Dietary Polyunsaturated Fatty Acids Improve Histological and Biochemical Alterations in Rats with Experimental Ulcerative Colitis[1]

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ABSTRACT The aim of the present study was to determine whether dietary intake of monounsaturated (MUFA) and/or polyunsaturated fatty acids (PUFA) of the (n- 3) and (n-6) series could improve intestinal damage and reduce inflammation in experimental ulcerative colitis (UC). Rats were treated with 80 mg/kg body of 2,4,6-trinitrobenzenesulfonic acid and fed for 1 or 2 wk diets enriched in olive oil (OO), fish oil (FO), or purified pig brain phospholipids (BPL), as sources of monounsaturated and PUFA of the (n-3) and (n-3) + (n-6) series. Evaluation of macroscopic and microscopic colonic damage was assessed. Ultrastructural and histologic changes were analyzed as well as plasma and colonic mucosa fatty acid profiles and some biochemical markers of injury and inflammation [alkaline phosphatase (AP), mieloperoxidase (MPO), prostaglandin E_2 (PGE_2) and leukotriene B_4]. Fatty acid profiles of both plasma and mucosa mostly reflected the dietary fatty acid composition. Plasma MUFA proportions were higher in UC animals fed the OO diet compared with FO or BPL groups 1 and 2 wk and (n-3) long chain PUFA (LC-PUFA) were higher in the FO than in the OO and BPL groups. At 1 wk, UC led to lower MUFA mucosa levels and (n-3)LC-PUFA were higher in the FO group compared with the OO and BPL groups. Rats with UC fed FO at 1 wk showed significantly less macroscopic and microscopic colonic damage. They also have lower AP and MPO activities and PGE_2 levels compared with the OO and BPL groups and showed enhanced histological repair, less necrotic areas within the mucosa, and more goblet cells with mature mucin granules. These results suggest that the use of balanced diets containing (n-3) LC-PUFA could ameliorate the inflammation and mucosal damage in UC. J. Nutr. 132: 11–19, 2002.

KEY WORDS: • *trinitrobenzenesulfonic acid* • *inflammatory bowel disease* • *ulcerative colitis* • *fatty acids*

Inflammatory bowel disease (IBD)[3] is a disorder characterized by diffuse inflammation of the gastrointestinal tract. There are two basic disorders, ulcerative colitis (UC) and Crohn's disease. UC affects mainly the colon, where inflammatory changes are limited to the mucosa. Medical therapy using pharmacological agents can induce remission; however, in the long-term it may result in adverse side effects. Dietary management of UC provides effective therapy without the adverse effects of either surgery or medications (1) and exclusive enteral nutrition using formulated food is efficacious primary therapy for active IBD, although the mode of action is poorly understood (2).

Although few clinical studies suggest a dramatic influence of diet or nutritional supplementation in UC because like many chronic diseases, it is multifactorial, some evidence indicates that a high intake of (n-3) PUFA such as eicosapentaenoic acid (EPA) may have anti-inflammatory effects in patients with UC (3). Previously, dietary fat restrictions due to steatorrhea associated with UC were recommended, but the many benefits of fat on the intestinal mucosa are now well-recognized and, in general, promoted. Most importantly, patients with UC need a balanced, nutritious diet (1). Shoda et al. (4) reported that high dietary intake of (n-6) PUFA, which lowers intake of (n-3) PUFA, may contribute to the development of the disease. Fish oil (FO) and flaxseed oil are two common sources of (n-3) PUFA. Belluzi et al. (5) administered an enteric-coated FO preparation, containing a high percentage of (n-3) PUFA, which are taken up in competition with (n-6) PUFA, lowering the induction of inflammatory eicosanoids such as leukotriene B_4 (LTB_4) while favoring the synthesis of LTB_5, controlling inflammation, and reducing the relapse rate in adults considered to be at risk for disease exacerbation. More recently, in patients with proctocolitis receiving (n-3) PUFA supplementation, there is evidence of suppression of immune reactivity and concurrent reduction in disease activity, which may have important implications for therapy in patients with UC (6).

In previous work we have observed that administration of (n-3) PUFA to rats with UC led to a minimum stenosis score, lowered alkaline phosphatase (AP) and γ-glutamyltranspeptidase activities in the colon, and mucosal levels of prostaglandin E_2 (PG E_2) and LTB_4 compared with rats fed olive oil

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[3] Abbreviations used: AP, alkaline phosphatase; BPL, brain phospholipids; FAME, fatty acid methyl esters; FO, fish oil; IBD, inflammatory bowel disease; LC-PUFA, long-chain polyunsaturated fatty acids with more than 18 carbon atoms; LTB_4, leukotriene B_4; MPO, mieloperoxidase; MUFA, monounsaturated fatty acids; OO, olive oil; PAS, peryodic acid-Schiff reagent; PGE_2, prostaglandin E_2, PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; TNBS, 2,4,6-trinitrobenzenesulfonic acid; UC, ulcerative colitis.

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(OO) or an enriched source of (n-6) + (n-3) PUFA diet. However, glutathione transferase, glutathione reductase, glutathione peroxidase, and catalase activities in rats with UC were lower in the group treated with (n-3) PUFA than in the groups fed either the monounsaturated- or the (n-6) + (n-3) PUFA-enriched diets (7).

To date, little information has been reported on the plasma and colon mucosa fatty acid composition in rats with UC after feeding diets supplemented with different sources of fatty acids. Therefore, the aim of the present study was to examine the fatty acid profile of plasma and colon mucosa in rats with experimental UC induced by trinitrobenzene sulfonic acid (TNBS) and fed three diets quite similar in their content of saturated-, monounsaturated- and essential fatty acids (EFA) but differing in their content of long-chain PUFA (LC-PUFA) of the (n-6) and (n-3) series [(n-6)>18 or (n-3)>18 carbon atoms] to determine whether the source of PUFA could ameliorate the intestinal damage in UC. One of the difficulties in studying the anti-inflammatory effects of each diet in the mucosa is the absence of easily quantifiable morphometric variables. Therefore, we performed a histological and ultrastructural study together with morphometric analysis to determine the number of goblet cells per crypt and the proportion of cells secreting mature-acidic and immature-neutral mucins.

