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Exercise training improve leptin sensitivity in peripheral tissue of obese rats

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ABSTRACT

The present study examined thechange to the effect of the leptin sensitivity by leptin resistance-induced leptin receptor (ObRb) and leptin-related suppressor of cytokine signaling 3 (SOCS3) mRNA levels in hypothalamic, liver, muscle and leptin protein levels in blood after eight 8 weeks of exercise training and/or dietary control of high fat induced obese rats. After 2 weeks of adaptation maintenance, four-week-old male SD rats ($n = 42$) were randomly divided into control (CO) ($n = 8$) and high-fat diet (HF) ($n = 32$) groups. The HF group randomly divided into HF, HF + exercise training (HFT), changed to normal diet (HFND) and changed to normal diet and exercise training (HFNDT) groups. 13 weeks of HF group average body weight significantly increased in comparison to the CO group ($p < 0.05$). Plasma leptin levels of the HFT, HFND and HFNDT group were significantly decreased in comparison to the HF group ($p < 0.05$). The mRNA expression of ObRb and SOCS3 in the liver and muscle of the HF group was significantly decreased comparison to that of the HFT, HFND and HFNDT group after 8 weeks intervention ($p < 0.05$). In addition, the mRNA expression of ObRb and SOCS3 in the hypothalamus of the HF group was significantly increased comparison to that of the HFT, HFND and HFNDT group ($p < 0.05$). HFND group also was significantly reduced comparison to of the HFT and HFNDT group ($p < 0.05$).

These findings suggest that the effect of leptin sensitivity in peripheral may primarily the more relate to combined dietary control and exercise training more than effect of dietary control.

1. Introduction

Central leptin resistance occurs during the growth and development of obese mice [1] and human [2]. Central leptin resistance can either be caused by reduced leptin transport across the blood brain barrier [3,4] or by reduced activation of leptin receptor signaling [5]. Leptin resistance is development as a permissive condition for obesity [6], and efforts to enhance leptin sensitivity could be a determinant in the treatment and prevention of this metabolic disorder.

Leptin is produced by adipocytes in proportion to their triglyceride content, links changes in body energy stores to adaptive responses in the central control of energy balance [7–10]. The hypothalamus can gather information on the body's nutritional status by integrating multiple signals, including potent hormonal signals such as insulin and leptin [8,10]. Obesity is associated with hypothalamic endoplasmic reticulum (ER) stress, which impairs leptin receptor b (ObRb) signaling in cultured cell; conversely, attenuation of ER stress improves leptin signaling and leptin action *in vivo*. Increased activity of inflammatory signaling pathways in the hypothalamus of obese animals can impair leptin signaling both *in vivo* and in cultured cell models, whereas genetic or pharmacological blockade of inflammatory signals in the brain of obese rodents promotes leptin action and protects against diet induced obesity [11–13].

High fat diet and sedentary lifestyle are the central factors that lead to the prevalence of obesity without precedent increase. However, exercise training plays an important role as a cornerstone of obesity treatment. Exercise has long been reported to reduce body weight and visceral adiposity, increasing the energy expenditure and improving glycaemic control in overweight or T1D and T2D patients [14–16]. No well-established study has been reported, at least to our knowledge, on the effects of exercise training and dietary control tissue on leptin sensitivity through cross-talk of hypothalamus, liver and muscle tissue in high fat diet induced obese rats.

Thus, we hypothesized that exercise training and dietary control could improve the central and peripheral leptin sensitivity modulating in hypothalamic, liver and skeletal muscle for the control of energy metabolism. In the present study, we investigated the alteration of the leptin sensitivity on ObRb and SOCS3 in hypothalamic, liver and muscle as well as leptin levels in blood after

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8 weeks exercise training and dietary control in high fat induced obese rat.

