EFFECTS OF AEROBIC EXERCISE TRAINING ON OXIDATIVE STRESS IN THE SKELETAL MUSCLES OF OBESE RATS

EFEITOS DO TREINAMENTO AERÓBICO SOBRE O ESTRESSE OXIDATIVO EM MÚSCULOS ESQUELÉTICOS DE RATOS OBESOS

EFECTOS DEL ENTRENAMIENTO AERÓBICO SOBRE EL ESTRÉS OXIDATIVO EN MÚSCULOS ESQUELÉTICOS DE RATONES OBESOS

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ABSTRACT

Introduction: Obesity is a complex and multifactorial metabolic disorder characterized by the accumulation of body fat; physical exercise increases energy expenditure and promotes a reparative effect through modulation of endogenous antioxidant defenses. Objective: To evaluate the effects of the high-fat diet (HFD) on oxidative stress parameters in skeletal muscles of rats using aerobic exercise training protocols (AETP), moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT). Methods: The study was quantitative and experimental. Animals received 8 weeks of HFD or normal diet (ND), followed by 9 weeks of HFD or ND and the two AETPs. Results: HFD did not alter the formation of thiobarbituric acid reactive substances (TBA-RS), total sulfhydryl and protein carbonyl content in the soleus and plantaris muscles; in contrast, the protocols caused a decrease in TBA-RS levels in the plantaris muscle and increased the sulfhydryl content in the soleus muscle, while MICT increased the sulfhydryl content in the plantaris muscle and reduced protein carbonyl content in both muscles. HFD reduced SOD activity in the plantaris muscle while the MICT protocol enhanced SOD in the soleus muscle and both protocols reversed the decrease in SOD in the plantaris muscle. HFD increased CAT activity in the soleus muscle, the HIIT protocol prevented this alteration and both protocols increased CAT in the plantaris muscle. HFD reduced GSH-Px activity in both muscles, and the MICT protocol prevented this reduction in the soleus muscle, while the HIIT protocol partially prevented this decrease. The MICT protocol did not prevent the reduction of GSH-Px and the HIIT protocol partially prevented this decrease in the plantaris muscle. Conclusions: HFD elicited oxidative stress in the skeletal muscle of rats, and both protocols were able to prevent most of the alterations in oxidative stress parameters caused by the HFD. ***Level of evidence IV; Investigation of treatment outcomes.***

Keywords: Protocols; Oxidative stress; Skeletal muscle.

RESUMO

*Introdução: Obesidade é uma desordem metabólica complexa e multifatorial, caracterizada pelo acúmulo de gordura corporal. O exercício físico tem a capacidade de aumentar o gasto energético e promover efeito reparador por meio da modulação das defesas antioxidantes endógenas. Objetivo: Avaliar os efeitos da dieta hiperlipídica (DHL) sobre parâmetros de estresse oxidativo em músculos esqueléticos de ratos, por protocolos de treinamento físico aeróbico (TFA), treinamento contínuo de intensidade moderada (TCIM) e treinamento intervalo de alta intensidade (HIIT). Métodos: O estudo foi quantitativo e experimental. Animais receberam 8 semanas de DHL ou dieta normal (DN), seguidas por 9 semanas de DHL ou DN e os dois TFA. Resultados: A DHL não alterou a formação de substâncias reativas ao ácido tiobarbitúrico (TBA-RS), conteúdo total de sulfidrilas e de proteínas carboniladas nos músculos sóleo e plantar. Em contraste, os protocolos diminuíram TBA-RS no músculo plantar e aumentaram o conteúdo de sulfidrilas no músculo sóleo. TCIM aumentou o conteúdo de sulfidrilas no músculo plantar e reduziu o conteúdo de proteínas carboniladas em ambos os músculos. A DHL reduziu a atividade da SOD no músculo plantar; o TCIM aumentou a SOD no músculo sóleo e ambos os protocolos reverteram a diminuição da SOD no músculo plantar. A DHL aumentou a CAT no músculo sóleo, o HIIT preveniu essa alteração e ambos os protocolos aumentaram a CAT no músculo plantar. A DHL diminuiu a atividade da GSH-Px em ambos os músculos, e o TCIM preveniu esta diminuição no músculo sóleo, enquanto que o HIIT preveniu parcialmente esta diminuição. O TCIM não preveniu a redução da GSH-Px, e o HIIT preveniu parcialmente esta diminuição no músculo plantar. Conclusão: A DHL causou estresse oxidativo nos músculos esqueléticos de ratos, e ambos os protocolos foram capazes de prevenir a maioria das alterações nos parâmetros de estresse oxidativo causadas pela DHL. **Nível de evidência IV; Investigação dos resultados do tratamento.***

