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Zinc Deficiency and the Desaturation of Linoleic Acid in Rats Force-Fed Fat-Free Diets

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ABSTRACT

Recent studies with rats force-fed zinc-deficient diets containing various types of fat failed to demonstrate a role of zinc in desaturation of linoleic acid. The present study was conducted to investigate the effect of zinc deficiency on desaturation of linoleic acid in rats that were initially force-fed fat-free diets to stimulate activity of desaturases. Therefore, rats were fed zinc-adequate and zinc-deficient fat-free diets for 6 d. After that period, the groups were divided and half of the rats continued feeding the fat-free diet for another 3.5 d whereas the other half was switched to a fat diet by supplementing the fat-free diet with 5% safflower oil. In order to assess desaturation of linoleic acid, fatty acid compositions of liver phosphatidylcholine, -ethanolamine, and -serine were considered, particularly levels of individual (n-6) polyunsaturated fatty acids (PUFA). Levels of total and individual (n-6) PUFA were similar in zinc-adequate and zinc-deficient rats fed the fat-free diet throughout the experiment. Addition of 5% safflower oil increased levels of total and individual (n-6) PUFA in both zinc-adequate and zinc-deficient rats. However, total (n-6) PUFA in all types of phospholipids were higher in zinc-adequate rats than in zinc-deficient rats. Additionally, in zinc-deficient rats there were changes of (n-6) PUFA levels typical for impaired Δ5 and Δ6 desaturation: linoleic acid and dihomo-γ-linolenic acid were elevated; arachidonic acid, docosatetraenoic acid, and docosapentaenoic were lowered by zinc deficiency. Therefore, the study shows that zinc deficiency impairs desaturation of linoleic acid in rats force-fed fat-free diets and therefore supports results from for-

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mer convential zinc deficiency experiments suggesting a role of zinc for desaturation of linoleic acid.

Index Entries: Zinc deficiency; force-feeding; desaturation; liver; fat-free diet; fatty acid composition; rat.

INTRODUCTION

Zinc deficiency has been shown to accentuate essential fatty acid (EFA) deficiency in rats, and thus an interaction between zinc and EFA deficiency has been proposed *(1)*. Some studies suggested that zinc deficiency affects metabolism of EFA by impaired desaturation *(2–5)*. In contrast, other studies could not support a role of zinc in fatty acid desaturation *(6–10)*. One reason for the contradiction might be that the effects of zinc deficiency are confounded by the low food intake in zinc-deficient rats *(6)*. In order to overcome the problems of low food intake, in a series of experiments *(11–14)*, we used a force-feeding technique that has been shown to be a convenient technique to induce severe zinc deficiency, provide rats with sufficient nutrients, and guarantee identical food intake and feeding pattern in control and zinc-deficient rats *(15–17)*. Those studies that used either a coconut oil/safflower oil mixture or linseed oil as a source of dietary fat demonstrated that zinc deficiency impairs Δ9-desaturation but does not affect Δ5- and Δ6-desaturation *(11–13)*.

Several studies have shown that the activities of Δ5- and Δ6-desaturase depend on the dietary fat. Fats with high levels of polyunsaturated fatty acids (PUFA) suppress activities of desaturases, whereas administration of a fat-free diet markedly elevates activities of desaturases *(18–21)*. The aim of the present study was to investigate whether zinc deficiency affects Δ5- and Δ6-desaturation in force-fed rats if activities of desaturases are raised by feeding a fat-free diet. Therefore, a fat-free diet was fed for 6 d, and after that period the diet was supplemented with safflower oil for another 3.5 d. As a measure for fatty acid desaturation, fatty acid composition of liver phospholipids was determined and levels of individual (n-6) PUFA were considered to assess desaturation of linoleic acid.

MATERIALS AND METHODS

Animals and Diets

Forty-four male Sprague-Dawley rats weighing 122 ± 5 g were divided into two groups containing 20 rats (zinc-adequate group) and 24 rats (zinc-deficient group). Throughout the experiment, all the rats were fed 4 times/day (0800, 1300, 1800, 2300) by intragastric tube *(11–14,17)*. The zinc-adequate group received a semisynthetic basal fat-free (FF) diet supplemented with 40 mg zinc/kg (as zinc sulfate) for 6 d. The zinc-defi-

cient group received the same diet without zinc supplementation; the zinc concentration of that diet was 0.5 mg/kg. The zinc-deficient group contained a higher number of animals than the zinc-adequate group because of the higher risk of mortality during the experiment. At the morning of the seventh day, both groups were divided in 2 of 10 (zinc-adequate group) resp. 12 rats (zinc-deficient group). One-half continued feeding the fat-free diet whereas the other half was switched to the same diet added with 5% safflower oil. This feeding period included 3.5 d. After that, the experiment was terminated because the rats fed the zinc-deficient diets became severely ill; they showed signs of severe zinc deficiency such as sparse and coarse hair, skin lesions around mouth, paws and eyes, ataxia and lethargy. After the last feeding, the rats were starved for 3 h and killed by decapitation after a light anestesia with diethyl ether.

