Fenofibrate Prevents Obesity and Hypertriglyceridemia in Low-Density Lipoprotein Receptor-Null Mice

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Our previous study demonstrated that fenofibrate improves both lipid metabolism and obesity, in part through hepatic peroxisome proliferator-activated receptor α (PPARα) activation, in female ovariectomized, but not in sham-operated, low-density lipoprotein receptor-null (LDLR-null) mice. The aim of this study was to determine whether fenofibrate prevents obesity and hypertriglyceridemia in male LDLR-null mice. Mice fed a high-fat diet for 8 weeks exhibited increases in body and white adipose tissue (WAT) weights and developed severe hypertriglyceridemia compared with mice fed a low-fat control diet. However, these effects were effectively prevented by fenofibrate. Mice given a fenofibrate-supplemented high-fat diet showed significantly reduced body weight, WAT weight, and serum triglycerides versus high-fat diet-fed animals. Triton WR1339 study showed that fenofibrate-induced reduction in circulating triglycerides was due to the decreased secretion of triglycerides from the liver. Moreover, the administration of fenofibrate not only resulted in liver hypertrophy and reduction in hepatic lipid accumulation, but also regulated the transcriptional expression of PPARα target genes, such as hepatic acyl-coenzyme A (CoA) oxidase and apolipoprotein C-III (apoC-III). Therefore, our results suggest that alterations in hepatic PPARα action by fenofibrate seem to suppress diet-induced obesity and severe hypertriglyceridemia caused by LDLR deficiency in male mice.

FIBRATES ARE A class of hypolipidemic drugs used to treat dyslipidemic patients. At the molecular level, fibrates act as peroxisome proliferator-activated receptor α (PPARα) ligands that regulate the expression of a number of genes critical for lipid and lipoprotein metabolism.[1-3] Fibrate-bound PPARα heterodimerizes with retinoid X receptor and then modulates the expression of target genes with a PPAR response element (PPRE) in their promoter regions.[4] The known targets of PPARα include acyl-coenzyme A (CoA) oxidase (ACOX), enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase (HD), and thiolase used for peroxisomal fatty acid β-oxidation,[5-7] carnitine palmitoyltransferase I used for mitochondrial fatty acid β-oxidation,[8] and apolipoprotein C-III (apoC-III) and lipoprotein lipase used for the hydrolysis of plasma triglycerides.[9]

Fibrates seem to regulate energy homeostasis. Excess energy intake increases the concentrations of plasma triglycerides and cholesterol, and lipids accumulated in the adipose tissue are believed largely to derive from circulating triglycerides.[10-12] Thus, increased hepatic fatty acid oxidation and decreased hepatic triglycerides by fenofibrate may inhibit an increase in body weight, indicating that PPARα may be involved in the regulation of obesity. This is supported by a report that PPARα-deficient mice have abnormal triglyceride and cholesterol metabolism and become obese with age.[11] Other studies have produced evidence that fenofibrate can modulate the body weight of animal models, such as fatty Zucker rats, high–fat-fed C57BL/6 mice, and high–fat-fed obese rats, although the reported effects of fibrates are contradictory.[12-15]

Mice with targeted disruption of the low-density lipoprotein receptor gene (LDLR-null mice), an animal model of homozygous familial hypercholesterolemia, develop severe hypercholesterolemia and massive atherosclerosis when fed a high-cholesterol diet.[16,17] Moreover, it has recently been shown that LDLR-null mice fed a high-fat, high-carbohydrate diet become obese and exhibit severe hypertriglyceridemia.[18] Our previous work suggests that fenofibrate inhibits high-fat diet-induced body weight gain and adiposity in female ovariectomized (OVX) LDLR-null mice. Interestingly, these effects were not observed in female sham-operated (Sham) LDLR-null mice.[19]

Therefore, the objective of the present study was to determine whether fenofibrate treatment prevents obesity and hypertriglyceridemia in male LDLR-null mice. Our data demonstrate that increased hepatic PPARα activity by fenofibrate decreases high-fat diet-induced obesity and hypertriglyceridemia in male LDLR-null mice and suggest that fenofibrate regulates obesity by LDLR deficiency in a sexually dimorphic manner.

