Differential effect of dietary fish oil and vegetable oil on lipid and lipoprotein metabolism

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Summary

The present experiment was designed to clarify the effect of dietary fish oil (rich in eicosapentaenoic acid n-3), corn oil (rich in linoleic acid n-6) or a mixture of fish and corn oils on the cholesterol and triglyceride concentration of plasma and liver, and on the plasma lipoprotein profile in male Wistar strain rats. Alteration of phospholipid composition in liver microsomal membranes by consumption of these fats was also determined. Fish oil consumption resulted in a decrease in the plasma triglyceride and cholesterol levels, whereas corn oil consumption produced an increase in the plasma triglyceride and cholesterol levels compared with the control group fed standard chow diet. Replacement of 50% of corn oil by fish oil, however, reduced the accumulation of plasma lipids. The decrease in plasma triglyceride by fish oil was attributed by a decrease in very low density lipoprotein (VLDL)-triglyceride. The type of dietary fat had no influence on liver triglyceride and cholesterol content. Fish oil consumption decreased the proportion of phosphatidylcholine at the expense of phatidylethanolamine in liver microsomal membranes, suggesting a decreased synthesis of phosphatidylcholine or a decreased N-methylation of phosphatidylethanolamine to phosphatidylcholine by n-3 polyunsaturated fatty acids. Feeding of fish oil also increased the proportion of phosphatidic acid in the microsomal membranes, suggesting the inhibition of phosphatidate hydrolysis by fish oil. Taken together, the present study and the previous studies support the hypothesis that lipid-lowering effect of fish oil might be caused by the diminished lipogenesis, enhanced fatty acid oxidation and diminished secretion of VLDL from the liver.

Key words: fish oil, cholesterol, triacylglycerol, lipoprotein, membranes

INTRODUCTION

The two types of polyunsaturated fatty acids (PUFA) are n-6 and n-3. The principal n-6 fatty acid, linoleic acid (18:2), is found in vegetable oil. In human, 18:2 n-6 is a necessary component of cell membranes as well as a precursor of prostaglandins. The primary n-3 fatty acid, linolenic acid α-18:3, is present in large amounts in perilla and linseed oils and in lesser amounts in soybean and rapeseed oils. Linolenic acid is a
precursor to the longer chain n-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3), found in fish oils.

There have been repeated demonstrations that oils of vegetable origin and marine origin containing a large proportion of polyunsaturated fatty acids lower plasma lipid level in comparison with saturated fatty acids\(^1\). However, fish oil, rich in n-3 fatty acids, appears to be more effective in lowering the concentration of plasma triglyceride than vegetable oil, generally rich in n-6 fatty acids\(^2\). The mechanisms responsible for the hypotriglyceridemic effects of fish oil are currently under intense investigation. In addition, controlled human clinical and animal feeding trials have supported the epidemiological data that dietary long chain n-3 polyunsaturated fatty acids both decrease the incidence of cardiovascular diseases and prevent the formation of atherogenic lesions\(^3\)\(^-\)\(^8\). These effects of dietary long chain n-3 polyunsaturated fatty acids on cardiovascular diseases rate have been attributed to changes in circulating lipid levels as well as modified eicosanoid production resulting in altered platelet and leukocyte reactivity\(^1\), \(^9\)\(^-\)\(^10\).

It is also suggested that the decrease in plasma triglyceride (TG) observed in fish oil consumption may be related to increased mitochondrial fatty acid oxidation\(^11\), but not peroxisomal oxidation. Other studies have shown that dietary fish oil decreased the capacity for TG production by affecting hepatic enzymes involved in TG synthesis\(^12\)\(^-\)\(^17\). We have recently reported that rats fed fish oil rich in EPA resulted in a decrease of CTP:phosphocholine cytidylyltransferase activity, the rate limiting enzyme for phosphatidylcholine synthesis, concomitant with the decrease in output of VLDL\(^18\), \(^19\). As newly synthesized phosphatidylcholine is required for the VLDL assembly and secretion\(^20\), the inhibition of PC synthesis by fish oil may link to the reduced assembly of VLDL in the liver\(^18\), \(^19\).

