Effect of environmental enrichment associated or not with physical activity on nociceptive and motor functions in an animal model of fibromyalgia

Efeito do enriquecimento ambiental associado ou não a atividade física nas funções nociceptivas e motoras em um modelo animal de fibromialgia

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ABSTRACT

BACKGROUND AND OBJECTIVES: Fibromyalgia is a complex syndrome, characterized by chronic widespread musculoskeletal pain and the reduction of physical/functional performance as a major comorbidity. Pharmacological treatment of fibromyalgia has limited effectiveness, making it important to study non-pharmacological therapies, emphasizing physical activity, cognitive behavioral therapy and distracting techniques. Environment enrichment and physical activity have been used in the treatment of diseases associated with increases in peripheral and central nociceptive activity. The objective of this study was the investigation of environmental enrichment, a technique based on physical, sensory and cognitive stimulation, and voluntary physical activity for hyperalgesia prevention in an experimental model of fibromyalgia.

METHODS: Twenty-four male Wistar rats were split into four groups: 1. environmental enrichment, 2. physical activity, 3. environmental enrichment plus physical activity and 4. control and kept in these protocols for 4 weeks. Next, diffuse chronic muscle pain was induced by a double injection of acidic saline in the left gastrocnemius muscle. Mechanical paw withdrawal threshold, thermal latency, neuromuscular activity and ambulation in six different moments were assessed: baseline, after the 1st, 2nd, 3rd and 4th weeks and 24 hours after chronic muscle pain induction.

RESULTS: Animals kept in the environmental enrichment plus physical activity protocol showed increased mechanical threshold, thermal latency, neuromuscular activity and ambulation even after the acidic saline injections.

CONCLUSION: These results suggest association between environmental enrichment and physical activity as a strategy for chronic musculoskeletal pain prevention and physical performance optimization in a diffuse chronic muscle pain model.

Keywords: Exercise, Fibromyalgia, Hyperalgesia, Pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A fibromialgia é uma síndrome complexa, caracterizada por dor musculoesquelética crônica generalizada, tendo como principal comorbidade a redução do desempenho físico/funcional. O tratamento farmacológico da fibromialgia tem eficácia limitada, tornando importante o estudo de terapias não farmacológicas, enfatizando a atividade física, terapia cognitivo-comportamental e técnicas de distração. O enriquecimento ambiental e a atividade física têm sido utilizados no tratamento de doenças associadas ao aumento da atividade nociceptiva periférica e central. O objetivo deste estudo foi investigar o enriquecimento ambiental, uma técnica baseada na estimulação física, sensorial e cognitiva e atividade física voluntária para prevenção de hiperalgesia em um modelo experimental de fibromialgia.

MÉTODOS: Vinte e quatro ratos Wistar machos foram divididos em quatro grupos: 1. enriquecimento ambiental, 2. atividade física, 3. enriquecimento ambiental somado a atividade física e 4. controle, e mantidos nesses protocolos por 4 semanas. A dor muscular crônica difusa foi induzida por uma injeção dupla de salina ácida no músculo gastrocnêmio esquerdo. Foram avaliados o limiar mecânico de retirada da pata, latência térmica, atividade neuromuscular e deambulação em seis momentos diferentes: basal, após a 1ª, 2ª, 3ª e 4ª semanas e 24h após a indução crônica da dor muscular.

RESULTADOS: Os animais mantidos no protocolo de enriquecimento ambiental somado a atividade física apresentaram aumento do limiar mecânico, latência térmica, atividade neuromuscular e deambulação mesmo após injeções de salinas ácidas.

CONCLUSÃO: Esses resultados sugerem a associação entre enriquecimento ambiental e atividade física como estratégia para prevenção da dor musculoesquelética e déficit motor em modelo de fibromialgia.

Descritores: Dor, Exercício, Fibromialgia, Hiperalgesia.