The composition of the basal diet is shown in Table 1. The concentration of total lipids in the fat-free diets was 1.3 mg/kg. The rats were housed in Macrolon cages. A daily 12-h light/dark cycle, a temperature of 23°C, and 60% humidity were maintained. Diet slurries were freshly prepared before each feeding by mixing 100 g of dry diet with 60 mL of double-distilled water (fat-free diet) and additionally 5 g of safflower oil (5% safflower oil diet). The safflower oil used was composed (in g/100 g fatty acids) of palmitic acid (16:0) 7.5, stearic acid (18:0) 2.5, oleic acid (18:1) 13.7, and linoleic acid (18:2 n-6) 75.2; other fatty acids existed only in traces (< 0.2 g/100g fatty acids). Immediately before feeding, the slurry was warmed in a glass bottle at 50°C for a few minutes. The intragastric tube consisted of a 5-mL syringe connected with a slide catheter. During tube feeding, the conscious rat was hand-held. The catheter was then inserted into the stomach of the rat, and the slurry was slowly injected. To avoid contamination, zinc-deficient rats were always fed before zinc-adequate rats. Each rat was fed 4 mL of slurry per feeding (fat-free diet, representing 12.8 g of dry matter per day) resp. 4.16 mL (5% safflower oil diet, representing 13.4 g of dry matter per day). The rats had free access to drinking water (double-distilled water, supplemented with 0.14 g/L sodium chloride to adapt osmolarity to that of tap water).

Lipid Analyses

Liver lipids were extracted with a hexane/isopropanol mixture (3:2, v/v, containing BHT to prevent degradation of PUFA) *(22)*. Phospholipids of the extracts were separated with high performance-liquid chromatography. The major phospholipids (PC, PE, and PS) were collected with a fraction collector *(23)*. The PE fraction consisted of diacyl and plasmalogen PE glycerophospholipids. Fatty acids of phospholipid fractions were converted into methyl esters by transesterification with boron fluoride/methanol reagent *(24)*. Fatty acid methyl esters were separated by gas chromatography using a Hewlett-Packard HP 5890A gas chro-

Table 1
Composition of the Fat-Free Basal Diets

Ingredient	Amount
	g/kg diet
Casein (EDTA purified)	200
Sugar	408
Corn starch	300
Fiber (cellulose)	30
Mineral mixture[1]	40
Vitamin mixture[2]	20
DL-Methionine	2

[1]Mineral mixture supplied the following (per kg diet): 10.74 g $Na_2HPO_4 \cdot 2H_2O$; 8.20 g KH_2PO_4; 6.00 g KCl; 3.40 g $MgCl_2 \cdot 6H_2O$; 13.6 g $CaCO_3$; 248.8 mg $FeSO_4 \cdot 7H_2O$; 47.2 mg $CuSO_4 \cdot 7H_2O$; 46.1 mg $MnSO_4 \cdot 5H_2O$; 9.0 mg KI; 4.48 mg $NiSO_4 \cdot 6H_2O$; 0.50 mg $NaMoO_4 \cdot 2H_2O$; 0.57 mg $SnCl_2 \cdot 2H_2O$; 0.67 mg $Na_2SeO_3 \cdot 5H_2O$; 0.51 mg $CrCl_3 \cdot 6H_2O$; 0.23 mg NH_4VO_3; 1.51 mg $NaSiO_3 \cdot 5H_2O$; sugar to 40 g.

[2]Vitamin mixture supplied the following (per kg diet): 1.7 mg all-*trans*-retinol; 7.5 µg cholecalciferol; 150 mg all-*rac*-α-tocopherol acetate; 5 mg menadione sodium bisulfite; 5 mg thiamin·HCl; 10 mg riboflavine; 6 mg pyridoxine·HCl; 20 mg Ca pantothenate; 50 mg nicotinic acid; 1000 mg choline chloride; 0.2 mg folic acid; 0.025 mg cyanocobalamine; sugar to 20 g.

matographic system (Hewlett-Packard, Taufkirchen, Germany), fitted with an automatical on-column injector, a flame ionization detector, and a CP-Sil 88 capillary column (50 m × 0.25 mm internal diameter, film thickness 0.2 µm; Chrompack, Middleburg, The Netherlands). The oven temperature program was as follows: 75°C, initial temperature; raised to 160°C with 30°C/min; 160°C held for 1 min; raised to 200°C with 15°C/min; 200°C held for 1 min; raised to 225°C with 10°C/min. The detector temperature was 300°. FAMEs were identified by comparing their retention times with those of individual purified standards and quantified with heptadecanoic acid methyl ester as internal standard.