2. Methods

2.1. Animals

Four-week-old male Sprague Dawley (SD) rats ($n = 42$) (Central Lab Animal Inc., Korea) were kept in individual cages and fed freely with standard rat chow and water. It contained on average calories 40% as fat, 20% protein, 35% carbohydrates. All rats were cared for during the entire period of experimentation in accordance the Guidelines of Animal Experiments recommended by Institutional Animal Care and Use Committee, which the Care and Use of Laboratory Animals of the Institute for Laboratory Animal Research [17,18].

After 2 weeks of adaptation maintenance, SD rats were randomly divided into two groups. One group was fed freely with standard rat chow (CO group) ($n = 8$); while the other group (HF group) ($n = 32$) was fed with high fat diet for 13 weeks. The HF group randomly divided into four groups, the HF + T group (continued to accept high fat diet and did exercise training for additional 8 weeks), HF-ND group (changed to normal diet and did not do exercise training for additional 8 weeks), HF-ND + T group (changed to normal diet and did exercise training for additional 8 weeks), and the HF group (continued to accept high-fat diet and did not do exercise training for additional 8 weeks). All rats were sacrificed when they were 29-week-old.

2.2. A 8-week treadmill training program

Our rats in the exercise groups were made to run on animal treadmill for 40 min once a day for 7 consecutive days. The exercise load during 1–4 weeks used for the mld-intensity exercise group consisted of running at 2 m/min for the first 5 min, at 5 m/min for the next 5 min, and then at 8 m/min for the last 30 min at 0° of inclination. The exercise load used during 5–8 weeks for the moderate-intensity exercise group consisted of running at 8 m/min for the first 5 min, at 11 m/min for the next 5 min, and then at 14 m/min for the last 30 min at 0° at inclination.

2.3. Measurement of body weight, FBS and plasma leptin levels

Body weight was measured every day during the experimental period. The fasting blood sugar (FBS) was measured using blood drawn from the tail vein after overnight fasting. The plasma leptin level was analyzed with leptin ELISA kit for rat (Linco Research, Inc., USA).

2.4. Measurement of plasma lipid profiles

Plasma was collected by centrifugation of heparinized blood at 2000×g for 15 min. Plasma total cholesterol (TC) and triglyceride (TG) levels were analyzed with rat TC and TG kits (Asan Pharmaceutical, Korea). The plasma free fatty acid (FFA) level was analyzed with rat FFA kits (Shinyang Diagnostics, Korea).

2.5. Reverse transcription polymerase chain reaction analysis

In the hypothalamus, liver and muscle total RNA was isolated with Trizol reagent (Invitrogen, Inc., USA), and single-stranded cDNA was synthesized from 5 μg of total RNA with oligo(dT)15 primers, M-MLV reverse transcriptase, M-MLV 5× reaction buffer, dNTPs, and ribonuclease inhibitor (Promega Corporation, Inc., USA). The sequences of the sense and antisense primers used for amplification were as follows: ObRb, 5′-TCCACCCAAAATTCTGACGA-3′, and 5′-AATTCAGCGTAGCGGTGATG-3′; SOCS3, 5′-TGGTCACCCACAGCAAGTTT-3′, and 5′-TGTCGCGGATAAGAAAGGTG-3′; 18S rRNA, 5′-GATGGTAGTCGCCGTGCCT-3′, and 5′-CCTTCCTTGGATGTGGTAGCC-3′. PCR analyses were performed using a GeneAmp PCR System 2400 (Perkin Elmer, USA). Each reaction was carried out with 10 μL of 2× Prime Taq Premix, 1 μL of cDNA, 1 μL of forward primer, 1 μL of reverse primer, and 7 μL of distilled water. The invariant control used for all studies was 18S.

2.6. Statistical analyses

Statistical data was analyzed using SPSS/+PC Windows version 18.0 statistical package, for which all measurements were expressed as mean ± standard error (SE). To demonstrate the statistically significant difference in measurements between ND and HF group, an independent t-test was performed. In addition, to make a comparison of the difference after exercise and dietary control, one-way ANOVA was performed. In cases in which there was a statistical significance, post hoc analysis was performed using Duncan's test. Differences were considered significant when their p-values were less than 0.05.

