Modulating Effect of Amount and Types of Dietary Fat on Colonic Mucosal Phospholipase A₂, Phosphatidylinositol-specific Phospholipase C Activities, and Cyclooxygenase Metabolite Formation during Different Stages of Colon Tumor Promotion in Male F344 Rats

Chinthalapally V. Rao, Barbara Simi, Tin-Tin Wynn, Kathy Garr, and Bandaru S. Reddy


ABSTRACT

Epidemiological and laboratory animal model studies suggest that the effect of dietary fat in colon carcinogenesis depends not only on the amount but on its fatty acid composition. Animal model studies demonstrated that high dietary corn oil or safflower oil rich in omega-6 fatty acids increased the colon tumor promotion, whereas diets containing fish oil high in omega-3 fatty acids had no such enhancing effect. One of the mechanisms by which high dietary fat enhances colon carcinogenesis may be through the modulation of colonic mucosal phospholipase A₂ (PLA₂) and phosphatidylinositol-specific phospholipase C (PI-PLC), which are dominant pathways for arachidonic acid release and formation of eicosanoids. PI-PLC is also responsible for diacylglycerol formation and protein kinase C-dependent signal transduction and cell proliferation. In the present study, we investigated the modulating effect of high fat diets rich in omega-3 and omega-6 fatty acids on colonic mucosal PLA₂, PI-PLC activities, and eicosanoid (prostaglandins and thromboxane B₂) formation from arachidonate via cyclooxygenase (COX) during different stages of azoxymethane (AOM)-induced colon carcinogenesis in male F344 rats. After 5 weeks of age, groups of animals were fed the low-fat diet containing 5% corn oil. Beginning at 7 weeks of age, all animals except those intended for vehicle treatment received AOM s.c. once weekly for 2 weeks at a dose rate of 15 mg/kg body weight. Vehicle-treated groups received an equal volume of normal saline. One day after the second AOM or vehicle treatment, groups of animals were transferred to experimental diets containing 23.5% corn oil and 20.5% fish oil + 3% corn oil, whereas one group continued on the low-fat diet containing 5% corn oil. Groups of animals were then sacrificed at weeks 1, 12, and 36 after the second AOM or saline-treatment. Colonic mucosa harvested at weeks 1, 12, and 36 and colonic tumors obtained at week 36 were analyzed for PLA₂, PI-PLC, and eicosanoid formation from arachidonic acid via cyclooxygenase (COX). The results demonstrate that colon carcinogenesis treatment increases the activities of colonic mucosal PLA₂ and PI-PLC and the formation of prostaglandins and thromboxane A₂ from arachidonic acid through COX throughout the study period compared to saline-treated animals fed similar diets. The activities of PLA₂, PI-PLC, and COX were significantly higher in colon tumors compared to colonic mucosa. These results also demonstrate that a high-fat diet containing corn oil increases colonic mucosal and tumor PLA₂ and PI-PLC and the formation of prostaglandins and thromboxane B₂ by the action of COX as compared to low dietary corn oil or a diet high in fish oil. The results of our study offer one of the mechanisms by which the amount and types of dietary fat modulate colon carcinogenesis.

INTRODUCTION

Significant variations in dietary habits among populations of different cultures and life-styles have been associated with a risk for the development of cancer. Among the dietary habits, dietary fat has received considerable attention as a risk factor in the etiology of colon cancer (1–5). Several animal model studies have provided additional evidence that the fatty acid composition of dietary fat is one of the determining factors in colon carcinogenesis (6–8). The high levels of highly polyunsaturated omega-3 fatty acids such as EPA (c20:5, n-3) and DHA (c22:6, n-3) present in marine oils make them unique dietary fats. Most commonly consumed vegetable oils in the United States, such as corn oil and safflower oil, contain high levels of polyunsaturated fatty acids of the omega-6 type, i.e., LA (c18:2, n-6). Recently, researchers have sought to determine the relative tumor-promoting capabilities of different types of dietary fat, such as fish oil and corn oil. Available data indicated that diets containing high proportions of omega-3 polyunsaturated fatty acids had minimal or no colon tumor-promoting effect, whereas diets containing increased levels of omega-6 polyunsaturated fatty acids such as LA enhanced colon tumorigenesis in laboratory animal models (9–11). Recent Phase II clinical trials in patients with polyps demonstrate that dietary fish oil supplements decreased the rectal cell proliferative pattern (12).

