Peroxisome Proliferator-activated Receptor α Is Not Rate-limiting for the Lipoprotein-lowering Action of Fish Oil*

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Similar to fibrate hypolipidemic drugs, long chain polyunsaturated fatty acids contained in fish oil are activators of peroxisome proliferator-activated receptor α (PPARα). The goal of this study was to assess the contribution of PPARα in mediating the effect of fish oil on plasma lipid, lipoprotein, and apolipoprotein levels. To this end, PPARα-deficient mice and wild-type littermates were fed isocaloric fish oil or coconut oil diets, the content of which varied reciprocally between 0, 3, 7, and 10% for 1 week. In both wild-type and PPARα-deficient mice, fish oil feeding was associated with a dose-dependent decrease in triglycerides, cholesterol, and phospholipids associated with lower levels of very low density lipoprotein (VLDL) triglycerides and high density lipoprotein (HDL) cholesterol. The lowering of triglycerides and VLDL triglycerides was associated with a significant decrease of plasma apoC-III in both genotypes. Fish oil treatment did not influence hepatic apoC-III mRNA levels in either genotype indicating that apoC-III is not under transcriptional control by fish oil. The lowering of HDL cholesterol observed in both genotypes was associated with reduced plasma apoA-II without changes in liver apoA-II mRNA levels. In contrast, plasma apoA-I and liver apoA-I mRNA levels were decreased in wild-type but not in PPARα-deficient mice after fish oil feeding indicating that PPARα contributes to the effect of fish oil on apoA-I gene expression. In conclusion, PPARα is not rate-limiting for fish oil to exert its triglyceride- and HDL-lowering action. Furthermore, PPARα mediates, at least partly, the decrease of apoA-I after fish oil treatment, whereas apoC-III and apoA-II levels are affected in a PPARα-independent manner. Altogether, these results show major molecular differences in action between fibrates and fish oil providing a molecular rationale for combination treatment with these compounds.

Fish oil treatment efficiently lowers lipids in patients with hypertriglyceridemia (1, 2). In addition to its effect on triglyceride-rich lipoproteins, fish oil decreases HDL1 levels in rodents and to a lesser extent in humans (2, 3). Fish oil acts by modulating the activity of several enzymes of lipid and carbohydrate metabolism, such as diacylglycerol acyltransferase, fatty-acid synthase, carnitine palmitoyltransferase, glucose-6-phosphate dehydrogenase, glucose-6-phosphatase, acetyl-CoA carboxylase and Δ⁹-desaturase (4). Fish oil and its major long chain fatty acids, eicosapentaenoic (EPA) and docosahexaenoic (DHA) acid, appear to affect most hepatic enzyme activities by regulating the expression of their genes (4). The resultant effect is a decrease in triglyceride synthesis (5) and an increase in fatty acid mitochondrial β-oxidation (6–8). This, in turn, results in decreased formation and production of VLDL (9).

High fat diets also increase peroxisome proliferation in liver, kidney, and heart of rodents (10). Coincident with an increase in the number of peroxisomes, peroxisomal enzymes are induced by transcriptional activation. Several of these enzymes are controlled by the peroxisome proliferator-activated receptor α (PPARα) (11–13). PPARα belongs to the superfamily of nuclear receptors that function as ligand-activated transcription factors. In addition to PPARα, the PPAR family comprises PPARγ and PPARδ. PPARs heterodimerize with the retinoid X receptor and alter transcription of target genes after binding to peroxisome proliferator response elements. In vitro PPAR is activated by fatty acids that bind to a ligand binding domain in its C-terminal region (14–20). In addition, compounds such as fibrates, certain prostaglandins and leukotrienes, and oxidized fatty acid derivatives also bind to and activate PPARs. These observations suggest that fish oil may exert its metabolic and lipid-lowering properties by activating PPARs. In agreement with this hypothesis, studies in PPARα-deficient mice have demonstrated that PPARα is necessary for fish oil to activate gene expression of enzymes of fatty acid oxidation such as acyl-CoA oxidase and cytochrome P450–4A2 but is not necessary to inhibit gene expression of fatty-acid synthase and S14 protein (21, 22).

To date, the exact contribution of the PPARα pathway to the lipid- and lipoprotein-lowering properties of fish oil has not been defined. Moreover, its contribution to the changes in circulating apolipoprotein levels after fish oil treatment has not been described. Therefore, the goal of the present study was to assess the role of the PPARα pathway in mediating the fish oil-dependent lipid, lipoprotein and apolipoprotein alterations. To this end, the effects of increasing consumption of fish oil on lipid and apolipoprotein levels were assessed in wild-type and very low density lipoprotein; PPARα, peroxisome proliferator-activated receptor α, EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; FPLC, fast protein liquid chromatography; PIPES, 1,4-piperazinediethanesulfonic acid.

