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ORIGINAL ARTICLE

The effects of exercise on hippocampal inflammatory cytokine levels, brain oxidative stress markers and memory impairments induced by lipopolysaccharide in rats

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Abstract

The exercise effects on behavioral tests, hippocampal and cortical oxidative stress, and hippocampal inflammatory cytokines of lipopolysaccharide (LPS) administered rats were investigated. The rats were divided into four groups ($N = 8$): (1) control; (2) moderate training (MT, 15 m/min, 30 min/day, 9 weeks); (3) LPS (1 mg/kg LPS) and (4) LPS + MT (1 mg/kg LPS; 15 m/min, 30 min/day, 9 weeks). LPS was injected 2 h before the behavioral experiments during the last week of training. Finally, the rats' brain were removed for biochemical assessments. LPS increased escape latency and traveled distance to reach the platform in Morris water maze (MWM) test ($P < 0.05$–$P < 0.001$). In the passive avoidance (PA) test, LPS decreased the latency to enter the dark compartment and the time spent in the light compartment and increased the time spent in the dark compartment ($P < 0.01$–$P < 0.001$), while MT improved the rats performances in MWM and PA tests ($P < 0.01$–$P < 0.001$). Additionally, LPS increased tumor necrosis factor α (TNF-α), interleukin 1 beta (IL-1β) and C-reactive protein levels in the hippocampal tissues, malondialdehyde (MDA) and nitric oxide metabolite in hippocampal and cortical tissues, and decreased thiol contents and catalase (CAT) and superoxide dismutase (SOD) activity in hippocampal and cortical tissues compared to the control group ($P < 0.01$-$P < 0.001$); while moderate training decreased the levels of TNF-α, IL-1β and MDA; increased thiol contents, and SOD and CAT activity in the LPS + MT compared to the LPS group ($P < 0.001$). These results indicated that moderate training improved LPS-induced learning and memory impairments by attenuating the hippocampal cytokine levels and brain oxidative damage.

Keywords Moderate training · Lipopolysaccharide · Learning · Memory · Cytokine · Oxidative damage

Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder, which is related to learning and memory impairments and it decrease the individual's quality of life (Yirmiya and Goshen 2011). During the past century, AD had been proposed as a new challenge of world organization systems (Bishop et al. 2010). The underlying mechanisms of AD are poorly understood. However, chronic neuroinflammation, increase in brain-reactive oxygen species and hypoxia, insulin resistance, mitochondrial dysfunction, and vascular diseases are pre-pathological conditions which is resulted in tau and amyloid-β plaque formation as the main histopathological marker of AD (Nazem et al. 2015). There is a causal relationship between chronic low-grade inflammation and tau formation. Tau and amyloid-β oligomers activate microglia and reactive astrocytes, stimulate inflammatory responses, and release chemokine and cytokines (Wes et al. 2016) through activation of nuclear factor kappa B (NF-κB) related pathway as well as induction of the expression of pro-inflammatory genes by stimulating mitogen-activated protein kinase (MAPK) and extracellular signal-regulated protein kinase (ERK) pathways which are associated with neuronal apoptosis. Also, pro-inflammatory cytokines affect the amyloid-β formation and increase the amyloid deposition. In addition, it has been

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suggested that systemic inflammation (Donzis and Tronson 2014), oxidative stress (Kanamaru et al. 2015) and overproduction of inflammatory cytokines in the hippocampus, such as TNF-α, IL-1β, and IL-6 have a critical role in learning and memory impairments (Donzis and Tronson 2014). Also, in a human study it was reported that an increase in the levels of plasma C-reactive protein (CRP) may elevate the risk of AD and cognitive impairments (Ravaglia et al. 2007). Oxidative stress, which reflects the imbalance between the generated reactive oxygen and nitrogen species (ROS/RNS) is one of the deleterious processes common in brain aging, neurodegenerative diseases, and human cognitive disorders (Diniz et al. 2018). The brain is very susceptible to oxidative stress due to its high metabolic activity, high oxidation substrates and modest antioxidant defense (Cobley et al. 2018). Lipopolysaccharide (LPS) is a potent bacterial endotoxin derived from the cell wall of gram-negative bacteria, and neuroinflammation induced by LPS administration is a common animal model of AD (Zarifkar et al. 2010). It was showed that systemic injection of LPS causes spatial memory impairment and decreases neurogenesis in the animal hippocampus (Valero et al. 2014) through the generation of inflammatory cytokines, which lead to the excessive production of free radicals and oxidative stress (Zarifkar et al. 2010). It was reported that LPS administration in animal experiments is able to activate immune cells, such as macrophages and neutrophils, which release inflammatory cytokine (Fruhauf et al. 2015). Some studies suggest that administration of LPS causes spatial memory impairment in Morris water maze (MWM), increased hippocampal levels of inflammatory cytokines such as TNF-α and IL-1β and reduced antioxidant defense (Anaeigoudari et al. 2015; Anaeigoudari et al. 2016a).

Physical exercise and lifestyle modification have an effective role to improve neurodegenerative diseases. Moderate exercise training has an anti-inflammatory and beneficial effects on immunological functions and it mediate an important role in protecting against diseases that are associated with low-grade inflammation, as shown in AD animal models (Cassilhas et al. 2016). Also, physical exercise can prevent AD through the reduction of oxidative damage (Radak et al. 2010). During exercise, the oxygen flow increases in the active skeletal muscle thereby causing the production of reactive oxygen species (ROS) and free radicals (Peake and Suzuki 2004). It was proposed that in physical activity, free radicals stimulate the important parts of the endogenous antioxidant defense system, such as superoxide dismutase (SOD) and glutathione peroxidase (GPX). Moreover, regular physical activity, especially moderate exercise which doesn't lead to exhaustion, can activate the endogenous antioxidant defense system (Ji et al. 2006). In addition, both human and animal studies reported that regular moderate exercise have an anti-inflammatory role and lead to reduction of inflammatory cytokines such as TNF-α, IL-1β, IL-6 and CRP (Chen et al. 2012; Dvorakova-Lorenzova et al. 2006) and elevation of IL-10 as an anti-inflammatory cytokine (Gholamnezhad et al. 2014).

Few experiments studied the beneficial effects of exercise on different aspects of LPS mediated memory impairments. Therefore, the effects of moderate exercise on LPS-induced learning and memory impairments, hippocampal cytokine levels and brain tissues oxidative damage in rats were investigated in the present study.

