Effects of Fenofibrate on High-Fat Diet–Induced Body Weight Gain and Adiposity in Female C57BL/6J Mice

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Our previous study suggested that fenofibrate affects obesity and lipid metabolism in a sexually dimorphic manner in part through the differential activation of hepatic peroxisome proliferator-activated receptor α (PPARα) in male and female C57BL/6J mice. To determine whether fenofibrate reduces body weight gain and adiposity in female sham-operated (Sham) and ovariectomized (OVX) C57BL/6J mice, the effects of fenofibrate on not only body weight, white adipose tissue (WAT) mass, and food intake, but also the expression of both leptin and PPARα target genes were measured. Compared to their respective low-fat diet–fed controls, both Sham and OVX mice exhibited increases in body weight and WAT mass when fed a high-fat diet. Fenofibrate treatment decreased body weight gain and WAT mass in OVX, but not in Sham mice. Furthermore, fenofibrate increased the mRNA levels of PPARα target genes encoding peroxisomal enzymes involved in fatty acid β-oxidation, and reduced apolipoprotein C-III (apo C-III) mRNA, all of which were expressed at higher levels in OVX compared to Sham mice. However, leptin mRNA levels were found to positively correlate with WAT mass, and food intake was not changed in either OVX or Sham mice following fenofibrate treatment. These results suggest that fenofibrate differentially regulates body weight and adiposity due in part to differences in PPARα activation, but not to differences in leptin production, between female OVX and Sham mice.

FIBRATES ACT as nuclear peroxisome proliferator-activated receptor α (PPARα) ligands, and regulate the expression of a number of genes that are critical for lipid and lipoprotein metabolism, thereby leading to lipid homeostasis.[1-3] Fibrate-activated PPARα heterodimerizes with retinoid X receptor (RXR) and binds to PPAR response elements (PPREs) in the promoter region of target genes.[4] PPARα target genes include those involved in the hydrolysis of plasma triglycerides, such as lipoprotein lipase and apolipoprotein C-III (apo C-III),[5-7] fatty acid uptake and binding, such as fatty acid transport protein and acyl-CoA synthetase,[8] and fatty acid β-oxidation, such as fatty acyl-CoA oxidase (ACOX), enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase (HD), and thiolase.[9-11] The activation of PPARα target genes therefore promotes increased hepatic oxidation of fatty acids, as well as the increased breakdown and reduced synthesis and secretion of triglycerides.

Fibrate-activated PPARα is also suggested to be involved in the regulation of energy balance. Since fenofibrate increases hepatic fatty acid oxidation and thus decreases the levels of plasma triglycerides responsible for adipose cell hypertrophy and hyperplasia,[12-14] it may inhibit an increase in body weight, suggesting that PPARα may be important in obesity due to its ability to restore an overall energy balance. This is supported by a report that PPARα-deficient mice showed abnormalities in triglyceride and cholesterol metabolism, and became obese with age.[13] Furthermore, recent studies have suggested that fenofibrate can modulate body weight in animal models, such as fatty Zucker rats, high-fat diet–fed C57BL/6 mice, and high-fat–fed obese rats.[14-16]

Energy balance seems to be influenced by gonadal sex steroids.[17] Gonadal steroids have been the subject of intense investigation over the last several decades because of the role that these ovarian hormones have in the regulation of food intake, body weight and lipid metabolism. For example, it is well known that ovariectomized (OVX) animals and postmenopausal women show increased food intake, body weight, and adipose tissue mass, indicating the involvement of gonadal steroids in the modulation of obesity.[18-22] Moreover, our previous results demonstrated that fenofibrate reduced body weight and WAT mass in male mice, but did not decrease them in female mice, showing the sexually dimorphic effects of fenofibrate on obesity.[23] Accordingly, we thought it plausible that fenofibrate may influence obesity differentially depending on the presence of gonads.

The aims of this study were to determine whether or not fenofibrate regulates body weight gain and adiposity in high-fat diet–fed sham-operated (Sham) and OVX female mice, and to investigate the involvement of PPARα in this process. Thus we examined body weight, white adipose tissue (WAT) mass, food intake, leptin, and PPARα target gene expression. Here we report that fenofibrate reduces body weight gain and WAT mass in high-fat diet–fed OVX mice, but not in Sham mice, which suggests that these differences may in part be attributed to the differences in hepatic expression of PPARα target genes.