Descritores: *Protocolos; Estresse oxidativo; Músculo esquelético.*

RESUMEN

Introducción: La obesidad es un desorden metabólico complejo y multifactorial caracterizado por la acumulación de grasa corporal. El ejercicio físico tiene la capacidad de aumentar el gasto energético y promover efecto reparador por medio de la modulación de las defensas antioxidantes endógenas. Objetivos: Evaluar los efectos de la dieta hiperlipídica (DHL) sobre parámetros de estrés oxidativo en los músculos esqueléticos de las ratas, por protocolos de entrenamiento físico aeróbico (TFA), entrenamiento continuo de intensidad moderada (TCIM) y entrenamiento de intervalo de alta intensidad (HIIT). Métodos: El estudio fue cuantitativo y experimental. Los animales recibieron ocho semanas de DHL o dieta normal (DN), seguidas por nueve semanas de DHL o DN

y los dos TFA. Resultados: La DHL no alteró la formación de sustancias reactivas al ácido tiobarbitúrico (TBA-RS), contenido total de sulfhidrilos y de proteínas carboniladas en los músculos sóleo y plantar. En contraste, los protocolos disminuyeron TBA-RS en el músculo plantar y aumentaron el contenido de sulfhidrilos en el músculo sóleo. TCIM aumentó el contenido de sulfhidrilos en el músculo plantar y redujo el contenido de proteínas carboniladas en ambos músculos. La DHL redujo la actividad de la SOD en el músculo plantar, el TCIM aumentó la SOD en el músculo sóleo y ambos protocolos revirtieron la disminución de la SOD en el músculo plantar. La DHL aumentó la CAT en el músculo sóleo, el HIIT previno esa alteración y ambos protocolos aumentaron la CAT en el músculo plantar. La DHL disminuyó la actividad de GSH-Px en ambos músculos, y el TCIM previno esta disminución en el músculo sóleo, mientras que el HIIT previno parcialmente esta disminución. El TCIM no previno la reducción de la GSH-Px y el HIIT previno parcialmente esta disminución en el músculo plantar. Conclusión: La DHL causó estrés oxidativo en los músculos esqueléticos de ratones y ambos protocolos fueron capaces de prevenir la mayoría de las alteraciones en los parámetros de estrés oxidativo causados por DHL. ***Nivel de evidencia IV; Investigación de los resultados del tratamiento.***

Descriptores: *Protocolos; Estrés oxidativo; Músculo esquelético.*

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INTRODUCTION

Obesity is a chronic disease characterized by the excessive accumulation of triglycerides in adipose tissue, due to the energy imbalance between a high intake of foods with high fat and sugar content and a reduced energy consumption. This condition, which can be measured by the Index Body mass (BMI), has a complex etiology, as a result of interactions between genetic, metabolic and environmental factors.[1]

Simultaneously, obesity is also a risk factor for cardiovascular diseases, such as hypertension and atherosclerosis, and metabolic endocrine-diseases, such as diabetes mellitus type 2. This interaction occurs as a consequence of abnormal bio-metabolic processes, including endothelial dysfunction. [2] Obesity is also associated with the induction of cellular events that can lead to the mitochondrial production of reactive oxygen species (ROS), via the respiratory chain.[3,4] According to Pimenta et al.,[5] diets that are high in fat exacerbate the deleterious effects of free radicals in the animal model.

