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Troglitazone Regulates white Adipose Tissue Metabolism by Activating Genes Involved in Fatty Acid β-Oxidation in High Fat Diet-fed C57BL/6J Mice

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This study aimed to determine whether troglitazone stimulates genes related to fatty acid β-oxidation, leading to modulation of white adipose tissue (WAT) metabolism in high fat diet-fed mice. Female C57BL/6J mice were randomly divided into two groups (n=10/group). After they received either a high fat diet or the same high fat diet supplemented with troglitazone for 4 weeks, the effects of troglitazone on gene expression and physiology of WAT were measured using Northern, histological and serological analyses. Administration of troglitazone induced the expression of genes involved in mitochondrial and peroxisomal fatty acid β-oxidation in mesenteric WAT. Troglitazone also significantly increased uncoupling protein 2 mRNA levels. The changes in WAT gene expression were accompanied by reductions in circulating levels of free fatty acids and triglycerides as well as glucose and insulin. Histological studies showed that troglitazone treatment decreased the average size of adipocytes in mesenteric WAT. These results suggest that troglitazone-stimulated WAT expression of genes associated with fatty acid β-oxidation regulates WAT metabolism of high fat diet-fed mice, contributing to improvement of insulin sensitivity.

Key Words: Troglitazone, PPARγ, White adipose tissue, Fatty acid β-oxidation, Uncoupling protein 2

INTRODUCTION

The thiazolidinediones (TZDs) are a class of antidiabetic drugs for the treatment of type II diabetes on the basis of their ability to lower glucose levels. TZDs mediate their therapeutic effects through direct interactions with perosome proliferator-activated receptor γ (PPARγ) (Hauner, 2002; Lehmann et al., 1995; Spiegelman, 1998). Activated PPARγ modulates target gene expression by binding to DNA response elements composed of a direct repeat of the hexameric core motif AGGTCA separated by a single base pair after heterodimerization with retinoid X receptor (RXR). The PPARγ/RXR heterodimer plays a crucial role in adipogenesis and insulin sensitization (Camp et al., 2002; Rangwala and Lazar, 2004; Rosen and Spiegelman, 2000; Willson et al., 2001). It has been also reported to be invloved in a number of physiological processes including inflammation, carcinogenesis, and development (Barbier et al., 2002; Debril et al., 2001; Willson et al., 2001).

The primary action of TZDs is thought to be on adipose tissue because PPARγ is highly expressed in adipose tissue compared with muscle and liver. In contrast to TZD-improved glucose homeostasis and insulin sensitization in muscle and liver (Inzucchi et al., 1998), adipose tissue is responsible for only a small part of insulin-mediated glucose clearance (James et al., 1985). Although, a crucial role of PPARγ in adipose tissue is suggested by the finding that mice lacking adipose tissue are resistant to the antidiabetic actions of TZDs (Chao et al., 2000). TZD-mediated effects on adipose tissue have therefore been now recognized to be implicated in the alleviation of insulin resistance although how TZDs improve insulin sensitivity through regulating white adipose tissue (WAT) metabolism remains unclear. It has been shown that circulating free fatty acids (FFAs) are a major factor responsible for insulin resistance (Chaput et al., 2000; Way et al., 2001), suggesting that TZD lowering

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of serum FFAs increases glucose uptake in muscle and decreases insulin resistance (Boden et al., 2003; Way et al., 2001). Accordingly, it is likely that TZDs are involved in the metabolic pathways for fatty acid catabolism.

Therefore, the objective of the present study was to determine whether troglitazone activates WAT expression of genes involved in fatty acid β-oxidation and to examine the subsequent effects in WAT physiology, using troglitaozne as a PPARγ ligand since it is experimentally suitable for investigating TZD effects although it is no longer available clinically due to its hepatic toxicity. Our data demonstrate that troglitazone increased the adipocyte expression of genes involved in fatty acid β-oxidation and that these changes may lead to improved lipid and glucose metabolism and increased number of small adipocytes in WAT, showing that insulin resistance can be alleviated through increases in fatty acid β-oxidation of WAT by troglitazone.

