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Fenofibrate regulates obesity and lipid metabolism with sexual dimorphism

Michung Yoon[1,4], Sunhyo Jeong[1], Christopher J. Nicol[3], Hyunghee Lee[1], Miyoung Han[1], Jung-Jae Kim[2], Yun-Jeong Seo[2], Chilyeol Ryu[1] and Goo Taeg Oh[2]

[1]Department of Life Sciences
Mokwon University
Taejon 302-729, Korea
[2]Genetic Resources Center
Korea Research Institute of Bioscience and Biotechnology
Taejon 305-600, Korea
[3]Laboratory of Metabolism
Division of Basic Sciences
National Institutes of Health
Bethesda, MD, 20892, U.S.A.
[4]Corresponding author: Tel, 82-42-829-7585;
Fax, 82-42-829-7580; E-mail, yoon60@mokwon.ac.kr.

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Abbreviations: ACOX, acyl-CoA oxidase; HD, enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase; PPARα, peroxisome proliferator-activated receptor α; RXR, retinoid X receptor; WAT, white adipose tissue

Abstract

To determine whether the PPARα agonist fenofibrate regulates obesity and lipid metabolism with sexual dimorphism, we examined the effects of fenofibrate on body weight, white adipose tissue (WAT) mass, circulating lipids, and the expression of PPARα target genes in both sexes of high fat diet-fed C57BL/6J mice. Both sexes of mice fed a high-fat diet for 14 weeks exhibited increases in body weight, visceral WAT mass, as well as serum triglycerides and cholesterol, although these effects were more pronounced among males. Feeding a high fat diet supplemented with fenofibrate (0.05% w/w) reduced all of these effects significantly in males except serum cholesterol level. Females on a fenofibrate-enriched high fat diet had reduced serum triglyceride levels, albeit to a smaller extent compared to males, but did not exhibit decreases in body weight, WAT mass, and serum cholesterol. Fenofibrate treatment resulted in hepatic induction of PPARα target genes encoding enzymes for fatty acid β-oxidation, the magnitudes of which were much higher in males compared to females, as evidenced by results for acyl-CoA oxidase, a first enzyme of the β-oxidation system. These results suggest that observed sexually dimorphic effects on body weight, WAT mass and serum lipids by fenofibrate may involve sexually related elements in the differential activation of PPARα.

Keywords: fenofibrate; lipid; obesity; PPARα; sex

Introduction

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 metabolism (Schoonjans *et al.*, 1996a; Staels *et al.*, 1998; Kliewer *et al.*, 1999). Activated PPARα heterodimerizes with retinoid X receptor (RXR) and then increases the expression of target genes that have a peroxisome proliferator-responsive element (PPRE) in their promoter regions (Dreyer *et al.*, 1992). PPARα target genes include those involved in hydrolysis of plasma triglycerides such as lipoprotein lipase and apolipoprotein C-III (Hertz *et al.*, 1995; Auwerx *et al.*, 1996; Schoonjans *et al.*, 1996b), fatty acid uptake and binding such as fatty acid transport protein and acyl-CoA synthetase (Martin *et al.*, 1997), and fatty acid β-oxidation acyl-CoA oxidase (ACOX), enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase (HD) and thiolase for (Zhang *et al.*, 1992; Osumi *et al.*, 1996; Nicolas-Frances *et al.*, 2000), all of which participate in lipid catabolism.

Fibrate are also suggested to be involved in the regulation of obesity. Obesity is the result of an imbalance between caloric intake and energy expenditure. Excess caloric intake promotes the elevated circulating concentrations of plasma triglycerides and cholesterol, the former of which is responsible for hypertrophy and hyperplasia of adipose cells (Bourgeois *et al.*, 1983; Costet *et al.*, 1998; Chaput *et al.*, 2000). The fenofibrate-induced reduction of plasma triglycerides as well as free fatty acids (Schoonjans *et al.*, 1996a; Staels *et al.*, 1998) may thus inhibit a rise 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 serum triglycerides and cholesterol, and became obese with age (Costet *et al.*, 1998). Furthermore, several recent studies suggest that fenofibrate can modulate obesity in several experimental animal systems such as fatty Zucker rats, high fat fed C57BL/6J mice, and high fat fed obese rats (Chaput *et al.*, 2000; Guerre-Millo *et al.*, 2000; Mancini *et al.*, 2001).