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INTRODUCTION

Fibromyalgia (FM) is a chronic pain syndrome with unknown etiology, characterized by non-inflammatory widespread musculoskeletal pain due to several factors that sensitize the central nervous system (CNS). Other characteristics of FM are the presence of tender points sensitive upon palpation, sleep disturbances, increased oxidative stress, muscle and joint stiffness, among others that contribute to reduced quality of life in this population[1-3]. Due to Its complexity, treatment for FM must comprise of a complex clinical multidisciplinary approach that can articulate pharmacological and non-pharmacological aspects[4,5].

Pharmacologic treatment of FM focuses, in general, on reducing the action of stimulating neurotransmitters, such as glutamate by gabapentinoids and potentiate the action of neurotransmitters that inhibit the CNS such as noradrenaline, serotonin and gamma-aminobutyric acid by tricyclic compounds and inhibitors of serotonin and norepinephrine reuptake[6,7]. It is noteworthy that the pharmacological therapy for FM caters effectively to a small portion of the affected population[6-10]. As for the non-pharmacological therapies cognitive behavioral therapy, hydrotherapy, electrical stimulation currents and exercise, their main objective is to improve the functional performance of FM patients[7,11]. In many situations, non-pharmacological therapy is more effective than drug therapy. However, there are limitations on the implementation of non-pharmacological therapies in clinical practice, such as lack of access, patient adherence, low methodological rigor and lack of evidence from well-designed studies[7,11-13].

Reiterating the need for expansion of therapeutic possibilities in FM, environmental enrichment (EE) is presented in this study. EE is a widely used concept in animal research that proposes an increase in the stimulation of physical and social aspects physical, sensory and cognitive activities. EE has shown significant evidence as a neuroprotective tool, presenting benefits in physical performance, learning, neuroplasticity and sensory modulation. It is noteworthy that no studies showing the use of EE in FM animal models were found by the time this study was conducted[14-16].

This study aims to investigate prophylactic effects of EE, associated or not to physical activity, in nociceptive function, ambulation and motor control in an animal model of diffuse chronic muscle pain.

METHODS

Twenty-four male Wistar rats, two months old, weighing 250-350g, were included in this study. Animals were kept in a light-dark cycle of 12h, and all tests were performed during the light cycle. Temperature was set at 22°C, food and water was available ad libitum. All procedures were in line with the ethical principles of the Colégio Brasileiro de Experimentação Animal (COBEA - Brazilian College of Animal Experimentation) and the International Association for the Study of Pain (IASP).

Widespread chronic muscle pain induction

In order to mimic FM diffuse chronic muscle pain, an animal model consisting of two injections of acidic saline solution (pH 4.0; 100µL, each) administered five days apart and applied on the rats left gastrocnemius muscle was used. Animals were anesthetized with vaporized isoflurane (2% - 4%) prior to injection. This is a model of non-inflammatory muscle pain capable of producing lasting hyperalgesia without significant damage of muscle tissue[17].

Study groups

Sample size was determined based on previously published studies in this field that investigated antinociceptive effects of EE[16,18]. Animals were split into 4 study groups (n=6, per group): 1. enriched environment alone (EE); 2. enriched environment plus physical activity (EE + PA); 3. physical activity without EE (PA); and 4. control (CTRL), with animals kept in standard housing (Figure 1).

In the EE group, structural changes in the physical environment were carried, increasing the explorable area (100x40x60cm) and adding rattles, pipes, sheds, stairs, chewable wooden objects and a top floor in the cage. The EE+PA group received, in addition to the same structural changes, a running wheel (Insight™, Ribeirão Preto, SP, Brazil). The PA group received a running wheel and expansion of the exploration area (100cmx40cmx60cm), but no external objects. CTRL group was placed in standard cages (30x20x23cm), without any modification.

