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REVIEW

Sesamin, a Sesame Lignan, as a Potent Serum Lipid-Lowering Food Component

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Abstract

Effect of sesamin, a sesame lignan, on the hepatic fatty acid metabolism was examined in the rat. Increase of the dietary level of sesamin progressively increased the mitochondrial and peroxisomal fatty acid oxidation rate. Mitochondrial activity almost doubled in rats fed a 0.5% sesamin diet. Peroxisomal activity became more than 10 times higher in rats fed a 0.5% sesamin diet, compared to those fed a sesamin-free diet. Dietary sesamin also markedly increased the hepatic activity and mRNA levels of various fatty acid oxidation enzymes. In contrast, dietary sesamin decreased the hepatic activity and mRNA abundance of lipogenic enzymes. This was associated with the down-regulation of sterol regulatory element-binding protein-1, a transcriptional factor that regulates the lipogenic enzyme gene expression. Dietary sesamin significantly decreased the triacylglycerol secretion accompanying the increase in ketone body production by the perfused rat liver. It is apparent that sesamin affects the fatty acid metabolism and lipoprotein production in the liver, and hence lowers the serum lipid levels. We also developed several sesame lines with seeds containing sesamin and sesamolin at twice the concentration of conventional cultivars. Compared to a conventional cultivar, these lignan-rich sesame seeds increased the hepatic fatty acid oxidation rate and lowered the serum triacylglycerol level in the rat. Therefore, it is considered that enrichment of the lignans potentiates the characteristics of sesame in improving human health.

Discipline: Food
Additional key words: sesame, fatty acid oxidation, fatty acid synthesis, lipoprotein production, rat

Introduction

Sesamin, one of the lignans present most abundantly in sesame seed and oil (Fig. 1), markedly influences the lipid metabolism in experimental animals. Sesamin feeding is associated with a reduction of serum lipid levels in rodents[7,8,22]. This compound is also effective in preventing an increase in the serum triacylglycerol level following ethanol consumption in the rat[1]. The cholesterol-lowering effect of sesamin has also been demonstrated in humans[6]. However, the mechanism(s) underlying the lipid-lowering effect of sesamin remains to be clarified. The changes in the rate of fatty acid synthesis and oxidation in the liver may possibly modify serum lipid concentrations. Alterations in fatty acid synthesis[25] and oxidation[10,11] which affect the availability of fatty acids for triacylglycerol synthesis, and in turn modify the very low density lipoprotein production by the liver, may affect the serum lipid levels. In this context, we examined the physiological activity of sesamin in relation to the hepatic fatty acid metabolism in the rat.

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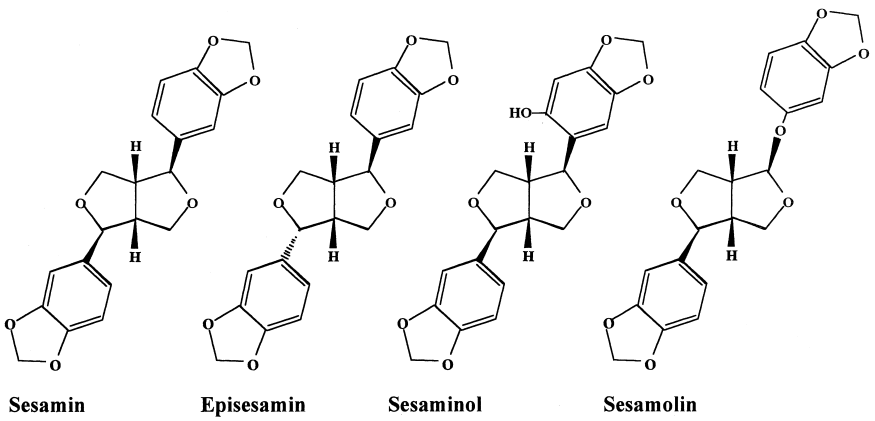

