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The Regulation of the Concentrations of Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha and Sirtuin 1 Protein in the Soleus Muscle by Aerobic Exercise Training in Obese Wistar Rats

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Abstract

Background: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a) and Sirtuin 1 (SIRT1) are significant indicators of obesity and other metabolic disorders.
Objectives: The present study aimed to investigate the regulation of the concentrations of PGC-1a and SIRT1 protein in the soleus muscle by aerobic exercise training in obese Wistar rats.
Methods: This study was conducted on 24 obese male rats, which were randomly categorized into three groups of control, medium-intensity training (28 m/min), and high-intensity training (34 m/min) after obesity induction through a high-fat diet. A series of aerobic trainings in five sessions of 60-minute aerobic training per week was performed for eight weeks. Data analysis was performed using one-way ANOVA to examine the mean differences between the groups. In addition, Tukey's post-hoc test was used for the paired comparisons of the groups.
Results: Significant differences were observed in the concentrations of the PGC-1a ($P < 0.001$) and SIRT1 proteins between the study groups ($P < 0.001$). Tukey's post-hoc test revealed a significant difference between the moderate-intensity aerobic exercise and control groups ($P < 0.01$) regarding their mean concentration of the PGC-1a protein. However, the high- and moderate-intensity groups showed no difference in this regard ($P < 0.028$). Moreover, there was a significant difference in the concentration of the SIRT1 protein between the moderate-intensity aerobic exercise and control groups ($P < 0.02$), and the high-intensity training and control groups ($P < 0.005$).
Conclusions: According to the results, aerobic exercise training could activate SIRT1 and PGC-1a and might enhance mitochondrial biogenesis in the subcutaneous fat. Therefore, aerobic training is recommended as a therapeutic approach to obesity and several other metabolic diseases.

Keywords: Aerobic Training, PGC-1a, SIRT1, Obese Rat

1. Background

Obesity is considered to be a significant health concern across the world, and one of its main consequences is epigenetic changes, which has not been investigated adequately (1). The transformation of the white adipose tissue into the brown adipose tissue is a solution for increased energy consumption and obesity. Contrary to the white dispose tissue, the brown dispose tissue is where heat is produced (2). The white dispose tissue produces heat through expressing unpaired protein-1 (UCP-1) and increasing mitochondrial density (3). Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1a) regulates heat production by inducing UCP-1 expression and the mitochondrial respiratory chain key enzymes (4). Numerous transcription factors are involved in metabolic and physiological adaptations, leading to mitochondrial biogenesis; such examples are transcription factors PGC-1a (5) and Sirtuin 1 (SIRT1) (6). PGC-1a factor plays a key role in increasing energy consumption and mitochondrial biogenesis as a co-activator (7) and is expressed in the brown dispose tissue of the heart, kidneys, skeletal muscles, brain, and other oxidative tissues. The expression of PGC-1a in the

heart and skeletal muscles increases under the impact of physical training (8). In addition, PGC-1a regulates numerous genes in the metabolic pathway, including glycogen genesis, glycolysis, and fatty acid oxidation (9). The SIRT1 protein residing in the nucleus is among the first genes known to impact the cellular responses to stress (10) and fatty acid excursion from the fat cells (11) This is also one of the essential nuclear factors contributing to PGC-1a activation (deacetylation). In fact, the increased mitochondrial activity suggests the deacetylase activation of the SIRT1 protein (12). SIRT1-increasing stimuli contribute to PGC-1a activation, the increased mitochondrial enzymes attributed to the fat oxidation process, and energy metabolism alternation in the hepatocytes, white adipocytes, and hepatocytes (13).