Acclimatization

Animals were acclimated to the behavioral tests for two consecutive days right before each experiment. For the mechanical skin sensitivity test, animals were placed on the assessment apparatus transparent cubicles, for 20 minutes and stimulations were performed in the plantar surface of their hind paws. For the thermal sensitivity test, animals were acclimated in the test apparatus for 5 minutes without thermal stimulation. For the dynamic balance test, animals were acclimated in the appa-

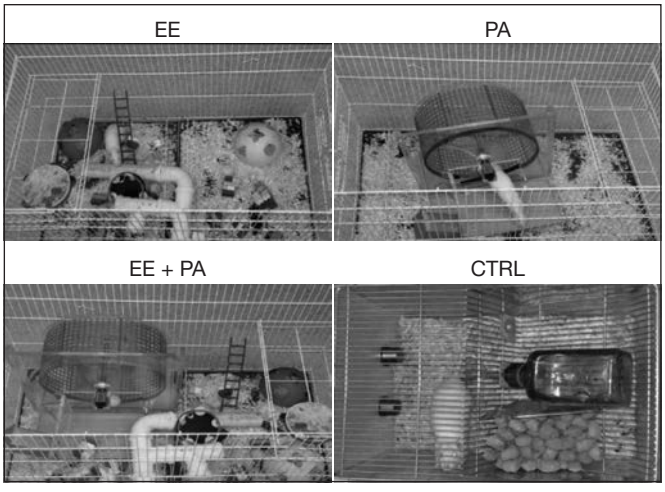

Figure 1. Study groups
EE = enriched environment; PA = physical activity; CTRL = control.

ratus at a low rotation speed (5 rpm) for three attempts, with five-minutes intervals between them.

Nociception assessment

Mechanical paw withdrawal threshold was measured by an electronic von Frey device (Insight™, Ribeirão Preto, SP, Brazil), applied directly on their hind paws. Prior to the measurement, animals were acclimated for 20 minutes at the assessment room. To measure thermal hyperalgesia, the Hot Plate (Insight™, Ribeirão Preto, SP, Brazil) was used, which consists of a heated surface with an open acrylic tube to confine the animals. For the test, temperature was set to 50°C[19].

Motor function assessment

To assess neuromuscular activity, the Rota Rod test, which measures balance alterations and neuromuscular coordination[19,] was used (AVS™, São Carlos, SP, Brazil). To assess motor activity, Open Field Test (OPT Insight™, Ribeirão Preto, SP, Brazil) was used. The testing protocol started with animal acclimatization (D-1, D0). Two days after, mechanical hyperalgesia, thermal latency, dynamic balance and motor activity tests were performed (D1, D2). The animals were randomly assigned into the different study groups and kept in their assigned cages for four weeks. Then, starting at day 9, the behavioral tests were reassessed four times with a week interval between them (D9-10; D16-17; D23-24, D30-31). The first and second acidic saline injections were applied at days 32 and 37, respectively.

On days nine and ten (D9, D10), the behavioral reassessment was performed, respectively. Then the reassessment was repeated at days 16 and 17 (D16, D17), 23 and 24 (D23, D24), and 30 and 31 (D30, D31). At day 32 and 37 (D32, D37), the first and second acidic saline injections were applied, respectively.

Approval by the Ethics Committee on Animal Research of the Federal University of Sergipe (protocol number 39/2012). All participants provided written Free Informed Consent Term (FICT) before study procedures were initiated.

Statistical analysis

For non-parametric data analysis, Kruskal-Wallis, Friedman and Tukey tests were used for comparisons between groups on mechanical and thermal threshold tests. Two-way ANOVA and Bonferroni test were used to analyze samples from dependent parametric data at each time of assessment before and after injury, comparing differences between groups. P value <0.05 was considered as statistically significant.

RESULTS

Mechanical paw withdrawal latency

Mechanical paw withdrawal threshold was significantly higher in the group treated with a combination of enriched environment and physical activity (EE + PA) compared to the other groups from the third reassessment (p<0.001). This effect was sustained at the fifth assessment post-induction. It is noteworthy that even after diffuse chronic muscle pain induction, the EE + PA group maintained a significant increase in mechanical withdrawal threshold (p<0.01), while the other groups showed a significant reduction when compared to EE + PA group post-induction and also when compared to its own previous assessments (Figure 2).

