Effects of sesamin-supplemented dietary fat emulsions on the ex vivo production of lipopolysaccharide-induced prostanoids and tumor necrosis factor α in rats[1,2]

Tohru Utsunomiya, Sambasiva R Chavali, W William Zhong, and R Armour Forse

ABSTRACT

Background: Sesamin, a nonfat constituent of sesame oil, inhibits Δ^5-desaturase activity, resulting in accumulation of dihomo-γ-linolenic acid (DGLA), which displaces arachidonic acid (AA) and consequently decreases the formation of proinflammatory 2-series prostaglandins.

Objective: We sought to determine whether dietary supplementation with sesamin augments the antiinflammatory effects of dietary linseed oil in rats.

Design: We investigated the effects of continuous tube feedings of emulsions containing safflower oil or linseed oil with sesamin (SO+ and LO+) or without sesamin (SO and LO) on liver fatty acid composition and on endotoxin-induced production of prostaglandin E_2, 6-keto-prostaglandin $F_{1\alpha}$, and tumor necrosis factor α (TNF-α) by whole blood from rats (n = 6 per diet group).

Results: We found a significant accumulation of DGLA only in the liver phospholipids of animals fed SO+ and LO+ (1.8 ± 0.2 and 1.4 ± 0.3 mol%, respectively), which suggests that sesamin inhibited Δ^5-desaturation of n−6 fatty acids. These changes were associated with significant reductions in plasma prostaglandin E_2 concentrations in animals fed SO+ compared with those fed SO ($P < 0.05$). Despite a significant reduction in tissue AA content in the LO group, the prostaglandin E_2 concentrations did not differ significantly from those of the SO group. Plasma concentrations of TNF-α were significantly lower ($P < 0.05$) in the animals fed LO+ than in those fed SO (199 ± 48 and 488 ± 121 ng/L, respectively).

Conclusion: These data indicate that in rats, tube feedings of diets containing sesamin exerted antiinflammatory effects that were augmented by concurrent consumption of linseed oil. *Am J Clin Nutr* 2000;72:804–8.

KEY WORDS Sesamin, short-term continuous feeding, prostanoids, septic shock, rats, antiinflammatory effects, linseed oil, prostaglandins, tumor necrosis factor α, lipopolysaccharides

INTRODUCTION

Sesame oil has long been used as an edible fat and is considered a health food in Asia (1). The nonfat portion of the oil contains considerable amounts of sesamin, sesamol, and other related lignans (2). Consumption of diets supplemented with sesamol (3) or sesamin results in significant inhibition of Δ^5-desaturation of n−6 fatty acids and increases the accumulation of dihomo-γ-linolenic acid (DGLA), with a concomitant decrease in arachidonic acid (AA) concentrations, in mice (4, 5) and in rats (6, 7). Therefore, consumption of sesamin could increase the production of the less-inflammatory 1-series prostaglandins and decrease synthesis of proinflammatory 2-series prostaglandins, which depends on the availability of specific fatty acid precursors (8, 9). Dietary fats rich in γ-linolenic acid, α-linolenic acid, or eicosapentaenoic acid (EPA) were used to modulate inflammatory responses in animal models (10–12) and in clinical trials (13, 14). Consumption of diets rich in n−3 polyunsaturated fatty acids (PUFAs) also reduces production of proinflammatory 2-series prostaglandins while concomitantly increasing formation of 3-series prostaglandins during infection and some disease states (15).

Therefore, it is plausible to suggest that consumption of dietary n−3 PUFAs supplemented with sesamin could reduce the synthesis of 2-series prostaglandins and enhance the production of 1-series and 3-series prostaglandins, both of which are favored during several inflammatory disorders (16, 17). It was shown that consumption of sesamin-supplemented diets for 3 wk had no significant effect on the Δ^5-desaturation of n−3 PUFAs (5, 7) and the consequences of continuous feeding for a shorter duration are unknown. We reported previously that after continuous tube feeding of emulsions containing n−3 PUFAs from menhaden oil for 5 d, a significant reduction in the tissue AA content was associated with a significant decrease in the production of proinflammatory prostanoids (18). By using the same established animal model, we investigated the effects of feeding linoleic acid–enriched safflower oil (SO) and α-linolenic acid–enriched linseed oil (LO) emulsions supplemented with sesamin on the phospholipid fatty acid composition of the liver and on the lipopolysaccharide-induced production of prostanoids and tumor necrosis factor α (TNF-α).