According to the literature, the adaptations achieved through physical training could contribute to the changes in the function and structure of contractile proteins (14), mitochondrial function (15), metabolic regulation (16), intracellular signaling (17), and transcriptional responses (18). In this regard, regular high-intensity training has been reported to activate the signaling pathway that contributes to the mitochondrial biogenesis in the skeletal muscles (19). Suwa et al. (20) explored the impact of severe endurance training and both high-intensity and low-intensity training on the expression of the SIRT1 and PGC-1a proteins in the skeletal muscles of rats, reporting that severe endurance training with a treadmill (20 m/min with 18.5% elevation for 45 minutes) could improve the expression of the PGC-1a protein for 18 hours after the training, as well as the expression of the SIRT1 protein in the horseshoe muscles for two hours after the training.

In another study, Gurd et al. (21) investigated the impact of three training sessions per week containing 10 sets of training at 90% of the peak oxygen consumption level with two minutes of rest between every two sets for six weeks, discovering that the SIRT1 activity increased along with the mitochondria biogenesis in the skeletal muscles after the training program. In addition, the mentioned study indicated that the SIRT1 levels had no significant changes after six weeks of regular training at the intensity of 90% of the peak oxygen consumption (21).

2. Objectives

According to the literature, aerobic training is among the important influential factors in the phenotypic conversion of the white dispose tissue into the brown dispose tissues, while it also plays a pivotal role in weight loss. On the other hand, the association of aerobic exercises with PGC-1a and SIRT1 could influence obesity. Considering the diversity of the findings in this regard, there seems to be no coherent knowledge of the general impact of aerobic training and trainings with various intensities on PGC-1a and SIRT1. The present study aimed to determine which aerobic training intensities could possibly alter the SIRT1 and PGC-1a levels in obese male Wistar rats. A comparative experiment was also performed to assess the impact of high-intensity and moderate-intensity aerobic training over eight weeks the SIRT1 and PGC-1a proteins levels of the rats.

3. Methods

3.1. Experimental Animals

In the present experimental study, 24 Wistar rats, healthy, male, 14 weeks old, weighing from 250 to 300 grams, and with a body mass index more than 30 g/cm^2, acquired from Razi Institute of Iran and fed/grown on/with a set diet from Behparvar Company and thus adapted to laboratory research, were used as models. After the week 6, the rats began to receive a calorie-rich diet to gain weight/become obese, leading to them weighing from 250 to 300 grams at the week 14. Their living conditions consisted of polycarbonate cages, and a controlled environment (the average temperature = 23 $\pm$ 1°C; humidity = 50 $\pm$ 3%; and kept in a cycle of light and darkness for 12 hours each). Also, for 14 days, the rats were provided with unlimited water and food, specially made for Wistar rats. After the 14-day period, the rats were separated in three groups, randomly: moderate-intensity aerobic exercise (n = 8); high-intensity aerobic exercise (n = 8); and control (n = 8).

3.2. Induction of Obesity in the Rat

The obese group continued to receive a fat- and calorie-rich diet, containing 4.8 kcal in g energy and 39% fat, in comparison to the standard food, containing 3.9 kcal in g, and 3.5% fat. The rats' unlimited access to water and food continued for another 14 weeks. The normal range of body mass index (BMI) of rats, which is the definitive measure of their obesity, is 0.45 to 0.68 g/mc^2 (22). When the rats finished the obesity phase at 14 weeks of age and before training, their BMI had exceeded the normal range at 0.84 g/cm^2.

3.3. Familiarization Stage and Exercise Protocol

The rats underwent 60-minute-long high- and medium-intensity aerobic training sessions, lasting eight weeks, five times per each (week). The rat rodent treadmills used for the training were provided by Mobin Company (Iran), with an adjustable 15 - 15 degrees elevation range and various consecutive trainings with different

speeds, shocks, elevations, and accelerations. First, the rats were accustomed to the program and learned the aerobic training protocol. At the start of the program, they began to walk on the treadmill with no elevation and at the speed of 10 meters/minute. The training became steadily longer and faster in the course of the second and the third weeks. The rats in the medium-intensity group could run on the treadmill with a speed of 28 meters/minute (70% - 75% VO2max), and those in the high-intensity group with a speed of 34 meters/minute (80% - 85% VO_{2max}) (23). For the rats to cool off, the treadmill would stop (inversely to zero) after each session was finished.