Energy balance seems to differ depending on the gonadal sex steroids (Mystkowski and Schwartz, 2000). Gonadal steroids are widely recognized to influence food intake, energy expenditure, body weight, and body fat composition, although the specific mechanisms underlying these effects are not clear. Androgens are generally accepted as anabolic agents that promote food intake, whereas estrogens are catabolic agents that decrease food intake and body weight (Wade, 1975; Roy and Wade, 1977; Chai *et al.*, 1999; Geary and Asarian, 2001). Based on these previous reports, the role of the PPARα ligand fenofibrate in obesity and lipid metabolism suggests that energy homeostasis and body weight can be regulated with sexual dimorphism.

To test this hypothesis, we measured the effects of fenofibrate on the changes in body weight, adipose tissue mass, circulating lipids, and the expression of PPARα target genes in both sexes of C57BL/6J mice. Here we report that fenofibrate may exert sexually dimorphic control of body weight, white adipose tissue (WAT) mass and serum lipids, but its effect on obesity may be associated with differential induction of hepatic PPARα- target genes.

Materials and Methods

Animals and treatments

For all experiments, eight-week-old mice (C57BL/6J) were housed and bred at the Korea Research Institute of Bioscience and Biotechnology under specific pathogen-free conditions with a standard 12-h light/dark cycle. Prior to the administration of special diets, mice were fed standard rodent chow and water *ad libitum*. Female and male mice were each randomly divided into three groups (n = 5/group) and received either a regular chow fat diet (4.5% fat w/w, CJ Corp., Korea), a high fat diet containing 15% fat (w/w, Oriental Yeast Co. Ltd., Japan), or a high fat diet supplemented with fenofibrate (0.05% w/w, Sigma) for 14 weeks. In all experiments, body weight and food intake were monitored throughout the treatment period. At the end of the study, blood samples were collected, from which serum was isolated and stored at -20°C until further analysis. 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).

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 and Schuell, Inc., Dassel, Germany) by downward capillary transfer in the presence of 20×SSC buffer (3 M NaCl, 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 were 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 (Sinal *et al.*, 2001). Densitometric analysis of the mRNA signals was performed using ImageQuant image analysis software (Molecular Dynamics).

Statistics

Unless otherwise noted, all values are expressed as mean±SD. All data were analyzed by ANOVA for statistically significant differences between each group.

Results

Effects of fenofibrate on body weight and WAT mass

To determine whether fenofibrate regulates obesity in both sexes of animals, C57BL/6J mice, which became obese when fed a high fat diet were used. C57BL/6J mice fed a high fat diet had body weights that were increased by 11% in males (33.3±0.96 *g* in high fat diet group and 30.1±0.76 *g* in low fat diet group) and 6% in females (25.5±0.60 *g* in high fat diet group and 24.5±0.50 *g* in low fat diet group) (Figure 1). In contrast, fenofibrate treatment reduced body weight by 12% (29.8±0.36 *g* in high fat/fenofibrate diet group) in male mice, but failed to decrease body weight in female mice.

