Effects of Dietary Corn Oil and Salmon Oil on Lipids and Prostaglandin E_2 in Rat Gastric Mucosa

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Three groups of male rats were fed either a corn oil-enriched diet (17%, w/w), a salmon oil-enriched diet (12.5%) supplemented with corn oil (4.5%) or a low-fat diet (4.4%) for eight wk to investigate the possible relationships between dietary fatty acids and lipid composition, and prostaglandin E_2 level and phospholipase A_2 activity in the rat gastric mucosa.

High-fat diets induced no important variation in total protein, phospholipid and cholesterol contents of gastric mucosa.

Compared with a low-fat diet, corn oil produced a higher n-6/n-3 ratio in mucosal lipids, whereas this ratio was markedly lowered by a fish oil diet.

In comparison with the low-fat diet, the production of prostaglandin E_2(PGE_2) in gastric mucosa of rats fed salmon oil was significantly decreased by a factor of 2.8. In the corn oil group, PGE_2 production tended to decrease, but not significantly.

In comparison with the low-fat diet, both specific and total gastric mucosal phospholipase A_2 activities were increased (+ 18 and 23%, respectively) in the salmon oil group; they were unchanged in the corn oil group.

It is suggested that the decrease of gastric PGE_2 in rats fed fish oil is not provoked by a decrease in phospholipase A_2 activity but may be the result of the substitution of arachidonic acid by n-3 PUFA or activation of PGE_2 catabolism.

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It now is well accepted that prostaglandins can protect the gastric mucosa from becoming injured by various irritants and that this effect is mediated by two distinct mechanisms: inhibition of gastric acid secretion (1,2) and cytoprotection (3,4). It recently has become evident that exogenous and endogenous prostaglandins, mostly of the E-series (PGE_2), exert cytoprotective properties (3) and are effective in the treatment of peptic ulcer disease (5).

Synthesis of prostaglandins is initiated by the release of arachidonic acid through the action of phospholipase A_2 on the 2-position of membrane phospholipids. Such an activity has been described in rat gastric mucosa (6–8), and we recently have shown that this enzyme is mostly associated with microsomal and plasma membranes (8).

Prostaglandin synthesis can be affected by ingestion of fish oils. Fish oils are rich in n-3 polyunsaturated fatty acid (PUFA), which were demonstrated to be efficient in lowering plasma cholesterol and preventing atherosclerosis (9–14). Another beneficial effect of fish oils is to lower platelet aggregability through modifications of prostaglandin I_2 and thromboxane A_2 production (9,15). However, modification of the prostaglandin level in various tissues may lead to nonbeneficial effects. For example, Lokesh et al. (16) have recently reported that menhaden oil fed to mice altered the spleen prostaglandin production, which in turn may affect the immune function of this organ. In the same way, ingestion of cod liver oil by rats resulted in a reduction in kidney PGE_2 generation, which may influence blood pressure regulation (17).

In regard to the importance of prostaglandins in gastric cytoprotection and to the marked effect of the dietary n-3 PUFA on prostaglandin level in various tissues, we investigated the effect of n-3 PUFA (salmon oil) in comparison with n-6 PUFA (corn oil) on gastric prostaglandin production in rat. Possible relationships between dietary fatty acids and lipid composition of gastric mucosa, gastric phospholipase A_2 activity and prostaglandin production were studied.

MATERIAL AND METHODS

Animals and feeding procedures. Three groups of male Wistar rats (IFFA-Credo, L'Arbresle, France) weighing 190–210 g were used. Each group was divided into cages of two rats. One group (10 rats) was fed a low-fat diet containing (4.4%, w/w) of fat consisting of a lard and corn oil mixture giving a P/S ratio of 1.2. A second group (10 rats) received a corn oil-enriched diet (17%, w/w) with a P/S ratio of 5. The third group was fed a salmon oil-enriched diet (12.5%, w/w) supplemented with 4.5% of corn oil, with a P/S ratio of 2.0. The composition of the diets and their fatty acid compositions are given in Tables 1 and 2, respectively.