MATERIALS AND METHODS

Animal Treatments

For all experiments, 8-week-old mice (C57BL/6J) were housed and bred at the Korea Research Institute of Bioscience and Biotechnology under pathogen-free conditions with a standard 12-hour light/dark cycle. Prior to the administration of special diets, mice were fed standard rodent chow and water ad libitum. Female Sham and OVX

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mice were each randomly divided into 3 groups (n = 5 per group), which showed the uniformity in response to each treatment in the pilot study. The mice received a low-fat diet (fat, 0.4 kcal/g; protein, 0.8 kcal/g; carbohydrate, 1.8 kcal/g; CJ Corp, Inchon, Korea), a high-fat diet (fat, 1.8 kcal/g; protein, 0.8 kcal/g; carbohydrate, 1.8 kcal/g; Oriental Yeast Co, Tokyo, Japan), or a high-fat diet supplemented with fenofibrate (0.05% wt/wt) for 13 weeks.

In all experiments, body weights were measured daily using top-loading balance and the person measuring the body weight blinded to each treatment group. Food intake was determined by estimating the amount of food consumed by the mice throughout the treatment period. Cages were inspected for food spillage, but only a little spillage was noticed and collected to measure the food intake. Animals were killed by cervical dislocation, and tissues were harvested, weighed, snap frozen in liquid nitrogen, and stored at −80°C until use.

Analysis of Target Gene Expression

Total RNA from liver and parametrial WAT was prepared using Trizol reagent (Gibco-BRL, Grand Island, NY) and Northern blot analysis was performed using mouse PPARα, human RXRα, rat ACOX, rat HD, rat thiolase, mouse apo C-III, mouse leptin, and internal control mouse β-actin probes. Total RNA was 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 20x SSC buffer (3 mol/L NaCl, 0.3 mol/L sodium citrate, pH 7.0), 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.[24] Densitometric analysis of the mRNA signals was performed using ImageQuant image analysis software (Molecular Dynamics).

Statistics

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

RESULTS

Effects of Fenofibrate on Body Weight Gain and WAT Mass in Female Mice

To determine whether fenofibrate reduces body weight gain and adiposity in female mice, the influence of fenofibrate treatment on body weight and WAT mass was examined in diet-induced obese female Sham and OVX C57BL/6J mice. Compared to their respective low-fat diet controls, the administration of a high-fat diet for 13 weeks increased body weight by 15.7% ± 0.7% in OVX mice and by 8.4% ± 0.5% in Sham mice, as shown in Fig 1. In contrast, compared to their respective high-fat diet–fed groups, fenofibrate treatment reduced high-fat diet–induced body weight gain by 17.3% ± 1.5% in OVX mice, but no change was observed in Sham mice.

Compared to chow-fed animals, feeding mice with a high-fat diet for 13 weeks significantly increased WAT mass by 70.1% ± 13.1% in OVX mice and by 41.1% ± 8.3% in Sham mice (Table 1). In contrast, compared to their respective high-fat diet–fed controls, fenofibrate treatment reduced WAT mass by 78.4% ± 4.5% in OVX mice, but WAT mass increased slightly in Sham mice. In addition, compared to the chow-fed controls, OVX mice given a fenofibrate-supplemented high-fat diet had lower body weights and WAT masses. These results demonstrate that fenofibrate affects body weight and WAT mass differently in female Sham and OVX mice.