Multiple therapies have been suggested as approaches to reduce the harmful results of obesity and its comorbidities, among these are the conducts that aim to minimize its deleterious effects at the cellular and systemic levels.[6-9] Studies have proven that regular and systematic physical activity is beneficial in the prevention and rehabilitation of damage to health, since it can regulate metabolic control, activating and amplifying the functioning of all organs. Among the models of exercises, we highlight interval and continuous exercise.[10,11] Interval training is performed intermittently, and is characterized by alternating periods of exercise, combined with rest intervals, while continuous training is characterized by the execution of low and medium intensity exercise, for a period of time, with recovery only after termination of exercise.[5, 12-13] Considering the high global rates of obesity, in association with physical inactivity and the dietary changes that result from popular lifestyles[14], this study aimed to evaluate the effects of two aerobic exercise training protocols (AETP), moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT), on the alterations caused by a high-fat diet (HFD) on oxidative stress parameters in the soleus and plantaris muscles of rats.

MATERIALS AND METHODS

Adult male Wistar rats (70 days old) were obtained from the UNIVALI (Universidade do Vale de Itajaí, Brazil) and were randomly assigned into groups fed on a HFD (protein, 20%; carbohydrate, 20%; lipid, 60% - Prag Soluções Biosciências, Jaú-SP) or normal diet (ND) (protein, 20 kcal%; carbohydrate, 70 kcal%; lipid, 10 kcal%; - Nuvital Nutrientes, Curitiba-PR) for 8-weeks. The rats were maintained on a light-dark inverted cycle (12:12-h light-dark cycle), controlled temperature (22 ±1°C) and free access to the respective diets and tap water. Upon completion of the 8-weeks of diet, animals from the HFD were randomly assigned to the untrained group (HFD-UNT; n=6) or one of the groups that were trained with the different AETPs (HFD-MICT, n=6 and HFD-HIIT, n=6). Animals from the ND were assigned to an untrained group (ND-UNT; n=6). After, these 4 experimental groups were submitted to 9 more weeks of diet and training. Rats were euthanized three days after the last day of training. This study was performed in accordance with the "Principles of Laboratory Animal Care" (NIH publication 85–23, revised 1985), and was approved by the UNIVILLE (Universidade da Região de Joinville, Joinville, Brazil) Ethics Committee (Protocol No. 002/213 – COEA). All chemicals used in the analysis of oxidative stress parameters were purchased from Sigma Chemical Co., St Louis, MO, USA.

Before the AETP, rats were conditioned to Graded treadmill exercise test, the rats were placed on the treadmill and allowed to acclimatize for at least 10 minutes, later the rats run until exhaustion at 20° inclination; the speed was started at 6 m/min and was increased by 3 m/min every 3 min until rats were unable to run.[15] Both AETPs consisted of an 8-weeks program of running, 5 days a week.

(1) MICT: was performed at a treadmill speed corresponding to 60% of the maximum running speed, which was kept unchanged throughout the entire session. (2) HIIT: the rats ran for 3 min at 60% of the maximum running speed, followed by 4-min intervals at 85% of the maximum running speed, which was repeated seven times, session lasted for 49 min., the MICT and HIIT protocols were of matched volume.[16] HFD-UNT and ND-UNT animals were placed on the treadmill twice a week for 10 min each day at 40% of the maximum running speed to maintain running skills.

After decapitation, the skeletal muscle soleus and plantaris were removed and kept in ice-cold buffered sodium phosphate. The skeletal muscles were homogenized in ten volumes (1:10w/v) of 20.0 mM sodium phosphate buffer, pH 7.4, containing 140.0 mM KCl. Homogenates were prepared by passing 5 pulses and were centrifuged at 750 x g for 10 min at 4°C.[17] The pellet was discarded and the supernatant was saved in aliquots and stored at -80 ° C.