Statistical Analysis

Treatment effects were analyzed by two-way analysis of variance (ANOVA). Classification factors were zinc supply and addition of safflower oil, as well as their interaction. Means of the four treatment groups were compared by Fisher's multiple range test. All data in the

present text are expressed as mean ± SD. Significantly different means ($P < 0.05$) are marked by different superscript letters.

RESULTS

Weight Gain and Zinc Status

The intial body weight was 122 ± 5 g for both the zinc-deficient and zinc-adequate group. During the first 6 d of the experiment in which the rats were fed the fat-free diets, growth of the rats was not influenced by the zinc supply. Daily body weight gain during this period was 4.78 ± 0.82 g for the zinc-adequate rats and 4.55 ± 0.75 g for the zinc-deficient rats. During the remaining 3 d of the experiment growth was significantly affected by zinc deficiency. Daily body weight gain during this period was: zinc-adequate rats on fat-free diet, 6.00^a ± 0.55 g; zinc-adequate rats on the 5% safflower oil diet, 6.57^a ± 0.63 g; zinc-deficient rats on the fat-free diet, 0.87^b ± 1.70 g; zinc-deficient rats on the 5% safflower oil diet, 2.90^b ± 2.87 g. Activity of alkaline phosphatase as well as zinc concentration in serum were markedly decreased by zinc deficiency (Table 2).

Fatty Acid Composition of Liver Phospholipids

The fatty acid composition of liver phospholipids is shown in Tables 3–5. In the rats fed both the fat-free and the 5% safflower oil diet, zinc deficiency increased levels of saturated fatty acids in PC, PE, and PS slightly, but significantly. Levels of monounsaturated fatty acids (MUFA) were not affected by zinc deficiency.

In the groups fed the fat-free diets throughout the experiment, the levels of total (n-6) PUFA were similar in zinc-adequate and zinc-deficient individuals. The level of arachidonic acid was slightly lowered by zinc-deficiency compared with the zinc-adequate group; this effect was significant in PE and PS. The levels of most of the other individual (n-6) PUFA were not influenced by zinc deficiency. The levels of (n-3) PUFA in the main were also not influenced by zinc deficiency. An exception for this was an elevated level of total (n-3) PUFA in PS of zinc-deficient rats compared to zinc-adequate rats.

Regardless of the zinc status, feeding the diet supplemented with 5% safflower oil elevated the levels of total and individual (n-6) PUFA compared to the fat-free diets; levels of MUFA and (n-3) PUFA were lowered by supplementation with 5% safflower oil. However, concerning the levels of (n-6) PUFA, there were marked differences between the zinc-adequate and the zinc-deficient rats. Zinc-deficient rats fed the 5% safflower oil diet had markedly lower levels of total (n-6) PUFA in all types of phospholipids than the equivalent zinc-adequate rats. Additionally, zinc deficiency caused a shift between (n-6) PUFA with two and three double

Table 2
Activity of Alkaline Phosphatase and Zinc Concentration in Serum

Treatment group	Alkaline Phosphatase (U/L)[1]	Zinc concentration (μM/L)[1]
Zn+, FF (10)	428 ± 95[a]	18.8 ± 1.5[a]
Zn+, 5% SO (9)	431 ± 107[a]	17.9 ± 1.8[a]
Zn-, FF (9)	246 ± 83[b]	3.91 ± 0.46[b]
Zn-, 5% SO (12)	311 ± 70[b]	3.63 ± 0.66[b]

Results are mean ± SD. Means with different superscript letters ([a], [b]) within one column differ significantly by Fisher's multiple range test ($p < 0.05$). The number of analyses is given in parentheses. Results of ANOVA: [1]significant effect of factor zinc ($p < 0.05$); FF, fat-free; SO, safflower oil.

bonds and those with four and five double bonds. Zinc-deficient rats had higher levels of linoleic acid (in PC and PE) and dihomo-γ-linolenic acid (in PC, PE, and PS) but lower levels of arachidonic acid and docosatetraenoic acid (in PC, PE, and PS) as well as docosapentaenoic acid (in PC and PE) than zinc-adequate rats. In all types of phospholipids, levels of (n-3) PUFA were higher in zinc-deficient than in zinc-adequate rats.