Although the mechanism(s) of colon tumor-promoting effect of high dietary corn oil and lack of tumor promotion by high dietary fish oil is not completely understood, the tumor-promoting effect of high dietary fat has been associated with increased concentrations of colonic lumenal secondary bile acids, i.e. deoxycholic acid and lithocholic acid (4). Laboratory animal model studies demonstrated that these secondary bile acids increase colonic mucosal ornithine decarboxylase (a rate-limiting enzyme in polyamine biosynthesis) activity, colonic epithelial polyamine levels, and cell proliferation and act as colon tumor promoters (13–15). Our recent study demonstrated that dietary fish oil suppressed colonic mucosal ornithine decarboxylase and tyrosine-specific protein kinase activities as compared to dietary corn oil (16). Elevated levels of these enzymes have been associated with increased tumor promotion (17, 18). Another related mechanism by which high dietary fat can modulate colon carcinogenesis is through alteration of membrane phospholipid turnover and prostaglandin synthesis as shown in Fig. 1 (19, 20). Several previous studies have established that AA metabolites may modulate the pathogenesis of several immunological and inflammatory diseases (21, 22). Activities of PLA₂ and PI-PLC, which are dominant pathways for the AA release, play a significant role in the outcome of formation of AA metabolites in colon mucosa and tumors. It is noteworthy that elevated levels of PLA₂ and PI-PLC and arachidonic metabolites were observed in human colon tumors compared to normal colonic mucosa, indicating that increased levels or expression of these enzymes may play a role in colon carcinogenesis (23–26). A recent

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3The abbreviations used are: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; DAG, diacetylglycerol; AOM, azoxymethane; AA, arachidonic acid; LA, linoleic acid; COX, cyclooxygenase; LPCO, low-fat diet containing 5% corn oil; HPCO, high-fat diet containing 23.5% corn oil; HPFO, high-fat diet containing 20.5% fish oil and 3% corn oil; PI-PLC, phosphatidylinositol-specific phospholipase C; PG, prostaglandin; TXB₂, thromboxane B₂; PAPC, l-α-1-palmitoyl-2-arachidonyl phosphatidylcholine; PIP₂, l-3-phosphatidylinositol 4,5-bisphosphate; PKC, protein kinase C; HPLC, high-performance liquid chromatography; PLA₂, phospholipase A₂.
study demonstrated that deoxycholic acid, which is implicated as a promoter of colon carcinogenesis, is a potent activator of PI-PLC in human colon mucosa and tumors (23). One of the pathways leading to the generation of AA involves a direct action of PLA2 on a phospholipid that could include 1,2-diacylglycerol or 1-O-alkyl-2-acyl-phosphatidylglycerol, phosphatidylethanolamine, or phosphatidylcholine. The second pathway, mediated by PI-PLC, involves the degradation of phosphatidylglycerol 4,5-biphosphate via a sequence of reactions beginning with PI-PLC, followed by diacylglyceride lipase and monoaoylglycerol lipase (Fig. 1; Refs. 27 and 28). Also, PI-PLC hydrolyzes phosphatidylglycerol 4,5-biphosphate to DAG, which activates PKC that upon activation can phosphorylate proteins and regulate cellular events, including cell proliferation and differentiation (27). Only after liberation from phospholipid is arachidonate available as a substrate for further enzymatic modification by COX, lipoxygenase, and cytochrome P450 (22). COX converts arachidonate to PGs and thromboxane (22). In this connection, it is interesting that administration of nonsteroidal antiinflammatory drugs, such as indomethacin, piroxicam, sulindac, and aspirin, which are inhibitors of COX activity, inhibited chemically induced colon tumor development in rats (29–32). Thus, these findings clearly suggest the importance of COX activity and formation of increased levels of eicosanoids in colon tumor promotion.