MATERIALS AND METHODS

Experimental design and composition of the diets. The protocol for the present study was approved by the University of Granada (Spain) and rats received humane treatment according to the European Union regulations. The experimental design is shown in **Figure 1**. A total of 120 male Wistar rats (200 ± 20 g), supplied by the Animal Laboratory of the University of Granada, were fed with a standard nonpurified diet (Panlab, Barcelona, Spain) for 4 wk. Then, 60 rats were treated with TNBS as described below (UC groups), and 60 rats with 9 g/L NaCl solution (control groups) and were randomly assigned to six subgroups of 10 rats each. After induction of UC, rats were fed semipurified diets differing in their type of lipids (designated as OO, FO and BPL) for 1 or 2 wk. The fat supplied about 10% of the total energy of the diet. The composition of the semipurified diets is shown in **Table 1**. The OO fat consisted of a mixture of OO (62.5 g/100 g), soybean oil (11.1 g/100 g) and refined coconut oil (26.4 g/100 g). The FO fat contained 26.26 g/kg of the OO fat (70 g/100 g total fat) and 11.25 g/kg FO (30 g/100 g total fat). The BPL fat contained 26.26 g/kg of the OO fat (70 g/100 g total fat) and 11.25 g/kg of pig brain purified phospholipids (30 g/100 g total fat). Diets were supplemented with DL-α-tocopherol (1g/kg of fat) to prevent oxidation. The fatty acid composition of the diets is shown in **Table 2**. The OO diet had a (n-6):(n-3) PUFA ratio of 12.5; the FO diet, 1.72 and the BPL diet, 7.3. The OO diet was practically devoid of LC-PUFA, whereas the FO diet was enriched in (n-3) LC-PUFA and the BPL diet was enriched in both (n-6) and (n-3) LC-PUFA (Table 2).

TABLE 1

Composition of the experimental diets

Component	Amount, *g/kg*
Casein	220.5
Corn starch	455.8
Oil[1]	37.5
Saccharose	150.0
Cellulose	80.0
L-methionine	4.0
Choline chloride	2.0
Mineral supplement	50.0
Vitamin supplement	0.2

[1] The oil type varied for the three considered experimental diets. The olive oil-enriched diet (OO) contained 37.51 g/kg of a mixture of olive oil (62.5 g/100 g), soybean oil (11.1 g/100 g and refined coconut oil (26.4 g/100 g); the enriched fish oil diet (FO) contained 26.26 g/kg OO fat (70 g/100 g total fat) and 11.25 g/kg fish oil (30 g/100 g total fat); the enriched brain phospholipid diet (BPL) contained 26.26 g/kg OO fat (70 g/100 g total fat) and 11.25 g/kg of purified pig brain phospholipids (30 g/100 g total fat). All diets [as described in (7)] were supplemented with *dl*-α-tocopherol (1 g/kg of fat) to prevent oxidation.

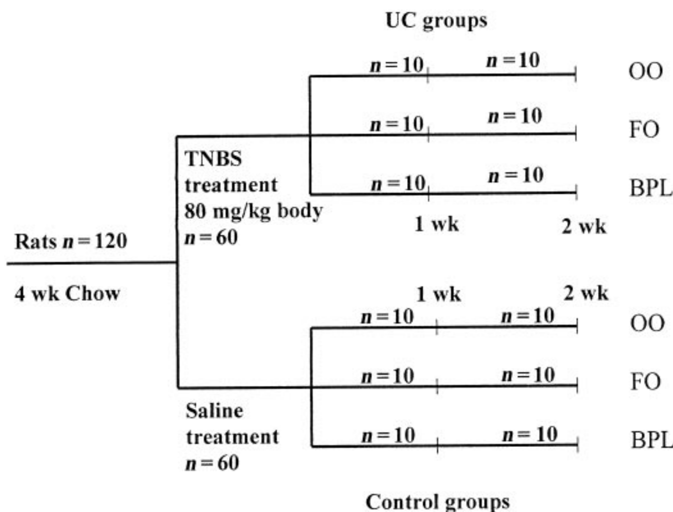

FIGURE 1 Experimental design for the study of influences of different diets differing in their PUFA contents in rats with experimental ulcerative colitis (UC) induced by trinitrobenzene sulfonic acid (TNBS). OO, FO and BPL are groups fed with the enriched olive oil, fish oil and purified brain phospholipids diets, respectively.

To study not only the influence of TNBS treatment but also the effect of time of recovery, one-half of the rats was killed at 1 wk after UC induction and the other half at 2 wk.

Induction of UC and collection of samples. Rats were food deprived for 24 h, and UC was induced as previously described (8). Briefly, rats were anesthesized with 200 g/L urethane (1 mL/100 g body), and a 2.6-mm diameter polyurethane catheter (Corpak, Chicago, IL) was inserted into the colon at 8 cm from the anus at the splenic flexure. TNBS (Sigma, St. Louis, MO) in 30% ethanol (v/v) was instilled into the lumen at a dose of 80 mg/kg body, and rats were kept in the *Trendelenburg* position for 1 min. Then, rats were maintained in cages with free access to water and the experimental diets for 1 or 2 wk until they were killed. Blood was collected from the abdominal aorta using a heparinized syringe and plasma was obtained by centrifugation of heparinized blood at 3000 × *g*. Colon sections were excised, slit longitudinally, measured, weighed and rinsed with cold 9 g/L NaCl and the excess solution dried using a filter paper; the colon was measured at a constant weight (5 g). Samples of colon were collected for light and electron microscopy and mucosa from the remnant colon was immediately scraped off using a glass slide, frozen in liquid nitrogen and used later for biochemical analysis.

Assessment of colonic damage. The degree of damage was scored macroscopically by one of the authors (N.N.) who was unaware of the experimental groups, according to the criteria of Lugea et al. (9) based on the presence of adhesions, strictures, ulcers and wall thickness of the colon.

The degree of microscopic damage was evaluated by two histologists (M.I.T. and A.R.) who also were unaware of the experimental groups, diets and extent of macroscopic damage. Colonic inflammation was assessed using the histopathological grading system of Ameho et al. (10).

Histological studies. Colon mucosa samples (distal section) were examined under light microscopy at a magnification of 100X. Biopsy specimens were fixed in 4 g/L paraformaldehyde, paraffin-embedded,

TABLE 2

Fatty acid composition of diets[1]

Fatty acid	Diet OO	Diet FO	Diet BPL
	mol/100 mol total fatty acid methyl esters		
8:0	2.85	2.10	2.41
10:0	2.34	1.72	2.00
12:0	1.13	0.86	1.01
14:0	0.62	2.40	0.70
15:0	ND	0.20	ND
16:0	11.33	12.46	12.50
17:0	ND	0.34	0.11
18:0	3.27	3.59	5.07
24:0	ND	0.10	0.27
16:1(n-7)	0.35	2.44	0.37
18:1(n-7)	1.41	2.25	1.83
16:1(n-9)	0.10	0.23	0.17
18:1(n-9)	49.60	38.78	44.33
20:1(n-9)	0.24	ND	ND
20:3(n-9)	ND	ND	ND
22:1(n-9)	ND	ND	ND
24:1(n-9)	ND	0.12	0.12
18:2(n-6)	22.78	16.71	19.55
18:3(n-6)	ND	ND	0.10
20:2(n-6)	0.19	0.20	0.21
20:3(n-6)	0.21	0.10	0.10
20:4(n-6)	ND	0.37	0.85
22:4(n-6)	ND	0.22	0.44
22:5(n-6)	ND	ND	0.11
18:3(n-3)	2.25	1.77	1.87
18:4(n-3)	ND	0.49	0.10
20:5(n-3)	ND	4.16	0.12
22:5(n-3)	ND	0.80	0.11
22:6(n-3)	ND	3.01	0.72
(n-6) > 18C	0.40	0.89	1.71
(n-3) > 18C	—	10.23	0.95
(n-6)/(n-3)	12.5	1.7	7.3

