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Fenofibrate improves lipid metabolism and obesity in ovariectomized LDL receptor-null mice

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Abstract

We investigated whether fenofibrate improves lipid metabolism and obesity in female ovariectomized (OVX) or sham-operated (SO) low density lipoprotein receptor-null (LDLR-null) mice. All mice fed a high-fat diet exhibited increases in serum triglycerides and cholesterol as well as in body weight and white adipose tissue (WAT) mass compared to mice fed a low fat control diet. However, fenofibrate prevented high-fat diet-induced increases in body weight and WAT mass in female OVX LDLR-null mice, but not in SO mice. In addition, administration of fenofibrate reduced serum lipids and hepatic apolipoprotein C-III mRNA while increasing the mRNA of acyl-CoA oxidase in both groups of mice, however, these effects were more pronounced in OVX LDLR-null mice. The results of this study provide first evidence that fenofibrate improves both lipid metabolism and obesity, in part through PPARα activation, in female OVX LDLR-null mice.

Keywords: Adipose tissue; Body weight; Fenofibrate; Lipid; LDLR-null; PPARα

The fibrates are widely used hypolipidemic drugs that activate the nuclear peroxisome proliferator-activated receptor α (PPARα), and thereby regulate the expression of a number of genes critical for lipid and lipoprotein metabolism [1–3]. Activated PPARα heterodimerizes with retinoid X receptor (RXR) and then increases the expression of target genes that contain a peroxisome proliferator-responsive element (PPRE) in their promoter regions [4]. The targets for PPARα action include lipoprotein lipase and apolipoprotein C-III (apoC-III) used for the hydrolysis of plasma triglycerides [5–7], fatty acid transport protein, and acyl-CoA synthetase in the fatty acid uptake and binding [8], and acyl-CoA oxidase (ACOX), enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase (HD), and thiolase used for fatty acid β-oxidation [9–11].

The fibrates have also been suggested to be involved in the regulation of energy homeostasis. Excess energy intake causes elevated concentrations of plasma triglycerides and cholesterol, and the resulting triglycerides in the circulation are responsible for the hypertrophy and hyperplasia of adipose cells [12–14]. Reduced levels of plasma triglycerides and of fatty acids by fenofibrate may thus inhibit an increase in body weight, indicating that PPARα may be involved in obesity due to its ability to regulate energy balance. This is supported by the report that PPARα-deficient mice show abnormalities in triglyceride and cholesterol metabolism, and become obese with age [13]. In addition, other results suggest the possibility that fenofibrate can modulate body weight in 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 [14–17].

The low density lipoprotein receptor (LDLR)-deficient mouse is an animal model of homozygous familial hypercholesterolemia, characterized by an absence of

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functional LDL receptors, leading to delayed clearance of triglyceride-rich lipoproteins and elevated circulating cholesterol, which results in atherosclerosis [18,19]. Moreover, it has recently been shown that LDLR-null mice fed a high-fat, high-carbohydrate diet become obese and develop severe hypertriglyceridemia [20]. Given the effects of treatment with the PPARα ligand, fenofibrate, on the lipid metabolism and the role of circulating triglycerides in the regulation of lipids in adipose tissue, it is likely that fenofibrate improves dyslipidemia and obesity in LDLR-null mice on a high-fat diet. However, whether or not fenofibrate prevents both lipid disorder and obesity in LDLR-deficient mice remains unknown.

The objective of this study was to analyze whether fenofibrate improves lipid profiles and obesity through the transcriptional activation of PPARα in female LDLR-null mice. Our data demonstrate that alterations in PPARα target expression by fenofibrate can reduce body weight, WAT mass, and serum lipids in female OVX LDLR-null mice although this improvement is not shown by female SO mice.