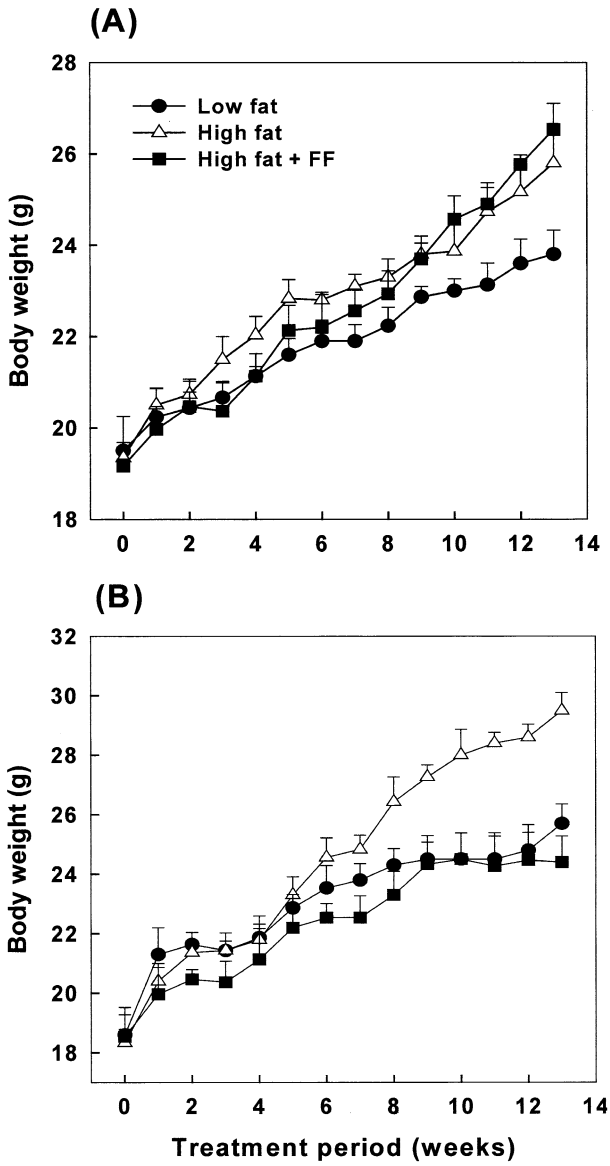

Fig 1. Regulation of high-fat diet–induced body weight gain by fenofibrate in female (A) Sham and (B) OVX mice. Female Sham and OVX mice received a low-fat, high-fat, or fenofibrate-supplemented (FF; 0.05% wt/wt) high-fat diet for 13 weeks. All values are expressed as the mean ± SD. Body weights at the end of the treatment period are significantly different not only when comparing the low-fat group to either the high-fat ($P < .05$) or high-fat plus FF ($P < .01$) groups in female Sham mice, but also when comparing the high-fat group to either the low-fat ($P < .01$) or high-fat plus FF ($P < .005$) groups in female OVX mice.

Table 1. Effects of Fenofibrate on Body and WAT Weights in Diet-Induced Obese Female C57BL/6J Mice

Treatment Group	Body Weight (g)		WAT Weight (g)	WAT/Body Weight (%)
	Baseline	13 Weeks		
Sham				
Low fat	19.5 ± 0.7	23.6 ± 0.5	0.35 ± 0.08	1.49 ± 0.21
High fat	19.4 ± 0.3	25.8 ± 0.7*	0.49 ± 0.06*	1.98 ± 0.13*
High fat + FF	19.2 ± 0.2	26.5 ± 0.6*	0.52 ± 0.10*	1.95 ± 0.28
OVX				
Low fat	18.6 ± 0.8	25.7 ± 0.6	1.10 ± 0.18	3.52 ± 0.79
High fat	18.3 ± 0.5	29.5 ± 0.6*	1.86 ± 0.28*	6.32 ± 0.94*
High fat + FF	18.5 ± 0.7	24.4 ± 0.8†	0.44 ± 0.17†	1.77 ± 0.66†

NOTE. Female Sham and OVX mice received a low-fat, high-fat, or fenofibrate-supplemented (FF; 0.05% wt/wt) high-fat diet for 13 weeks. In all experiments, body weights were recorded throughout the treatment period and WAT weights were measured at the end of the treatment period. All values are expressed as the mean ± SD.

*Significantly different *v* low-fat group ($P < .05$).

†Significantly different *v* high-fat group ($P < .05$).

Effects of Fenofibrate on Leptin mRNA Levels in Female Mice

Leptin is a long-term satiety signal that often reflects changes in body weight and WAT mass. To evaluate whether the observed differential effects of fenofibrate on obesity are caused by differences in leptin gene expression in adipose tissue and/or by differences in food intake, leptin mRNA levels and food consumption were measured. In both Sham and OVX animals, leptin mRNA levels were found to positively correlate with WAT mass (Fig 2) and body weight (data not shown). Thus, fenofibrate treatment does not seem to influence leptin synthesis. By daily monitoring, Sham and OVX female mice were found to have similar food consumption profiles after fenofibrate treatment throughout the study (Fig 3). Interestingly, OVX mice fed the fenofibrate-supplemented diet did not show an increase in food intake despite a striking reduction in leptin mRNA levels, compared to high-fat diet alone controls, indicating that fenofibrate did not have a differential influence on food intake between these 2 groups. These data further show that the differential effects of fenofibrate on body weight and WAT mass are not driven by differences in energy intake. In addition, leptin mRNA levels were significantly higher in Sham versus OVX mice for all dietary regimens, perhaps due to the estrogen-mediated increase of leptin gene expression in Sham mice.

