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Liver PPARα and UCP2 are Involved in the Regulation of Ovariectomy-Induced Adiposity and Steatosis by Swim Training

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It is suggested that ovariectomy induces body weight gain primarily in the form of adipose tissue in rodents. Since liver peroxisome proliferator-activated receptor α (PPARα) and uncoupling 2 (UCP2) are involved in the regulation of energy expenditure, it was investigated whether swim training regulates ovariectomy-induced adiposity and steatosis through liver PPARα and UCP2 activation in female ovariectomized mice, an animal model of postmenopausal women. Swim-trained mice had significantly decreased adipose tissue weights compared with sedentary control mice. Histological analysis showed that hepatic lipid accumulation was inhibited by swim training. Concomitantly, swim training significantly increased mRNA levels of PPARα and its target genes responsible for peroxisomal fatty acid β-oxidation, such as acyl-CoA oxidase, enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase and thiolase in the liver. Moreover, swim training induced the mRNA expression of UCP2. These results suggest that swim training can effectively prevent adiposity and steatosis caused by ovariectomy, in part through activation of liver PPARα and UCP2 in female obese mice.

Key Words: Ovariectomy, Adiposity, Steatosis, Liver, Swim training, PPARα, UCP2

INTRODUCTION

Obesity is the result of an energy imbalance caused by an increased ratio of caloric intake to energy expenditure. Obesity is characterized by increased adipose tissue mass that results from both increased fat cell number (hyperplasia) and increased fat cell size (hypertrophy) (Couillard et al., 2000). In particular, accumulation of visceral fat is thought to play a major role in the pathogenesis of metabolic syndrome, such as hypertension, hyperlipidemia, obesity and type 2 diabetes, because the occurrence of the syndrome correlates with the amount of intra-abdominal fat and intra-abdominal adipose tissue is lipolytically active (Kissebah, 1997; Enevoldsen et al., 2000; Jensen, 2006).

Energy balance seems to be influenced by gonadal sex steroids (Mystkowski and Schwartz, 2000). Gonadal steroids have been the subject of intense investigation over the last several decades because of the role that these ovarian hormones play in regulating food intake, body weight and lipid metabolism. Menopause, which is characterized by ovarian steroid withdrawer, also tends to be a risk factor for metabolic disease including obesity (Park et al., 2003; Rossi et al., 2008). For example, postmenopausal women and ovariectomized (OVX) animals not only show increased body weight and fat mass, but also develop insulin resistance and cardiovascular disease maybe due to the development of obesity (Heine et al., 2000; Gasse et al., 2001).

Physical exercise rapidly increases energy expenditure and has been associated with improved weight control (Brook et al., 1995; King et al., 2001; Wier et al., 2001). Exercise also causes a preferential utilization of fat, resulting in less fat in active individuals compared with sedentary controls. Whereas food restriction alone tends to cause loss of lean as well as fat tissue, physical activity appears to have a protein-sparing effect (Walberg et al., 1982).

The family of peroxisome proliferator-activated receptors (PPARs) is known to be involved in the control of lipid metabolism and obesity. Among the three PPAR isoforms,

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PPARα seems to be important in fat catabolism and obesity (Yoon et al., 2002; Yoon et al., 2003; Jeong et al., 2004). Uncoupling proteins (UCPs) including UCP1, 2 and 3 are thought to play roles in the regulation of energy expenditure, body weight, body temperature and fatty acid metabolism. As chemical uncoupling of mitochondrial membrane reduces weight gain and adiposity, UCPs can potentially be used in the treatment of human obesity (Lentes et al., 1999; Nakatani et al., 2002). Since menopause is often associated with a rise in obesity (Tan et al., 2010) and our previous study demonstrated that swim training improves genetically-induced obesity and lipid disorders through liver PPARα and UCP2 (Oh et al., 2006), it can be hypothesized that swim training improves ovariectomy-induced obesity through liver PPARα and UCP2 activation.