Materials and methods

Animal treatments. Eight week old, homozygous low density lipoprotein receptor-null (B6,129-LDLR^{tm1Her}–/– mice) purchased from the Jackson Laboratory (ME, USA) and bred at the Korea Research Institute of Bioscience and Biotechnology under specific pathogen free conditions were used in all experiments. Female mice were sham-operated (SO) or ovariectomized (OVX) and then randomly assigned to three different diets, a low fat diet (4.5% fat, w/w, CJ, Korea), a high-fat diet containing 15% fat (w/w, Oriental Yeast, Japan), or the same high-fat diet supplemented with fenofibrate (0.05%, w/w) for 8 weeks. In all experiments, body weights were monitored throughout the treatment period. At the end of the study period, animals were sacrificed by cervical dislocation, tissues were harvested, weighed, snap frozen in liquid nitrogen, and stored at −80 °C until use.

Serum assays. Serum concentrations of total cholesterol and triglycerides were measured using an automatic blood chemical analyzer (CIBA corning, OH, USA).

Analysis of target gene expression. Total RNA was prepared using Trizol reagent (Gibco-BRL, Grand Island, NY) and analyzed by electrophoresis on 0.22 M formaldehyde-containing 1.2% agarose gels. The separated RNA was transferred to Nytran membranes (Schneicher & Schuell, Dassel, Germany) by downward capillary transfer in the presence of 20× SSC buffer (3 M NaCl and 0.3 M sodium citrate, pH 7.0), UV-crosslinked, and baked for 2 h 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 [21]. Densitometric analysis of the mRNA signals was performed using ImageQuant image analysis software (Molecular Dynamics, Sunnyvale, CA).

Statistics. Unless otherwise noted, all values are expressed as means ± standard deviation (SD). All data were analyzed by ANOVA for statistically significant differences between groups.

Results

Changes in lipid profiles by fenofibrate in female LDLR-null mice

Since fenofibrate has a beneficial effect on lipid profiles and acts as an efficient lipid-lowering drug, the effects of fenofibrate on serum total cholesterol and triglycerides were examined in LDLR-null mice, which show delayed clearance of triglyceride-rich lipoproteins and severe hypercholesterolemia. Compared to a low fat diet, a high-fat diet increased serum total cholesterol and triglycerides in both female OVX and SO LDLR-null mice ($p < 0.01$) (Fig. 1). However, the fenofibrate-containing high-fat diet caused a significant reduction in the serum triglyceride concentrations ($p < 0.01$), compared with the high-fat diet, and this reduction was more prominent in female OVX LDLR-null mice than in female SO mice. Treatment with fenofibrate also signifi-

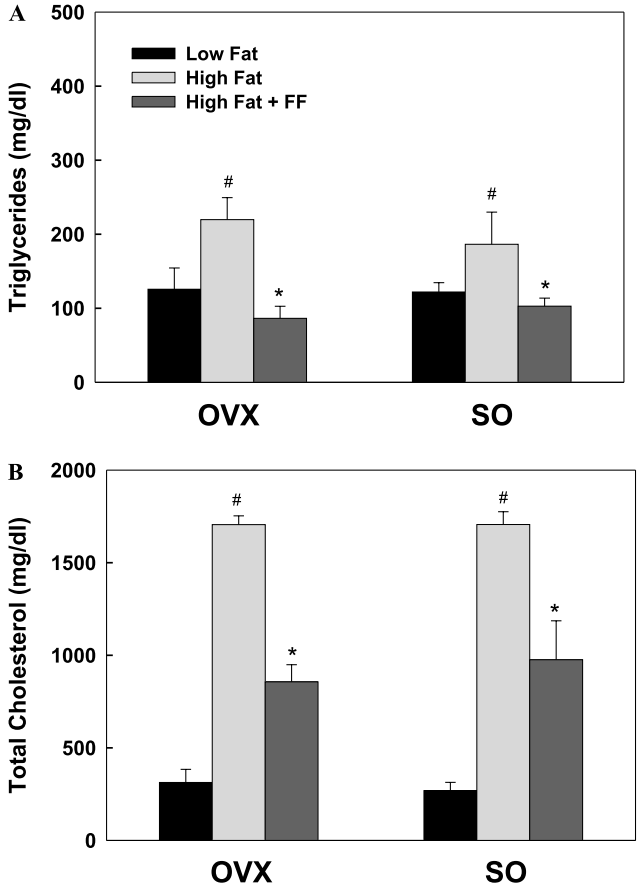

Fig. 1. Changes in circulating triglycerides and total cholesterol by fenofibrate in female LDLR-null mice. Female ovariectomized (OVX) or sham-operated (SO) LDLR-null mice received a low fat, a high-fat or the same high-fat diet supplemented with fenofibrate (FF; 0.05% w/w) for 8 weeks. Serum concentrations of triglycerides (A) and total cholesterol (B) were measured and all values are expressed as means ± SD. #, Significantly different versus a low fat group, $p < 0.01$. *, Significantly different versus a high-fat group, $p < 0.01$.

