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NEUROPROTECTOR EFFECT OF STRENGTH TRAINING IN AN NEUROINFLAMMATION ANIMAL MODEL

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ABSTRACT

Background: The preventive role of muscular strength in the diminishing of a neuroinflammation is yet unknown. In this study, the role of the prophylactic muscular strength exercise was investigated, whether it would diminish cognitive alterations and modify the antioxidant intracellular scenery in an animal neuroinflammation model of the CA1 region of the hippocampus. **Methods:** The animals received muscular strength training for eight weeks, three times a week. Subsequently, the stereotaxic surgery, with intra-hippocampal infusion of either saline solution or lipopolysaccharide (LPS) was performed. Next, behavioral tests were performed: objects and social recognition. At last, the animals were euthanized and the collect of the hippocampus and the prefrontal cortex were performed and, later, the dosage of the antioxidant activity was performed. **Results:** The results showed that the muscular strength exercises was capable of showing a beneficial prophylactic effect in the oxidative stress caused by an acute neuroinflammation. There was diminishing of the reduced glutathione concentration (GSH) and increase of the activity of the catalase enzyme (CAT)

in the group (SE + LPS), regarding the control groups. In the prefrontal cortex, there was only an increase of the CAT activity in the group (SE + LPS), regarding the groups (CT) and (SE + SAL). As for the cognitive alterations there were found in the (SE + LPS) group, diminishing the mnemonic hazard of the discriminative and social memories, when compared to the control groups. **Conclusion:** We concluded, therefore, that the induction of a local inflammatory process in the hippocampus leads to mnemonic deficits in behavioral activities and increase of the GSH concentration, and that the muscular strength exercise performed prophylactically presents a protective effect capable of minimizing such mnemonic deficits and increasing the antioxidant defenses in mice that suffered a local neuroinflammatory process in the hippocampus.

KEYWORDS

Neuroinflammation; strength training; oxidative stress; memory.

ABBREVIATION LIST3

AP – antero-posterior

BBB – blood-brain barriers

BDNF – neurotrophic factor

CAT – catalase

CCL2 – C-C chemokine ligand 2

CNS – central nervous system

CO2 – cyclooxygenase 2

CT – control group

DTNB – 5,5'-dithio-bis-[2-nitrobenzoic acid

DV – dorsum-ventral

ECM – elevated crossway maze

GSH – glutathione

GSH-Px – glutathione-peroxidase

GSH-Rd – glutathione-redutase

GST – S-transferase glutathione

HTAB – hexadecyltrimethylammonium bromide

IGF-1 – insulin-like growth factor 1

LT – lateral tilting

LTM – long term recent memory duration

MD – mid-lateral

MLD – memory of long duration

MP – miloperoxidase enzymes

PGC-1α – transcriptional coactivator peroxisome proliferator-activated receptor-γ coactivator 1α

OD – optical density

ROS – reactive oxygen species

SD – superoxide-dismutase

STM – short term memory

TMB – tetramethylbenzene

INTRODUCTION

Neuroinflammation is a complex process which consists in the answer of immune cells, specialized in the central nervous system (CNS) to stimulation that affects the basal activity of the parenchyma of such tissue [1]. However, the brain is considered an immune privileged organ, since peripheral immune cells are unable to cross the blood-brain barriers (BBB), limiting the neuroinflammatory response to the CNS. Therefore, its interaction with the peripheral immune system is little known [1, 2, 3].

Microglia cells are considered the immune cells of the CNS, and express pro and anti-inflammatory effects, promoting the brain homeostasis [3]. In its physiological basal activity, the microglia expresses an anti-inflammatory phenotype and their ramifications go through continuous extension cycles, with the purpose of monitoring the environment [2, 4].

However, when detecting a pathological stimulation, such as infections, mechanical trauma, poorly folded proteins and ischemia [4], microglia quickly modifies its morphology, expressing a reactive phenotype with pro-inflammatory effects, synthesizing and secreting cytokines, such as TNF-α and IL-1β [5], and activating nitric oxide synthesis -2 enzyme, cyclooxygenase 2 (COX2) and C-C chemokine ligand 2 (CCL2), which produce reactive oxygen species (ROS) [6], aiming at eliminating the aggressive stimulation and reparing the tissue damage [1, 7].

It is known that the neuroinflammatory process is a needed mechanism and important in the brain homeostasis [3]. However, when outside (environmental) harmful persistent stimulation and/or internal stimulation are recognized by the microglia [8], a system of positive retro-feeding is sustained,

over-elevating the production of pro-inflammatory factors, which promote cell death and atrophy of local neural synapses, inducing symptoms such as cognitive decline, movement alterations and memory loss [4].

The constant activation of the microglia, the increase of the oxidative stress, the reduction of the neurotrophic support, the alteration of the metabolism of neurotransmitters and the rupture of the brain-blood barrier are described in the literature as associated mechanisms to pathologies and neuropsychiatric disorders, including Alzheimer's disease [6, 9], Parkinson disease and depression [5].

It is foreseen that neuroinflammatory/neurodegenerative diseases will be the biggest health concerns of this century and the second main cause of death by 2050 [10]. Being aware of such facts, several studies are performed with the purpose of developing therapeutic and preventive strategies that may mold the neuroinflammatory process. The practice of physical exercise, a non-pharmacological action, has shown to be promising in the search of reaching such goals [11], and has been proposed as an anti-oxidant and natural anti-inflammatory strategy, which stimulates the increase of the hippocampal neuroplasticity [12, 3], hippocampal neurogenesis and cell proliferation [13], as well as it increases the synthesis of growth factors such as the brain derived neurotrophic factor (BDNF) [14, 15], insulin-like growth factor 1 (IGF-1) [16] and the production of enzymatic and non-enzymatic antioxidants [3].

All such benefits have a direct action in the symptomatology of patients with neuroinflammatory diseases, diminishing the cognitive decline, specially memory loss [3, 11]. However, most relevant studies are focused on the benefits

of aerobic exercises, and few studies approach the influence of muscular strength training, specially when practiced prophylactically, with the purpose of preventing a possible progression of a neuroinflammation, and how such effects are modulated, and what the best strategy of physical training is, evaluating intensity, training and recovery period.

This way, in the present study, we propose the investigation of the neuroprotective effect of muscular strength training at a moderate intensity, practiced prophylactically, in a neuroinflammation-induced model, induced by lipopolysaccharide (LPS). For such, we analyzed the discriminative, averse and social memory, and the activity of antioxidant enzymes in the hippocampus and in the prefrontal cortex of mice which were submitted to the hippocampus intra-CA1 infusion of LPS after 8 weeks of physical training.

METHODS

Animals and experimental design

Male *Wistar* mice, of approximately 2 months old and with weight of 250 – 350g were used. The animals were conditioned in controlled room temperature at 22 ºC with bright/dark cycles of 12 hours and kept in appropriate boxes with capacity for 5 animals, covered with shaving, which was switched every two days. They received water and food at ease. The maximum concern was deliberated with the purpose of minimizing the suffering of the animals and reducing the number of animals to be used in the research. All the experiments were according

to the rules of the CEUA/UNIPAMPA and of the “Principles of laboratory animal care” (NIH publication N° 85-23, revised in 1996), under the report #046/2017.

For the experiments, the animals were divided into six groups, having ten animals per group. The groups were divided into control groups: group naive, group submitted to the intra-hippocampal infusion of saline, group submitted to the hippocampus infusion of LPS; and groups which practiced muscular strength exercises: group which performed only muscular strength exercises (CT), group which performed muscular strength exercises and was submitted to the infra-hippocampal infusion of saline (exercise + saline), and group that performed muscular strength exercise and was submitted to the intra-hippocampal infusion of LPS (exercise + LPS).

The animals were submitted to eight weeks of training, three times a week. After the final day of training, all animals performed the muscular strength testing by gripping through the Grip Strength equipment. After training, the surgery was performed to induce an initially acute neuroinflamation through LPS, which was infused in the CA1 region of the hippocampus. The post-operative period was of 5 days, followed by the beginning of the behavioral testings in the following sequence: open field, object recognition, social recognition, plus maze and hot plate. At last, the animals were euthanized, and then, the removal of the heart, the hippocampus and the prefrontal cortex was performed, to obtain the analysis of the activity of antioxidant enzymes.

Strength exercise protocol

Muscular strength training was performed using a personalized vertical scale made of wood and iron (1.1 × 0.18 m, 2 cm grip, inclination of 80°) with a wooden box (20 × 20 × 20 cm) put in the upper part of the stairs. Initially, the animals were familiarized with the exercise, performing four attempts of climbing per day during three days. Once they were able to climb to the wooden box, they could rest inside the wooden box for 120 s. The strength training started a week after the familiarization. In the first week, the load that corresponded to 50% of the mouse's body mass was fixed at the base of the animal's tail. In the second week of training, the test of maximum load was performed to determine the load of exercise for each animal individually. To determine the maximum load corresponding to 75% of the body mass and 30 g were added to each repetition of addition climb until the mouse was not able to finish the exercise. The heavier load transported successfully was considered the maximum load. The maximum load was determined on the first day of each week of training. The training sessions consisted of eight climbs in the stairs with 2 repetitions for each load of 50%, 75%, 90% and 100% of the individual result of the maximum load, resulting in 8 climbs with rest interval of 1 minute between the repetitions, with 3 training sessions per week (one day for the maximum load and 2 days for the training sessions), during 8 weeks [17].

Grip Strength Meter

After the final day of training, all animals performed the muscular strength test by gripping through the equipment Grip Strength. The grip gauge was positioned horizontally facing the equipment. The animals were put in the metal

grid and, next, were pulled backwards in the horizontal plan by the tail. The forces applied to the grid through the animal's legs were measured in grams and immediately before losing the adherence the maximum tension was recorded. Three tests were performed and as result, a mean value was obtained [18].