Materials and methods

Animals

Thirty-two adult male Wistar rats (6–8 weeks old and weighing 150–200 g) were obtained from the animal house of Mashhad University of Medical Sciences, Mashhad, Iran. Animals were housed in standard conditions (temperature (22 ± 2 °C) and 12 h light/dark cycle) and food and water were available throughout the experiment. Animals were allowed to adjust to new condition for 1 week. All experiments were approved (IR.MUMS.fm.REC.1396.468) by the Committee on Animal Research of Mashhad University of Medical Sciences. The rats were randomly divided into four groups ($n = 8$): control, moderate trained (MT), LPS, and LPS + moderate trained (LPS + MT). The animals of LPS and LPS + MT groups received 1 mg/kg of LPS intraperitoneally (i.p.) (Bargi et al. 2017) that was injected 2 h before training trails in MWM test in the last week of exercise training for 5 consecutive days. LPS was purchased from Sigma (Sigma-Aldrich Chemical Co). The chemical agents that were used for biochemical assessments were purchased from Merck Company.

Exercise protocol

A motorized treadmill with 4 individual lanes was used. A shock grid at the back of the treadmill provided a mild shock (2 mA, 2 s) if the rat's pace went below the treadmill rate. The animals experienced 1 week familiarizing (10 min/day for 5 days at a speed of 12 m/min at 0% degree inclination) prior to the start of the experiments for eliminating exercise-induced stress.

The animals of control and LPS groups placed on the treadmill with the aim of experiencing the stress of treadmill environment. Exercise groups undertook a progressive load of training 6 days/week to enhance cardiorespiratory fitness and a 5 min warm up and cool down were included in each session. The animals of MT and LPS + MT groups run at a speed of 15 m/min for 30 min, 6 days/week for 9 weeks (Kim et al. 2003) (Fig. 1).

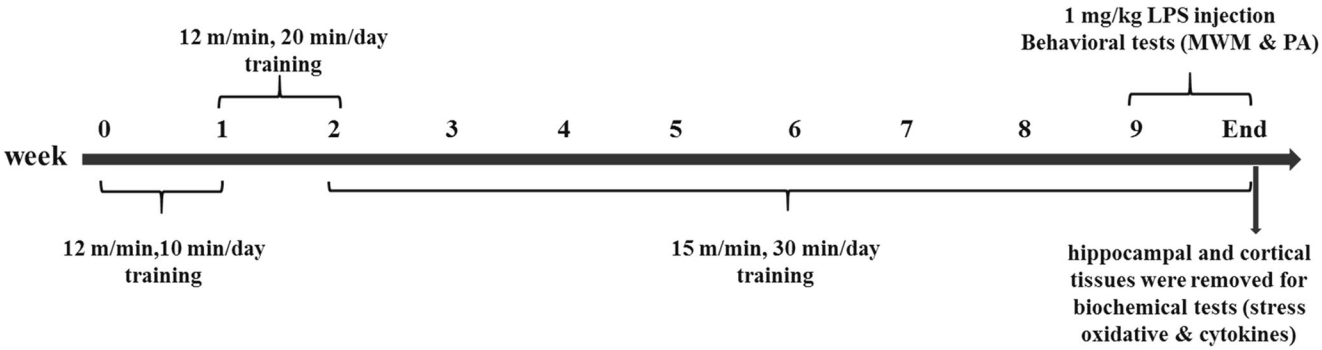

Fig. 1 Time table of animal training

Behavioral assessments

Behavioral assessments included Morris water maze (MWM) and passive avoidance test (PA) began in the last week of exercise training. All behavioral tests were conducted in a noiseless room, under modest illumination and the rats were kept in the room for at least 1 h before the test.

MWM test

MWM apparatus was used for evaluating spatial learning and memory similar to the previously described method (Bargi et al. 2017). Briefly, a circle shaped black pool was divided into four quadrants with boundaries labeled north (N), east (E), south (S) and west (W). There was a circular platform was hidden in the southeast quadrant (target quadrant or Q_4) about 2 cm below the water surface. The animals were released into the pool at one of four positions (north, east, south, and west). The rats were allowed to swim freely to find the platform within 60 s and remained on the platform for 15 s. The position of the animals was detected by a camera. The experiments were repeated with four trials in each day for four consecutive days. The time spent and traveled distance were measured using software to evaluate the spatial learning ability. Twenty-four hours later, the platform was removed and a probe test was performed. The time spent and the traveled path in Q_4 was compared between groups.

PA test

PA apparatus (including light and dark compartments) was used for evaluating passive avoidance memory similar to the previously described method (Anaeigoudari et al. 2015).

Biochemical assessments

After the behavioral assessments, the animals were anesthetized widely by urethane and were euthanized, their hippocampal and cortical tissues were removed and the tissues were homogenized with phosphate buffer solution (PBS) (pH 7.4). The homogenates were centrifuged at 1500 rpm for 10 min, then submitted to determine biochemical assessments. Total thiol (SH), malondialdehyde (MDA), SOD, catalase (CAT) and nitric oxide metabolite (NO^{2-}) were measured in both the hippocampal and cortical tissues. TNF-α, IL-1β and CRP concentrations were determined in hippocampal tissues.

Measurement of TNF-α, IL-1β and CRP

Hippocampal tissues TNF-α, IL-1β and CRP contents determination were performed with specific rat ELISA kits (TNF-α: Diaclone Co, France; IL-1β, CRP: Zellbio Co, Germany) according to the manufacturer instructions. The measured absorbance of the samples in a microplate reader (Biotek, USA) was compared with an established standard curve in the same measurement and the concentrations were calculated.