In view of the potential significance of secondary bile acids and activities of PLA2, PI-PLC, and COX in colon tumorigenesis and of differences in tumor-promoting effects of high dietary corn oil and fish oil, we assessed the modulating effect of diets containing LFCO, HFCO, and HFFO on colonic mucosal and tumor PLA2, PI-PLC, and COX activities, and formation of eicosanoids such as PGE2, PGF2α, PGD2, 6-keto PGF1α, and TXB2 from AA through COX activity to understand the biochemical mechanisms of the effect of types and amount of dietary fat during the promotional stage of colon carcinogenesis in male F344 rats.

### MATERIALS AND METHODS

#### Materials

AOM (CAS:25843-45-2) was purchased from Ash Stevens (Detroit, MI). [14C]AA and PAPC were purchased from NEN-Dupont (Boston, MA). PIP2 was obtained from Amersham (Arlington Heights, IL). AA, PGE2, PGF2α, 6-Keto PGF1α, PGD2, AND TXB2 and fatty acid standards were procured from the Cayman Chemical Company (Ann Arbor, MI). The reverse-phase HPLC µ Bondpak C18 column was from Waters Associates (Milford, MA). Precoated Silica-G plastic TLC plates were from Fisher Scientific Co. (Springfield, NJ).

#### Animals and Diets

Weanling male F344 rats were purchased from Charles River Breeding Laboratories (Kingston, NY). Fish oil was donated by Menhaden Oil Refinery of Zapata Protein (USA), Inc. (Reedville, VA). The ingredients of semipurified diets were purchased from Dyets, Inc. (Bethlehem, PA). A total of 216 male F344 rats received at weaning were quarantined for 7 days and then randomly assigned to one of three dietary groups of LFCO, HFCO, and HFFO. Each dietary group (72 animals) was then divided into AOM-treated and vehicle-treated subgroups. They were housed three each in a plastic cage with filter tops and maintained under controlled conditions of 21°C at 50% humidity and a 12-h light/dark cycle. All animals were fed ad libitum. The food cups were replenished every day.

The composition of experimental diets was based on modified AIN-76A diet (9) and is shown in Table 1. HFFO diet was formulated to contain 3% corn oil to alleviate any essential fatty acid deficiency. The percentage composition of all experimental diets was adjusted so that the animals in all dietary groups would consume the same amount of calories, protein, vitamins, minerals, and fiber (33). All diets were prepared in our laboratory three times weekly and stored in air-tight containers filled with nitrogen in a cold room at 4°C under dark. Aliquots of experimental diets were analyzed for their fatty acid composition.

#### Fatty Acid Analysis

The methods for the extraction and separation of lipids from diet samples were as described by Bligh and Dyer (34) using chloroform:methanol (2:1)
containing butyldihydroxytoluene (0.005%). Fatty acid phenacyl esters from lipids were prepared according to the method of Borch (35). These fatty acid derivatives were analyzed by a HPLC method using a Waters HPLC system driven by model 510 system controller (Waters Associates, Milford, MA). Briefly, the fatty acid derivatives were separated on a Waters Bondpak C18 column (30 cm length × 4 mm diameter) with a step-wise gradient of acetonitrile and water at a flow rate of 1.5 ml/min. Elutions of fatty acid phenacyl esters were monitored at 240 nm wavelength in a Waters 990 photodiode array detector. Identification of individual fatty acids was made with authentic standards derivatized and analyzed under the same conditions.