DISCUSSION

The results of the present study clearly demonstrate that zinc deficiency impairs the desaturation of linoleic acid in rats fed initially a fat-free diet. This is evident by a shift of individual (n-6) PUFA levels in zinc-deficient rats typical for impaired Δ5- and Δ6-desaturation *(25,26)*. This shift includes elevated levels of substrates for Δ6- and Δ5-desaturation, linoleic acid, and dihomo-γ-linolenic acid whereas levels of desaturation products, arachidonic acid, decosatetraenoic acid and docosahexaenoic acid were markedly lowered.

Some conventional zinc deficiency experiments with ad libitum feeding already suggested a role of zinc in desaturation of linoleic acid *(2–5)*. However, other experiments could not confirm this suggestion *(6–10)*. The reason for the contradictory results may be that the low food intake in zinc-deficient rats confounds the effects of zinc deficiency on fatty acid metabolism. The present results clearly support a role of zinc in Δ5- and Δ6-desaturation in rats with sufficient food and energy intake. In contrast with the present study, recent studies using rats force-fed diets with either coconut oil, linseed oil, or fish oil could not find an impairment of Δ5- and

Table 3
Fatty Acid Composition of Liver Phosphatidylcholine (mol/100 mol)

Fatty acid	Treatment group			
	Zn+, FF (10)	Zn-, FF (9)	Zn+, 5%SO (9)	Zn-, 5%SO (12)
ΣSFA[1]	47.1 ± 0.6[b]	49.4 ± 1.6[a]	46.4 ± 1.2[b]	48.6 ± 1.3[a]
ΣMUFA[1,2]	19.0 ± 2.1[a]	20.2 ± 2.4[a]	9.86 ± 1.09[b]	11.8 ± 2.1[b]
Σn-6 PUFA[1,2,3]	24.2 ± 1.9[c]	22.4 ± 1.8[c]	39.1 ± 1.1[a]	34.3 ± 2.2[b]
18:2[2,3]	6.03 ± 0.39[c]	5.65 ± 0.43[c]	10.9 ± 1.5[b]	12.3 ± 1.0[a]
20:3[1,3]	1.59 ± 0.13[b]	1.66 ± 0.22[b]	1.22 ± 0.25[c]	2.33 ± 0.52[a]
20:4[1,2,3]	14.4 ± 1.8[c]	12.8 ± 1.1[c]	23.5 ± 1.9[a]	17.4 ± 2.4[b]
22:4[2,3]	0.33 ± 0.02[d]	0.41 ± 0.11[c]	0.57 ± 0.09[a]	0.48 ± 0.04[b]
22:5[1,2,3]	1.60 ± 0.27[b]	1.59 ± 0.37[b]	2.70 ± 0.50[a]	1.53 ± 0.38[b]
Σn-3 PUFA[2,3]	6.19 ± 0.81[a]	5.49 ± 1.19[a]	4.30 ± 0.40[b]	4.82 ± 0.58[ab]
22:5	0.22 ± 0.06	0.22 ± 0.04	0.16 ± 0.04	0.24 ± 0.09
22:6[2,3]	5.97 ± 0.82[a]	5.27 ± 1.17[ab]	4.14 ± 0.39[c]	4.58 ± 0.57[bc]

Results are mean ± SD. Means with different superscript letters ([a], [b], [c], [d]) within one row differ significantly by Fisher's multiple range test ($p < 0.05$). The number of analyses is given in parentheses. Results of ANOVA: [1]significant effect of factor zinc ($p < 0.05$); [2]significant effect of factor fat ($p < 0.05$); [3]significant interaction between factors zinc and fat ($p < 0.05$).

FF, fat-free; SO, safflower oil; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

Table 4
Fatty Acid Composition of Liver Phosphatidylethanolamine (mol/100 mol)