Fig. 1. Chemical structure of sesame lignans

Sesamin is a potent inducer of hepatic fatty acid oxidation[2]

Rats were fed purified experimental diets containing varying amounts of sesamin (0–0.5%) for 15 days. Dietary sesamin increased the mitochondrial and peroxisomal fatty acid oxidation rates dose-dependently (Fig. 2). A diet containing 0.5% sesamin nearly doubled the mitochondrial activity, and increased the peroxisomal activity more than 10 times compared to a diet free of sesamin. Sesamin also increased the activities of various hepatic fatty acid oxidation enzymes dose-dependently (data not shown). The activity of peroxisomal acyl-CoA oxidase progressively increased as the dietary level of sesamin increased, and the enzyme activity in rats fed a 0.5% sesamin diet became 12-fold higher than in those fed a sesamin-free diet. The diet containing 0.5% sesamin caused a 2–4 fold increase in the activities of other fatty acid oxidation enzymes, including acyl-CoA dehydrogenase, enoyl-CoA hydratase, carnitine palmitoyltransferase, 3-hydroxyacyl-CoA dehydrogenase, 3-ketoacyl-CoA thiolase, 2,4-dienoyl CoA reductase and Δ^3, Δ^2-enoyl CoA isomerase.

Dietary sesamin increased the mRNA levels of various fatty acid oxidation enzymes dose-dependently (Fig. 3). The mRNA abundances of mitochondrial fatty acid oxidation enzymes, including carnitine palmitoyltransferases I and II, long-chain specific acyl-CoA dehydrogenase mitochondrial trifunctional enzyme subunits α and β, mitochondrial 3-ketoacyl-CoA thiolase, 2,4-dienoyl-CoA reductase, and Δ^3, Δ^2-enoyl-CoA isomerase were 2–9 times higher in rats fed a 0.5% sesamin diet than in those fed a sesamin-free diet. Dietary sesamin also increased the abundance of mRNA for peroxisomal enzymes. The mRNA abundance of acyl-CoA oxidase became more than 15 times higher with 0.5% sesamin

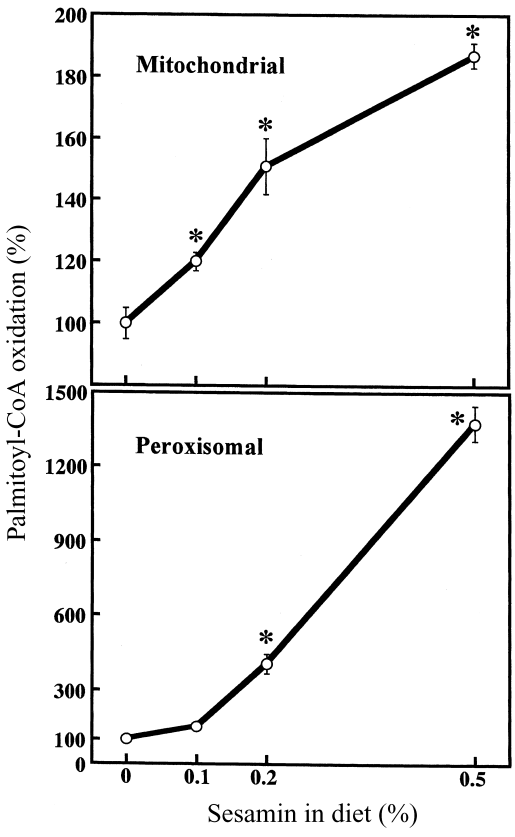

Fig. 2. Effect of sesamin on mitochondrial and peroxisomal palmitoyl-CoA oxidation rates in rat liver

Rats were fed experimental diets containing varying amounts of sesamin (0–0.5%) for 15 days. Activities were calculated as total activity (μmol/min per liver per 100 g body weight), and presented as percentages of the activities in rats fed a sesamin-free diet. Values represent means ± SE of 7–8 rats. *P< 0.05 v. sesamin-free group.