Key enzymes involved in the synthesis of glycerolipid have shown to be present, but not exclusively, on endoplasmic reticulum membranes. It is suggested that these enzymes are influenced by the property of membrane phospholipids\(^21\). Assembly, intracellular transport, storage in Golgi, and secretion of VLDL are all membrane-associated phenomenon. In the present study, we sought to determine if phospholipid composition in liver microsomal membranes and plasma lipoprotein profiles in response to dietary fats was affected. We also determined interactions between PUFA of the n-3 and n-6 families. Possible mechanisms by which dietary fish oil induced changes in circulating lipid levels were discussed.

**METHODS**

**Materials and reagents**

Male Wistar rats, (100-120 g) were purchased from Kyudo Animal Labs (Tosu, Saga). Fish oil was kindly donated from Nippon Yushi Co. Corn oil was from Wako Co. Standard laboratory chow (powder, CE-II) was from Nihon Clea (Osaka). All other chemicals and reagents were analytical grade.
Animals and diets

Male Wistar rats were allotted to individual stainless steel cages and provided water and standard laboratory chow for 4 days before starting the experimental diet treatment. The animals were housed under a normal light-dark cycle, with light on from 0700 to 1900. Food and water were available to the animals *ad libitum* for a feeding period.

In experiment 1, rats were weighed and divided into 4 groups of 6 rats per group in a manner ensuring that the average body weight was similar in each group. Each group of animals was fed a semi-synthetic diet supplemented with 10% by weight of either a corn oil, fish oil or a mixture of fish oil and corn oil (1:1, w/w) for 3 weeks. Control rats were fed the standard commercial chow diet. In experiment 2, rats were divided into 2 groups of 5 rats per group and were fed a semi-synthetic diet supplemented with 10% by weight of either corn oil or fish oil for 10 days. Serum was collected after fasting for 5 hours and provided for the lipoprotein analysis.

Composition of semi-purified diet was, in weight % of total: casein, 20; vitamin mixture²², 1.0; mineral mixture²³, 4.0; choline chloride, 0.2; nonnutrient cellulose, 5.0; and sucrose to make 100 as described elsewhere²⁴). Diets were prepared weekly and stored at −40°C.

The fatty acid composition of dietary lipids were shown in Table 1.

Blood and liver samples

On the morning of the experiments, animals were exsanguinated between 0900 and 1000hr and blood was collected in heparinized tubes from the abdominal aorta and the plasma was separated by centrifugation (1500×g for 15 min.).

Four ml of 0.9% NaCl was layered over 4 ml of pooled plasma in 9 ml polycarbonate centrifuge bottles and centrifuged in Beckman 40 rotor at 12000 rpm for 30 min at 13°C. The floating chylomirion fractions were removed (0.5 ml)²⁶.

Livers were flushed with cold 0.9% NaCl, removed and weighed. Samples were taken for the preparation of microsomal fractions and for lipid analysis.

Preparation of liver microsomes

Microsomal fraction of the liver was prepared as reported previously²⁴). In briefly, a 20% liver homogenate was prepared at 4°C in 250 mM sucrose with Tris-buffer

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Fatty acid composition of dietary fats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty acid</td>
<td>Fish oil</td>
</tr>
<tr>
<td>14 : 0</td>
<td>6.9</td>
</tr>
<tr>
<td>16 : 0</td>
<td>8.1</td>
</tr>
<tr>
<td>16 : 1 n-7</td>
<td>10.2</td>
</tr>
<tr>
<td>18 : 0</td>
<td>2.1</td>
</tr>
<tr>
<td>18 : 1 n-9</td>
<td>11.8</td>
</tr>
<tr>
<td>18 : 2 n-6</td>
<td>6.6</td>
</tr>
<tr>
<td>18 : 3 n-3</td>
<td>2.9</td>
</tr>
<tr>
<td>18 : 4 n-3</td>
<td>6.2</td>
</tr>
<tr>
<td>20 : 4 n-6</td>
<td>2.0</td>
</tr>
<tr>
<td>20 : 5 n-3</td>
<td>28.1</td>
</tr>
<tr>
<td>22 : 1</td>
<td>1.2</td>
</tr>
<tr>
<td>22 : 3 n-3</td>
<td>2.1</td>
</tr>
<tr>
<td>22 : 6 n-3</td>
<td>11.4</td>
</tr>
</tbody>
</table>

| Total n-6 | 8.6 | 32.1 | 55.5 |
| Total n-3 | 50.7 | 25.3 | — |

* A mixture of fish oil and corn oil (1 : 1, w/w).
(pH 7.4), 1 mM EDTA and 1 mM dithiothreitol, using a Potter-Elvehjem homogenizer. The post-mitochondrial supernatant was centrifuged at 105,000 × g for 60 min to sediment microsomes. The microsomal fraction was suspended in the same buffer.