Experimental Procedure

Beginning at 5 weeks of age, all animals were fed the modified AIN-76A (LFCO) diet. At 7 weeks of age, animals allotted to carcinogen treatment were given AOM s.c. once weekly for 2 doses at a rate of 15 mg/kg body weight, whereas the animals intended for the vehicle treatment were given normal saline. One day after the second AOM or saline treatment, groups of individual rats at weeks 1, 12, and 36 and colon tumors harvested at week 36 were analyzed by Student's t test and ANOVA. Differences were considered statistically significant at P < 0.05.

Membrane-bound PI-PLC activity was measured by the method of Bleasdale et al. (37) with some modifications using [3H]PIP2 (5 Ci/mmol) as a substrate (36). PI-PLC activity of membrane proteins (100–200 µg) was determined in a total volume of a 250-µl reaction mixture containing 30 mM HEPES-NaOH buffer (pH 7.2), 5 mM DTT, 4 mM CaCl2, 2 mM EDTA, 0.9 mM MgSO4, and 50 µM [3H]PIP2 (50 µCi/mmol). The reaction was initiated by adding substrate to the mixture and incubating at 37°C for 20 min in a shaking water bath. The reaction was terminated by the addition of 0.2 ml of chloroform:methanol (1:2, v/v) and then 0.3 ml of 1 M HCl. The incubation mixture was mixed vigorously and centrifuged to yield two phases. An aliquot of 0.3 ml of the aqueous layer containing [3H]inositol 1,4,5-triphosphate was transferred into a scintillation vial containing 10 ml of scintillation cocktail. Radioactivity was counted in a Beckman model LS6800 scintillation counter. The activity is expressed as pmoles of [3H]inositol 1,4,5-triphosphate formed from [3H]PIP2/mg protein/15 min.

Results

PLA2 and PI-PLC Activities. Samples of colonic mucosa collected from individual rats at weeks 1, 12, and 36 and colon tumors collected at week 36 were homogenized in 1:3 (w/v) volumes of homogenizing buffer containing 30 mM Tris-HCl (pH 7.4), 140 mM NaCl, 5 mM KCl, 20 µM EDTA, 10 µg/ml leupeptin, 50 µg/ml trypsin inhibitor, and 1 mM phenylmethylsulfonyl fluoride, and the homogenates were centrifuged at 100,000 × g at 4°C for 1 h. The resulting supernatant fraction was used for cytosolic PLA2 activity, and the pellet fraction was redissolved in 30 mM HEPES-NaOH buffer (pH 7.2) containing 0.2% Triton X-100 and used for the analysis of membrane-bound PI-PLC activity.

Cytosolic PLA2 activity was measured by our method published previously using [14C]PA (40–60 mCi/mmol) as substrate (36). PLA2 activity of cytosolic protein was carried out in a total volume of a 100-µl reaction mixture containing 50 mM sodium HEPES (pH 7.3), 0.8 mM CaCl2, 0.02% Triton X-100, and 20–30 µg of cytosolic protein. The reaction was initiated by adding 40 µM of PA (10 µCi/µmol, adjusted with cold substrate), and the reaction mixture was incubated at 37°C in a shaking water bath for 30 min. Reaction was terminated by adding 300 µl chloroform:methanol (3:2, v/v). An additional 200 µl of chloroform were added to each sample and mixed thoroughly. The samples were then centrifuged, and the chloroform layer was separated and evaporated to dryness under N2. Five µg of AA was added to the dried extract and redissolved in chloroform. An aliquot of the chloroform extract was then subjected to chromatography on precoated plastic TLC plates (Silica-G). The TLC plates were developed with a solvent system containing chloroform:methanol:acetic acid:water (90:12:2:1, v/v/v/v). An iodide chamber for 5 min showed visualization of AA. The area of each [14C]AA metabolite was determined with a Bioscan System 200 image-scanning counter (Bioscan, Inc., Washington, DC) equipped with a β-detector. Protein content was determined by the Bio-Rad method. Results are expressed as pmoles of [14C]AA released/mg protein/min.