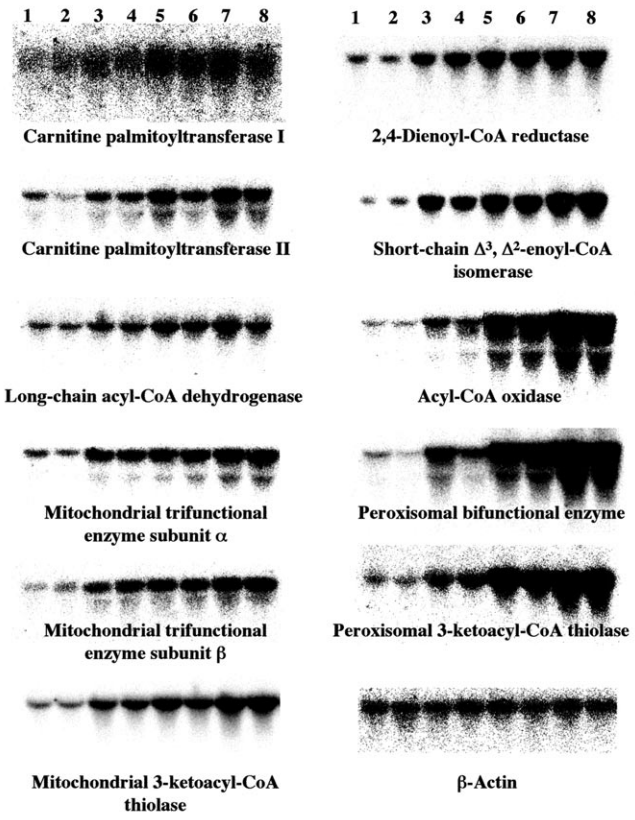

Fig. 3. Northern-blot analysis of mRNA of fatty acid oxidation enzymes in rat liver
Lanes 1 and 2: RNA from rats fed a sesamin-free diet, 3 and 4: 0.1% sesamin diet, 5 and 6: 0.2% sesamin diet, 7 and 8: 0.5% sesamin diet.

diet than that observed with a sesamin-free diet. The mRNA level of the peroxisomal bifunctional enzyme exhibiting both enoyl-CoA hydratase and 3-hydroxyacyl-CoA dehydrogenase activities was 50 times higher in rats fed a 0.5% sesamin diet than in those fed the control diets free of sesamin. The level of peroxisomal 3-ketoacyl-CoA thiolase mRNA became 6 times higher with a 0.5% sesamin diet than with a sesamin-free diet.

The present study unequivocally demonstrated that sesamin strongly induced the activity and gene expression of hepatic enzymes involved in fatty acid oxidation. Sesamin-dependent increase in fatty acid oxidation activity was detectable at dietary levels as low as 0.1%. Polyunsaturated fatty acids of the n-3 series have been demonstrated to induce hepatic fatty acid oxidation[12,23,24], but considerably higher amounts are required to obtain a detectable increase in hepatic fatty acid oxidation compared to sesamin. Thus, sesamin appears to be the most potent inducer of hepatic fatty acid oxidation among the various naturally occurring compounds reported so far. The potential role of the peroxisome proliferator-activated receptors (PPARs) in regulating the lipid metabolism has been well documented[16]. Various types of PPARs (α, γ_1, γ_2 and δ) have been identified in rodents and humans. PPARα is highly expressed in the liver and may play a crucial role in regulating the lipid metabolism in this tissue[16]. Diverse chemicals called peroxisome proliferators, which include the hypolipidemic drug clofibrate and related compounds, activate PPARα to induce the gene expression of the hepatic fatty acid oxidation enzymes and consequently lower the serum lipid levels[11,16]. It is considered that sesamin, like other peroxisome proliferators, induces the gene expression of the hepatic fatty acid oxidation enzymes through a PPAR-dependent mechanism.

