ABSTRACT

It has been suggested that linoleic acid (LA) is responsible for the promoting effect of dietary polyunsaturated fat on pancreatic carcinogenesis via an accelerated prostaglandin synthesis, caused by metabolism of LA-derived arachidonic acid in (pre)neoplastic tissue. The purpose of the present study was to investigate whether dietary LA is the cause of pancreatic tumor promotion by a high fat diet. Five groups of 30 azaserine-treated rats and 5 groups of 30 N-nitrosobis(2-oxopropyl)amine-treated hamsters were maintained for 6 months (rats) and 12 months (hamsters) on high fat (25 weight %) AIN diets containing 2, 4, 6, 10, or 15 weight % LA. The results indicated that the strongest enhancing effect on the growth of pancreatic (pre)neoplastic lesions in rats and hamsters was obtained with 4 and 2 weight % of dietary LA, respectively. At higher LA levels the tumor response seemed to decrease rather than increase. In both rats and hamsters the fatty acid profiles of blood plasma and pancreas showed an accurate reflection of the dietary fatty acid profiles: a proportional increase in LA levels was observed in plasma and pancreas with increasing dietary LA. In both species plasma and pancreatic AA levels remained constant, except for arachidonic acid levels in rat plasma, which significantly increased with increasing dietary LA levels. Fatty acid profiles in hamster pancreatic tumors did not differ from fatty acid profiles in nontumorous pancreatic tissue from hamsters fed the same diet. Prostaglandin (PG) E2, 6-keto-PGF1α, PGF2α, and thromboxane B2-concentrations in nontumorous pancreatic tissue were similar among the diet groups. Ductular adenocarcinomas from hamster pancreas showed significantly higher levels of 6-keto-PGF1α, PGF2α, and thromboxane B2, but not of PGE2, in comparison with nontumorous pancreas. It is concluded that the strongest pancreatic tumor promotion by dietary LA is 4 weight % in rats and 2 weight % or less in hamsters, and that PGs may be involved in the development of ductular adenocarcinomas induced in hamster pancreas by N-nitrosobis(2-oxopropyl)amine.

INTRODUCTION

Initiation of cancer is generally caused by a primary genetic event, followed by a series of genetic and/or epigenetic alterations that promote development from precancerous cells to malignant tumors. It has been demonstrated that high levels of dietary PUFA3 promote tumor growth in several animal models (1–3), including pancreatic cancer models (4–6). LA has been implicated to cause this effect (4, 7, 8). One hypothesized mechanism involves an accelerated prostaglandin synthesis, caused by metabolism of LA-derived AA, in (pre)neoplastic tissue (9–11). This theory is supported by a frequently seen tumor growth inhibition concurrent with biochemical inhibition of the prostaglandin-synthesizing enzyme cyclooxygenase by indomethacin (12) or by competitive inhibition by n–3 fatty acids from fish oils (13–15).

To study the specific role of PUFA in dietary fat-promoted pancreatic carcinogenesis, experiments with asaizerine-treated rats (model for acinar pancreatic cancer) and BOP-treated hamsters (model for ductular pancreatic cancer) were performed. Rats and hamsters were maintained on a high fat diet (25 weight %) with increasing LA concentrations, in order to find the dietary LA level with the strongest enhancing effect on pancreatic carcinogenesis, and to evaluate the involvement of prostaglandins in this process by determination of the fatty acid composition of blood plasma and pancreas as well as the prostaglandin content of the pancreas.

MATERIALS AND METHODS

Animals

Fifty-five 1-week pregnant female Wistar rats were obtained from Harlan-CPB, Austerlitz, The Netherlands. During pregnancy the rats were kept solitary, in stainless steel cages fitted with wire mesh fronts and floors and were fed a standard laboratory chow. Two weeks (±1 day) after arrival the rats gave birth to a mean of eight pups. After 4 days the pups were sexed. All females, the surplus of male pups, and 33 mothers were killed and a total of 175 male pups were divided among the remaining 22 mothers. At 14 and 21 days of age 150 pups were given an i.p. injection of 30 mg azageline (Calbiochem-Behring Corp., La Jolla, CA) per kg body weight, which was dissolved freshly in 0.9% NaCl solution. Twenty-five control animals received injections with 0.9% NaCl solution only. Directly after the second injection the animals were weaned and randomly allocated to 5 groups of 35 animals each (5 0.9% NaCl solution-treated controls plus 30 azaserine-treated animals).

