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Differential Regulation of Obesity by Swim Training in Female Sham-operated and Ovariectomized Mice

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The peroxisome proliferator-activated receptor α (PPARα) is a nuclear transcription factor that plays a central role in lipid and lipoprotein metabolism. To investigate whether swim training improves obesity and lipid metabolism through PPARα activation in female sham-operated (Sham) and ovariectomized (OVX) mice, we measured body weight, visceral adipose tissue mass, serum free fatty acid at 6 weeks as well as the expression of hepatic PPARα target genes involved in fatty acid oxidation. Swim-trained mice had decreased body weight, visceral adipose tissue mass and serum free fatty acid levels compared to high fat diet fed control mice in both female Sham and OVX mice. These reductions were more prominent in OVX than in Sham mice. Swim training significantly increased hepatic mRNA levels of PPARα target genes responsible for mitochondrial fatty acid β-oxidation, such as carnitine palmitoyltransgerase-1 (CPT-1), very long chain acyl-CoA dehydrogenase (VLCAD), and medium chain acyl-CoA dehydrogenase (MCAD) in OVX mice. However, swim trained female Sham mice did not increase hepatic mRNA levels of PPARα target genes responsible for mitochondrial fatty acid β-oxidation compared to Sham control mice. These results indicate that swim training differentially regulates body weight and adipose tissue mass between OVX and Sham mice, at least in part due to differences in liver PPARα activation.

Key Words: Female, Obesity, Ovariectomized mice, Ovary, PPARα, Swim training, Liver

INTRODUCTION

Excess energy and fat intake, combined with low levels of physical activity in modern societies, have led to an increased prevalence of the metabolic syndrome, characterized by obesity, type 2 diabetes, hypertension, cardiovascular disease, and dyslipidemia (Wilson et al., 1999; Park et al., 2003).

Regular exercise is highly recommended for disease prevention and understanding exercise physiology is important for the maintenance of our health. Exercise training decreases fat deposition and enhances insulin sensitivity (James et al., 1984; Saengsirisuwan et al., 2009). Swim trained mice decrease visceral fat accumulation and serum triglycerides, and exercise training decreases body weight and total fat mass in overweight and obese adults (Murase et al., 2005; Maki et al., 2009). This is achieved especially through alterations in metabolism caused by modifications in the activity and quantity of specific proteins (Tunstall et al., 2002; Pillard et al., 2010). However, the mechanisms by which exercise alters obesity and lipid metabolism are unclear.

There is rapidly accumulating knowledge on the roles of the peroxisome proliferator-activated receptors (PPARs). The family of PPARs is thought to be involved in the control of lipid metabolism and obesity. Among the three PPAR isoforms, PPARα seems to be important in fat catabolism and obesity (Yoon et al., 2002; Yoon et al., 2003; Jeong et al., 2004a). PPARα is expressed predominantly in tissues that have a high level of fatty acid catabolism such as liver, heart, and muscle (Schoonjans et al., 1996; Staels et al., 1998; Kliewer et al., 1999). PPARα induces enzymes involved in fatty acid oxidation, the hydrolysis of plasma triglycerides, fatty acid uptake and energy expenditure

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(Schoonjans et al., 1996; Lentes et al., 1999; Ferré, 2004). Moreover, PPARα activation regulates female lipid metabolism and obesity in a ovary-dependent manner (Yoon et al., 2003; Jeong et al., 2004b).

Peroxisome proliferator-activated receptor α (PPARα) has a potential role in the metabolic response to exercise training (Horowitz et al., 2000; Iemitsu et al., 2002; Morifuji et al., 2006). Because the capacity for fat utilization may be related to the development of obesity, understanding fat oxidation during exercise may assist in preventing obesity and in prescribing effective body or fat weight-loss strategies in obese individuals.

Since PPARα has a potential role in the metabolic response to exercise training and has different activities in a functional ovaries-dependent manner, this study was focused to investigate that swim training may improve obesity through PPARα activation depending on the presence of ovaries in females.