[1] From the Department of Surgery, Harvard Institutes of Medicine, Boston; Beth Israel Deaconess Medical Center, Boston; and Harvard Medical School, Boston.

[2] Address reprint requests to RA Forse, Department of Surgery, Boston University, One Medical Place C-5, Boston, MA 02218. E-mail: armour.forse@bmc.org.

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TABLE 1
Composition of liquid emulsions enriched with safflower oil (SO) or linseed oil (LO): amount per 60 mL of liquid emulsion

	SO	LO
Lipophilic phase[1]		
Safflower oil (g)	1.38	0
Linseed oil (g)	0	1.50
Palm oil (g)	0.48	0.18
Coconut oil (g)	0	0.18
Span 80 (μL)	104	104
Hydrophilic phase[2]		
Criticare HN (mL)[3]	35	35
Amynosyn II 10% (mL)	18	18
Distilled water (mL)	5	5
Tween 20 (μL)	16	16

[1] Safflower oil rich in linoleic acid (18:2n−6) was used as a source of n−6 polyunsaturated fatty acids (PUFAs) and linseed oil rich in α-linolenic acid (18:3n−3) was used as a source of n−3 PUFAs. Palm oil and coconut oil were used as filler oils to keep the ratio of polyunsaturated to saturated fatty acid constant at 3. The SO diet provided 3.8 g linoleic acid·kg^{-1}·d^{-1} and the LO diet provided 1.2 g linoleic acid·kg^{-1}·d^{-1} and 2.6 g α-linolenic acid·kg^{-1}·d^{-1}.

[2] pH was adjusted to 3.9 before mixing with the lipophilic phase.

[3] The basal enteral formula provides (in g/100 mL) the following: protein, 3.8; fat (corn oil), 0.53; carbohydrate, 22; minerals, 0.7; water, 83.

MATERIALS AND METHODS

Animals

We used male Sprague-Dawley rats (n = 6 per group) that weighed 225–250 g (Taconic Farms, Germantown, NY). Rats were allowed free access to the nonpurified stock diet (ProLab RMH 3000; Agway, Syracuse, NY). They were housed in our animal facility, which had a controlled environment with a cycle of 12 h dark and 12 h light.

Diets

Liquid emulsions enriched with SO (SVO Enterprises, Eastlake, OH) or LO (Novartis Nutrition, St Paul) were prepared according to procedures described previously (18); the composition of the emulsions is shown in **Table 1**. The hydrophilic-lipophilic balance of the emulsifying agents (Tween 20 and Span 80; Sigma Chemical Co, St Louis) was adjusted to 6 and was used at a final concentration of 0.2% (vol:vol) to yield stable emulsions. The sesamin (a mixture of sesamin and episesamin in equal proportions by weight) was a gift from Suntory Ltd (Osaka, Japan) and was added (0.25 wt%) to the lipid phase. Other constituents of the emulsions included palm oil and coconut oil (both from Fuji Vegetable Oil, Savannah, GA), Amynosyn II (Abbott Laboratories, North Chicago), and Criticare HN (Bristol Meyers Co, Evansville, IN). The diets provided 836.8 kJ (30% of total energy from fat) with 1.6 g N in 192 mL·kg^{-1}·d^{-1} (energy density = 4.35 kJ/mL). The fatty acid composition of the liquid emulsions is shown in **Table 2**.

Experimental protocol

The rats were anesthetized with ether, and a 0.76-mm silastic feeding tube was inserted into the duodenum through the stomach. The free end was tunneled subcutaneously to exit through a stab wound in the midscapular region and was attached to a flow-through swivel (Spalding Medical Products, Birmingham, AL). Later, the rats were housed individually and the diets were infused continuously at 8 mL·kg^{-1}·h^{-1} with a multiple-head syringe pump (Harvard Apparatus, Natick, MA).