LPS administration

To induce the neuroinflammation process, the animals were submitted to a stereotaxic surgery and subsequently the intra-hippocampal bilateral administration (CA1 region) administration of vehicle (saline solution) or LPS (from *Escherichia coli* 055:B5; Sigma) dissolved in PBS in the concentration of 10 mg/ml and administrated in the dose of 40 g/side, through the infusion of 4 l/side during 10 min. The coordinated used for the stereotaxic surgery was adapted from the Paxinos & Watson Anatomic Atlas, being as follows: antero-posterior (AP) = - 4.2 mm; mid-lateral (MD) = ± 3.0 mm; dorsum-ventral (DV) = -3.0 mm; lateral tilting (LT) = 0° starting from the Bregma point. The LPS infusion was performed using a Hamilton (5 µl) syringe. All the procedures were performed with previously anesthetized animals with 75 mg/kg of ketamine and 10 mg/kg of xylazine through the intra-peritoneal route. After the surgery, the mice were put in housing boxes, under smooth heating, to avoid hypothermia.

Object recognition memory test

To evaluate the discriminative memory, the object recognition test was performed. From the first to the fourth day of the experiment of such task, considering the habituation period, the animal was put in the left superior corners

of the device, a 50 cm × 50 cm × 50 cm box, made of compensated, acrylic transparent polyvinyl chloride, and then left it there for 5 minutes, without a single object inside the box, so that the animal could get used to the environment.

During the training session, one day after the last day of the habituation day, the animal was once again put in the box with two equal objects, A and B, located right at the center of the box, and the animal was left there for 5 minutes, so it could explore the environment freely. The exploration time of each object was clocked for posterior evaluation. After 3 hours, the short term memory was tested, in which the animal was replaced in the box, with two objects, object A and object C, relieving the previous object B, in a period of time of 5 minutes for free exploration. The long term memory duration was tested 24 h after the previous test, in which the animal as once again placed inside the box, with two objects, being one object A and the other, object D, different from objects A, B and C, and the animal had 5 minutes for free exploration [20].

Social recognition memory test

The task of evaluating the social memory is an adaptation of the social interaction test proposed by [21]. The task was performed in 3 days. First, the animals were placed in a habituation field (the same size and characteristics described in the previously described task of object recognition) with two small cages during 20 minutes for free exploration. In the following day, the training was performed with the inclusion of a juvenile mouse in one of cages for 1 h of free exploration, being, at the same period, one cage left empty. After 24 h, the test was performed when the same mouse of the training (which means, the

mouse that became familiar) and a new mouse were put for exploration for 5 min. The time spent exploring the new mouse and the familiar mouse was registered. The exploration of the animal was defined as smelling or touching the cages with the nose and/or front legs [19].

Open field

To verify whether the effects of the LPS or the vehicle infusion either harmed or not the exploratory and moving activities, the animals were put for 5 minutes in the open field arena. The apparatus is from the same size and characteristics previously described in the object recognition task. The experiments were held in a low sound room under low intensity lighting. Each mouse was placed in the center of the open field and the number of squares crossed and rearing were registered [22].

Elevated plus maze

To evaluate the state of anxiety and to assure that the LPS or the vehicle infusion did not harm such state, the mice were put in an elevated crossway maze (ECM), and the number of entries and the time spent in the open and close ailes were registered during a 5 minute session [23].

Hot plate

To evaluate the nociceptive response and the sensitivity of the animal's legs and to assure that the LPS or the vehicle infusion would not harm the nociceptive sensibility and, consequently, in the task of elusive inhibition, the hot

plate test was use. The mouse was placed in a device with a warm metal sheet of paper (55 ± 0,5 °C) and the time until the animal showed reaction to the thermal stimulation by raising or licking one's leg was determined [24].

Heart mass

After all the behavioral tasks, the animals were euthanized, and then the collect of the hippocampus, prefrontal cortex and heart mass was performed. For the heat mass collect, the open chest procedure was performed and blood was drawn by cardiac puncture, followed by the removal of the heart. After such removal, the heart was washed with saline solution (0.9%) to remove the excess of blood and, immediately the heart mass was weighed using an analytic scale. The index of cardiac hypertrophy was calculated through the reason between heart mass (mg) and body mass (g).

Preparation of the homogenate and protein analysis

Tissue samples of the hippocampus and from the prefrontal cortex were weighed and homogenized with 200 mM phosphate buffer. This homgenate was used for the analysis of the quantification of the reduced glutathione (GSH) concentration and of the miloperoxidase enzymes (MP), dismutase superoxide (SD), catalase (CAT) and S-transferase glutathione (GST).

The protein concentration was measured with a spectrophotometer at 590nm using Bradford (Biorard®) reactant, and bovine albumin (0.012 – 0.100 mg/ml) was used for the standard curve.

309

310 **Determination of MPO activity**

311 The homogenate obtained according to the previous description was
312 centrifuged at 10000 rpm for 20 minutes. The obtained precipitate was re-
313 suspended with 500 µL of 80 mM potassium phosphate buffer with 0.5% of
314 hexadecyltrimethylammonium bromide (HTAB). After the homogenization, the
315 samples were once again centrifuged at 12000 rpm, 20 minutes at 4°C of
316 temperature in a high speed refrigerated microcentrifuge. In a 96-well plate in
317 triplicate, aliquotes of 60 µl of the supernatant of each sample, or distilled water
318 for the white, and then 200 µl of a reactional solution (100 µL of 80 mM phosphate
319 buffer, 85 µl of 22 mM phosphate buffer and 15 µl of 0.017% H_2O_2) was added.
320 The reaction stated with the addition of 20 µl of tetramethylbenzene (TMB), an
321 enzymatic substrate that results in a colorful product in each well. The plaque
322 with the samples was incubated for 3 min at 37ºC, and the reaction was
323 interrupted by the addition of 30 µl of 1,46 M sodium acetate (pH = 3.0) in each
324 well. The enzymatic activity was determined in a spectrophotometer at 620 nm.
325 The results were expressed as units of optical density (OD)/mg of protein,
326 according to [25].

327

328 **Quantification of the GSH and LOOH levels**

329 As described by [26, 27], 50 µl of the homogenate was added to 40 µL of
330 12,5% of thrichloroacetic. Next, the material was centrifuged at 1.4 G / 15 min.
331 After the centrifuge, 20 µl of the supernatant was added to 270 µl of TRIS buffer
332 (pH 8.9) and 10 µl of 5,5'-dithio-bis-[2-nitrobenzoic acid (DTNB). The absorbance

was measured after 5 min in wavelength of 415 nm and the values were interpolated in a standard deviation curve of GSH (1.25-10.00 µg/mL). The results are expressed in µg/g of tissue.

Determination of SOD, CAT and GST activities

The obtained homogenates were used to verify the participation of the SOD, and it was based on the capacity of the SOD in inhibit the auto-oxidation of the pirogalol. In a conic tube, the following were added: 442,5 µl of Tris -EDTA buffer and 20 µl of the sample. After agitation in a vortex, 25 µl of 1 mM pirogalol was added and incubated. Then, they were centrifuged and 300 µL of the supernatant was pippeted in a microplate for the reading in the spectrophotometer at 205 nm. The results were compared with the control group (Tris-EDTA buffer with pirogalol without incubation + mean of the triplicate without the sample and without incubation), being such value equal to 100%. The amount of protein that inhibits the reaction in 50% (IC 50) is equal to one unit (U) of SOD. The results were expressed in U of SOD/mg of protein [28].

The homogenate was also used to verify the participation of the catalase enzyme (CAT). In a 96-well microplate 10 µL of the sample (homgenate) was placed, added to 290 go of the reaction broth (5 mM Tris/EDTA buffer, pH 8.0 + 30% H_2O_2 + ultra pure water) [29]. After being added all the elements, three readings in the spectrophotometer were performed, at the wavelength of 240 nm, and the results were expressed in µmol of H_2O_2 consumed/min/g of tissue.

The supernatant was used to verify the presence of the S-transferase glutathione enzyme. After centrifuge of the homogenate, the precipitate of the

supernatant was separated. 50 µL of the supernatant and 250 µL of the reaction broth (0,1M phosphate buffer, 3 mM CDMB and 3 mM GSH) were added in a 96-well microplate. After such step, three reading in a spectrophotometer were performed at the wavelength of 340 mn, and the results were expressed in µmol/min./mg of protein [30].

Data analysis

The latency and the time percentage of the behavioral experiments and the mean numbers obtained in the biochemical experiments were compared between the different groups through the parametric Student test (two groups) or ANOVA (more than two groups) with the post-hoc Newman-Keuls test for multiple comparisons, or Dunnett's test for the comparisons with the control group. P values < 0.05 were considered statistically significant.