Therefore, we investigated whether swim training reduces visceral fat mass and steatosis in female OVX mice, an animal model of postmenopausal women, and examined whether hepatic PPARα and UCP2 activation is involved in this regulation.

MATERIALS AND METHODS

Animals and swim training

For all experiments, eight-week-old female mice (C57BL/6J) were housed and bred at Mokwon University under 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 OVX and each randomly divided into two groups (a non-swim control group and a swim group, n=8/group). Mice in swim group swam for 2 h daily for 6 weeks in a 35±1℃ water bath (1 × 1 m, Jeiotech, Seoul, Korea); during the first two weeks, the duration of daily training was increased from 10 min to 2 h. All the animals received a high fat diet (45% kcal fat, Research Diets, New Brunswick, NJ) for 6 weeks and were sacrificed by cervical dislocation. Tissues were harvested, weighed, snap frozen in liquid nitrogen and stored at -80℃ until use. Additional sections of liver were fixed in phosphate-buffered formalin for histological analysis. All animal experiments were approved by the Institutional Animal Care and Use Committees of Mokwon University, and followed National Research Council Guidelines.

Histological analysis

The right lobe of the liver was fixed in 10% phosphate-buffered formalin for 1 day and processed in a routine manner for paraffin section. Five-micrometer thick sections were stained with hematoxylin and eosin (HE) for light microscopic examination.

RT-PCR

Total cellular RNA was prepared using the Trizol reagent (Invitrogen, Carlsbad, CA). After 2 μg total RNA was reverse-transcribed using Moloney murine leukemia virus reverse transcriptase (MMLV-RT) and an antisense primer, cDNA was generated. The RNA was denatured for 5 min at 72℃ and then immediately placed on ice for 5 min.

Table 1. Sequences of oligonucleotide primers and PCR conditions

Genes	Size (bp)	Primer sequences	Annealing (℃)	Cycle
PPARα	202	F: 5'-gcagctcgtacaggtcatca-3' R: 5'-ctcttcatccccaagcgtag-3'	56	37
ACOX	195	F: 5'-actatatttggccaattttgtg-3' R: 5'-tgtggcagtggtttccaagcc-3'	58	34
HD	355	F: 5'-caaaaagatcggaaagattg-3' R: 5'-ctgataccaccgtttacctg-3'	58	45
Thiolase	294	F: 5'-ggataacctcggagaatgtggc-3' R: 5'-cactcacctgactggagttt-3'	52	45
UCP2	310	F: 5'-ctgagctggtgacctatgac-3' R: 5'-caagctgctcaataggtgac-3'	56	38
β-actin	350	F: 5'-tggaatcctgtggcatccatgaaac-3' R: 5'-taaaacgcagctcagtaacagtccg-3'	58	28