Similarly, WAT mass was increased by 93% (1.38±

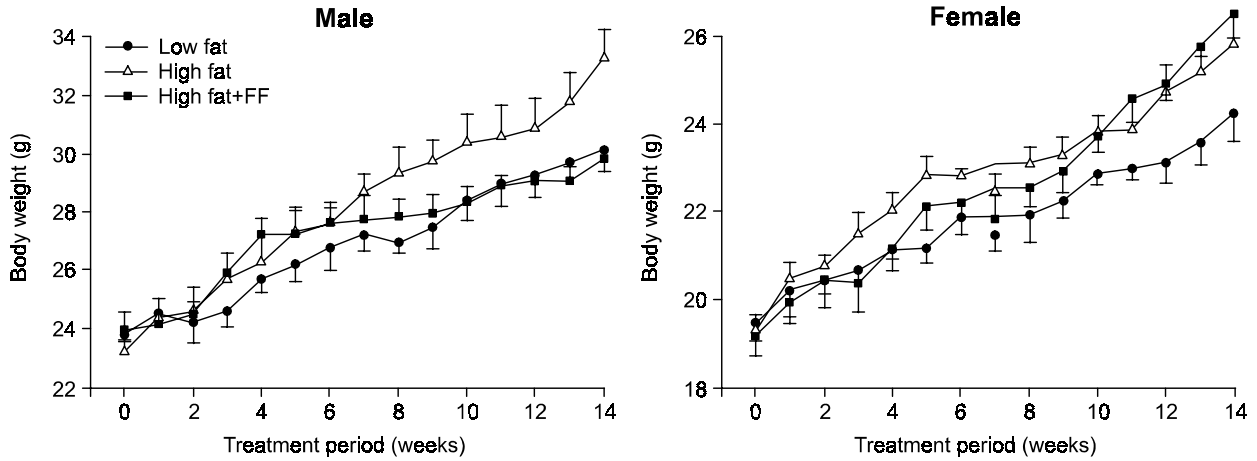

Figure 1. Differential regulation of high fat diet-induced body weight gain by fenofibrate in both sexes of C57BL/6J mice. Male and female C57BL/6J mice received a low fat, a high fat or the same high fat diet supplemented with fenofibrate (FF; 0.05% w/w) for 14 weeks. All values are expressed as the mean ± SD. Body weights at the end of the treatment period are statistically significant between the low fat group and the high fat ($P<0.05$) and high fat plus fenofibrate ($P<0.01$) groups in female mice, and between the high fat group and the low fat ($P<0.05$) and high fat plus fenofibrate ($P<0.01$) groups in male mice.

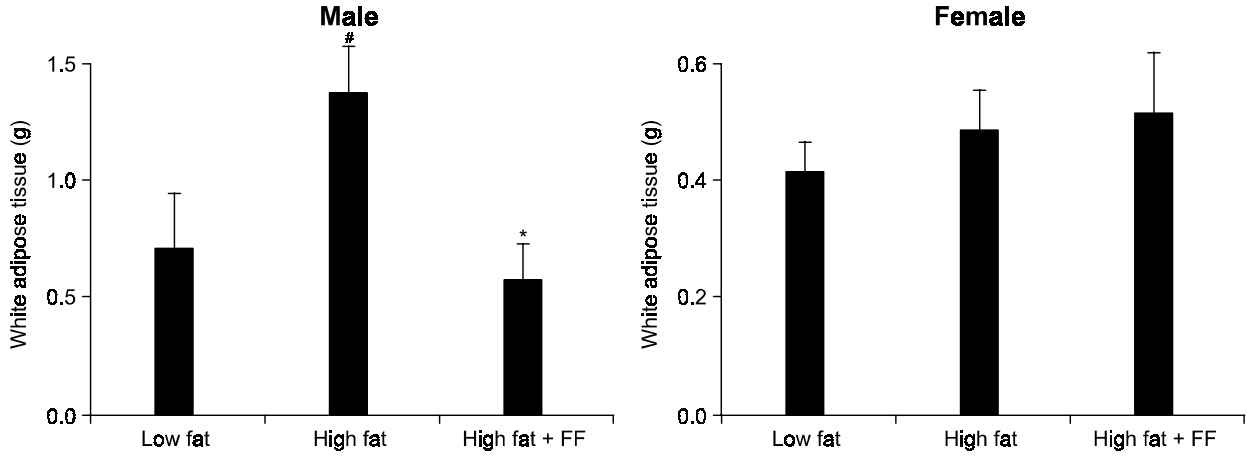

Figure 2. Modulation of high fat diet-induced visceral adipose tissue mass by fenofibrate in both sexes of C57BL/6J mice. Male and female C57BL/6J mice received a low fat, a high fat, or the same high fat diet supplemented with fenofibrate (FF; 0.05% w/w) for 14 weeks. All values are expressed as the mean ± SD. #, Significantly different *versus* low fat group, $P<0.05$. *, Significantly different *versus* high fat group, $P<0.01$.