MATERIALS AND METHODS

Animal Treatments

All experiments were performed on male homozygous LDLR-null (B6,129-LDLR^{tm1Her}-/-) mice, 8-weeks-old at the start of the experiments, which were purchased from the Jackson Laboratory (Bar Harbor, ME) and bred at the Korea Research Institute of Bioscience and Biotechnology under specific pathogen-free conditions. Mice were randomly assigned to 3 different diets, a low-fat diet (4.5% fat, wt/wt, CJ Corp, Inchon, Korea), a high-fat diet containing 15% fat (wt/wt,

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Oriental Yeast, Tokyo, Japan), or the same high-fat diet supplemented with fenofibrate (0.05%, wt/wt) for 8 weeks.

Body weight and food intake of the animals were monitored at regular intervals throughout the treatment period. At the end of study period, food was removed and blood samples were collected 4 hours later. Animals were killed by cervical dislocation, liver and white adipose tissue (WAT) were harvested, weighed, snap frozen in liquid nitrogen, and stored at −80°C until use.

In Vivo Triglyceride Secretion Studies

For the determination of triglyceride secretion rates, 4-hour fasted mice were injected intravenously with Triton WR1339 (500 mg/kg body weight) in normal saline (0.9% NaCl). Blood samples were collected at base line (preinjection) and at 60 minutes and 120 minutes after injection for the determination of triglyceride levels. Because Triton coats lipoprotein particles and prevents their lipolysis,[20] the rate of increase of circulating triglycerides indicates the secretion rate of triglycerides from the liver.[21] Serum was isolated and stored at −20°C until required for further analysis.

Serum Assays

Serum triglyceride and total cholesterol concentrations were measured using an automatic blood chemical analyzer (Hitachi Ltd, Tokyo, Japan).

Analysis of Target Gene Expression

Total RNA was prepared using Trizol reagent (Gibco-BRL, Grand Island, NY) and analyzed by electrophoresis on 0.22 mol/L formaldehyde-containing 1.2% agarose gels. The separated RNA was then transferred to Nytran membranes (Schneicher & Schuell, Dassel, Germany) by downward capillary transfer in the presence of 20 × SSC buffer (3 mol/L NaCl, 0.3 mol/L sodium citrate, pH 7.0), ultraviolet (UV)-crosslinked, and baked for 2 hours at 80°C. Probe hybridization and washing were performed using standard techniques. Blots were exposed to PhosphorImager screen cassettes and visualized using a Molecular Dynamics Storm 860 PhosphorImager system (Sunnyvale, CA). The probes used in this study were ^{32}P-labeled by the random-primer method using a Ready-to-Go DNA Labeling kit (Amersham-Pharmacia Biotech, Piscataway, NJ) as previously described.[22] Densitometric analysis of the mRNA signals was performed using ImageQuant image analysis software (Molecular Dynamics).

Histologic Analysis

Liver tissues were fixed in 10% phosphate-buffered formalin for 1 day and processed in a routine manner for paraffin section. Sections (5 μm) were stained with hematoxylin and eosin for microscopic examination.

Statistics

Unless otherwise noted, all values are expressed as mean ± SD. All data were analyzed by analysis of variance (ANOVA) for statistically significant differences between groups.

RESULTS

Fenofibrate Reduces Body and WAT Weights in High-Fat Diet–Fed Male LDLR-Null Mice

LDLR-null mice were fed the chow, high fat, or high-fat diet supplemented with fenofibrate for 8 weeks. Mice fed a chow diet had a final body weight of 28.05 ± 0.5 g. After 8 weeks of high-fat diet, the body weight was 30.24 ± 0.6 g (7.8% higher than that of the chow-fed control mice, $P < .05$). By contrast, the body weight of mice fed a fenofibrate-enriched high-fat diet was 28.3 ± 0.8 g (6.4% lower than that of the high-fat diet-fed mice, $P < .05$) (Fig 1A). Thus, fenofibrate treatment significantly reduced body weight gain in LDLR-null mice.