3. Results

3.1. Effect of high-fat diet on metabolic parameters in SD rats before exercise training

There was no difference in body weight between the CO and HF group before start high-fat diet (290 ± 3 vs. 280 ± 8 g). The body weight in the HF group significantly increased after 3 weeks high fat diet (13 weeks: 579.61 ± 13.42 vs. 532.56 ± 9.75 g, $p < 0.05$) (Fig. 1). Plasma FFA, TG and leptin levels of the HF group were significantly increased in comparison to the CO group after 13 weeks of high fat diet. Plasma TC level and FBS did not change between both groups after 13 weeks high fat diet (Table 1).

3.2. Effect of eight-weeks exercise training on body weights in SD rats

Body weight was not significantly different among the HF and HFT, HFND, HFNDT groups before exercise training. After 8 weeks exercise training, the average body weight seemed to be decreased in the HFT group compared with the HF group, but there was no significant difference. The average body weight of the HFND and HFNDT groups were significantly decreased in comparison to those of the HF group ($p < 0.05$) (Fig. 2).

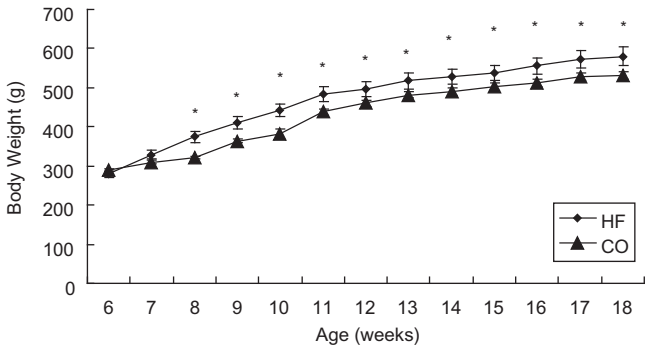

Fig. 1. Changes of body weight in experimental rats before exercise training. *$p < 0.05$ vs. CO.

Table 1
Metabolic parameters.

	CO (n = 16)	HF (n = 32)
Body weight (g)	532.56 ± 9.75	579.61 ± 13.42*
FFA (uEq/L)	619.28 ± 46.80	823.36 ± 36.94*
TG (mg/dL)	126.95 ± 2.67	166.83 ± 9.57*
TC (mg/dL)	111.55 ± 3.32	117.15 ± 4.29
FBS (mg/dL)	144 ± 3	150 ± 3
Leptin (pg/mL)	644.75 ± 26.86	1066.07 ± 84.74*

Values are means ± SE, CO; control, HF; high fat diet, FFA; free fat acid, TG; triglycerol, TC; total cholesterol, FBS; fasting blood sugar.
* $p < 0.05$ vs. CO.

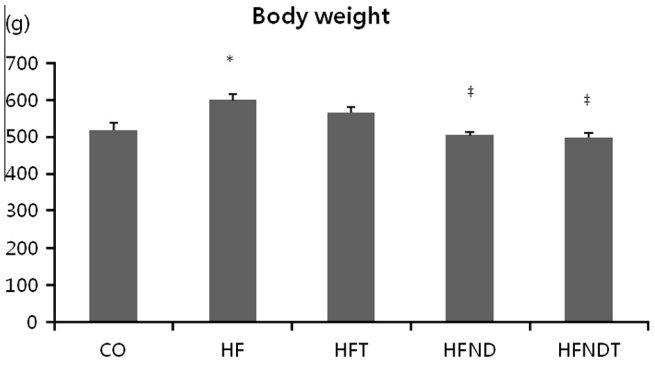

Fig. 2. Effects of 8 weeks exercise training on body weight. CO; control, COT; control and training, HF; high fat diet, HFT; high fat diet and training, HFND; high fat diet and normal diet, HFNDT; high fat diet and normal diet and training. Values are means ± SE, *$p < 0.05$ vs. CO, ‡$p < 0.05$ vs. HF.