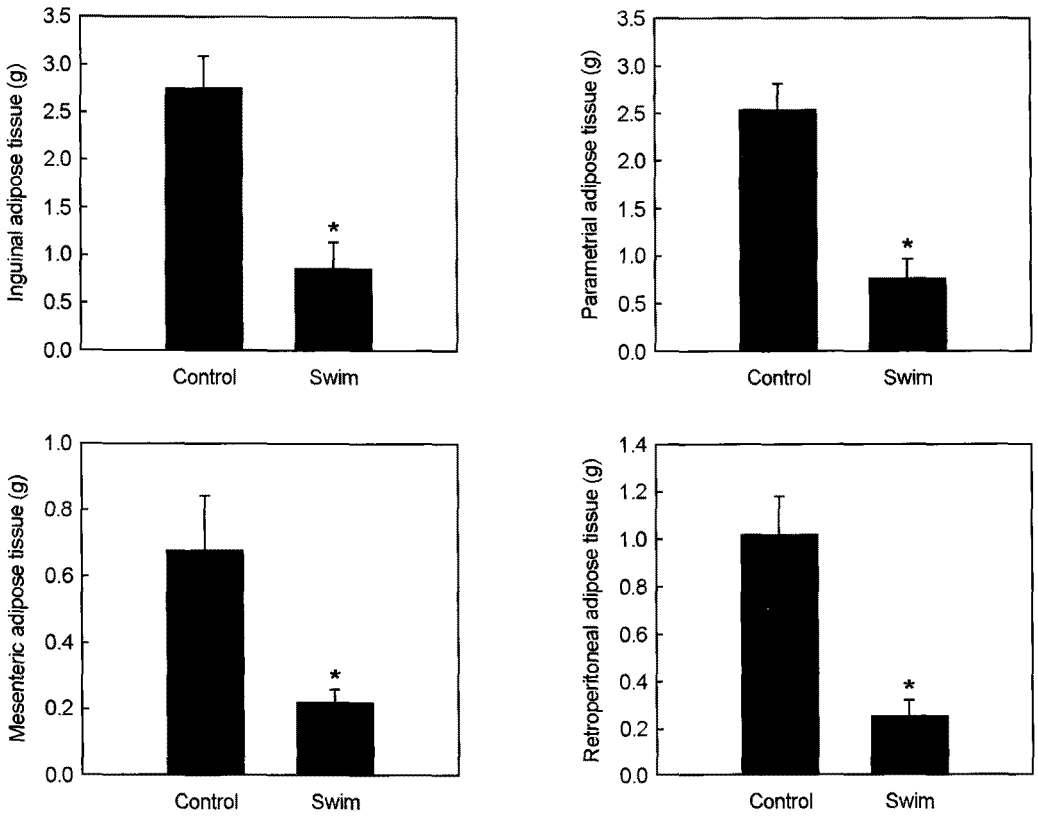

Fig. 1. Effects of swim training on white adipose tissue mass in OVX obese mice. Female OVX mice (n=8/group) were subjected to swim training for 2 h daily in a 35±1℃ water bath for 6 weeks; during the first 2 weeks, the duration of daily training was increased from 10 min to 2 h. Control mice of similar initial body weights were kept sedentary for 6 weeks. White adipose tissue weight was measured at the end of the study. All values are expressed as mean ± SD. *P<0.05 Significantly different from control mice.

Denatured RNA was mixed with MMLV-RT, MMLV-RT buffer, and a dNTP mixture, and incubated for 1 h at 42℃. Synthesized cDNA fragments were amplified by PCR in an MJ Research Thermocycler (Waltham, MA, USA). The PCR primers used for gene expression analysis are shown in Table 1. The cDNA was mixed with PCR primers, *Taq* DNA polymerase (Solgent, Daejon, Korea), and a dNTP mixture. The reaction consisted of 28~45 cycles of denaturation for 1 min at 94℃, annealing for 1 min at 52~58℃, and elongation for 1 min at 72℃. The PCR products were analyzed by electrophoresis on a 1% agarose gel. Relative expression levels were presented as a ratio of target gene cDNA versus β-actin cDNA. PCR products were quantified from agarose gels using the GeneGenius (Syngene, Cambridge, UK).

Statistics

Unless otherwise noted, all values are expressed as mean ± standard deviation (SD). All data were analyzed by the unpaired student's *t*-test for statistically significant differences between two groups.

RESULTS

Effects of swim training on adipose tissue mass

Swim training for 6 weeks reduced ovariectomy-induced adipose tissue mass. Compared with sedentary controls, swim training significantly decreased inguinal, parametrial, mesenteric, and retroperitoneal adipose tissue weights by 68.7%, 70.8%, 67.6%, and 76.5%, respectively (Fig. 1). These results indicate that swim training effectively inhibits ovariectomy-induced adiposity in female mice.