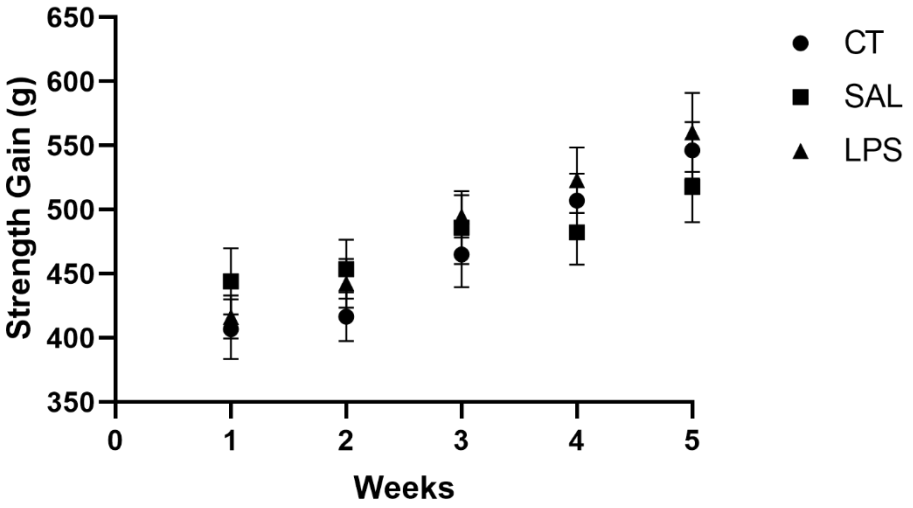
RESULTS

Data from the body weight were expressed in grams. All animals gained weight throughout the experiment. However, there was no significant difference regarding weight gain among the different groups: CT (442.7 ± 20.43), saline + exercise (419.8 ± 16.47), LPS + exercise (378.7 ± 14.90), Naive (445.4 ± 14.88), saline (429.4 ± 11.37) and LPS (425.7 ± 14.70) ($p > 0.05$).

With the purpose of evaluating the animal's maximum muscular strength and posteriorly prescribe the maximum load that the animal would use during the exercise, the animals submitted to the strength exercise protocol performed the

maximum load test, once a week, during all the muscular strength training protocol.

Figure 1. Eight weeks of strength exercise previously to the intra-CAI dorsal bilateral infusion of LPS (40 µg/side) or saline improved the muscular strength of the animals.



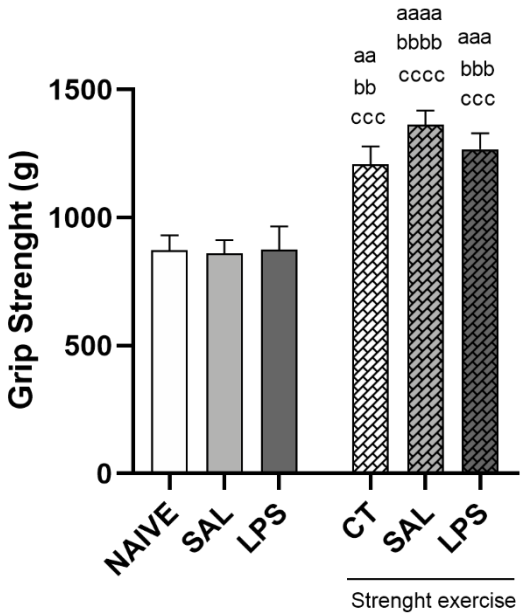
The animals were submitted to the maximum load test once a week during all the muscular strength training protocol. The animals achieved gradual muscular gain. However, there was not statistical differences among the groups ($p > 0.05$, two-way ANOVA, followed by the Newman-Keuls multiple comparison test).

As seen in figure 1, the prophylactic intervention with exercise resulted in progressive muscular strength increase in the animals that trained for 8 weeks. However, it was not verified significant difference among the trained groups that received LPS/saline or the control group (CT).

GRIP STRENGTH TESTING

After the final day of muscular strength training, the animals were submitted to the grip strength testing through the equipment Grip Strength Meter. The results of the outcome of the test for all the groups are shown in Figure 2.

Figure 2. Eight weeks of strength exercise previously to the infusion of intra-CA1 dorsal bilateral infusion of LPS (40 µg/side) induced an increase in the grip strength.



The mice were submitted to eight weeks of strength exercise training protocol. As followed, they received intra-CA1 dorsal bilateral infusion of either saline (SAL) or LPS (40 µg/side). Groups NAIVE and control (CT) were not submitted to the procedure of intra-CA1 infusion. One day after the final day of

412 training, the animals were submitted to the grip strength test (g), through the
413 equipment Grip Strength Meter. Analysis of variance two-way ANOVA, followed
414 by Newman-Keuls multiple comparison test. aa $P < 0.01$; aaa $P < 0.001$; aaaa P
415 < 0.0001, when compared with the group NAIVE. bb $P < 0.01$; bbb $P < 0.001$;
416 bbbb $P < 0.0001$ when compared with the SAL group, when not submitted to
417 exercise. ccc $P < 0.001$; cccc $P < 0.0001$ when compared to the LPS group, when
418 not submitted to exercise.

419 As expected, the prophylactic intervention with exercised resulted in grip
420 strength increase in the trained animals, demonstrating that the proposed training
421 protocol in the present study was efficient, significantly increasing the muscular
422 strength of the animals that were trained, when compared to the animals which
423 were not trained.

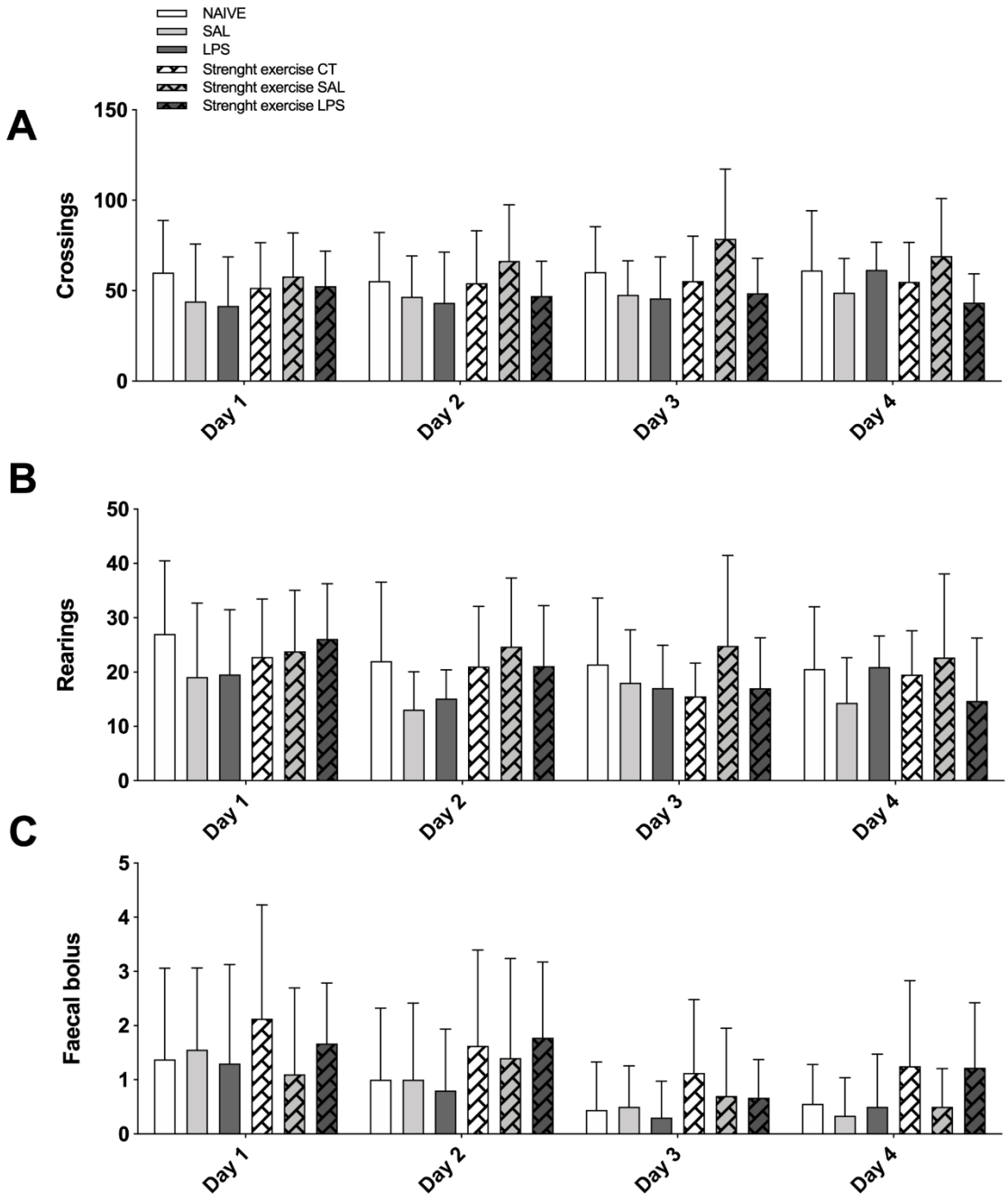
424

425 **OPEN FIELD**

426 The animals had their locomotor and exploratory capacity analyzed in the
427 open field task, during the habituation phase which preceded that object
428 recognition task. The results of the performance in such task for all the groups
429 are shown in Figure 3.

430

431 **Figure 3.** Eight weeks of strength exercise previous to the intra-CA1 dorsal
432 bilateral infusion of LPS (40 µg/side) does not affect the locomotion and
433 exploratory activity of mice in the open field task.



The mice were submitted to two weeks of training in the strength exercise protocol. As followed, they received intra-CA1 dorsal bilateral infusion of either saline (SAL) or LPS (40 µg/side). The groups NAIVE and control (CT) were not submitted to the procedure of intra-CA1 infusion. After 5 days of postoperative

recovery, these mice were submitted to several behavioral tasks, among them the open field task, as part of the habituation process which preceded the object recognition task. Four sessions were performed, one by day, during 4 consecutive days. (A) Number of crossings among internal squares of the open field box (B) Number of times that the mouse lifted its back legs. (C) Number of feces expelled by the mouse during the period of session in open field. Data are expressed as mean numbers (± EM) from the previous variables. There was not significant statistical difference among the groups, after two-way ANOVA with repeated measurements, followed by the Newman-Keuls multiple comparison test.