One hundred seventy-five 4-week-old Syrian golden hamsters were obtained from Harlan-CPB. The hamsters were kept in Macrolon cages, 5 animals/cage, on a softwood bedding and under standard laboratory conditions. During the initiation phase the hamsters were fed a standard laboratory chow. At 5, 6, and 7 weeks of age 150 hamsters received a s.c. injection of 20 mg BOP (Nacalai Tesque Inc., Kyoto, Japan) per kg body weight, which was dissolved freshly in 0.9% NaCl solution. Twenty-five control animals received injections with 0.9% NaCl solution only. Directly after the third injection the animals were randomly allocated to 5 groups of 35 animals each (5 0.9% NaCl solution-treated controls plus 30 BOP-treated animals).

Diets

One week after the last injection the animals were maintained on an AIN-76 diet high in fat (25 weight %; Table 1). The fat was blended to contain an increasing percentage of linoleic acid by mixing high linoleic safflower oil (Unilever, Vlaardingen, the Netherlands) with high oleic sunflower oil (Trisen; Contined, Bennekem, the Netherlands). The (calculated) dietary levels of linoleic acid over the five experimental groups were 2, 4, 6, 10, and 15 weight %. After reextraction of the oil mixtures, the prepared diets actually contained 2.0, 3.8, 5.9, 9.9, and 15.0 weight % of linoleic acid, respectively. Their cause of death could not be established due to severe autolysis and cannibalism. Sixty-seven hamsters (38%), involving all groups, died of tumor growth inhibition concurrent with biochemical inhibition of the prostaglandin-synthesizing enzyme cyclooxygenase by indomethacin (12) or by competitive inhibition by n–3 fatty acids from fish oils (13–15).

Monitoring and Autopsy

Body weights and food intake were recorded weekly during the first 3 months and monthly thereafter. The general condition and behavior of the animals were checked daily. Two rats died during the study (at days 54 and 104, respectively). Their cause of death could not be established due to severe autolysis and cannibalism. Sixty-seven hamsters (38%), involving all groups, did not reach the end of the study. Forty-seven of these animals (20 found dead and 27 killed in extremis) were included in the results. Their effective stay in
the results due to very early death (before day 171), autolysis, or cannibalism.

Nitrogen-flushed plastic bags at —20°C until use.

The study was at least 250 days. The 20 remaining animals were excluded from the study.

Gross lesions were excised. The pancreas and liver (rats) or the pancreas only was kept at —80°C until analysis. The entire pancreas, liver, kidneys, and all containing tubes and centrifuged at 1700 X g at 4°C for 20 mm. The plasma was separated from blood clots by centrifugation at 10,000 X g for 30 mm and the supernatant was discarded after centrifugation at 105,000 X g for 60 mm. The microsomal pellet was resuspended in 300 μl buffer and stored at —30°C until fatty acid analysis. Total lipids were extracted from 50-μl aliquots of pancreatic microsomes as described by Folch et al. (21). Fatty acid composition was determined by gas-liquid chromatography. The samples were eluted on a capillary BD23 column (J&W Scientific) after saponification with NaOH in methanol and transmethylation of the fatty acids with boron trifluoride methanol.

**Prostaglandins.** Pancreatic tissue (100–200 mg) was homogenized in 0.1 M phosphate-buffered saline (pH 7.4) containing 15% methanol and was applied to Sep-Pak C18 columns (J. T. Baker Inc., Phillipsburg, NJ). After washing with 6 ml 15% methanol/phosphate-buffered saline and 6 ml petroleum ether, the samples were eluted with 6 ml methanol. After evaporation of the methanol under N2, the samples were dissolved in 1.0 ml buffer and subsequently analyzed by using enzyme immunoassay kits for PGE2, PGF2α, 6-keto-PGF1α, and TXB2 (Cascade Biochem. Ltd, Reading, United Kingdom).

