table V). However, there was no effect of diet on fatty acid synthesis in the postabsorptive period. Triglyceride secretion, studied using Triton method, was lower in SBF-fed rats than in FF diet-fed rats in both periods studied (Table V).

Discussion

The hypocholesterolemic effects of food rich in some fibers, especially water-soluble fibers, have been frequently reported in humans and animals (for reviews, see Refs. 8 and 21–24). The other aspect of dietary fiber that is very interesting is its hypotriglyceridemic effect. However, the effects of fibers on triglyceride levels have not been consistent in the previous studies and have not been as extensively investigated as the effects on cholesterol level. Variable responses of plasma cholesterol and triglyceride concentrations to dietary fiber have been reported and appear to be related to the experimental conditions and the source of fiber used (for reviews, see Refs. 8 and 21–24). We have reported previously the effects of dietary fermentable fibers on plasma lipid and lipoprotein levels and on overall lipoprotein metabolism (12, 13). When fermentable fibers are substituted for easily digested car-

Table V. Lipogenesis and Triglyceride Secretion Rate in Rats Fed Fiber-Free or Sugar-Beet Fiber Diets[a]

	Lipogenesis[b]		Triglyceride secretion rate[c]
	Liver	Adipose tissue	
0800 hr			
Fiber-free	100 ± 13	60 ± 12	508 ± 26
Sugar-beet fiber	19 ± 2[d]	11 ± 3[e]	361 ± 56[f]
1600 hr			
Fiber-free	7 ± 1	7 ± 2	350 ± 34
Sugar-beet fiber	6 ± 1	5 ± 2	237 ± 11[f]

[a] Values are means ± SE of six determinations. Results were compared using a Student's *t* test to determine the effect of adding fiber to fructose-based diet.
[b] Lipogenesis is expressed as μmol of ^3H_2O incorporated into saponified lipid/hr per g fresh wt of tissue.
[c] Triglyceride secretion rates are expressed as nmol of triglyceride/min per 100 g body wt.
[d] $P < 0.001$.
[e] $P < 0.01$.
[f] $P < 0.05$.

bohydrates, triglyceride and cholesterol plasma levels are markedly decreased, even in animals fed high-fat diets (12) or in hyperlipidemic obese Zucker rats (13).

In the present study, we have used a diet rich in sugar-beet fiber. The biological properties of SBF, which is rich in pectin and hemicelluloses, have recently been investigated by Johnson *et al.* (25). Their study demonstrated that the SBF combines some of the useful biological characteristics of both insoluble and soluble dietary fiber.

It has been shown by Johnson *et al.* (25) and also in the present study that SBF diet has a lowering effect on plasma cholesterol in the rat. In the present work, we have also shown that SBF feeding to rats fed a fructose-based diet resulted in significantly lower plasma triglyceride concentrations than those in FF diet-fed rats, both in postprandial and postabsorptive periods. SBF supplementation resulted in a decreased lipogenesis in the postprandial period and decreased secretion in both periods studied. Taken together, these observations suggest that there is a lower triglyceride storage pool formation in SBF-fed rats compared with FF diet-fed rats during the postprandial period, when the rate of hepatic fatty acid synthesis reaches its peak. It is well known (26) that newly synthesized triglycerides may be either channeled into the liver cytosol as lipid droplets or packaged into nascent VLDL for secretion into the plasma. However, even in well-fed animals, newly synthesized fatty acids constitute only less than 10% of the total VLDL triglyceride fatty acids secreted *in vivo* (27). Thus, the liver triglyceride storage pool plays an important role in triglyceride secretion during the postabsorptive period and, in turn, in the maintenance of plasma triglyceride level.

We also found that weight of fat pad was reduced in animals fed SBF diet compared with those fed FF diet. A considerable portion of newly synthesized fatty acids found in adipose tissue is made in the liver, but it is well known that fructose feeding reduces the capacity of the adipose tissue to synthesize fatty acids and increases fatty acid synthesis in the liver compared to glucose-fed animals (28). However, analysis over a period of 1 hr revealed that the transfer of newly made fatty acids from liver to adipose tissue has no significant effect on adipose tissue lipogenesis (29). Thus, the results presented here show the actual lipogenic activities of tissues *in situ*. Therefore, since triglyceride secretion and adipose tissue lipogenesis are reduced by SBF feeding, it can be inferred that both these mechanisms are involved in fatty reduction in fiber-fed rats.