Effects of Fenofibrate on Hepatic PPARα Target Gene mRNA Levels in Female Mice

To determine whether differential PPARα actions in the liver can induce the observed different effects of fenofibrate on obesity, we measured the mRNA levels of the PPARα target enzymes ACOX, HD, and thiolase in the livers of the different groups (Fig 4). Fenofibrate-treated mice showed elevated PPARα target gene expression for peroxisomal fatty acid β-oxidation versus high-fat diet–fed mice, and the mRNA levels of ACOX, HD, and thiolase were respectively 1.2-, 1.2-, and 1.9-fold higher in OVX compared to Sham mice. Furthermore, OVX mice had significantly higher mRNA levels of these enzymes than Sham mice after a fenofibrate-enriched high-fat diet.

In addition to the enzymes required for fatty acid β-oxidation, the apo C-III gene contains a PPRE and plays a critical role in the control of circulating triglyceride metabolism.[5,6] Consistent with the regulation of triglycerides by fenofibrate (data not shown), apo C-III mRNA levels were found to be reduced by fenofibrate treatment in both groups, but this reduction was more prominent in OVX mice (Fig 4). Analysis of the hepatic mRNA expression of PPARα revealed no significant association with any dietary regimen in either female OVX or Sham mice. These results suggest that PPARα activation following fenofibrate differs between these 2 groups and is influenced in the presence of the ovaries.

DISCUSSION

This study was undertaken to verify whether fenofibrate prevents body weight gain and adiposity in female OVX and Sham C57BL/6J mice on a high-fat diet, and to determine whether PPARα is associated with these events.

Our results demonstrate that fenofibrate reduces body weight gain and WAT mass in high-fat diet–fed OVX mice, but fails to do so in Sham mice. Body weights of OVX mice were found to be higher than those of Sham mice 6 weeks after commencing the high-fat diet. Compared to high-fat diet–fed OVX mice, fenofibrate-treated OVX mice had significantly decreased body weight gain by 6 weeks into the treatment regimen, and had significantly lower body weight at 13 weeks. In addition to changes in body weight, WAT mass was significantly reduced after fenofibrate treatment, and the final WAT mass of the fenofibrate-treated OVX animals was lower than that of the OVX animals on a chow diet. Interestingly, reductions in body weight gain correlated well with WAT mass reductions (data not shown), indicating that reduced WAT may lead to a reduced body weight. In contrast to the OVX mice, fenofibrate did not decrease high-fat diet–induced body weight gain and WAT mass increases in Sham mice. These results suggest that obesity is differentially affected in response to fenofibrate in Sham and OVX mice. According to recent reports, fenofibrate seems to act as a weight-stabilizer through PPARα; however, these results were obtained using male animal models.[14-16] Nevertheless, these reports suggest that fenofibrate not only prevents excessive weight gain, but is also able to mobilize