Thermal latency

Thermal latency was significantly higher in the EE + PA group compared to the other groups, starting from the second evaluation (p<0.001). This increase remained at the 3rd, 4th and 5th week. Differently, the other groups had a significant decrease in thermal latency at the 5th revaluation (after acidic saline injections) compared to EE + PA group (p<0.003) and when compared to its previous assessments (p<0.003; Figure 3).

Neuromuscular activity

Neuromuscular activity significantly increased in the EE + PA group compared to the others starting from the 1st evaluation (p<0.01). This increase was significantly kept in the following as-

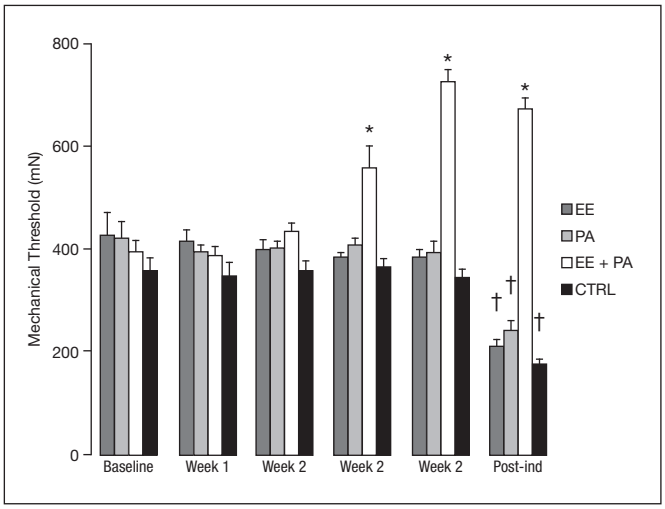

Figure 2. Mechanical paw withdrawal latency (mN) of groups EE, EE + PA, PA and CTRL, at baseline and 1st, 2nd, 3rd, 4th and 5th weeks
* p<0.001 when compared to the other groups (One-way Anova). † p<0.01 when compared to EE + PA group and the previous assessments (paired T test).
EE = enriched environment; PA = physical activity; CTRL = control.

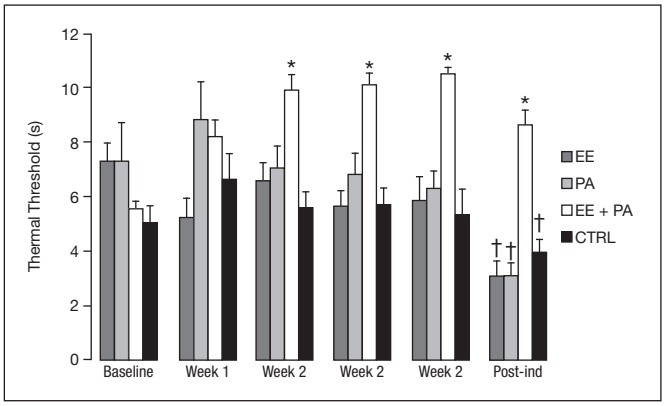

Figure 3. Thermal latency (s) of groups EE, EE + PA, PA and CTRL, at baseline and 1st, 2nd, 3rd, 4th and 5th week.
* p<0.001 when compared to the other groups (One-way Anova). † p<0.003 when compared to EE + PA group and the previous assessments (paired T test).
EE = enriched environment; PA = physical activity; CTRL = control.

sessments (2nd, 3rd, 4th and 5th week) when compared to the other groups (p<0,01). The other groups showed significant reduction in neuromuscular activity when compared to EE + PA group at the 5th assessment (after injections), and when compared to its own previous assessments (Figure 4).