Measurement of oxidative stress markers

Measurement of MDA

MDA as an indicator of lipid peroxidation was measured based on MDA reaction with thiobarbituric acid (TBA), which produces a pink complex with a peak absorbance at 535 nm (Janero 1990). TBA 375 mg was dissolved in 2 ml of hydrochloric acid (HCl), then 15 g trichloroacetic acid (TCA) was added, and the total volume was reached to 100 ml with distilled water. 1 ml of homogenized tissue mixed with 2 ml of TBA + TCA + HCl solution and the solution was incubated in a boiling water bath for 45 min. After reaching the room temperature, the solution was centrifuged at 1000 rpm for 10 min and its absorbance was measured at 535 nm. MDA level was calculated based on the following formula: (Kaveh et al. 2017)

$$C\ (M) = A/1.65 \times 10^5$$

Measurement of total thiol content

Total thiol contents was measured by the method of Ellman (Habeeb 1972). At first, 50 μl of homogenized tissue and

1 mL of tris- ethylenediaminetetraacetic acid (EDTA) buffer (pH = 8.6) were mixed and the absorbance was read at 412 nm against tris-EDTA buffer alone (A_1). 2, 2′-dinitro-5, 5′-dithiodibenzoic acid (DTNB) reacts with the SH groups to produce a yellow complex which has a peak absorbance at 412 nm. Then, 20 μL of 10 mM solution of DTNB was added and it was stored in room temperature for 15 min and the absorbance was read again (A_2). The absorbance of DTNB alone was also read as blank (B). The following equation was used for calculation of total thiol concentration (Khodabandehloo et al. 2013).

$$\text{Total thiol concentration (mM)} = (A_2 - A_1 - B) \times 1.07/0.05 \times 13.6$$

Measurement of SOD activity

The SOD activity was determined by the method of Madesh and Balasubramanian. The procedure involving the production of superoxide through auto-oxidation of pyrogallol and the inhibition of superoxide-dependent reduction of the tetrazolium dye, MTT (3-(4, 5-dimethylthiazol-2-yl) 2, 5-diphenyltetrazolium bromide) conversion to formazan. The homogenized tissue was pipetted into 96-well plates and incubated at room temperature for 5 min. The reaction was stopped by adding dimethyl sulfoxide (DMSO) and then SOD activity was measured at 570 nm. One unit of SOD was defined as the amount of protein required to inhibit the rate of MTT reduction by 50% (Madesh and Balasubramanian 1997).

Measurement of CAT activity

The activity of CAT was determined according to the method of Aebi. 30 mM hydrogen peroxide (H_2O_2) was used as a substrate and 50 mM phosphate buffer (pH = 7) was used as an alternative substrate in the blank. The reaction was started by adding H_2O_2 and the reduction of absorption was measured at 240 nm for 3 min (Aebi 1984).

Measurement of NO metabolite

NO metabolite (nitrite) were measured according to the Griess reagent methods. Briefly, 50 μl of homogenized tissue was added to the Griess reagents, sulfanilamide, and Naphthylethylenediamine (NED) solutions. Then, absorbance was measured at 520 nm using a microplate reader and the level of NO metabolite were calculated from standard calibration plots (Hosseini et al. 2014).

Statistical analysis

The data were presented as mean ± standard error of the mean (SEM) using SPSS 16 software. The data of the MWM test during 4-days were compared using repeated measures analysis of variance (ANOVA) and One-way ANOVA. The data of the MWM test in probe trial, the data of the PA test and the biochemical data were compared using One-way ANOVA followed by LSD post hoc comparisons test. Statistical significance was considered at $P < 0.05$.

Results

Behavioral results

MWM test

The results of the MWM test were presented for two parameters: the time latency and the traveled distance to reach the platform during the 4-day training, and the time spent and the traveled distance in target quadrant (Q_4) in probe day when the platform was removed.

On the first day, there was no significant difference in the time latency to reach the platform between the groups in the first trial (Fig. 2a). Also, there were no significant difference in the time latency and traveled distance to reach the platform of MT, LPS, and LPS + MT groups compared to the control group. In the animals of MT and LPS + MT groups, these parameters were lower than the LPS group ($P < 0.05$-$P < 0.01$). On the second day, time latency and traveled distance in the LPS group were higher than the control group ($P < 0.01$ and $P < 0.05$, respectively). There were no significant differences between these parameters of MT and LPS + MT groups compared to the control group. Also, these parameters in MT and LPS + MT groups were lower than the LPS group ($P < 0.001$ and $P < 0.01$, respectively). The results of the third day showed that time latency to reach the platform in the animals of the LPS group was higher than the control group ($P < 0.05$), while there was no significant difference in the traveled distance of the LPS group compared to the control group. Also, these parameters decreased in the animals of the LPS + MT group compared to the control group ($P < 0.05$). There were no significant differences between these parameters of the MT group compared to the control group. The results also showed that time latency and traveled distance in MT and LPS + MT groups were lower than the LPS group ($P < 0.001$ and $P < 0.01$, respectively). On the fourth day, time latency and traveled distance in the LPS group were higher than the control group ($P < 0.001$ and $P < 0.01$, respectively). There were no significant differences between these parameters of MT and LPS + MT groups compared to the control group. Also, the results showed that time latency and traveled