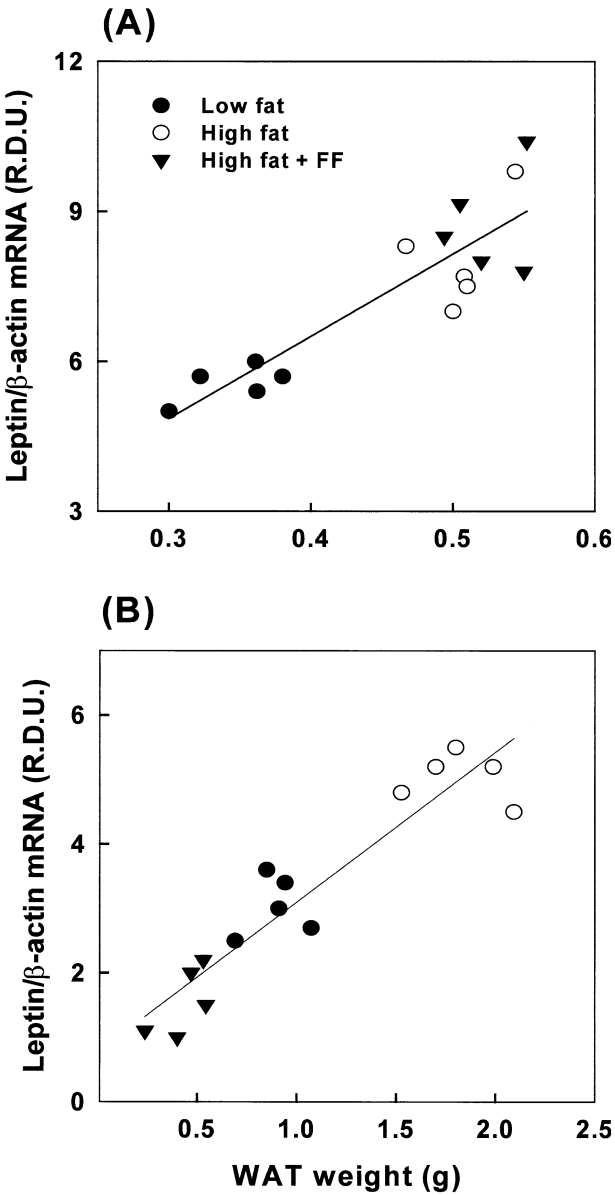

Fig 2. Correlation between leptin mRNA levels and WAT weight after fenofibrate treatment in female (A) Sham and (B) OVX mice. Female Sham and OVX mice received a low-fat, high-fat, or fenofibrate-supplemented (FF; 0.05% wt/wt) high-fat diet for 13 weeks. WAT weights were measured at the end of the treatment period. RNA was extracted from adipose tissue, and leptin and β-actin mRNA levels were measured as described in the Methods. mRNA results are expressed as the R.D.U. (relative density units) using β-actin as a reference.

fat from adipose tissue by increasing fat catabolism in the liver, which supports the findings of present study. Therefore, it is noteworthy that reductions in body weight gain and WAT mass by fenofibrate in male mice are also shown by female OVX mice, but that these effects were absent in female Sham mice.

However, fenofibrate seems to differentially affect body weight and adiposity among Sham and OVX mice by a mechanism other than the modulation of leptin gene expression. Although leptin is produced only in adipose tissue and elicits satiety responses by binding to leptin receptors in the brain,[25,26] our data show that changes in leptin mRNA levels are in accordance with those in body weight and WAT mass in both female OVX and Sham mice following fenofibrate treatment. Consistent with this finding, Guerre-Millo et al[15] reported that serum leptin concentrations positively correlated with body weight and epididymal adipose tissue mass in fenofibrate-treated male mice, suggesting that fenofibrate may modulate body weight not by influencing leptin gene expression and food intake, but by enhancing the energy expenditure.[27,28]

By stimulating hepatic fatty acid oxidation and by reducing apo C-III expression, fibrates are known to lower plasma triglyceride levels in a PPARα-mediated manner,[4] which is responsible for lipid accumulation in adipose tissue. We thus studied the effects of fenofibrate on the hepatic expression of

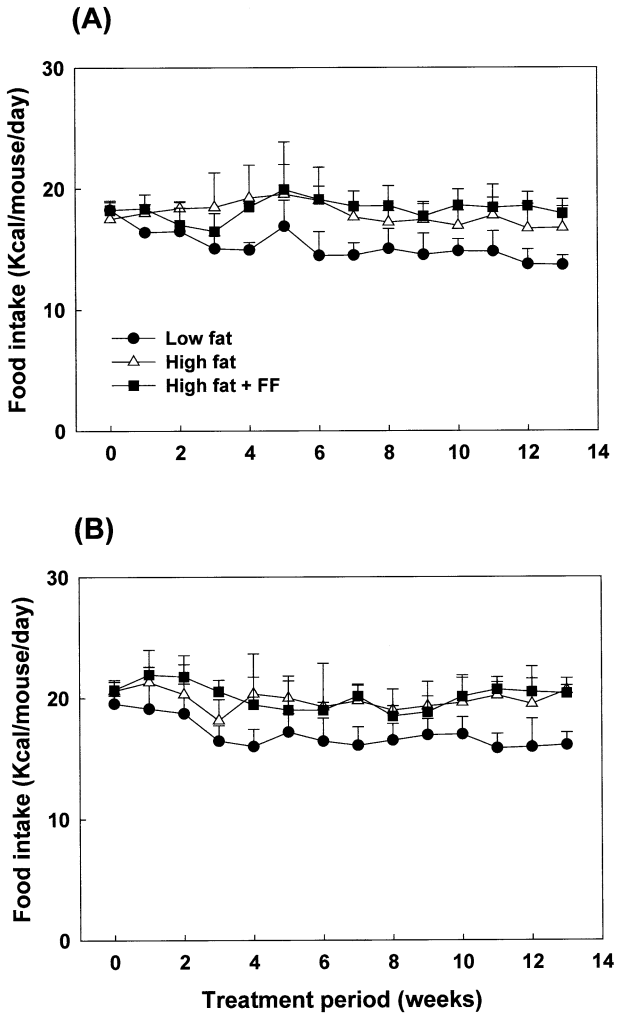

Fig 3. Effects of fenofibrate on food intake in female (A) Sham and (B) OVX mice. Female Sham and OVX mice received a low-fat, high-fat, or fenofibrate-supplemented (FF; 0.05% wt/wt) high-fat diet for 13 weeks. Food intake was measured daily using special metal food containers. All values are expressed as the mean ± SD.