Table 1 Percentage composition of experimental diets

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<thead>
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<th>Diet ingredients</th>
<th>Corn oil diets</th>
<th>Fish oil diets</th>
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<td>Low fatb</td>
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<tr>
<td>Casein</td>
<td>20.0</td>
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<td>Corn starch</td>
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<td>Vitamin mix</td>
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<td>Choline bitarurate</td>
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a Diet was formulated on the basis of the American Institute of Nutrition standard reference diet with the modification of various sources of carbohydrate (9).
b Additional corn oil and fish oil were added at the expense of starch. The composition of high-fat diets was adjusted so that all animals in various dietary groups would consume approximately the same amount of protein, minerals, vitamins, fiber, and calories (9).

Statistical Analysis

Differences in body weights and biochemical parameters between the groups were analyzed by Student's t test and ANOVA. Differences were considered statistically significant at P < 0.05.

RESULTS

As expected, corn oil diet contained LA as major fatty acid, whereas fish oil diet contained primarily DHA and EPA (Table 2). HFFO diet, which was formulated to contain 3% corn oil, showed reduced levels of LA relative to HFCO diet. The body weights of animals treated with vehicle or AOM and fed the control and experimental diets were comparable throughout the study (data not shown). However, animals fed LFCO diet gained about 10% lesser body weight when compared to those fed HFCO and HFFO diets in both

Table 2 Percentage composition of experimental diets

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a Polytron tissue homogenizer. The samples were then centrifuged at 9000 × g at 4°C for 1 h. The resulting mesosomal pellet was resuspended in 50 mM potassium phosphate buffer (pH 7.4) for the assay of COX activity. The COX activity of colon mucosa and of tumors was measured by methods published previously (36). Briefly, a 150-µl reaction mixture containing 12 µM [14C]AA (420,000 dpm), 1 mM epinephrine, 1 mM glutathione in 30 mM phosphate buffer, and 25–35 µg of mucosal or tumor microsomal protein was incubated at 37°C for 15 min. The reaction was then terminated by the addition of 40 µl of 0.2 M HCl. The COX metabolites of AA were extracted three times with 0.5 ml of ethyl acetate. The combined extracts were evaporated to dryness under N2, redissolved in chloroform, and subjected to TLC using Silica-G plates, which were developed in a solvent system containing chloroform:methanol:acetic acid:water (100:15:1:25:1, v/v/v/v). They were then exposed in an iodide chamber for 5 min for visualization of the standards. The metabolites of [14C]AA corresponding to PGE2, PGF2α, PGD2, 6-keto PGF1α, and TXB2 were detected by their comigration (Rf values) with authentic standards. The area of each metabolite was determined with the Bioscan System 200 image-scanning counter equipped with a β-detector.

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AOM- and saline-treated groups. Since the aim of this study was to understand the mechanisms of types and amount of dietary fat in colon tumor promotion, the tumors harvested at week 36 were used to assay the biochemical parameters that are involved in colon tumorigenesis and not subjected to histopathology. However, the gross colon tumor incidences (% animals with tumors) in animals fed the experimental diets were as follows: LFCO, 48%; HFCO, 82%; and HFFO, 52%.

PLA₂ Activity. The activity of PLA₂ analyzed in colonic mucosa at weeks 1, 12, and 36 and in tumors at week 36 is summarized in Table 3. Carcinogen administration significantly elevated the activities of colonic mucosal PLA₂ as compared to saline treatment, irrespective of dietary regimen throughout the period. It is noteworthy that there was a 2—3-fold increase in the PLA₂ activity of the colon tumors when compared to surrounding colonic mucosa. The activity of PLA₂ in the colonic mucosa was higher in AOM-treated animals fed the HFCO diet when compared to those fed the LFCO and HFFO diets. In saline-treated animals, dietary HFCO produced a significant decrease in colonic mucosal and tumor PLA₂.