As shown in Fig 1B, the WAT weight was 2.50 ± 0.36 g for chow-fed mice. However, mice fed a high-fat diet had a WAT weight of 4.12 ± 0.40 g and a WAT weight increase of 65% versus the mice fed a low-fat diet ($P < .01$). In response to

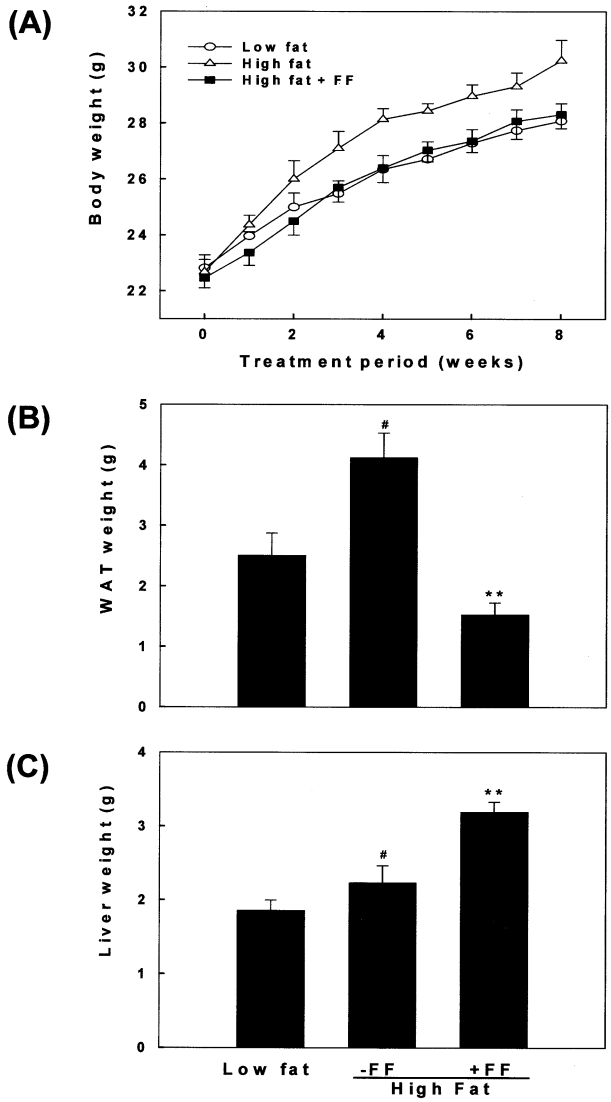

Fig 1. Modulation of (A) body, (B) epididymal WAT, and (C) liver weights by fenofibrate in male LDLR-null mice. Adult male LDLR-null mice received a low fat, a high fat, or the same high-fat diet supplemented with fenofibrate (FF, 0.05% wt/wt) for 8 weeks. All values are expressed as mean ± SD for n = 8 mice. Body weights at the end of the treatment period were significantly different in the high-fat and low-fat groups ($P < .05$) and in the high-fat and high-fat plus FF groups ($P < .05$) groups. #Significantly different *v* the low-fat group, $P < .01$. *Significantly different *v* the high-fat group, $P < .05$. **Significantly different *v* the high-fat group, $P < .01$.