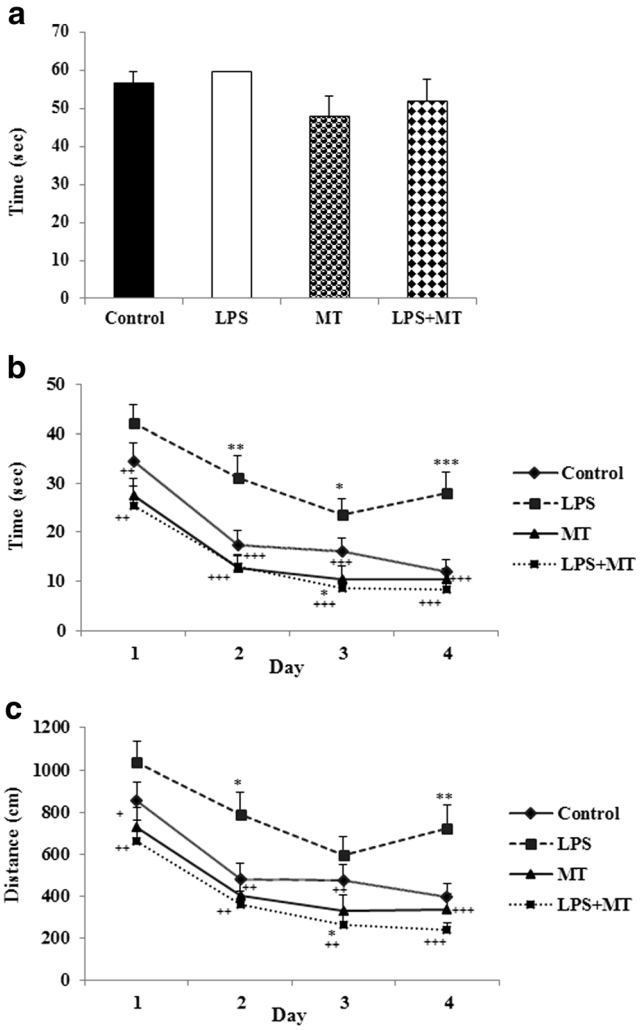

Fig. 2 Comparison of time latency in the first trial of the first day (**a**), time latency (**b**) and traveled distance (**c**) to reach the platform during 4-days of Morris water maze test between control, LPS, MT (moderate trained) and LPS + MT (LPS+ moderate trained) groups. The data are presented as mean ± standard error of the mean ($n = 8$ in each group). $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ compared to the control group, and $^{+}P < 0.05$, $^{++}P < 0.01$ and $^{+++}P < 0.001$ compared to the LPS group

distance in MT and LPS + MT groups were lower than the LPS group ($P < 0.001$) (Fig. 2b and c).

The results of repeated measures ANOVA showed that time latency and traveled distance to reach the platform in the animals of the LPS group were significantly higher than the control animals ($P < 0.001$), while these parameters were significantly reduced in the animals of the LPS + MT group compared to the control group ($P < 0.05$). There were no significant differences in time latency and traveled distance of the MT group compared to the control group. Also, the results indicated that the animals of MT and LPS + MT groups had lower time latency and traveled less distance in comparison to the LPS group ($P < 0.001$) (Fig. 2b and c).

In the probe trial, the animals of the LPS group spent lower time and traveled less distance in target quadrant (Q_4) compared to the control group ($P < 0.05$), while the animals of the LPS + MT group spent more time and traveled a longer distance in Q_4 compared to the control group ($P < 0.01$ and $P < 0.05$, respectively). There were no significant differences in the time spent and traveled distance in Q_4 of the MT group compared to the control group. Additionally, MWM results demonstrated that the time spent and traveled distance in Q_4 of the MT and LPS + MT groups were significantly higher than the LPS group ($P < 0.001$) (Fig. 3a and b).

PA test

The latency to enter the dark compartment, the time spent in the dark compartment and the time spent in the light compartment at 2, 24 and 48 h after receiving the electric shock, were presented.

In the animals of the LPS group, the latency to enter the dark compartment was significantly lower than the control group ($P < 0.01$–$P < 0.001$). There were no significant differences between the latency to enter the dark compartment of

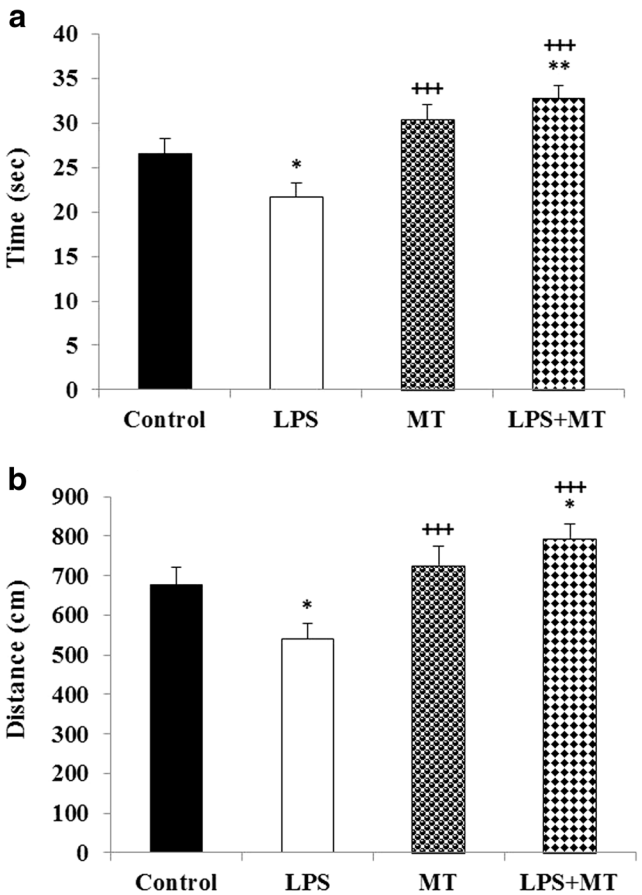

Fig. 3 Comparison of time spent (**a**) and traveled distance (**b**) in target quadrant between control, LPS, MT (moderate trained) and LPS + MT (LPS+ moderate trained) groups in probe day. The data are presented as mean ± standard error of the mean ($n = 8$ in each group). $^{*}P < 0.05$ and $^{**}P < 0.01$ compared to the control group and $^{+++}P < 0.001$ compared to the LPS group

MT and LPS + MT groups compared to the control group. In the animals of MT and LPS + MT groups; the latency to enter the dark compartment was significantly increased compared to the LPS group ($P < 0.01$–$P < 0.001$) (Fig. 4a).

The time spent in the dark compartment in the animals of the LPS group was significantly higher than the control group ($P < 0.01$–$P < 0.001$). There were no significant differences between the time spent in the dark compartment of MT and LPS + MT groups compared to the control group. In the animals of MT and LPS + MT group, the time spent in the dark compartment was significantly decreased compared to the LPS group ($P < 0.01$–$P < 0.001$) (Fig. 4b).