3.4. Muscle Tissue Biopsy

The rats were anesthetized using a combination of xylazine (3 - 5 mg/kg of body weight) and ketamine (30 - 50 mg/kg of body weight) 48 hours after the last training session and 12 hours of fasting. After confirming the anesthesia by examining leg retraction, an incision (5 - 6 cm) was made through the abdominal area of the rats, Moreover, the horseshoe muscle was removed quickly, transferred to a microtube (1.5 mL), immersed in liquid nitrogen immediately, and preserved at the temperature of -80°C until examination (24). The tissue samples were initially pulverized using a mortar and pestle and mixed with a radioimmunoprecipitation assay buffer solution in homogenizer tubes for 15 minutes. Following that, the samples were retrieved from the tube using a sampler, poured in microtubes (1.5 mL), and centrifuged at 20,000 rpm and the temperature of 4°C for four minutes. At the next stage, the microtubes were removed from the centrifuge device, drawn from the tubes using a supernatant sampler with the contents poured into another tube, and preserved in a freezer at the temperature of-80°C. The levels of PGC-1a and SIRT1 (intra-assay: CV < 10%) were measured using the special Rat ELISA Kit.

3.5. Statistical Analysis

SPSS version 16 was used for data analysis (significance level = $P \leq 0.05$). First, the normal distribution of the data was attested by the Shapiro-Wilk test, and the variance homogeneity confirmed by Levene's test. Next, the differences between the three groups were investigated using One-way ANOVA and the paired comparisons between the groups was performed using Tukey's post-hoc test.

4. Results

According to the information in Table 1, eight weeks of moderate-intensity and high-intensity aerobic exercises caused significant differences in the protein concentrations of PGC-1a ($F [2,29] = 11.81$; $P < 0.001$) and SIRT1 ($F [2,28] = 5.34$; $P < 0.001$] between the three groups. Tukey's post-hoc test revealed that there was a significant difference between the moderate-intensity aerobic exercise and control groups ($P < 0.01$) regarding their mean concentration of the PGC-1a protein. However, the high- and moderate-intensity groups showed no such difference ($P < 0.028$). Moreover, the concentration of the SIRT1 protein between the high-intensity training and control groups ($P < 0.005$), and moderate-intensity aerobic exercise and control groups ($P < 0.02$), was significantly different, and the high-intensity training and control groups ($P < 0.005$). However, the high-intensity and moderate-intensity training groups had a significant difference in this regard ($P < 0.37$).

Table 1. Variation of PGC-1a and SIRT1 Levels in Study Groups[a]

Variable	C	MI	HI
PGC-1a, ng/mL	0.27 ± 0.01	0.31 ± 0.01[b]	0.30 ± 0.008[b]
SIRT1, ng/mL	0.73 ± 0.08	0.82 ± 0.09[b]	0.86 ± 0.11[b]

Abbreviations: C, control; HI, high-intensity aerobic exercise; MIl moderate-intensity aerobic exercise.
[a]Data expressed as mean ± standard deviation.
[b]The level of significant at 0.05.

5. Discussion

The present study aimed to regulation of the concentrations of PGC-1a and SIRT1 protein in the soleus muscle by aerobic exercise training in obese Wistar rats. According to the obtained results, the moderate- and high-intensity aerobic exercise program significantly increased the PGC-1a protein concentration in the obese male rats compared to the control group. The results of the present study are consistent with some studies (25, 26) and inconsistent with the results of Alvehus et al. (27) and Ikeda et al. (12). By altering the NADH/NAD ratio, aerobic physical activity could stimulate the SIRT1 activity in rat muscles (12). Furthermore, upstream mechanisms seem to be stimulated by the physical activity, thereby leading to the stimulation of SIRT1 and PGC-1a activity, increased AMPK activity, and activation of the cell surface receptors by epinephrine (26, 28). In this process, SIRT1 interacts physically and functionally with PGC-1a (29). In addition, hormonal stimulation plays a pivotal role in enhancing PGC-1a expression in the visceral and subcutaneous white adipose tissues, so that chronic physical activity would increase the level of thyroid hormone secretion, which in turn may increase PGC-1a expression and stimulate UCP-1 expression (30).