3.3. High fat diet induced peripheral leptin resistance in SD rat

The plasma leptin of the HF group was significantly increased comparison to that of the CO group ($p < 0.05$). However, the mRNA expression of ObRb and SOCS3 in the liver and muscle of the HF group was significantly decreased comparison to that of the CO group ($p < 0.05$). However, the mRNA expression of ObRb and SOCS3 in the hypothalamus of the HF group was significantly increased comparison to that of the CO group ($p < 0.05$). High fat diet in Fig. 3 induced peripheral tissue leptin resistance in SD rat, but not induced central it.

3.4. Effect of exercise training on plasma leptin and ObRb and SOCS3 mRNA expressions in liver and muscle

The plasma leptin of the HF group was significantly increased comparison to that of the HFT, HFND and HFNDT groups ($p < 0.05$). In addition, HFNDT group was significantly reduced comparison to of the HFND and HFT groups ($p < 0.05$).

The mRNA expression of ObRb and SOCS3 in the liver and muscle of the HF group was significantly decreased comparison to that of the HFT, HFND and HFNDT groups after 8 weeks intervention ($p < 0.05$). In addition, the mRNA expression of ObRb and SOCS3 in the hypothalamus of the HF group was significantly increased comparison to that of the HFT and HFND groups ($p < 0.05$). HFND group also was significantly reduced comparison to of the HFT and HFNDT groups ($p < 0.05$) (Fig. 4).

4. Discussion

In this study, we demonstrated that high fat diet induced obese rat during 13 weeks was presented only leptin resistance in peripheral tissue. Our observed that dietary control and combined dietary control and exercise training was effected the reduced body weight and the improved peripheral tissue leptin resistance and leptin sensitivity. However, the resulted our study showed that combined exercise and dietary control was not increased ObRb and SOCS3 mRNA expression but improved the reduction plasma leptin in hypothalamus. These findings suggest that exercise/or diet control changed positively leptin resistance and sensitivity.

It is widely accepted that the prevalent lifestyle model of Western societies characterized by limited physical activity, excessive caloric intake, and repetitive behavioral patterns contributes to the dysregulation of the otherwise homeostatic control of body weight [19]. The leptin play a role important in the system, a hormone secreted in the periphery by fat cells [20], which signals the status of body energy stores, down-regulates feeding behavior, and promotes energy expenditure by activating signal transduction mediated by JAK-STAT pathway in the hypothalamic arcuate nucleus through its receptor (ObRb). Leptin is required for energy stores to be sensed in the central nervous system and is thus essential for the functions such as normal energy homeostasis and reproduction.

Leptin resistance often reported in standard housed mice [21], especially if obese, was partially rescued by genetic modifications [22] or physical exercise [23]. Although the energy expenditure aspects of such exercise training may contribute to the effects of weight loss, it has been suggested that combined exercise and dietary control may also contribute to the energy balance by altering appetite and reducing food intake. In other studies, it was showed a significant effect of exercise. The previous study showed that the exercise intervention was either longer than 10 weeks [24–26] or the exercise intervention period over the period of diet-induced obesity [27]. The relatively during 8 weeks intervention in our study was explained that exercise and diet intervention was effected at altering indices of reduction body weight and plasma leptin levels.

Central leptin resistance can either be caused by reduced leptin transport across the blood-brain barrier or by reduced activation of leptin receptor signaling [1–4]. Thus leptin resistance was regarded as disorder central nervous system. Recently, study reported that leptin resistance is reduced in diet-induced obese rats exposed to postweaning voluntary exercise as compared with control sedentary rats, thus attenuating the development of obesity typical of this model [23]. The other study suggested the same in line, although obtained in a pathological model genetically predisposed to become obese and characterized by leptin resistance [6]. However, our study showed that high fat diet induced obese rat during 13 weeks was not induced central leptin resistance but was presented peripheral leptin resistance.