cantly decreased the circulating cholesterol level in both groups of LDLR-null mice ($p < 0.01$).

Modulation of body weight and WAT mass by fenofibrate in female LDLR-null mice

To examine whether fenofibrate reduces body weight gain and adiposity in female LDLR-null mice, we analyzed the influence of fenofibrate on body weight and adipose tissue mass. Feeding mice with a high-fat diet resulted in increased body weight by 10.6% in female OVX and by 6.3% in female SO LDLR-null mice (Fig. 2). In contrast, as compared to high-fat diet-fed groups, fenofibrate treatment reduced body weight by 11.3% in female OVX LDLR-null mice, but slightly increased body weight by 2.7% in female SO mice.

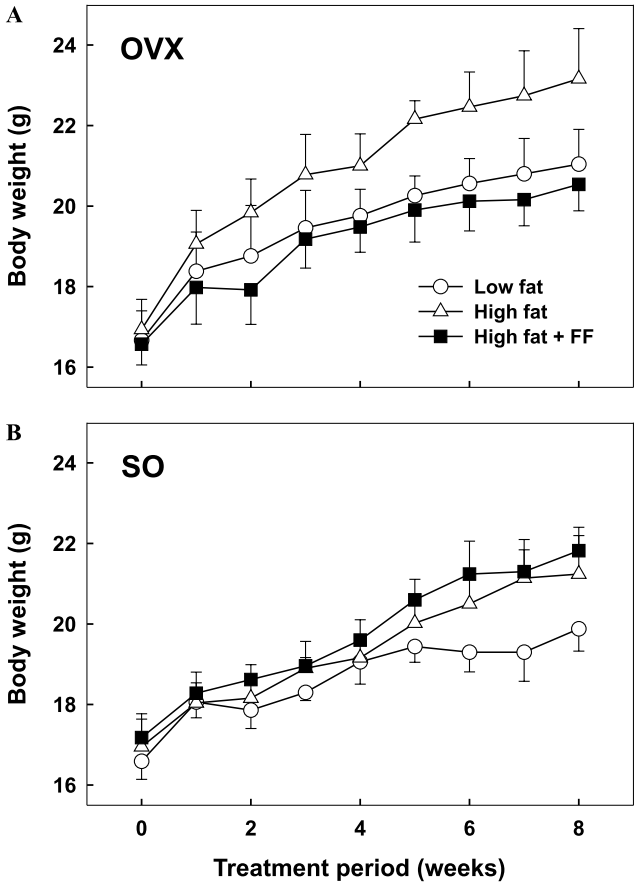

Fig. 2. Regulation of body weight by fenofibrate in female ovariectomized (A) and sham-operated (B) LDLR-null mice. Female ovariectomized (OVX) or sham-operated (SO) LDLR-null mice received a low fat, a high-fat or the same high-fat diet supplemented with fenofibrate (FF; 0.05% w/w) for 8 weeks. All values are expressed as means ± SD. Body weights at the end of the treatment period are statistically significant between the high-fat group and the low fat ($p < 0.01$) and high-fat plus fenofibrate ($p < 0.01$) groups in OVX mice, and between the low fat group and the high-fat ($p < 0.05$) and high-fat plus fenofibrate ($p < 0.01$) groups in SO mice.