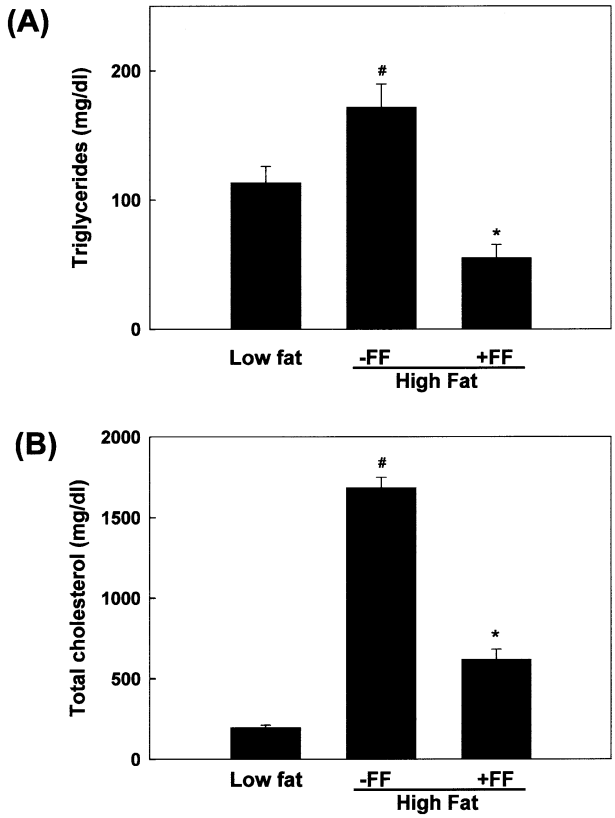

Fig 2. Changes in circulating (A) triglycerides and (B) total cholesterol by FF in male LDLR-null mice. Adult male LDLR-null mice received a low fat, a high fat, or the same high-fat diet supplemented with FF (0.05% wt/wt) for 8 weeks. Serum concentrations of triglycerides and total cholesterol were measured, and all values are expressed as the mean ± SD for n = 8 mice. #Significantly different *v* the low-fat group, *P* < .01. *Significantly different *v* the high-fat group, *P* < .01.

fenofibrate, high fat diet-induced increase in WAT weight was decreased by 63% to 1.53 ± 0.20 g ($P < .05$). The administration of fenofibrate resulted in liver hypertrophy, and liver weights were significantly higher, by 44%, after fenofibrate administration versus the high-fat diet ($P < .01$), suggesting that the increased liver activity is paralleled by a large reduction in WAT mass (Fig 1C).

Moreover, fenofibrate-enriched high-fat diet-fed LDLR-null mice showed similar food consumption to the high-fat diet-fed animals throughout the study, suggesting that fenofibrate does not influence food intake (data not shown). Therefore, the lower body and WAT weights of fenofibrate-administered LDLR-null mice cannot be due to reduced food intake.

Fenofibrate Prevents High-Fat Diet–Induced Hypertriglyceridemia in Male LDLR-Null Mice

Hypertriglyceridemia is a risk factor of cardiovascular disease and has been implicated indirectly in the progression of atherosclerosis.[23] Moreover, increased adiposity in LDLR-null mice can result from increased triglyceride availability from circulating lipoproteins. Thus, fenofibrate is likely to prevent obesity and hypertriglyceridemia in LDLR-null mice, because it can stimulate hepatic fatty acid oxidation and reduce hepatic triglycerides. To test this possibility, serum triglyceride levels were measured in mice fed a chow, high fat, or high fat plus fenofibrate diet. Mice fed the low-fat diet had a serum triglyceride level of 113 ± 12 mg/dL (Fig 2A). Mice fed the high-fat diet had a triglyceride level of 172 ± 18 mg/dL (52% higher than that of the low-fat–fed mice, $P < .01$). However, a high-fat diet containing fenofibrate significantly reduced the serum concentration of triglycerides (55 ± 10 mg/dL) by 68% compared with a high-fat diet ($P < .01$). In addition to serum triglycerides, a fenofibrate-enriched high-fat diet also significantly decreased serum total cholesterol (618 ± 63 mg/dL) by 64% compared with a high-fat diet alone (1,684 ± 65 mg/dL) ($P < .01$), suggesting that fenofibrate prevents hypertriglyceridemia and hypercholesterolemia as well as obesity in LDLR-null mice.