MATERIALS AND METHODS

Animals and swim training

For all experiments, eight-week-old female mice (C57BL/6J) were housed and bred Mokwon University 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 sham-operated (Sham) and ovariectomized (OVX) and randomly divided into four groups (n=8/group); a non-swim trained Sham control group, a swim trained Sham group, a non-swim trained OVX group, and a swim trained OVX group. Mice in swim group swam for 2 h daily for 6 weeks in a 35±1℃ water bath (1 m × 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 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. All animal experiments were approved by the Institutional Animal Care and Use Committee of Mokwon University and followed National Research Council Guidelines.

Serum assays

Serum concentrations of free fatty acids are committed to and measured in Samkwang Medical Laboratories (Seoul, Korea).

RNA preparation and analysis

Total cellular RNA was prepared using Trizol reagent (Gibco-BRL, Grand Island, NY) and relative levels of specific mRNA were assessed by reverse transcription-polymerase chain reaction (RT-PCR). Complementary DNA was synthesized from RNA samples by mixing 2 μg of total RNA and 0.5 μg of the reverse primer in a total volume of 14 μl in water, heating the mixture at 75℃ for 15 min, cooling the mixture immediately on ice for 5 min, and adding 5× Moloney murine leukemia virus reverse transcriptase (MMLV-RT) buffer, 10 mM dNTP mixture (Promega) and 200 units MMLV-RT (Promega) in total volume of 25 μl. Samples were incubated at 42℃ for 60 min. A five μl aliquot of the RT reaction was then used for subsequent PCR amplification with specific primers.

Twenty five μl PCR sample contained 5 μl of the RT

Table 1. Sequences of oligonucleotide primers and PCR conditions

Genes	Size (bp)	Primer sequences	Annealing (℃)	Cycle
CPT-1	587	F: 5'-tatgtgaggatgctgcttcc-3' R: 5'-ctcggagagctaagcttgtc-3'	58	43
VLCAD	268	F: 5'-cgtcagaggtgtactttgatgg-3' R: 5'-catggactcagtcacatactgc-3'	58	45
MCAD	321	F: 5'-gacatttggaaagctgctagtg-3' R: 5'-tcacgagctatgatcagcctctg-3'	58	43
β-actin	350	F: 5'-tggaatcctgtggcatccatgaaac-3' R: 5'-taaaacgcagctcagtaacagtccg-3'	58	28

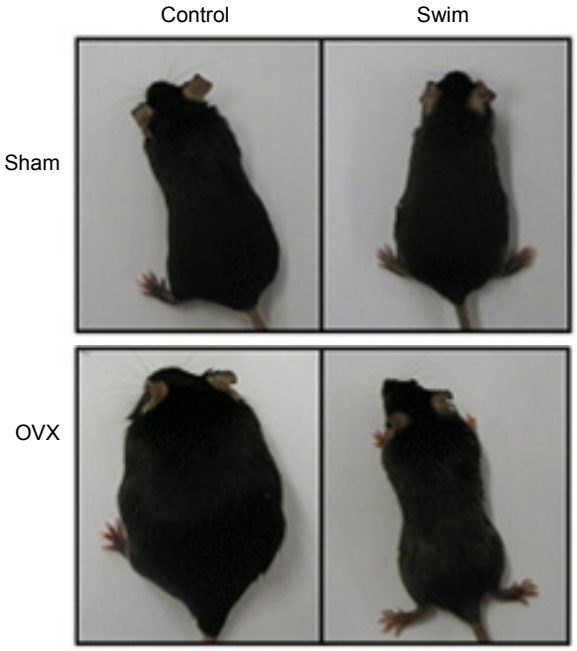


Fig. 1. Appearance of female sham-operated and ovariectomized mice at 6 weeks. Female sham-operated (Sham) or ovariectomized (OVX) C57BL/6J mice (n=8/group) were subjected to swim training for 2h daily in a 35±1℃ water bath for 6 weeks; during the first two weeks, the duration of daily training was increased from 10 min to 2 h. Control mice of similar initial body weights were kept sedentary for 6 weeks.