Sesamin decreases fatty acid synthesis in rat liver accompanying the down-regulation of sterol regulatory element-binding protein-1[13]

The effect of sesamin on the hepatic fatty acid synthesis was examined in rats. Rats were fed experimental diets containing varying amounts of sesamin (0 to 0.4%) for 15 days. A diet containing 0.1% sesamin caused a 20–40% decrease in the activity and mRNA level of the enzymes involved in fatty acid synthesis, except for the

Table 1. Effect of sesamin on the activity and mRNA level of hepatic enzymes involved in fatty acid synthesis

	Enzymes					
	Acetyl-CoA carboxylase	Fatty acid synthase	ATP-citrate lyase	Glucose 6-phosphate dehydrogenase	Malic enzyme	Pyruvate kinase
Expt. 1						
Enzyme activity (μmol/min per liver per 100 g body weight)						
0% Sesamin	14.4 ± 1.0^{c}	29.7 ± 2.1^{b}	59.4 ± 2.9^{c}	93.8 ± 3.9^{c}	81.3 ± 3.5	232 ± 7^{c}
0.1% Sesamin	9.26 ± 0.93^{b}	20.2 ± 1.7^{a}	41.5 ± 3.0^{b}	54.3 ± 3.4^{b}	76.2 ± 3.9	187 ± 6^{b}
0.2% Sesamin	6.16 ± 0.66^{a}	16.1 ± 1.0^{a}	31.5 ± 2.3^{a}	38.8 ± 2.8^{a}	91.9 ± 8.0	130 ± 7^{a}
mRNA level (%)						
0% Sesamin	100 ± 4^{c}	100 ± 8^{b}	100 ± 6^{c}	100 ± 10^{c}	100 ± 9	100 ± 4^{c}
0.1% Sesamin	64.9 ± 2.9^{b}	63.9 ± 6.4^{a}	71.6 ± 3.2^{b}	64.4 ± 5.9^{b}	102 ± 10	74.7 ± 4.7^{b}
0.2% Sesamin	48.0 ± 2.2^{a}	50.5 ± 3.3^{a}	52.2 ± 4.4^{a}	36.5 ± 8.9^{a}	93.1 ± 8.2	45.4 ± 5.2^{a}
Expt. 2						
Enzyme activity (μmol/min per liver per 100 g body weight)						
0% Sesamin	13.5 ± 0.5^{b}	27.2 ± 2.8^{b}	55.2 ± 4.4^{b}	85.6 ± 6.7^{b}	74.3 ± 6.4^{a}	260 ± 18^{b}
0.2% Sesamin	7.62 ± 0.47^{a}	14.4 ± 1.3^{a}	31.6 ± 2.7^{a}	34.1 ± 5.9^{a}	92.5 ± 7.1^{a}	130 ± 5^{a}
0.4% Sesamin	7.96 ± 0.61^{a}	16.7 ± 1.7^{a}	30.0 ± 3.1^{a}	38.3 ± 5.6^{a}	146 ± 13^{b}	115 ± 9^{a}
mRNA level (%)						
0% Sesamin	100 ± 5^{b}	100 ± 6^{b}	100 ± 5^{b}	100 ± 5^{b}	100 ± 6^{a}	100 ± 8^{b}
0.2% Sesamin	51.0 ± 2.6^{a}	40.7 ± 4.1^{a}	56.1 ± 3.6^{a}	51.5 ± 3.2^{a}	116 ± 9^{a}	34.0 ± 2.6^{a}
0.4% Sesamin	52.8 ± 3.4^{a}	42.8 ± 8.8^{a}	59.6 ± 5.9^{a}	51.1 ± 2.5^{a}	192 ± 17^{b}	35.3 ± 4.6^{a}

Values are means ± SE of 7–8 rats. mRNA level was expressed by assigning a value of 100 for mRNA in rats fed 0% sesamin diet. Values in a column with different superscript letters are significantly different at $P<0.05$.

malic enzyme (Table 1, Expt. 1). Diets containing 0.2 and 0.4% sesamin further decreased these parameters to approximately one-half of the values obtained with sesamin-free diets (Expts. 1 & 2). The malic enzyme activity and gene expression in rats fed 0.1 and 0.2% sesamin diets were indistinguishable from those in the animals fed sesamin-free diets (Expts. 1 & 2). However, these values became significantly higher in rats fed a 0.4% sesamin diet than in those fed sesamin-free and 0.2% sesamin diets (Expt. 2).

