ORIGINAL ARTICLE

Effects of low-intensity training on the brain and muscle in the congenital muscular dystrophy 1D model

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Abstract

Introduction Congenital Muscular Dystrophy type 1D (MDC1D) is characterized by a hypoglycosylation of α-dystroglycan protein (α-DG), and this may be strongly implicated in increased skeletal muscle tissue degeneration and abnormal brain development, leading to cognitive impairment. However, the pathophysiology of brain involvement is still unclear. Low-intensity exercise training (LIET) is known to contribute to decreased muscle degeneration in animal models of other forms of progressive muscular dystrophies.

Aim The objective of this study was to analyze the effects of LIET on cognitive involvement and oxidative stress in brain tissue and gastrocnemius muscle.

Methods Male homozygous (Large$^{myd-/-}$), heterozygous (Large$^{myd+/-}$), and wild-type mice were used. To complete 28 days of life, they were subjected to a low-intensity exercise training (LIET) for 8 weeks. After the last day of training, 24 h were expected when the animals were submitted to inhibitory avoidance and open-field test. The striatum, prefrontal cortex, hippocampus, cortex, and gastrocnemius were collected for evaluation of protein carbonylation, lipid peroxidation, and catalase and superoxide dismutase activity.

Results LIET was observed to reverse the alteration in aversive and habituation memory. Increased protein carbonylation in the striatum, prefrontal cortex, and hippocampus and lipid peroxidation in the prefrontal cortex and hippocampus were also reversed by LIET. In the evaluation of the antioxidant activity, LIET increased catalase activity in the hippocampus and cortex. In the gastrocnemius, LIET decreased the protein carbonylation and lipid peroxidation and increased catalase and superoxide dismutase activity.

Conclusion In conclusion, it can be inferred that LIET for 8 weeks was able to reverse the cognitive damage and oxidative stress in brain tissue and gastrocnemius muscle in MDC1D animals.

Keywords Large^{myd} mice · Low-intensity exercise training · Memory · Oxidative stress · Central nervous system

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Introduction

Progressive muscular dystrophies (PMD) describe a set of clinical and genetically heterogeneous pathologies with common features such as progressive muscle atrophy, loss of muscle strength, bone deformities, and progressive pattern of degeneration [1, 2]. Congenital Muscular Dystrophy type 1D (CMD1D) is characterized by a hypoglycosylation of α-dystroglican protein (α-DG) due to the abnormal functioning of the LARGE gene. It affects the skeletal muscles associated with atrophy and loss of muscle fibers and function. Hypoglycosylation of α-DG protein is also strongly implicated in abnormal central nervous system (CNS) development, leading to cognitive impairment in patients [3, 4] and in animal models [5, 6]. Several therapeutic strategies have been proposed to reduce the progression of PMD, including the implementation of a low-intensity exercise program [7]. However, there are no definitive studies on the implementation of exercise in this population group [8].

Exercise has been cited in studies and the literature as an important factor for quality of life by reducing oxidative stress and promoting neurogenesis [9]. Studies have shown that low-intensity exercise training (LIET) is able to slow the progression of some types of dystrophies, such as Duchenne muscular dystrophy (DMD) [10, 11]. A study found that, using LIET, there was a decrease in oxidative damage in skeletal muscle in mdx mice (animal model for DMD) [12]. However, in the animal model of MDC1D, the Large$^{myd-/-}$ mouse, there are no scientific data that clarify the effects of exercise on changes in skeletal muscle or in the CNS. Recently, it has been demonstrated that abnormal glycosylation of α-DG can affect the memory storage process, causing impaired memory and learning [6] associated to increased oxidative damage in brain tissue [5]. An increase of BBB permeability associated with an increase in the protein of MMP-2 and MMP-9 levels in the brain can also be observed in Large$^{myd-/-}$ mice [13].

In this context, the focus of this study is to verify the effects of LIET on CNS impairment in Large$^{myd-/-}$ animals. The hypothesis is that the LIET is able to reduce or reverse cognitive impairment and oxidative stress in the brain tissue without altering the pathophysiological pattern in skeletal muscles, i.e., without increasing disease progression in muscle tissue.

Methods

Animals

Large$^{myd-/-}$ homozygous (mutation in Large), Large$^{myd+/-}$ heterozygous, and wild-type (C57BL/6) male mice used in this study were genotyped using tail DNA via PCR. Only male mice weighing 25 and 30 g were used. They were housed as five in a cage with food and water available ad libitum and were kept on a 12-h light/dark cycle (lights on at 7:00 a.m.). All experimental procedures were approved by the Unisul Animal Experimentation and Treatment Committee (protocol number 13.035.4.08.IV, Brazil). When the animals were 28 days old, they were submitted to LIET.

Exercise protocol

At approximately 28 days of age, the mice ($n = 10$ per group) were randomly assigned to either a low-intensity exercise training (LIET) group or a sedentary (SED) group. LIET mice were trained with exercise on a motorized treadmill. Large$^{myd-/-}$, Large$^{myd+/-}$, and wild-type mice were divided into two groups: one group performed LIET (treadmill running, 30 min/day, 2 times a week for 8 weeks at 9 m/min, while the other group was sedentary. Although this exercise intensity was a very low intensity compared to regimens in healthy mice, it was still above the 6 m/min, since others have reported early exhaustion and a decline in full-body strength of mice following acute treadmill running. However, the 9 m/min is below the maximal intensity in which the enhanced pathology in mdx mice was observed [12].