0.19 *g* in high fat diet group and 0.71±0.23 *g* in low fat diet group) and 18% (0.49±0.06 *g* in high fat diet group and 0.42±0.05 *g* in low fat diet group) respectively in high fat fed male and female mice (Figure 2). In response to fenofibrate, the high fat diet-induced increase in WAT mass was significantly decreased by 135% (0.59±0.14 *g* in high fat/fenofibrate diet group) ($P<0.01$) in male mice, but showed little changes in female mice. In addition, male mice given a fenofibrate-supplemented high fat diet had smaller body weights and WAT, the magnitudes of which were well correlated with each other (data not shown). These data demonstrate not only that the effects of fenofibrate are different between sexes, but also that fenofibrate can prevent obesity in male mice.

Daily monitoring of chow (low fat, high fat and high fat containing 0.05% fenofibrate diets) uptake by both male and female mice showed similar food consumption profiles regardless of diet types animals were fed throughout the study (12.5±0.27 *g* per mouse per day), indicating that fenofibrate did not have any differential influences on food intake between two sexes (data not shown).

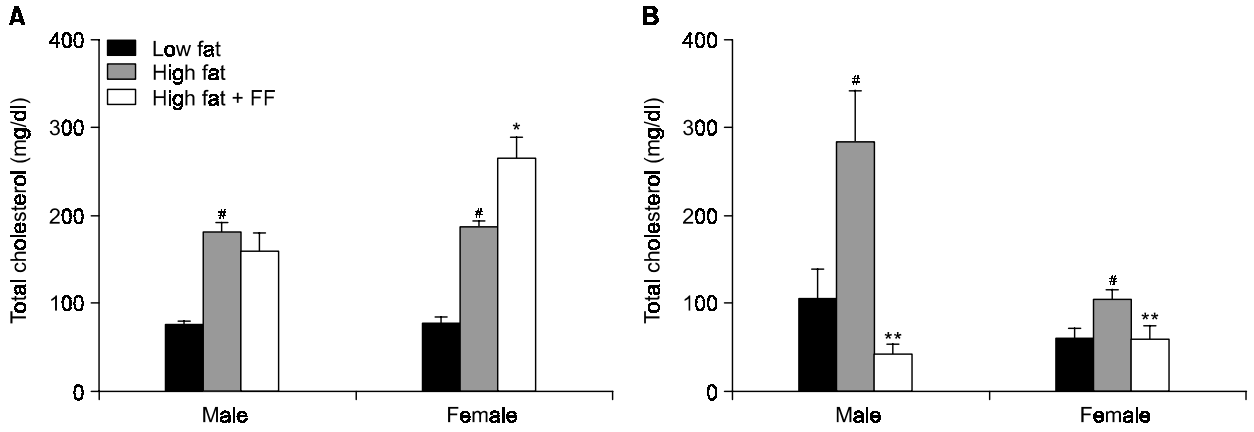

Figure 3. Changes in circulating total cholesterol and triglycerides by fenofibrate in both sexes of C57BL/6J mice. Male and female C57BL/6J mice received a low fat, a high fat, or the same high fat diet supplemented with fenofibrate (FF; 0.05% w/w) for 14 weeks. Serum concentrations of total cholesterol (A) and triglycerides (B) were measured and all values are expressed as the mean ± SD. #, Significantly different *versus* low fat group, $P<0.001$. *, Significantly different *versus* high fat group, $P<0.01$. **, Significantly different *versus* high fat group, $P<0.001$.

Effects of fenofibrate on lipid levels

Since fenofibrate has beneficial effects on lipid profiles and acts as an efficient lipid-lowering drug, its effects on serum total cholesterol and triglycerides were examined in high fat diet-induced obese C57BL/6J mice (Figure 3). In comparison with respective low fat diet fed control animals, the high fat diet fed mice increased serum total cholesterol and triglycerides in both sexes ($P<0.001$). Serum triglycerides and total cholesterol were significantly decreased among fenofibrate-treated male mice, respectively reduced by 86% ($P<0.001$) and 12%; moreover, triglycerides were lower than those of chow fed male mice. Fenofibrate treatment of female mice also decreased circulating triglycerides by 31% ($P<0.001$), but to a much smaller extent compared to similarly treated males, and in contrast, increased total cholesterol by 30% ($P<0.01$). Our data show a strong correlation between decreased serum triglycerides, body weights and WAT mass following fenofibrate treatment in male mice, which is supported by the information that WAT lipids are largely derived from serum triglycerides (Lupien *et al.*, 1991; Yano *et al.*, 1997; Fruchart *et al.*, 1998). Nevertheless, it appears that lowering serum triglycerides does not directly control obesity in female mice.