Effects of swim training on hepatic lipid accumulation

OVX obese controls showed considerable hepatic lipid accumulation compared with sham-operated female mice

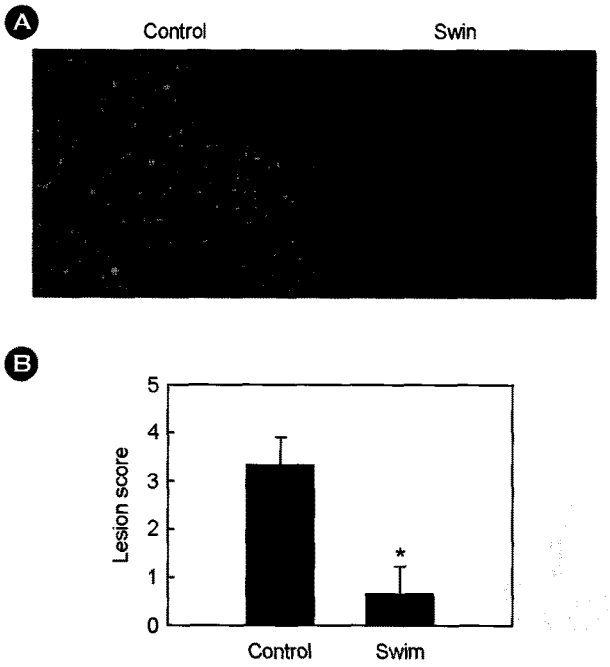

Fig. 2. Effects of swim training on hepatic lipid accumulation in OVX obese mice. (A) Representative hematoxylin and eosin-stained liver sections are shown (original magnification ×200). OVX mice were subjected to swim training as described in the legend of Fig. 1, with control mice of similar initial body weights kept sedentary, for 6 weeks. Arrows indicate the lipid droplets in hepatocytes. (B) Histological analysis of hepatic lipid accumulation. Pathological scores of hepatic lipid accumulation are as follows: 0, no lesion; 1, mild; 2, moderate; 3, severe; 4, very severe. All values are expressed as mean ± SD. *P<0.05 Significantly different from control mice.

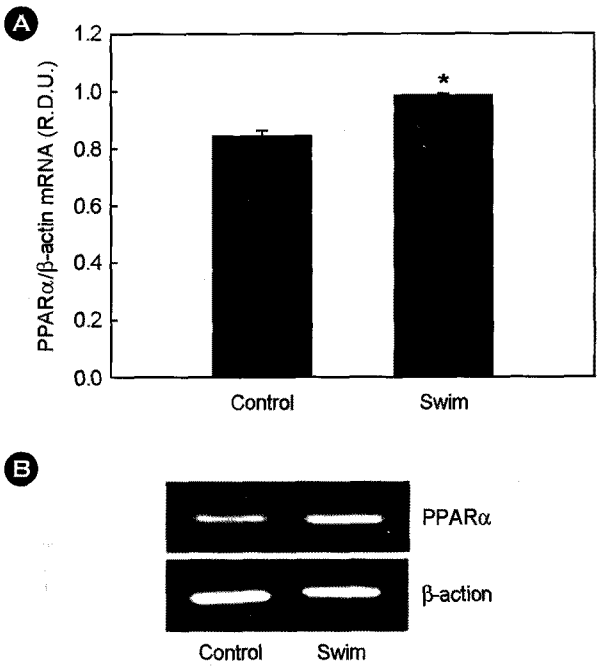

Fig. 3. Effects of swim training on the mRNA levels of PPARα in the livers of OVX obese mice. (A) OVX mice (n=8/group) were subjected to swim training as described in the legend of Fig. 1, with control mice of similar initial body weights kept sedentary, for 6 weeks. RNA was extracted from the liver, and all values are expressed as mean ± SD of R.D.U. (relative density units) using β-actin. *P<0.05 Significantly different from control mice. (B) Representative RT-PCR photographs from one of three independent experiments are shown.

with functioning ovaries (data not shown). However, it was found that hepatic lipid accumulation was markedly lower in swim-trained mice than in sedentary controls (Fig. 2). These results indicate that swim training suppresses ovariectomy-induced steatosis in female mice.