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‡ The abbreviations used are: HDL, high density lipoprotein; VLDL,
**PPARα-deficient mice.** The results of the present study indicate that PPARα has a minor role in the fish oil-induced lowering of triglyceride and HDL cholesterol levels in mice. In this respect, fish oil acts differently than synthetic PPARα activators such as fibrates.

**MATERIALS AND METHODS**

**Animals—**The studies were performed with wild-type and PPARα-deficient mice (23) in the SV129 genetic background. Before dietary experiments all animals were acclimatized for more than 2 weeks under conditions of controlled temperature (20 ± 1 °C) and lighting (dark from 8 p.m. to 8 a.m.) in a room of low background noise. The average age of the mice was 8 weeks.

**Experiments—**For all experiments, male wild-type and PPARα-deficient mice were used. Before each dietary experiment a blood sample was drawn for randomization on triglyceride levels. Animals were housed in cages (2–3 per cage) and given free access to a fat-free semi-purified diet (UAR, Villemonais sur Orge, France) supplemented with coconut oil, fish oil, or fenofibrate (Sigma). Fish oil and coconut oil were obtained from menhaden and copra, respectively, and were purchased from Sigma. Fish oil contained 30% of n-3 fatty acid, and the EPA to DHA ratio was 1.2. Duration of experimental dietary exposure was 1 week in all experiments. For experiment 1, three groups of 6 SV129 mice were supplemented with an isocaloric diet containing either 10% (w/w) coconut oil alone, 10% (w/w) coconut plus 0.2% (w/w) fenofibrate, or 10% (w/w) fish oil alone. For experiment 2, wild-type or PPARα-deficient mice were fed an isocaloric diet supplemented with either 10% (w/w) coconut oil alone, 7% coconut oil plus 3% fish oil, 3% coconut oil plus 7% fish oil, or 10% fish oil alone. The other major nutrient components were carbohydrate (50.4 g/100 g), casein (18 g/100 g), cellulose (4.9 g/100 g), salt mixture (5.6 g/100 g), and vitamins (0.8 g/100 g). At the end of each dietary experiment, mice were food-deprived for 4 h and were exsanguinated under diethyl ether anesthesia by cardiac puncture. Blood samples were collected on EDTA tubes.

**Lipoprotein Separation and Measurements—**Plasma was separated by centrifugation (630 x g) for 20 min at 4 °C. Lipids were determined enzymatically using commercially available kits for triglycerides (Triglycerides GPO-PAP or Cholesterol PAP 150, BioMérieux, Lyon, France). Phospholipids (g/liter) 3.04 Triglycerides (g/liter) 0.61 Cholesterol (g/liter) 1.62

**RESULTS**

**Effect of Fenofibrate and Fish Oil on Lipid Levels in SV129 Mice Strain—**To test whether mice of the SV129 strain respond to PPARα activators, we tested the effect of fenofibrate (0.2% w/w) and fish oil (10% w/w) on lipid metabolism in this mouse strain. Plasma triglycerides, cholesterol, and phospholipids were lower in SV129 mice supplemented with fish oil than in those on the coconut oil diet (Table I). These effects were accounted for by lower levels of both the large triglyceride-rich and the small cholesterol-rich lipoprotein fraction as assessed by gel filtration chromatography (data not shown). In contrast, fenofibrate decreased triglyceride levels but not cholesterol and phospholipid concentrations in the SV129 mice.

**Effect of Fenofibrate and Fish Oil on Liver Acyl-CoA Oxidase, ApoA-I, ApoA-II, and ApoC-III mRNA Levels in SV129 Mice Strain—**To test whether mice of the SV129 strain respond to PPARα activators by peroxisomal proliferation and apolipoprotein gene expression changes, the effect of fenofibrate (0.2% w/w) and fish oil (10% w/w) on liver acyl-CoA oxidase, apoC-III, apoA-I, and apoA-II mRNA levels were analyzed (Fig. 1). Liver acyl-CoA oxidase mRNA levels were higher in SV129 mice treated with fenofibrate (approximately ×10) than in those supplemented with coconut oil. In contrast, liver acyl-CoA oxidase mRNA levels was mildly induced (approximately ×1.4) by fish oil feeding. Liver apoC-III and apoA-I mRNA levels were lower in the fenofibrate group than in the coconut oil group, whereas apoA-I, but not apoC-III, was decreased by fish oil feeding in this mice strain. Finally, liver apoC-II mRNA levels were markedly increased by fenofibrate feeding but not affected by fish oil treatment.