MATERIALS AND METHODS

1. Animal treatments

For all experiments, eight-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-h light/dark cycle. Prior to the administration of special diets, mice were fed standard rodent chow and water *ad libitum*. Female mice were each randomly divided into two groups and received either a high fat diet (15% fat, w/w, Oriental Yeast Co. Ltd., Japan) or the same high fat diet supplemented with troglitazone (0.2% w/w, Sankyo Co., Ltd., Tokyo, Japan) for 4 weeks. In all experiments, body weights were monitored throughout the treatment period. At the end of the study, blood samples were collected, from which serum was isolated and stored at -80℃ until further analysis. Animals were sacrificed by cervical dislocation, tissues were harvested, weighed, snap frozen in liquid nitrogen and stored at -80℃ until use.

2. Northern analysis

Total RNA was prepared using Trizol reagent (Gibco-BRL, Grand Island, NY, USA) and analyzed by electrophoresis on 0.22 M formaldehyde-containing 1.2% agarose gels. The separated RNA was transferred to Nytran membranes (Schleicher & 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℃. 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, USA). 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, USA), as previously described (Oh et al., 2006). Densitometric analysis of the mRNA signals was performed using ImageQuant image analysis software (Molecular Dynamics, Sunnyvale, CA, USA).

3. Serum assays

Serum concentrations of triglycerides and glucose were measured using an automatic blood chemical analyzer (CIBA Corning, Oberlin, OH, USA). Serum insulin and FFAs were measured using Rat Insulin RIA kit (Linco Research, Inc., MO, USA) and SICDIA NEFAZYME (Shinyang Chemical Co., Seoul, Korea), respectively.

4. Histological analysis

For hematoxylin and eosin (HE) staining, female mesenteric WAT was fixed in 10% phosphate-buffered formalin for 1 day and processed in a routine manner for paraffin sections. Sections of thickness 5 μm were cut and stained with HE for microscopic examination. To quantitate the number and size of adipocytes, the sectional areas of adipose tissues in the HE-stained preparations were analyzed with an image analysis system (Image Pro-Plus, Silver Spring, MD, USA).

5. Statistics

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

RESULTS

1. Gene expression in WAT

Troglitazone administration dramatically stimulated the expression of genes involved in fatty acid β-oxidation. Compared with controls, troglitazone-treated mice showed