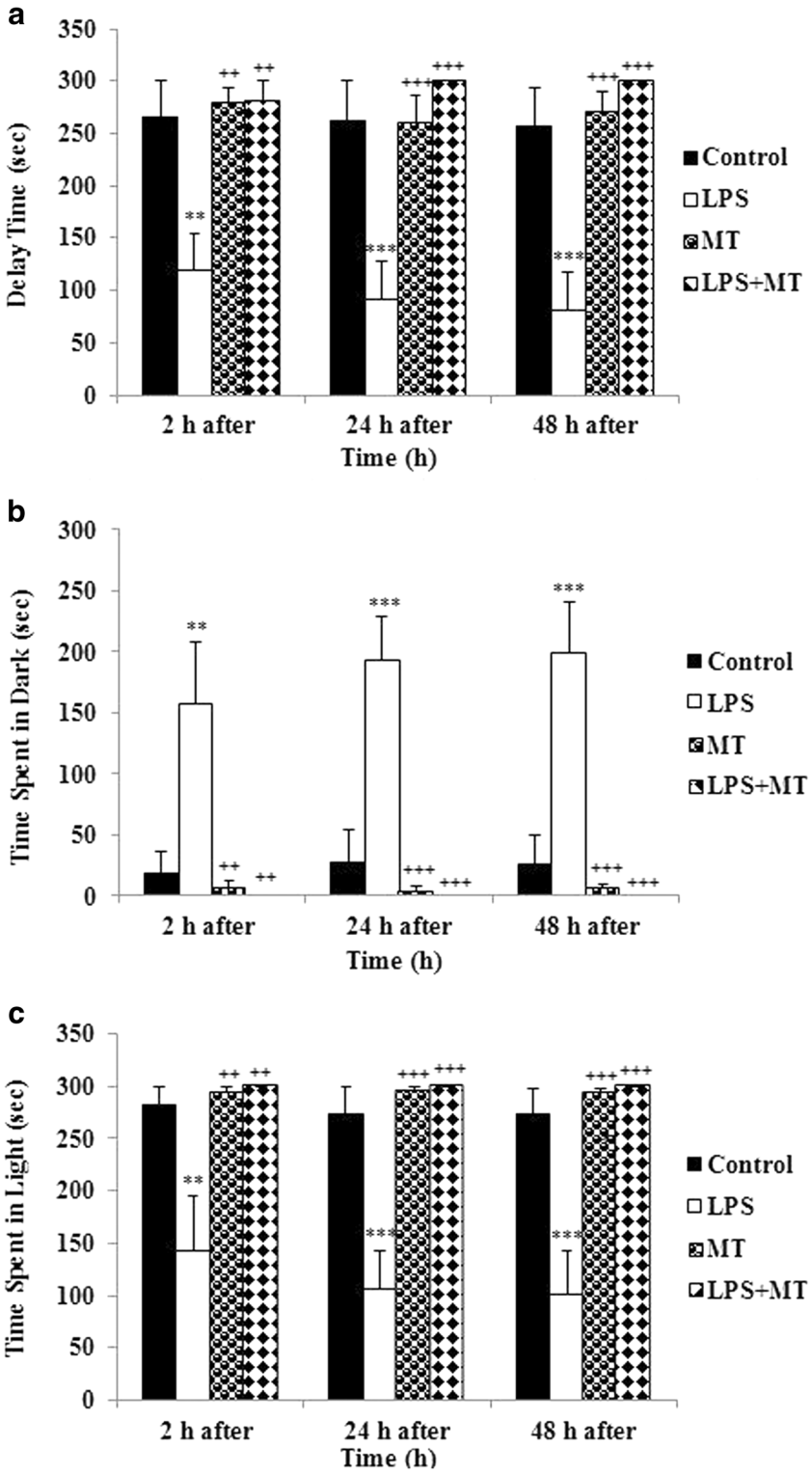

Fig. 4 Comparison of latency to enter the dark compartment (**a**), time spent in dark compartment (**b**) and time spent in light compartment (**c**) at 2, 24 and 48 h after receiving the electric shock between control, LPS, MT (moderate trained) and LPS + MT (LPS+ moderate trained) groups. The data are presented as mean ± standard error of the mean ($n = 8$ in each group). $^{**}P < 0.01$ and $^{***}P < 0.001$ compared to the control group and $^{++}P < 0.01$ and $^{+++}P < 0.001$ compared to the LPS group. Latency to enter the dark compartment of LPS + MT group: 280.62 ± 19.37 for 2 h, 300 ± 0 for 24 h, 300 ± 0 for 48 h. Time spent in dark compartment of LPS + MT group: 0.375 ± 0.375 for 2 h, 0 ± 0 for 24 h, 0 ± 0 for 48 h. Time spent in light compartment of LPS + MT group: 299.62 ± 0.375 for 2 h, 300 ± 0 for 24 h, 300 ± 0 for 48 h

The time spent in the light compartment in the animals of the LPS group was significantly lower than the control group ($P < 0.01$–$P < 0.001$). There were no significant differences between the light compartment time spent in the MT and LPS + MT groups compared to the control group. In the animals of MT and LPS + MT group, the time spent in the light compartment was significantly increased compared to the LPS group ($P < 0.01$–$P < 0.001$) (Fig. 4c).

Biochemical results

Hippocampal cytokine levels

The hippocampal levels of TNF-α in LPS and LPS + MT groups were significantly higher than the control group ($P < 0.05$–$P < 0.001$). There were no significant differences between the TNF-α levels of the MT group compared to the control group. The hippocampal levels of TNF-α in MT and LPS + MT groups were lower than the LPS group ($P < 0.001$) (Fig. 5a).

The hippocampal levels of IL-1β in MT and LPS groups were significantly higher than the control group ($P < 0.05$–$P < 0.001$). There were no significant differences in the IL-1β levels of the LPS + MT group compared to the control group. IL-1β hippocampal levels in MT and LPS + MT groups were lower than the LPS group ($P < 0.01$–$P < 0.001$) (Fig. 5b).

Our results showed that the hippocampal levels of CRP in the animals of the LPS group were significantly higher than the control group ($P < 0.01$). There were no significant differences in the CRP levels of MT and LPS + MT groups compared to the control group. Hippocampal levels of CRP in the LPS + MT group were lower than the LPS group, but these differences were not significant. Also, the hippocampus of the animals of the MT group had lower CRP levels compared to the LPS group ($P < 0.01$) (Fig. 5c).

Hippocampal stress oxidative markers

The MDA concentrations of the hippocampal tissues in MT, LPS, and LPS + MT groups were significantly higher and the thiol contents were lower than the control group ($P < 0.001$). In the hippocampal tissues of MT and LPS + MT groups, the MDA levels were significantly lower than the LPS group ($P < 0.001$) but in these groups, thiol contents were higher than the LPS group ($P < 0.001$) (Fig. 6a and b).