To determine whether the decreased circulating triglycerides

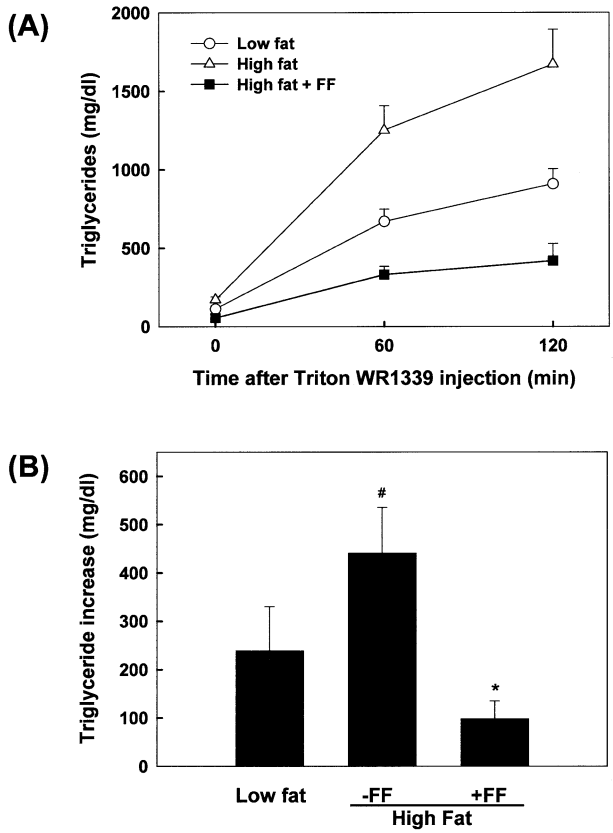

Fig 3. Hepatic triglyceride secretion after FF treatment in male LDLR-null mice. Adult male LDLR-null mice received a low fat, a high fat, or the same high-fat diet supplemented with FF (0.05% wt/wt) for 8 weeks. Triton WR1339 (500 mg/kg body weight) was injected into fasted mice after 8 weeks of treatment. Mice were bled before injection and at 60 and 120 minutes postinjection. The values for serum triglyceride concentrations are expressed as the mean ± SD for n = 8 mice. #Significantly different *v* the low-fat group, *P* < .01. *Significantly different *v* the high-fat group, *P* <.001.

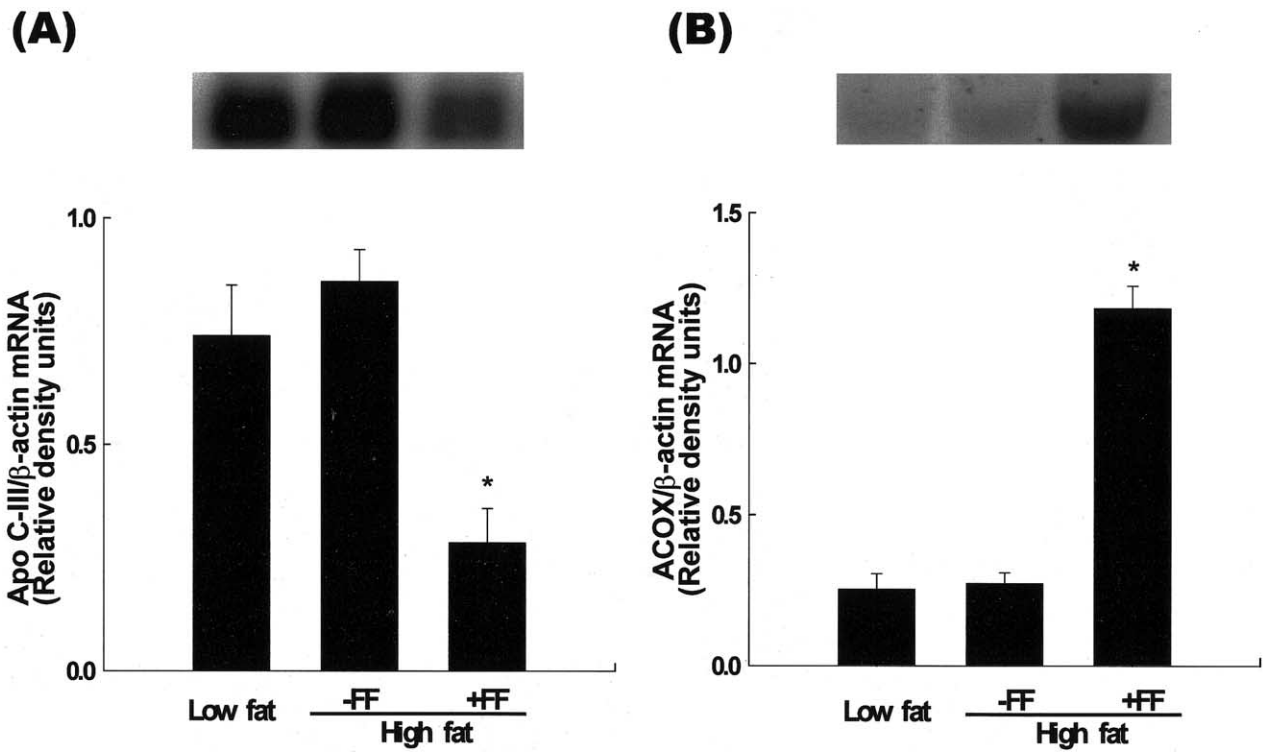

Fig 4. Modulation of (A) apoC-III and (B) ACOX mRNA levels by FF in male LDLR-null mice. Adult male LDLR-null mice received a low fat, a high fat, or the same high-fat diet supplemented with FF (0.05% wt/wt) for 8 weeks. RNA was extracted from livers, and apoC-III and ACOX mRNA levels were measured as described in Materials and Methods. The mean ± SD for 3 animals is shown, and all values are expressed in relative density units using β-actin as a reference. *Significantly different *v* the high-fat group, $P < .01$.