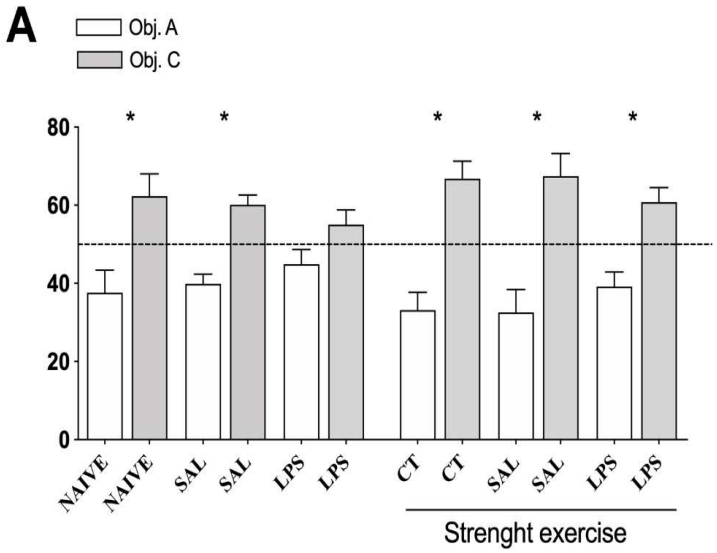
There were not significant differences among the groups throughout the days in the analyzed parameters analyzed in the open field task. Therefore, neither the resistance exercise nor the neuroinflammation induced by the LPS in the CA1 hippocampus region were able to alter the locomotor and exploratory activity of mice in the open field task regarding the control group.

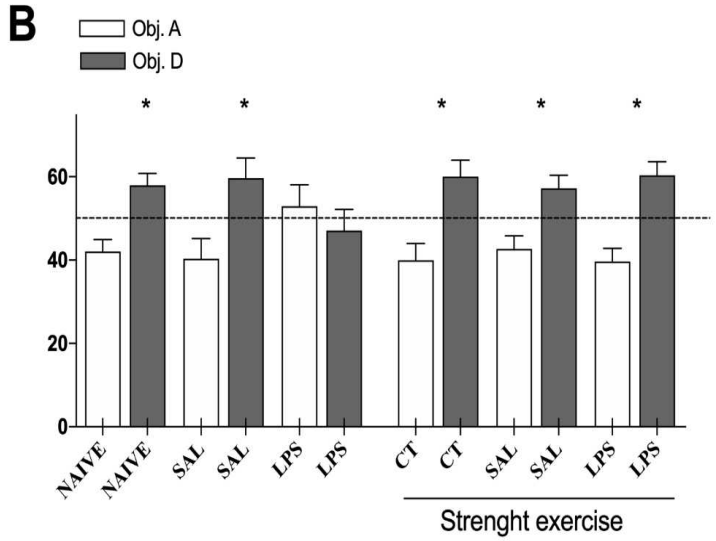
OBJECT RECOGNITION

The animals had their short and long term retention duration of the discriminative memory analyzed in the object recognition task. The results of the performance in such task are shown in Figure 4.

Figure 4. Eight weeks of strength exercise previous to the intra-CA1 dorsal bilateral infusion of LPS (40 µg/side) improves the performance of mice in the

retention of the short term memory (STM) or long term recent memory duration (LTM) of discriminative memory relative to the object recognition task.





The mice were submitted to eight weeks of training in the strength exercise training protocol. As followed, they received intra-CA1 dorsal bilateral infusion of either saline (SAL) or LPS (40 µg/side). After 5 days of postoperative recovery, these mice were submitted to several behavioral tasks, among them the object

recognition task. (A) Test performed 3 hours after the training session with the objects A and B. (B) Second test, performed 24 hours after the training session. Data are expressed as mean numbers (± EM) from the exploration percentage of each of the objects presented regarding the total time of the exploration of the objects. * $p < 0.05$ vs. Theoretical percentage of 50% in Student's t test. (n = 7 – 10 per group).

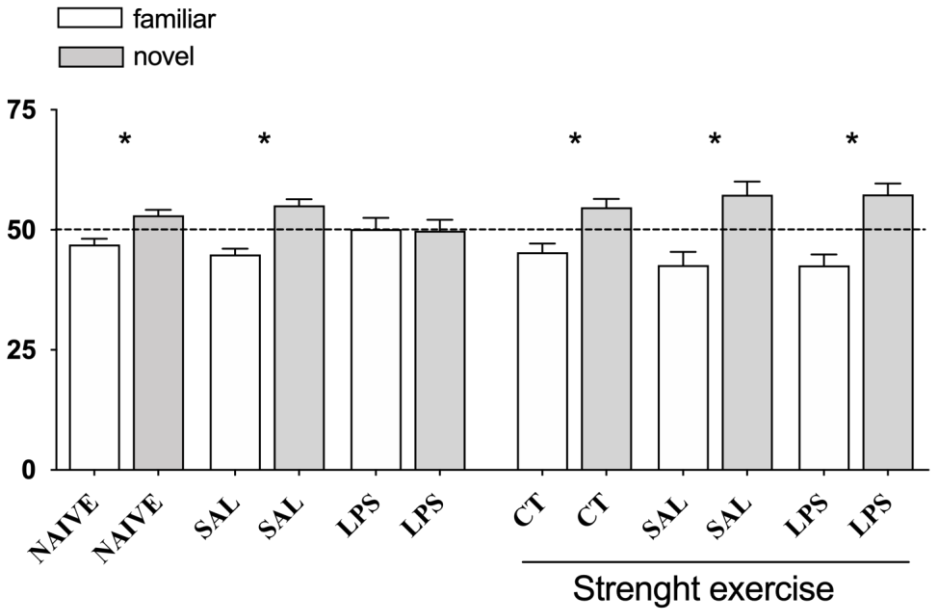
As expected, the locally provoked neuroinflammation in the CA1 hippocampus region harmed the mice capacity to form and retain descriminitative short and long term duration regarding object recognition task. The prophylactic intervention with strength exercise resulted in a protection effect, which was verifiable both in the retention of the discriminating short term memory and recent long duration. Therefore, in this cognitive task, as well as what happened in the social recognition task, the strength exercise has shown to have potential prophylactic mnemonic neuroptrotector in face of a local neuroinflammatory effect.

SOCIAL RECOGNITION

The animals had their retention capacity of short and long duration of social memory analyzed in the social recognition task. The results of the performance in such task for all the groups are shown in Figure 5.

Figure 5. Eight weeks of strength exercise, previously to the intra-CA1 dorsal bilateral infusion of LPS (40 µg/side), improves the performance of mice in the

retention of social recent memory of long duration (MLD) regarding the task of social recognition.



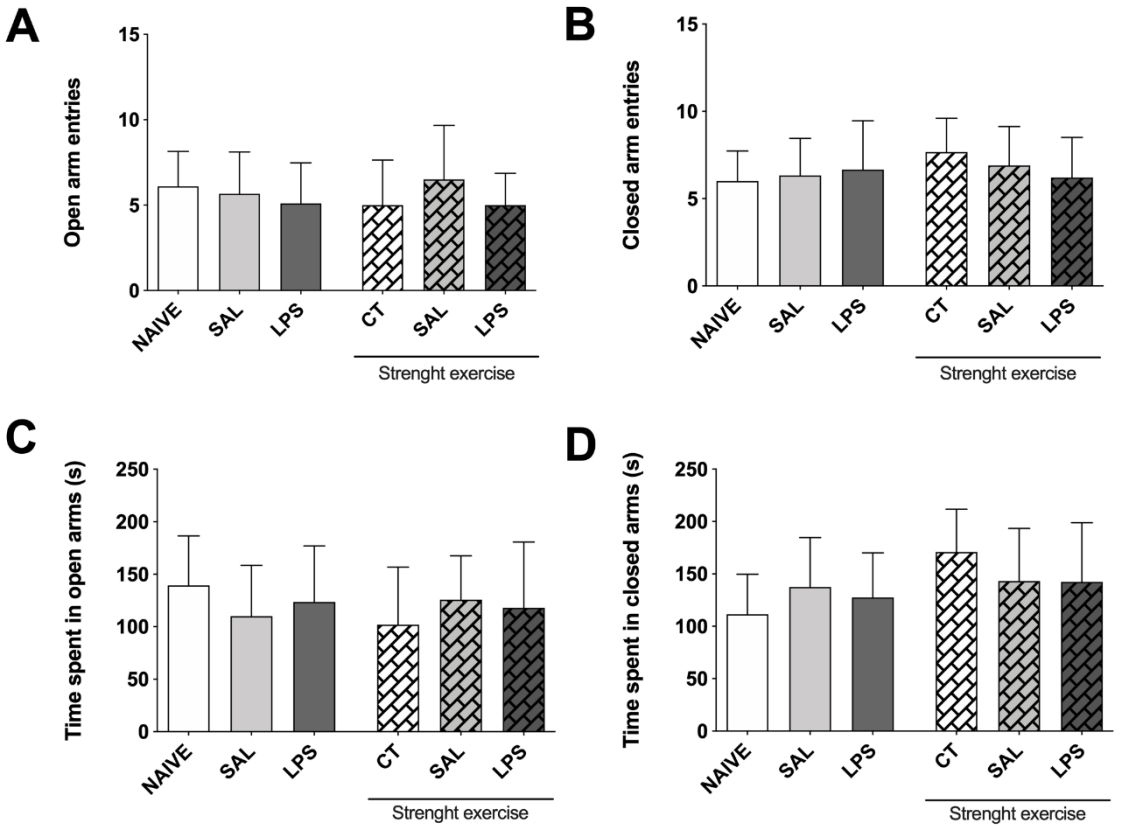
The mice were submitted to eight weeks of training in the strength exercise protocol. As followed, they received intra-CA1 dorsal infusion of either saline (SAL) or LPS (40 µg/side). The groups NAIVE and control (CT) were not submitted to the intra-CAI infusion procedure. After 5 days of post-operative recovery, these mice were submitted to several behavioral tasks, among them the social recognition task. Test performed 24 hours after the training session. Data are expressed as mean numbers (± EM) from the percentage of the exploration of each of one of the juvenile mice regarding the total time of exploration of such mice. * $p < 0.05$ vs. Theoretical percentage in 50% in t Student test. (n = 7 – 10 per group).