TBA-RS were determined according to the method described by Ohkawa et al.[18] Tissues were mixed with 20% trichloroacetic acid and 0.8% thiobarbituric acid and heated in a boiling water bath for 60 min. TBA-RS were determined by the absorbance at 535 nm. TBA-RS content was calculated as nanomoles of MDA formed per milligram of protein.

The sulfhydryl content was determined by the method of Aksenov and Markesbery.[19] 50 µL of homogenate were added to 1mL of phosphate-buffered saline (PBS), pH 7.4, containing 1mM ethylenediaminetetraacetic acid. The reaction was started by the addition of 30 µL of 10mM 5,5´-dithiobis-(2-nitrobenzoic acid) (DTNB) and incubated for 30 min at room temperature in a dark room. Total sulfhydryl content was determined by the absorbance at 412 nm. Results were reported as nmol 3-thio-2-nitrobenzoic acid (TNB)/mg protein.

Carbonyl content was assayed by a method of Reznick and Packer.[20] 200 µL of homogenate were added containing 400 µL of 10 mM dinitrophenylhydrazine (prepared in 2M HCl). Samples were kept in the dark for 1 h and vortexed every 15 min., 500 µL of 20% trichloroacetic acid were added, was vortexed and centrifuged at 14,000 x *g* for 3 min.The pellet was washed with 1mL ethanol/ethyl acetate, vortexed and centrifuged at 14,000 x *g* for 3 min. The pellet re-suspended in 600µL of 6 M guanidine (prepared in a 20 mM potassium phosphate solution, pH 2.3), before vortexing and incubating at 60 ° C for 15 min. Samples were then centrifuged at 14,000 x *g* for 3 min and the supernatant was used to measure absorbance at 370 nm. Results are reported as carbonyl content (nmol/mg protein).

CAT activity was assayed by the method of Aebi.[21] The method is based on the disappearance of H_2O_2 at 240 nm in a reaction medium containing 20mM H_2O_2, 0.1 % Triton X-100, 10 mM potassium phosphate buffer, pH 7.0, and 0.1–0.3mg protein/mL. The specific activity is calculated as CAT units/mg protein.

GSH-Px activity was measured by the method of Wendel.[22] The medium contained 2mM GSH, 0.15 U/mL GSH reductase, 0.4 mM azide, 0.5 mM *tert*butyl- hydroperoxide and 0.1 mM NADPH. The activity is presented as GSH-Px units/mg protein.

SOD activity is based on the capacity of pyrogallol to autoxidize.[23] The medium contained 15 µL of sample, 215 µL of a mixture containing 50 µM Tris buffer, pH 8.2, 1 µM EDTA, 30 µM CAT and 20 µL of pyrogallol. The absorbance recorded every 30 seconds for 3 minutes at 420 nm spectrophotometer. The specific activity is reported as SOD units/mg protein.

Protein was measured by the method of Lowry et al.,[24] using serum bovine albumin.

Statistical analysis

The data are presented as means and standard error of the means (mean ± SEM). One-way ANOVA with post hoc testing by Duncan was used. Statistical significance was considered achieved when the p-value was <0.05. We used the statistical program SPSS for Windows version 12.

RESULTS

We initially verified the effects of two protocols of AET, HIIT and MICT, on TBA-RS and total sulfhydryl content and total carbonyl content in the soleus and plantaris muscles of rats submitted to HFD.

Figure 1A shows that HFD did not alter TBA-RS in the soleus and plantaris muscles. The HIIT and MICT did not alter this parameter in the soleus muscle, but caused a decrease in TBA-RS levels in the plantaris muscle, when compared to the HFD-UNT group (p<0.05). HFD did not alter the total sulfhydryl content (Figure 1B) in the muscles. Both protocols increased total sulfhydryl content in the soleus muscle, while the MICT protocol also increased total sulfhydryl content in the plantaris muscle of rats. HFD did not alter protein carbonyl content (Figure 1C) in the soleus and plantaris muscles, when compared to the control groups (ND-UNT). The HIIT protocol did not alter protein carbonyl content in the plantaris and soleus muscles; the MICT protocol significantly reduced the levels of protein carbonyl content in both types of skeletal muscles, when compared to the HFD-UNT group (p<0.05).