Isolation of plasma lipoproteins

The plasma lipoproteins were separated by sequential ultracentrifugation26, with minor modifications. The fractions at 4<1.006 g/ml (VLDL), d 1.006-1.063 g/ml (LDL), and d 1.063-1.210 g/ml (HDL2 + HDL3) were isolated using L-80 ultracentrifuge equipped with 40 Ti rotor (Beckman Instruments, Fullerton, CA). Lipoprotein fractions were dialyzed for 48 h in Spectapore #1 tubing (Spectrum Medical Industries). Lipid (triglyceride, cholesterol, and phospholipid) and protein contents were assayed in each lipoprotein fraction.

Lipid analysis

Livers were homogenized in chloroform methanol (2:1 v/v)26. Aliquots of the total lipid extracts from the liver were taken for determination of total cholesterol, triglyceride and phospholipid by colorimetrically27. Phospholipids from liver homogenates and microsomal fractions were separated by thin-layer chromatography on Silica gel H plates using a solvent system composed of chloroform/methanol/acetic acid/water (25:15:4:2 v/v/v/v)28, and then assayed individually24, 27-30).

Serum cholesterol, triglyceride and phospholipid concentrations were assayed enzymatically.

Fatty acid composition of liver phospholipid and triglyceride

Hepatic phospholipids and triglyceride were separated by thin-layer chromatography on Silica gel G plates using a solvent system composed of petroleum ether/diethyl ether/acetic acid (80:20:1, v/v/v), transmethylated by methanolic HCl and the fatty acid composition was determined by capillary gas chromatography27, 30).

Statistical analysis

Values are reported as means±SEM. Statistical evaluation of differences between treatment groups were made by using a one-way ANOVA at the 95% probability level.

RESULTS

(1) Body weight, liver weight and food intake.

The average body weight gain, liver weight, liver weight to body weight percentages, and amount of food consumed per day for the animals fed the diets for a 3 week period in experiment 1 are presented in Table 2. There are no significant differences in body weight gain among the groups. Animals consumed similar amounts of food per day irrespective of fat quality, although it was somewhat lower in the fish oil diet fed group. The wet weight of the livers and liver weight to body weight ratios were also unaffected by the
Table 2 Effect of dietary fats on the body weight, food intake and liver weight

<table>
<thead>
<tr>
<th>Groups**</th>
<th>Final body weight (g)</th>
<th>Liver weight (g)</th>
<th>Liver weight (g/100g body wt)</th>
<th>Food intake (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chow</td>
<td>254.4±2.6*</td>
<td>14.21±1.74</td>
<td>4.88±0.09</td>
<td>16.2±0.24</td>
</tr>
<tr>
<td>Corn oil</td>
<td>261.4±3.2</td>
<td>12.70±0.40</td>
<td>4.75±0.17</td>
<td>18.2±0.26</td>
</tr>
<tr>
<td>Fish oil</td>
<td>249.6±5.2</td>
<td>12.10±0.35</td>
<td>4.84±0.35</td>
<td>16.9±0.44</td>
</tr>
<tr>
<td>Mixture***</td>
<td>259.8±2.5</td>
<td>12.57±0.28</td>
<td>4.84±0.07</td>
<td>15.3±0.37</td>
</tr>
</tbody>
</table>

* Values are the mean ± SEM of 6 rats.  
** Rats were fed commercial chow diet or semi-synthetic diets containing corn oil, fish oil or a mixture of corn oil and fish oil (1:1, w/w) as a sole of fat for 21 days. Average initial body weight of rats were 113.0 ± 1.5 g.  
*** A mixture of corn oil and fish oil (1:1, w/w)

dietary fatty acid composition. There were no significant changes of these parameters in experiment 2 (data not shown).

(2) The effect of dietary fats on plasma cholesterol, triglyceride and phospholipid.

Table 3 showed the effect of dietary fats on plasma lipids in rats (3 weeks). Compared to the control group, feeding of fish oil diet for 21 days also decreased significantly both cholesterol and triglyceride content in plasma. The decrease was detected at 3, 7 and 14 days after starting the experiment (data not shown). In contrast, corn oil intake increased plasma cholesterol, triglyceride and phospholipid concentrations compared with control group fed chow diet. Replacement of 50% of corn oil by fish oil reduced accumulation of triglyceride and cholesterol in plasma (Table 3). Neither triglyceride nor cholesterol content of the liver was affected by changes in the dietary fats.