Sterol regulatory element-binding proteins (SREBPs) are membrane-bound transcriptional factors which regulate the gene expression of the enzymes involved in fatty acid and cholesterol biosynthesis[9]. Three types of SREBPs have been identified (SREBP-1a, -1c, and -2). SREBPs are synthesized as approximately 1,150 amino acid precursors bound to the endoplasmic membrane and nuclear envelope. To be active, an NH_2-terminal sequence approximately 500 amino acids long containing the basic-helix-loop-helix-leucine zipper region is released by a sequential two-step proteolytic cleavage process. The liberated NH_2-terminal, the mature SREBP, enters the nucleus and activates the gene. SREBP-1 is mainly involved in the regulation of the gene expression of the fatty acid synthesis enzymes, while SREBP-2 activates the genes of the enzymes involved in cholesterol biosynthesis and the low-density lipoprotein receptor[9]. To test the hypothesis that sesamin decreases the lipogenic enzyme gene expression through the SREBP-1-dependent mechanism, we analyzed the mRNA and protein levels of this transcriptional factor.

Diets containing 0.1 and 0.2% sesamin caused 25–30% decreases in the SREBP-1 mRNA levels (data not shown). The value in rats fed a 0.4% sesamin diet became less than one-half of that in the animals fed a sesamin-free diet. Dietary sesamin dose-dependently decreased the amount of the membrane-bound precursor SREBP-1, as determined by Western-blotting (Fig. 4). The value in rats fed a 0.4% sesamin diet was 37% lower than in those fed a sesamin-free diet. Dietary sesamin also markedly decreased the amount of the soluble mature nuclear form of SREBP-1. The values were more than 80% lower in rats fed 0.2 and 0.4% sesamin diets than in those fed a sesamin-free diet.