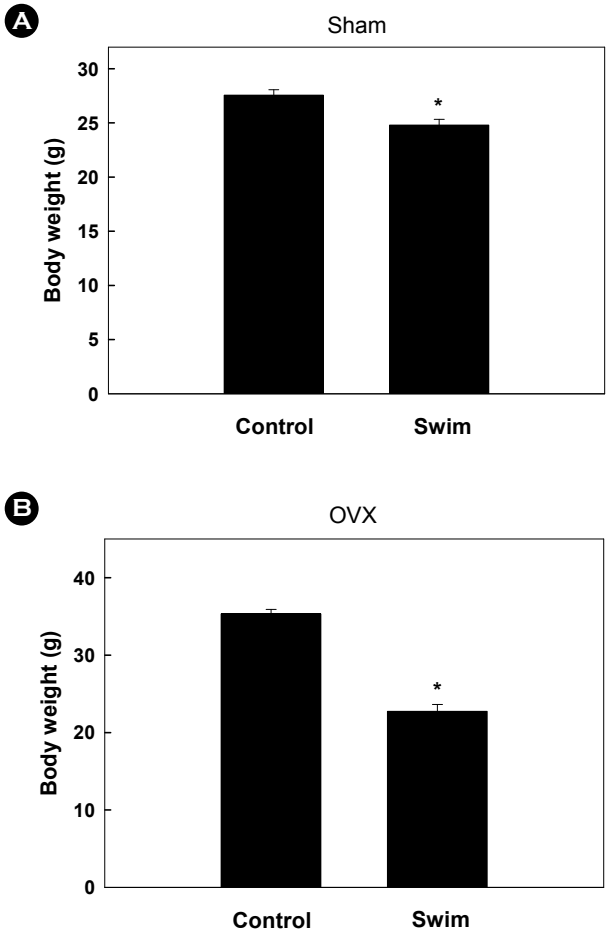


Fig. 2. Effects of swim training on body weight in female sham-operated and ovariectomized mice at 6 weeks. Female (A) sham-operated (Sham) or (B) ovariectomized (OVX) C57BL/6J mice (n=8/group) were subjected to swim training as described in the legend of Fig. 1, with control mice of similar initial body weights were kept sedentary, for 6 weeks. All values are expressed as mean ± SD. $^{*}P<0.05$ significantly different from the control mice.

reaction, 10× buffer with $MgCl_2$, 10 mM dNTP, 5 units of Tag polymerase (Solgent, Daejon, Korea) and 10 μM of each primer. Primer sequences and PCR conditions are shown in Table 1. PCR was performed in a PTC-100^{TM} Programmable Thermal Controller (MJ Research, Watertown, MA, USA). PCR products were electophoresed on a 1% agarose gel.

Statistics

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

RESULTS

To determine whether swim training regulates obesity in both female Sham and OVX C57BL/6J mice, we preferentially observed appearance and measured body weight and visceral adipose tissue mass. Swim trained mice were visibly leaner than control mice in OVX mice, but not in Sham mice (Fig. 1). Body weight was decreased by swim training in both Sham and OVX mice, by 9.8% and 35.7%, respectively ($P<0.05$) (Fig. 2). Similar to the results of body weight, swim trained mice significantly decreased visceral adipose tissue mass compared to control mice in both Sham mice and OVX mice, by 12.9% and 69.9%, respectively ($P<0.05$) (Fig. 3). Swim training also significantly lowered serum free fatty acid levels in both Sham and OVX mice, by 26.1% and 41.7%, respectively ($P<0.05$) (Fig. 4).