As expected, the locally provoked neuroinflammation in the CA1 hippocampus region harmed the capacity of the mice to form and retain social memory of short and long duration related to the social recognition task. The prophylactic intervention with strength exercise resulted in a verifiable protecting effect in the retention of the discriminating memory of recent long duration. Therefore, in this cognitive tasks, the strength exercise has shown to be have prophylactic neuroprotective potential in face of an acute neuroinflammatory context.

PLUS MAZE

The animals had their level of anxiety analyzed in the elevated plus maze. The results of the performance in such task for all groups are shown in Figure 6.

Figure 6. Eight weeks of strength exercise previously to the intra-CA1 dorsal bilateral infusion of LPS (40 µg/side) does not affect the level of anxiety of mice in the plus maze elevated task.



525

526

527 The mice were submitted to two weeks of training protocol in the strength
528 exercise. As followed, they received intra-CA1 dorsal bilateral infusion of saline
529 (SAL) or LPS (40 µg/side). The groups NAIVE and control (CT) were not
530 submitted to the intra-CA1 infusion procedure. After 5 days of postoperative
531 recovery, these mice were submitted to several behavioral tasks, among them
532 the elevated plus maze task. (A) Number of entries in the open arms. (B) Number
533 of entries in the closed arms. (C) Time spent within the open arms. (D) Time spent
534 within the closed arms. Data are expressed as mean numbers (± EM) from
535 previous variables. There were no significant difference among the groups,
536 whether after one-way ANOVA followed by multiple comparison Student-

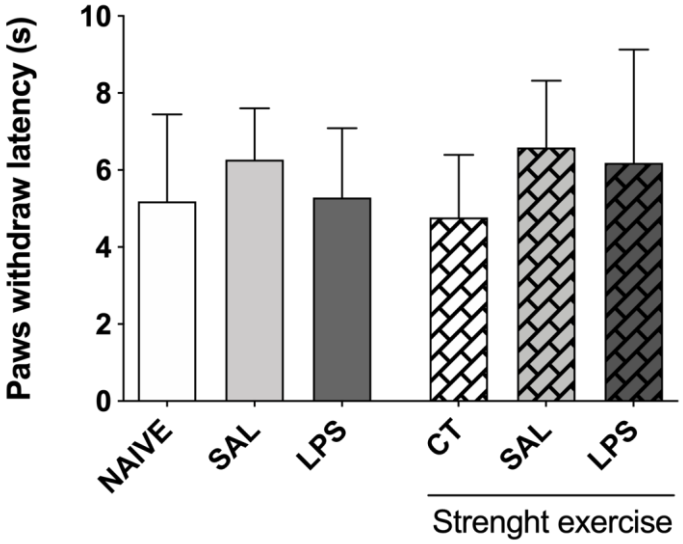
Newman-Keuls test, whether after comparisons with the NAIVE group, according to the test of Dunnett.

There were no significant differences among the groups in the analyzed parameters in the elevated plus maze task. Therefore, neither the strength exercise nor the neuroinflammation induced by the LPS in the CA1 hippocampus region were able to alter the level of anxiety in the mice in such task regarding to the control groups.

HOT PLATE

The animals had their nociception analyzed in the hot plate task. The results of the performance in such task for all the groups are shown in Figure 7.

Figure 7. Eight weeks of strength exercise previously to the itra-CA1 dorsal bilateral infusion of LPS (40 µg/side) does not affect the nociception of mice in the hot plate task.



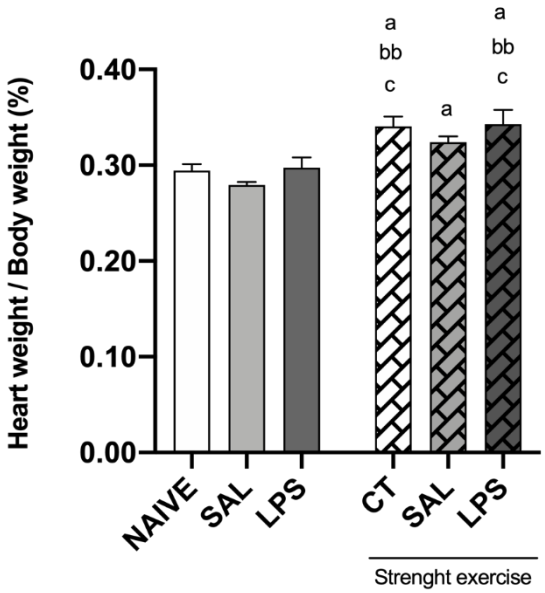
The mice were submitted to eight weeks of training in the strength exercise protocol. As followed, they received the intra-CA1 dorsal bilateral infusion of saline (SAL) or LPS (40 µg/side). The groups NAIVE and control (CT) were not submitted to the intra-CA1 infusion procedure. After 5 days of post-operative recovery, these mice were submitted to several behavioral activities, among them the hot plate task. The data are expressed as mean numbers (± EM) of the reaction time to the thermal stimulation (removal and lick of the legs). There was not statistical significant difference among the groups, whether after one-way ANOVA followed by the Student-Newman-Keuls multiple comparison test, or after the comparisons with the NAIVE group, according to the Dunnett's test.

There was not significant statistical difference among the groups regarding the reaction time to the thermal stimulation, by removing and licking the legs. Therefore, neither the strength exercise nor the induced neuroinflammation by the LPS in the CA1 hippocampus region were able to alter the nociception of the mice in this task regarding the control groups.

HEART MASS

Figure 8 presents the data referring to the heart mass, presented as reason between mass of the heart by body mass of the animal, index which determines the occurrence of cardiac hypertrophy. The reason heart mass/body mass from the group CT, SAL + exercise and LPS + exercise was significantly higher than the respective groups NAIVE, SAL without exercise and LPS without exercise.

Figure 8. Eight weeks of strength exercise previously to the intra-CA1 dorsal bilateral infusion of (40 µg/side) induces a physiological cardiac hypertrophy caused by muscular training.



The mice were submitted to eight weeks of training in the strength exercise protocol. As followed, they received the intra-CA1 dorsal bilateral infusion of saline (SAL) or LPS (40 µg/side). The groups NAIVE and control (CT) were not submitted to the intra-CA1 infusion procedure. After being euthanized, the heart of the animals was removed and then weighted. The heart mass was corrected by the body mass. For such correction, the following formula was used: (Total weight of the heart/body weight) x 100. Two-way ANOVA, followed by Newman-Keuls multiple comparison test, a $P < 0.05$ when compared to the group NAIVE. bb $P < 0.01$ when compared to the group SAL not exercised. c $P < 0.05$ when compared to the group LPS not exercised.

The prophylactic intervention of muscular strength exercise was able to induce a physiological hypertrophy, compensatory/adaptation, needed to

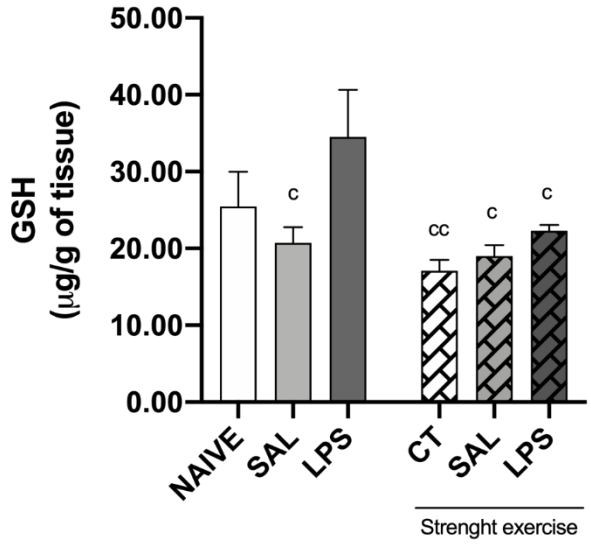
maintain a cardiac performance in increased condition of circulatory overload during the animals' training. It is known that the intensive and long-lasting physical training induces cardiovascular adaptations, including a cardiac hypertrophy, which allows the heart an exceptional physical performance. We noticed, in this study, a statistical difference in the heart mass of the animals which trained, when compared to the ones that did not train, which shows that the heart of the trained animals became adapted to the muscular strength training, showing that the proposed training protocol in the present study was efficient.

Evaluation of the effect of strength exercise on GSH level in rat hippocampus after intra-hippocampal infusion of LPS.

With the purpose of knowing whether the maintenance of the intracellular level of GSH is influenced by the practice of prophylactic strength exercise, after a local neuroinflammatory condition, the hippocampus concentration of GSH was evaluated in hippocampus samples of mice. Figure 9 shows that the hippocampus concentration of GSH in animals which were submitted to the strength exercise was smaller than in the group that received LPS intra-hippocampus infusion, when compared to the group that received only LPS intra-hippocampus infusion ($p < 0.05$) but was not previously submitted to the strength exercise.