Behavioral tests

The animals were submitted to behavioral tests 24 h after last exercise training session.

Habituation to an open-field task

The purpose of performing this task is to assess motor performance during the training session and also non-associative memory with the retention test. The open-field habituation was carried out in a 40×40-cm open field surrounded by 40-cm-high brown plywood walls with a glass front wall. To carry out the test, the floor of the open field was divided into 12 equal rectangles by black lines. The animals were gently placed in the left rear quadrant and left to explore the arena for 5 min (training session). Immediately after, the animals were taken back to their home cage and, 24 h later, submitted again to a similar open-field session (test session). Black line crossings and rearrangements performed in both sessions were counted. The decrease in the number of crossings and rearings between the two sessions was taken as a measure of habituation retention.

Step-down inhibitory avoidance task

This task evaluates aversive memory. In the training session, the animals were placed on the platform, and their latency to step down on the grid with all four paws was measured with an automatic device. Immediately after stepping down on the grid, the animals received a 0.3-mA, 2.0-s paw shock and were returned to their cage. A retention test session was performed 24 h after training. It was procedurally identical to the training, except that no paw shock was performed. It was used as a measure of retention of inhibitory avoidance for the lowering latency of the retention test (maximum 180 s).

Substance, dose, via

The animals were submitted to painless-assisted death by anesthetic overdose (xylazine hydrochloride (20 mg/kg) associated with an intraperitoneal administration of dextrocetamine hydrochloride (100 mg/kg)) according to Resolution no. 1000 of May 12, 2012—Federal Council of Veterinary Medicine (CFMV), under the supervision of the responsible veterinarian. All procedures involving handling, surgical procedure, collection of material, and administration of drugs were performed by the veterinarian responsible for the sector.

Oxidative stress

The animals were sacrificed at 90 days of age. LIET mice were sacrificed 24 h after training in an attempt to avoid the potential effect of the last exercise training session. The mice were anesthetized with isoflurane and were kept under general anesthesia as the tissue was collected. Gastrocnemius, hippocampus, striatum, and total cortex were removed and dissected. The tissues were immediately stored at -80 °C until analysis.

Lipid peroxidation

Lipid peroxidation was measured by the formation of thiobarbituric acid (TBA) reactive substances (TBARS) [14]. Brain structures were washed with PBS, harvested, and lysed after dissection. TBA 0.67% was added to each tube and vortexed. A spectrophotometer at 535 nm was used to measure the optical density of each solution. Data were expressed as equivalent nanomoles of TBARS per milligram of protein.

Protein carbonyl formation

The protein carbonyl content was measured in brain homogenates using 2,4-dinitrophenylhydrazine (DNPH)

in a spectrophotometric assay [15]. The absorbance was recorded in a spectrophotometer at 370 nm for both DNPH-treated and HCl-treated samples. Protein carbonyl levels were expressed as nanomoles of carbonyl per milligram of protein.

Catalase activity

To determine catalase (CAT) activity, brain tissue was sonicated in 50 mmoL/L phosphate buffer (pH 7.0) and the resulting suspension was centrifuged at 3000 g for 10 min. The supernatant was used for enzyme assay. The rate of decrease in hydrogen peroxide absorbance at 240 nm was used to measure CAT activity [16].

Superoxide dismutase activity

Superoxide dismutase (SOD) activity was assessed by measuring the inhibition of adrenaline auto-oxidation, as previously described [17].

Protein mensuration

All biochemical measurements were normalized for protein content, with bovine albumin as standard [18].

Statistical analyses

Data from biochemical analyses and habituation to the open field are reported as mean and SEM, and comparisons between groups were performed using the Tukey post hoc ANOVA and intra-individual groups were analyzed by paired t-test. Data from the inhibitory avoidance task are reported as median and interquartile ranges, and comparisons between groups were performed using Mann–Whitney U tests. Intra-individual groups were analyzed by the Wilcoxon tests. In all comparisons, $p < 0.05$ indicated statistical significance.

Results

Figure 1 shows the results obtained after LIET on habituation (Fig. 1A) and aversive (Fig. 1B) memory. In habituation memory, there was no difference in the number of crossings and rearings ($p > 0.05$) between training and test in the SED Large$^{myd-/-}$ group. After LIET, there was a significant difference between training and test in the number of crossings and rearings ($p < 0.05$) in Large$^{myd-/-}$ mice (Fig. 1A). In the SED group, there was no statistically significant difference in the latency time between training and test in Large$^{myd-/-}$ mice ($p > 0.05$). In the LIET group, there was a