after fenofibrate treatment were due to the decreased triglyceride secretion from the liver, we measured the triglyceride secretion rates over 120 minutes in LDLR-null mice fed a chow, high fat, or high-fat plus fenofibrate diet after the administration of Triton WR1339. As shown in Fig 3, the increase in triglycerides between 60 and 120 minutes was found to be 85% higher in high-fat diet-fed mice versus chow diet-fed mice ($P < .01$) and 78% lower in mice fed a fenofibrate-enriched high-fat diet versus high-fat diet-fed mice ($P < .001$), suggesting that a fenofibrate-enriched high-fat diet significantly decreased the triglyceride secretion rate compared with a high-fat diet alone.

Fenofibrate Alters the PPARα Target Gene Expression in Male LDLR-Null Mice

The expression levels of PPARα target genes were determined in liver of LDLR-null mice by Northern analysis. We measured the amounts of apo C-III and ACOX mRNA; these have crucial roles in the control of triglyceride metabolism and in fatty acid β-oxidation, respectively. The fenofibrate-containing high-fat diet-fed mice exhibited substantially lower expression of hepatic apo C-III mRNA levels by 66% compared with the high-fat diet treated mice ($P < .01$) (Fig 4A). In response to fenofibrate administration, hepatic ACOX mRNA levels increased significantly versus the high-fat diet groups ($P < .01$). The expression level of ACOX was 327% higher in the fenofibrate-treated mice than in their high-fat diet-fed counterparts (Fig 4B). These results suggests that fenofibrate faithfully modifies hepatic mRNA levels of apoC-III and ACOX and thereby prevents hypertriglyceridemia, resulting in decreased adiposity and body weight gain in LDLR-null mice.

Fenofibrate Reduces Hepatic Lipid Accumulation in High-Fat Diet–Fed Male LDLR-Null Mice

The hepatic accumulation of lipids was determined after fenofibrate treatment in LDLR-null mice by light microscopy. As shown in Fig 5, the hepatic accumulation of lipids was considerably higher in the high-fat diet-fed mice than in the low-fat diet controls. However, a fenofibrate-supplemented high-fat diet inhibited this accumulation, showing that fenofibrate increases fat catabolism in liver.

DISCUSSION

LDLR-null mice exhibit a genetic disorder called familial hypercholesterolemia, an autosomal dominant disorder characterized by the absence of active LDLR. This defect elevates serum LDL and results in premature atherosclerosis. Moreover, the loss of LDLR increases susceptibility to diet-induced obesity and hypertriglyceridemia. Therefore, because our previous results demonstrated the role of PPARα in the regulation of lipid metabolism and obesity in female OVX LDLR-null mice,