**Statistics.** Food and energy intake and body and pancreatic weights were statistically evaluated by 2-way analysis of variance followed by Dunnett’s test, prostaglandin levels were evaluated by analysis of variance followed by Student’s t test, the number of pancreatic lesions was evaluated by 2-sample t test, or by 1-way analysis of variance followed by linear trend tests with orthogonal contrasts. The number of tumor-bearing animals (incidence) was analysed by χ² test. Fatty acid compositions were evaluated by 2-way analysis of variance by using percentage of dietary linoleic acid and carcinogen treatment as factors, and by 1-way analysis of variance followed by linear trend tests with orthogonal contrasts.

**RESULTS**

**Food Consumption and Body and Pancreatic Weights**

Mean food consumption was similar among the experimental groups (rats, 12.7–13.0 g/animal/day; hamsters, 5.1–6.0 g/animal/day). Mean body weight gain showed no significant differences among groups (Fig. 1). Body and pancreatic weights at autopsy were similar among the diet groups and are summarized in Table 2.

**Microscopy**

**Rats.** Both acidophilic and basophilic AACF were identified in pancreatic tissue of azaserine-treated rats. Basophilic AACF were not scored because they were too scarce to justify evaluation. The microscopic data on acidophilic AACF, which are summarized in Table 3, show that the area and volume as percentage of pancreas occupied by AACF tissue is highest in the group fed 4% dietary LA. At higher levels of LA in the diet the area as percentage of pancreas occupied by acidophilic nodule tissue had decreased rather than increased in comparison with the 4% LA diet group. Furthermore, rats maintained on the 4% LA diet developed significantly (P < 0.05) more acidophilic AACF with a diameter between 1 and 3 mm than rats in the diet groups containing more than 4% LA (Table 4). The number of

### Table 1: Weight percentage composition of the AIN76 diet and percentage of fatty acid composition of the oils

<table>
<thead>
<tr>
<th>Diet component</th>
<th>Fatty acid</th>
<th>Safflower oil</th>
<th>Sunflower oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casein</td>
<td>25.0</td>
<td>C14:0</td>
<td>0.1</td>
</tr>
<tr>
<td>ot-Methionine</td>
<td>0.38</td>
<td>C16:0</td>
<td>7.0</td>
</tr>
<tr>
<td>Wheat starch</td>
<td>35.72</td>
<td>C16:1</td>
<td>0.1</td>
</tr>
<tr>
<td>Cellulose</td>
<td>6.25</td>
<td>C18:0</td>
<td>2.6</td>
</tr>
<tr>
<td>Choline bitartrate</td>
<td>0.25</td>
<td>C18:1</td>
<td>13.1</td>
</tr>
<tr>
<td>AIN-76 minerals</td>
<td>4.38</td>
<td>C18:2</td>
<td>76.0</td>
</tr>
<tr>
<td>AIN-76 vitamins</td>
<td>1.25</td>
<td>C18:3</td>
<td>0.3</td>
</tr>
<tr>
<td>Ca3H2PO4</td>
<td>1.77</td>
<td>C20:0</td>
<td>0.3</td>
</tr>
<tr>
<td>Fat</td>
<td>25.0</td>
<td>C20:1</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C22:0</td>
<td>0.2</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
<td>99.9</td>
<td>99.9</td>
</tr>
</tbody>
</table>

*The diets were prepared every 2 months. All diets were stored in sealed, nitrogen-flushed plastic bags at —20°C until use.*

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**Fig. 1.** Body weight gain of azaserine-treated rats and BOP-treated hamsters maintained on a high fat diet containing increasing levels of binoleic acid for 6 and 12 months, respectively. 2% LA; △, 4% LA; □, 6% LA; ▽, 10% LA; △, 15% LA.
cancerous tumors was also higher in the 4% LA group in comparison with the other groups, although the difference did not reach the level of statistical significance. No significant linear trend could be observed in number of lesions in rat pancreas with increasing dietary LA.

**Hamsters.** The total number of ductular carcinomas in hamster pancreas was highest in the group fed 2% dietary LA and was significantly (P < 0.05) higher as compared to the group maintained on 6% LA (Table 4). No significant linear trend could be observed in number of pancreatic lesions with increasing dietary LA. The incidence of pancreatic tumors (carcinoma in situ plus adenocarcinomas) was also highest in the 2% LA group in comparison with the other groups, although no significant differences were observed when analyzed by \( \chi^2 \) test.