[1] The OO group fat contained 37.51 g/kg of a mixture of olive oil (62.5 g/100 g), soybean oil (11.1 g/100 g and refined coconut oil (26.4 g/100 g); the FO group fat contained 26.26 g/kg OO fat (70 g/100 g total fat) and 11.25 g/kg fish oil (30 g/100 g total fat); the BPL group fat contained 26.26 g/kg OO fat (70 g/100 g total fat) and 11.25 g/kg of purified pig brain phospholipids (30 g/100 g total fat). All diets were supplemented with *dl*-α-tocopherol (1 g/kg of fat) to prevent oxidation.
[2] ND, not detected.

cut at 5 μm, step-sectioned and stained with peryodic acid-Schiff reagent (PAS)-Alcian blue (AB) at pH 2.5. Samples for electron microscopy were fixed in 25 g/L glutaraldehyde per 0.1 mol/L of cacodylate buffer at pH 7.4, postfixed in 15 g/L osmium tetroxide, dehydrated in acetone, and embedded in Epon 812 resin. Ultrathin sections stained with uranil acetate and lead citrate were examined under a Zeiss 902 electron transmission microscope.

Morphometric analysis. Ten serial sections of 5-μm thickness, separated by 20 μm, were obtained from fixed colon samples for each rat in the UC and control groups. Fifteen arbitrarily chosen whole crypts for each section were studied. In each crypt the total numbers of whole goblet cells, PAS-positive cells (stained in pink), PAS-negative/AB-positive cells (stained in blue), and AB-positive cells (stained in purple) were counted using a magnification of 100X. The slides were read twice by two of the authors (M.I.T. and A.R.) for consistency. Results were expressed as the percentages of PAS-positive/AB negative, PAS-negative/AB-positive, and AB-positive goblet cells per crypt. We used the PAS and AB stains to distinguish between neutral and acidic mucins. Goblet cells containing neutral mucins are PAS-positive in contrast with those AB-positive cells which have acidic mucins. Acidic mucins are due to the presence of syalil and sulfated sugar residues, whereas neutral mucins are less mature proteglycans and glycoproteins.

Biochemical markers of colon injury. Mucosal AP activity was determined using a commercial kit (Boehringer-Mannheim, Germany). One unit of specific activity of AP is defined as the amount of the enzyme that produces 1 mmol of *p*-nitrophenol per milligram of protein per min at 37°C. Mieloperoxidase (MPO) activity was determined as previously described (7). One unit of specific activity of MPO is defined as the amount of enzyme that decomposes 1 μmol H_2O_2 per mg of protein per min at 30°C.

Markers of inflammation, prostaglandin E_2 (PGE_2) and LTB_4, were determined using solid phase extraction followed by an enzyme immunoassay determination (Amersham, Buckinghamshire, UK), according to the instructions provided by the manufacturer and as described previously (7).

Quantification of plasma and mucosa fatty acids. Total fatty acids were transesterified according to Lepage and Roy (11) with some modifications. Plasma (100 μL) or 500 μL of colon mucosa homogenates (100 g/L in saline solution), 3 mL of methanol:benzene (4:1), and 200 μL of acetyl chloride were added in the same tube and mixed with a Votex mixer for 3 min. Pentadecaenoic acid was used as an internal standard in plasma samples, at a final concentration of 60 μg/L. Methanolysis was performed at 100°C for 1 h. Samples were cooled, and 5 mL of 0.4 mol/L K_2CO_3 were added to stop the reaction and neutralize the pH. After centrifugation at 2500 × *g*, the upper phase was collected and frozen at −80°C.

Fatty acid methyl esters (FAME) were analyzed in a 30-m DB-2330-N fused silica column (Folsom, CA) using a Hewlett-Packard 5890 Series II gas chromatograph (Avondale, PA) with flame ionization detector. Nitrogen was used as the auxiliary gas and hydrogen as the mobile phase. The gas fluxes were 30 mL/min of nitrogen, 30 mL/min of hydrogen, and 400 mL/min of air. The split ratio was 17:1, the injection port temperature, 225°C and the detector temperature, 240°C. The column was kept at 150°C for 5 min, followed by an initial increase to 190°C at a rate of 2°C/min, and a second increase to 211°C at a rate of 3°C/min, maintaining 211°C for 3 min, and a third increase to 235°C at a rate of 4°C/min, maintaining 235°C for 35 min. The gas chromatograph was calibrated daily using a mixture of commercially available FAME (Sigma). Fatty acid response factors were used to consider the interaction of the fatty acids with the column, according to their carbon chain length, and the number and position of the double bonds.

Statistical analysis. Results are expressed as the mean ± SEM. To evaluate the three main effects tested (diet × time × treatment) two-way ANOVA was used. When significant effects ($P < 0.05$) were found, post hoc comparisons of means were done using the adjusted Bonferroni *t* test. When variances were heterogeneous, nonparametric ANOVA was conducted. All statistical analyses were done with the BMDP PC-90 version software (BMDP Statistical Software, Los Angeles, CA) (12).

RESULTS

Plasma fatty acids in rats with UC and controls mostly reflected the dietary fatty acid composition and no major changes were observed due to TNBS treatment or time (**Table 3**). All groups fed with the OO diet had significantly higher proportions of saturated fatty acids (SFA) than FO- and BPL-fed groups but SFA were unaffected by both TNBS treatment and time of recovery. MUFA proportions were higher in rats with UC fed the OO diet compared with those fed FO or BPL at both 1 and 2 wk; this effect was mainly due to differences in oleic acid [18:1 (n-9)]. No major differences were observed between FO and BPL groups regardless of treatment or time of recovery. LC-PUFA of the (n-6) series were higher in BPL than in OO groups at 1 and 2 wk and the FO group showed slightly lower means than the BPL groups. LC-PUFA of the (n-3) series were higher in the FO than in OO and BPL groups, with the latter exhibiting intermediate values. The proportion of (n-3) LC-PUFA was lower in UC rats fed with BPL compared with its healthy control at 2 wk.

