Effect of Sesame Seeds Rich in Sesamin and Sesamolin on Fatty Acid Oxidation in Rat Liver

Satoko Sirato-Yasumoto,† Masumi Katsuta,† Yoshinao Okuyama,‡ Yoko Takahashi,§ and Takashi Ide*,§

National Food Research Institute, Ministry of Agriculture Forestry and Fisheries, 2-1-2 Kannondai, Tsukuba 305-8642, Japan; National Agriculture Research Center, Ministry of Agriculture Forestry and Fisheries, 2-1-2 Kannondai, Tsukuba 305-8666, Japan; and Chugoku National Agriculture Experimental Station, Ministry of Agriculture Forestry and Fisheries, Nishifukatsu 6-12-1, Fukuyama 721-8514, Japan

Activities of enzymes involved in hepatic fatty acid oxidation and synthesis among rats fed sesame (*Sesamum indicum* L.) differing in lignan content (sesamin and sesamolin) were compared. Sesame seeds rich in lignans from two lines, 0730 and 0732, lines established in this laborary, and those from a conventional cultivar (Masekin) were employed. Seeds from the 0730 and 0732 lines contained sesamin and sesamolin at amounts twice those from Masekin. Sesame seeds were added at levels of 200 g/kg to the experimental diets. Sesame increased both the hepatic mitochondrial and the peroxisomal fatty acid oxidation rate. Increases were greater with sesame rich in lignans than with Maskin. Noticeably, peroxisomal activity levels were >3 times higher in rats fed diets containing sesame seeds from the 0730 and 0732 lines than in those fed a control diet without sesame. The diet containing Masekin seed caused only a 50% increase in the value, however. Diets containing seeds from the 0730 and 0732 lines, compared to the control and Masekin diets, also significantly increased the activity of hepatic fatty acid oxidation enzymes including acyl-CoA oxidase, carnitine palmitoyltranferase, 3-hydroxyacyl-CoA dehydrogenase, and 3-ketoacyl-CoA thiolase. In contrast, diets containing sesame lowered the activity of enzymes involved in fatty acid synthesis including fatty acid synthase, glucose-6-phosphate dehydrogenase, ATP-citrate lyase, and pyruvate kinase. No significant differences in enzyme activities were, however, seen among diets containing sesame from Masekin cultivar and lines 0730 and 0732. Serum triacylglycerol concentrations were lower in rats fed diets containing sesame from lines 0730 and 0732 than in those fed the control or Masekin diet. It is apparent that sesame rich in lignans more profoundly affects hepatic fatty acid oxidation and serum triacylglycerol levels. Therefore, consumption of sesame rich in lignans results in physiological activity to alter lipid metabolism in a potentially beneficial manner.

Keywords: *Sesame; lignans; hepatic fatty acid oxidation; serum lipids; rat*

INTRODUCTION

Sesame lignans including sesamin and sesamolin have physiological effects including antioxidant (*1*−*3*), anticarcinogen (*4*), blood pressure lowering (*5*, *6*), and serum lipid lowering (*7*−*10*) activities in experimental animals and humans. Previous findings suggested that consumption of sesame seeds has health benefits, and enrichment of the lignans would potentiate the characteristics of sesame in improving human health. Taking this into consideration, we have bred and established several sesame lines with seeds containing sesamin and sesamolin at twice the levels of conventional cultivars (*11*). We also confirmed that crop yields of these lines are comparable to those of conventional cultivars. However, the physiological activity of sesame seeds from these lines rich in lignans remained to be clarified. In the present study, we examined the physiological activity of sesames rich in sesamin and sesamolin focusing on their effects on tissue lipid levels and the activity of enzymes involved in fatty acid oxidation and synthesis in rat liver.

* Corresponding author (telephone 81-298-38-8083; fax 81-298-38-7996; e-mail idetaka@nfri.affrc.go.jp).

† National Agriculture Research Center.

‡ Chugoku National Agriculture Experimental Station.

§ National Food Research Institute.