Effects of swim training on mRNA expression of PPARα, PPARα target genes and UCP2 in the liver

To evaluate whether the inhibitory effects of swim training on adiposity in OVX mice were caused by PPARα activation in the liver, we measured the mRNA levels of hepatic PPARα and its target genes. Swim training increased the mRNA expression levels of PPARα and its target fatty acid oxidative enzymes. Compared with sedentary controls, swim-trained mice showed significantly elevations in mRNA levels of PPARα by 16.7% (P<0.05) (Fig. 3). Swim training increased the mRNA levels of PPARα targets, such as acyl-CoA oxidase (ACOX), enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase (HD), and thiolase, by 22.1%, 32.4%, and 15.6%, respectively (P<0.05) (Fig. 4).

We also tested the effects of swim training on the mRNA expression of UCP2 in ovariectomy-induced obese mice. Swim training significantly increased the levels of UCP2 mRNA by 16.2% compared with control mice (P<0.05) (Fig. 5). These results suggest that swim training prevents adiposity by activating liver PPARα and UCP2, resulting in the improvement of obesity in OVX animals and post-menopausal women.

DISCUSSION

It is known that ovariectomy increases body weight and fat accumulation. Similarly, menopause also accentuates obesity, which frequently accompanies insulin resistance, type 2 diabetes, lipid disorders, and hypertension. The in-