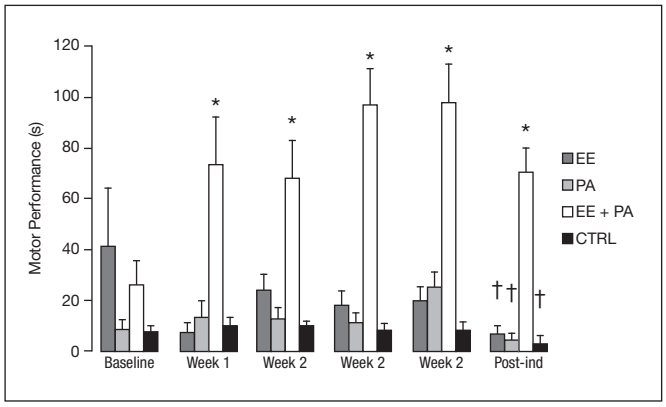

Figure 4. Neuromuscular activity (s) of groups EE, EE + PA, PA and CTRL, at baseline and 1st, 2nd, 3rd, 4th and 5th week
*p<0.01 when compared to the other groups (One-way Anova). †p<0.01 when compared to EE+PA group and previous assessments (paired T test).
EE = enriched environment; PA = physical activity; CTRL = control.

Motor activity

Open field test analysis showed a significant increase in the total number of quadrants (central and peripheral) of EE + PA group, when compared to the other groups from the first week. This increase was maintained in the following assessments, even after chronic muscle pain induction (Figure 5).

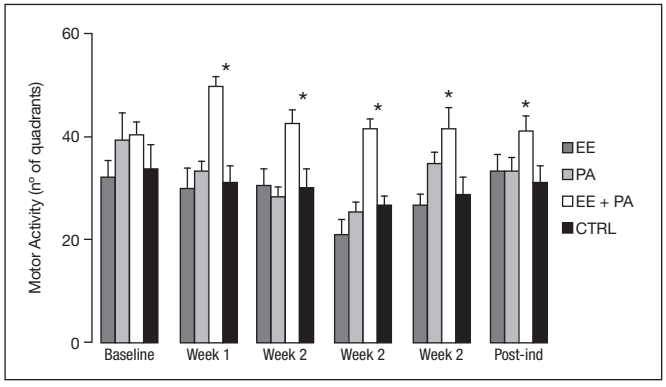

Figure 5. Motor activity (nº of quadrants) of groups EE, EE + PA, PA and CTRL, at baseline and 1st, 2nd, 3rd, 4th and 5th week.
*p<0.01 when compared to the other groups (One-way Anova)
EE = enriched environment; PA = physical activity; CTRL = control.

There was no statistical difference between post-induction and the previous assessments (paired T test).

DISCUSSION

There are few studies investigating the effects of EE in animal models of pain, specifically regarding the model investigated in this study. As far as known, this is the first study that investigated the effects of combining PA and EE for preventing the development of cutaneous hyperalgesia mechanical and thermal, in an animal model of diffuse chronic muscle pain. After four consecutive weeks of exposure to PA and EE combined, there was a prevention of the mechanical hyperalgesia response that would be expected after the two injections of acidic saline. However, animals treated individually with either EE or PA separately showed mechanical hyperalgesia after the second acid saline injection, suggesting that the analgesic effect was attributed to the combination of the two forms of intervention.

Although currently there is no previous study investigating the effect of PA combined with an EE in the diffuse chronic muscle pain model, study[18] examined the effects of physical and social stimulation in an animal model of inflammatory pain. Similar to the findings of the present study, the authors observed reduced mechanical hyperalgesia after four weeks of environmental and physical enrichment tunnels, running wheel, extra nesting material. Furthermore, there was a decrease in the duration of mechanical hyperalgesia[18]. It is noteworthy that differently from this protocol, in the present study animals were exposed to the combined intervention prior to hyperalgesia induction, suggesting a potential prophylactic analgesic effect. Authors[20] also used the exposure to physically and socially EE before abdominal surgery by cecal manipulation, revealing that EE promoted a decrease of analgesic self-administration during postoperative recovery.

Study[18] tested four housing conditions for mice physical enrichment, social enrichment, social and physical enrichment, and standard housing. There was a reduction of mechanical hyperalgesia in animals exclusively treated with either physical enrichment size of cages, insertion of objects, tunnels, or social enrichment increasing the number of animals in cages. Anti-hyperalgesia was even more pronounced when an association between physical and social aspects was performed, suggesting that this effect is due to increased physical activity and reduced stress levels, simultaneously[18]. The intimate relationship between stress and nociceptive function has been reported in the literature, especially considering that pain is a complex process that integrates emotional and physical components of the perception of noxious stimuli[21]. In rats, previous studies have shown that chronic stress increases nociceptive response[22,23].