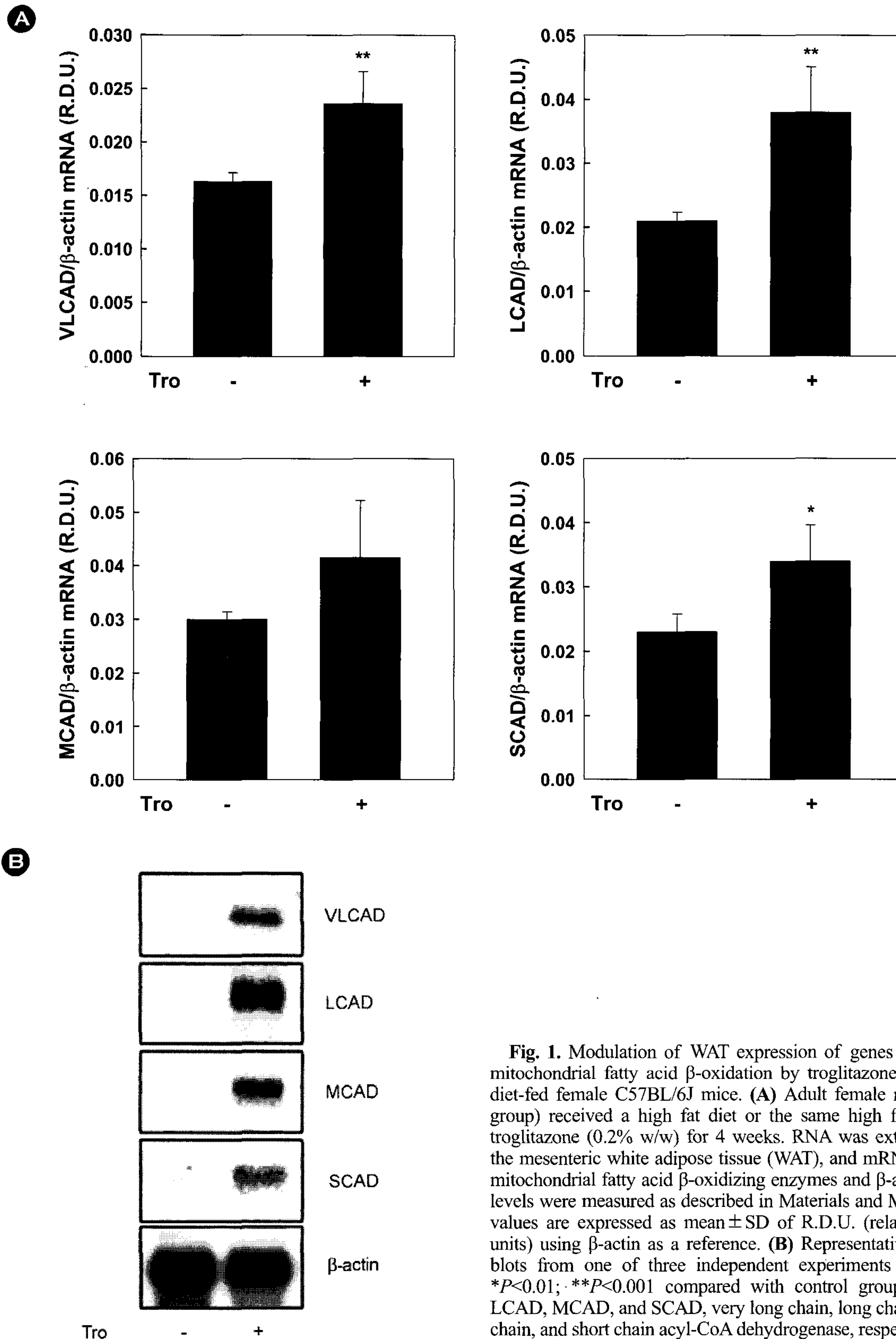

Fig. 1. Modulation of WAT expression of genes involved in mitochondrial fatty acid β-oxidation by troglitazone in high fat diet-fed female C57BL/6J mice. **(A)** Adult female mice (n=10/group) received a high fat diet or the same high fat diet with troglitazone (0.2% w/w) for 4 weeks. RNA was extracted from the mesenteric white adipose tissue (WAT), and mRNA levels of mitochondrial fatty acid β-oxidizing enzymes and β-actin mRNA levels were measured as described in Materials and Methods. All values are expressed as mean±SD of R.D.U. (relative density units) using β-actin as a reference. **(B)** Representative Northern blots from one of three independent experiments are shown. **P*<0.01; ***P*<0.001 compared with control group. VLCAD, LCAD, MCAD, and SCAD, very long chain, long chain, medium chain, and short chain acyl-CoA dehydrogenase, respectively.

significant elevations in mRNA levels of WAT mitochondrial fatty acid β-oxidizing enzymes, such as very long chain, long chain, medium chain and short chain acyl-CoA dehydrogenase, by 44.8% (*P*<0.001), 80.95% (*P*<0.001),