Fig. 1 Effects of LIET on habituation (**A**) and aversive (**B**) memory. Data are expressed by mean and standard deviation. *$p < 0.05$ versus training
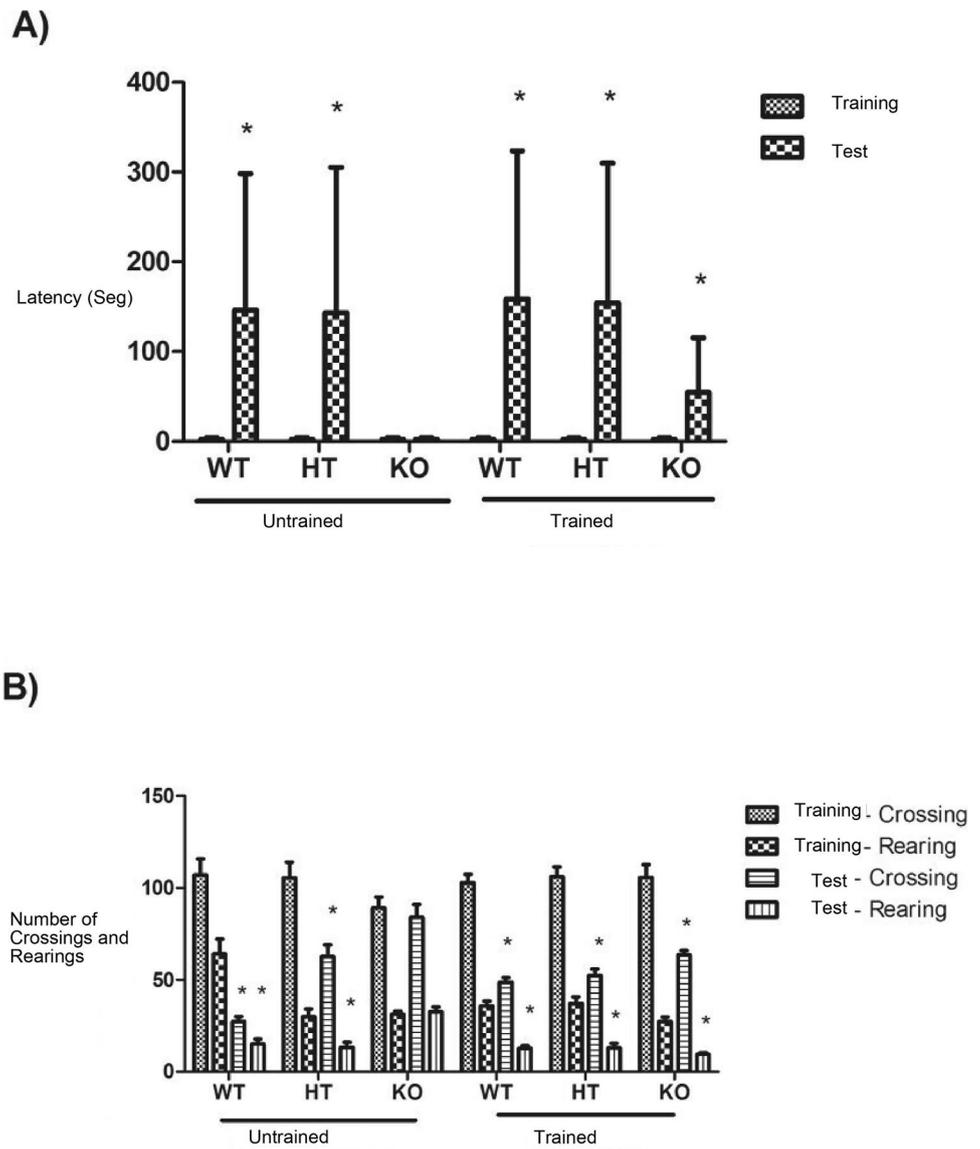
statistical difference in the latency time between training and test ($p < 0.05$) in Large$^{myd-/-}$ mice (Fig. 1B).

Figure 2 shows the results of LIET on protein carbonylation (Fig. 2A), lipid peroxidation (Fig. 2B), catalase activity (Fig. 2C), and superoxide dismutase activity (Fig. 2D) in the gastrocnemius. It can be observed that SED Large$^{myd-/-}$ mice group showed increased protein carbonylation in gastrocnemius when compared to the wild-type SED mice group ($p < 0.05$). After LIET, Large$^{myd-/-}$ mice presented lower protein carbonylation levels when compared to SED Large$^{myd-/-}$ mice ($p < 0.05$) (Fig. 2A). Figure 2B shows the results of the lipid peroxidation in the gastrocnemius. It was observed that SED Large$^{myd-/-}$ mice had a high level of lipid peroxidation in the gastrocnemius when compared to SED wild-type animals ($p < 0.05$). However, LIET Large$^{myd-/-}$ mice

showed a reduction in these levels when compared to SED Large$^{myd-/-}$ mice ($p < 0.05$). The catalase activity in the gastrocnemius is shown in Fig. 2C. It can be observed that there is a decrease in the CAT activity in the gastrocnemius of SED Large$^{myd-/-}$ mice when compared to wild-type SED mice ($p < 0.05$). When Large$^{myd-/-}$ mice were submitted to LIET, there was an increase in CAT activity in gastrocnemius when compared to SED Large$^{myd-/-}$ mice. Figure 2D demonstrates the results obtained in the evaluation of SOD activity in the gastrocnemius. It is observed that SED Large$^{myd-/-}$ mice showed a decrease in superoxide dismutase activity when compared to SED wild-type mice ($p < 0.05$). After LIET, Large$^{myd-/-}$ mice showed an increase in superoxide dismutase activity when compared to SED Large$^{myd-/-}$ mice ($p < 0.05$), demonstrating that the protocol was beneficial for the gastrocnemius muscle.