**Fatty Acid Composition of Blood Plasma and Pancreatic Microsomes**

**Untreated versus Carcinogen-treated Animals.** Two-way analysis of variance revealed significant differences between control animals and carcinogen-treated animals for most fatty acids in both plasma and pancreas (Tables 5 to 9). Azaserine-treated rats exhibited a higher level of C18:2 along with lower levels of C18:3 (n — 6) and C20:4 in plasma in comparison with controls. Remarkably, in hamsters the opposite was observed: BOP-treated hamsters demonstrated a lower level of C18:2 along with higher levels of C18:3 (n — 6) and C20:4 in both plasma and pancreas, in comparison with controls. Azaserine treatment caused almost no differences in fatty acid profiles of rat pancreas.

**Effects of Dietary LA on Fatty Acid Composition of Plasma and Pancreas.** The complete fatty acid profiles of plasma and pancreas of rats and hamsters are given in Tables 5, 6, 7, and 8, respectively. In plasma as well as pancreatic microsomes of both species LA significantly increased (P < 0.001) with increasing dietary LA, whereas AA significantly (P < 0.001) with increasing LA concentration in the feed. This dose-related increase of LA was accompanied by a significant decrease (P < 0.001) in OA. AA in rat plasma increased significantly (P < 0.001) with increasing dietary LA, whereas AA levels in pancreatic tissue of rats as well as in plasma and pancreatic

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**Table 2 Body and pancreatic weights at autopsy**

<table>
<thead>
<tr>
<th>Diet group</th>
<th>Body wt (g)</th>
<th>Pancreatic wt (g)</th>
<th>Body wt (g)</th>
<th>Pancreatic wt (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls (N)</td>
<td>Aza-treated (N)</td>
<td>Controls (N)</td>
<td>Aza-treated (N)</td>
</tr>
<tr>
<td>2% LA</td>
<td>493.5 ± 7.3 (5)</td>
<td>500.3 ± 7.0 (30)</td>
<td>1.14 ± 0.06 (5)</td>
<td>1.23 ± 0.04 (30)</td>
</tr>
<tr>
<td>4% LA</td>
<td>483.4 ± 5.6 (5)</td>
<td>488.9 ± 8.2 (29)</td>
<td>1.01 ± 0.08 (5)</td>
<td>1.26 ± 0.04 (28)</td>
</tr>
<tr>
<td>6% LA</td>
<td>479.7 ± 8.4 (5)</td>
<td>495.7 ± 8.0 (30)</td>
<td>1.21 ± 0.16 (5)</td>
<td>1.21 ± 0.05 (30)</td>
</tr>
<tr>
<td>10% LA</td>
<td>482.2 ± 9.0 (5)</td>
<td>491.7 ± 5.7 (29)</td>
<td>1.07 ± 0.05 (5)</td>
<td>1.20 ± 0.04 (29)</td>
</tr>
<tr>
<td>15% LA</td>
<td>502.7 ± 8.5 (5)</td>
<td>504.5 ± 6.7 (30)</td>
<td>0.96 ± 0.08 (5)</td>
<td>1.24 ± 0.05 (30)</td>
</tr>
</tbody>
</table>

**Table 4 Number of pancreatic lesions in azaserine-treated rats and BOP-treated hamsters maintained on a high fat diet containing increasing levels of linoleic acid for 6 or 12 months, respectively**

<table>
<thead>
<tr>
<th>No. of lesions</th>
<th>2% LA</th>
<th>4% LA</th>
<th>6% LA</th>
<th>10% LA</th>
<th>15% LA</th>
<th>P linear trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Pre)neoplastic lesions observed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of animals</td>
<td>30</td>
<td>29</td>
<td>30</td>
<td>29</td>
<td>30</td>
<td>0.112</td>
</tr>
<tr>
<td>No. of tumor-bearing animals (%)</td>
<td>4 (13)</td>
<td>6 (21)</td>
<td>1 (3)</td>
<td>4 (14)</td>
<td>3 (10)</td>
<td></td>
</tr>
<tr>
<td>AACF (1 &lt; Ø &lt; 3 mm)</td>
<td>19&lt;sup&gt;c&lt;/sup&gt;</td>
<td>30&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Adenoma (Ø &gt; 3 mm)</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0.347</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>3</td>
<td>7</td>
<td>0</td>
<td>6</td>
<td>3</td>
<td>0.678</td>
</tr>
<tr>
<td>Acinar adenocarcinoma</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.615</td>
</tr>
</tbody>
</table>

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<sup>a</sup> Values are means ± SEM. Statistics: analysis of variance plus Dunnett's tests.