Fatty acid analysis

Liver tissues were homogenized and extracted with a 2:1 (vol:vol) chloroform:methanol mixture containing 0.01% butylated hydroxytoluene as an antioxidant (19). The solvent fraction was isolated and evaporated to dryness under nitrogen gas and was reconstituted in a convenient volume of chloroform. The total phospholipids were separated by thin-layer chromatography on silica gel H plates (Analtech Inc, Newark, DE). The fatty acid methyl esters were derived (20) and analyzed on a fused-silica capillary column (100 m, 0.25-mm inside diameter, 0.20-μm thickness; SP-2560; Supelco Inc, Bellefonte, PA) by using a gas chromatograph (5890 Series II) equipped with a mass selective detector (5971; Hewlett-Packard, Palo Alto, CA). The results were expressed as the relative percentage of identified fatty acids on a molar basis; we used heptadecanoic acid (17:0) as an internal standard.

Ex vivo stimulation of whole blood

With the rats under ether anesthesia, venous blood was collected from the inferior vena cava. The blood was mixed with lipopolysaccharide (50 mg/L) in sterile tubes (Eppendorf, Hamburg, Germany) and was incubated for 15 or 120 min at 37°C. Care was taken to prevent the cells from settling by placing the tubes on a Varimix platform (Barnstead/Thermolyne, Dubuque, IA) oscillating at a low angle (15°) and very low speed. Plasma was separated and stored at −70°C until analyzed.

Concentrations of prostaglandin E_2, 6-keto-prostaglandin $F_{1\alpha}$, and TNF-α

The concentrations of prostaglandin E_2 and 6-keto-prostaglandin $F_{1\alpha}$ in the ethyl acetate extracts of plasma (5) were determined with use of a radioimmunoassay according to procedures described elsewhere (21). The polyclonal rabbit anti-prostaglandin E_2 and 6-keto-prostaglandin $F_{1\alpha}$ antisera were obtained from Advanced Magnetics (Cambridge, MA). According to the supplier's technical information, the prostaglandin E_2 antiserum has 50% cross-reactivity with prostaglandin E_1 and we determined that it has 10% cross-reactivity with prostaglandin E_3 (18). A double antibody sandwich enzyme-linked immunosorbent assay was used to determine the plasma concentrations of TNF-α according to procedures described previously (18).

TABLE 2
Fatty acid composition of liquid emulsions containing safflower oil (SO) or linseed oil (LO)[1]

Fatty acid	SO	LO
	mol%	
12:0	0	1.3
14:0	0	1.3
16:0	16.5	8.5
18:0	4.4	3.4
18:1n−9	24.2	20.3
18:2n−6	5.3	14.7
18:3n−3	0	50.4

[1] The fatty acid composition of each diet was determined as described in Materials and Methods.

TABLE 3
Fatty acid composition of liver membrane phospholipids in rats after a 5-d continuous tube feeding of a liquid emulsion diet containing safflower oil or linseed oil with sesamin (SO+ or LO+) or without sesamin (SO or LO)[1]

	SO	SO+	LO	LO+
			mol%	
Fatty acids				
SFAs	43.4 ± 1.4	45.5 ± 1.0	44.3 ± 1.1	45.9 ± 1.8
MUFAs	3.8 ± 0.6	3.2 ± 0.7	4.4 ± 1.0	4.7 ± 0.8
18:2n−6	20.7 ± 1.6	20.5 ± 1.5	22.4 ± 1.2	21.0 ± 1.3
20:3n−6	ND	1.8 ± 0.2[2]	ND	1.4 ± 0.3[2]
20:4n−6	22.1 ± 0.9	20.6 ± 1.3	16.3 ± 0.4[2]	15.9 ± 1.3[2]
20:5n−3	ND	ND	1.9 ± 0.3[2]	1.3 ± 0.1[2,3]
22:6n−3	5.8 ± 1.2	5.3 ± 0.4	5.1 ± 0.5	5.9 ± 0.9
AI index[4]	26.4 ± 1.0	32.6 ± 6.3	40.3 ± 4.9[2]	52.7 ± 6.9[2,3]

[1] $\bar{x}$ ± SD. n = 6 per group. ND, not detectable. The amounts of individual saturated fatty acids (SFAs: 14:0, 16:0, and 18:0) and monounsaturated fatty acids (MUFAs: 16:1 and 18:1) did not differ significantly between the groups of animals and are therefore shown as total SFAs and MUFAs.
[2] Significantly different from SO, $P < 0.05$ (one-way factorial ANOVA).
[3] Significantly different from LO, $P < 0.05$ (one-way factorial ANOVA).
[4] Antiinflammatory index = [20:3n−6 + 20:5n−3 + 22:6n−3/20:4n−6] × 100.