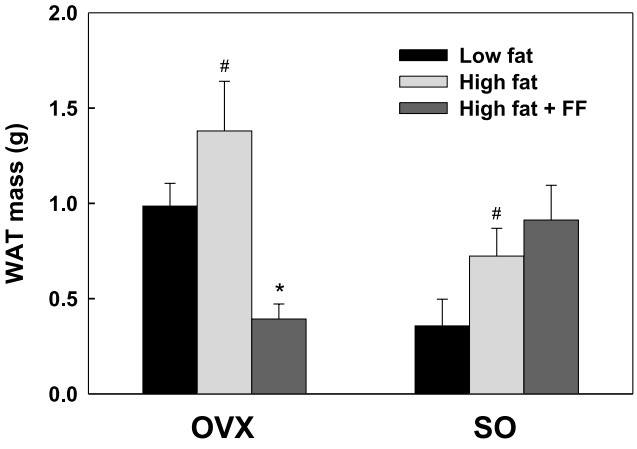

Fig. 3. Modulation of visceral adipose tissue mass by fenofibrate in female LDLR-null mice. Female ovariectomized (OVX) or sham-operated (SO) LDLR-null mice received a low fat, a high-fat or the same high-fat diet supplemented with fenofibrate (FF; 0.05% w/w) for 8 weeks. All values are expressed as means ± SD. #, Significantly different versus a low fat group, $p < 0.01$. *, Significantly different versus a high-fat group, $p < 0.01$.

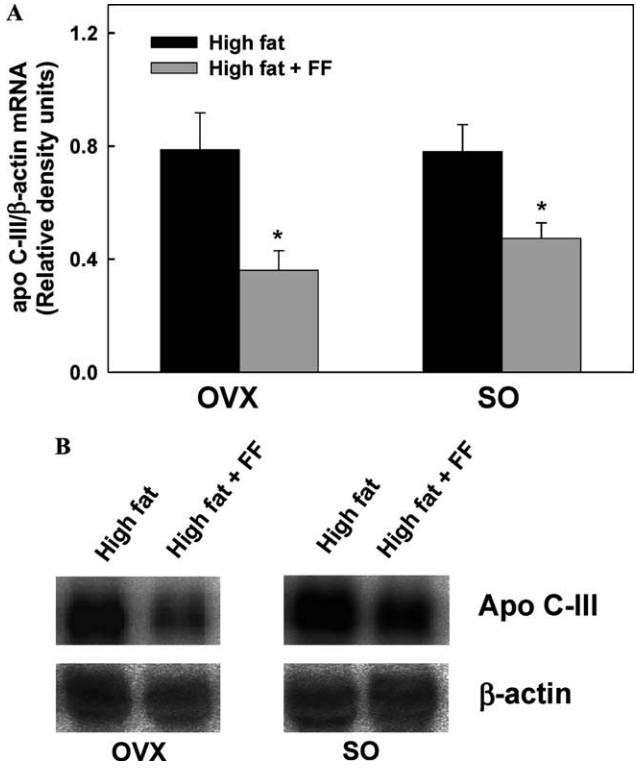

Fig. 4. Modulation of apo C-III mRNA by fenofibrate in female LDLR-null mice. (A) Female ovariectomized (OVX) or sham-operated (SO) LDLR-null mice received a low fat, a high-fat or the same high-fat diet supplemented with fenofibrate (FF; 0.05% w/w) for 8 weeks. RNA was extracted from liver and, apo C-III and β-actin mRNA levels were measured as described under "Materials and methods." The mean ± SD for three animals is shown and all values are expressed in RDU (relative density units) using β-actin as a reference. *, Significantly different versus a high-fat group, $p < 0.05$. (B) Representative Northern blots, from an independent experiment.

As shown in Fig. 3, WAT mass was also significantly increased in the high-fat diet groups versus the low fat diet. In response to fenofibrate, high-fat diet-induced increases in WAT mass were significantly decreased by 71% in female OVX LDLR-null mice ($p < 0.01$), but rather increased by 26% in female SO mice. In addition, compared to the chow-fed OVX controls, female OVX mice given a fenofibrate-supplemented high-fat diet had lower body weights and WAT mass. Our data show a strong correlation between serum triglycerides, body weights, and WAT mass reductions following fenofibrate treatment in high-fat diet-fed female OVX mice, which is supported by the finding that WAT lipids are largely derived from serum triglycerides [22–24].