TABLE 3

Selected plasma fatty acid levels in rats with ulcerative colitis (UC) induced by intrarectal administration of 2,4,6-trinitrobencenesulfonic acid (TNBS) fed for 1 or 2 wk diets containing different lipids[1]

		Time, wk			
		1		2	
Fatty acid	Diet[2]	Control[3]	UC	Control	UC
		mol/100 mol			
16:0	OO	27.8 ± 1.0[b]	31.1 ± 0.9[a]	29.5 ± 1.5[ab]	31.9 ± 0.5[a]
	FO	21.9 ± 1.1[cd]	21.3 ± 0.1[cd]	21.2 ± 0.4[cd]	22.1 ± 0.3[c]
	BPL	20.8 ± 0.3[d]	19.9 ± 0.2[d]	21.5 ± 0.4[cd]	21.9 ± 0.2[c]
18:0	OO	16.0 ± 0.9[a]	15.3 ± 0.7[a]	16.3 ± 0.9[a]	15.7 ± 0.6[a]
	FO	11.0 ± 0.4[b]	10.1 ± 0.3[b]	11.3 ± 0.7[b]	9.4 ± 0.3[bc]
	BPL	10.8 ± 0.3[b]	10.7 ± 0.2[b]	8.8 ± 0.2[c]	8.8 ± 0.2[c]
16:1(n-7)	OO	2.9 ± 0.2[d]	3.9 ± 0.3[bc]	3.7 ± 0.2[bc]	4.7 ± 0.2[a]
	FO	3.3 ± 0.3[bc]	3.1 ± 0.2[cd]	2.9 ± 0.2[d]	3.6 ± 0.2[bc]
	BPL	3.3 ± 0.1[bc]	3.2 ± 0.2[cd]	3.4 ± 0.2[bc]	4.0 ± 0.2[ab]
18:1(n-9)	OO	13.6 ± 0.5[c]	20.9 ± 0.8[a]	17.9 ± 1.3[ab]	20.2 ± 0.6[a]
	FO	12.0 ± 0.7[cd]	11.9 ± 0.4[cd]	12.1 ± 0.6[cd]	13.5 ± 0.5[c]
	BPL	12.5 ± 0.3[cd]	11.4 ± 0.5[d]	14.9 ± 0.6[bc]	16.3 ± 0.5[b]
18:2(n-6)	OO	15.5 ± 1.6[ab]	13.4 ± 0.8[bc]	10.3 ± 0.8[bc]	9.45 ± 0.7[c]
	FO	13.9 ± 1.1[b]	17.9 ± 1.6[ab]	11.7 ± 0.7[bc]	17.2 ± 1.9[ab]
	BPL	12.3 ± 0.4[bc]	15.4 ± 0.8[ab]	19.3 ± 1.0[a]	16.3 ± 0.8[ab]
20:4(n-6)	OO	12.4 ± 1.9[cd]	7.3 ± 1.1[cd]	10.4 ± 1.0[cd]	6.3 ± 0.7[d]
	FO	21.7 ± 1.7[ab]	22.1 ± 0.6[ab]	21.4 ± 0.9[ab]	18.9 ± 0.6[b]
	BPL	26.8 ± 0.5[a]	25.8 ± 0.9[a]	23.2 ± 1.0[ab]	20.9 ± 0.4[b]
20:5(n-3)	OO	0.4 ± 0.1[c]	0.2 ± 0.0[c]	0.2 ± 0.0[c]	0.4 ± 0.0[c]
	FO	3.4 ± 0.4[b]	3.8 ± 0.4[b]	3.8 ± 0.4[b]	5.7 ± 0.5[a]
	BPL	0.4 ± 0.1[c]	0.7 ± 0.1[c]	0.7 ± 0.1[c]	0.8 ± 0.1[c]
22:6(n-3)	OO	0.8 ± 0.2[b]	0.5 ± 0.1[b]	0.8 ± 0.3[b]	0.5 ± 0.1[b]
	FO	4.4 ± 0.4[a]	4.6 ± 0.2[a]	5.0 ± 0.3[a]	4.8 ± 0.2[a]
	BPL	3.4 ± 0.1[a]	3.6 ± 0.1[a]	3.7 ± 0.3[a]	3.8 ± 0.1[a]
SFA	OO	50.1 ± 2.2[a]	48.0 ± 1.6[a]	47.6 ± 2.5[a]	49.6 ± 1.2[a]
	FO	34.4 ± 1.6[b]	32.7 ± 0.5[b]	33.7 ± 1.2[b]	32.6 ± 0.6[b]
	BPL	32.5 ± 0.6[b]	31.8 ± 0.5[b]	31.9 ± 0.9[b]	31.9 ± 0.5[b]
MUFA	OO	22.3 ± 1.0[bc]	31.0 ± 1.3[ab]	27.7 ± 1.8[ab]	30.7 ± 1.0[a]
	FO	19.9 ± 1.2[c]	19.6 ± 0.8[c]	19.4 ± 0.9[c]	21.5 ± 0.9[c]
	BPL	21.7 ± 0.8[c]	20.9 ± 1.0[c]	24.1 ± 1.2[bc]	26.3 ± 0.9[b]
(n-6) > 18C	OO	14.1 ± 2.0[bc]	8.3 ± 1.2[c]	10.4 ± 1.0[c]	7.9 ± 0.9[c]
	FO	22.7 ± 1.8[ab]	23.3 ± 0.7[ab]	22.1 ± 1.1[ab]	20.0 ± 0.7[b]
	BPL	28.5 ± 0.6[a]	28.2 ± 1.1[a]	25.3 ± 1.2[ab]	23.2 ± 0.6[ab]
(n-3) > 18C	OO	1.7 ± 0.3[d]	1.0 ± 0.1[d]	1.4 ± 0.4[d]	1.3 ± 0.2[d]
	FO	8.7 ± 0.9[b]	9.5 ± 0.7[b]	10.1 ± 0.7[ab]	11.8 ± 0.7[a]
	BPL	4.3 ± 0.2[c]	4.8 ± 0.2[c]	5.0 ± 0.2[c]	1.2 ± 0.2[d]

[1] Values are mean ± SEM, $n = 10$. Means for a variable without a common letter differ, $P < 0.05$.
[2] Rats were fed diets enriched in olive oil (OO), fish oil (FO) and brain phospholipids (BPL).
[3] Control, groups treated with 9 g/L NaCl; UC, groups treated with 80 mg/kg body TNBS.

Colon mucosa fatty acid profiles also reflected the dietary composition (**Table 4**). At 1 wk experimental UC led to lower MUFA levels in all groups but by 2 wk, rats with UC did not differ from controls. LC-PUFA of the (n-6) series tended to be higher in all groups with UC at 1 wk (OO, $P = 0.09$; FO, $P = 0.09$; BPL, $P = 0.06$), but values at 2 wk did not differ among groups. LC-PUFA of the (n-3) series were higher in all rats fed FO compared with those fed OO and BPL at both times.

The colonic macroscopic score showed that FO-fed rats with UC were significantly less affected by the TNBS treatment than OO- and BPL-fed groups, both at 1 and 2 wk (**Table 5**). Interestingly, BPL-fed rats were the most affected. Total score decreased significantly in the OO group but not in BPL or FO groups between 1 and 2 wk. The grade of colitis showed the same pattern as the macroscopic score of colon damage (Table 5). The activities of AP and MPO were higher in rats with UC than in saline-treated controls after 1 wk of treatment. However, the activity of AP was significantly lower in FO-fed rats than in those fed OO or BPL at both 1 and 2 wk. The AP activity remained high only in the BPL group at 2 wk. The MPO activities in OO and FO groups did not differ and activity was highest in rats with UC fed BPL after 1 wk of treatment (**Table 6**). Mucosa PGE_2 levels were higher at 1 wk in all UC groups compared with controls and were higher in BPL group compared with rats fed the OO and FO diets (**Table 7**). At 2 wk PGE_2 remained higher in BPL than in the OO-fed group with UC. LTB_4 was higher in OO and BPL than in the FO group at both 1 and 2 wk of TNBS treatment (Table 7).