MATERIALS AND METHODS

Animals and Diets. Male Sprague−Dawley rats obtained from Charles River Kanagawa, Japan, were housed individually in a room with controlled temperature (20−22 °C), humidity (55−65%), and lighting (lights on from 7:00 a.m. to 7:00 p.m.) and fed on a commercial nonpurified diet (type NMF, Oriental Yeast Co., Tokyo, Japan). After 7 days of acclimatization to the housing conditions, rats were randomly divided into groups and fed experimental diets for 16 days. The compositions of the experimental diets are shown in Table 1. The diet for the control group contained 200 g/kg casein, 83 g/kg corn oil, 50 g/kg cellulose, and 617 g/kg sucrose as protein, fat, dietary fiber, and carbohydrate sources, respectively. Sesame seed powders were added at a level of 200 g/kg. We used sesame seed powder from a conventional cultivar that is popular in Japan (Masekin) and lines rich in sesamin and sesamolin (0730 and 0732) (*11*). Analyses revealed that sesame from Masekin cultivar and lines 0730 and 0732 contained 240, 221, and 209 g of protein/kg and 383, 353, and 414 g of fat/kg, respectively. On the basis of this information, the amounts of casein and corn oil were reduced in diets containing sesame to adjust protein and fat contents and were indistinguishable among the diets. Casein contained 942 g of protein/kg. Sesame is reported to contain 132 g of dietary fiber/kg (*12*). Therefore, the cellulose contents of the diets containing sesame were reduced accordingly. Thus, the various experimental diets served similar amounts of protein, fat, and dietary fiber. Fatty acid compositions of sesame in grams per kilogram of fatty

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Table 1. Composition of Experimental Diets and Their Fatty Acid Composition and Lignan Content[a]

	exptl diets			
	control	Masekin	0730	0732
ingredients (g/kg)				
sesame seed powder	0	200	200	200
casein	200	149	153	156
corn oil	83	6	12	0
cellulose	50	24	24	24
mineral mixture	35	35	35	35
vitamin mixture	10	10	10	10
choline bitartrate	2	2	2	2
DL-methionine	3	3	3	3
sucrose	617	571	561	571
fatty acid composition (g/kg fatty acid)				
14:0	0.6	0.4	0.4	0.3
16:0	110	97.1	85.8	84.4
16:1	0.4	0.5	1.1	1.1
18:0	20.2	47.9	48.6	49.4
18:1	299	399	387	373
18:2	552	443	467	483
18:3	17.8	11.8	10.4	9.2
lignans (g/kg)				
sesamin	0	0.82	1.64	2.02
sesamolin	0	0.44	0.86	0.88

[a] Protein and fat contents of sesame were determined, and amounts of casein and corn oil were reduced in diets containing sesame to adjust protein and fat contents and are indistinguishable among diets. Also, amounts of cellulose contents were reduced in diets containing sesame according to the information on dietary fiber content of sesame provided by Resources Council, Science and Technology Agency of Japan (*12*). Fatty acid compositions of diets were determined in triplicate, and average values are shown.

acids were as follows: 14:0, 0.4; 16:0, 96.1; 16:1, 0.5; 18:0, 50.1; 18:1, 407; 18:2, 435; and α-18:3, 11.4, for Masekin; 14:0, 0.3; 16:0, 81.6; 16:1, 1.2; 18:0, 53.4; 18:1, 402; 18:2, 453; and α-18:3, 9.2, for line 0730; and 14:0, 0.3; 16:0, 84.4; 16:1, 1.1; 18:0, 49.4; 18:1, 373; 18:2, 483; and α-18:3, 9.2, for line 0732, respectively. The sesamin and sesamolin contents of sesame seeds were determined as described previously (*11*) and were 4.1 and 2.2 g/kg for Masekin, 8.2 and 4.3 g/kg for line 0730, and 10.1 and 4.4 g/kg for line 0732, respectively. Corn oil did not contain measurable amounts of sesamin and sesamolin. The compositions of mineral and vitamin mixtures were the same as those recommended by the American Institute of Nutrition (*13*). Fatty acid compositions of the experimental diets were determined and are shown in Table 1.