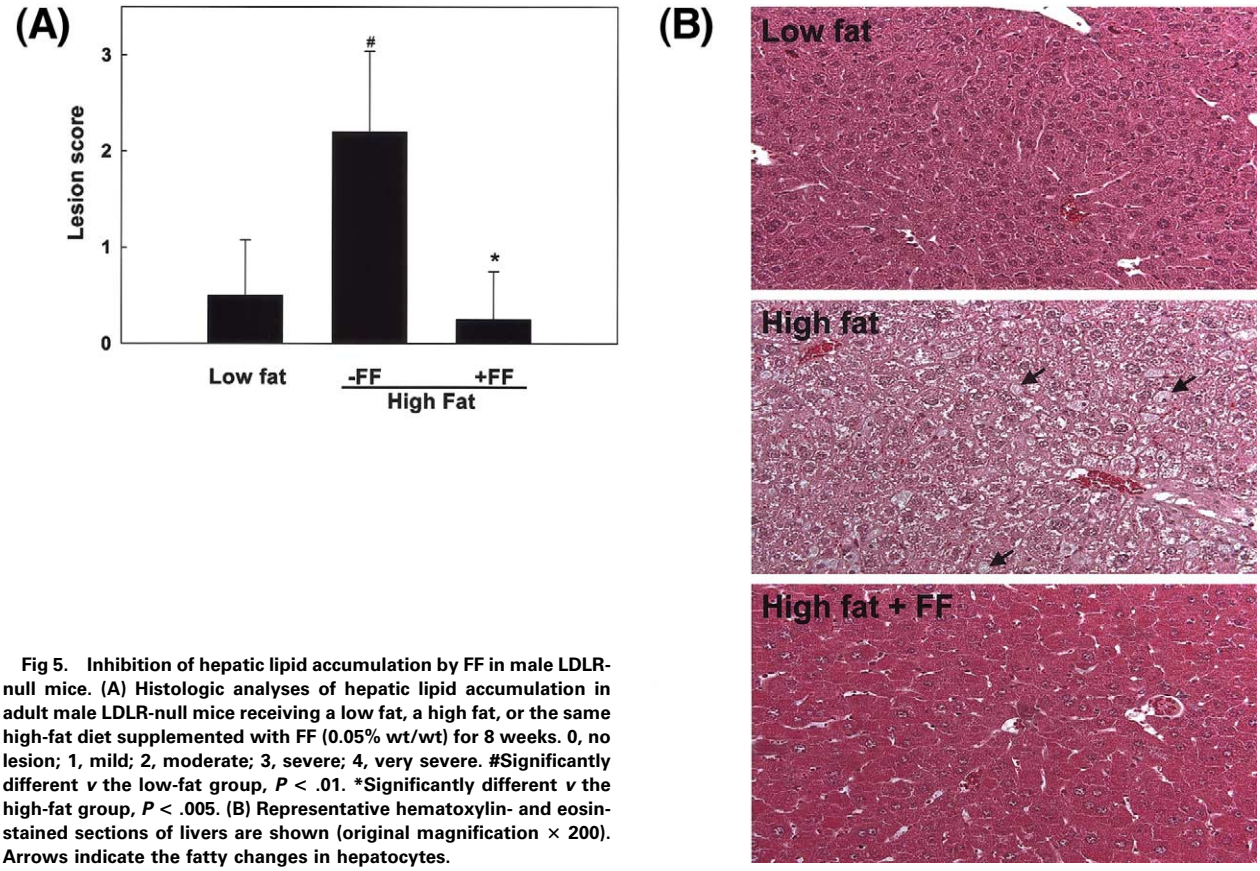

Fig 5. Inhibition of hepatic lipid accumulation by FF in male LDLR-null mice. (A) Histologic analyses of hepatic lipid accumulation in adult male LDLR-null mice receiving a low fat, a high fat, or the same high-fat diet supplemented with FF (0.05% wt/wt) for 8 weeks. 0, no lesion; 1, mild; 2, moderate; 3, severe; 4, very severe. #Significantly different *v* the low-fat group, $P < .01$. *Significantly different *v* the high-fat group, $P < .005$. (B) Representative hematoxylin- and eosin-stained sections of livers are shown (original magnification × 200). Arrows indicate the fatty changes in hepatocytes.

we speculated that fenofibrate may influence body weight gain, adiposity, and dyslipidemia caused by LDLR deficiency in male mice.

Body weights and WAT mass were found to be increased in LDLR-null mice on a high-fat diet compared with low-fat diet controls. As shown in our previous studies of wild-type C57BL/6J mice[24] and female LDLR-null mice,[19] the body weight gain of male LDLR-null mice is largely due to an increased WAT mass, whereas the weights of other organs and tissues remain unchanged, except for the liver, which showed steatosis and a 21% weight increase. Schreyer et al[18] also provided evidence that the loss of LDLR expression directly contributes to increased triglyceride uptake in adipose, or more likely, that loss of hepatic LDLR expression increases circulating lipoproteins and probably increases triglyceride substrate for uptake by adipocytes.