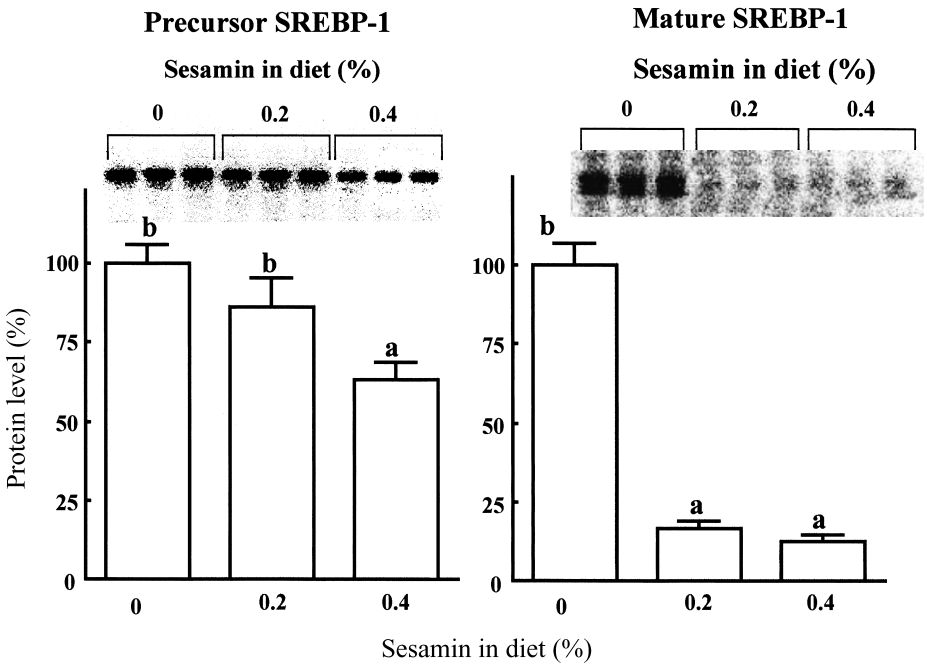

Fig. 4. Western-blot analysis of the content of membrane-bound precursor and the mature nuclear forms of SREBP-1 in the liver of rats fed diets containing 0, 0.2 and 0.4% sesamin

Values are expressed relative to a value of 100 for rats fed a sesamin-free diet. Values are means for 7–8 rats with standard errors indicated by vertical lines. Mean values not sharing a common letter are significantly different at $P<0.05$.

The present study showed that sesamin lowered the activities and mRNA levels of all the lipogenic enzymes, except for the malic enzyme. Among the various lipogenic enzymes, only the malic enzyme gene harbors a peroxisome proliferator response element, and its expression is up-regulated when PPARα is activated[5]. In the present study, dietary sesamin not only increased the gene expression of many enzymes involved in fatty acid oxidation, but also that of the malic enzyme. This observation further suggests that sesamin increases the gene expression of the hepatic fatty acid oxidation enzymes through the activation of PPARα. Available evidence indicates that the gene expression of the lipogenic enzymes, except for the malic enzyme, is under a control mechanism independent of PPARα[18].

The current finding that a dietary sesamin-dependent decrease in the gene expression of the enzymes involved in fatty acid synthesis accompanied a down-regulation of the mRNA level and protein content of SREBP-1 in the rat liver supports the assumption[15,19] that SREBP-1 plays a significant role in the nutritional regulation of hepatic fatty acid synthesis. The extent of the decrease in the protein content of mature SREBP-1 was larger than expected from the reductions in the SREBP-1 mRNA level and the protein content of the precursor form. This observation indicated that sesamin not only affects the gene expression of SREBP-1, but also modifies the proteolytic process for the production of the mature form, and thus down-regulates the gene expression of the hepatic enzymes involved in fatty acid synthesis.

Sesamin decreases the triacylglycerol secretion accompanying the enhanced production of ketone bodies by perfused rat liver[3,4]

Our studies unequivocally demonstrated that sesamin increases the activity and gene expression of the hepatic fatty acid oxidation enzymes, while it down-regulates these parameters for lipogenesis. These changes may reduce the hepatic triacylglycerol synthesis and consequently decrease the assembly and secretion of triacylglycerol-rich lipoproteins by the liver[10,11,25]. To confirm this hypothesis, we examined the effect of dietary sesamin on the triacylglycerol secretion and ketone body production by perfused rat liver. Rats were fed either a commercial diet containing 0.2% sesamin or a control diet free of sesamin for 14 to 16 days. The liver was isolated under pentobarbital anesthesia and perfused with recirculating Krebs-Henseleit buffer (pH 7.4) containing 25 mM glucose, 1.5% bovine serum albumin and 25% washed bovine erythrocytes with continuous supply