Corn oil, as supplied, contained 45 mg/100 g of α-tocopherol and salmon oil was supplemented with 100 mg/100 g of α-tocopherol as antioxidant. So, the total amounts supplied by the control diet, corn oil diet and salmon oil diet were 171 mg, 246 mg and 315 mg/kg of diet, respectively. The low-fat and corn oil diets were prepared to last one month and stored at −20 C in plastic bags, and the salmon oil diet was prepared every two wk and stored at −20 C in sealed containers flushed with nitrogen.

The rats were fed ad libitum, and uneaten food was discarded in the morning. They had free access to water, and the feeding period was for eight wk.

Procedures for stomach. The animals were fasted overnight, weighed and guillotined. Their stomachs were removed, opened and extensively washed at 4 C with the homogenization buffer (5 mM Tris HCl, pH 7.4, 0.25 M sucrose). The upper portion of the stomach, the forestomach, was discarded, and the glandular part (antrum plus fundus) was gently scraped on an ice-cold glass plate, the mucosa was weighed and suspended in the same homogenization buffer (10%, w/v) and homogenized by

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Abbreviations: FAME, fatty acid methyl esters; PA_2, phospholipase A_2; PGE_2, prostaglandin E_2; PGI_2, Prostacycline I_2; PGI_3, Prostacycline I_3; PUFA, polyunsaturated fatty acids; ANOVA, analysis of variance; GLC, gas liquid chromatography; P/S ratio, polyunsaturated to saturated fatty acid ratio; RIA, radioimmunoassay.

TABLE 1

Composition of Experimental Diets

	Low fat g/100 g	Corn oil g/100 g	Salmon oil g/100 g
Casein[a]	27.3	27.3	27.3
Lard[a]	2.2	—	—
Salmon oil[b]	—	—	12.5
Corn oil[c]	2.2	17.0	4.5
Starch[a]	34.0	26.9	26.9
Glucose[a]	23.5	18.0	18.0
Minerals[a]	5.0	5.0	5.0
Vitamins[a]	1.0	1.0	1.0
Cellulose[a]	4.8	4.8	4.8
BHT[d]	0.05	0.05	0.05

[a]From Unité Alimentation Rationnelle (UAR) (Villemoisson, France).

[b]From SEAH International (Boulogne/Mer France).

[c]From CPC Europe Consumer Products (Heilbronn, FRG).

[d]Butylated Hydroxytoluene, Sigma, Coger (Paris, France).

Vitamins, given in g/kg diet: retinol, 19.8 IU; cholecalciferol, 6 IU; thiamin, 0.02; riboflavin, 0.015; nicotinamide, 0.035; pyridoxine, 0.01; carnitine, 0.15; cyanocobalamin, 5×10^{-5}; ascorbic acid, 0.8; α-tocopherol, 0.17; menadione, 0.04; nicotinic acid, 0.10; choline, 1.36; pteroylmonoglutamic acid, 5×10^{-4}; p-aminobenzoic acid, 0.05; biotin, 3×10^{-4}. Minerals given in g/kg diet: $CaHPO_4$ 21.5; KCl, 5; NaCl, 5; $MgSO_4$, 2.50; Fe_2O_3, 0.15; $FeSO_4 \cdot 7H_2O$, 0.25; $MnSO_4 \cdot H_2O$, 0.12; $CuSO_4 \cdot 5H_2O$, 0.025; $CoSO_4 \cdot 7H_2O$, 2×10^{-4}; $ZnSO_4 \cdot 7H_2O$, 0.1; stabilized KI, 4×10^{-4}; NaF, 0.012. UAR, Villemoisson/Orge, France. On the basis of UAR information, the selenium content of the diets was estimated at 50–60 μg/kg.