Alterations in PPARα target gene expression by fenofibrate in LDLR-null mice

To test whether PPARα is involved in the fenofibrate regulation of lipid metabolism and obesity in female LDLR-null mice, the effects of fenofibrate on the expression of the PPARα-mediated hepatic genes, apo C-III, and ACOX were examined. In line with other results, fenofibrate was found to significantly reduce the expression of hepatic apo C-III mRNA levels in both OVX and SO LDLR-null animals as compared with the respective high-fat diet-treated mice ($p < 0.05$) (Fig. 4). In addition, the extent of reduction in apo C-III mRNA were found to be higher in female OVX mice than in SO mice following fenofibrate treatment, consistent with the serum triglyceride levels.

In response to fenofibrate administration, mRNA levels of ACOX, which is involved in fatty acid β-oxidation, was found to be higher in OVX ($p < 0.01$) and SO LDLR-null mice ($p < 0.05$) compared with the respective mice treated with high-fat diet (Fig. 5). However, the expression level of ACOX was 1.6-fold higher in female OVX mice than in SO females, suggesting that differences in fenofibrate-mediated hepatic fatty acid β-oxidation and the resulting fatty acids available for adipose triglycerides may contribute to the differences in body weight and adipose tissue mass of the two groups.

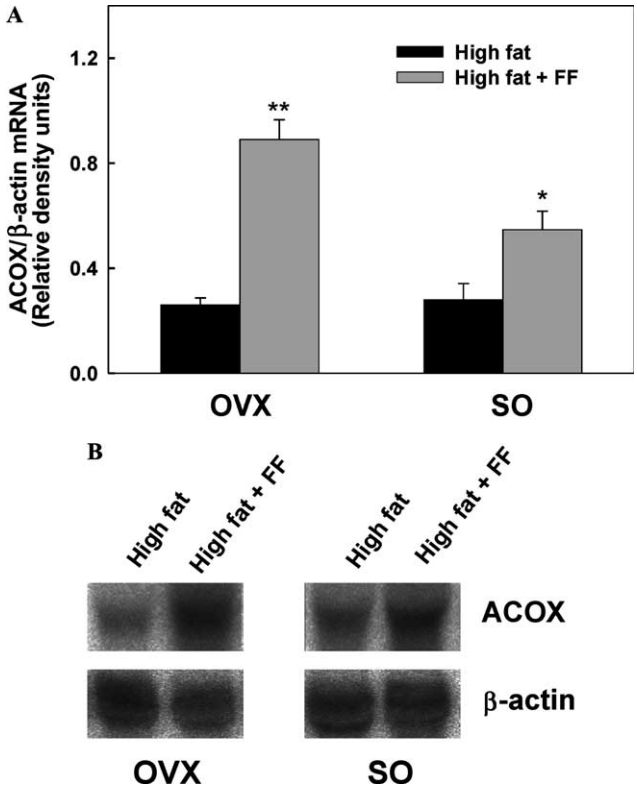

Fig. 5. Modulation of ACOX mRNA by fenofibrate in female LDLR-null mice. (A) Female ovariectomized (OVX) or sham-operated (SO) LDLR-null mice received a low fat, a high-fat or the same high-fat diet supplemented with fenofibrate (FF; 0.05% w/w) for 8 weeks. RNA was extracted from liver and ACOX and β-actin mRNA levels were measured as described under "Materials and methods." The mean ± SD for three animals is shown and all values are expressed in RDU (relative density units) using β-actin as a reference. *, Significantly different versus a high-fat group, $p < 0.05$. **, Significantly different versus a high fat group, $p < 0.01$. (B) Representative Northern blots, from an independent experiment.

Discussion

Based on the suggestion that LDLR-null mice exhibit hypertriglyceridemia and obesity when fed a high-fat, high-carbohydrate diet, and the documented role of PPARα in the regulation of lipid metabolism and energy balance, we hypothesized that fenofibrate improves lipid metabolism and obesity in LDLR-null mice on a high-fat diet. This study was thus undertaken to examine the effects of fenofibrate on obesity and lipid profiles in OVX LDLR-null mice, an animal model of postmenopausal women with familial hyperlipidemia, which show increased body weight and adipose tissue mass as well as lipid disorder.