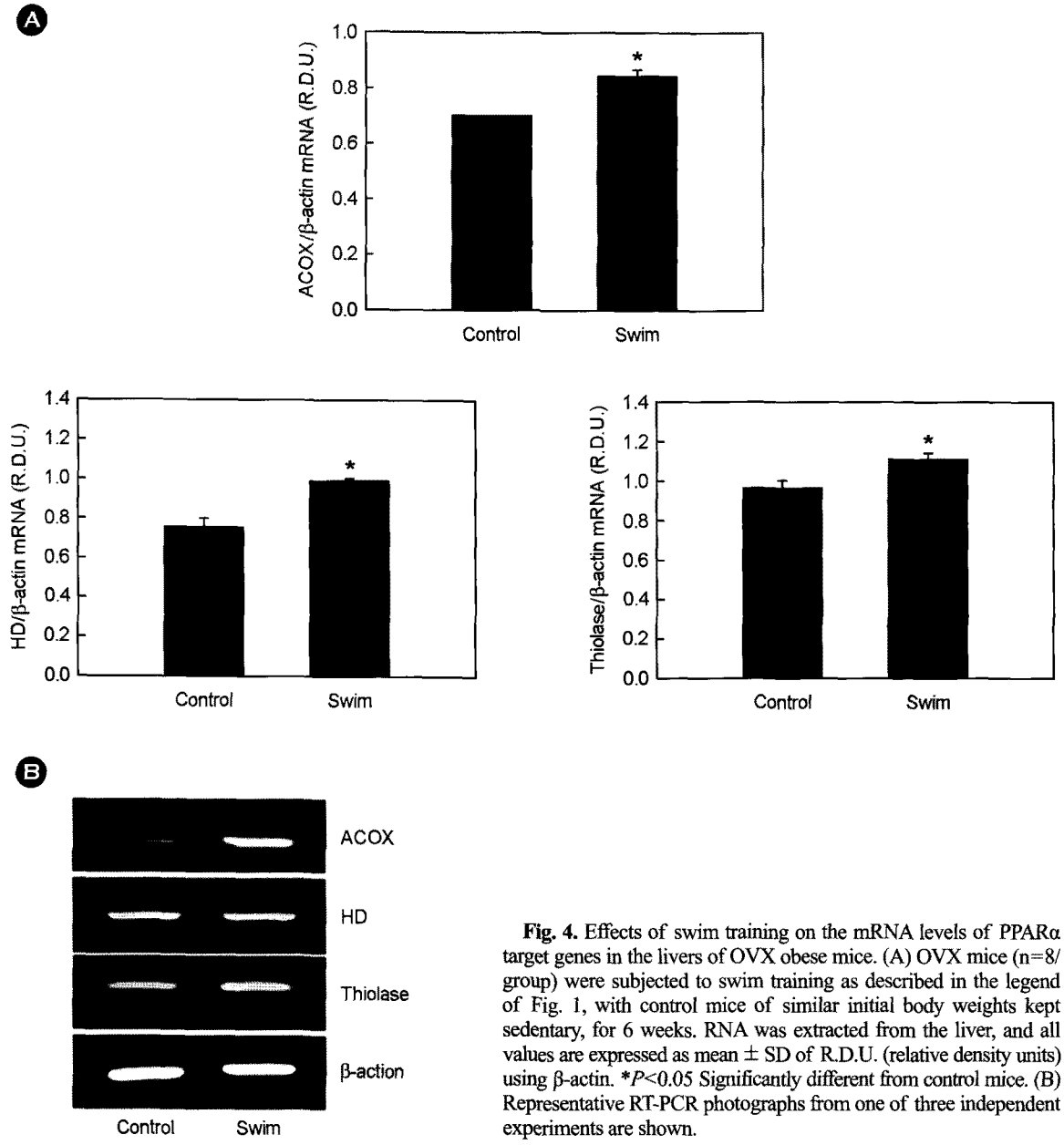

Fig. 4. Effects of swim training on the mRNA levels of PPARα target genes in the livers of OVX obese mice. (A) OVX mice (n=8/group) were subjected to swim training as described in the legend of Fig. 1, with control mice of similar initial body weights kept sedentary, for 6 weeks. RNA was extracted from the liver, and all values are expressed as mean ± SD of R.D.U. (relative density units) using β-actin. *$P<0.05$ Significantly different from control mice. (B) Representative RT-PCR photographs from one of three independent experiments are shown.

cidence of obesity increases with age and is higher in postmenopausal women than in age-matched premenopausal women (Svendsen et al., 1995; Tchernof et al., 2000). Since our previous study suggested that liver PPARα and UCP2 are involved in the regulation of genetically induced obesity (Oh et al., 2006; Oh et al., 2007), it was hypothesized that swim training regulates ovariectomy-induced adiposity through liver PPARα and UCP2 in female OVX mice, an animal model of postmenopausal women.

The present study demonstrated that swim training decreased ovariectomy-induced adipose tissue mass. In particular, visceral adipose tissues, such as mesenteric, retroperitoneal, and parametrial adipose tissues were substantially reduced by swim exercise, indicating that swim training can effectively regulate visceral obesity in OVX mice and that swim training demonstrates the potential to be used for the treatment of postmenopausal obese women. In this respect, since visceral obesity is thought to play a major role in the pathogenesis of metabolic syndrome, swim training is likely to be useful in treating diseases associated with visceral adiposity, such as hypertension, hyperlipidemia, obesity and type 2 diabetes in postmeno-