TABLE 2

Fatty Acid Composition of the Diets (%)

Fatty acid	Low fat	Corn oil	Salmon oil
14:0	—	—	4.6
15:0	—	—	0.3
16:0	20.2	11.6	12.6
16:1n-7	0.3	—	5.4
17:0	—	—	0.6
18:0	8.0	0.2	1.8
18:1n-9	35.1	26.8	14.8
18:1n-7	—	—	2.6
18:2n-6	33.6	60.0	16.9
18:3n-3	0.7	0.8	0.6
18:4n-3	—	—	2.0
20:0	0.3	0.4	0.3
20:1n-9	0.5	—	2.6
20:1n-11	—	—	7.8
20:4n-6	0.3	0.1	0.4
20:4n-3	—	—	0.6
20:5n-3	—	—	9.8
22:1n-11	—	—	6.6
22:1n-9	—	—	0.6
22:5n-3	—	—	1.2
22:6n-3	—	—	7.2
24:1n-9	—	—	0.4
Saturated	28.6	12.2	20.0
Polyunsaturated	34.5	61.3	39.8
P/S	1.2	5.0	2.0
n-6/n-3	46.0	75.0	0.8

using a polytron tissue processor (Kinematica PT-10, Luzern, Switzerland) for 10 sec at the rheostat setting of 6.0.

Fractions for the prostaglandin E_2 assay were diluted with a same volume (v/v) of a Tris HCl 0.1 M, pH 7.4, buffer to obtain a final concentration of 50 mM Tris HCl, pH 7.4, 0.125 M sucrose. Then they were stored at −60 C until use, and undiluted fractions were stored at −20 C pending biochemical analysis.

Protein assay. Proteins were measured by the dye-binding method of Bradford (18) using rabbit γ-globulin as standard (protein assay kit, Bio-Rad, Richmond, CA).

Phospholipase A_2 assay. Gastric phospholipase A_2 was assayed as recently described (8). Incubation mixtures contained 0.2 mM 1-palmitoyl-2[1-^{14}C]oleoylphosphatidylcholine (Amersham, France) with a specific radioactivity of 59.2 KBq/μmol and 50 mM sodium cacodylate at pH 7.0 in a final volume of 0.2 ml. Radioactivity was counted by liquid scintillation spectrometry (Beckman LS 9000, Palo Alto, CA) in 10 ml of Readysolve MP (Beckman) scintillation fluid. The results were corrected for a control incubated without protein. All the assays were done in duplicate.

Prostaglandin E_2 assay. Prostaglandin E_2 was extracted with ethylacetate from gastric mucosa homogenates (5 mg protein) according to the method of Lokesh et al. (16). Prostaglandin E_2 was quantified by radioimmunoassay (RIA), using a [^{125}I]prostaglandin E_2 RIA kit (NEK-020) purchased from NEN (Paris, France).

Appropriate blanks for nonspecific binding and tubes for total binding determinations were included. All the assays were done in duplicate (two extractions). All the measurements were in the linear portion of the standard curve.

Lipid analysis. Lipids were extracted from the gastric mucosa homogenate by the method of Folch et al. (19).

A fraction of this extract was used for lipidic phosphorus determination (20). Another part of this extract was used to determine total lipid fatty acid composition. Fatty acid methyl esters (FAME) of total lipids were prepared according to a rapid and convenient method used for vegetable oils (21). FAME recovered in hexane were stored under nitrogen at −20 C pending gas liquid chromatography (GLC) analysis. Separation of FAME was performed as described (22), using a gas liquid chromatograph (Girdel 3000, Paris, France) equipped with a peak integrator (Delsi, Enica 10, Suresne, France) and a 50 m capillary column (Spirawax FS, 1493, Spiral, Dijon, France).

The cholesterol content of gastric mucosa was determined with the cholesterol esterase-cholesterol oxidase kit (Boehringer Mannheim, Mannheim, FRG) using a two-point kinetic method. Measurements were made with an automatic Multistat III (Instrumentation Laboratory, Lexington, MA) at 30 C.

Statistical analysis. Results presented in the tables are mean ±SD. Statistical significance of mean differences between dietary groups was investigated by analysis of variance (ANOVA) and by the multiple comparison of Scheffé at $p < 0.05$ or $p < 0.01$.

RESULTS

Over the eight-wk feeding period, there was no significant difference ($p > 0.05$) in body weight gains. They were (in

g): 180.5 ± 19.3, 203.1 ± 35.0 and 218.0 ± 25.0 for rats fed low-fat, corn oil and salmon oil diets, respectively. Also, gastric mucosa weights were not significantly different among the three groups of rats: they weighed (in g) 0.37 ± 0.03, 0.33 ± 0.06 and 0.37 ± 0.06 in rats fed low fat, corn oil and salmon oil, respectively. No visible gastric ulceration was observed among the three groups of rats.