Figure 9. Evaluation of the influence of the strength exercise in the hippocampal concentration of GSH. Eight weeks of strength exercise previously to the intra-CA1 dorsal bilateral infusion of LPS (40 µg/side) diminished the hippocampus

concentration of GSH in the mice hippocampus previously submitted to the strength exercise, when compared to the non-exercised mice.

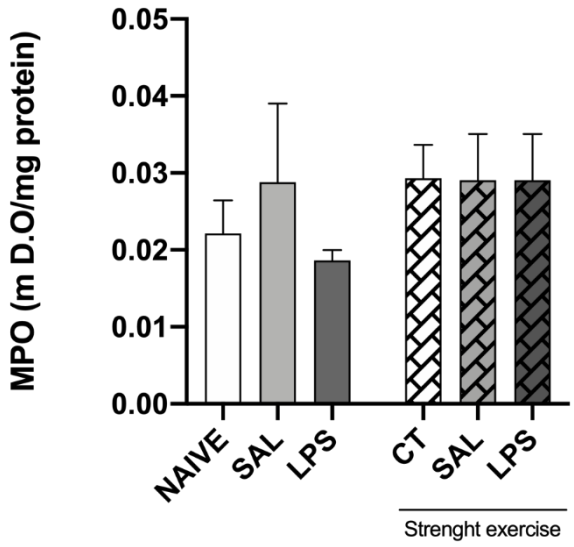


The mice were submitted to eight weeks of training in the strength exercise protocol. As followed, they received intra-CA1 dorsal bilateral infusion of either saline (SAL) or LPS (40 µg/side). The groups NAIVE and CT were not submitted to the intra-CA1 infusion procedure. After 5 days of post-operative recovery, such mice were submitted to several behavioral tasks, followed by euthanasia and then the removal of the hippocampus was performed. Results expressed in mean numbers ± EPM. (n = 7-10 per group). c $P < 0.05$, cc $P < 0.01$ when compared to the non-exercised LPS group (One way ANOVA followed by Newman-Keuls multiple comparison test).

Effect of strength exercise on MPO expression in rat hippocampus after intra-hippocampal infusion of LPS

As shown in Figure 10, the strength exercise was not able to alter the MPO activity in the hippocampus in animals submitted to the intra-hippocampal infusion of LPS when compared to the respective control group (LPS without exercise).

Figure 10. Influence of the strength exercise in the activity of MPO in the hippocampus. Eight weeks of strength exercise previously to the intra-CA1 dorsal bilateral of LPS (40 µg/side) does not affect the activity of MPO in the hippocampus.



The mice were submitted to eight weeks of training in the strength exercise protocol. As followed, they received intra-CA1 dorsal bilateral infusion of either saline (SAL) or LPS (40 µg/side). The groups NAIVE and CT were not submitted to the intra-CA1 infusion procedure. After 5 days of post-operative recovery, such mice were submitted to several behavioral tasks, followed by euthanasia and then

652 the removal of the hippocampus was performed. Results expressed in mean
653 numbers ± EPM. (n = 7-10 per group) and statistical analysis was performed by
654 one-way ANOVA, followed by Newman-Keuls multiple comparison test.

655

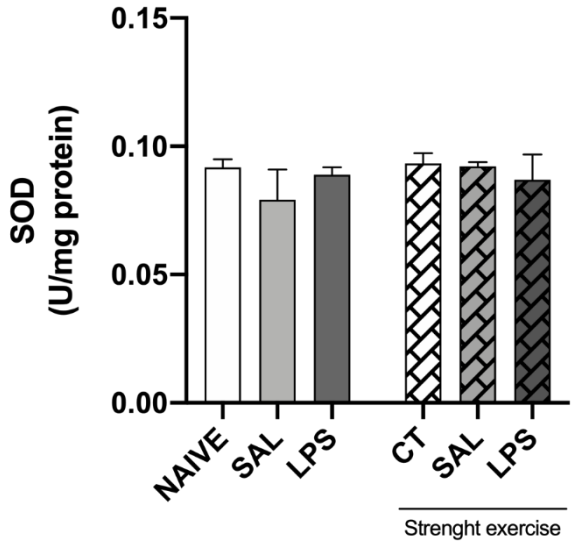
656 **Effect of strength exercise on the expression of the SOD enzyme in the**
657 **hippocampus of rats after intra-hippocampal infusion of LPS**

658

659 As shown in Figure 11, the strength exercise was not able to re-establish
660 the activity of the enzyme SOD in mice submitted to the intra-hippocampal
661 infusion of LPS when compared to the control group.

662

663 **Figure 11.** Influence of the strength exercise in the activity of the enzyme SOD.
664 Eight weeks of strength exercise previously to the intra-CA1 dorsal bilateral
665 infusion of LPS (40 µg/side) does not affect the activity of SOD in the
666 hippocampus of mice.



667

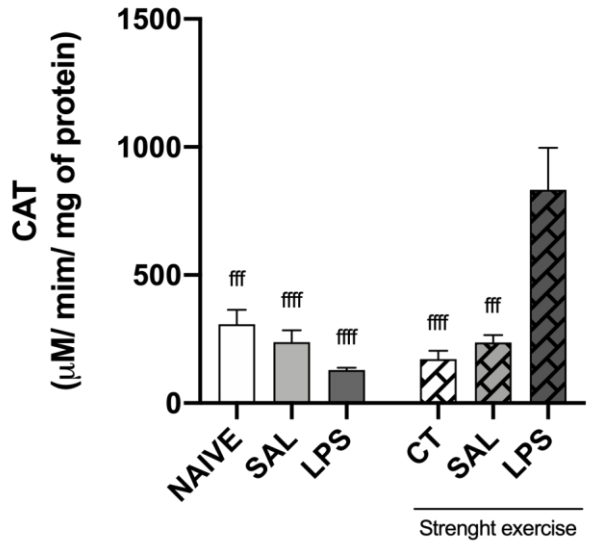
668

The mice were submitted to eight weeks of training in the strength exercise protocol. As followed, they received intra-CA1 dorsal bilateral infusion of either saline (SAL) or LPS (40 µg/side). The groups NAIVE and CT were not submitted to the intra-CA1 infusion procedure. After 5 days of post-operative recovery, such mice were submitted to several behavioral tasks, followed by euthanasia and then the removal of the hippocampus was performed. Results expressed in mean numbers ± EPM. (n = 7-10 per group) and statistical analysis was performed by one-way ANOVA, followed by Newman-Keuls multiple comparison test..

Effect of strength exercise on the expression of the CAT enzyme in hippocampus in rats after intra-hippocampal infusion of LPS

As shown in Figure 12, the strength exercise has shown to have influence in the enzyme CAT in the hippocampus. The animals that performed strength exercise prophylactically and were submitted to the intra-hippocampal infusion of LPS showed higher activity of the enzyme CAT in the hippocampus when compared to the group which practiced exercise and received intra-hippocampal infusion of saline, to the group that practiced only exercise and the sedentary group that received either LPS or saline ($p<0.001$).

Figure 12. Influence of the strength exercise in the activity of the enzyme CAT. Eight weeks of strength exercise previously to the intra-CA1 dorsal bilateral infusion of LPS (40 µg/side) increased the activity of CAT in the hippocampus of mice which received local induction of neuroinflammation.



692

693

694 The mice were submitted to eight weeks of training in the strength exercise
695 protocol. As followed, they received intra-CA1 dorsal bilateral infusion of either
696 saline (SAL) or LPS (40 µg/side). The groups NAIVE and CT were not submitted
697 to the intra-CA1 infusion procedure. After 5 days of post-operative recovery, such
698 mice were submitted to several behavioral tasks, followed by euthanasia and then
699 the removal of the hippocampus was performed. Results expressed in mean
700 numbers ± EPM. (n = 7-10 per group) fff $P < 0.001$, ffff $P < 0.0001$ when compared
701 to the exercised LPS group, in one-way ANOVA followed by Newman-Keuls
702 multiple comparison test.

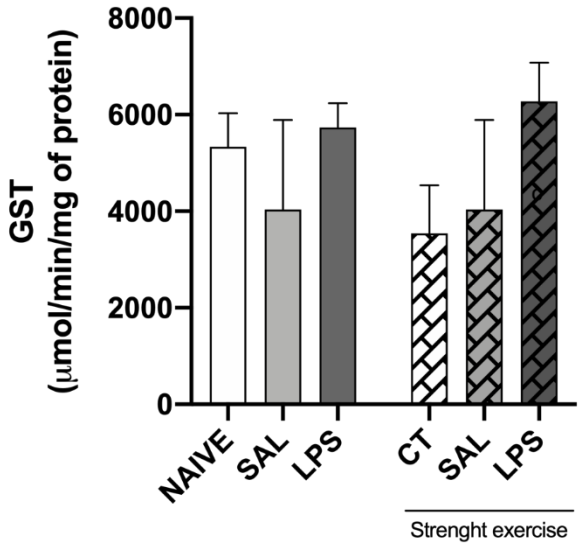
703

704 **Effect of strength exercise on the expression of the GST enzyme in**
705 **hippocampus in rats after intra-hippocampal infusion of LPS**

706 Figure 13 shows that the strength exercised influenced the activity of the
707 enzyme GST. We observed that the group which performed strength exercise
708 and was submitted to the intra-hippocampal infusion of LPS showed higher

activity of the enzyme GST when compared to the group which practiced strength exercise and received intra-hippocampal infusion of saline and the group that only practiced physical strength. ($P<0.05$).

Figure 13. Influence of the strength exercise in the activity of the enzyme GST. Eight weeks of strength exercise previously to the intra-CA1 dorsal bilateral infusion of LPS (40 µg/side) does not affect the activity of GST in the hippocampus of mice.