(3) The effect of dietary fats on very low density lipoprotein (VLDL) and HDL (high density lipoprotein) content

Fig. 1 shows the effect of dietary fats on lipoprotein pattern in plasma in experiment 2. The hepatic release of VLDL was depressed in animals fed fish oil–supplemented diet compared with those fed corn oil. HDL fraction decreased by consumption of fish oil.

(4) Liver cholesterol, triglyceride and phospholipid

Table 4 showed the concentrations of total cholesterol, triglyceride and phospholipid in the liver of experiment 1. Neither the cholesterol, triglyceride nor phospholipid in livers
was affected by changes in the dietary fat composition.

(5) **Phospholipid composition of hepatic microsomal membranes**

Table 5 showed the phospholipid composition of liver microsomal membranes in experiment 1. Consumption of fish oil diet increased the proportion of phosphatidic acid (approximately 28% compared with the group fed corn oil). Consumption of fish oil decreased the proportion of phosphatidylcholine (28% compared with the group fed corn oil) at the expense of phosphatidylethanolamine in the membranes.

(6) **Fatty acid composition of hepatic phospholipid and triglyceride**

The fatty acid composition of hepatic phospholipid reflected the differences in dietary fatty acid composition (Table 6). Consumption of diet containing either fish oil or a mixture of fish and corn

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**Table 4** Effect of dietary fats on liver lipids in rats

<table>
<thead>
<tr>
<th>Groups**</th>
<th>Cholesterol (mg/g liver)</th>
<th>Triglyceride (mg/g liver)</th>
<th>Phospholipid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chow</td>
<td>2.11±0.19</td>
<td>8.52±0.78</td>
<td>27.74±0.79</td>
</tr>
<tr>
<td>Corn oil</td>
<td>2.14±0.14</td>
<td>9.39±0.82</td>
<td>20.53±0.96</td>
</tr>
<tr>
<td>Fish oil</td>
<td>1.95±0.06</td>
<td>9.66±1.49</td>
<td>22.68±1.41</td>
</tr>
<tr>
<td>Mixture</td>
<td>1.93±0.23</td>
<td>9.38±0.44</td>
<td>23.67±1.41</td>
</tr>
</tbody>
</table>

* Values are the mean ± SEM of 6 rats.
** Rats were fed commercial chow diet or semi-synthetic diets containing corn oil, fish oil or a mixture of corn oil and fish oil (1:1, w/w) as a sole of fat for 3 weeks.
*** A mixture of corn oil and fish oil (1:1, w/w)

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**Table 5** Effect of dietary fats on the phospholipid composition in liver microsomes

<table>
<thead>
<tr>
<th>phospholipid</th>
<th>Chow ( % of total phospholipids)</th>
<th>Corn oil ( % of total phospholipids)</th>
<th>Fish oil ( % of total phospholipids)</th>
<th>Mixture oil ( % of total phospholipids)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LYSO-PC</td>
<td>1.02±0.18a</td>
<td>1.96±0.16b</td>
<td>1.36±0.20a</td>
<td>1.54±0.13ab</td>
</tr>
<tr>
<td>SPM</td>
<td>3.67±0.14a</td>
<td>4.39±0.35b</td>
<td>4.08±0.20ab</td>
<td>3.63±0.16a</td>
</tr>
<tr>
<td>PC</td>
<td>60.63±0.70a</td>
<td>56.73±0.94b</td>
<td>47.11±0.78c</td>
<td>50.77±0.68d</td>
</tr>
<tr>
<td>PI+PS</td>
<td>9.96±0.21a</td>
<td>13.05±0.97b</td>
<td>16.02±1.14c</td>
<td>14.79±0.18bc</td>
</tr>
<tr>
<td>PE</td>
<td>19.30±0.37a</td>
<td>20.75±0.61ab</td>
<td>22.40±0.94b</td>
<td>21.59±0.37b</td>
</tr>
<tr>
<td>PA</td>
<td>5.33±0.94a</td>
<td>4.13±0.13a</td>
<td>9.03±0.40b</td>
<td>7.67±0.21b</td>
</tr>
<tr>
<td>PC/PE</td>
<td>3.15±0.06</td>
<td>2.70±0.15</td>
<td>2.12±0.09</td>
<td>2.36±0.07</td>
</tr>
</tbody>
</table>