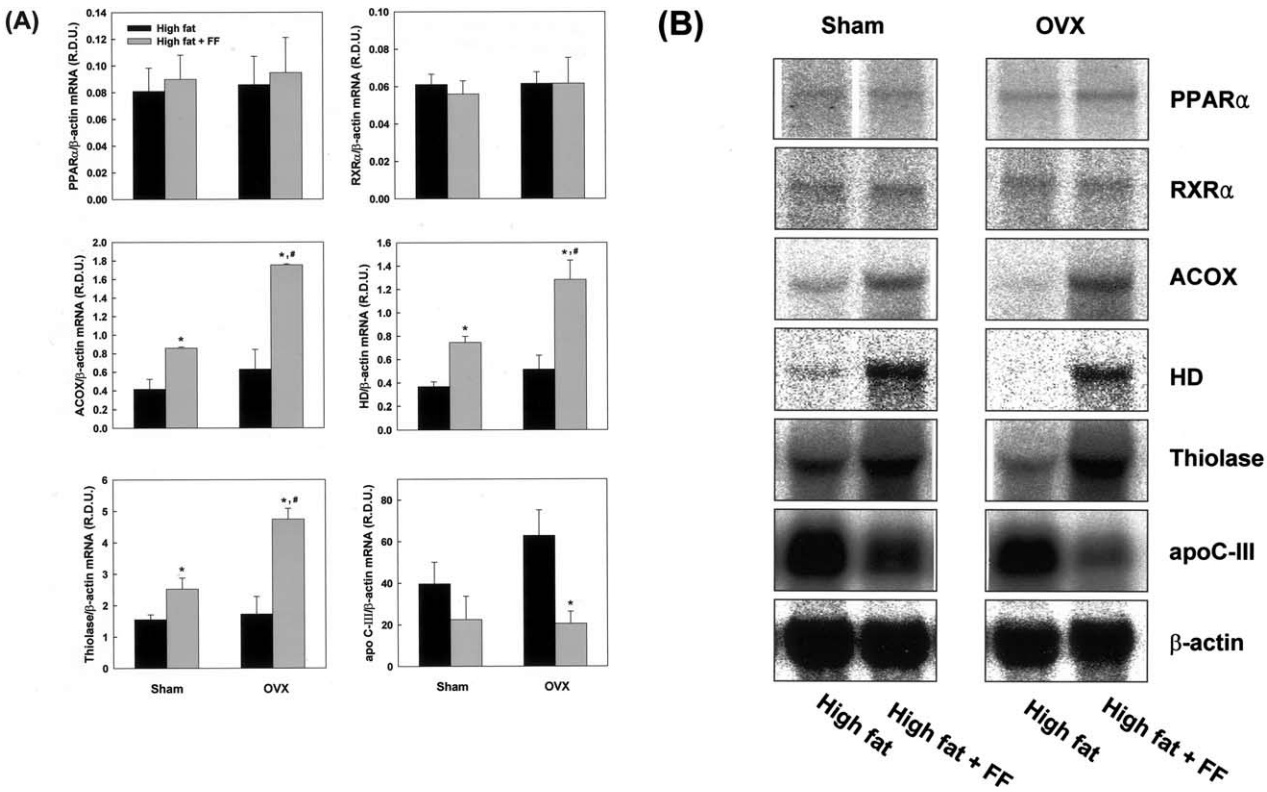

Fig 4. Effects of fenofibrate on the hepatic mRNA levels of PPARα target genes. (A) Female Sham and OVX mice received a low-fat, high-fat, or fenofibrate-supplemented (FF; 0.05% wt/wt) high-fat diet for 13 weeks. RNA was extracted from the liver, and PPARα target genes and β-actin mRNA levels were measured as described in the Methods. All values are expressed as the mean ± SD of R.D.U. (relative density units) using β-actin as a reference. *Significantly different *v* the high fat group, $P < .05$. #Significantly different *v* the Sham group, $P < .05$. (B) Representative Northern blots, from an independent experiment.