PI-PLC Activity. As summarized in Table 3, carcinogen treatment significantly (P < 0.05) increased the colon PI-PLC activity at all time points. PI-PLC activity was also found to be increased (P < 0.001) in colonic tumors compared to mucosa. Dietary LFCO and HFFO resulted in decreased colonic mucosal and tumor PI-PLC activity as compared to HFCO diet (P < 0.05—0.001) in both saline- and AOM-treated groups. Since PI-PLC is involved in the generation of AA from phospholipids through the modulation of DAG and monoacylglycerol lipase (Fig. 1), decreased levels of colonic mucosal and tumor PI-PLC observed in animals fed HFFO as compared to those fed HFCO may suggest that the availability of AA for eicosanoid synthesis may be reduced in animals fed HFFO diet.

COX Activity. COX activity was analyzed by quantitating the rate of formation of PGs and TXB₂ from [⁴C]AA. The levels of formation of PGE₂, PGF₂, PGD₂, 6-keto PGF₁, and TXB₂ in colonic mucosa and tumor tissues are summarized in Table 4. The results indicate that there was a 3—6-fold surge in the formation of all COX metabolites during the first week after AOM administration in all dietary groups as compared to their respective saline-treated groups. These levels were reduced to about 75% at weeks 12 and 36. Carcinogen-treated animals exhibited significantly (P < 0.05—0.001) enhanced colonic mucosal COX activity, as indicated by the formation of PGS and TXB₂ from AA as compared to those treated with saline in all dietary groups. Colonic PGE₂, PGF₂, PGD₂, and TXB₂ levels were significantly (P < 0.05—0.001) higher in animals treated with AOM and fed HFCO diet compared to those fed LFCO or HFFO diets at all time points; somewhat similar trends were observed in the saline-treated groups. In general, the formation of colonic mucosal 6-keto PGF₁ was not affected (P > 0.05) by types and amount dietary fat. The COX activity was 3—4-fold higher in colonic tumors than in mucosa. Animals fed HFFO diet showed significantly (P < 0.05—0.001) lower COX activity in the tumors as compared to those fed HFCO diet. The results of this study indicate that the formation of eicosanoids from AA via COX can be influenced by the types and amount of dietary fat. Dietary fat rich in omega-3 fatty acids decreased the formation of colonic mucosal and tumor PGs and TXB₂, which are products derived from AA via COX when compared to a diet high in omega-6 fatty acids.
DISCUSSION

The results of the present study demonstrate that administration of AOM enhanced the activities of colonic mucosal PLAr and PI-PLC and the formation of PGs and TXB2 via COX activity (38, 39). Furthermore, because of additional double bonds within EPA compared to AA, COX enzyme metabolizes EPA to PGE3 and TBA3 instead of PGE2 and TXB2 (Fig. 1), suggesting altered biological properties compared with the eicosanoids derived from AA (20, 40).

Increased colon tumor content of eicosanoids and the formation of PGs and TXB2 from AA by COX in the colon tumors through the activation of COX. It is also noteworthy that the activities of PLAr and PI-PLC and the formation of PGs and TXB2 were higher in colon tumors than in mucosa, suggesting an enhanced release of arachidonate from the phospholipids and increased formation of eicosanoids in colon tumors through the activation of COX.