Enzyme Assays. At the termination of the experiment, rats were anaesthetized using diethyl ether and killed by bleeding from the abdominal aorta. The livers were then quickly excised. About 2 g of each liver was homogenized with 15 mL of 0.25 M sucrose containing 1 mM EDTA and 3 mM Tris-HCl (pH 7.0) and centrifuged at 9000*g* for 10 min. The supernatant fraction was centrifuged at 200000*g* for 30 min. The mitochondrial and peroxisomal fatty acid oxidation rates were measured using the whole liver homogenate as an enzyme source and employing [1-^{14}C]palmitoyl-CoA as a substrate (*14*). The activity of hepatic fatty acid oxidation enzymes was analyzed using whole liver homogenate as an enzyme source as detailed previously (*14*, *15*). The activity of the enzymes in fatty acid synthesis was measured using a 200000*g* supernatant fraction. Fatty acid synthase, malic enzyme, glucose-6-phosphate dehydrogenase, and pyruvate kinase activities were measured as detailed previously (*14*–*16*). The activity of ATP-citrate lyase was measured according to the procedure described by Takeda et al. (*17*).

Lipids Analysis. Liver triacylglycerol and phospholipid concentrations were determined as described previously (*18*). The liver cholesterol concentration was analyzed as detailed elsewhere (*19*). Serum triacylglycerol, cholesterol, and phospholipid concentrations were assayed using commercial enzyme kits (Wako Pure Chemical, Osaka, Japan).

Statistical Analysis. Data were analyzed according to the method of Snedecor and Cochran (*20*) as detailed elsewhere (*21*), and significant differences of the means were evaluated at the level of $p < 0.05$.

RESULTS

Average body weight at the start of the experiments was 134 g (SE of 1 g). There were no significant differences in food intake, body weight at time of sacrifice, and growth among groups (Table 2). Liver weights were significantly higher in rats fed line 0730 and 0732 diets than in those fed control and Masekin diets. When normalized to those in the animals of 100 g body weight, no significant differences were detected among the values in rats fed control, 0730, and 0732 diets. However, the normalized values were still significantly higher in the animals fed 0730 and 0732 diets than in those fed Masekin diet.

Activity of Hepatic Fatty Acid Oxidation Enzymes. As significant differences were seen in the liver weight of rats, the activities of enzymes were expressed in total activity (micromoles per minute per liver of 100 g body weight). Diets containing sesame increased both the mitochondrial and the peroxisomal palmitoyl-CoA oxidation rates (Figure 1). Among the groups of animals fed diets containing sesame, the mitochondrial rate was higher in the animals fed 0730 and 0732 diets than in those fed the Masekin diet, and a significant difference was detected between the animals fed 0730 and Masekin diets. More clear-cut differences among groups were seen in the peroxisomal fatty acid oxidation rate. The diet containing sesame from Masekin cultivar only slightly and insignificantly increased the peroxisomal fatty acid oxidation rate compared to the control diet. However, diets containing sesame seed from lines 0730 and 0732 caused a 3–4-fold increase in the peroxisomal fatty acid oxidation rate. The results on enzyme activity in fatty acid oxidation further confirmed the observation made regarding palmitoyl-CoA oxidation rate (Table 3). The diet containing sesame seed from the Masekin cultivar only slightly increased the activity of acyl-CoA oxidase, a rate-limiting enzyme in peroxisomal fatty acid oxidation. However, the activity in rats fed 0730 and 0732 diets was >4-fold that in those fed the control diet. Diets containing sesame from lines 0730 and 0732 relative to the Masekin cultivar also significantly in-

Table 2. Growth Parameters and Liver Weight[a]

	groups			
	control	Masekin	0730	0732
food intake (g/day)	18.8 (0.4)	18.5 (0.3)	19.2 (0.5)	19.2 (0.6)
body wt at time of sacrifice (g)	262 (4)	267 (5)	270 (5)	275 (10)
growth (g/16 days)	128 (3)	134 (4)	134 (3)	141 (8)
liver wt (g)	13.6b (0.4)	13.0b (0.3)	15.3c (0.7)	15.3c (0.5)
liver wt (g/100 g of body wt)	5.18bc (0.12)	4.88b (0.11)	5.65c (0.18)	5.62c (0.23)

[a] Values represent means of seven to eight rats, with SE in parentheses. Values with different letters significantly differ at $p < 0.05$.