Our previous report showed that hepatic lipid accumu-

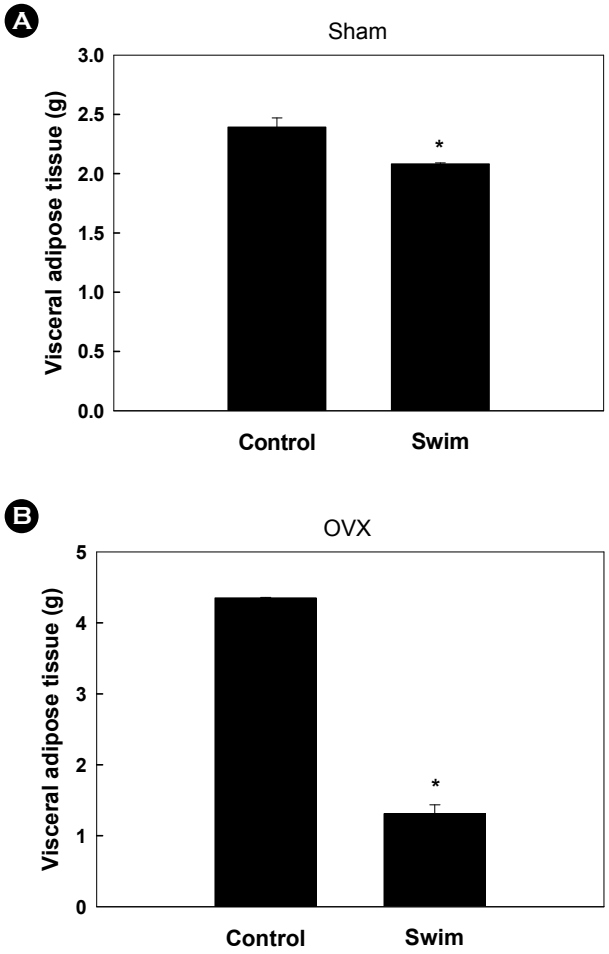


Fig. 3. Effects of swim training on visceral adipose tissue mass in female sham-operated and ovariectomized mice at 6 weeks. Female (A) sham-operated (Sham) or (B) ovariectomized (OVX) C57BL/6J mice (n=8/group) were subjected to swim training as described in the legend of Fig. 1, with control mice of similar initial body weights were kept sedentary, for 6 weeks. All values are expressed as mean ± SD. $^{*}P<0.05$ significantly different from the control mice.