The effects of the two AET protocols were also investigated by evaluating the activities of the antioxidant enzymes. As can be seen in Figure 2A, HFD did not alter SOD activity in the soleus muscle of the HFD-UNT group, but reduced this enzyme's activity in the plantaris muscle, when compared to the ND-UNT group (p<0.05).The MICT protocol enhanced SOD activity in the soleus muscle, when compared to the HFD-UNT group (p<0.5). Both protocols reversed the decrease in SOD activity caused by HFD in the plantaris muscle of rats (p<0.05). Figure 2B shows that HFD increased CAT activity in the soleus muscle of the HFD-UNT group, when compared to the ND-UNT group, (p<0.05) and did not alter this enzyme activity in the plantaris muscle. The HIIT protocol prevented this alteration

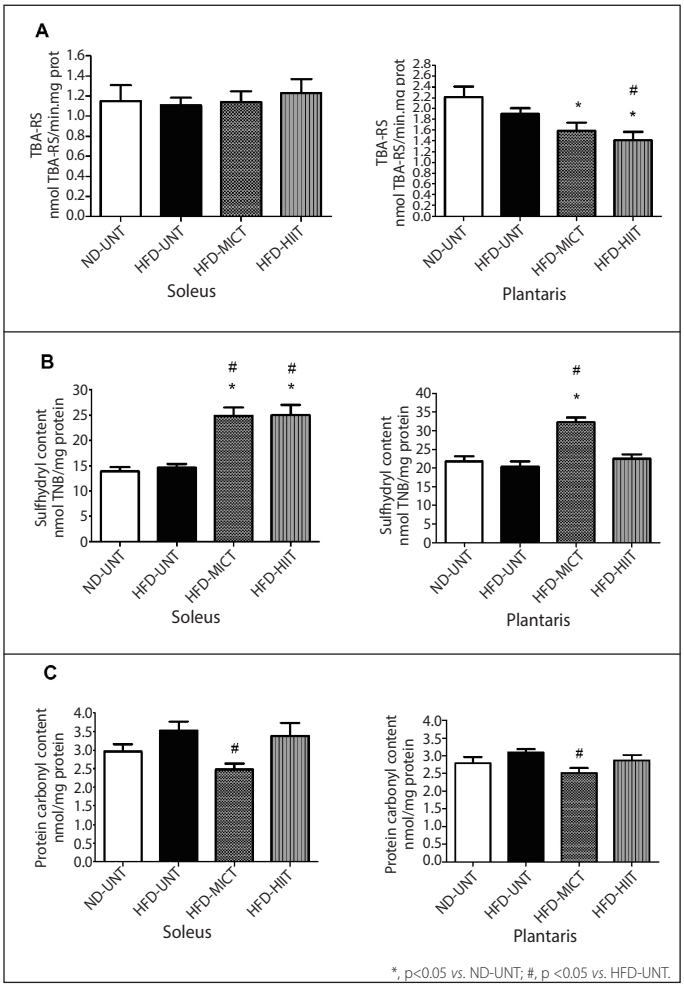

Figure 1. Oxidative stress parameters, (A) thiobarbituric acid reactive substances (TBA-RS); (B) total sulfhydryl content; and (C) protein carbonyl content in the soleus and plantaris muscles of rats from four groups: ND-UNT (normal diet and untrained; n=6), HFD-UNT (high-fat diet and untrained; n=6), HFD-MICT (high-fat diet and moderate-intensity continuous training; n=6) and HFD-HIIT (high-fat diet and high-intensity interval training; n=6). Data are presented as means ± SEM and were compared between groups by one-way analysis of variance (ANOVA) with a post-hoc Duncan test.