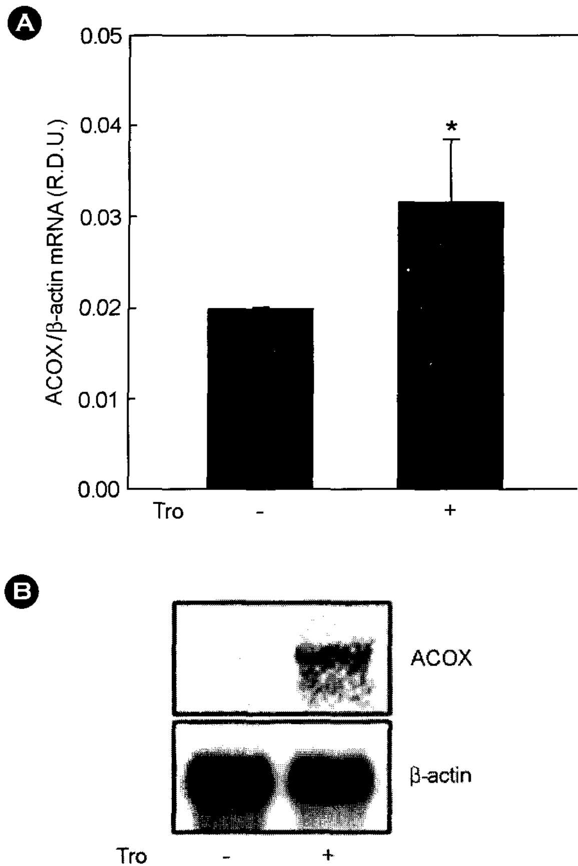

Fig. 2. Modulation of WAT ACOX mRNA by troglitazone in high fat diet-fed female C57BL/6J mice. **(A)** Adult female mice (n=10/group) received a high fat diet or the same high fat diet with troglitazone (0.2% w/w) for 4 weeks. RNA was extracted from the mesenteric white adipose tissue (WAT), and acyl-CoA oxidase (ACOX) and β-actin mRNA levels were measured as described in Materials and Methods. All values are expressed as mean ± SD of R.D.U. (relative density units) using β-actin as a reference. **(B)** Representative Northern blots from one of three independent experiments are shown. *P<0.01 compared with control group.

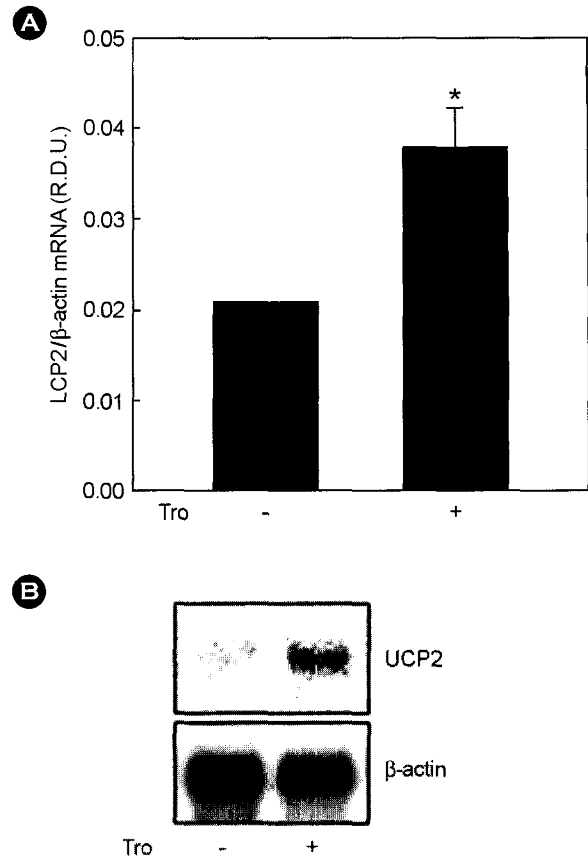

Fig. 3. Modulation of WAT UCP2 mRNA by troglitazone in high fat diet-fed female C57BL/6J mice. **(A)** Adult female mice (n=10/group) received a high fat diet or the same high fat diet with troglitazone (0.2% w/w) for 4 weeks. RNA was extracted from the mesenteric white adipose tissue (WAT), and uncoupling protein 2 (UCP2) and β-actin mRNA levels were measured as described in Materials and Methods. All values are expressed as mean ± SD of R.D.U. (relative density units) using β-actin as a reference. **(B)** Representative Northern blots from one of three independent experiments are shown. *P<0.01 compared with control group.