The results of this study demonstrate that high dietary corn oil increased colonic mucosal and tumor PLA2 and PI-PLC activities as compared to a low corn oil diet, whereas high dietary fish oil distinctly inhibited the activities of these enzymes as compared to a high corn oil diet. Although the mechanism of alteration of mucosal PLA2 and PI-PLC activities by the types and amount of dietary fat is not clearly known, it is possible that the increased levels of omega-6 fatty acids or omega-3 fatty acids may exert their enhancing or inhibitory effect by directly acting on the PLA2 and PI-PLC, or alternatively by acting on their regulators. Also, colonic secondary bile acids have been shown to activate colonic mucosal PLA2 (42) and PI-PLC (43). In this context, it is noteworthy that high dietary corn oil increases the colonic luminal (or fecal) secondary bile acids as compared to a low-fat diet containing corn oil (4). Our recent unpublished results indicate that the luminal concentrations of secondary bile acids such as deoxycholic acid and lithocholic acid in the animals fed the diets containing low and high amounts of corn oil and high fish oil were 1.56, 3.18, and 1.74 mg/g dry sample, respectively, suggesting that high dietary fish oil had no enhancing effect on the production of secondary bile acids in the lumen of the colon as compared to a high corn oil diet. Therefore, the feeding of a diet rich in corn oil results in increased levels of secondary bile acids and increased colonic mucosal and tumor PLA2 and PI-PLC activities as compared to a low corn oil diet, whereas high dietary fish oil distinctly inhibited the activities of these enzymes as compared to a high corn oil diet. Although the mechanism of alteration of mucosal PLA2 and PI-PLC activities by the types and amount of dietary fat is not clearly known, it is possible that the increased levels of omega-6 fatty acids or omega-3 fatty acids may exert their enhancing or inhibitory effect by directly acting on the PLA2 and PI-PLC, or alternatively by acting on their regulators. Also, colonic secondary bile acids have been shown to activate colonic mucosal PLA2 (42) and PI-PLC (43). In this context, it is noteworthy that high dietary corn oil increases the colonic luminal (or fecal) secondary bile acids as compared to a low-fat diet containing corn oil (4). Our recent unpublished results indicate that the luminal concentrations of secondary bile acids such as deoxycholic acid and lithocholic acid in the animals fed the diets containing low and high amounts of corn oil and high fish oil were 1.56, 3.18, and 1.74 mg/g dry sample, respectively, suggesting that high dietary fish oil had no enhancing effect on the production of secondary bile acids in the lumen of the colon as compared to a high corn oil diet. Therefore, the feeding of a diet rich in corn oil results in increased levels of secondary bile acids and omega-6 fatty acids in the lumen of the colon, which activate colonic mucosal PLA2 and PI-PLC activities (42, 43) for the release of free AA and other products of phospholipid breakdown. AA is metabolized via the COX pathway to a number of prostanooids. Products of the COX pathway modulate the proliferation rates of a variety of cell types (40). Consistent with these fatty acids. In addition, it was also reported that omega-3 fatty acids, i.e., EPA and DHA present in fish oil, inhibit the formation of PGs and TXB2 via COX activity (38, 39). Furthermore, because of additional double bonds within EPA compared to AA, COX enzyme metabolizes EPA to PGE3 and TBA3 instead of PGE2 and TXB2 (Fig. 1), suggesting altered biological properties compared with the eicosanoids derived from AA (20, 40).
results were several investigations that demonstrated that PG synthesis inhibitors, such as nonsteroidal antiinflammatory agents, inhibit colon carcinogenesis in laboratory animal models (29–32). These interesting observations suggest the potential importance of AA metabolism and PGs in modifying tumor promotion by omega-6 and omega-3 fatty acids in colon carcinogenesis. In conclusion, the results of the present study provided evidence that high-fat diets containing corn oil significantly enhanced the colonocytic PL-PL and PL-PLC activities, indicating PL-PL and PL-PLC-dependent cellular activities may play an important role in the promotion of high dietary corn oil-induced colon tumor promotion. The results of our current and earlier studies from our laboratory and of others demonstrate that a high-fat diet containing corn oil as compared to a low-fat diet and high dietary fish oil increase the colonocytic luminal secondary bile acids that modulate the colonocytic mucosal PL-PL and DAG (Fig. 1). This in turn directly activates the PKC and PKC-dependent cell proliferation and/or is responsible for the increase of cellular AA levels through the mediation of DAG and monoacylglycerol lipases as proposed in Fig. 1 (43–47). Also, diets rich in corn oil activate colonocytic mucosal PL-PL, thereby increasing phospholipid turnover and the release of free AA and other products of phospholipid breakdown. The increased levels of AA are metabolized via the COX pathway to a number of prostanoids that enhance tumor promotion.

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References

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