<sup>b</sup> Azaserine.


Table 5 Fatty acid composition of plasma of untreated and azaserine-treated rats maintained on a high fat diet containing increasing levels of linoleic acid for 6 months

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>2%</th>
<th>4%</th>
<th>6%</th>
<th>10%</th>
<th>15%</th>
</tr>
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<tbody>
<tr>
<td>C14:0</td>
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<td></td>
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<tr>
<td>C16:0</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>C16:1 trans</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>C16:1 cis</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>C18:0</td>
<td></td>
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<td></td>
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<tr>
<td>C18:1</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>C18:2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C18:3 cis 6, 9, 12</td>
<td></td>
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<tr>
<td>C20:0</td>
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<tr>
<td>C20:1</td>
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<tr>
<td>C20:2</td>
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<td>C20:3</td>
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<tr>
<td>C20:4</td>
<td></td>
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<tr>
<td>C22:6</td>
<td></td>
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<tr>
<td>C18:2</td>
<td></td>
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<tr>
<td>C18:1</td>
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<tr>
<td>C16:1 cis</td>
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<td>C16:1 trans</td>
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<td>C18:0</td>
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<tr>
<td>C18:1</td>
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<tr>
<td>C20:0</td>
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<tr>
<td>C20:1</td>
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<td>C20:2</td>
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<td>C20:3</td>
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<td>C20:4</td>
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<tr>
<td>C22:6</td>
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</tbody>
</table>

**DISCUSSION**

The main purpose of the present study was to find out whether increasing levels of essential polyunsaturated fatty acid (in fact LA) proportionally enhance the development of putative (pre)neoplastic lesions in the pancreas of azaserine-treated rats and ductular (pre)neoplastic lesions in the pancreas of BOP-treated hamsters. Since dietary fat has a strong promoting effect on pancreatic carcinogenesis, the amount of fat in the diets of the various groups was kept at a constant high (25 weight %) level. To obtain an increasing concentration of LA in the high fat diet without influencing the chain length of the fatty acids, high linoleic safflower oil (approximately 75% LA) was blended with high oleic Trisun sunflower oil (approximately 80% OA). The results of the present studies demonstrate that 2 and 4 weight % LA in a high fat diet of hamsters and rats, respectively, give the strongest tumor response. Higher concentrations of LA resulted in a decrease rather than an increase in tumor response, indicating that above a certain threshold a dose-effect relationship between dietary LA and tumor response does not exist as far as the growth of pancreatic AACF (rat) and pancreatic ductular lesions (hamster) are concerned. The present results are in contrast to those of Roebuck.
et al. (22), who found that in azaserine-treated rats the acidophilic ACF increased in number and size as the LA content in the diet increased. This promoting effect of LA was particularly apparent from 4 up to 8 weight % LA is required for optimal enhancement of azaserine-induced pancreatic carcinogenesis by a high fat diet. The difference between the present results and those obtained by Roebuck et al. (22) are most probably caused by differences in the composition of the diets used. Roebuck et al. (22) used diets compounded by blending corn oil with a high percentage of LA with coconut oil containing mainly short chain saturated fatty acids (C10:0, C12:0, C14:0, and C16:0) and only 10% C18:0, C18:1, and C18:2. In the present study LA (C18:2) was exchanged for OA (C18:1). OA forms a large part of many natural dietary lipid sources but in contrast to LA and AA cannot be converted by mammals to n — 6 fatty acids which are known to stimulate tumor growth. Short chain saturated fatty acids are differently absorbed and metabolized than long chain unsaturated fatty acids, leading to a difference in the fatty acid composition of the membranes of the pancreatic cell and hence a difference in the modulating effects on carcinogenesis. It is not illogical to assume that the difference observed between our results and those of Roebuck et al. (22) is caused by this phenomenon, since our data clearly demonstrate that feeding increasing levels of LA to
rats or hamsters altered the composition of fatty acids in the plasma and the incorporation of fatty acids in the microsomes of normal pancreatic cells as well as of pancreatic tumor cells. Apart from changes in membrane structure and function, metabolic processes that take place in the cell membranes and in the cytoplasm of the cell, utilizing liberated membrane constituents may very well be influenced by alteration of the fatty acid profile of the cell membrane. It is hypothesized that the promoting effect of a high fat diet on carcinogenesis is the result of an accelerated formation of AA and subsequently of PGs (10). Our results, however, indicate that AA is not formed in direct proportion to tissue LA which may point to elongation and desaturation of fatty acids as a strictly regulated mechanism. Furthermore, the present results are indicative of an impaired LA metabolism in plasma due to carcinogen treatment: an inhibited LA conversion to C18:3 (n - 6) and C20:4 in rats and an accelerated LA metabolism in hamsters. This alteration may be caused by the presence of (pre)neoplastic lesions in the tissue of carcinogen-treated animals, but no direct evidence is available for this assumption. However, the observation points to a contrasting species difference.