Table 3. Activity (Micromoles per Minute per Liver of 100 g of Body Weight) of Hepatic Enzymes in Fatty Acid Oxidation[a]

	enzymes			
group	acyl-CoA oxidase	carnitine palmitoyltransferase	3-hydoxyacyl-CoA dehydrogenase	3-ketoacyl-CoA thiolase
control	1.35b (0.09)	4.06b (0.58)	293b (25)	195b (13)
Masekin	2.15b (0.17)	9.11c (0.76)	981c (38)	329c (28)
0730	6.29c (0.31)	17.6d (1.2)	1770d (62)	636d (36)
0732	7.32c (0.52)	14.7d (1.4)	1729d (96)	538d (23)

[a] Values represent means of seven to eight rats, with SE in parentheses. Values with different letters significantly differ at $p < 0.05$.

Table 4. Activity (Micromoles per Minute per Liver of 100 g of Body Weight) of Hepatic Enzymes in Fatty Acid Synthesis[a]

	enzymes				
group	fatty acid synthase	glucose-6-phosphate dehydrogenase	malic enzyme	ATP-citrate lyase	pyruvate kinase
control	11.7c (1.6)	36.3c (5.5)	51.4b (5.3)	36.3c (5.5)	268c (17)
Masekin	3.45b (0.82)	8.57b (0.95)	34.7b (5.0)	8.57b (0.95)	118b (6)
0730	4.02b (1.05)	13.5b (1.4)	93.1c (5.6)	13.5b (1.4)	107b (15)
0732	3.41b (0.44)	11.5b (0.7)	78.7c (8.5)	11.5b (0.7)	100b (10)

[a] Values represent means of seven to eight rats, with SE in parentheses. Values with different letters significantly differ at $p < 0.05$.

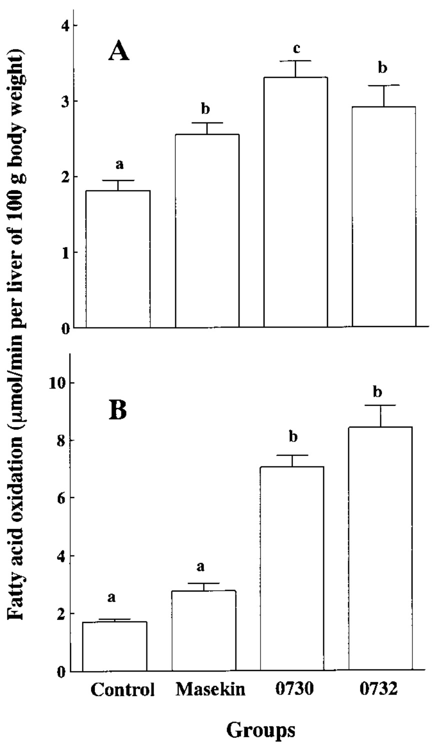

Figure 1. Effect of sesame seeds differing in lignan contents on mitochondrial (A) and peroxisomal (B) palmitoyl-CoA oxidation rate in rat liver. Rats were fed a control diet without sesame seed or diets containing 200 g/kg sesame seed powder from Masekin cultivar and lines 0730 and 0732. Values represent means ± SE of seven to eight rats. Values with different letters significantly differ at $p < 0.05$.

creased the activity of carnitine palmitoytransferase, 3-hydroxyacyl-CoA dehydrogenase, and 3-ketoacyl-CoA thiolase. The Masekin diet relative to the control diet increased the enzyme activity 1.7−3.3-fold, whereas 0730 and 0732 diets increased the enzyme activity 2.8−6.0-fold.

Activity of Enzymes in Fatty Acid Synthesis. All of the diets containing sesame significantly decreased fatty acid synthase, glucose-6-phosphate dehydrogenase, ATP-citratle lyase, and pyruvate kinase activities relative to the control diet (Table 4). No significant differences were, however, found among the three groups of rats fed diets containing sesame. The diet containing Masekin sesame did not affect malic enzyme activity, but the 0730 and 0732 diets significantly increased it.