Ultrastructural studies revealed severe alterations in colonocytes of rats with UC with areas of necrosis, desquamated epithelial cells as well as loss of intercellular junctions, and lobulated nuclei with heterochromatin accumulated in the nuclear envelope. Reduced endoplasmic reticulum and

TABLE 4

Selected colonic mucosa fatty acids in rats with ulcerative colitis (UC) induced by intrarectal administration of 2,4,6-trinitrobencenesulfonic acid (TNBS) fed for 1 or 2 wk diets containing different lipids[1]

		Time, wk			
		1		2	
Fatty acid	Diet[2]	Control[3]	UC	Control	UC
		mol/100 mol			
16:0	OO	24.9 ± 1.0[a]	23.8 ± 0.8[a]	23.3 ± 0.8[a]	23.9 ± 0.8[a]
	FO	24.8 ± 1.0[a]	22.7 ± 0.4[a]	24.6 ± 0.7[a]	23.8 ± 1.2[a]
	BPL	25.6 ± 0.6[a]	23.1 ± 0.4[a]	25.6 ± 0.7[a]	24.8 ± 0.9[a]
18:0	OO	6.2 ± 0.7[ab]	7.8 ± 0.7[a]	7.1 ± 0.5[ab]	6.4 ± 0.6[ab]
	FO	6.4 ± 0.6[ab]	7.7 ± 0.6[a]	7.0 ± 0.8[ab]	7.7 ± 0.7[a]
	BPL	6.1 ± 0.4[ab]	8.1 ± 0.6[a]	5.3 ± 0.3[b]	5.6 ± 0.7[b]
16:1(n-7)	OO	6.7 ± 0.7[ab]	4.8 ± 0.6[b]	5.9 ± 0.6[ab]	6.5 ± 0.6[ab]
	FO	6.3 ± 0.6[ab]	4.7 ± 0.3[b]	6.3 ± 0.4[ab]	5.9 ± 1.0[ab]
	BPL	7.2 ± 0.4[a]	5.0 ± 0.4[b]	7.7 ± 0.4[a]	6.7 ± 0.6[ab]
18:1(n-9)	OO	27.4 ± 1.5[a]	21.2 ± 1.3[a]	26.9 ± 1.2[a]	27.1 ± 1.1[a]
	FO	28.8 ± 1.1[a]	21.5 ± 1.0[a]	25.0 ± 1.5[a]	23.3 ± 1.3[a]
	BPL	26.4 ± 1.0[a]	20.8 ± 0.7[a]	26.8 ± 0.6[a]	25.7 ± 1.0[a]
18:2(n-6)	OO	12.9 ± 0.6[ab]	14.4 ± 0.9[a]	10.7 ± 0.4[b]	12.1 ± 0.5[b]
	FO	14.9 ± 1.0[a]	14.2 ± 0.7[a]	13.2 ± 0.7[ab]	11.2 ± 0.7[b]
	BPL	12.3 ± 0.5[b]	13.9 ± 0.6[a]	12.4 ± 0.5[b]	12.5 ± 0.6[ab]
20:4(n-6)	OO	5.8 ± 1.2[ab]	7.9 ± 1.0[a]	7.4 ± 0.1[a]	6.9 ± 1.0[ab]
	FO	5.5 ± 0.8[ab]	7.8 ± 0.7[a]	5.1 ± 0.9[ab]	6.6 ± 1.0[ab]
	BPL	4.7 ± 0.7[b]	6.6 ± 0.5[ab]	4.2 ± 0.5[b]	4.3 ± 0.6[b]
20:5(n-3)	OO	0.2 ± 0.0[c]	0.2 ± 0.0[c]	0.1 ± 0.0[c]	0.3 ± 0.0[c]
	FO	0.8 ± 0.1[b]	1.0 ± 0.1[b]	1.2 ± 0.1[ab]	1.5 ± 0.2[a]
	BPL	0.1 ± 0.0[c]	0.2 ± 0.0[c]	0.1 ± 0.0[c]	0.1 ± 0.0[c]
22:6(n-3)	OO	0.5 ± 0.1[b]	0.7 ± 0.1[b]	0.6 ± 0.1[b]	0.6 ± 0.1[b]
	FO	1.1 ± 0.1[a]	1.4 ± 0.1[a]	1.3 ± 0.1[a]	1.5 ± 0.2[a]
	BPL	0.6 ± 0.1[b]	1.1 ± 0.1[a]	0.7 ± 0.1[b]	0.8 ± 0.1[b]
SFA	OO	32.6 ± 2.0[a]	33.6 ± 1.7[a]	32.0 ± 1.0[a]	31.8 ± 1.2[a]
	FO	32.9 ± 1.7[a]	32.2 ± 1.1[a]	33.0 ± 1.7[a]	33.2 ± 2.1[a]
	BPL	27.6 ± 1.0[a]	33.2 ± 1.0[a]	32.2 ± 1.1[a]	31.7 ± 1.8[a]
MUFA	OO	39.9 ± 2.8[a]	32.5 ± 2.4[b]	39.3 ± 2.4[a]	39.7 ± 2.1[a]
	FO	40.9 ± 1.6[a]	31.9 ± 1.4[b]	37.3 ± 2.8[ab]	35.7 ± 2.4[ab]
	BPL	39.5 ± 01.6[a]	32.2 ± 1.6[b]	40.5 ± 1.6[a]	38.7 ± 1.6[ab]
(n-6) > 18C	OO	8.4 ± 1.6[ab]	11.7 ± 1.5[a]	10.4 ± 0.4[a]	9.8 ± 1.5[ab]
	FO	7.5 ± 1.1[ab]	10.5 ± 1.1[a]	7.7 ± 1.1[ab]	9.0 ± 1.6[ab]
	BPL	6.8 ± 0.9[b]	9.9 ± 0.2[ab]	6.3 ± 1.0[b]	5.6 ± 1.1[b]
(n-3) > 18C	OO	0.7 ± 0.2[d]	1.3 ± 0.2[cd]	1.1 ± 0.1[cd]	1.2 ± 0.2[cd]
	FO	2.5 ± 0.5[b]	3.3 ± 0.4[ab]	3.3 ± 0.1[ab]	4.1 ± 0.5[a]
	BPL	1.0 ± 0.1[cd]	1.6 ± 0.1[c]	1.2 ± 0.3[cd]	1.2 ± 0.2[cd]

[1] Values are mean ± SEM, $n = 10$. Means for a variable without a common letter differ, $P < 0.05$.
[2] Rats were fed diets enriched in olive oil (OO), fish oil (FO) and brain phospholipids (BPL).
[3] Control, groups treated with 9 g/L NaCl; UC, groups treated with 80 mg/kg body TNBS.