Fig. 2 Effects of LIET on protein carbonylation (**A**), lipid peroxidation (**B**), catalase activity (**C**), and superoxide dismutase activity (**D**) in the gastrocnemius. Data are expressed by mean and standard deviation. *$p < 0.05$ versus wild-type + SED; #$p < 0.05$ versus Large$^{myd-/-}$ + SED
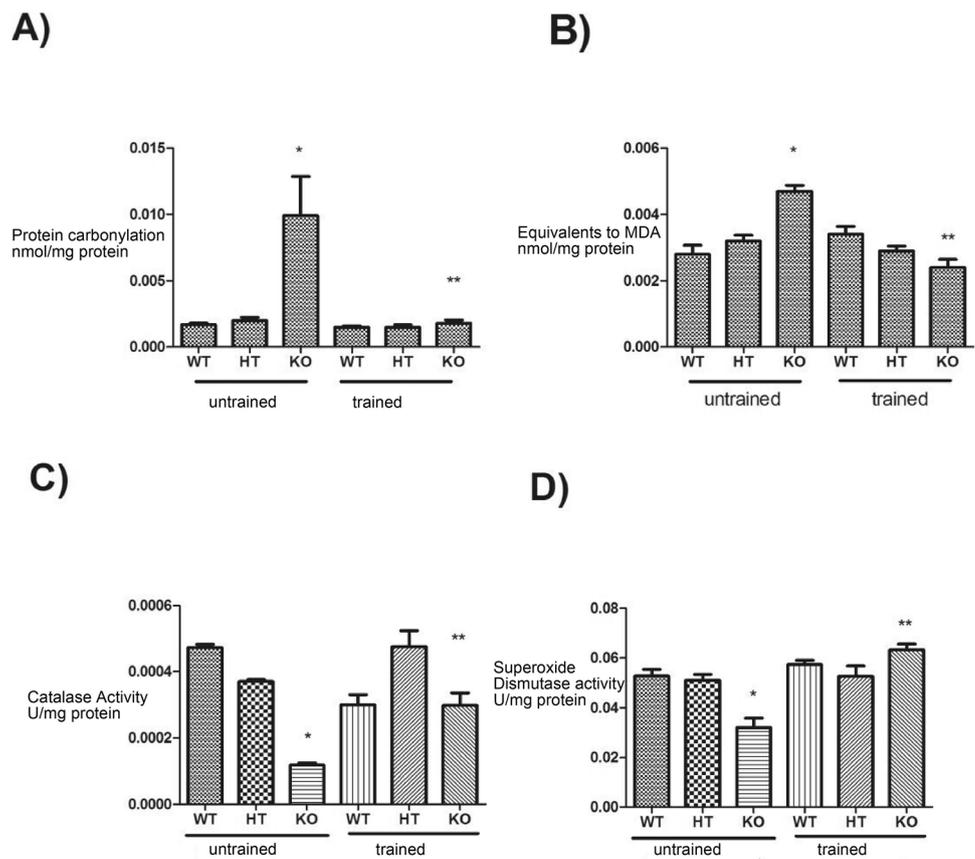

Figure 3 shows the evaluation of protein carbonylation in the striatum (Fig. 3A), prefrontal cortex (Fig. 3B), hippocampus (Fig. 3C), and cortex (Fig. 3D). There was an increase in protein carbonylation in the striatum, prefrontal cortex, and hippocampus in SED Large$^{myd-/-}$ mice when compared to SED wild-type animals ($p < 0.05$). However, LIET Large$^{myd-/-}$ mice showed a decrease in protein carbonylation in the striatum and hippocampus when compared to SED Large$^{myd-/-}$ mice ($p < 0.05$). In the prefrontal cortex, there was no decrease in levels in the LIET Large$^{myd-/-}$ group of mice compared to SED Large$^{myd-/-}$ mice ($p > 0.05$). In the cortex, there was no change in the experimental groups of SED animals. There was only a decrease in protein carbonylation in LIET Large$^{myd+/-}$ and Large$^{myd-/-}$ mice compared to SED wild-type animals ($p < 0.05$).

The evaluation of lipid peroxidation is shown in Fig. 4 through the analyses of the striatum (Fig. 4A), prefrontal cortex (Fig. 4B), hippocampus (Fig. 4C), and cortex (Fig. 4D). It can be observed that there was an increase in lipid peroxidation in the prefrontal cortex and hippocampus of SED Large$^{myd-/-}$ mice compared to SED wild-type mice ($p < 0.05$). In LIET mice, there was a decrease in lipid peroxidation in the prefrontal cortex of Large$^{myd+/-}$ and Large$^{myd-/-}$ mice when compared to the same SED groups ($p < 0.05$). These results show that LIET decreased the high

levels of lipid peroxidation in the prefrontal cortex and hippocampus of Large$^{myd-/-}$ mice ($p < 0.05$).