**Dose-dependent Effects of Fish Oil on Lipid and Lipoprotein Levels in Wild-type and PPARα-deficient Mice—**To assess whether PPARα mediates the effect of fish oil on plasma lipids, a dose-response study was performed in wild-type and PPARα-deficient mice (Table II). Plasma cholesterol, triglycerides, and phospholipids were lower in both wild-type and PPARα-deficient mice fed fish oil than in those fed coconut oil (Table II). The lowering effect of fish oil on cholesterol, triglyceride, and primed labeling (Roche Molecular Biochemicals). Filters were hybridized to 1 × 106 cpmm-1 of each probe as described (28). They were washed in 300 ml of 75 m M NaCl, 7.5 m M sodium citrate, pH 7.4, and 0.1% SDS for 10 min at room temperature and twice for 30 min at 65 °C and subsequently exposed to x-ray film (Kodak X-Omat-AT, Eastman Kodak Co.). Autoradiograms were obtained by quantitative scanning densitometry (Bio-Rad GS870 Densitometer, Bio-Rad) in the linear range of film sensitivity. Curves were plotted on a log/log scale relating the density measurements to the amounts of mRNA in the corresponding dots. The relative amounts of mRNAs were calculated using the parallel, linear parts of these curves as described elsewhere (28, 29).

![Table I](https://www.sciencedirect.com/science/article/pii/S003961098890895X)

| SV129 wild-type mice | Coconut oil | Cholesterol (g/liter) | Triglycerides (g/liter) | Phospholipids (g/liter) |
|----------------------|-------------|-----------------------|------------------------|-------------------------|
| Fish oil             |-------------|                       |                        |                         |
| Cholesterol (g/liter)| 1.62 ± 0.1  | 1.82 ± 0.16           | 0.61 ± 0.08            |                         |
| Phospholipids (g/liter)| 0.30 ± 0.12 | 0.30 ± 0.24           | 0.34 ± 0.05*           |                         |

* Student’s t test was used for mean comparisons with coconut oil, the p value is p < 0.001.

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The effect of fish oil on acyl-CoA oxidase and CYP450 mRNA levels—To assess whether fish oil and PPARα deficiency affect peroxisomal proliferation, liver acyl-CoA oxidase and CYP450 mRNA levels were measured (Fig. 3). Liver acyl-CoA oxidase mRNA levels were induced by ~1.4-fold and in liver CYP450 mRNA levels by 3-fold in wild-type but not in PPARα-deficient mice.

Effect of Fish Oil on Plasma ApoC-III and Liver ApoC-III mRNA Levels—The effect of fish oil on circulating apolipoprotein C-III levels in wild-type and PPARα-deficient mice was assessed (Fig. 4). Plasma apoC-III levels were lower in both PPARα-deficient and in wild-type mice fed fish oil than in those fed with coconut oil. There was no evidence for a statistically significant effect of fish oil on liver apoC-III mRNA levels in either genotype.

Effect of Fish Oil on Plasma and Liver mRNA Levels of Apolipoprotein A-I and A-II—Next, we examined the effect of fish oil on the major HDL apolipoproteins (Fig. 5). Fish oil supplementation was associated with a decrease in plasma apoA-I levels in both mice strains. This decrease was less pronounced in the PPARα-deficient mice. Similarly, liver apoA-I mRNA levels were lower after fish oil feeding in wild-type but not in PPARα-deficient mice suggesting that PPARα contributes to the fish oil-mediated lowering of plasma apoA-I and liver apoA-I mRNA levels. Plasma apoA-II levels were lower in both PPARα-deficient and in wild-type mice fed with fish oil than in those fed with coconut oil (Fig. 6). However, fish oil had mild liver apoA-II mRNA levels raising effect in both wild-type and PPARα-deficient mice.

**DISCUSSION**

The results of the present study show that fish oil has similar effects on cholesterol, triglyceride, and HDL cholesterol levels in wild-type and PPARα-deficient mice suggesting that PPARα is not rate-limiting for fish oil to lower plasma lipid and lipoprotein levels. This finding is different to what is observed with fibrates (32) and suggests that fibrates and fish oil affect lipoprotein metabolism through different mechanisms of action. The lowering of plasma triglyceride was associated with decreased levels of apoC-III in both wild-type and PPARα-deficient mice suggesting a contribution of PPARα. These results indicate that, in contrast to fibrates, fish oil has different molecular mechanisms of action on triglyceride and HDL metabolism.