Golgi apparatus, vacuoles, and electrodense and dilated mitochondria were observed. Mucin was released to the cytoplasm due to hypertrophy of goblet cells (**Fig. 2**). Rats fed the OO (Fig. 2*A*) and BPL (Fig. 2*C*) diets for 2 wk displayed desquamation and necrosis. Mitochondria, Golgi apparatus, and the endoplasmic reticulum were still damaged with loss of the cellular apycal microvilli. However, rats fed the FO diet (Fig. 2*B*) showed significant repair at the histological level with a large number of goblet cells containing inner mucin granules surrounded by membranes.

Rats with UC fed the OO or the FO diets had a significantly higher number of goblet cells per crypt compared with their corresponding control groups at 2 wk (**Table 8**). However, rats fed the BPL diet had fewer goblet cells/crypt compared with their control group. In control rats, the type of mucin contained in the goblet cells was mainly PAS-negative/AB-positive (stained in blue) with some cells PAS-positive/AB-negative (stained in pink), reflecting a better maturation of mucin than in rats with UC. The difference, in type of mucin present in the cells of TNBS-treated rats compared with their controls, was smaller in FO-fed rats compared with OO- or BPL-fed rats, indicating maturation of mucins as well as recovery. The BPL group exhibited the lowest proportion of mature goblet cells.

DISCUSSION

To date, encouraging results have been obtained in patients with UC by the oral administration of FO and primrose oil, which replace the LC-PUFA of the (n-6) series with those of the (n-3) series, especially arachidonic acid by eicosapentaenoic and docosahexaenoic acids (5,6,13,14). The rationale for supplementation with (n-3) fatty acids to promote the health of the gastrointestinal tract lies in the anti-inflamma-

TABLE 5

Colon macroscopic and microscopic scores of rats with ulcerative colitis induced by intrarectal administration of 2,4,6-trinitrobencenesulfonic acid fed for 1 or 2 wk diets containing different lipids[1]

Parameter	Diet[2]	Time, wk 1	Time, wk 2
Macroscopic score[3]			
Adhesions	OO	1.2 ± 0.4[b]	1.0 ± 0.0[b]
	FO	0.9 ± 0.3[b]	1.0 ± 0.0[b]
	BPL	2.0 ± 0.0[a]	1.6 ± 0.5[a]
Strictures	OO	1.9 ± 0.7[b]	0.4 ± 0.5[c]
	FO	0.4 ± 0.8[c]	0.4 ± 0.9[c]
	BPL	2.9 ± 0.3[a]	2.4 ± 0.7[ab]
Ulcers	OO	1.8 ± 0.6[b]	1.2 ± 0.8[bc]
	FO	1.1 ± 0.9[c]	0.9 ± 0.3[c]
	BPL	2.8 ± 0.7[a]	2.2 ± 1.0[ab]
Wall thickness	OO	1.2 ± 0.4[ab]	0.9 ± 0.3[b]
	FO	0.3 ± 0.7[c]	0.3 ± 0.5[c]
	BPL	1.7 ± 0.7[a]	1.4 ± 0.8[ab]
Total score	OO	6.1 ± 1.6[b]	3.5 ± 1.4[c]
	FO	2.7 ± 2.4[c]	2.7 ± 1.3[c]
	BPL	9.3 ± 1.7[a]	7.6 ± 2.8[ab]
Microscopic score[3]			
Grade of colitis	OO	4.2 ± 0.5[ab]	3.8 ± 0.4[ab]
	FO	3.0 ± 0.0[c]	2.4 ± 0.5[d]
	BPL	5.1 ± 0.5[a]	4.2 ± 0.4[ab]

[1] Values are mean ± SEM, $n = 10$. Means for a variable without a common letter differ, $P < 0.05$.
[2] Rats were fed diets enriched in olive oil (OO), fish oil (FO) and brain phospholipids (BPL).
[3] Macroscopic and microscopic scores were evaluated according to Lugea et al. (9) and Ameho et al. (10), respectively.

tory effects of these lipid compounds, although there are controversial results that may reside in the different study designs used as well as in the various formulations and dosages used (3).

We studied plasma and colonic mucosa fatty acids profiles as well as colonic mucosa ultrastructural features in rats with experimental UC induced by the intrarectal administration of TNBS. After induction of UC, rats were fed diets enriched with different sources of PUFA, such as OO rich in fatty acids of the (n-9) series and practically devoid of LC-PUFA, FO rich in LC-PUFA of the (n-3) series, and purified pig brain phospholipids (BPL) rich in both (n-6) and (n-3) LC-PUFA, to determine whether manipulating the source of LC-PUFA could ameliorate the inflammation and mucosal damage, the main features of this disease. We used OO as the basis of diets as a neutral oil in various respects. However, OO may also have consequences on the responsiveness of the UC model, compared with other MUFA sources, because it contains relatively high levels of antioxidants, namely tocopherols and phenolic acids, which exhibit antioxidant properties. Although phospholipids may have different bioavailabilities than triglycerides, we used BPL as a source of both (n-3) and (n-6) LC-PUFA because its addition to OO makes it possible to maintain the proportions of the rest of the fatty acids close to those in the other two experimental diets.

As expected, higher levels of 18:1(n-9)were found in rats fed the OO diet due to its relatively high content of oleic acid; in contrast, plasma (n-6) PUFA levels were higher in BPL-fed rats. It has been reported that during malnutrition, high plasma MUFA levels coexist with a reduction in PUFA due to metabolic stress in response to intestinal ulceration (15), although these same investigators have also shown, in colectomized patients with UC, higher levels of plasma SFA and lower levels of MUFA with no changes in LC-PUFA (16). Likewise, they also observed that in humans with IBD, the more severe the inflammation, the lower the concentration of (n-6) fatty acids in plasma (17). Rats fed the FO diet had higher levels of (n-3) PUFA at 1 and 2 wk compared with the other dietary groups. The (n-3) series of fatty acids have anti-inflammatory function because they lead to PGE_3 and LTB_5 production, which have 1/30 the potency of PGE_2 and LTB_4. The latter is a chemotactic factor that facilitates accumulation of neutrophils within the mucosa with the consequent production of reactive oxygen species and oxidative stress damage (18). Conversely, LTB_4, which derives from arachidonic acid [(20:4 (n-6)], alters the absorptive and secretory functions of the intestine as well as cellular immmunity, leading to cell damage (7,19). In this study we observed higher

TABLE 6

Enzymatic markers of colon injury in rats with ulcerative colitis (UC) induced by intrarectal administration of 2,4,6-trinitrobencenesulfonic acid (TNBS) acid fed for 1 or 2 wk diets containing different lipids[1]