Table 5. Serum and Liver Lipid Levels[a]

	lipid components		
group	triacylglycerol	cholesterol	phospholipid
serum lipids (μmol/dL)			
control	339c (46)	300c (11)	250cb (10)
Masekin	294c (37)	246b (15)	223b (14)
0730	176b (22)	264b (14)	262cb (14)
0732	177b (11)	254b (8)	272c (16)
hepatic lipids (μmol/liver of 100 g body wt)			
control	178 (42)	34.3 (2.0)	162b (4)
Masekin	151 (8)	30.7 (0.8)	177b (5)
0730	131 (14)	33.4 (0.9)	253c (7)
0732	153 (18)	34.7 (1.6)	247c (9)

[a] Values represent means of seven to eight rats, with SE in parentheses. Values with different letters significantly differ at $p < 0.05$.

Serum and Liver Lipid Levels. Serum triacylglycerol concentrations were significantly lower in rats fed 0730 and 0732 diets than in those fed control and Masekin diets (Table 5). All of the diets containing sesame significantly reduced serum cholesterol concentration relative to the control diet. However, no significant differences were seen among the three groups of rats fed sesame seeds. Serum phospholipid concentration was significantly lower in rats fed the Masekin diet than in those fed a control diet. No other significant difference in this parameter was seen among the groups. Hepatic triacylglycerol and cholesterol contents were the same among groups. Hepatic phospholipid contents were significantly higher in rats fed 0730 and 0732 diets than in those fed control and Masekin diets.

DISCUSSION

It has been demonstrated that sesame seed lignans including sesamin and sesamolin show various beneficial physiological activities in experimental animals and humans (*1*−*10*). Given that the enrichment of sesame with lignans will potentiate the beneficial effect on human health, we have established several sesame lines with seeds rich in sesamin and sesamolin (*11*). Seeds from these lines contained sesamin and sesamolin in twice the amount of common cultivars popular in Japan and other countries such as Masekin, Kanto-1, Kumashiba-1, and Tima-1 (*11*). We also confirmed that the harvest of seeds from these lines was comparable to that in common cultivars (*11*). We showed in the present study that sesame seeds from lines rich in sesamin and sesamolin significantly increased hepatic fatty acid oxidation accompanying the lowering of serum triacylglycerol levels compared to those from a conventional cultivar (Masekin). Therefore, the consumption of sesame seeds rich in lignans exerted a profound effect on lipid metabolism in the rat.

Diets containing sesame seed from Masekin cultivar and lines 0730 and 0732 caused 40, 80, and 60% increases in the mitochondrial fatty acid oxidation rate, and 60, 400, and 500% increases in the peroxisomal fatty acid oxidation rate, respectively. The physiological activity of sesame seeds rich in lignans in increasing hepatic fatty acid oxidation was confirmed by the measurements of enzyme activity in fatty acid oxidation. It has been demonstrated that sesamin is a potent inducer of hepatic fatty acid oxidation in the rat (*10*). Evidence indicates that sesamin is an activation of peroxisomal proliferator activated receptor (PPAR), a transcriptional factor that regulates gene expression of fatty acid oxidation enzymes (*10*, *22*, *23*). Both the mitochondrial and the peroxisomal fatty acid oxidation rates increased with the dietary level of sesamin. Diets containing 1, 2, and 5 g/kg sesamin caused 20, 50, and 90% increases, respectively, in mitochondrial fatty acid oxidation rate. These diets caused 50, 400, and >1000% increases, respectively, in the peroxisomal fatty acid oxidation rate. In the present study, sesamin and sesamolin contents were 0.82 and 0.42 g/kg for the Masekin diet, 1.64 and 0.86 g/kg for the 0730 diet, and 2.02 and 0.88 g/kg for the 0732 diet, respectively. Therefore, the alterations in hepatic fatty acid oxidation in the present study well paralleled those predicted from the differences in sesamin contents of diets. It is possible that sesamolin in addition to sesamin contributes to the enhancement of hepatic fatty acid oxidation, but the information regarding the physiological activity of sesamolin in altering hepatic fatty acid oxidation has hitherto been lacking.