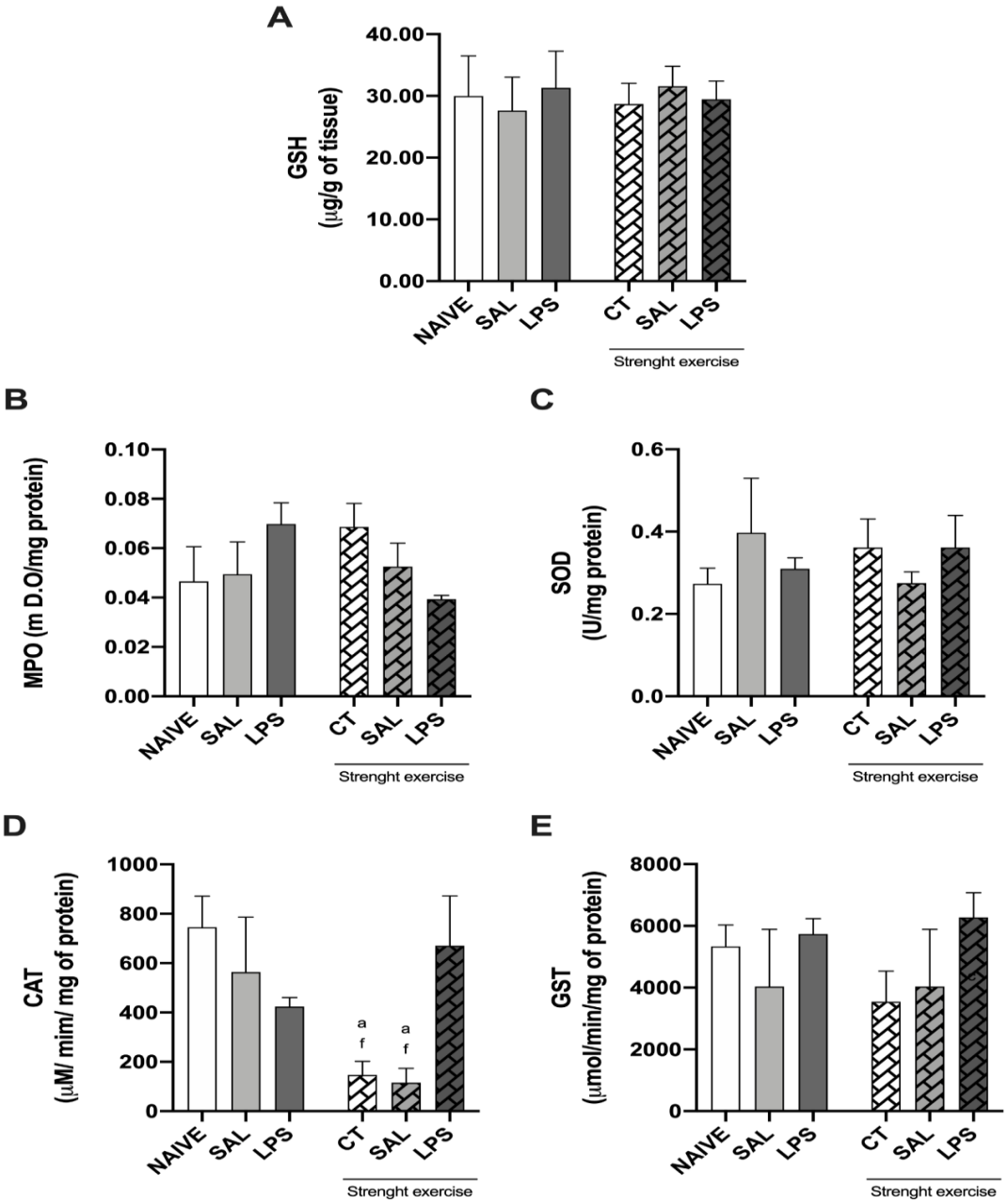
The mice were submitted to eight weeks of training in the strength exercise protocol. As followed, they received intra-CA1 dorsal bilateral infusion of either saline (SAL) or LPS (40 µg/side). The groups NAIVE and CT were not submitted to the intra-CA1 infusion procedure. After 5 days of post-operative recovery, such mice were submitted to several behavioral tasks, followed by euthanasia and then the removal of the hippocampus was performed. Results expressed in mean

numbers ± EPM. (n = 7-10 per group) and statistical analysis by one-way ANOVA and Newman-Keuls multiple comparison test.

Effect of strength exercise on the expression of MPO E GSH and CAT, SOD and GST enzymes in the prefrontal cortex of rats after infusion of LPS in the CA1 region of the hippocampus

As shown in Figure 14, only the activity of CAT was diminished in animals which practiced strength exercise without the induction of intra-CA1 hippocampal neuroinflammation, when compared to the group NAIVE ($p < 0.05$) and the group LPS exercised ($p < 0.05$).

Figure 14. Expression of GSH and from the enzymes SOD, CAT, GST and MPO in prefrontal cortex of mice. Eight weeks of strength exercise diminished the activity of CAT in the prefrontal cortex of mice, in relation to non-exercised mice, except when the mice were submitted to intra-CA1 dorsal bilateral infusion of LPS (40 µg/side) soon after the period of exercise.



742

743

744 The mice were submitted to eight weeks of strength exercise training
745 protocol. As followed, they received intra-CA1 dorsal bilateral infusion of either
746 saline (SAL) or LPS (40 µg/side). The groups NAIVE and CT were not submitted
747 to the intra-CA1 infusion procedure. After 5 days of post-operative recovery, such
748 mice were submitted to several behavioral tasks, followed by euthanasia and then

749 the removal of the prefrontal cortex was performed. Panel (A-E) showing the
750 concentration of GSH GSH (A) and the activity of the enzymes MPO (B), SOD
751 (C), CAT (D) and GST (E). Results expressed as mean numbers ± EPM. (n = 7-
752 10 per group). Figure D: a $P < 0.05$ when compared to the group NAIVE; f $P <$
753 0.05, when compared to the group LPS which practiced strength exercise. One-
754 way ANOVA followed by Newman-Keuls multiple comparison test.
755

756 **DISCUSSION**

757 With the purpose of investigation the influence of muscular strength
758 exercise practiced prophylactically on the parameters of oxidative stress and
759 memory deficits caused by local neuroinflammation in a key brain structure to the
760 formation and consolidation of memories [31], we showed that the muscular
761 strength exercise has neuroprotective effect on the short term social and
762 discriminative memories (STM) and of recent long term memory (LTM), and on
763 markers of oxidative stress in the hippocampus (target structure in which the
764 neuroinflamation process occurred) and in the prefrontal cortex of mice (control
765 structure).

766 Regarding the biochemical tests, we observed that the muscular strength
767 exercise was able to promote increase of the activity of the antioxidant enzyme
768 CAT in the hippocampus in mice, in which there was induction of local
769 neuroinflammation in the CA1 hippocampal region, both regarding the exercised
770 control groups, as well as regarding the group that had also induced local
771 neuroinfammation, but which did not suffer the previous protocol of strength
772 exercise. In the prefrontal cortex, it was verified that the muscular strength

773 exercise reduced the activity of the enzyme CAT in such brain region, compared
774 with the mice that were not exercised, except for the reduction in the activity of
775 CAT in the exercised group.

776 In the object recognition test, we discovered that the prophylactic strength
777 exercise was able to revert the amnesia deficit caused by the LPS regarding both
778 types of memory, STM and LTM. Regarding social memory, the exercise
779 prevented amnesia deficit in LTM.

780 The oxidative stress, the mitochondrial dysfunction and the hyperactivity
781 of microglia are key-processes involved in the neuroinflammatory physio-
782 pathology of different brain diseases [8]. As a response to a lesion, during
783 maximum activation of microglia, an increase in its cell metabolism occurs, as
784 well as synthesis of pro-inflammation factors, in order to eliminate the stressful
785 stimulation and maintain the tissue homeostasis. However, associated to an
786 increase in the cell metabolism, it also occurs the production of different reactive
787 species of oxygen, such as super-oxide radicals (O_2^-), hydroxyl (OH^-) and, yet,
788 hydrogen peroxide (H_2O_2).

789 The excessive formation of such free radicals may lead to DNA alterations
790 and lipidic peroxidation, key-factors in the acceleration of the neuroinflammation
791 process related to age and to the development of neurodegenerative diseases
792 [10].

793 The hippocampus is highly vulnerable to an increase in the formation of
794 free radicals due to its reduced capacity of keeping the redox homeostasis [32].
795 Since the hippocampus is involved in certain ways of learning and memory
796 consolidation [33], a chronic local formation of reactive species of oxygen may

797 cause impairment of the mnemonic functions. Therefore, the maintenance of a
798 redox normal state in the hippocampal microglia is important for the prevention
799 of a cognitive decline [32].

800 To protect itself from these reactive species, the microglia reacts through
801 anti-oxidant mechanisms of defense, and one of such mechanisms acts through
802 specialized enzymes, such as glutathione-peroxidase (GSH-Px), superoxide-
803 dismutase (SOD) and CAT [34]. The second line of defense has the function of
804 repairing a possible damage which has occurred in the cell, being constituted by
805 substances such as glutathione-redutase (GSH-Rd), GSH-Px, among others.

806 Physical exercise has shown to be promising in attenuation of an oxidative
807 stress. During the practice of the physical exercise, there is an increase of around
808 40% to 70% in the brain blood flow to supply the metabolic demand of oxygen
809 [32]. Such increase in the consumption of oxygen results in the microglia in an
810 increase in the synthesis of reactive species of oxygen as a response to the
811 intensity of the exercise.