The simultaneous treatment with a high-fat diet with fenofibrate prevented the high-fat diet-induced increases in body weight and WAT mass in male LDLR-null mice, which concurs with the results of our previous study, namely that fenofibrate decreases body weight and WAT mass in female OVX LDLR-null mice without ovarian steroids. The body weights of male LDLR-null mice were significantly reduced after 1 week of fenofibrate administration, whereas wild-type mice showed weight decreases after 7 weeks of fenofibrate, as we described previously,[24] suggesting that fenofibrate more effectively reduces body weight gain in LDLR-null mice than in wild-type mice. Interestingly, the final body weight of the fenofibrate-treated animals was very similar to that of untreated animals on a standard low-fat diet. This indicates not only the prevention of body weight gain and the increased fat mobilization from WAT due to fenofibrate-induced increases of fat catabolism in the liver, but also a strong correlation between reduced body weight and decreased WAT mass by fenofibrate. In fact, the liver weight was significantly increased in fenofibrate-treated LDLR-null mice versus high-fat diet-fed LDLR-null mice due to the proliferation of peroxisomes.[25,26] High-fat diet-fed LDLR-null mice showed hepatic lipid accumulation, which was absent in the hepatocytes of mice on a low-fat diet and which disappeared after fenofibrate treatment, mainly due to peroxisomal and mitochondrial β-oxidation of fatty acids.[25,26] In addition, fenofibrate did not affect the food intake in high-fat diet-induced obese LDLR-null mice. These results indicate that the increased liver activity may be paralleled by a large reduction in WAT mass, which accounts for most of the body weight reduction.

Serum triglycerides were significantly higher in male LDLR-null mice on a high-fat diet for 8 weeks than in mice on a low-fat control diet, which is supported by other reports that LDLR-null mice are highly susceptible to high-fat diet-induced hypertriglyceridemia.[18,27,28] However, fenofibrate treatment substantially decreased high-fat diet-induced increases in tri-

glycerides in the present study and in other reports,[12,19,24] indicating that fenofibrate efficiently regulates triglyceride metabolism in male LDLR-null mice. In addition, high-fat diet-increased serum total cholesterol was also decreased by fenofibrate treatement. In this respect, fenofibrate may be useful for treating patients with both familial hypercholesterolemia and hypertriglyceridemia.

Circulating triglyceride levels are thought to be regulated by the balance between its secretion and clearance. With lipoprotein catabolism suppressed, the increase in circulating triglyceride over time is indicative of the rate at which triglyceride is being secreted from the liver.[29-31] As shown in Fig 3, the hepatic triglyceride secretion rate was significantly lowered in fenofibrate-supplemented high-fat diet-fed mice compared with high-fat diet-fed mice when Triton WR1339 was used to prevent lipolysis. These observations suggest that the reduced circulating triglycerides after fenofibrate treatment are due to the decreased secretion of triglycerides from the liver.

To gain insight into the molecular mechanisms underlying the effects described above, we investigated genes involved in lipid metabolism and found that apoC-III and ACOX gene expression was respectively downregulated and upregulated by fenofibrate treatment in the presence of a high-fat diet. Although the combined action of fenofibrate and a high-fat diet is not known, its effect on apoC-III and ACOX expression was partly expected, because these are targets of fenofibrate-activated PPARα. In parallel with the serum triglyceride levels, LDLR-null mice fed fenofibrate showed significantly lowered mRNA levels of hepatic apoC-III, an apolipoprotein that limits tissue triglyceride clearance, compared with those of the high–fat-fed mice.[4,19,32,33] In addition to apoC-III-mediated effects on the clearance of triglyceride-rich lipoproteins by fenofibrate, fenofibrate-activated PPARα in the liver increased mRNA levels of ACOX, the first and rate-limiting enzyme of PPARα-mediated fatty acid β-oxidation, which resulted in reduced triglyceride production.[32]

In conclusion, our data demonstrate the effects of fenofibrate on obesity and hypertriglyceridemia in male LDLR-deficient mice. Fenofibrate treatment was found to prevent the body weight gain, adiposity, and hypertriglyceridemia caused by LDLR deficiency in male mice, which is consistent with its effects in female OVX LDLR-null mice. In addition, the action of fenofibrate on obesity seems to differ in male and female LDLR-null mice, suggesting the involvement of ovarian steroid hormones in the regulation of obesity by fenofibrate.

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