apo C-III gene and PPARα target genes involved in fatty acid β-oxidation to determine whether differences in gene expression might explain the different effects of fenofibrate on gonad-dependent weight gain in females. As expected, a high-fat diet containing fenofibrate not only elevated the transcriptional activation of PPARα target genes, ACOX, HD, and thiolase, but also reduced apo C-III mRNA levels versus a high-fat diet alone in both groups of mice. Moreover, these alterations in expression levels were found to be more prominent in female OVX than in Sham mice after fenofibrate treatment. Our results are supported by findings that the effect of fenofibrate on obesity may involve its action on fatty acid β-oxidation in the liver, and that the body weights of PPARα-null mice are higher than those of PPARα wild-type mice.[13,16] These reports and the findings of the present work suggest that fenofibrate influences obesity via the differential activation of PPARα in female Sham and OVX mice.

It has also been reported that ovarian steroids can affect obesity and lipid metabolism, and that these effects are probably mediated by estradiol.[17] Estrogen insufficiency is thought to be largely responsible for increased adiposity and circulating lipids in OVX rodents, because such animals do not display obesity, adiposity, and lipid disorders when they are administered estrogen.[29,30] Although the administration of estrogen or fenofibrate alone effectively reduces body weight gain and WAT mass in high-fat–fed female OVX mice, our present data show that fenofibrate treatment does not prevent them in female Sham mice with functioning ovaries. Our findings suggest the possibility that signal cross-talk may exist between PPARα and estrogen receptor in their effects of obesity, and that the action of fenofibrate may be influenced by estrogen in females.[31-33]

In conclusion, our results provide evidence that treatment with fenofibrate has different effects on body weight and WAT mass, in part due to differentially activating hepatic β-oxidation and apo C-III gene expression between female Sham and OVX mice. These differences may provide important information about the mechanisms modulating obesity, and about the actions of other lipid-lowering drugs, such as fenofibrate, which are PPARα ligands in females. Further work is needed to identify the mechanism by which fenofibrate effects obesity, in an ovarian steroid-dependent manner, in order to understand the actions of PPARα with respect to female obesity. In addition, these results also suggest that the administration of fenofibrate may effectively prevent obesity in overweight postmenopausal women.