The content of proteins, total phospholipids and total cholesterol of gastric mucosa is shown in Table 3. In comparison with a low-fat diet, only corn oil induced a moderate increase of 15% in proteins and a slight decrease of 14% in total phospholipids. Total cholesterol was unchanged among the three dietary groups.

To estimate the respective contribution of fatty acid originated from phospholipids and triglycerides, we gravimetrically determined the total amount of gastric mucosa lipids obtained from the Folch extraction. The quantification of lipidic phosphorus and cholesterol in this extract allowed us to estimate the amount of neutral lipids. It showed that the phospholipids represented about 75% (w/w) of the lipids esterified by fatty acids.

The fatty acid composition of total lipids is shown on Table 4. It can be observed that in comparison with the low fat diet, both corn oil and salmo • oil induced profound modifications in the fatty acid composition of gastric lipids. Corn oil diet provoked a significant decrease in both saturated (−40%) and monounsaturated (−20%) fatty acids, whereas PUFA increased two-fold. This rise was due mostly to a three-fold increase in linoleic acid. However, arachidonic acid was significantly decreased by a factor of 1.4. All of these modifications led to a 1.7-fold increase in the n-6/n-3 ratio. Salmon oil–enriched diet provoked a less-pronounced decrease in saturated and monounsaturated fatty acids than corn oil did. In comparison with a low-fat diet, PUFA were 45% higher. In the PUFA, the most pronounced effect of salmon oil was a 2.4-fold decrease in arachidonic acid, whereas n-3 PUFA were drastically increased, particularly the 20:5n-3 and 22:6n-3. Consequently, in comparison with the two other dietary groups, a drastic reduction in the n-6/n-3 ratio and in the 20:4n-6/20:5n-3 ratio was obtained in this dietary group, whereas the unsaturation index was augmented by about 38%.

The activity of gastric phospholipase A_2 and the PGE_2 production under the various dietary conditions were investigated. Results presented in Table 5 show that in comparison with the low-fat diet, only the salmon oil–enriched diet induced a slightly significant increase (+18%) in the specific activity of phospholipase A_2. In the same way, the total phospholipase A_2 activity (μmol/hr/g mucosa) also was slightly increased (+23%) in the salmon oil group. In this last group, compared with the low-fat group, PGE_2 production was considerably lowered by a factor of 2.8. Although the PGE_2 level tended to decrease in the corn oil group, the difference was not significant ($p > 0.05$) compared with the low-fat diet group. However, this PGE_2 level still was significantly ($p < 0.01$) higher (2.1 times) than that of the salmon oil group.

DISCUSSION

Throughout the feeding period, all the diets were well-accepted by the rats as judged by their growth rates. The diets induced no visible ulceration of the gastric mucosa. Protein and lipid composition of mucosa showed no important variation under the different dietary conditions.

Significant modifications were seen in the fatty acid composition of total lipids. Generally speaking, the modifications observed seem to reflect the fatty acid composition of the diet. For the corn oil diet, the decrease in saturated fatty acids was associated with a high increase in linoleic acid. This may be the result of a high affinity of acyl-CoA:lysophosphatidylcholine-acyltransferase for the linoleoyl-CoA during reconstitution of membrane phospholipids initially hydrolyzed by the active gastric phospholipase A_2 (8). Curiously, this increase in linoleic acid was not correlated with a higher conversion into arachidonic acid, the final level of which even decreased. This phenomenon also has been observed in various tissues like kidney (17), heart (22) and platelets (23,24) of animals fed linoleic-rich vegetable oils. This could indicate that, at some point, a balance is reached between the increased availability of linoleic acid and its conversion into arachidonic acid. The results obtained with salmon oil–enriched diet show that n-3 PUFA of the diet are easily incorporated in gastric mucosa lipids, drastically reducing

TABLE 3

Effects of Dietary Corn Oil and Salmon Oil on Protein, Lipidic Phosphorus and Total Cholesterol Content of Rat Gastric Mucosa