In contrast to fibrates, fish oil decreased triglyceride levels to a similar extent in wild-type and PPARα-deficient mice suggesting that fish oil exerts its triglyceride-lowering properties through mechanisms that are independent of PPARα. There are a number of possible hypotheses to explain these differences between fish oil and fibrates. First, although long chain fatty acids, including EPA and DHA, bind and activate PPARα, the affinity and the ability of these fatty acids to activate PPARα is much smaller than that of pharmacological activators such as fibrates (15–20). For example the effect of fish oil on acyl-CoA oxidase expression is much lower than that of fibrates suggesting that the contribution of fatty acid oxidation to the triglyceride-lowering activity of fish oil treatment is minor in mice. In fact, fish oil fatty acids might not be potent enough to activate PPARα to a level where it exerts a significant metabolic effect in vivo. However, in our experiments fish oil treatment regulated apoA-I, acyl-CoA oxidase, and CYP450 gene expression in a PPARα-dependent manner indicating that this hypothesis is unlikely to be true. Second, fish oil may regulate the same genes controlling triglyceride metabolism as...
For example, the activity of a number of lipogenic enzymes such as the S14 protein and fatty-acid synthase which are conspicuously decreased by fish oil treatment (33, 34) are under the control of the SREBP1 transcription factor (35, 36). Recent studies have shown that SREBP1 expression is decreased by long chain polyunsaturated fatty acids (36–39). Third, in contrast to fibrates EPA and DHA activate PPARγ, which induces lipoprotein lipase in a tissue-specific manner in adipose tissue, it is likely that a part of the triglyceride-lowering activity of fish oil treatment occurs through activation of this nuclear receptor in adipose tissue. Finally, PPARα agonists and fish oil may affect different subsets of genes, by currently unknown mechanisms, that are important for triglyceride metabolism.

ApoC-III plays a crucial role in triglyceride metabolism. Earlier studies have demonstrated that apoC-III inhibits VLDL lipolysis and uptake by cellular receptors (40–42) and that overexpression of apoC-III in mice is associated with elevated levels of triglycerides due to a defective clearance of VLDL (43). Fibrate treatment has been shown to decrease hepatic apoC-III mRNA and plasma apoC-III levels, an effect contributing to the triglyceride-lowering activity of these drugs. Interestingly, although plasma apoC-III concentrations are also reduced by ~80% by fish oil, this diet did not decrease hepatic apoC-III mRNA levels, an observation that is in sharp contrast to fibrates (32). These observations further point out a difference between fibrates and fish oil. Thus, the major reduction of plasma apoC-III levels (~80%) as compared with the lack of effect of fish oil on liver apoC-III mRNA suggests that nontranscriptional mechanisms contribute to the lowering of plasma apoC-III after fish oil treatment.

Previous studies have shown that replacing saturated by polyunsaturated fatty acids results in the lowering of HDL cholesterol in rodents as well as in humans (44–46). The mechanism of this effect is not clear since either decreased production rates or increased catabolic rates of apoA-I were described depending on the experimental models, the type of diets, and the metabolic parameters that were measured (47–50). Moreover, hepatic apoA-I mRNA levels were either lowered or not
affected by the substitution of saturated by polyunsaturated fatty acids in the diet (44, 48–53). In this study, fish oil supplementation resulted in lower levels of HDL cholesterol and HDL phospholipids in both genotypes, indicating a PPARα-independent lowering action of fish oil on HDL lipids. In contrast with this finding, plasma apoA-I and liver apoA-I mRNA levels were decreased in wild-type mice, but not in the PPARα-deficient mice, after fish oil feeding. These observations indicate that PPARα contributes to the effect of fish oil on apoA-I expression. Previous studies in our laboratory have shown that fibrates decrease apoA-I mRNA levels by a (post) translational repression of its transcriptionally induced by activation of PPARα in mice and humans (25, 32, 57). However, in contrast to fibrate treatment, apoA-II levels were lowered by fish oil feeding as well in wild-type and PPARα-deficient mice. Furthermore and in contrast to apoA-I, liver apoA-II mRNA levels were not affected by fish oil treatment. The observed changes in plasma apoA-II concentrations might be due to a (post) translational repression of its production or secondary to intravascular metabolic changes. Although further studies are required to elucidate the molecular mechanisms involved therein, our results clearly demonstrate a distinct regulation of apoA-II by fibrates and fish oil.

In conclusion, the results of the present study indicate that fish oil decreases triglyceride and HDL levels to a similar extent in wild-type and PPARα-deficient mice suggesting that PPARα is not rate-limiting for fish oil to exert its lipid- and lipoprotein-lowering action. The decrease in triglyceride levels was associated with a decrease in plasma apoA-I, apoA-II, and liver apoA-I mRNA. The effect on plasma apoA-I and liver apoA-I mRNA levels was abolished by PPARα deficiency indicating a contribution of PPARα to this effect. Altogether, these data suggest that although fibrates and fish oil have a very similar lipid- and apolipoprotein-lowering profile, they exert their lipid-lowering action through different molecular mechanisms of action.

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