Effects of fenofibrate on hepatic expression of PPARα target genes

To evaluate whether the dimorphic effects of fenofibrate on obesity and lipid profiles between male and female C57BL/6J mice were caused by differential PPARα actions in the liver, mRNA levels were measured for the PPARα targets ACOX, HD, and thiolase. Analysis of the hepatic mRNA expression of PPARα and its heterodimerization partner RXRα revealed no significant effects by any dietary regimens in both male and female mice (Figure 4A, B). However, both sexes of fenofibrate treated mice had elevated PPARα target gene expression for peroxisomal fatty acid β-oxidation. The expression levels of ACOX, HD, and thiolase were respectively 460%, 320%, and 115% higher in males compared to females. In addition, for ACOX, which is the first and rate-limiting enzyme in the β-oxidation system, fenofibrate treated male mice showed significant increases in mRNA expression in comparison with high fat diet controls, but these changes were not detected among similar female treated groups, demonstrating a marked sexual dimorphism in fenofibrate actions.

Discussion

The present study demonstrates that PPAR activator fenofibrate influences body weight, WAT, and circulating lipids in both sexes of mice through the differential activation of PPARα. Fenofibrate treatment reduces body weight gain and WAT in high fat diet-fed male mice, but fails to do so in female mice. In males, body weight and WAT mass were respectively increased over low fat controls by 11% and 93% after 14-week administration of high fat diet. These parameters began to decrease 7 weeks into the fenofibrate treatment regimen, and were significantly lowered compared to low fat diet controls by 14 weeks. In addition, reductions in body weight correlated well with a fall in WAT mass (data not shown), indicating that a decreased WAT may lead to a reduced body