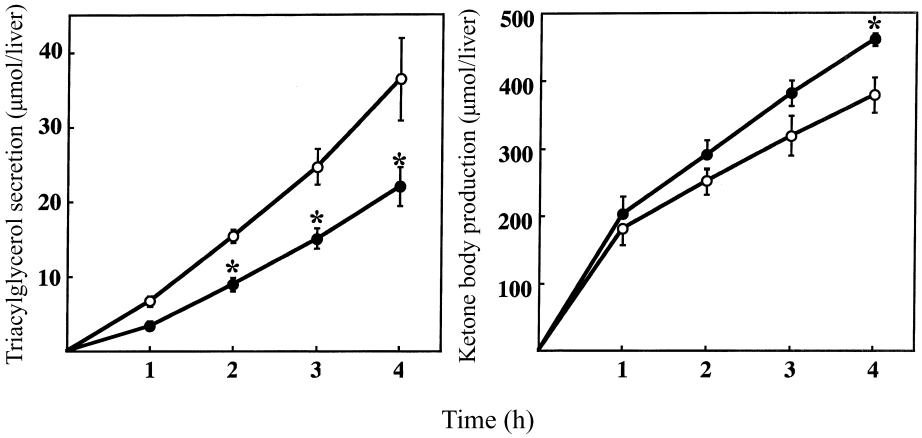

Fig. 5. Triacylglycerol secretion and ketone body production by the liver in rats fed diets containing 0 (○) and 0.2% sesamin (●)

Values are means for 6 rats with standard errors indicated by vertical lines.
*P< 0.05 v. sesamin-free group.

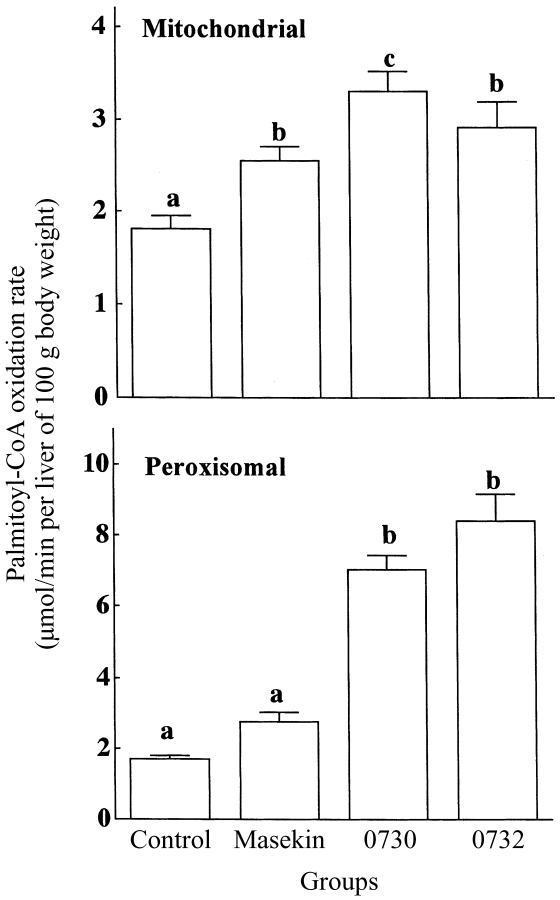

Fig. 6. Effect of sesame seeds differing in lignan contents on mitochondrial and peroxisomal palmitoyl-CoA oxidation rates in rat liver

Rats were fed a control diet without sesame seed or diets containing 20% sesame seed powder from Masekin cultivar, and 0730 and 0732 lines. Values represent means ± SE of 7–8 rats. Values with different letters significantly differ at P<0.05.

of oleate substrate. The triacylglycerol secretion by the liver of rats fed control and sesamin diets linearly increased during the 4 h experimental period (Fig. 5). Dietary sesamin caused a 40% decrease in the rate of hepatic triacylglycerol secretion. On the contrary, livers of rats fed sesamin produced more ketone bodies than did the livers of rats fed a control diet, and a significant difference was observed at 4 h of the experimental period. It is therefore apparent that up-regulation of hepatic fatty acid oxidation by sesamin is associated with a lower rate of lipoprotein production by the liver. The reduction in the hepatic lipoprotein production may account for the serum lipid-lowering effect of sesamin.