Statistical analysis

Differences between the experimental groups were determined by using one-way factorial analysis of variance with Scheffe's method as a post hoc test. $P < 0.05$ was considered statistically significant.

RESULTS

Body weight and liver fatty acid composition

There were no significant differences between the 4 groups of animals in average body weight after continuous tube feedings of the liquid emulsions for 5 d (data not shown). Changes in the fatty acid composition ($\bar{x}$ ± SD and mol%) of liver membrane phospholipids resulting from the ability of sesamin to inhibit Δ^5-desaturase activity (5, 7) were determined after continuous infusion of the emulsions; these data are summarized in **Table 3**. The amounts of saturated fatty acids (palmitic + stearic acids) and monounsaturated fatty acids (mainly oleic acid) did not differ significantly among the 4 groups of animals. Appreciable amounts of DGLA were detectable only in the 2 groups of rats fed diets supplemented with sesamin (1.8 ± 0.2 and 1.4 ± 0.3 mol% for SO+ and LO+, respectively). Tissue AA concentrations were significantly lower in the groups of rats fed diets enriched with LO (16.3 ± 0.4 and 15.9 ± 1.3 mol% in LO and LO+, respectively; $P < 0.05$) than in the groups fed SO diets (22.1 ± 0.9 and 20.6 ± 1.3 mol% in SO and SO+, respectively). However, concentrations of EPA were detectable only in the groups of rats fed diets containing LO (1.9 ± 0.3 and 1.3 ± 0.1 mol% in LO and LO+, respectively). Although DGLA is an n−6 PUFA, because of its antiinflammatory properties it is included with n−3 PUFAs when the antiinflammatory fatty acid index is calculated [(docosahexaenoic acid + EPA + DGLA)/AA] (Table 3). Thus, the antiinflammatory index in the group of rats fed LO+ was significantly higher than that of rats fed SO (52.7 ± 6.9 compared with 26.4 ± 1.0, respectively).

Prostaglandin E_2 and 6-keto-prostaglandin $F_{1\alpha}$

We determined the effects of consuming SO+ and LO+ diets on the lipopolysaccharide-induced production of prostaglandin E_{1+2} (**Figure 1**) and 6-keto-prostaglandin $F_{1\alpha}$ (**Figure 2**). Before lipopolysaccharide exposure, the mean concentrations of prostaglandin E_{1+2} and 6-keto-prostaglandin $F_{1\alpha}$ did not differ significantly between the groups of animals. After 15 min of exposure to lipopolysaccharide, the mean concentration of prostaglandin E_{1+2} in the whole blood samples from rats fed LO+ was significantly lower than that of rats that received SO (197 ± 88 and 335 ± 82 ng/L, respectively). Furthermore, 120 min after lipopolysaccharide exposure, the average plasma concentrations of prostaglandin E_{1+2} (ng/L) in the groups of animals fed the sesamin-supplemented diets were significantly lower than those of rats fed SO (SO+ = 205 ± 98; LO+ = 212 ± 85; SO = 376 ± 103). The mean plasma concentrations of 6-keto-prostaglandin $F_{1\alpha}$ (ng/L) in the SO+ group (165 ± 82) and the LO+ group (175 ± 67) were also significantly lower than that of rats receiving the SO diet (296 ± 52).

TNF-α

Dietary PUFAs can influence the production of cytokines (22, 23), and overproduction of TNF-α is associated with an increase in mortality during sepsis (24, 25). Thus, we determined the concentrations of lipopolysaccharide-induced TNF-α in rats that received the SO, SO+, LO, and LO+ diets (**Figure 3**). TNF-α was not detectable in the plasma samples before or 15 min after lipopolysaccharide exposure. However, 120 min after lipopolysaccharide exposure, the mean plasma concentration of TNF-α in the LO+ group was significantly lower than that of the SO group (199 ± 48 compared with 488 ± 121 ng/L, respectively).