in the soleus muscle, when compared the result to the HFD-UNT group (p<0.05) and both protocols increased the activity of CAT in the plantaris muscle (p<0.05). Figure 2C shows that HFD reduced GSH-Px activity in both muscles in the HFD-UNT group, when compared to the ND-UNT group (p<0.05). The MICT protocol prevented this reduction in the soleus muscle, while the HIIT protocol partially prevented it when compared to the HFD-UNT group**.** The MICT protocol did not prevent the reduction in GSH-Px activity in the plantaris muscle, but the HIIT protocol was able to partially prevent the reduction in GSH-Px activity that was observed in the HFD-UNT group (p<0.05).

DISCUSSION

Obesity is strongly related to oxidative stress; as physical exercise increases the body's energy expenditure and stimulates endogenous antioxidant defenses, it is considered to be an important resource to provide a balance for pro oxidant damage and impaired antioxidant repair mechanisms.[25,26] The aim of the present study was to investigate the effect of two different protocols of AET, HIIT and MICT, on the oxidative stress profiles of the soleus and plantaris muscles of rats submitted to a HFD.

Our recent study showed that HFD causes oxidative stress in the blood and liver of rats and that both AET protocols (MICT and HIIT) prevented most of the alterations elicited by HFD on oxidative stress parameters. [27] According to our results, although HFD did not alter TBA-RS levels, nor total

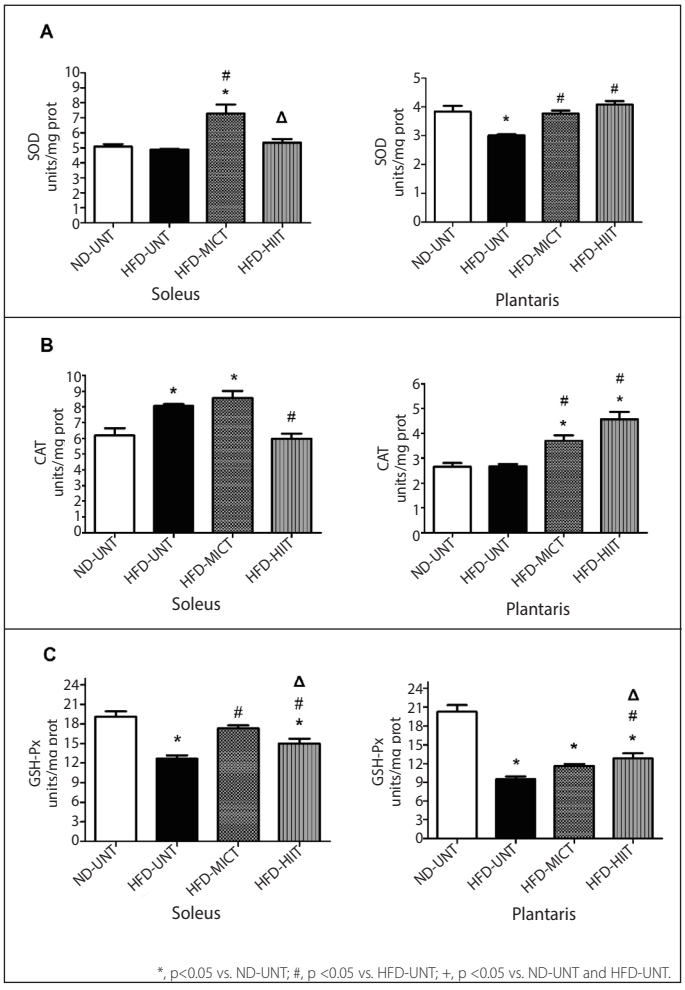

Figure 2. Activities of the antioxidant enzymes, (A) superoxide dismutase (SOD), (B) catalase (CAT) and (C) glutathione peroxidase (GSH-Px) in the soleus and plantaris muscles of rats from four experimental groups: ND-UNT (normal diet and untrained; n=6), HFD-UNT (high-fat diet and untrained; n=6), HFD-MICT (high-fat diet and moderate--intensity continuous training; n=6) and HFD-HIIT (high-fat diet and high-intensity interval training; n=6). Data are presented as means ± SEM and were compared between groups by one-way analysis of variance (ANOVA) with a post-hoc Duncan test.