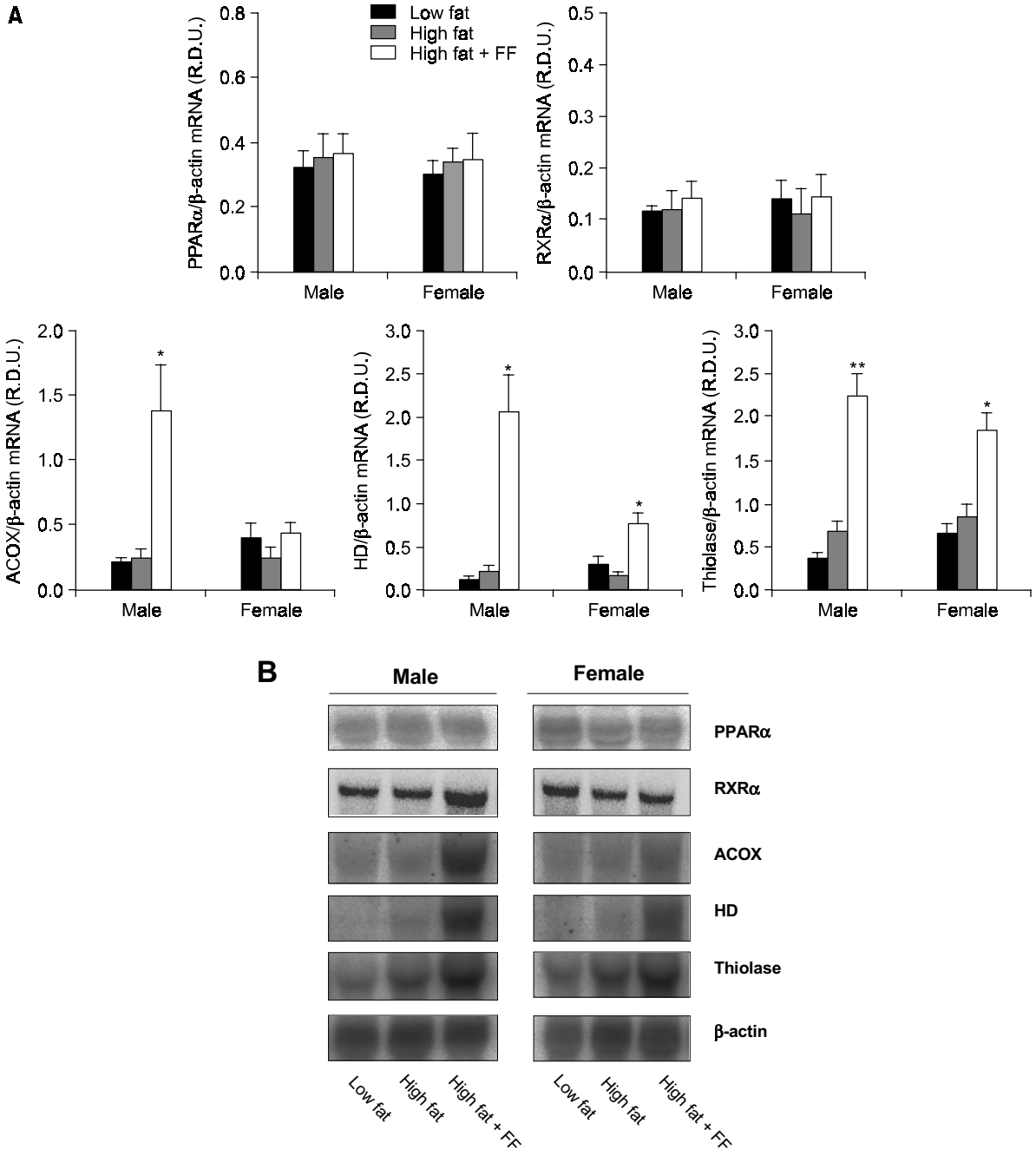

Figure 4. Modulation of PPARα target gene expression by fenofibrate in both sexes of C57BL/6J mice. (A) Male and female C57BL/6J mice received a low fat, a high fat, or the same high fat diet supplemented with fenofibrate (FF; 0.05% w/w) for 14 weeks. RNA was extracted from liver and PPARα target genes and β-actin mRNA levels were measured as described under Materials and Methods. The mean ± SD for 3 animals is shown and all values are expressed in relative density units (RDU) using β-actin as a reference. *, Significantly different *versus* high fat group, $P < 0.01$. **, Significantly different *versus* high fat group, $P < 0.001$. (B) Representative autoradiograms of Northern blot analysis.

weight. In contrast to males, compared with high fat diet controls, fenofibrate did not decrease high fat diet-induced increases in body weight and WAT mass. This data suggests a difference in the response to PPARα ligands between females and males in the control of obesity. Previous studies reported fenofibrate may be an effective regulator of energy homeostasis in males by showing that fenofibrate can modulate body weight and WAT among animal models such as fatty *fa/fa* Zucker rats, and

high fat-fed C57BL/6 mice, and Wistar rats (Chaput *et al.*, 2000; Guerre-Millo *et al.*, 2000; Mancini *et al.*, 2001). Our present data provide the first direct evidence that male and female C57BL/6J mice respond differently to fenofibrate and that these differences may provide important information for understanding the mechanisms regulating obesity and the actions of other lipid lowering drugs such as fenofibrate which are PPARα ligands.

Furthermore, fenofibrate reduced serum concentrations of total cholesterol and triglycerides significantly in male mice similar to previous reports (Lupien *et al.*, 1991; Fruchart *et al.*, 1998), and lowered circulating levels of triglycerides, but to a much smaller extent but failed to decrease total cholesterol in female mice. These data show that fenofibrate controls lipid metabolism with sexual dimorphism, although fenofibrates are drugs widely used to control elevated plasma triglycerides and cholesterol. In old PPARα-knockout mice, deficient females exhibited a 250.5% higher level of serum triglycerides *versus* control values, and deficient males showed a 154.6% higher level of serum triglycerides *versus* control values, which support our results that PPARα regulation on lipid metabolism may be different between sexes, although the increase of triglycerides in deficient female mice is higher than that of deficient male mice (Costet *et al.*, 1998). Based on the information that accumulated lipids in WAT are largely derived from circulating triglycerides, differential regulation of obesity by fenofibrate may be partly due to different levels of circulating lipids between sexes.