Values are the mean ± SEM of 6 samples.
Sea also Table 2.
Valves not sharing the same surescript letter within the same row are significantly different at p<0.05 at least.
Table 6  Fatty acid composition of hepatic phospholipids
(Experiment 1)

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Corn oil (%)</th>
<th>Fish oil (%)</th>
<th>Mixture oil (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 : 0</td>
<td>0.37±0.06a</td>
<td>0.58±0.08b</td>
<td>0.31±0.05a</td>
</tr>
<tr>
<td>16 : 0</td>
<td>23.78±0.71a</td>
<td>25.24±1.51a</td>
<td>23.14±1.54a</td>
</tr>
<tr>
<td>16 : 1</td>
<td>1.83±0.83a</td>
<td>4.85±1.00b</td>
<td>2.05±0.39a</td>
</tr>
<tr>
<td>18 : 0</td>
<td>18.69±1.62a</td>
<td>17.28±1.30a</td>
<td>18.47±1.66a</td>
</tr>
<tr>
<td>18 : 1 n-9</td>
<td>9.86±6.01a</td>
<td>4.13±0.27a</td>
<td>5.04±0.55a</td>
</tr>
<tr>
<td>18 : 2 n-6</td>
<td>12.38±1.42a</td>
<td>1.44±0.12b</td>
<td>13.28±1.27a</td>
</tr>
<tr>
<td>20 : 4 n-6</td>
<td>24.46±1.06a</td>
<td>11.16±0.47b</td>
<td>13.97±0.95c</td>
</tr>
<tr>
<td>20 : 5 n-3</td>
<td>—</td>
<td>9.37±0.37b</td>
<td>4.77±0.39c</td>
</tr>
<tr>
<td>22 : 5 n-3</td>
<td>—</td>
<td>3.03±0.34b</td>
<td>1.52±0.18c</td>
</tr>
<tr>
<td>22 : 6 n-3</td>
<td>3.68±0.58a</td>
<td>11.12±1.41b</td>
<td>8.73±1.34b</td>
</tr>
<tr>
<td>Unknown</td>
<td>5.06±0.78a</td>
<td>6.28±0.78a</td>
<td>5.71±1.42a</td>
</tr>
</tbody>
</table>

Values are the mean ± SEM of 6 animals.
Values not sharing superscript letter within the same row are significantly different at p<0.05 at least.
See Tables 2 and 4.

Oils decreased the proportion of 20:4 n-6, whereas increased in the proportion of 20:5 n-3 and 22:6 n-3 in rat liver phospholipids. The 18:2 n-6 content of hepatic triglyceride was significantly decreased by feeding of fish oil and the mixture diets (Table 7).

**DISCUSSION**

The present study confirm that dietary vegetable oil rich in 18:2 n-6 and fish oil rich in n-3 PUFA had different effect on lipid metabolism in rats. A slight decrease in the body weight after fish oil consumption was found although the amount of food consumed was not statistically different among the groups. Liver weight remained unchanged by the dietary fat treatment (Table 2). Therefore, the changes observed in lipid concentration in plasma and livers, and phospholipid composition of hepatic microsomal membranes are apparently as a result of dietary treatment and do not stem from the differences in growth rate.

The reduction in plasma triglyceride and cholesterol content following consumption of fish oil diet was observed in the present experiment (Table 3), in agreement with previous reports (1-6). In contrast, consumption of corn oil diet increased plasma lipid content compared to chow diet. However, the replacement of 50% of corn oil with fish oil produced a decrease in plasma lipids with similar magnitude to that observed in animals fed fish oil. In subsequent experiment, we found that the decrease in plasma triglyceride was attributed to a decrease in VLDL-triglyceride (Fig. 1). In spite of the remarkable change of plasma lipids, liver triglyceride content remained unaltered by the composition of the fat fed. On the other hand, cholesterol content in the liver decreased slightly by fish oil consumption.