In a mice model of neuropathic pain, authors[16] promoted increased exploration area, insertion of playful and chewable objects, tunnels and running wheels when the protocol was administered after the induction of hyperalgesia, showing reduced mechanical hyperalgesia only after two months of exposure to this protocol. The present study results showed that a four weeks exposure was enough to prevent the development of hyperalgesia. This lower exposure time required to promote the antinociceptive effect is possibly attributed to the different experimental models used, considering that the treatments applied to neuropathic pain usually have a greater duration[24,25].

Authors[16,18] also showed a reduction in thermal hyperalgesia after exposure to an EE physically and socially. Changes in housing cages were also used[26] showing decreased thermal hyperalgesia four weeks after complete Freund's adjuvant induced inflammation in rats. It is noteworthy that, in this same study, there was no change in mechanical hyperalgesia, unlike the study[18]. Both studies used an inflammatory pain model, however, the study[26]

had no increase in the exploration area / animal housing, only insertion of objects, which can justify the opposing results. In the present study, the animals housing area was also increased, however, this only proved effective in the studied variables when associated with a running wheel.

Regarding the motor component, animals treated with EE and voluntary PA showed an optimization of dynamic balance on the Rota Rod test, even after induction of diffuse muscle chronic pain. Contrarily to the findings of the present study, studies[15,16] showed that the EE associated to PA did not reduce motor impairment in neuropathic pain and ischemia-hypoxia models. Study[27] also examined the effects of EE in motor function in a neuropathic pain model, by using the Basso, Beatie and Bresnahan scale (BBB scale). In this study, EE was effective in motor impairment recovery after spinal cord injury. After 12 weeks of EE exposure, the BBB scale signaled a recovery of motor impairment, suggesting the use of EE to promote motor control optimization in sensory dysfunctions.

Authors[28] also developed a study on spinal cord injury using EE for motor control recovery. In this study, beyond the conventional EE tools (objects and activity wheel), the animals were stimulated to increased PA by placing food and water on opposite sides of the cage. Results showed that exposure to EE improves the recovery of gross and fine locomotor activity as measured by the BBB scale. In the present study, the association of EE and PA was effective for motor impairment prevention and optimization of motor control in a model of chronic muscle pain. It is speculated that such effects can be justified by an increased proprioceptive activity trough the activities provided by the EE associated with PA overcoming obstacles, climbing stairs, coordinated movement of fore and hind limbs.

Curiously, dynamic balance showed very low latencies in all groups at baseline and only the group exposed to EE and PA had an effective motor control optimization even after induction of diffuse chronic muscle pain. Reduced values at baseline can be justified by the speed used in the Rota Rod apparatus, whereas speeds below 15 rpm may result in better test results. However, the effect of EE on dynamic balance is still not clear, mainly if strain and age of the animals are considered.

Animal exposure to an EE has also been used to increase the exploratory behavior[29]. In the open field test, the findings of the present work indicated increased locomotor activity in animals receiving EE and PA protocol, even after the saline injections. Study[30] showed increased locomotor activity on animals exposed to an enriched environment immediately after birth. Authors argue that this increase in mobility is due to an increase in motivation and better processing of spatial information both resulting from the activation of dopaminergic receptors, and similarly to the findings of the present study, exposure to an enriched environment was effective in increasing mobility. It is worth highlighting that this study exposure for four weeks, was carried on two-month-old rats and the study[30] was carried on immediately after birth.

EE can act in the functioning of neurotransmitters intimately related to the variables investigated in this study. It is pointed out that the environmental enrichment can increase the expression of serotoninergic receptors. Study[31] showed increased levels of serotonin at the hippocampus and frontal cortex, in animals submitted to EE. Serotoninergic activity was also increased in the hippocampus positively associated with PA swimming and negatively to immobility[31]. This suggests a possible analgesic effect promoted by the therapeutic combination of EE and PA performed in this study.