Aerobic activity has been shown to decrease adenosine triphosphate (ATP) levels and increase intracellular calcium levels, thereby triggering the activation of the AMPK and CaMK pathways (31). The activation of these pathways results in the activation of MEF2 transcription and increased synthesis of PGC-1a (32). By regulating the expression of both contractile and enzymatic proteins, the working capacity increases, thereby providing the required energy (33). Among the other potential benefits of aerobic exercises of varying intensities is the stimulation of the upstream of the mechanisms that influence mitochondrial production and diminish the adverse effects of obesity through increasing exothermicity and energy expenditure.

According to the results of the present study, the moderate and high-intensity aerobic exercise programs significantly increased the SIRT1 protein compared to the control group. The results of Huang et al. (34) and Vizvari et al. (35) are similar to the present study. Hence, findings of Marton et al. (36) is inconsistent with present study. Sirtuins regulate fat metabolism and lipogenesis. PPARγ is a nuclear receptor that regulates lipogenesis. SIRT1, along with N-CoR, suppresses PPARγ transcriptional activity, thereby inhibiting lipogenesis (37). Under starvation conditions, the activation of PGC-1a by SIRT1increases fatty acid oxidation and ketogenesis (38). PGC-1a stimulates fatty acid oxidation enzymes, such as MCAD, CPT1, and PDK-4, acting as a key regulator of metabolic transition to fatty acid oxidation under nutrient depletion conditions. SIRT1 also binds to PPARα and enhances its transcriptional activity along with its coactivator (i.e., PGC-1a), thereby improving fatty acid oxidation (39). LXRS and FXRS are hepatic X receptors and the nuclear receptors that regulate lipid metabolism. LXRS regulates lipid and cholesterol metabolism and increases the transfer of cholesterol from the peripheral tissues to the liver, while FXR decreases serum lipid and glucose levels by regulating glucose, fat, and acidic metabolism. SIRT1 deacetylates and activates this nuclear receptor and improves the metabolic status. The deacetylation of LXRS and FXR by SIRT1 also increases ubiquitinase and its degradation (40). However, the activation of these nuclear receptors by this rapid modernization remains unclear, which also deacetylates SIRT1, SREBP-18, and SREBP-2; these are the transcription factors that increase the expression of cholesterogenic and lipogenic genes for fat storage and are also active in nutrition and satiety, and deacetylation renders them as targets for ubiquitinase, thereby decreasing their activity (41). Through deacetylation and the subsequent activation of LCAD (fatty acid oxidation pathway), SIRT3 increases fatty acid oxidation during starvation (42). Therefore, the substances that activate syringes (especially SIRT1) have the potential to be used in the treatment of metabolic disorders such as obesity. Furthermore, sirtuin is able to regulate energy metabolism. Physical exercise activates AMPK, which increases oxidative phosphorylation to produce ATP and reduce its consumption by inhibiting anabolic pathways, such as protein synthesis pathways (43).

5.1. Conclusions

According to the results, the PGC-1a and SIRT1 proteins significantly increased in the obese male Wistar rats of the moderate-intensity and high-intensity aerobic training groups compared to the control group. However, therapeutic interventions and exercise activities (e.g., aerobic exercises) are recommended for the activation of PGC-1a and SIRT1 as a treatment for obesity and several other metabolic diseases.

Footnotes

Authors' Contribution: The contributions of the authors were in accordance with the research regulations.

Conflict of Interests: None declared.

Ethical Approval: The study protocol was approved by the Ethics Committee of Ferdowsi University of Mashhad, Iran (code: MUMS.REC.2016.131).

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