38.3% and 47.8% (P<0.01), respectively, in mesenteric WAT (Fig. 1). In addition to elevated expression of genes related to mitochondrial fatty acid β-oxidizing enzymes, troglitazone also affects WAT peroxisomal fatty acid β-oxidation. WAT mRNA expression of acyl CoA-oxidase, known to be a first and rate-limiting enzyme for peroxisomal fatty acid β-oxidation, was significantly increased by 57.8% (P<0.01) in troglitazone-treated mice compared with controls (Fig. 2).

We also tested the effects of troglitazone on the expression of WAT uncoupling protein 2 (UCP2) gene, which is likely to be involved in the regulation of fatty acid β-oxidation. Troglitazone significantly increased the levels of UCP2 mRNA by 81.0% (P<0.01) in troglitazone-administered mice compared with controls (Fig. 3). Taken together, these changes in WAT gene expression suggest that troglitazone may contribute to the lowering of circulating FFAs through activation of WAT fatty acid β-oxidation.

2. Serum lipid and glucose metabolism

As expected, troglitazone decreased markedly serum levels of both FFAs and triglycerides. Serum FFA levels were decreased by 33% (P<0.001) (Fig. 4A) and serum triglycerides by 26% (P<0.01) (Fig. 4B) compared with controls. Troglitazone also decreased both serum glucose (P<0.001) and insulin levels although the reductions in serum insulin levels were not statistically significant (Figs. 4C and 4D). These results indicate that serum lipid and glucose metabolism may be improved by elevations in fatty