Figure 5 shows the results obtained from the evaluation of CAT activity in striatum (Fig. 5A), prefrontal cortex (Fig. 5B), hippocampus (Fig. 5C), and cortex (Fig. 5D). There was a decrease in CAT activity in the hippocampus and cortex of SED Large$^{myd-/-}$ mice when compared to SED wild-type mice ($p < 0.05$). However, LIET Large$^{myd-/-}$ mice demonstrated an increase in CAT activity when compared to SED Large$^{myd-/-}$ mice, showing that LIET was able to reverse the decrease of CAT in the hippocampus and cortex ($p < 0.05$). In the striatum and prefrontal cortex, there was no difference in the experimental groups ($p > 0.05$). In the striatum, there was only an increase in catalase activity in LIET Large$^{myd-/-}$ mice when compared to SED mice ($p < 0.05$).

SOD activity is shown in Fig. 6 by the analysis of the striatum (Fig. 6A), prefrontal cortex (Fig. 6B), hippocampus (Fig. 6C), and cortex (Fig. 6D). There was a decrease in SOD activity in SED Large$^{myd+/-}$ and Large$^{myd-/-}$ mice groups in the striatum when compared to SED wild-type mice ($p < 0.05$). There were no changes in the other structures analyzed in Large$^{myd+/-}$ and Large$^{myd-/-}$ mice ($p > 0.05$). However, there was no increase in superoxide dismutase activity in Large$^{myd+/-}$ and striatum Large$^{myd-/-}$ mice when compared to the SED ($p > 0.05$). In the cortex, there

Fig. 3 Effects of LIET on protein carbonylation in the striatum (**A**), prefrontal cortex (**B**), hippocampus (**C**), and cortex (**D**). Data are expressed by mean and standard deviation. *$p < 0.05$ versus wild-type + SED; #$p < 0.05$ versus Large$^{myd-/-}$ + SED
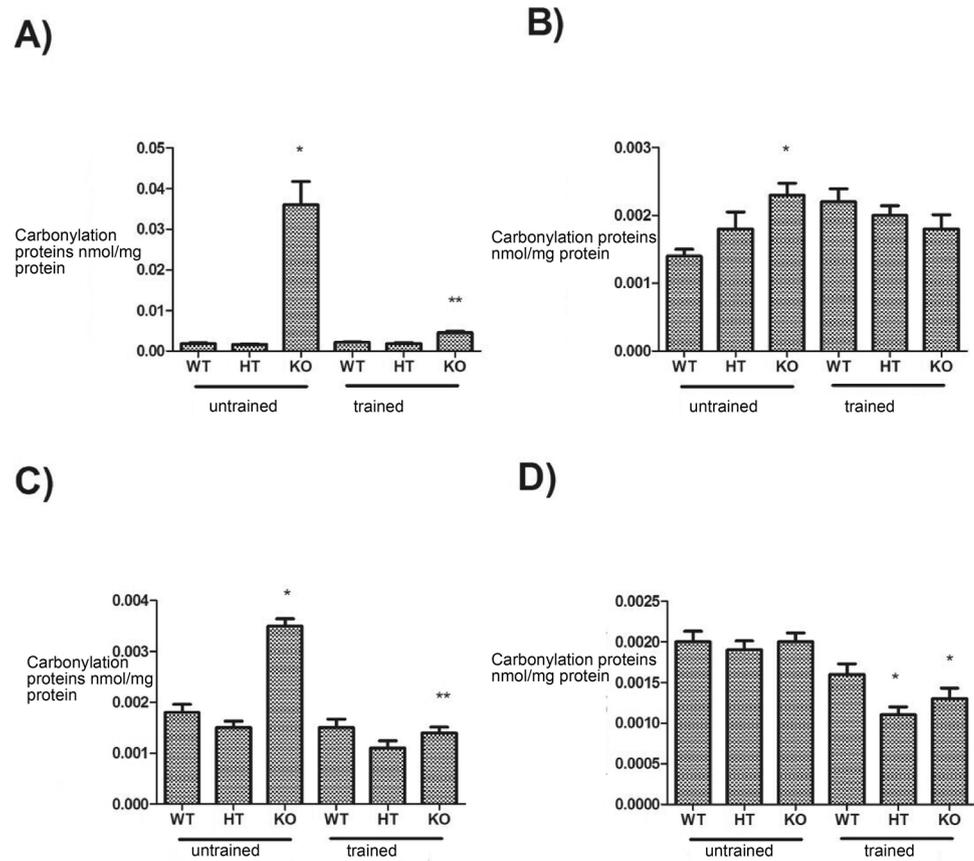
was only an increase in SOD in LIET Large$^{myd-/-}$ when compared to SED Large$^{myd-/-}$ mice ($p < 0.05$).

Discussion

In this study, it can be observed that LIET for 8 weeks, performed for 30 min and twice a week, was able to reverse the impairment of habituation and aversive memory as well as oxidative stress in the brain and in the gastrocnemius muscle. The analysis of the gastrocnemius muscle was of great value, since MDC1D is, in essence, a neuromuscular disease. Improving cognitive ability would not be important if LIET increased oxidative stress in skeletal muscle tissue, since oxidative stress is one of the pathophysiological events associated with progressive degeneration of PMD [19–21].