Fenofibrate is not likely to have a direct effect on adipose tissue, although it can reduce WAT mass and body weights in male mice, because fenofibrate does not exert a specific regulatory effect on leptin production related to body fat accumulation and PPARα-knockout mice that became obese with age are not hyperphagic (Martin *et al.*, 1997; Costet *et al.*, 1998; Guerre-Millo *et al.*, 2000, Lee *et al.*, 2001). Instead, many reports indicate that fenofibrate increases hepatic β-oxidation, resulting in decreased fatty acids available for triglyceride synthesis (Kalderon *et al.*, 1992; Rustan *et al.*, 1992; Skrede *et al.*, 1994). We studied the effect of fenofibrate on the hepatic expression of PPARα target genes involved in fatty acid β-oxidation to determine if differences of gene expression might explain the different effects of fenofibrate on obesity between sexes. A high fat diet containing fenofibrate elevated the transcriptional activation of PPARα target genes, ACOX, HD and thiolase, compared with high fat diet alone in both sexes of mice. However, the expression levels were much higher in males *versus* females. More interestingly, mRNA levels of ACOX, the rate-limiting step in the fatty acid β-oxidation system, were not changed by fenofibrate treatment in female mice whereas its expression was significantly increased in male mice, suggesting that fenofibrate exhibits sexually dimorphic activation of PPARα-mediated hepatic β-oxidation, resulting in a differential energy balance between sexes.

Consistent with the present study, Guerre-Millo *et al.* (2000) and Mancini *et al.* (2001) report that fenofibrate improves obesity due to its action on the fatty acid β-oxidation in the liver and seems to act as a weight-stabilizer through its effect on liver metabolism. Moreover, it was suggested that the body weights of PPARα deficient mice were greater than PPARα wild-type mice and a marked increased amount of intra-abdominal adipose tissue was examined in PPARα knockout mice (Costet *et al.*, 1998; Poynter and Daynes, 1998). In addition, Costet *et al.* (1998) suggested that the difference in body weight between male and female PPARα-null mice was attributed in part to differences in hepatic PPARγ expression and differences in hepatic lipid accumulation, but differences in hepatic lipid accumulation following fenofibrate was not detected between males and females in this study (data not shown). In contrast, Akiyama *et al.* (2001) provide evidence that PPARα regulates lipid metabolism, but is not associated with obesity. Suggesting that the conflicting accounts of phenotypes for PPARα-null mouse lines with respect to obesity seem to be due to the strain of congenic mouse used for analysis and the source of fat used for control and experimental diet (Akiyama *et al.* 2001). However, it is not likely that these factors have contributed to any significant degree on PPARα actions in our experimental condition (with the wild-type C57BL/6J mice, and the same source of fat). The results presente here does provide support that fenofibrate is involved in obesity through PPARα-mediated action. Especially, a noteworthy finding of this study is that fenofibrate treatment did not prevent body weight and dyslipidemia in female mice with healthy ovaries and further suggest possibilities of a cross-talk between fenofibrate and estrogen in the control of obesity and lipid metabolism. A notion that fenofibrate action may be influenced by estrogen in females is supported by the report showed that PPARs/RXRs interact with estrogen receptor (ER) which then inhibit transactivation by ER through competition for estrogen response element (ERE) (Keller *et al.*, 1995). PPRE and ERE have common consensus half-site sequence AGGTCA. However, a signaling cross-talk between PPARα/RXRα and ER is not known for the regulation of both lipid disorder and obesity of female mice.

Overall, the results of this study provide evidence that the treatment of fenofibrate affects body weight, WAT mass, lipid metabolism, and hepatic β-oxidation with sexual dimorphism, and that fenofibrate regulated obesity may be influenced by sex-related factors.

Further investigation of the mechanism by which fenofibrate exerts its differential effects on energy balance and obesity among the sexes is needed. Moreover, further work is also needed to determine the factors contributing to these sex differences following fenofibrate treatment, in order that the mechanisms leading to obesity may not only be better understood, but also therapeutically treated more effectively among different sexes.

Acknowledgements

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