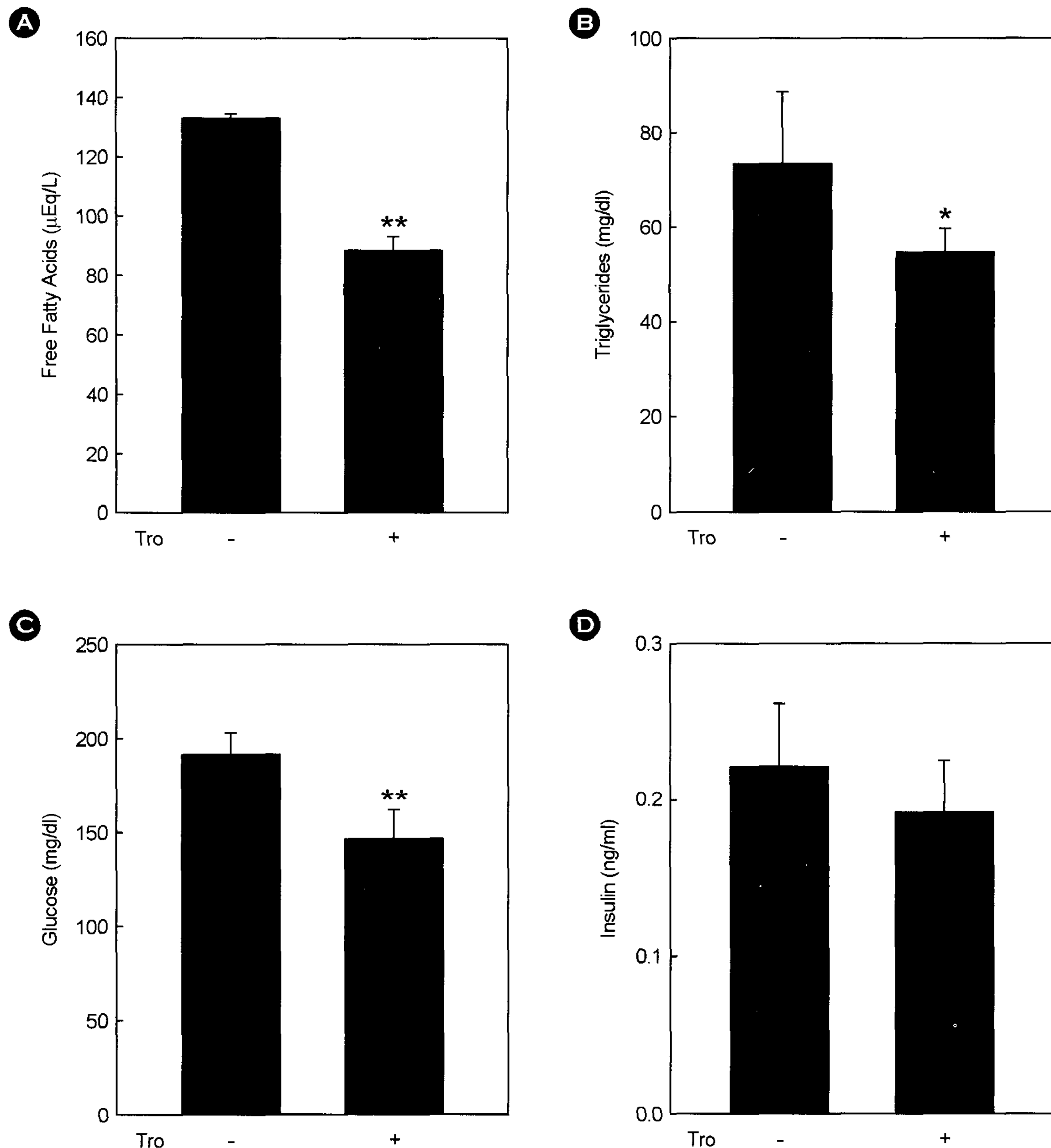

Fig. 4. Changes in circulating free fatty acids **(A)**, triglycerides **(B)**, glucose **(C)** and insulin **(D)** in high fat diet-fed female C57BL/6J mice. Adult female mice (n=10/group) received a high fat diet or the same high fat diet with troglitazone (0.2% w/w) for 4 weeks. All values are expressed as mean ± SD. **P*<0.01; ***P*<0.001 compared with control group.

acid β-oxidation by troglitazone.

3. Adipocytes in WAT

Since WAT lipids are largely derived from circulating triglycerides, adipocyte size seems to be influenced by serum triglycerides (Bourgeois et al., 1983). Consistent with the effects of troglitazone on fatty acid β-oxidation and serum lipid levels, histological analysis showed that the adipocyte size was significantly lower in mesenteric WAT of troglitazone-treated mice than in that of control mice ($P<0.00001$) (Figs. 5A and 5B). The average size of adipocytes was 1,258±72 μm^2 in vehicle-treated mice whereas 668±34 μm^2 in troglitazone-treated mice. In contrast, troglitazone caused a substantial increase in the number of adipocytes of mesenteric WAT by 88.2% compared with high fat diet only ($P<0.00001$) (Figs. 5A and 5C), suggesting that troglitazone increased the number of small adipocytes and concomitantly decreased that of large adipo-