The hippocampal levels of CAT and SOD in LPS and LPS + MT groups were significantly lower than the control group ($P < 0.001$). There were no significant differences between the hippocampal CAT levels of the MT group compared to the control group. However, the hippocampal SOD levels were lower than the control group ($P < 0.01$). Additionally, the levels of CAT and SOD in the hippocampal tissues of MT and LPS + MT groups were significantly higher than the LPS group ($P < 0.001$). Moreover, the hippocampal

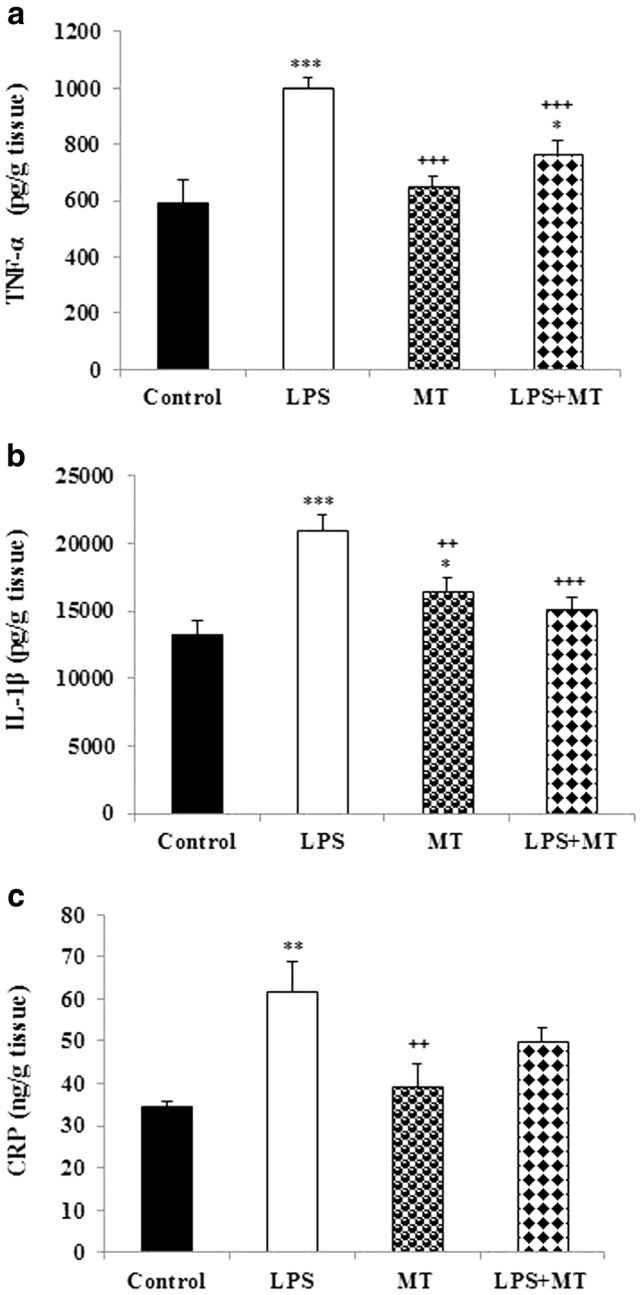

Fig. 5 Comparison of the hippocampal TNF-α (**a**), IL-1β (**b**) and CRP (**c**) levels between control, LPS, MT (moderate trained) and LPS + MT (LPS+ moderate trained) groups. The data are presented as mean ± standard error of the mean ($n = 8$ in each group). $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ compared to the control group and $^{++}P < 0.01$ and $^{+++}P < 0.001$ compared to the LPS group

CAT levels in the animals of the LPS + MT group were lower than the MT group ($P < 0.05$) (Fig. 6c and d).

Cortical stress oxidative markers

The MDA concentrations of cortical tissues were significantly higher and the thiol contents were lower in the LPS group compared to the control group ($P < 0.001$). There were no