Studies have shown that regular exercise influences cognitive improvement, neurochemistry, and mitochondrial and oxidative function on the CNS, favorably influencing brain plasticity and facilitating neurogenerative, neuroadaptive, and neuroprotective processes in experimental models [22]. Although the exact neurobiological underpinnings underlying the cognitive benefits of exercises have not been fully elucidated, there is evidence supporting the relevance of neuronal adaptive responses in the CNS, such as

increased synaptic plasticity [22–26] and neurogenesis [26, 27]. Exercise has been shown to increase the expression of many genes associated with synaptic function, involved in synaptic plasticity, memory formation, integration of multiple extracellular signals, and memory processes [28]. Corroborating these findings, Molteni et al. report that exercises increase neuronal protection in the hippocampus [25]. According to Spangenburg et al., the physiological response to training stimulates several signaling pathways, increasing gene expression and its protein products, associated with synaptic plasticity [29]. The underlying mechanism for MDC1D-related memory impairment is not fully understood. However, in this study, it is observed that habituation and aversive memory can be modulated by one of the pathways associated with the physiological changes caused by LIET.

In this context, this study also observed that LIET decreased protein carbonylation in the striatum and hippocampus, and lipid peroxidation in the prefrontal cortex and hippocampus, in addition to increasing the antioxidant activity of catalase in the hippocampus and cortex of Large^{myd} animals. Studies show that the increased activity of antioxidant enzymes in the brain is probably linked to the response to increased exercise-related free radical formation [30, 31]. In this context, there is evidence that low- or