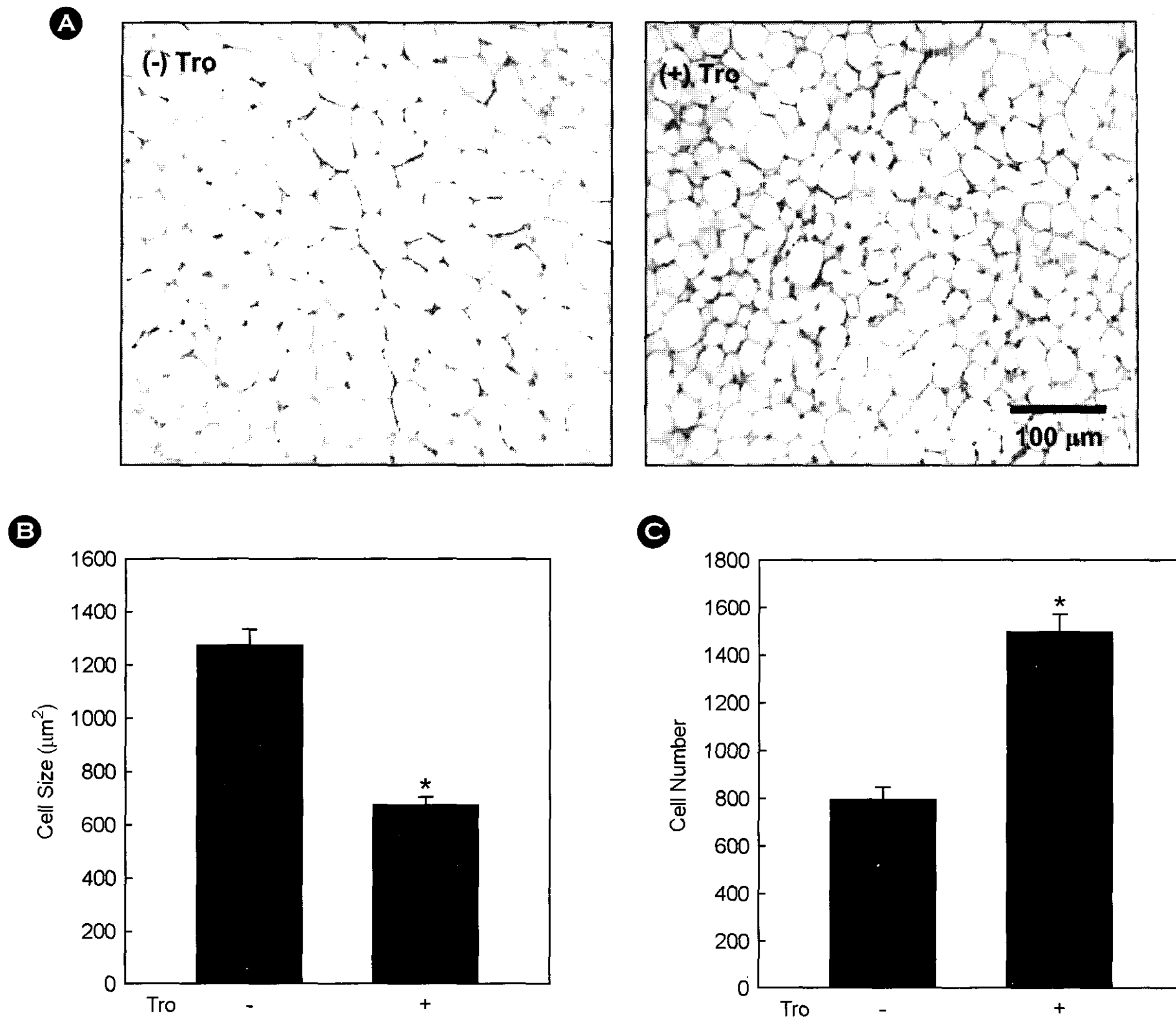

Fig. 5. Histological analyses of WAT in high fat diet-fed female C57BL/6J mice. **(A)** Adult female mice (n=10/group) received a high fat diet or the same high fat diet with troglitazone (0.2% w/w) for 4 weeks. Shown are representative hematoxylin- and eosin-stained sections (5 µm thick) of female mesenteric white adipose tissue (WAT). The size of adipocytes from troglitazone-treated groups was smaller than those from control groups. Hematoxylin and eosin-stained sections were analyzed with an image analysis system, and the size **(B)** and number **(C)** of adipocytes in a fixed area (1,000,000 μm^2) were quantified. All values are expressed as mean ± SD. *$P<0.00001$ compared with control.

cytes. With respect to the physiological significance of changes in adipocyte size, molecules generated or secreted by hypertrophic adipocytes have been implicated in the development of insulin resistance (Hotamisligil et al., 1993; Taylor et al., 1996). Moreover, small fat cells have the capacity to take up more glucose in the presence of insulin, compared to large fat cells (Olefsky, 1976). Thus, troglitazone may alleviate insulin resistance, at least in part due to its ability to reduce adipocyte size.

DISCUSSION

Since circulating FFAs are a major factor responsible for insulin resistance, a role of TZDs in WAT fatty acid β-oxidation can be hypothesized. Thus, we investigated whether troglitazone regulates WAT expression of genes involved in fatty acid β-oxidation and examined the resulting responses including adipocyte size of WAT, serum lipid and glucose metabolism in high fat diet-fed female C57BL/6J mice.