The overall high relative concentration of AA in rat plasma may be the result of a basically higher elongation and desaturation potency of rat liver in comparison with hamster liver. The significant dose-response relationship observed between the amount of LA in the diet and the AA concentration in the plasma of rats but not of hamsters may also be ascribed to a difference in hepatic metabolic activity between the two species.

Interestingly, the diet groups showing a relatively high incidence of (pre)neoplastic lesions in pancreas of both rats and hamsters contained a high percentage of OA. Recently, Khoo et al. (23) studied the effects of stearic and oleic acid on pancreatic fatty acids and the development of AACF in azaserine-treated rats and demonstrated an enhancing effect of oleic acid on pancreatic carcinogenesis. However, foci were absent in the group treated with azaserine alone and in the other groups the number of foci per pancreas observed was unusually low in comparison with the numbers of foci observed by other workers in this field (24, 25). Since OA cannot be metabolized to LA or other long chain PUFA and PGs, the findings by Khoo et al. (23) are hard to explain mechanistically. However, the presently observed absence of a concentration-related effect of LA on pancreatic carcinogenesis might be due to the presence of a high concentration of OA in the diets containing low concentrations of LA. Moreover, saturated fats such as lard and beef tallow contain 40–50% OA which may be responsible for the promoting effects of lard on pancreatic carcinogenesis in rats (26) and of beef tallow on pancreatic carcinogenesis in hamsters (27). The findings of Khoo et al. (23) and those presented in this paper warrant further elucidation of the role of OA in the process of carcinogenesis.

Notwithstanding the possible promoting effects of OA on pancreatic carcinogenesis, it is beyond doubt that a diet high in unsaturated fat and containing at least 2–4 weight % of LA has stronger promoting effects on pancreatic carcinogenesis than a diet high in saturated fat containing a high concentration of OA. Since LA and not OA can give rise to AA and the biologically active PGs, the role of these eicosanoids in carcinogenesis needs further study.

The n - 6 PUFA, particularly LA, may give rise to PGs of the 2-series via AA. It has been demonstrated that some of these PGs may
stimulate cell proliferation (PGF$_{2\alpha}$; Ref. 28) or have immunosuppressive properties (PGE$_2$; Ref. 29) and hence may either promote tumor growth or disturb inhibition of tumor development. Quantitative determination of PG levels in pancreatic tissue of rats and hamsters did not show any difference among the various diet groups, whereas PG levels in the ductular hamster tumors observed in the present study were significantly elevated in comparison with nontumorous tissue, despite unchanged tissue LA and AA levels.
This observation suggests that PGs play a role in development of pancreatic tumors but more research is needed to establish whether PGs are needed for the development of putative preneoplastic lesions to tumors and, moreover, to elucidate whether n-3 fatty acids have the potency to influence this process. Studies with combinations of LA and Max eicosapentaenoic acids are currently running in our Institute in order to find answers to these questions.

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Fig. 5. Prostaglandin levels in pancreatic tumors and nontumorous pancreas of BOP-treated hamsters maintained on a high fat diet containing increasing levels of linoleic acid for 12 months. □ 2% LA; □ 4% LA; □ 6% LA; □ 10% LA; □ 15% LA; □ tumor tissue. Values are means ± SEM (N = 3); *P < 0.05, ***P < 0.001.
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