The hypothalamus play a central role in integrating hormonal (leptin and insulin) and nutritional signals from the periphery and regulate food intake, energy expenditure, and peripheral metabolism [10]. Therefore, the mechanism for leptin increased responsiveness in exercise is of great and understanding this mechanism could lead to new approaches to prevent or treat obesity. Exercise training may be one of the preventive and therapeutic strategy against impaired leptin and insulin signal transduction in the hypothalamus of obese individuals [6]. One potential mediator of increased STAT3 activation in the hypothalamus of exercised rats may be expression of SOCS3 as a suppressor of cytokine signaling. A strong expression SOCS3 in mammalian cells antagonizes leptin signaling, probably by binding and antagonizing JAK activity [28,29]. In addition, the previous study reported that exercise training was associated with a markedly increased phosphorylation or activity of several proteins involved in leptin and insulin signal transduction in the hypothalamus [30]. Obese rats in other study are peripherally leptin resistant, while they retain sensitivity to centrally administered leptin [31].

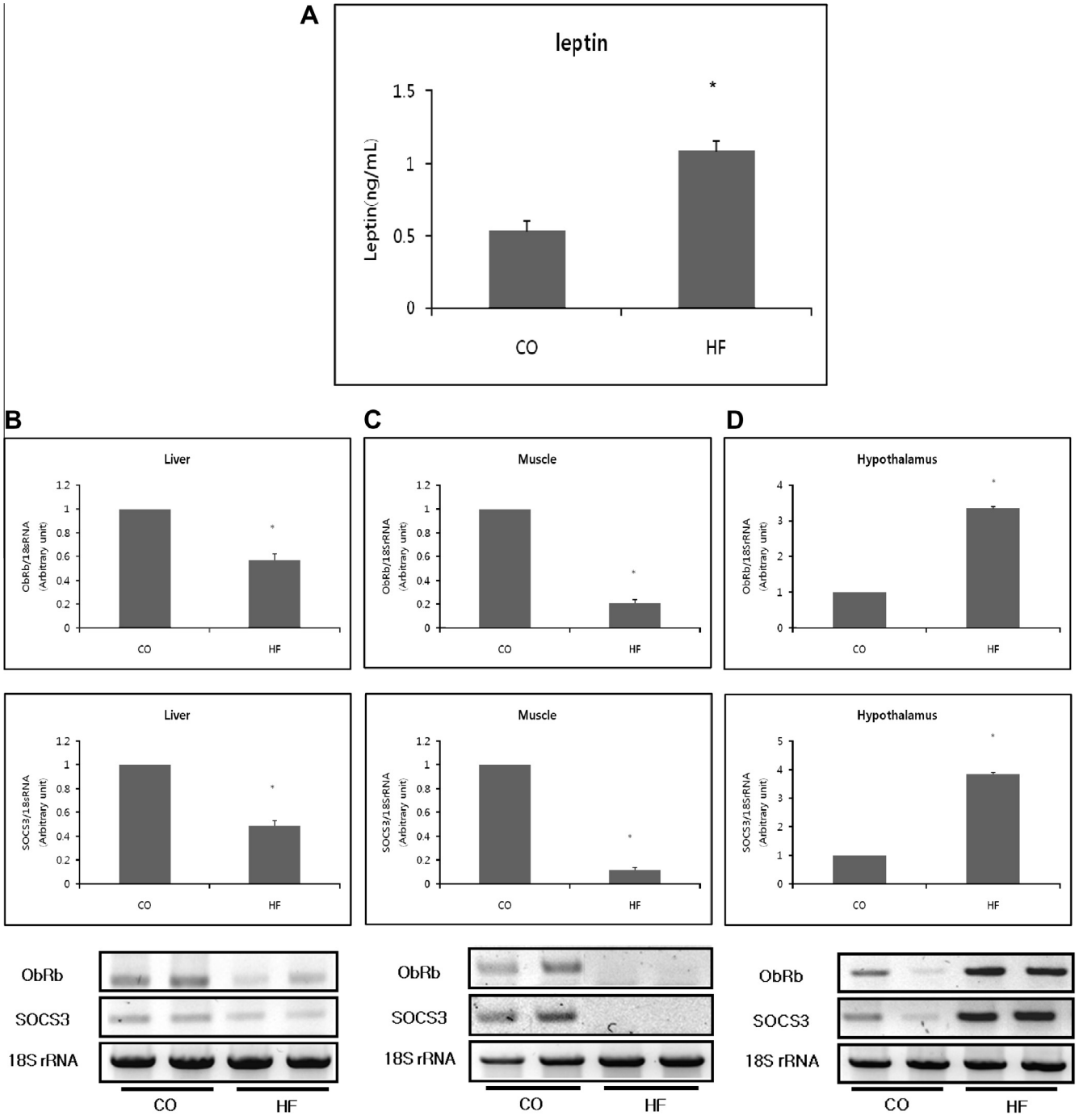

Fig. 3. Changes in plasma leptin for the CO ($n = 8$) and HF groups ($n = 8$) (A). Changes of ObRb and SOCS3 mRNA expression for the CO and HF groups in the liver (B), muscle (C), hypothalamus (D). High fat diet induced peripheral leptin resistance in SD rat. However, high fat diet was not induced central leptin resistance in SD rat. Values are means ± SE, $^{*}p < 0.05$ vs. CO.

In our study resulted, ObRb and SOCS3 expression in liver and muscle after 8 weeks intervention showed that HF group was decreased comparison to the HFT, HFND and HFNDT groups and HF group in hypothalamus was increased comparison to the HFT, HFND groups. However, HFNDT group was high expressed comparison to the HFND group. In addition, plasma leptin level of the HF group was significantly increased comparison to that of the HFT, HFND and HFNDT group. Thus, exercise and diet control during 8 weeks in our study was effected plasma leptin level, ObRb and SOCS3 expression.

Short and long term caloric restrictions without exercise training have been shown to dramatically reduce plasma leptin levels in obese human and rats [32–34]. Thus, components environment enrichment other than physical exercise could play a role in regulating feeding behavior and the related mechanisms in developing mice [35]. However, the molecular mechanisms by which exercise controls food intake are still unsolved. Several experimental studies have demonstrated that neither acute [30,36] nor regulatory [37] exercise per se change food intake, on the other hand, accumulating evidence showed that both exercise potentiate the anorexigenic effects of leptin in the hypothalamus.

In the present study, we showed that plasma leptin levels in HF group were significantly increased comparison to CO group. In addition, ObRb and SOCS3 mRNA expression was significantly