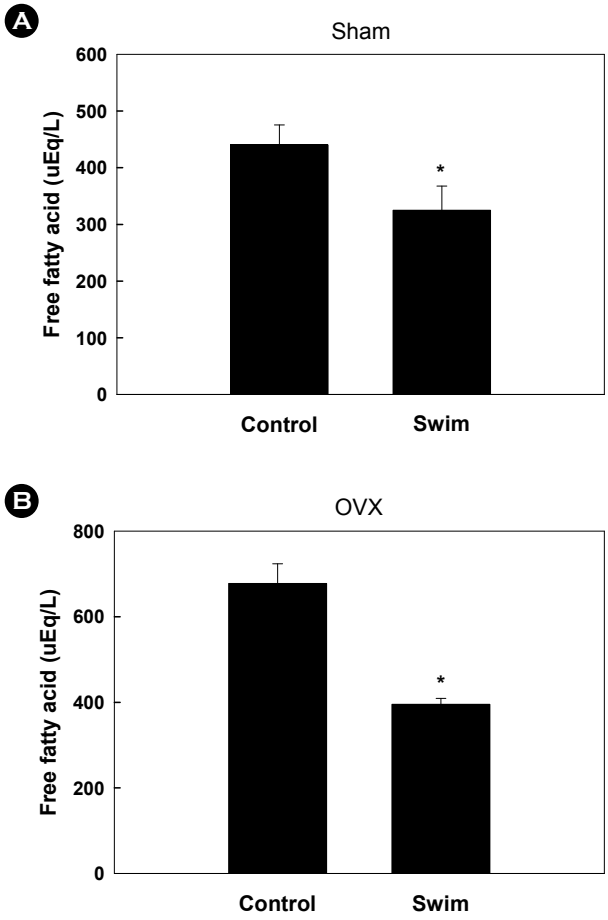


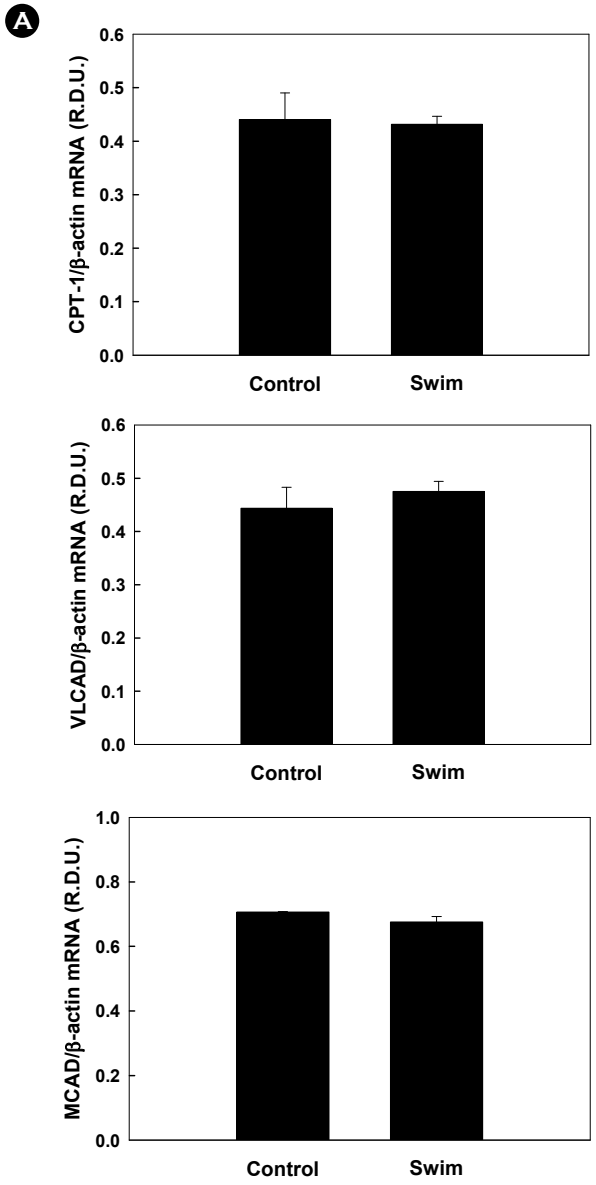
Fig. 4. Effects of swim training on circulating free fatty acids in female sham-operated and ovariectomized mice at 6 weeks. Female (A) sham-operated (Sham) or (B) ovariectomized (OVX) C57BL/6J mice (n=8/group) were subjected to swim training as described in the legend of Fig. 1, with control mice of similar initial body weights were kept sedentary, for 6 weeks. All values are expressed as mean ± SD. $^{*}P<0.05$ significantly different from the control mice.

lation was markedly lower in swim-trained OVX mice than in OVX control mice (Jeong and Yoon, 2010). However, swim training did not inhibit hepatic lipid accumulation in Sham mice (data not shown).

To evaluate whether the differential effects of swim training on obesity and lipid metabolism were caused by differences in hepatic PPARα activation, we measured mRNA levels of the PPARα target genes for mitochondrial fatty acid β-oxidation in livers (Fig. 5 and 6). Compared with OVX control mice, swim trained OVX mice showed significant elevations in mRNA levels of mitochondrial PPARα target genes, such as carnitine palmitoyltransferase-1 (CPT-1), very long chain acyl-CoA dehydrogenase (VLCAD) and medium chain acyl-CoA dehydrogenase (MCAD), by 29.1%, 18.3%, and 21.2%, respectively (Fig. 6). However, swim training did not increase hepatic PPARα target genes involved with mitochondrial fatty acid β-oxidation in Sham mice (Fig. 5).