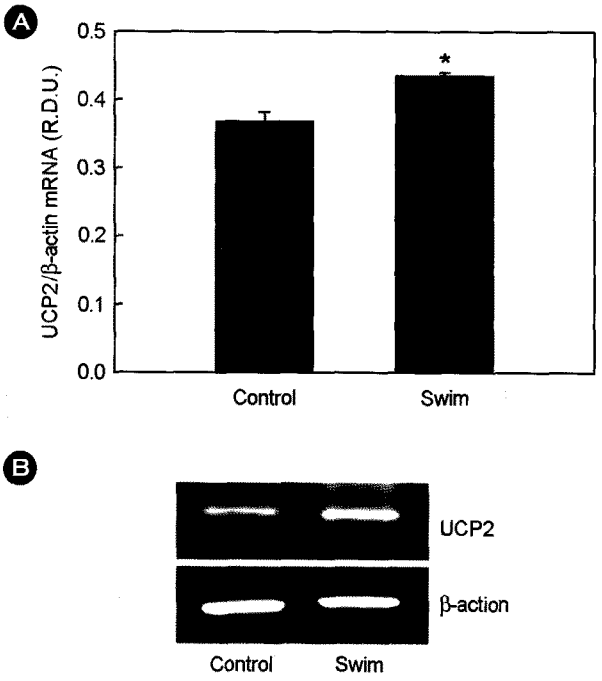

Fig. 5. Effects of swim training on the mRNA levels of UCP2 in the livers of OVX obese mice. (A) OVX mice (n=8/group) were subjected to swim training as described in the legend of Fig. 1, with control mice of similar initial body weights kept sedentary, for 6 weeks. RNA was extracted from the skeletal muscle, and all values are expressed as mean ± SD of R.D.U. (relative density units) using β-actin. *$P<0.05$ Significantly different from control mice. (B) Representative RT-PCR photographs from one of three independent experiments are shown.

pausal women with visceral obesity (Buemann and Tremblay, 1996).

In order to investigate whether swim training inhibits hepatic lipid accumulation, Hematoxylin and esosin staining of triglycerides was performed in the liver. Compared with sedentary control mice, lipid droplets were found to be substantially decreased in the livers of swim trained-mice. These results demonstrate that swim training stimulates fat catabolism in the liver. The present data are supported by our previous results showed that swim training significantly decreased serum levels of triglycerides and total cholesterol caused by ovariectomy. Loss of ovaries is associated with dyslipidemia, such as increased triglyceride levels (Pilot et al., 2007; Tan et al., 2010). 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 (Taghibiglou et al., 2000; Siri et al., 2001; Shimizugawa et al., 2002). These observations suggest that the reduced levels in circulating triglycerides after swim training is due to the fat catabolism in the liver.

To gain insight into the molecular mechanisms underlying the effects described above, we investigated genes likely to be involved in swim training-regulated adiposity and hepatic lipid metabolism. We found that swim training significantly increased the mRNA levels of PPARα and its target genes, such as ACOX, HD, and thiolase, all of which are responsible for fatty acid β-oxidation, in the liver of OVX mice. Although it was reported that exercise training may enhance skeletal muscle fatty acid oxidative capacity by PPARα regulation of gene expression (Horowitz et al., 2000), the results presented in this study suggest that hepatic PPARα-activated fatty acid β-oxidation may also be crucial in the regulation of adiposity by swim training. Other studies have also suggested that hepatic PPARα activation may be important in body weight control and lipid metabolism (Costet et al., 1998; Chaput et al., 2000; Guerre-Millo et al., 2000; Mancini et al., 2001). In particular, our previous study demonstrated that increased hepatic PPARα activation by swim training was in accordance with decreased fat mass in db/db mice, an animal model of obesity (Oh et al., 2006). Altogether, swim training may regulate obesity and lipid metabolism in part due to PPARα activation in liver.

In addition to swim training-induced expression of PPARα target enzymes for fatty acid oxidation, we examined alterations in the mRNA expression of liver UCP2, which is known to be involved in the energy homeostasis including fatty acid oxidation (Boss et al., 2000). It was found that liver UCP2 mRNA levels were significantly increased by swim training. Exercise has been shown to upregulate UCP2 gene expression in the liver of obese animals (Oh et al., 2006). These results suggest that liver UCP2 is involved in the improvement of ovariectomy-induced adiposity and steatosis by swim training in female mice.

In conclusion, these results suggest that swim training can effectively prevent adiposity and steatosis caused by ovariectomy in part through activation of PPARα and

UCP2 in the liver of female mice, which may contribute to alleviating obesity and lipid metabolism in postmenopausal women.

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