Parameter	Diet[2]	Time, wk 1 Control[3]	Time, wk 1 UC	Time, wk 2 Control	Time, wk 2 UC
		U/mg mucosa protein			
AP[4]	OO	0.15 ± 0.03[d]	2.23 ± 0.43[a]	0.22 ± 0.04[d]	0.57 ± 0.11[c]
	FO	0.10 ± 0.01[d]	0.50 ± 0.12[c]	0.13 ± 0.02[d]	0.18 ± 0.04[d]
	BPL	0.28 ± 0.04[cd]	1.53 ± 0.22[b]	0.28 ± 0.04[cd]	1.84 ± 0.45[ab]
MPO	OO	3.0 ± 0.3[c]	5.4 ± 1.1[b]	4.1 ± 0.3[c]	4.2 ± 2.0[bc]
	FO	4.0 ± 0.4[c]	6.4 ± 0.7[b]	3.8 ± 0.5[c]	4.1 ± 0.5[c]
	BPL	6.1 ± 0.5[b]	11.2 ± 1.0[a]	5.1 ± 0.4[b]	6.0 ± 0.6[b]

[1] Values are mean ± SEM, $n = 10$. Means for a variable without a common letter differ, $P < 0.05$.
[2] Rats were fed diets enriched in olive oil (OO), fish oil (FO) and brain phospholipids (BPL).
[3] Control, groups treated with 9 g/L NaCl; UC, groups treated with 80 mg/kg body TNBS.
[4] AP, alkaline phosphatase; MPO, myeloperoxidase.

TABLE 7

Prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB_4) levels in colonic mucosa of rats with ulcerative colitis (UC) induced by intrarectal administration of 2,4,6-trinitrobencenesulfonic acid (TNBS) fed for 1 or 2 wk diets containing different lipids[1]

		Time, wk			
		1		2	
Parameter	Diet[2]	Control[3]	UC	Control	UC
		pg/g mucosa			
PGE_2	OO	720 ± 230de	1630 ± 237^{c}	864 ± 111^{d}	574 ± 106^{e}
	FO	554 ± 126^{e}	2754 ± 328^{b}	922 ± 166^{d}	658 ± 183de
	BPL	906 ± 241^{d}	4054 ± 509^{a}	1034 ± 162^{cd}	1180 ± 367^{cd}
LTB_4	OO	17.6 ± 4.8^{bc}	24.2 ± 1.7^{a}	16.8 ± 1.3^{bc}	17.0 ± 2.7^{b}
	FO	17.0 ± 5.6^{bc}	13.4 ± 3.0^{c}	15.2 ± 3.9^{bc}	12.0 ± 1.7^{c}
	BPL	16.0 ± 1.4^{bc}	21.6 ± 3.8^{ab}	15.4 ± 3.8^{bc}	18.4 ± 0.8^{b}

1 Values are mean ± SEM, $n = 10$. Means for a variable without a common letter differ, $P < 0.05$.
2 Rats were fed diets enriched in olive oil (OO), fish oil (FO) and brain phospholipids (BPL).
3 Control, groups treated with 9 g/l NaCl; UC, groups treated with 80 mg/kg body TNBS.
4 PGE_2, prostaglandin E_2; LTB_4, leukotriene B_4.

levels of PGE_2 in mucosa of rats with UC fed the BPL diet compared with those fed the OO and FO diets after 1 wk of TNBS treatment. Levels of PGE_2 were higher in rats fed FO than in those fed OO at 1 wk. Mucosal LTB_4 was also higher of OO and BPL groups than in the FO group after 1 wk.

Several investigators have questioned the safety of using high doses of (n-3) series fatty acids for the nutritional therapy of IBD patients because they may increase oxidative damage due to the number of unsaturated double bonds that have in an organ whose antioxidant defense system is already depleted (5). However, dietary intake of (n-3) series PUFA inhibits hepatic and intestinal 20:4(n-6) synthesis, which may in turn down-regulate the production of pro-inflammatory eicosanoids.

Arachidonic acid regulates the synthesis of phospholipids in the intestine, and their packaging with the newly re-esterified tryglycerides into chylomicrons. LC-PUFA play an important role in fat absorption and transport at the intestinal level (20). Therefore, it was considered of interest to study the composition of fatty acids in the mucosa of rats with experimental UC fed different lipidic diets to determine whether external sources of long-chain PUFA could ameliorate intestinal inflammation because they affect absorption, the Na^+/K^+-ATPase and adenylate cyclase activities, and the morphology of the mucosa in vivo (21). Rats with UC fed diets enriched in FO and BPL had higher levels of mucosa (n-3) PUFA compared with those fed the OO diet at 1 and 2 wk, consistent with previous results reported in humans (5,22).

Part of the therapeutic strategy for UC aims at restoring intestinal integrity and function. Only rats fed the FO diet had significantly lower macroscopic and microscopic scores of damage, more histological repair, smaller necrotic areas within the mucosa, as well as more goblet cells with mature mucin granules. In addition, UC rats fed the FO diet exhibited the lowest

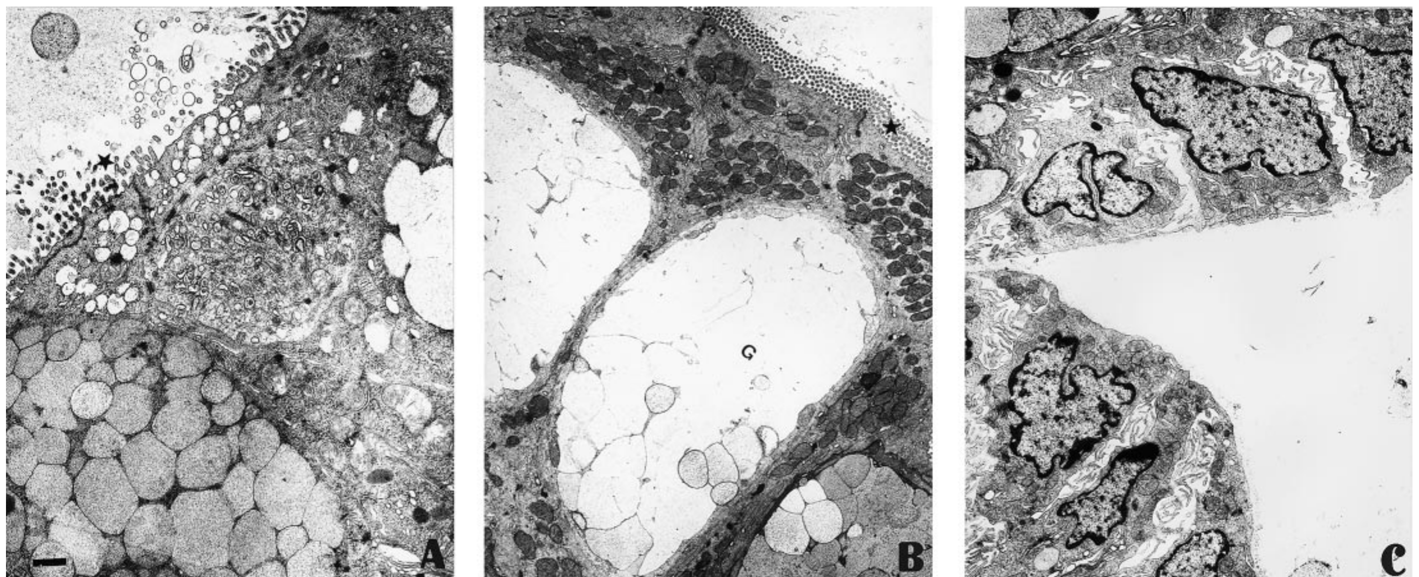

FIGURE 2 Electron micrographs of colonic mucosa of rats with ulcerative colitis fed different lipid diets: *A*, OO group; *B*, FO group; *C*, BPL group. G indicates goblet cell; star, loss of apical microvilli.