We observed that serum triglycerides and total cholesterol were significantly increased in both female OVX and SO LDLR-null mice on a high-fat diet for 8 weeks compared with mice on a low fat control diet. This finding agrees with those of other reports, which concluded that the loss of LDLR is associated with a rise in the total plasma cholesterol level and increases susceptibility to diet-induced hypertriglyceridemia [20,25,26]. However, fenofibrate treatment substantially decreased high-fat diet-induced increases of triglycerides and cholesterol, as evidenced by the present study and others [14,27], indicating that fenofibrate efficiently regulates the lipid metabolism in LDLR-null mice. In this respect, fenofibrate demonstrates the potential to be used for the treatment of patients with familial hypercholesterolemia and hypertriglyceridemia.

In parallel with their serum triglyceride levels, OVX and SO LDLR-null mice fed fenofibrate were found to

have significantly lower hepatic apo C-III mRNA levels (an apolipoprotein that limits tissue clearance of triglycerides) than the high-fat-fed mice [4,27,28]. In addition to the effect of apo C-III on the clearance of triglyceride-rich lipoproteins by fenofibrate, administration of fenofibrate increased mRNA levels of ACOX, which is the rate-limiting enzyme responsible for PPARα-mediated fatty acid β-oxidation, thus resulting in decreased triglyceride production [27]. Moreover, such changes in mRNA levels of apo C-III and ACOX by fenofibrate were greater in female OVX LDLR-null mice than in SO LDLR-null mice with functioning ovaries, thus showing that the action of fenofibrate on PPARα target gene expression and lipid metabolism may be affected by ovarian factors.

High-fat diet-fed LDLR-null mice had higher body weights and WAT mass than LDLR-null mice on a chow control diet, and the increases in body weight and WAT mass were higher in female OVX LDLR-null mice than in female SO mice [20]. However, interestingly, female OVX LDLR-null mice on a fenofibrate-enriched high-fat diet had lower body weights and WAT mass, which are similar to those found in several animal models [14,16,17], while female SO mice did not exhibit these reductions following fenofibrate treatment. Chaput et al. [14] provided evidence that the effect of fenofibrate on body weight depends on the utilization of fatty acid in *db*/*db* mice and fatty Zucker rats, as demonstrated by a fenofibrate-induced increase of ACOX mRNA. In agreement with the data presented by the present study and by Chaput et al. [14], PPARα-mediated fatty acid β-oxidation and hydrolysis of triglycerides by fenofibrate contribute to decreased body weight and WAT mass in OVX LDLR-null mice, suggesting that fenofibrate can act as an effective lipid-lowering drug and as a body weight-regulator.

However, it appears that PPARα-mediated reduction in serum triglycerides does not directly control obesity in fenofibrate-treated female SO LDLR-null mice, which exhibited simultaneously decreases in serum triglycerides and increases in body weight and WAT mass. Thus, the effect of fenofibrate on the body weight of female SO LDLR-null mice cannot be explained simply in terms of an altered and enhanced flux of fatty acids and triglycerides, since fenofibrate increased ACOX mRNA and decreased apo C-III gene expression in this group (although this expression was smaller than in the OVX group). Moreover, these changes in ACOX and apo C-III mRNA did not correlate with increased body weight and adiposity. Such conflicting data suggest the possibility that this discordance may be caused by ovarian factors, and may be attributed to signal cross-talk between the estrogen receptor and PPARα · RXR in the regulation of obesity of LDLR-null mice [29,30]. Further work is needed to determine which factors contribute to these differences following fenofibrate treatment in female LDLR-null mice, in order that the mechanisms leading to obesity may be better understood.

In conclusion, our data provide evidence that fenofibrate treatment prevents body weight gain, adiposity, and lipid disorder by activating hepatic PPARα in female OVX LDLR-null mice, although fenofibrate does not improve obesity in female SO mice. In addition, these results also suggest that the administration of fenofibrate may effectively regulate obesity and lipid metabolism in overweight postmenopausal women with elevated levels of triglycerides and cholesterol.

Acknowledgments

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