It has been demonstrated that dietary sesamin reduces hepatic activity of fatty acid synthase and pyruvate kinase, enzymes for the regulation of fatty acid synthesis (*10*). We showed, in the present study, that sesame lowered the activity of various enzymes involved in fatty acid synthesis including fatty acid synthase, glucose-6-phosphate dehydrogenase, ATP-citrate lyase, and pyruvate kinase. It is plausible that sesamin (and/or sesamolin) is responsible for reducing the activity of these enzymes in rats fed sesame. However, the activities were the same among rats fed sesame seeds from Masekin cultivar and lines 0730 and 0732. In this context, it has been demonstrated that sesamin at a dietary level as low as 1 g/kg exerts almost maximal physiological activity in reducing fatty acid synthase and pyruvate kinase activity (*10*). The response to dietary sesame of malic enzyme differs from that of other enzymes. The activities were comparable between rats fed the control and Masekin diets. However, the experimental diets containing sesame seeds from lines 0730 and 0732 significantly increased the value compared to both control and Masekin diets. Similar responses in enzyme activity and gene expression of this enzyme have been reported in rats fed diets containing various amounts of sesamin. Accordingly, at high dietary levels (2−5 g/kg), but not at a low dietary level (1 g/kg), sesamin increased the activity and gene expression of malic enzyme (*10*). This phenomenon may be a consequence of the activation by sesamin of PPAR. It has been demonstrated that the promoter region of the malic enzyme possesses a PPAR recognition element (*24*) and the transcriptional factor up-regulates expression of the gene encoding the malic enzyme without influencing that of other enzymes involved in hepatic fatty acid synthesis (*23*). Polyunsaturated fatty acids including linoleic acid are dietary components that reduce hepatic fatty acid synthesis (*25*). As the linoleic acid content is higher in the control diet than in the three types of diets containing sesame seeds, differences in the linoleic acid content of diets cannot account for the physiological activity of sesame seeds to reduce hepatic fatty acid synthesis.

There is still the possibility that a component or components other than lignans are also involved in the sesame-dependent changes in hepatic fatty acid metabolism. It is well demonstrated that the type and amount of dietary fiber are the crucial factors affecting lipid metabolism. We did not determine dietary fiber content in sesame and employed the reported value (*12*) for the construction of experimental diets in the present study. Therefore, not only the type but also the amount of dietary fiber may mutually differ among experimental diets. However, no information that dietary fiber affects hepatic fatty acid metabolism has hitherto been available. Also, there is the possibility that protein contained in sesame affects hepatic fatty acid metabolism. It has been reported that type of protein affects activity of hepatic enzymes in fatty acid synthesis (*26*).

Alterations in fatty acid synthesis (*27*) and oxidation (*19*, *28*) modify the availability of fatty acids for triacylglycerol synthesis and, in turn, alter the production of very low density lipoprotein by the liver. Therefore, the change in the rate of fatty acid synthesis and oxidation in the liver is a factor modifying serum lipid concentrations. We found in the present study that lines 0730 and 0732 lowered the serum triacylglycerol level more than did Masekin cultivar. The activities of enzymes in fatty acid synthesis were lower in the groups of rats fed sesame differing in lignan content than in those fed a control diet, but they were the same among the three groups of rats fed sesame. Activities of enzymes in fatty acid oxidation were, however, higher in the animals fed lines 0730 and 0732 than in those fed Masekin cultivar. Therefore, an alteration in very low density lipoprotein production through the change in hepatic fatty acid oxidation may primarily be responsible for the serum triacylglycerol lowering effect of sesame rich in lignans relative to a conventional cultivar. It has been demonstrated that dietary sesamin dose-dependently increases the hepatic phospholipid level accompanying liver hypertrophy (*10*). In the present study, we found that diets containing sesame rich in lignan relative to a control and Masekin diets significantly increased hepatic phospholipid content. This may represent proliferation of liver organelles including mitochondria and peroxisomes (*10*).

In conclusion, sesame seeds rich in sesamin and sesamolin from our established sesame lines compared to those from a conventional cultivar significantly increased the hepatic fatty acid oxidation rate and enzyme activity in fatty acid oxidation accompanying the lowering of serum triacylglycerol. The differences in the sesamin contents of sesame seeds accounts for the physiological activity to alter hepatic fatty acid oxidation. The possibility that differences in sesamolin content also contribute to the differential physiological activity of various sesame seeds remains to be clarified.

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