Conflicting data have been obtained concerning the effect of dietary fibers on plasma triglyceride levels, liver lipogenesis, and triglyceride secretion (8, 30–36). The extent of this effect may depend on the type and the quantity of fiber used, as well as on the time of adaptation. Specific effects of fermentable fibers on lipid synthesis in the liver remain to be elucidated. These may include: changes in carbohydrate and lipid absorption, modification in glucose metabolism, energy restriction, modifications in the hormonal pattern, or VFA influence on lipid metabolism. Since our study was carried out using a low-fat diet, changes in lipid absorption cannot be ascribed to the hypolipidemic effect of SBF. Therefore, decreased or delayed absorption of dietary lipid by fibers may occur in high-fat-fed animals (37). On the other hand, it is difficult to ascribe the triglyceride lowering effect of the SBF diet uniquely to their influence on lipid synthesis and secretion, since there may also have been a modification in the clearance of plasma triglycerides.

Because VFA production and absorption is very high in rats fed a diet rich in fermentable fibers, an interaction between VFA and lipid metabolism may occur. In particular, it has been suggested that propionate (which was markedly increased in the present study) may have an hypocholesterolemic effect by its action on peripheral cholesterol metabolism or on 3-hydroxy-3-methylglutaryl CoA reductase activity (38,

39). Data on the influence of dietary fiber on liver lipogenesis studied *in vivo* are conflicting. Some reports have shown an increased lipogenesis and indicated that there is a significant effect of VFA on lipogenesis, whereas other studies have reported the exact opposite (30–32, 34–36). In the recent study carried out on isolated hepatocytes from rats fed various fiber diets, Nishina and Freedland (40) have shown that pectin depresses sterol synthesis, although the fatty acid synthesis was unaffected by fiber feeding.

Recently, the effect of propionate on liver lipogenesis was studied in perfused rat liver (41) and isolated rat hepatocytes (42, 43). Studies with perfused livers from fed rats indicated that lipogenesis from tritiated water was depressed with increasing concentrations of propionate (41). This result has been confirmed by Nishina and Freedland (42) in isolated rat hepatocytes in the presence of 1 mmol/liter of propionate. However Wright *et al.* (43) have shown that propionate had no apparent effect on fatty acid biosynthesis from tritiated water. It appears that propionate could depress fatty acid synthesis, but the effect may be dependent upon experimental conditions (for example on basal lipogenesis in donor rats). At present, no direct mechanism for the effect of propionate on lipid synthesis has been demonstrated. Like lactate, acetate, and pyruvate derived from glycolysis, propionate is a potential substrate for lipogenesis. Additionally, propionate increases mitochondrial malate and this in turn may be a source of NADPH for lipogenesis (44). However, on the other hand, propionate could decrease utilization of other lipogenic substrates (for example lactate) (45). Finally, this may result in a negative effect of propionate on liver lipogenesis. Nishina and Freedland (42) have proposed that other mechanisms, i.e., direct action on lipogenesis enzyme activities, may also be involved in the action of propionate on lipogenesis.

It is difficult to say to what extent increased propionate availability could modify overall lipid metabolism in fiber-fed animals. In *in vivo* conditions, it seems that in the liver it may be the general orientation of metabolism rather than VFA themselves that conditions the impact of fiber diets on lipid metabolism. High-fiber-diet feeding causes low availability of exogenous glucose, increases propionate availability, and causes a low insulin to glucagon ratio. These conditions are known to stimulate hepatic glucose synthesis. This increase in gluconeogenesis may have a suppressive effect on lipogenesis (46, 47).

We have shown that substituting fermentable fiber for easily digested carbohydrate in fructose-based diet may decrease plasma triglyceride and cholesterol concentrations in concert with a decrease in lipid synthesis and secretion. It appears that some dietary fibers may play an interesting role in the prevention and treatment of hyperlipidemia and obesity.

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