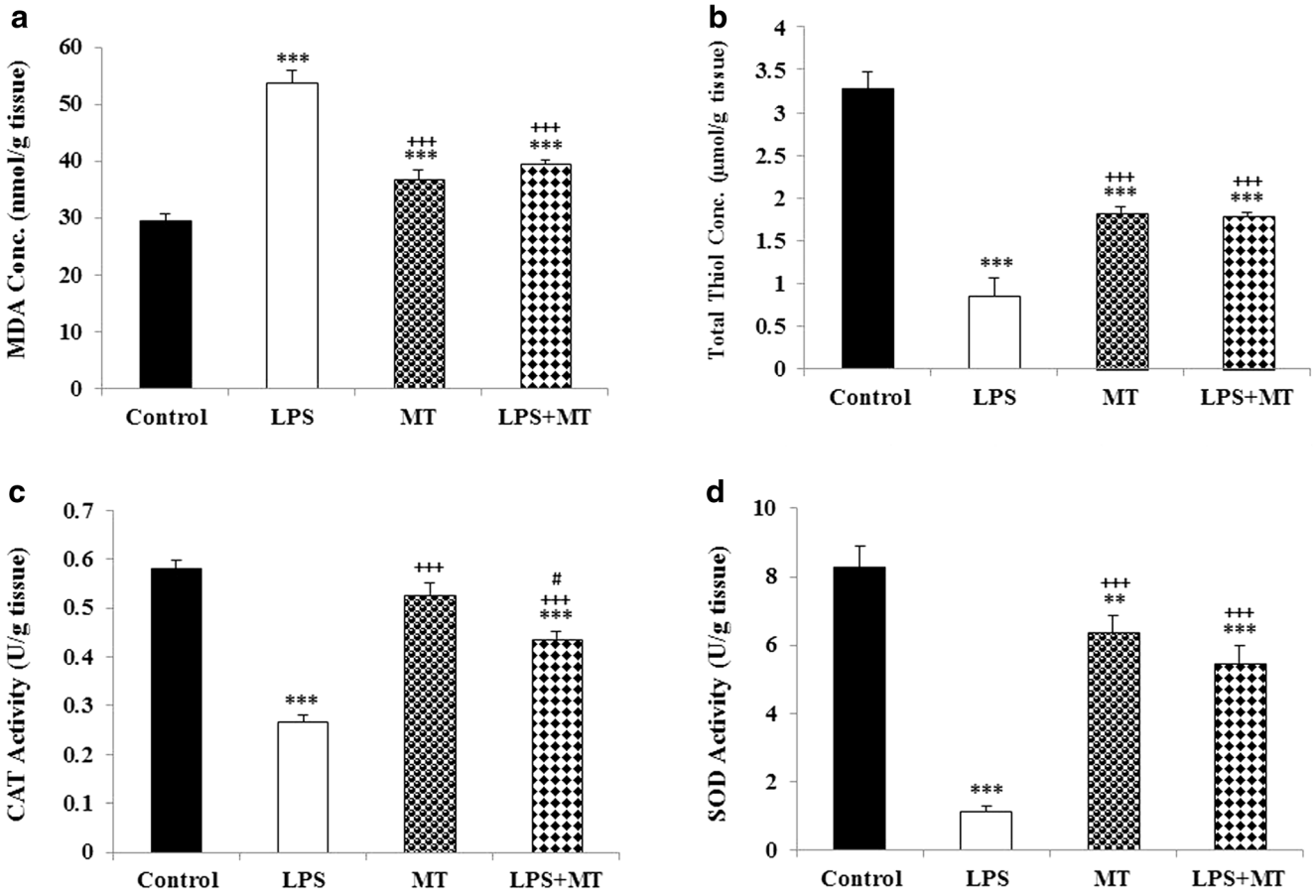

Fig. 6 Comparison of MDA concentrations (**a**), thiol contents (**b**), CAT (**c**) and SOD (**d**) levels in hippocampal tissues between control, LPS, MT (moderate trained) and LPS + MT (LPS+ moderate trained) groups. The data are presented as mean ± standard error of the mean ($n = 8$ in each group). $^{**}P < 0.01$ and $^{***}P < 0.001$ compared to the control group, $^{+++}P < 0.001$ compared to the LPS group and $^{\#}P < 0.05$ compared to the MT group

significant differences between the cortical MDA levels in MT and LPS + MT groups compared to the control group. However, the cortical thiol contents were lower than the control group ($P < 0.01$–$P < 0.001$). The animals of MT and LPS + MT groups had lower MDA concentrations and higher thiol contents in their cortical tissues compared to the LPS group ($P < 0.001$) (Fig. 7a and b).

The cortical levels of CAT and SOD in LPS and LPS + MT groups were significantly lower than the control group ($P < 0.01$–$P < 0.001$). There were no significant differences between the cortical CAT levels of the MT group compared to the control group. However, the cortical SOD levels were lower than the control group ($P < 0.05$). Additionally, the levels of CAT and SOD in the cortical tissues of MT and LPS + MT groups were significantly higher than the LPS group ($P < 0.001$) (Fig. 7c and d).

NO metabolite

The NO metabolite concentrations in the hippocampal tissues of LPS and LPS + MT groups were higher than the control group ($P < 0.05$–$P < 0.01$). There were no significant differences in the NO metabolite concentrations of the MT group compared to the control group. In the cortical tissues of the LPS group, the NO metabolite concentrations were higher than the control group ($P < 0.01$). There were no significant differences in the NO metabolite concentrations of MT and LPS + MT groups compared to the control group. Also, the NO metabolite concentrations in both hippocampal and cortical tissues of the MT group were lower than the LPS group ($P < 0.05$–$P < 0.01$) (Fig. 8).

Discussion

In the present study, the protective effects of moderate training against LPS-induced memory impairment in rats were evaluated. The behavioral test results showed that LPS administration induced impairment of spatial learning and memory, and passive avoidance memory in rats. Previous studies indicated that LPS is able to deteriorate spatial learning and memory in the MWM test and leads to cognitive impairments in PA test