The hypotriglyceridemic effect of n-3 fatty acids are proposed to mediate by several different mechanisms: a decrease in lipogenesis and an increase in fatty acid oxidation. We have recently found that in human liver-derived HepG2 cells, an addition of EPA to the
media decreased the synthesis of cellular triglyceride and the secretion of triglyceride from
cells to the media compared with oleic acid and linoleic acid\textsuperscript{32}. Furthermore, perfusion of
rat livers with EPA and DHA resulted in a decrease of phosphatidate phosphohydrolase
activity, considered to be the regulatory enzyme in triglyceride synthesis in the liver\textsuperscript{33-35}).
The activity of phosphatidate phosphohydrolase was significantly decreased in the liver of
rats consuming diet supplemented with 8% fish oil compared to unsupplemented diet\textsuperscript{15}).
More recently, Surette et al.\textsuperscript{11}) reported that a gradual decrease in hepatic phosphatidate
phosphohydrolase activity with n-3 fatty acids consumption was observed, and the diet
induced changes in plasma TG levels were also highly correlated with changes in hepatic
carnitine-palmitoyl transferase activity in humsters.

Consumption of dietary lipids altered the phospholipid composition in liver microsomal
membranes (Table 6). Feeding of fish oil increased the proportion of phosphatidic acid.
Phosphatidic acid is converted to diglyceride by phosphatidate phosphohydrolase, consid-
ered to be the regulatory enzyme in triglyceride synthesis. Therefore, our data is in good
agreement with the previous reports\textsuperscript{11, 13}) that n-3 PUFA inhibits the phosphatidate
phosphohydrolase activity. We also found the decrease in the ratio of phosphatidylycholine/
phosphatidylethanolamine in microsomal membranes (Table 6). Altered ratios of these
two major phospholipids were apparently the consequence of the activity of the CDP-
choline pathway and phosphatidylethanolamine methyltransferase pathway for the syn-
thesis of phosphatidylycholine\textsuperscript{36, 37}). Thus the balance of dietary fatty acids influencing
ratios of n-6 and n-3 fatty acids in membrane phospholipids appears to be an important
determinant of phosphatidylycholine synthesis. The assumption is supported by our previ-
ous report\textsuperscript{21}) that fish oil consumption depresses the CDP-choline: phosphocholine
cytidyltransferase activity in the liver. Thus, a reduced capability for phosphatidyly-
choline synthesis appears to contribute to the hypotriglyceridemic effect of n-3 fatty acid
consumption, because an active synthesis of phosphatidylycholine is required for the VLDL
assembly and secretion from the liver\textsuperscript{20}).

---

**Table 7** Fatty acid composition of hepatic triglyceride
(Experiment 1)

<table>
<thead>
<tr>
<th>Fatty acid Diet</th>
<th>Corn oil (%) of fatty acids</th>
<th>Fish oil (%) of fatty acids</th>
<th>Mixture oil (%) of fatty acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:0</td>
<td>2.13±0.24a</td>
<td>3.94±0.99a</td>
<td>2.45±0.52a</td>
</tr>
<tr>
<td>16:0</td>
<td>33.76±2.04a</td>
<td>27.83±2.01b</td>
<td>36.13±1.05a</td>
</tr>
<tr>
<td>16:1</td>
<td>8.45±0.90a</td>
<td>10.48±0.98a</td>
<td>8.13±1.05a</td>
</tr>
<tr>
<td>18:0</td>
<td>1.76±0.16a</td>
<td>2.41±0.25a</td>
<td>2.14±0.20a</td>
</tr>
<tr>
<td>18:1 n-9</td>
<td>30.74±1.43a</td>
<td>19.07±1.00b</td>
<td>28.41±1.89a</td>
</tr>
<tr>
<td>18:2 n-6</td>
<td>15.69±1.87a</td>
<td>1.87±0.33b</td>
<td>11.45±1.25c</td>
</tr>
<tr>
<td>20:4 n-6</td>
<td>1.05±0.35a</td>
<td>-</td>
<td>0.25±0.10</td>
</tr>
<tr>
<td>20:5 n-3</td>
<td>-</td>
<td>7.21±1.28b</td>
<td>1.41±0.30c</td>
</tr>
<tr>
<td>22:6 n-3</td>
<td>-</td>
<td>5.18±1.40b</td>
<td>0.99±0.10c</td>
</tr>
</tbody>
</table>

Values are the mean ± SEM of 6 animals.

Values not sharing superscript letter within the same row are significantly different at p<0.05 at least.