DISCUSSION

Consumption of diets containing DGLA, AA, and EPA results in the formation of 1-, 2-, and 3-series prostaglandins, respectively (26, 27). These prostaglandins influence a wide range of physiologic and pathologic processes, including inflammation and immunity (16, 28). For example, prostaglandin E_1 inhibits

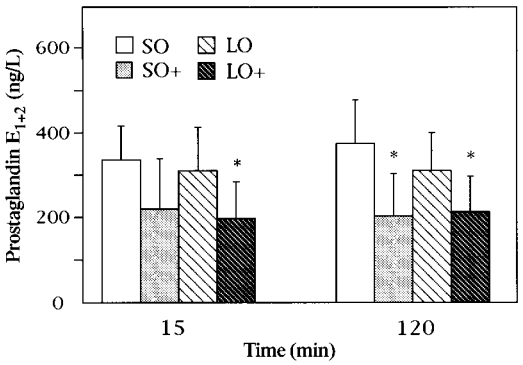

FIGURE 1. Mean (±SD) plasma concentrations of prostaglandin E_{1+2} 15 and 120 min after exposure to lipopolysaccharide in rats maintained for 5 d on liquid emulsions containing safflower oil or linseed oil with 0.25% sesamin (SO+ and LO+, respectively) or without sesamin (SO and LO); n = 6 per group. *Significantly different from the SO group, $P < 0.05$ (one-way factorial ANOVA).

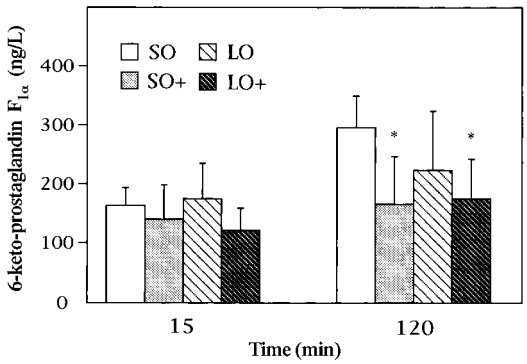

FIGURE 2. Mean (±SD) plasma concentrations of 6-keto-prostaglandin $F_{1\alpha}$ 15 and 120 min after exposure to lipopolysaccharide in rats maintained for 5 d on liquid emulsions containing safflower oil or linseed oil with 0.25% sesamin (SO+ and LO+, respectively) or without sesamin (SO and LO); n = 6 per group. *Significantly different from the SO group, $P < 0.05$ (one-way factorial ANOVA).

platelet aggregation, vascular smooth muscle cell proliferation, and superoxide anion generation. In contrast, prostaglandin E_2 is a proaggregatory and proinflammatory mediator with immunosuppressive properties (29, 30). Significant reductions in tissue concentrations of AA with concomitant accumulations of DGLA in the groups of animals fed sesamin-supplemented diets (SO+ and LO+) and accumulation of EPA in the LO group (Table 3) were consistent with the effects of ad libitum feeding of sesamin-supplemented diets (5, 7). Therefore, consumption of sesamin-supplemented LO diets, resulting in significantly increased accumulation of DGLA and EPA with a concomitant reduction of endotoxin-induced dienoic prostanoids and TNF-α, may have therapeutic potential to ameliorate clinical symptoms and complications that are secondary to excessive production of such proinflammatory mediators.

In the present study, a significant increase in the incorporation of EPA with a concomitant reduction of AA in rat liver membrane phospholipids, resulting from continuous tube feeding of emulsions containing LO, was consistent with the effects of menhaden oil (18). In response to an intravenous injection of lipopolysaccharide, the production of proinflammatory prostanoids is lower in rats fed menhaden fish oil (18). However, the lipopolysaccharide-induced ex vivo production of prostaglandin E_{1+2} in animals fed the LO diet was not significantly different from that of rats maintained on a control diet (Figures 1 and 2). These data suggest that in rats receiving a continuous infusion of the LO diet, a mere decrease in the AA content of the liver membrane phospholipids (Table 3) was not associated with changes in the circulating concentrations of prostanoids. However, the plasma concentrations of prostaglandin E_{1+2} were significantly lower in rats fed sesamin-supplemented SO or LO despite the fact that the tissue concentrations of AA did not differ significantly from those of rats fed diets containing SO or LO alone. These data suggest that sesamin could inhibit the enzymatic activity of cyclooxygenase, which is responsible for the formation of prostanoids.