DISCUSSION

The purpose of this study was to explore the effect of swim training on both obesity and the gene expression of PPARα target genes involved in lipid metabolism in both female Sham and OVX mice. We showed that swim training



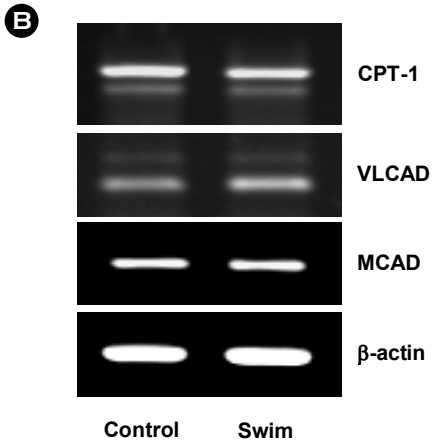


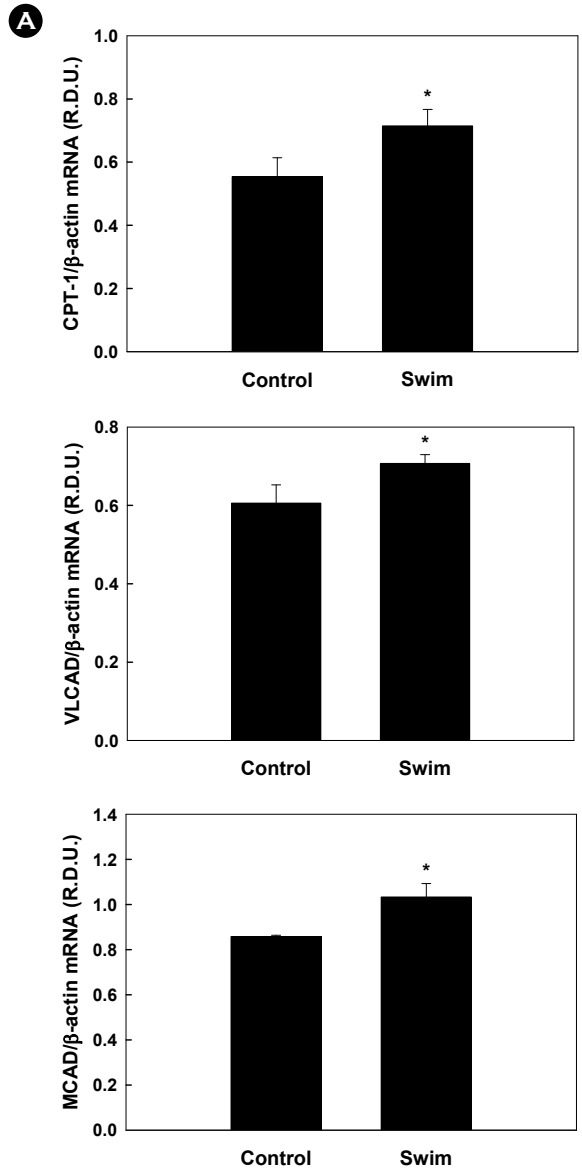
Fig. 5. Modulation of hepatic mRNA levels of PPARα target genes by swim training in female sham-operated mice at 6 weeks. (A) Female sham-operated (Sham) C57BL/6J mice (n=8/group) were subjected to swim training as described in the legend of Fig. 1, with control mice of similar initial body weights kept 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. (B) Representative RT-PCR photographs from one of three independent experiments are shown.

differentially regulates obesity and lipid metabolism between female Sham and OVX mice and this is attributed in part to differences in liver PPARα activation.

Regular exercise is highly recommended for disease prevention. Exercise is a powerful modifier of the manifestations of the metabolic syndrome in the direction of health enhancement (Pedersen and Saltin, 2006). 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). Indeed, physical exercise modifies the lipid metabolism and obesity in overweight men and animal models (Howley et al., 1995; Crampes et al., 2003; Morifuji et al., 2006; Pillard et al., 2010).