Fig. 4 Effects of LIET on lipid peroxidation in the striatum (**A**), prefrontal cortex (**B**), hippocampus (**C**), and cortex (**D**). Data are expressed by mean and standard deviation. *$p < 0.05$ versus wild-type + SED; #$p < 0.05$ versus Large$^{myd-/-}$ + SED
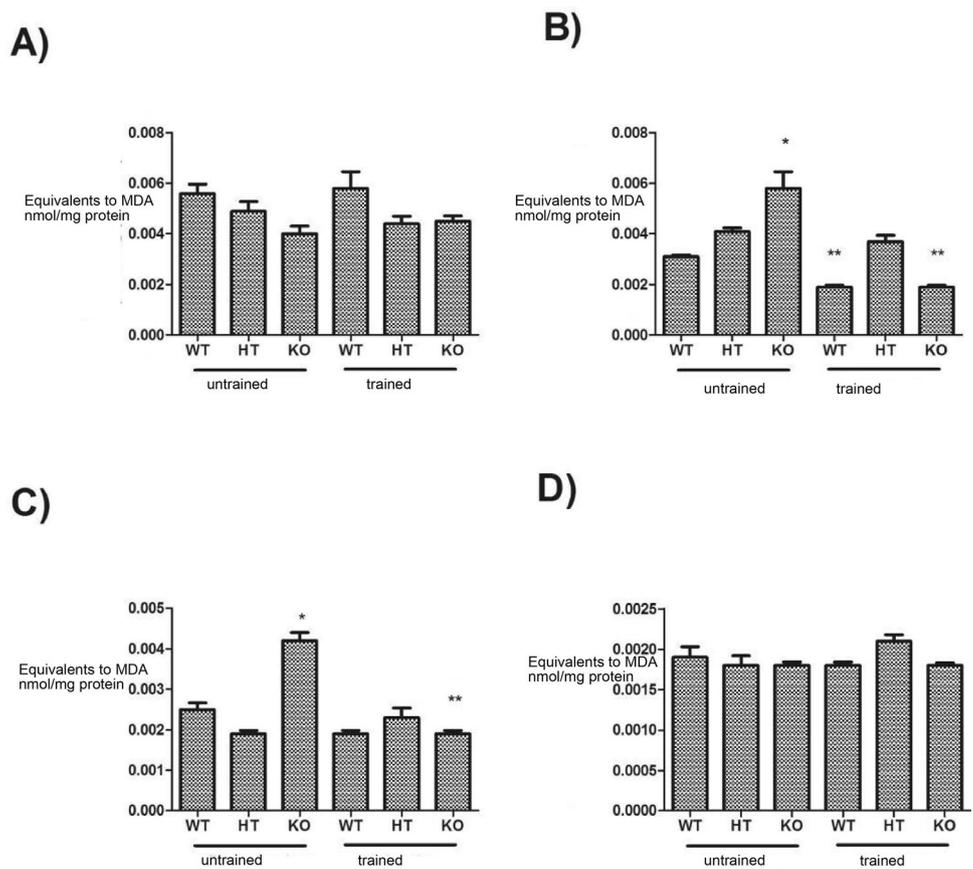
Fig. 5 Effects of LIET on catalase activity in the striatum (**A**), prefrontal cortex (**B**), hippocampus (**C**), and cortex (**D**). Data are expressed by mean and standard deviation. *$p < 0.05$ versus wild-type + SED; #$p < 0.05$ versus Large$^{myd-/-}$ + SED
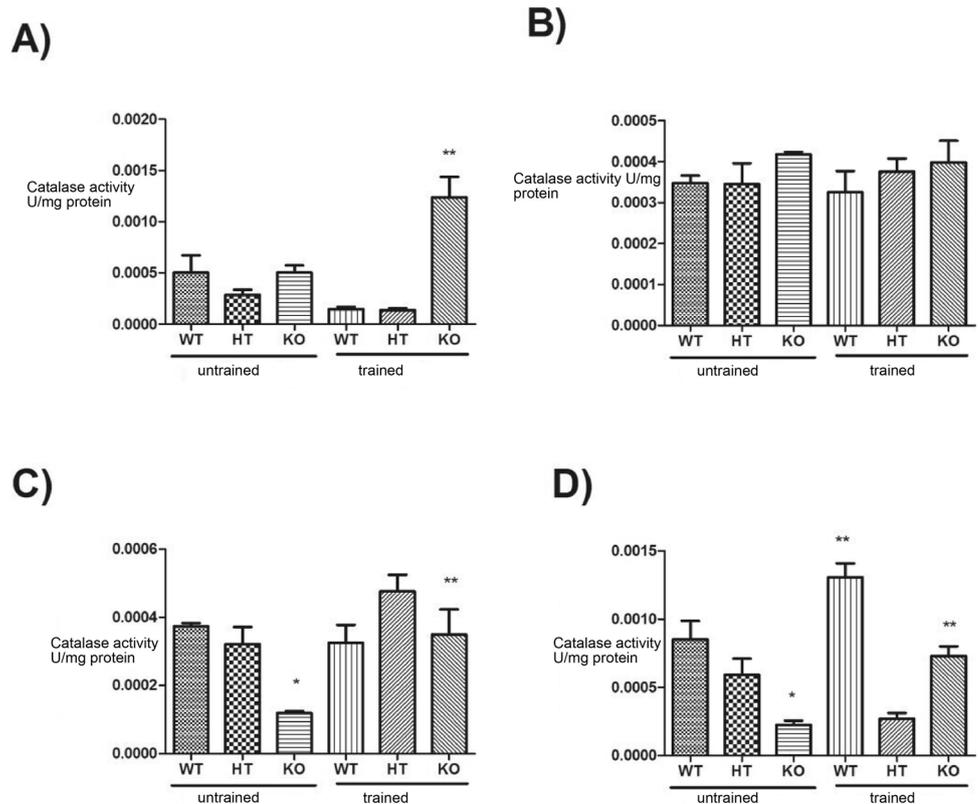
Fig. 6 Effects of LIET on superoxide dismutase activity is the striatum (**A**), prefrontal cortex (**B**), hippocampus (**C**), and cortex (**D**). Data are expressed by mean and standard deviation. *$p < 0.05$ versus wild-type + SED; #$p < 0.05$ versus Large$^{myd-/-}$ + SED
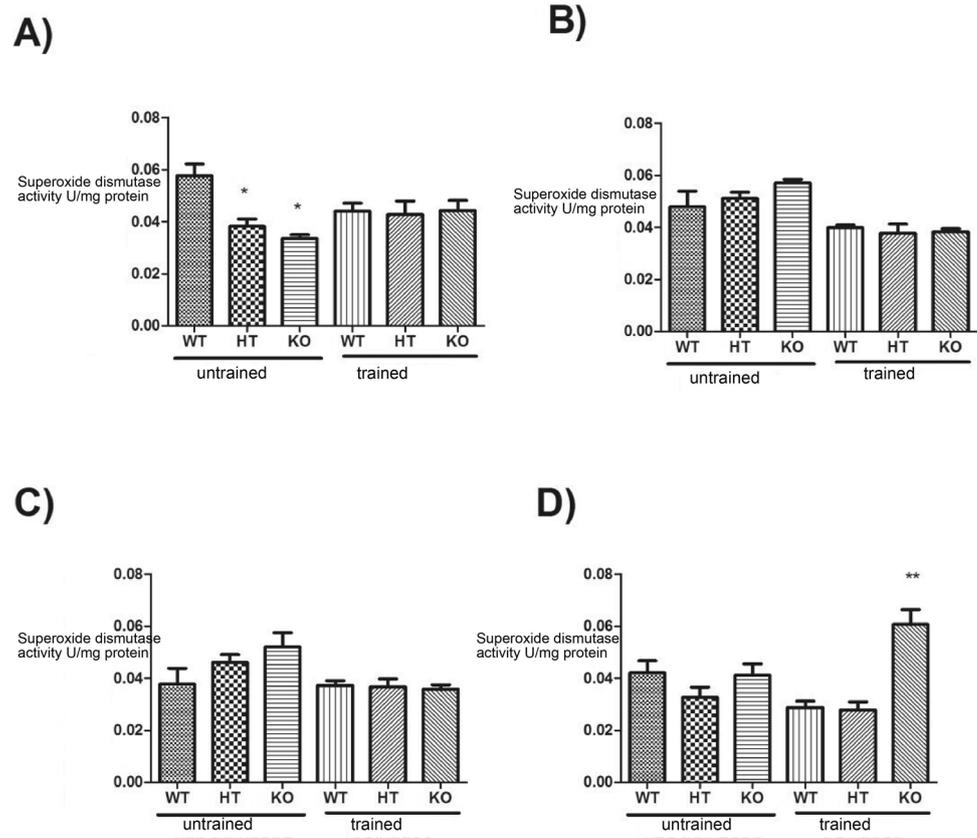
moderate-intensity aerobic exercise may delay the development of myopathies [11].