TABLE 8

Total number of goblet cells per crypt and percentage of goblet cells secreting mucin peryodic acid-Schiff reactive (PAS)-positive/Alcian blue (AB)-negative, PAS-positive/AB-positive and PAS-negative/AB-positive in rats with ulcerative colitis (UC) induced by intrarectal administration of 2,4,6-trinitrobencenesulfonic acid (TNBS) fed for 1 or 2 wk using diets containing different lipids[1]

Parameter	Diet[2]	Control[3]	UC
Goblet cells/crypt, *n*	OO	26.37 ± 1.39[c]	49.29 ± 5.88[a]
	FO	30.63 ± 0.87[bc]	44.23 ± 1.74[ab]
	BPL	37.60 ± 1.15[b]	16.38 ± 2.58[d]
PAS-positive/AB-negative cells	OO	4.81 ± 1.16[de]	12.10 ± 2.81[bc]
	FO	7.82 ± 2.04[cd]	2.81 ± 1.12[e]
	BPL	18.33 ± 1.76[b]	91.67 ± 5.69[a]
PAS-positive/AB-positive cells	OO	30.16 ± 4.45[b]	48.33 ± 6.90[a]
	FO	32.19 ± 3.26[b]	46.55 ± 5.38[a]
	BPL	40.00 ± 2.22[ab]	4.16 ± 2.80[c]
PAS-negative/AB-positive cells	OO	65.03 ± 4.95[a]	39.57 ± 8.99[b]
	FO	59.99 ± 4.80[a]	50.64 ± 5.76[ab]
	BPL	41.67 ± 2.10[b]	4.17 ± 2.85[c]

[1] Values are mean ± SEM, $n = 10$. Means for a variable without a common letter differ $P < 0.05$.
[2] Rats were fed diets enriched in olive oil (OO), fish oil (FO) and brain phospholipids (BPL).
[3] Control, groups treated with 9 g/L NaCl; UC, groups treated with 80 mg/kg body TNBS.

AP activity, a marker of damaged tissue. Moreover, the activity of MPO, a marker of inflammation, was also lower in UC rats fed the FO and OO diets than in those fed the BPL diet.

The intestinal epithelium is covered by a protective mucus gel composed predominantly of proteoglycanes and glycoproteins that are synthesized and secreted by goblets cells. Therefore, maintenance of its integrity plays a key role in preventing intestinal inflammation. Acidic mucins are indicators of adequate colonic epithelial secretory function and are mainly composed of sulfomucins and syalomucins, whereas neutral mucins are less mature and exhibit a lower content of sialyl and sulfated residues (23). The histochemical analysis of mucins may be a useful indicator of colonic epithelial damage.

In the present study, using histochemical techniques, which reveal the type and the maturation of mucins, we evaluated the changes in the chemical composition of intestinal mucus in response to the damage induced by TNBS and to the effect of the suplementation with different diets differing in their LC-PUFA composition. We showed that different sources of fatty acids alter the type of mucins in goblet cells. Supplementation of the diet with LC-PUFA of the (n-6) series altered mucin maturation, which could be due to an accelerated efflux of inmature mucin in response to TNBS. In contrast, rats fed the FO diet had a higher degree of maturation of mucins, which may be due to stimulation of goblet cells via prostaglandins that in turn activate synthesis and secretion of glycoproteins (24).

Taken together, these data suggest that dietary intake of (n-3) PUFA, even in low-fat diets, ameliorate the intestinal damage of UC. The possible beneficial effect of (n-3) fatty acids is not only attributed to their inhibition of PGE_2 and LTB_4 synthesis, but perhaps also to modulation of pro-inflammatory cytokines. Fats rich in (n-6) PUFA enhance interleukin-1 production and tissue responsiveness to cytokines whereas fats rich in (n-3) PUFA have the opposite effect. Likewise, MUFA diminish tissue responsiveness to cytokines and interleukin-6 production is enhanced by total unsaturated fatty acid intake (25). FO supplementation down-regulates pro-inflammatory cytokines, such as tumor necrosis factor-α, interleukin-1, and interleukin-6, which may in turn lessen activation of leukocytes and, therefore, oxidative damage (26). In this study we did not attempt to measure some inflammatory cytokines due to limitations in the amount of mucosa scraped off.

The supplementation of diets with FO, leading to a high content of (n-3) LC-PUFA in the intestinal mucosa, may lower membrane fluidity and change the activity of some carriers, enzyme-bound membranes and could contribute to the regulation of a number of transduction signals. In contrast, activation of protein kinase C, a key enzyme in signal transduction and growth regulation, provides a mechanism by which dietary components could be involved in carcinogenesis. Thus a high saturated fat diet enhances the membrane-associated PKC activity, compared with a low-fat diet (27). Moreover, some luminal factors, namely diacylglycerol and bile acids, can be affected by the lipid composition of the diet and in turn, the mucosal PKC and phosphatidylinositol-phospholipase C activities (28). These are several topics that should be investigated further to ascertain the mechanisms by which (n-3) fatty acids protect the intestinal mucosa in experimental UC.

To overcome lipid peroxidation by-products and cell damage from diets supplemented with long-chain PUFA, appropriate antioxidants should be provided. Dietary components such as α-tocopherol, ascorbate, carotenoids, or glucose have in vitro scavenging capabilities for reactive oxygen species. Furthermore, there are some indications that dietary lipids can improve the antioxidant defense system (13). In contrast, it has been reported that depletion of antioxidants, such as vitamin A and cysteine, a precursor of glutathione synthesis, plays a role in the pathophysiology of UC, and this deficiency might be a possible target for therapeutic intervention (29). It is important to mention that the three diets used in this particular model were stabilized using α-tocopherol (1 mg/kg dietary fat) to prevent oxidative damage. Therefore, balanced diets incorporating (n-3) fatty acids with adequate amounts of antioxidants improve the histology of the colon, decreasing inflammation in a specific tissue where low antioxidant defense has been previously described (7,30).

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