Fatty acid	Treatment group			
	Zn+, FF (10)	Zn-, FF (9)	Zn+, 5%SO (9)	Zn-, 5%SO (12)
ΣSFA[1]	46.3 ± 0.9[b]	47.9 ± 0.5[a]	46.1 ± 0.7[b]	48.4 ± 1.8[a]
ΣMUFA[2]	7.29 ± 0.97[a]	7.54 ± 1.18[a]	4.92 ± 0.66[b]	5.57 ± 0.92[b]
Σn-6 PUFA[1,2,3]	30.9 ± 0.6[c]	29.6 ± 0.9[d]	39.3 ± 0.7[a]	34.7 ± 1.3[b]
18:2[2]	2.23 ± 0.24[c]	2.03 ± 0.12[c]	3.96 ± 0.69[b]	4.70 ± 0.61[a]
20:3[1,3]	0.56 ± 0.08[b]	0.60 ± 0.09[b]	0.51 ± 0.11[b]	0.82 ± 0.20[a]
20:4[1,2]	25.0 ± 0.9[b]	23.4 ± 1.1[c]	28.1 ± 1.4[a]	25.1 ± 0.9[b]
22:4[2,3]	0.42 ± 0.10[c]	0.53 ± 0.12[c]	1.02 ± 0.19[a]	0.79 ± 0.16[b]
22:5[1,2,3]	2.65 ± 0.42[b]	3.04 ± 0.44[b]	5.61 ± 1.45[a]	3.27 ± 0.82[b]
Σn-3 PUFA[2,3]	14.2 ± 1.2[a]	13.8 ± 1.4[a]	9.53 ± 0.82[b]	11.1 ± 1.4[c]
22:5	0.43 ± 0.17	0.44 ± 0.12	0.34 ± 0.12	0.49 ± 0.24
22:6[2,3]	13.8 ± 1.2[a]	13.4 ± 1.3[a]	9.20 ± 0.76[c]	10.5 ± 1.3[b]

Results are mean ± SD. Means with different superscript letters ([a], [b], [c]) within one row differ significantly by Fisher's multiple range test ($p < 0.05$). The number of analyses is given in parentheses. Results of ANOVA: [1]significant effect of factor zinc ($p < 0.05$); [2]significant effect of factor fat ($p < 0.05$); [3]significant interaction between factors zinc and fat ($p < 0.05$).

FF, fat-free; SO, safflower oil; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

Table 5
Fatty Acid Composition of Liver Phosphatidylserine (mol/100 mol)

Fatty acid	Treatment group			
	Zn+, FF (10)	Zn-, FF (9)	Zn+, 5%SO (9)	Zn-, 5%SO (12)
ΣSFA	53.8 ± 3.1	54.4 ± 2.9	52.7 ± 1.3	53.6 ± 2.2
ΣMUFA[1,2,3]	6.72 ± 0.62[a]	4.95 ± 0.62[b]	4.15 ± 0.70[b]	4.05 ± 1.19[b]
Σn-6 PUFA[1,2,3]	29.6 ± 2.0[c]	28.0 ± 2.4[c]	37.4 ± 1.7[b]	32.7 ± 2.3[a]
18:2[2]	1.66 ± 0.40[b]	1.48 ± 0.13[b]	2.72 ± 0.37[a]	2.71 ± 0.45[a]
20:3[1,2,3]	1.37 ± 0.19[b]	1.25 ± 0.24[b]	1.21 ± 0.10[b]	1.72 ± 0.30[a]
20:4[1,2]	23.2 ± 2.0[b]	20.6 ± 2.6[c]	28.7 ± 1.0[a]	23.7 ± 2.2[b]
22:4[2,3]	0.80 ± 0.08[a]	1.12 ± 0.13[b]	1.30 ± 0.22[c]	1.08 ± 0.11[b]
22:5	2.52 ± 0.47	3.61 ± 1.39	3.42 ± 0.97	3.47 ± 0.76
Σn-3 PUFA[1,2]	9.90 ± 1.93[b]	12.6 ± 0.9[a]	5.85 ± 0.97[c]	9.63 ± 1.40[b]

Results are mean ± SD. Means with different superscript letters ([a], [b], [c]) within one row differ significantly by Fisher's multiple range test ($p < 0.05$). The number of analyses is given in parentheses. Results of ANOVA: [1]significant effect of factor zinc ($p < 0.05$); [2]significant effect of factor fat ($p < 0.05$); [3]significant interaction between factors zinc and fat ($p < 0.05$).

FF, fat-free; SO, safflower oil; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

Δ6-desaturation by zinc deficiency *(11–13)*. This difference suggests that zinc deficiency affects fatty acid desaturation mainly in rats with a high basal desaturase activity caused by feeding initially fat-free diets.

Long chain PUFA as constituents play a major role in maintaining the fluidity of biological membranes *(27)*. The present study suggests that zinc-deficient rats seek to compensate for reduced levels of long chain (n-6) PUFA, particularly of arachidonic acid by enhanced incorporation of (n-3) PUFA such as docosahexaenoic acid. On the other hand, PUFA with 20 carbon atoms, particularly arachidonic acid, are the products from which eicosanoids are derived *(28)*. The disturbed desaturation in zinc deficiency may cause a lower rate of eicosanoid formation, and possibly a shift between monoene, diene, and triene prostaglandins, influencing several physiological processes.

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