See also Table 2.
Fish oil consumption decreases in 20:4 n-6 and increases in EPA and DHA in hepatic phospholipids (Table 6), in agreement with previous report\textsuperscript{38}. As EPA present in fish oil has greater affinity than 20:4 n-6 for the glycerol-3-phosphate acyltransferase responsible for the synthesis of phospholipids\textsuperscript{39, 40}, EPA may replace some of 20:4 n-6 in the liver phospholipids\textsuperscript{41}. The increase in EPA subsequently competes with 20:4 n-6 at the level of cyclooxygenase\textsuperscript{42} in the formation of eicosanoids such as prostacyclin, prostaglandins, thromboxane and leukotrienes\textsuperscript{1-3}. In deed, it is well known that fish oil reduces synthesis of 20:4 n-6 by inhibiting the 6 desaturase enzyme\textsuperscript{43}, a rate-limiting enzyme in 20:4 n-6 biosynthetic pathway\textsuperscript{44}. In addition, consumption of fish oil lowers serum levels of thromboxane A\textsubscript{2} and thus has anti-aggregatory effect on the manifestation of thrombosis\textsuperscript{7-9}. While the exact mechanisms for the fish oil induced to decrease in plasma lipid levels are not clear, the platelet anti-aggregatory effects is most likely mediated via changes in the balance of eicosanoids formed from their common precursor, arachidonic acid (20:4 n-6)\textsuperscript{40}.

The most obvious observation in this study is that the replacement of 50% corn oil to fish oil lowers the plasma lipids to the same level as to fish oil, even though hepatic DHA content was not enough higher than that of fish oil diet. Therefore, the beneficial role of fish oil may be caused by keeping a moderate level of 20:4 n-6 and increasing amount of EPA in tissue lipids to ensure a proper balance of the different eicosanoids. If a higher level of DHA is important or not is presently not known, but it had been observed that hydroxylated products from this fatty acid are potent regulators of arachidonate metabolism\textsuperscript{46}.

We have found that n-3 fatty acids in fish oil decrease the concentration of plasma cholesterol in rats. However, the effect of fish oil on plasma cholesterol content in humans is still controversial. It is also suggested that hepatic cholesterol metabolism in rats is unlikely that in humans\textsuperscript{47}. Even though current evidence suggest that the n-3 fatty acids are the active agent in fish oil capable of influencing human lipid metabolism, the specific effect of fish oil supplementation on hepatic cholesterol metabolism remains elusive\textsuperscript{9}. In this context, we have recently found that 20:5 n-3 inhibits cellular cholesterol synthesis in Hep G\textsubscript{2} cells, but, we did not find any inhibitory effect of EPA on the secretion of cholesterol (both esterified- and free- forms) to the media.

The present study confirms that n-3 PUFA in fish oil has hypolipidemic effect in rats and supports the hypothesis that the decrease in the circulating lipoproteins following consumption of fish oil in rats may link to not only the depressed synthesis of triglyceride but also the change in the lipoprotein clearance from circulating plasma via lipoprotein receptors.

References

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食餌性魚油および植物油脂質代謝に及ぼす影響

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要　約
本研究は食餌中の植物油（リノール酸n-6）、魚油（エイコサペンタエン酸n-3）およびそれらの混合油が雄性Wistar系ラットの肝臓脂質濃度と血漿リポタンパク質像に及ぼす影響について検討した。肝臓ミクロソーム膜に及ぼす影響についても検討した。

標準chow食を摂取した対照群に比べて、魚油の摂取は血漿トリグリセリドとコレステロール濃度を低下させ、一方、コーン油食は血漿脂質濃度を増加させた。コーン油の50％を魚油で置き換えた食餌では血漿脂質の増加は顕著に抑制された。魚油による血漿トリグリセリドの減少は極低密度リポタンパク質（VLDL）の低下に起因することが認められた。食餌油脂のタイプは肝臓中のトリグリセリドとコレステロール濃度に影響しなかった。魚油はホスファチジルコレリンの合成の抑制あるいはホスファチジルエタノールアミンのN-メチル化の抑制により、肝臓ミクロソーム膜ホスファチジルコレリンの割合を低下させた。魚油食はホスファチジン酸の割合も増加させることから、魚油食によるホスファチジン酸異化代謝の阻害が示唆された。本研究とこれまでの研究から、魚油による脂質低下作用は脂質合成の低下、脂肪酸酸化の亢進および血漿VLDLの分泌抑制に起因すると考えられる。