The analysis of the gastrocnemius was performed in this study to ensure that the protocol used would not further impair the skeletal muscle, increasing disease progression, since MDC1D also progressively affects skeletal muscles. It was observed that there was a decrease in protein carbonylation and lipid peroxidation as well as an increase in the antioxidant activity of catalase and superoxide dismutase. In one study, it was seen that in an animal model of DMD, the use of the same protocol for 8 weeks obtained similar results to this study [12]. Increased muscle protein degradation may be related to the reduction of sarcolemmal membrane stability, intracellular calcium accumulation, which can activate apoptosis and cellular necrosis [32]. Kaczor et al. propose that LIET may induce calcium homeostasis in the dystrophic skeletal muscle and decrease mitochondrial calcium accumulation and reactive oxygen species (ROS) production [12].

The oxidative response to exercise is determined by type, frequency, duration, and intensity. Hence, it can make the antioxidant defense system more efficient by establishing a balance between ROS-induced damage and antioxidant defense systems [33]. In addition, exercise can modulate the activity of Krebs cycle enzymes and increase the availability of electron transport chain components and ATP activity in skeletal muscle [34–37]. Regular exercise promotes an adaptive increase in skeletal muscle defense mechanisms capable of protecting against ROS-produced injuries [38].

The results of different exercise models on the oxidative metabolism of the CNS are very controversial, but generally demonstrate gains in synaptic plasticity and cognitive function with moderate- and low-intensity exercises [39]. The physiological response to training stimulates some signaling pathways such as increased gene expression of several components of the MAPK cascade, the major TRK12 receptor signaling cascade. MAPK is involved in synaptic plasticity, memory formation, and integration of multiple extracellular signals [38] including learning [25, 29, 40] and increased expression of genes associated with synaptic function [25].

Some studies point to the beneficial effects of exercise in PMD [41, 42]. However, it has been debated whether exercise is beneficial or detrimental for PMD patients. After the completion of an experimental study in which a high-intensity exercise protocol induced muscle degeneration in mdx mice, the following hypothesis was formulated: the response to the therapeutic intervention stress is capable of generating damages and cellular degeneration in patients, suggesting the contraindication of physical activity [42–44]. In contrast, for Akimoto et al., there are currently insufficient data in the literature to justify the contraindication of LIET practice in DMP patients [45]. For Grange et al., exercise

may exacerbate the cellular damage of DMP patients [8]. In this context, it is necessary to establish limits to minimize the damage and determine which parameters can improve the muscle function of PMD patients.

In this scenario, Kaczor et al. questioned the lack of standardization of experimental studies, emphasizing the limitation of the number of experiments as well as the controversial results related to discrepancies regarding the methodology used in experimental studies such as the age of the mice; the intensity, type, and duration of the exercise; the divergent physiological, histological, and biochemical variables measured; and the measurement of the composition of the different cells analyzed in order to establish low-intensity exercise protocol that may be beneficial by reducing the cellular degenerative process and decreasing the progression of PMD [12].

Oxidative stress is known to be present in skeletal muscle tissue and brain tissue and to actively participate in the process of cell degeneration during the course of PMD. In an animal model of MDC1D, oxidative stress is present in adult animals in brain tissue [5]. LIET for 8 weeks is able to reverse oxidative stress in mdx mice [12]. It is already known that medium- and low-intensity exercise has antioxidant effects in both skeletal muscle and brain tissue of healthy animals or in animal models of psychiatric or neurodegenerative diseases, as mentioned throughout this work.

Some items should be considered. The protocol was initiated when the animals were 28 days old, that is, young animals. It was terminated when the animals were 90 days old. At 90 days of age, they had no memory impairment and showed little involvement of oxidative stress in brain tissue and gastrocnemius. Comim et al. showed that MDC1D animals at 60 days of age had cognitive impairment and oxidative stress [5].

Conclusion

It was observed in this study that the LIET performed for 8 weeks, 2 days a week, was able to reverse the impairment of aversive and habituation memory and decrease lipid peroxidation and protein carbonylation in gastrocnemius muscle and encephalic tissue. It was also observed that the protocol in question increased the enzymatic activity of catalase and superoxide dismutase in gastrocnemius muscle and partially in encephalic tissue.

This work provides possible evidence that LIET is able to slow down the process of cognitive impairment, possibly by reducing oxidative stress in brain tissue. It is known that oxidative stress is one of the causes of memory and learning impairment [46]. This study may contribute as a foundation for the development of future studies aimed at implementing regular exercise practices as adjunctive

methods of treatment, in patients with MCD1D or other forms of MPD, in order to try to slow down the progression of degeneration in both skeletal muscle and brain tissue. Further studies should be conducted to provide more evidence of this association and to substantiate the data obtained in this study.

Compliance with ethical standards

This research was supported by grants from Unisul (CMC), UNESC (JQ) and CNPq (CMC and JQ) and the UNIEDU/FUMDES (AA).

Ethical Approval None.

Consent to participate None.

Consent for publication None.

Conflict of Interest The authors declare no competing interests.

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