	Low fat	Corn oil	Salmon oil
Protein mg protein/g mucosa	195.7 ± 22.1^{a,*}	225.9 ± 15.2^{b,*}	204.4 ± 21.2^{a,b}
Lipidic phosphorus μmol/g mucosa	8.0 ± 1.8^{a,b}	6.9 ± 0.9^{a,**}	9.2 ± 1.2^{b,**}
Total cholesterol μmol/g mucosa	4.8 ± 1.2	4.9 ± 1.0	4.1 ± 1.1

Values without a common superscript are statistically different at *$p < 0.05$; **$p < 0.01$. If no superscript appears, values are not different ($p > 0.05$). Values are mean ± SD, and n = 10 for low-fat and corn oil diets, n = 12 for salmon oil diet.

TABLE 4

Effects of Dietary Corn Oil and Salmon Oil on Total Lipid Fatty Acid Composition of Rat Gastric Mucosa

Fatty acid %	Low fat	Corn oil	Salmon oil
14:0	1.43 ± 0.03^{a,**}	0.93 ± 0.07^{b,**}	3.15 ± 0.31^{c,**}
16:0	26.42 ± 0.65^{a,**}	15.25 ± 0.56^{b,**}	20.50 ± 1.67^{c,**}
16:1n-9	tr	0.85 ± 0.07	1.00 ± 0.22
16:1n-7	4.67 ± 0.74^{a,**}	1.10 ± 0.39^{b,**}	3.85 ± 0.35^{a,**}
18:0	10.06 ± 1.26^{a,**}	6.21 ± 0.85^{b,**}	9.50 ± 1.27^{a,**}
18:1n-9	29.34 ± 2.89^{a,**}	25.40 ± 0.66^{b,**}	21.20 ± 1.47^{c,**}
18:1n-7	4.27 ± 0.48^{a,*}	2.10 ± 0.15^{b,*}	3.90 ± 0.30^{a,*}
18:2n-6	10.33 ± 1.51^{a,**}	35.60 ± 0.97^{b,**}	13.90 ± 1.01^{c,**}
18:3n-3	0.10 ± 0.01	0.52 ± 0.01	0.50 ± 0.09
20:0	1.06 ± 0.70	0.93 ± 0.11	1.60 ± 0.37
20:4n-6[1]	9.53 ± 2.30^{a,*}	6.90 ± 1.23^{b,*}	4.00 ± 0.62^{c,*}
20:5n-3	0.16 ± 0.09^{a,**}	tr	5.00 ± 0.44^{b,**}
22:1n-11	tr	1.10 ± 0.15^{a,**}	2.50 ± 0.35^{b,**}
22:4n-6	1.69 ± 1.33	1.90 ± 0.27	1.50 ± 0.50
22:5n-3	tr	tr	1.70 ± 0.11
22:6n-3	1.02 ± 0.63^{a,**}	1.00 ± 0.19^{a,**}	6.40 ± 0.21^{b,**}
Saturated	38.97 ± 1.49	23.92 ± 1.49	34.75 ± 2.35
Monounsaturated	38.28 ± 3.60	30.55 ± 0.82	32.25 ± 2.22
Polyunsaturated	22.83 ± 0.97	45.92 ± 1.25	33.00 ± 1.48
n-6	21.55 ± 0.99	44.40 ± 1.12	19.40 ± 0.99
n-3	1.28 ± 0.57	1.52 ± 0.18	13.60 ± 0.73
n-6/n-3 ratio	16.83	29.21	1.42
$\frac{20:4n-6}{20:5n-3}$ ratio	59.56	∞	0.80
UI	111.70	114.51	155.45

Values without a common superscript are statistically different at $^{*}p < 0.05$; $^{**}p < 0.01$. If no superscript appears, values are not different ($p > 0.05$). Values are mean ± SD and n = 5 for low-fat and corn oil diet, n = 6 for salmon oil diet, and each n represents the pool of two gastric mucosa.

[1]For this fatty acid, salmon oil value and low-fat value are statistically different at $p < 0.01$.

tr, Traces < 0.1%.