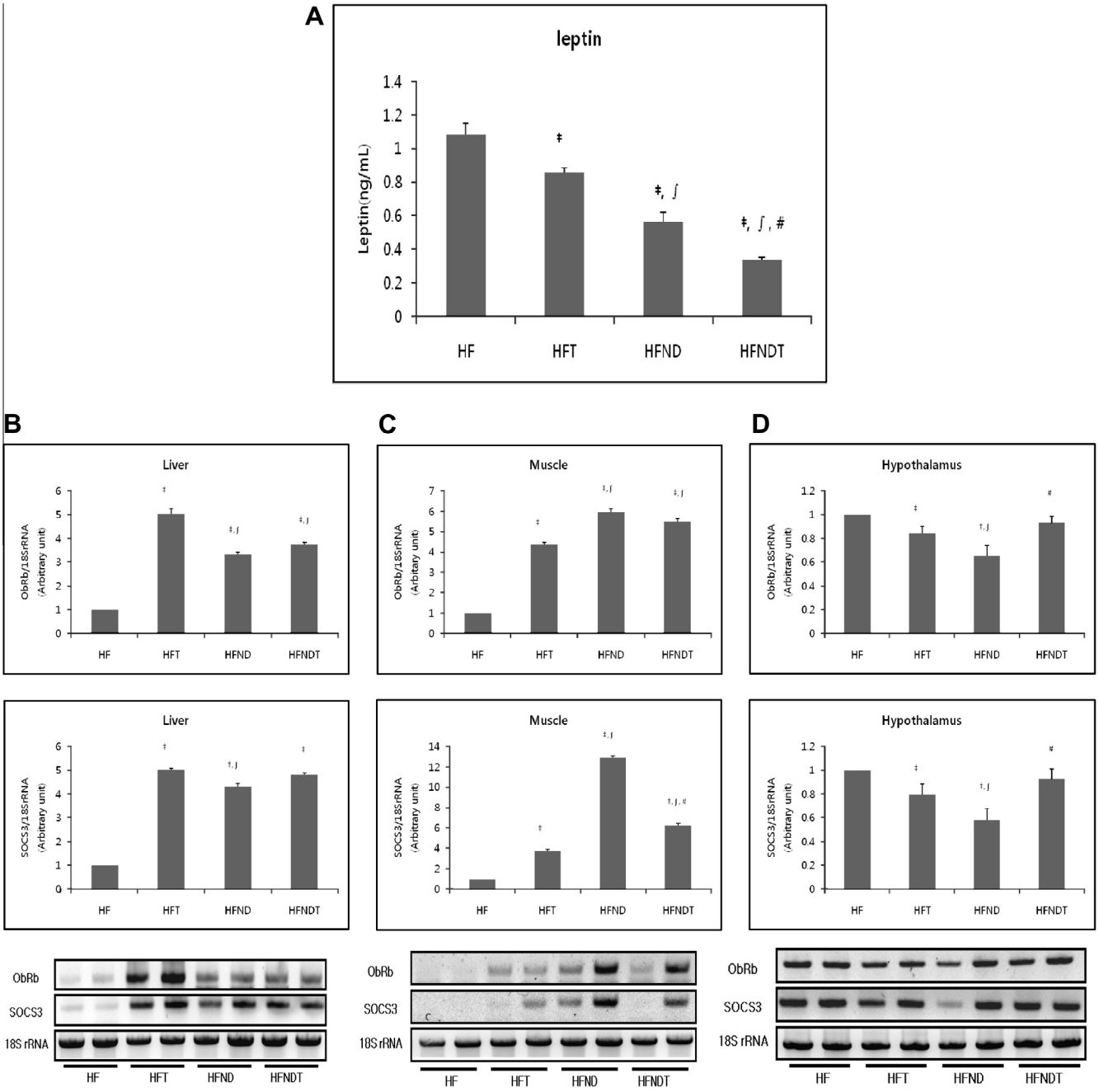

Fig. 4. Change in plasma leptin for the HF ($n = 8$), HFT ($n = 8$), HFND ($n = 8$) and HFNDT ($n = 8$) groups. ObRb and SOCS3 mRNA expression for the HF, HFT, HFND and HFNDT groups in the liver(B), the muscle (C) and hypothalamus (D) of each group after 8-week treatment. Values are means ± SE, $^{‡}p < 0.05$ vs. HF, $^{∫}p < 0.05$ vs. HFT, $^{\#}p < 0.05$ vs. HFND.

decreased of that in liver and muscle. This may leptin resistance of high fat diet induced in peripheral tissue. The plasma leptin after 8 weeks exercise and diet in peripheral tissue was decreased and leptin signaling pathway mRNA was increased all treated groups. Thus, exercise and diet intervention was improved leptin resistance and sensitivity in peripheral tissue. We cautiously suggest that the effect of leptin sensitivity in peripheral may primarily the more relate to combined dietary control and exercise training more than effect of dietary control.

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