Our results demonstrated that troglitazone had direct

effects on specific gene expression in WAT of high fat diet-fed female mice. Four weeks of treatment with troglitazone was associated with increased expression of genes critical for fatty acid β-oxidation in WAT. Messenger RNA levels of enzymes for mitochondrial and peroxisomal fatty acid β-oxidation were markedly increased after troglitazone treatment. It is however currently thought that PPARγ is critically important for adipocyte differentiation and fat storage in adipose tissue (Debril et al., 2001; Rosen and Spiegelman, 2000; Spiegelman, 1998), whereas PPARα plays an important role in fatty acid β-oxidation (Jeong et al., 2004a; Jeong et al., 2004b; Oh et al., 2006; Yoon et al., 2002; Yoon et al., 2003). Although fatty acid β-oxidation is generally reported to be regulated by PPARα, not by PPARγ, our results suggest that the PPARγ ligand troglitazone stimulates fatty acid β-oxidation in WAT similar to the PPARα effects on fatty acid β-oxidation.

In addition to troglitazone-induced expression of enzymes for fatty acid β-oxidation, we examined alterations in UCP2 gene expression in WAT, based on the role of UCP2 in the regulation of energy expenditure, body weight, and fatty acid metabolism (Boss et al., 2000). We found that WAT UCP2 mRNA levels were significantly increased by troglitazone administration. Similarly, our results are supported by other *in vitro* studies that TZDs stimulate UCP2 expressions in cell lines representing white and brown adipose tissues and skeletal muscle (Camirand et al., 1998; Viguerie-Bascands et al., 1999). In addition, several lines of observations show that UCP2 is induced in a state when fatty acid β-oxidation is likely to be increased and that overexpression of UCP2 increases oxidative activity (Wang et al., 1999). Moreover, Genes encoding UCPs contain PPAR response elements in their promoter regions (Acin et al., 1999; Lentes et al., 1999), suggesting that there may be an interaction of PPARγ and UCPs in fatty acid β-oxidation. Taken together, troglitazone may regulate WAT metabolism by increasing the UCP2 gene expression.

The troglitazone-mediated induction of expression of genes related to fatty acid β-oxidation in WAT was accompanied by significant decreases in circulating FFA and triglyceride levels. Consistent with the decreases in lipid levels by troglitazone, serum glucose and insulin levels were also decreased although the reductions in serum insulin levels were not statistically significant. Given the known role of circulating lipids such as FFA in inhibiting glucose uptake and use in muscle, troglitazone-induced fatty acid β-oxidation and the resulting decreases in serum FFA and triglycerides contribute to a decrease in skeletal muscle insulin resistance (Boden, 1997; Sugiyama et al., 1990).

Lipids accumulated in the adipocytes are largely derived from circulating triglycerides during high fat feeding. In parallel with the decreases in serum triglycerides by troglitazone, histological examination of WAT revealed that the average size of adipocytes was greatly decreased in WAT from troglitazone-treated mice compared with controls. The adipocyte size of mesenteric WAT was 47% lower in troglitazone-treated mice than in control mice. These cellular effects are also in agreement with PPARγ-mediated adipogenic effects of TZDs (de Souza et al., 2001; Hallakou et al., 1998; Okuno et al., 1998) and PPARγ agonist-induced apoptosis in adipocytes (Okuno et al., 1998). Small adipocytes have been shown to take up and oxidize more glucose than large adipocytes in the presence of insulin (Olefsky, 1976). Moreover, since small adipocytes are also more sensitive to the antilipolytic effects of insulin (Abbott and Foley, 1987), troglitazone-induced increases of small adipocytes in WAT may also promote lowering the serum FFA and triglyceride levels (de Souza et al., 2001; Okuno et al., 1998).

In conclusion, these studies demonstrate that 4 weeks of troglitazone treatment increases the expression of WAT genes involved in the fatty acid β-oxidation in high fat diet-fed female mice. These changes lead to decreases in serum FFA levels and adipocyte size, contributing to prevention of mice from becoming dyslipidemic and/or insulin-resistant.

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