sulfhydryl content and the levels of protein carbonyl content, both types of exercise reduced TBA-RS levels in the plantaris muscle, suggesting that aerobic physical activity, in the long term, can be effective in reducing lipid peroxidation in this muscle. In addition, our results suggest that aerobic exercise also prevents protein damage, since both protocols increased total sulfhydryl content in the soleus muscle, and the MICT protocol increased the total sulfhydryl content in the plantaris muscle of rats. In association with the prevention of protein damage, the MICT protocol also showed a tendency towards reducing the levels of protein carbonyl content in both types of skeletal muscles. These results corroborates a well-known positive effect of physical exercise on oxidative stress biomarkers.[28]

With regard to the antioxidant enzymes, results showed that HFD did not alter SOD activity in the soleus muscle, but reduced this enzyme's activity in the plantaris muscle. The MICT protocol enhanced SOD activity in the soleus muscle and both protocols reversed the decrease in SOD activity caused by HFD in the plantaris muscle of rats. With regard to the activity of CAT, HFD increased this enzyme's activity in the soleus muscle, but did not alter this enzyme's activity in the plantaris muscle. The HIIT protocol prevented this alteration in the soleus muscle and both protocols increased CAT activity in the plantaris muscle. HFD reduced the activity of the GSH-Px enzyme in both muscles and the MICT protocol was able to prevent this alteration completely in the soleus muscle, while the HIIT protocol partially prevented it. In contrast, the MICT protocol did not prevent the reduction in GSH-Px activity in the plantaris muscle, however, the HIIT protocol was able to partially prevented this reduction. This imbalance caused by HFD may represent a risk to the antioxidant system over the longer term, due to the important role that antioxidant enzymes play in the reduction of superoxide and hydrogen peroxide and in DNA protection.[29]

Pimenta et al.[5] reported that HFD exacerbates the deleterious effects of free radicals. In contrast, moderately intense exercise routines have been shown to increase immune defenses. Motta et al.[30] found an increased expression of antioxidant enzymes in a trained animal model, where a short-term HIIT protocol was seen to attenuate oxidative stress and regulate antioxidant activity, after nine training sessions. Oh et al.[31] and Delwing-de lima et al. [27] showed physical training to be effective in reducing serum levels of inflammatory and oxidative stress markers, such as TBA-RS. Additionally, Aguiar Júnior and Pinho[32] showed that aerobic exercise training increases antioxidant defenses and functional adaptations against oxidative stress by the organism.

The expressions of antioxidant enzymes by skeletal muscle are suggested to be modulated by patterns of activity, including intensity, duration and type, resulting in a variability of effects on the antioxidant enzymes.[33] Our results show that both types of AET protocols positively modulated the SOD and CAT enzymes in the skeletal muscles studied, but were less effective at modulating GSH-Px enzyme activity. Corroborating previous studies, both types of aerobic exercise diminished oxidative stress parameters in the soleus and plantaris muscles of rats submitted to HFD, by altering the activity of antioxidant enzymes and tending to reduce lipid peroxidation and protein damage. These positive results agree with recent studies showing adaptations of the antioxidant system following higher intensity exercise training.[34,35] Our results also suggest that the amount of daily training, the time of training and the type of aerobic exercise chosen are also essential for positively modulating this process.

CONCLUSION

In conclusion, our findings show that obesity alters the activity of antioxidant enzymes in the soleus and plantaris muscles, and that both types of AETP (MICT and HIIT) were effective at modulating the enzymatic system, providing greater protection to muscles against the oxidative damage caused by obesity.

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