Effect of sesame seeds rich in sesamin and sesamolin on fatty acid oxidation in rat liver[21]

Our studies showed that sesamin markedly affects the hepatic fatty acid metabolism and hence lowers serum-lipid levels. In addition, sesame lignans including sesamin and sesamolin exert physiological effects, by acting as anti-oxidant[14,26] and anti-carcinogen agents[8], and by lowering the blood pressure[17] in experimental animals and humans. Therefore, consumption of sesame seeds is beneficial to health, and enrichment of the lignans may potentiate the characteristics of sesame in improving human health. Therefore, we bred and established several sesame lines with seeds containing sesamin and sesamolin at twice the concentration of conventional cultivars[20]. We also confirmed that crop yields of these lines were comparable to those of conventional cultivars. In this study, we compared the activities of the enzymes involved in hepatic fatty acid metabolism, and

Table 2. Effect of sesame rich in sesamin and sesamolin on serum lipid levels

Groups	Serum lipids (μmol/dL)		
	Triacylglycerol	Cholesterol	Phospholipid
Control	339 ± 46[b]	300 ± 11[b]	250 ± 10[a b]
Masekin	294 ± 37[b]	246 ± 15[a]	223 ± 14[a]
0730	176 ± 22[a]	264 ± 14[a]	262 ± 14[a b]
0732	177 ± 11[a]	254 ± 8[a]	272 ± 16[b]

Values represent means ± SE of 7–8 rats.
Values in a column with different superscript letters are significantly different at $P<0.05$.

serum lipid levels in rats fed sesame rich in sesamin and sesamolin (0730 and 0732 lines), and in those fed a conventional sesame cultivar (Masekin) to determine whether the enrichment of lignans in sesame potentiates the physiological activity associated with the alteration of the lipid metabolism.

Rats were fed a control diet or diets containing 20% sesame seeds for 16 days. Sesame increased both the hepatic mitochondrial and peroxisomal fatty acid oxidation rates (Fig. 6). Increases were more conspicuous with sesame rich in lignans than with Masekin. Noticeably, the peroxisomal activity levels were more than 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 activity. Diets containing seeds from the 0730 and 0732 lines, compared to the control and Masekin diets, also significantly increased the activity of various hepatic fatty acid oxidation enzymes, including carnitine palmitoyltransferase, acyl-CoA oxidase, 3-hydoxyacyl-CoA dehydrogenase and 3-ketoacyl-CoA thiolase (data not shown). In contrast, diets containing sesame lowered the activity of the enzymes involved in fatty acid synthesis (fatty acid synthase, glucose 6-phosphate dehydrogenase, malic enzyme, ATP-citrate lyase and pyruvate kinase) (data not shown). No significant differences in enzyme activities were, however, observed among the diets containing sesame from the Masekin cultivar and, 0730 and 0732 lines. Serum triacylglycerol concentrations were lower in rats fed diets containing sesame from the 0730 and 0732 lines than in those fed the control or Masekin diets (Table 2). It is apparent that sesame rich in lignans affected more appreciably the hepatic fatty acid oxidation and serum triacylglycerol levels. Therefore, the consumption of sesame rich in lignans may result in physiological activity associated with the alteration of the lipid metabolism in a potentially beneficial manner.

Conclusion

Our studies clearly demonstrated that sesamin markedly influences the hepatic fatty acid oxidation and synthesis in the rat. Sesamin appears to be an active PPAR ligand and the most potent inducer of hepatic fatty acid oxidation among the various naturally occurring compounds so far reported. Moreover, we showed that sesamin decreases the hepatic lipogenic enzyme gene expression through the down-regulation of SREBP-1. The changes in the hepatic fatty acid metabolism by dietary sesamin were associated with a decrease in triacylglycerol secretion by perfused rat liver. Therefore, the reduction in the hepatic lipoprotein production may account for the serum lipid-lowering effect of dietary sesamin. We also developed sesame seed lines rich in sesamin and sesamolin that enhance hepatic fatty acid oxidation and lower the serum triacylglycerol level more than a conventional cultivar. Our studies using rats provided the scientific basis to demonstrate the health-promoting characteristics of sesame seeds and oil. We hope that the consumption of sesame will enable to improve the lipid metabolism and hence be beneficial to health by preventing arteriosclerosis in humans also.

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