In this study, we demonstrated that swim training reduces body weight and visceral adipose tissue mass in both high fat diet-fed female OVX and Sham C57BL/6J mice, but these decreases were found to be higher in OVX than in Sham mice. To our knowledge, this is the first report that obesity is differentially affected in response to swim training in Sham and OVX mice.

We previously showed that reductions in body weight gain could be correlated with reductions in fat mass, indicating that reduced fat may lead to reduced body weight, and that the capacity for fat utilization is related to the development of obesity (Yoon et al., 2002; Yoon et al., 2003; Jeong et al., 2004a). We thought that understanding fat oxidation during exercise may assist in preventing obesity and in prescribing effective body or fat weight-loss strategies, and have examined the effects of swim training on the expression of PPARα target genes involved in fat catabolism in livers of female mice. Swim training significantly increased mRNA levels of PPARα target genes responsible for mitochondrial fatty acid β-oxidation, such as CPT-1, VLCAD and MCAD in the liver of OVX mice. However, we found no differences in hepatic PPARα



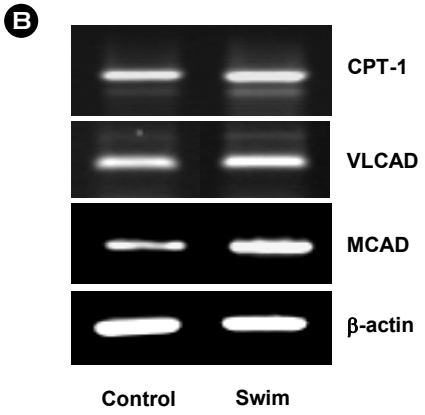


Fig. 6. Modulation of hepatic mRNA levels of PPARα target genes by swim training in female ovariectomized mice at 6 weeks. (A) Female ovariectomized (OVX) C57BL/6J mice (n=8/group) were subjected to swim training as described in the legend of Fig. 1, with control mice of similar initial body weights 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 the control mice. (B) Representative RT-PCR photographs from one of three independent experiments are shown.

activation between trained and untrained mice.

PPARα is known to be activated by fatty acids (Kliewer et al., 1997), whose concentrations in plasma increase immediately with exercise (Mougios et al., 2003). The binding of fatty acids to PPARα increases the DNA binding activity of PPARα (Mochizuki et al., 2006). Swim training increased mRNA expression of PPARα in skeletal muscle of male Sprague-Dawley rats and the lower hepatic PPARα mRNA levels in female OVX rats were reincreased by exercise training (Morifuji et al., 2006; Pighon et al., 2010). Exercise also causes a preferential utilization of fat, resulting in less fat in active individuals compared with sedentary controls (Morifuji et. al., 2006; Pillard et al., 2010). Thus, these report supported our suggestion that swim training stimulates fatty acid oxidation through hepatic PPARα, and that fat catabolism instead of fat storage into liver may contribute to reductions in adipose tissue mass and regulation of obesity in OVX mice.

However, the action of PPARα on lipid metabolism and obesity may be negative by estrogens, major ovarian factors in female mice (Yoon et al., 2003; Jeong et al., 2004b), because of a bidirectional signal cross-talk exists between PPARα and ERs (Wang and Kilgore, 2002; Jeong and Yoon, 2007). Accordingly, the unchanged expression levels of PPARα target genes by swim training in female Sham mice with functioning ovaries may be due to interference of estrogens, although serum fatty acids are increased during swim training. This is supported by the findings premenopausal women failed to increase PPARα gene expression by exercise in skeletal muscle, and that exercise training did not lead to increase the expression of PPARα in female rat skeletal muscle (Tunstall et al., 2002; Bruce et al., 2006; Kannisto et al., 2006).

In conclusion, this study provides evidence that swim training influences obesity and lipid metabolism via the differential activation of hepatic PPARα in female Sham

and OVX mice. Moreover our results show that swim training increases fat catabolism and decreases adipose tissue mass by stimulating hepatic PPARα target genes involved on fatty acid oxidation in female OVX mice, suggesting that swim training may prevent obesity in overweight postmenopausal women.

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