REFERENCES

1. Schoonjans K, Staels B, Auwerx J: Role of peroxisome proliferator-activated receptor (PPAR) in mediating the effects of fibrates and fatty acids on gene expression. J Lipid Res 37:907-925, 1996
2. Staels B, Dallongeville J, Auwerx J, et al: Mechanism of action of fibrate on lipid and lipoprotein metabolism. Circulation 98:2088-2093, 1998
3. Kliewer SA, Lehmann JM, Wilson TM: Orphan nuclear receptors: Shifting endocrinology into reverse. Science 30:757-760, 1999
4. Sander K, Beatrice D, Walter W: Roles of PPARs in health and disease. Nature 405:421-424, 2000
5. Hertz R, Bishara-Shieban J, Bar-Tana J: Mode of action of peroxisome proliferators as hypolipidemic drugs. Suppression of apolipoprotein C-III. J Biol Chem 270:13470-13475, 1995
6. Auwerx J, Schoonjans K, Fruchart JC, et al: Transcriptional control of triglyceride metabolism: Fibrates and fatty acids change the expression of the LPL and apo C-III genes by activating the nuclear receptor PPAR. Atherosclerosis 124:S29-S37, 1996 (suppl)
7. Schoonjans K, Peinado-Onsurbe J, Lefebvre AM, et al: PPARalpha and PPARgamma activators direct a distinct tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. EMBO J 15:5336-5348, 1996
8. Martin G, Schoonjans K, Lefebvre AM, et al: Coordinate regulation of the expression of the fatty acid transport protein and acyl-CoA synthetase genes by PPARalpha and PPARgamma activators. J Biol Chem 272:28210-28217, 1997
9. Zhang B, Marcus SL, Sajjadi FG, et al: Identification of a peroxisome proliferator-responsive element upstream of the gene encoding rat peroxisomal enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase. Proc Natl Acad Sci USA 89:7541-7545, 1992
10. Osumi T, Osada S, Tsukamoto T: Analysis of peroxisome proliferator-responsive enhancer of the rat acyl-CoA oxidase gene. Ann NY Acad Sci 804:202-213, 1996
11. Nicolas-Frances V, Dasari VK, Abruzzi E, et al: The peroxisome proliferator response element (PPRE) present at positions −681/−669 in the rat liver 3-ketoacyl-CoA thiolase B gene functionally interacts differently with PPARalpha and HNF-4. Biochem Biophys Res Commun 269:347-351, 2000
12. Bourgeois F, Alexiu A, Lemonnier D: Dietary-induced obesity: Effect of dietary fats on adipose tissue cellularity in mice. Br J Nutr 49:17-26, 1983
13. Costet P, Legendre C, More J, et al: Peroxisome proliferator-activated receptor alpha-isoform deficiency leads to progressive dyslipidemia with sexually dimorphic obesity and steatosis. J Biol Chem 273:29577-29585, 1998
14. Chaput E, Saladin R, Silvestre M, et al: Fenofibrate and rosiglitazone lower serum triglycerides with opposing effects on body weight. Biochem Biophys Res Commun 271:445-450, 2000
15. Guerre-Millo M, Gervois P, Raspe E, et al: Peroxisome proliferator-activated receptor alpha activators improve insulin sensitivity and reduce adiposity. J Biol Chem 275:16638-16642, 2000
16. Mancini FP, Lanni A, Sabatino L, et al: Fenofibrate prevents and reduces body weight gain and adiposity in diet-induced obese rats. FEBS Lett 491:154-158, 2001
17. Mystkowski P, Schwartz MW: Gonadal steroids and energy homeostasis in the leptin era. Nutrition 16:937-946, 2000
18. Wade GN: Some effects of ovarian hormones on food intake and body weight in female rats. J Comp Physiol Psychol 88:183-193, 1975
19. Czaja JA, Butera PC, McCaffrey TA: Independent effects of estradiol on water and food intake. Behav Neurosci 97:210-220, 1983
20. Garcia Rodriguez LA, Pfaff GM, Schumacher MC, et al: Replacement estrogen use and body mass index. Epidemiology 1:219-223, 1990
21. Wing RR, Matthews KA: Weight gain at the time of menopause. Arch Intern Med 151:97-102, 1991
22. Geary N, Asarian L: Estradiol increases glucagon's satiating potency in ovariectomized rats. Am J Physiol Regul Integr Comp Physiol 281:R1290-R1294, 2001
23. Yoon M, Jeong S, Nicol CJ, et al: Fenofibrate regulates obesity and lipid metabolism with sexual dimorphism. Exp Mol Med 34:481-488, 2002
24. Sinal CJ, Yoon M, Gonzalez FJ: Antagonism of the actions of peroxisome proliferator activated receptor-alpha by bile acids. J Biol Chem 276:47154-47162, 2001
25. Zhang Y, Proenca R, Maffei M, et al: Positional cloning of the mouse obese gene and its human homologue. Nature 372:425-432, 1994
26. Lee GH, Proenca R, Montez JM, et al: Abnormal splicing of the leptin receptor in diabetic mice. Nature 379:632-635, 1996
27. Kelly LJ, Vicario PP, Thompson GM, et al: Peroxisome proliferator-activated receptors gamma and alpha mediate in vivo regulation of uncoupling protein (UCP-1, UCP-2, UCP-3) gene expression. Endocrinology 139:4920-4927, 1998
28. Tsuboyama-Kasaoka N, Takahashi M, Kim H, et al: Up-regulation of liver uncoupling protein-2 mRNA by either fish oil feeding or fibrate administration in mice. Biochem Biophys Res Commun 257:879-885, 1999
29. Shearer GC, Joles JA, Jones H, et al: Estrogen effects on triglyceride metabolism in analbuminemic rats. Kidney Int 57:2268-2274, 2000
30. Shinoda M, Latour MG, Lavoie JM: Effects of physical training on body composition and organ weights in ovariectomized and hyperestrogenic rats. Int J Obes Relat Metab Disord 26:335-343, 2002
31. Nunez SB, Medin JA, Keller H, et al: Retinoid X receptor beta and peroxisome proliferator-activated receptor activate an estrogen response element. Recent Prog Horm Res 50:409-416, 1995
32. Nunez SB, Medin JA, Braissant O, et al: Retinoid X receptor and peroxisome proliferator-activated receptor activate an estrogen responsive gene independent of the estrogen receptor. Mol Cell Endocrinol 127:27-40, 1997
33. Wang X, Kilgore MW: Signal cross-talk between estrogen receptor alpha and beta and the peroxisome proliferator-activated receptor gamma1 in MDA-MB-231 and MCF-7 breast cancer cells. Mol Cell Endocrinol 194:123-133, 2002