Glutamatergic transmission is fundamental to the development of the animal pain model reproduced in the study[32]. Thus, it is pertinent to discuss the influence of EE in the glutamatergic system. A few authors pointed out an increased activity of glutamate receptors (NMDA and AMPA) in the hippocampus of animals submitted to EE[33]. However, no study on animal model of pain addressing the possible effect of EE on the glutamatergic system, especially in the rostral ventromedial medulla, was found. Increased glutamatergic activity suggests the increase in cognitive ability and memory[33], factors that can also act in preventing FM. Thus, the prevention of hyperalgesia in the present study would be explained, at last in part, by changes in the glutamatergic system, related to increased cognitive activity/distraction.

Concerning the opioid system, possible effects of environmental enrichment are not fully understood. However, study[34] showed increased sensitivity to the mu opioid receptor and no effect on kappa receptors in animals exposed to an enriched environment. Other studies show that the enriched environment increases the antinociceptive action of opioid drugs. These changes in opioid sensitivity may be mediated by changes in the mu-opioid receptors. Thus, it is speculated that the analgesic effect seen in the present work may also be explained by an activation of the opioid system, as shown in the study[17] through a low intensity aerobic exercise applied to the same diffuse muscle chronic pain model.

Enrichment conditions in this study were used alone or in combination with voluntary PA. Thus, it's possible to speculate the possibility of a synergistic antinociceptive effect between physical activity and environmental enrichment for the prevention of mechanical and thermal hyperalgesia, since only the simultaneous combination between the two interventions can prevent the decrease in mechanical and thermal threshold 24 hours after injection of acidic saline.

PA a concept that extends to a broad type of physical exercises, is a therapeutic tool commonly used in the treatment of fibromyalgia[13]. However, voluntary physical activity by itself presented no analgesic prophylactic effect in the present study. It is worth emphasizing that there is still no standardization on the type of exercise recommended for FM, and that association with other therapeutic interventions (as enriched environment) can be an effective approach for FM treatment, since it is a disease whose physiopathology is complex and affects more than one organ/system[7].

In the same experimental model of widespread muscle pain, previously published studies have shown reversal of mechanical hyperalgesia with low intensity aerobic exercises. In the study[17], a training exercise on treadmill at a slow speed (3m/min) was applied for 5 minutes. In the study[35] training was conducted

in a treadmill at alternating speeds 13, 14 ,15 and 16m/min, and at an increasing training duration 30, 40 and 45 minutes. In the present study, induction of voluntary physical activity alone was not enough to reverse mechanical and thermal hyperalgesia, although it was not a systematic training exercise as in the studies[17,35].

EE has been associated with the treatment of illnesses related to increases in peripheral and central nociceptive activity. Studies show that environmental enrichment can treat sensory dysfunctions and reduce hypersensitivity[16,18]. But a broader investigation into the nociceptive modulation mechanisms of environmental enrichment associated with physical activity is necessary, aiming to describe and correlate the possible antinociceptive effects on pain modulation pathways, the age in which animals should be exposed to the enriched environment and physical activity, and the amount of time of exposure.

Although the etiology of fibromyalgia is unknown, there are factors which are associated with the onset of the disease, considered as risky factors for FM, such as traumatic events, stress disorders, viral infections, genetic predisposition, obesity and decreased physical fitness[36]. Thus, among the cited factors, functional benefits such as stress reduction and increased physical fitness can be achieved through environmental enrichment as well as by regular physical activity. Thus, functional benefits and effects showed in the present study may be linked to a reduced predisposition to FM and thus preventing the development of diffuse chronic muscle pain, influencing not only nociceptive function, but also contributing to motor control optimization and increased ambulation.

CONCLUSION

The EE associated to voluntary PA showed a potential prophylactic effect on nociception, motor control and ambulation in an animal model of widespread chronic muscle pain.

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