812 Therefore, it is believed that other factors which increase the production of
813 ROS in the microglia, such as infections, mechanical traumas and ischemia, will
814 be more easily reduced by endogenous factors of protection in individuals who
815 practice physical exercise regularly, either by the positive regulation of anti-
816 oxidant enzymes and/or by increase in the number of mitochondria which allow
817 lower levels of respiratory activity for the same degree of ATP generation [35].

818 The studies of [36, 37] show that different factors in the mitochondria are
819 modulated by redox alterations associated to the exercise, through the activation
820 of the transcriptional coactivator peroxisome proliferator-activated receptor-γ

coactivator 1αo (PGC-1α), which induces and intensely coordinates the gene expression that stimulates the oxidative mitochondrial metabolism and may reduce in diminishing of the oxidative stress.

In fact, we observed that the animals that received the intra-hippocampal injection of LPS in the CA1 region of the hippocampus obtained an increase in the hippocampal concentration of GSH. Such increase that may have occurred as a local homeostasis answer that increased the production of such anti-oxidant as defense against the increase of free radicals unleashed by the inflammatory response. In addition, the increase of the concentration of GSH was the single antioxidant answer that we detected in this study, once the activities of the enzymes here evaluated were not altered in the hippocampus due to the local inflammation caused by the infusion of the LPS.

However, the muscular strength exercise showed to have positive influence on the activity of the anti-oxidant enzymes CAT in the animals which received LPS after having practiced the muscular strength exercise. Thus, once again, this did not have effect on the activity of the enzymes MPO, SOD and GST. Regarding the concentration of GSH, the muscular strength exercise caused a diminishing of such concentration in the hippocampus of mice which suffered the induction of hippocampal neuroinflammation, regarding the group of mice which also suffered such induction, but were not previously exercised. This may indicate that, in some way, consequent to the previous performance of the strength exercise, there has not been, after the induction of the hippocampal neuroinflammation, an oxidative unbalance strong enough to result in higher production of GSH to supply a higher demand for this antioxidant (hypothesis of

diminishing the production of GSH), or if there was a higher consumption of additional GSH produced precisely to diminish the concentration of the ROE resulting from the neuroinflammatory process (hypothesis of increased consumption of GSH). The increase in the activity of CAT and the diminishing of the mnemonic deficit observed in some behavioral tasks link with such suggested explanation.

We also verified that the strength exercise reduced the activity of the CAT in the prefrontal cortex, which by itself is an interesting result. Such result, perhaps, signs that the routine of muscular strength exercise diminishes the demand for the constitutive action of CAT in such brain region, which indicates that there would be a lower generation of ROE in the mice submitted to a muscular strength exercise routine. However, such reduction did not occur in mice that suffered induction of local neuroinflammation in the hippocampal region. In such mice, the activity of CAT was kept at the same level whether the mice had or had not been submitted to the prophylactic protocol of muscular strength exercise, which was a similar level to the groups NAIVE and SAL from the non-exercised animals. This is another interesting result, highlighting that an inflammatory process triggered in a brain region (hippocampus) rebounds in other regions, in this case, on the modulation of the effect of the routine of muscular strength physical exercise on the activity of CAT. Here, we may consider that the hippocampal neuroinflammation rebounded in several brain regions, including the prefrontal cortex, causing in increase in the activity of CAT, which would counterbalance the reduction of the CAT activity induced by the strength exercise. However, if that was the case, we should have noticed an

869 increase in the activity of CAT in the prefrontal CAT in non-exercised mice that
870 suffered local neuroinflammation in the hippocampus, which was not verified in
871 our results. Therefore, what we had here was that, in some way, the
872 neuroinflammation induction in the hippocampus provokes an increase of the
873 activity of CAT in the prefrontal cortex when it is already reduced regarding the
874 default levels (from the non-exercised groups), being such reduction attributed to
875 the previous routine of muscular strength exercise.

876 With the purpose of maintaining the basal levels of ROS and/or nitrogen,
877 the enzymactic and non-enzymactic antioxidants perform different functions. The
878 enzyme SOD catalyzes the desmutation of O_2^- converting it into H_2O_2, soon the
879 enzyme CAT catalyzes the conversion of hydrogen peroxide into water and
880 molecular oxygen, which is a function also performed by the enzyme glutathione-
881 peroxidase [38, 39]. Regarding the enzyme GST, it acts helping the conjugation
882 of eletrofilic substrates to glugathione (GSH) [40, 41]. Therefore, we believe that
883 the increase in the activity of the enzymes CAT in animals that performed
884 muscular strength exercise and after suffered the induction of hippocampal
885 neuroinflammation has been given by an increase in the production of hydrogen
886 peroxide, aiming at reducing it to water and oxygen and maintaining a
887 neuroprotector effect, thus, despite not being a free radical, by the absence of
888 unpaired electrons in the last layer, H_2O_2 is an extremely deleterious ROE,
889 capable of crossing lipid layers and reacting with transition metals and some
890 hemoproteins. It can also induce chromosomal alterations, by bursting the DNA
891 column and, in the absence of catalysts, oxidizing sulfhydryl composites.

892 The overproduction of H_2O_2, in addition to enabling the induction of the
893 increase in the activity of the enzymes CAT as a protection factor, can also
894 promote the inactivation of the enzymes SOD, which was verified in different
895 studies that suggest that high concentrations of H_2O_2 inactivated the enzyme
896 SOD [42, 43], corroborating our result, in which there were no statistical
897 differences in the quantification of the enzyme SOD among the groups.

898 The results found in the quantification of the enzyme CAT are coherent
899 with the results from the behavioral analysis evaluated in our study, since with
900 the increase/adaptation of the antioxidant enzyme given by the muscular strength
901 exercise, we verified a neuroprotective effect against the mnemonic deficits in
902 animals which suffered the intra-hippocampal infusion of LPS.

903 Corroborating with our study, it was investigated in [44] the effect of
904 strength exercise in mice after an induced neuroinflammation by monosodium
905 glutamate. The animals received monosodium glutamate in the dose of 4g/kg, on
906 the first day of life until the 10th day. After 60 days after the day of birth, the
907 animals initiated a strength exercise protocol for 7 weeks and, posteriorly, the
908 object recognition test was performed. The authors verified that the strength
909 exercise had effect in diminishing the deficit of discriminative memory.

910 According to [45], beneficial effects from the muscular strength exercise
911 were also related in the deficit of discriminative memory. The authors observed
912 that after eight weeks of muscular strength training, the animals received an
913 intracerebralventricular injection of the peptide $A\beta_{25-35}$ and practiced exercise
914 presented a significant improvement when compared to the control group
915 regarding deficit of the discriminative memory.

916 According to [46], the neuroprotective effects of three models of non-
917 pharmaceutical intervention, environmental enrichment, muscular strength
918 exercise and social enrichment were investigated in an animal model of
919 Alzheimer's disease. The authors demonstrated that eight weeks of muscular
920 strength exercise were able to revert the social and discriminative memory deficit
921 after the intra-hippocampal infusion of the beta amyloid Aβ in Wistar mice.

922 Several studies have shown the beneficial effects of aerobic exercise in
923 behavioral alterations face a neuroinflammation. However, studies that show the
924 influence of muscular strength exercise are seldom. For that reason, we found
925 few studies that showed the positive effects of strength exercise on social and
926 discriminative memory deficits. Still, when the studies here quoted showed the of
927 muscular strength exercise as a form of treatment, our study showed its
928 prophylactic action. We know that there is a consciousnesses by part of the
929 population on the beneficial effects of physical exercise, and in addition, the
930 practice of strength exercise has been rising. This way, researches on the
931 beneficial influence of such modality of physical exercise on the human
932 population regarding the diminishing of neurodegenerative diseases that have
933 neuroinflammation as a background.

934 Therefore, what was verified in the present study was that the
935 increase/adaptation of the antioxidant enzyme CAT in the hippocampus of
936 animals that received intra-hippocampal LPS in the group of animals that
937 practiced strength exercise may have contributed for the improvement of the
938 performance of such animals in the evaluation of the retention of discriminative
939 and social retention, possibly due to the diminishing of the ROE.

CONCLUSION

In conclusion, the present study reinforces evidences that the muscular strength exercise represents a useful prophylactic approach for the prevention of behavioral deficiencies and of oxidative stress associated to neuroinflammation, as it was induced in this study by LPS. We showed the beneficial effects of strength exercise in animals that suffered local hippocampal neuroinflammation, having avoided the mnemonic deficit in tasks of discriminative and social memory, promoting the increase of the activity of the enzyme CAT and the diminishing of the concentration of GSH (whether due to lower demand of GSH or by inducing its higher use) in the hippocampus.

DECLARATIONS

Ethics approval

All the experiments were conducted in accordance with the principles of laboratory animal care (National Research Council Committee for the Update of the Guide, 2011) and were approved by the Institutional Animal Care and Use Committee of the Local Institution (CEUA/UNIPAMPA) - Protocol #046/2017.

Consent for publication

Not applicable.

Availability of data and materials

964

965 The datasets used and/or analysed during the current study are available from
966 the corresponding author on reasonable request.

967

968 **Competing interests**

969 The authors declare that they have no competing interests.

970

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973 Científico e Tecnológico (CNPq).

974

975 **Authors' contributions**

976 EG was responsible for the acquisition of all research data,Writing- Original draft
977 preparation and Writing- Reviewing and Editing; GCM, LBS, LFL, KRL, GSC,
978 BHSN, SSP contributed largely to the research data acquisition; JSB contributed
979 revising the manuscript critically for important intellectual content and PBMC
980 supervised all research steps and contributed with Conception and design of
981 study; WCS performed the statistical analyzes, contributed with the design of
982 study,Writing- Original draft preparation and Writing- Reviewing and Editing. All
983 authors approved the version of the manuscript to be published.

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