UI, unsaturation index: addition of (percent of each fatty acid × double bond/fatty acid).

TABLE 5

Effects of Dietary Corn Oil and Salmon Oil on Phospholipase A_2 Activity and PGE_2 Production of Rat Gastric Mucosa

	Low fat	Corn oil	Salmon oil
Phospholipase A_2 Specific activity nmol/hr/mg protein	628.4 ± 44.0^{a,**}	568.5 ± 57.4^{a,**}	741.7 ± 35.0^{b,**}
Phospholipase A_2 Total activity μmol/hr/g mucosa	123.3 ± 18.8^{a,**}	126.5 ± 17.6^{a,*}	151.7 ± 19.4^{b,**}
PGE_2 ng/g mucosa	327.3 ± 75.4^{a,**}	250.8 ± 82.4^{a,**}	116.5 ± 40.9^{b,**}

Values without a common superscript are statistically different at $^{*}p < 0.05$; $^{**}p < 0.01$. If no superscript appears, values are not different ($p > 0.05$). Values are mean ± SD. For phospholipase A_2, n = 10 for low-fat and corn oil diets; n = 12 for salmon oil diet. For PGE_2 values: n = 9 for low-fat diet; n = 8 for corn oil diet; n = 12 for salmon oil diet.

both the n-6/n-3 and the 20:4n-6/20:5n-3 ratios. The marked reduction of arachidonic acid could not be attributed to the lack of the 18:2n-6 substrate in the precursor pool because an adequate amount of this fatty acid was added to the diet by supplementing with corn oil. Such a competitive incorporation of dietary n-3 PUFA also has been observed in various tissue phospholipids in rat (15–17,25,26). This enhanced incorporation of n-3 PUFA may be the result of several factors, including a better esterification of n-3 PUFA into membrane phospholipids by acyltransferase, or a competition between n-3 PUFA and 18:2n-6 at desaturation step (27) or a direct inhibition of the Δ6-desaturase by the 22:6n-3 (28).

Arachidonic acid is the precursor of the prostaglandins of the 2-series, whereas eicosapentaenoic acid is the precursor of the 3-series. The salmon oil–enriched diet sharply decreased the ratio 20:4n-6/20:5n-3 in gastric phospholipids, which may have important consequences on the gastric prostaglandin level. Among the gastric mucosal prostaglandins, PGE_2 was demonstrated to be more efficient in protecting (3,29) and in treating peptic ulcer diseases (5), therefore we focused our study on this prostaglandin. Clearly, fish oil induced a significant and sharp decrease in gastric PGE_2 production. Reduction of PGE_2 level also was observed in spleen (16) and kidney (17) of animals fed fish oils. The PGE_2 decrease is certainly not the result of a reduction in the release of the precursor 20:4n-6 from membrane phospholipids by the gastric phospholipase A_2, because its specific activity was slightly increased in this dietary group. This PGE_2 decrease can result from the drop in the arachidonic acid pool. Although not significant, this phenomenon also was observed in the corn oil group in which the drop in arachidonic acid might explain that PGE_2 tended to decrease. Reduction in PGE_2 levels also has been noted in other studies in which animals were fed linoleic acid-enriched oils (17,23,30) or in which endothelial cells were cultured with linoleic acid (31,32).

In addition to the diminution of the arachidonic pool, the presence in fish oil diet of n-3 PUFA may exert a direct inhibitory action on the cyclooxygenase (33,34). Combination of these effects may explain the drastic drop in gastric PGE_2 level production in rats fed salmon oil. Lastly, a PUFA-induced enhanced prostaglandin peroxisomal degradation also may lead to a lower PGE_2 level as judged by results in progress that show an increase in the activity of some peroxisomal enzymes in gastric mucosa of animals fed fish oil.

In conclusion, this study brings an additional and original demonstration of the inhibitory effect of high doses of n-3 PUFA on prostaglandin generation in organs. In the case of gastric mucosa, this diminution could impair the cytoprotective properties of PGE_2. This, in turn, may hamper the resistance of the stomach to various injuries like stress, lysolecithins or bile salts after a duodenal reflux.

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