In addition, consumption of diets supplemented with n−3 or n−6 PUFAs results in alterations in the production of cytokines, but the vast majority of published studies have produced contradictory results so far (10, 22, 23, 31). Previously, we reported that circulating TNF-α concentrations in rats infused with menhaden oil emulsions were not significantly different from those of rats fed the SO control diet (18). Plasma TNF-α concentrations are significantly elevated in animals fed diets enriched with EPA (fish oil) (10, 23, 32) or α-linolenic acid (5). Similarly, lipopolysaccharide-induced production of TNF-α increased significantly in resident macrophages from mice (32, 33) and in Kupffer cells from rats (34) that were maintained on fish oil diets. In contrast, dietary supplementation with fish oil caused significant reductions in the lipopolysaccharide-induced secretion of TNF-α in the peripheral blood mononuclear cells from healthy volunteers (22, 35) and patients with multiple sclerosis (36). Similarly, the production of TNF-α in response to a challenge with lipopolysaccharide was significantly lower in rats fed the LO+ diet, but not in those fed the SO+ or LO diets, than in the control rats that were fed SO (Figure 3).

Furthermore, increases in the amounts of both DGLA and EPA with a concomitant reduction of AA in the liver membrane phospholipids were observed only in the group of rats fed the LO+ diet. The ratio of the sum of fatty acids that have the ability to decrease the formation of dienoic eicosanoids [docosapentaenoic acid (22:5n−3), docosahexaenoic acid (22:6n−3), and DGLA (20:3n−6)] to AA was higher in livers from animals fed LO+ than in livers from the other animals (Table 3). As we reported elsewhere (4), an increase in an anti-inflammatory fatty acid index (Table 3) is associated with a significant decrease in the formation of prostaglandin E_2 (Figure 1) and 6-keto-prostaglandin $F_{1\alpha}$ (Figure 2). Furthermore, these data were consistent with similar effects resulting from a higher n−3-to-n−6 PUFA ratio in the liver, heart, aorta, lung, and platelets (37, 38). Alternatively, sesamin, which has antioxidant properties (1, 2), could decrease TNF-α production (Figure 3), as occurs with other antioxidants (31, 32, 39, 40).

In summary, a significant accumulation of DGLA in the tissue phospholipids of rats fed sesamin-supplemented diets was associated with significant reductions in the production of proinflammatory mediators (prostaglandin E_2, 6-keto-prostaglandin $F_{1\alpha}$, and TNF-α). Therefore, these data suggest that sesamin has an augmenting or synergistic effect on the antiinflammatory properties of enteral liquid emulsions containing n−3 PUFAs, and this effect may benefit patients with endotoxemia.

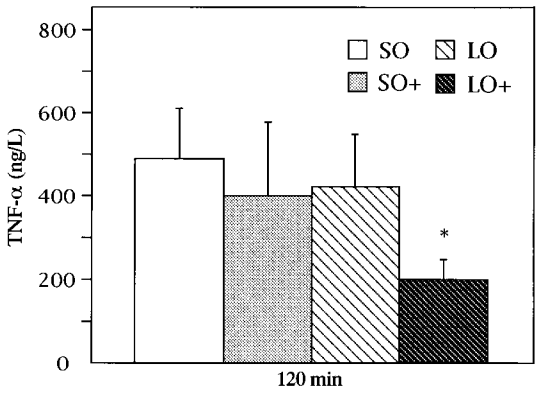

FIGURE 3. Mean (±SD) plasma concentrations of tumor necrosis factor α (TNF-α) 120 min after exposure to lipopolysaccharide in rats maintained for 5 d on liquid emulsions containing safflower oil or linseed oil with 0.25% sesamin (SO+ and LO+, respectively) or without sesamin (SO and LO); n = 6 per group. *Significantly different from the SO group, $P < 0.05$ (one-way factorial ANOVA).

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