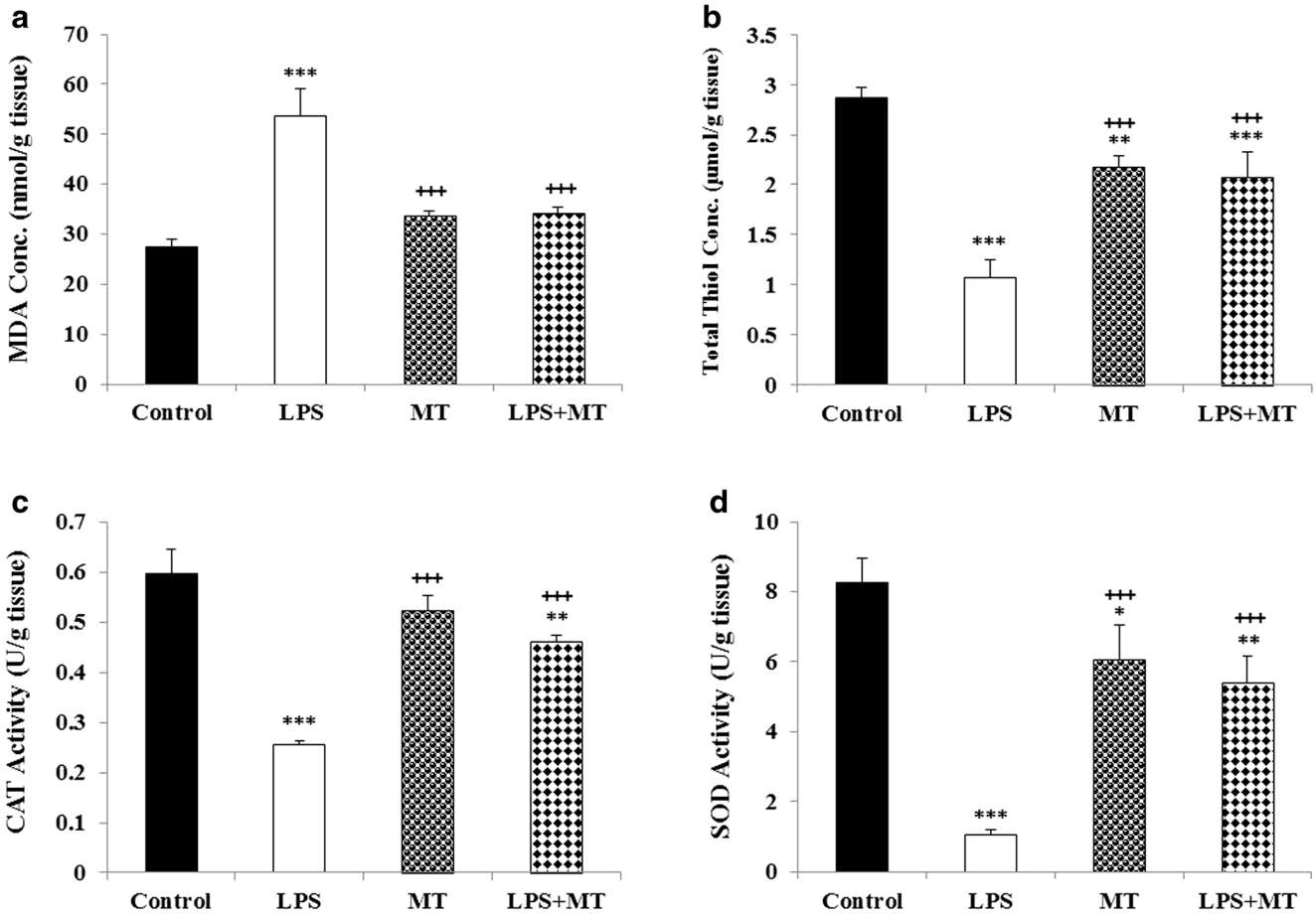

Fig. 7 Comparison of MDA concentration (**a**), thiol content (**b**), CAT (**c**) and SOD (**d**) levels in cortical tissues between control, LPS, MT (moderate trained) and LPS + MT (LPS+ moderate trained) groups. The data are presented as mean ± standard error of the mean ($n = 8$ in each group). $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ compared to the control group and $^{+++}P < 0.001$ compared to the LPS group

(Anaeigoudari et al. 2015; Anaeigoudari et al. 2016a; Bargi et al. 2017). Moreover, the direct injection of LPS into the hippocampus had a negative effect on spatial memory (Deng et al. 2012). Also, we did not observe any significant difference in the time latency to reach the platform between the groups in the first trial of the first day. These findings indicated that LPS administration (1 mg/kg, i.p.) did not impair the motor activity of rats in agreement with pervious study (Anaeigoudari et al. 2016b).

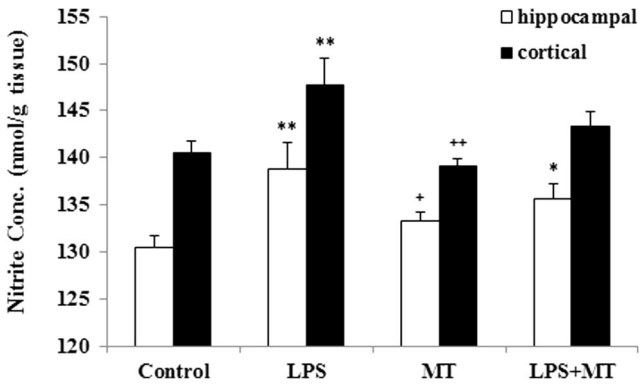

Fig. 8 Comparison of the hippocampal and cortical NO metabolite concentrations between control, LPS, MT (moderate trained) and LPS + MT (LPS+ moderate trained) groups. The data are presented as mean ± standard error of the mean ($n = 8$ in each group). $^{*}P < 0.05$ and $^{**}P < 0.01$ compared to the control group and $^{+}P < 0.05$ and $^{++}P < 0.01$ compared to the LPS group

It has been well-known that regular physical activity is very beneficial for brain health and function, by improving cognitive functions and delay the onset of memory decline (Rovio et al. 2005). In rodents, treadmill running reduced cognitive deficits, which have been induced by different brain damages through increasing the neuronal function, suppression neuronal loss, and increase in neurogenesis, long-term potentiation (LTP) and synaptic plasticity (Jahangiri et al. 2018; van Praag et al. 2005). In this study, moderate training improved LPS-induced memory impairment in the LPS + MT group while its effect on learning were not significant during 4-days of training. In agreement with these results, it was reported that moderate treadmill exercise (V = 10–14 m/min, 30–60 min/day for 4–5 weeks) attenuated cognitive impairments induced by LPS in MWM and PA tests (Kim et al. 2015b; Wu et al. 2007). The

positive effects of moderate intensity treadmill exercise were demonstrated in other models of memory deficit. In diabetic rats, treadmill exercise (V = 17 m/min, 40 min/day for 12 weeks) enhanced spatial memory performance in the MWM test (Reisi et al. 2009). It was also indicated that moderate treadmill exercise (V = 10 m/min, 30 min/day for 4 weeks) leads to better performance in PA test of aged gerbils after cerebral ischemia (Ahn et al. 2016).

The deleterious effects of LPS on learning and memory might be due to overproduction of inflammatory cytokines and induction of oxidative stress in the brain (Thomson and Sutherland 2005). In the current study, LPS administration increased the levels of TNF-α, IL-1β and CRP in the hippocampal tissues. It had been suggested that LPS impaired learning and memory through the induction of inflammatory responses and excessive production of TNFα, IL-6 and IL-1β (Hennigan et al. 2007; Thomson and Sutherland 2005). Other studies have shown that these inflammatory cytokines directly might affect the neuronal functions, LTP, glutamate release, glutamate receptor density and cellular signaling pathways associated with learning and memory (Czerniawski et al. 2015). Additionally, some studies determined that CRP contributes to memory deficit and the pathogenesis of AD (Lin et al. 2009).

In the present study, moderate exercise decreased the hippocampal levels of TNF-α and IL-1β in the animals of the LPS + MT group compared to the control group. Moreover, in the LPS + MT group, the hippocampal levels of CRP were lower than the LPS group, but these differences were not significant. Several studies had reported that regular physical activity might have an anti-inflammatory effect and ameliorated the increased levels of inflammatory cytokines such as TNF-α, IL-1β, IL-6 and CRP (Chen et al. 2012; Dvorakova-Lorenzova et al. 2006). The anti-inflammatory effects of exercise are mediated by reducing the pro-inflammatory cytokines levels, such as TNF-α, IL-1β and IL-6 as well as increasing the anti-inflammatory cytokine IL-10. During exercise training, contracting skeletal muscle IL-6 release induces production of anti-inflammatory cytokines, such as interleukin 1 receptor antagonist and IL-10, and inhibited TNF-α production (Gholamnezhad et al. 2014). Moreover, exercise increase the mitochondrial biogenesis and enzymatic activity (Steiner et al. 2011). It was demonstrated that mitochondrial lysates of microglial cell line in mice increased the production of NF-κB which is leading to the expression of pro-inflammatory cytokines mRNA, such as TNF-α and interleukin (IL)-8, and matrix metalloproteinase 8 (MMP-8) (Kovac et al. 2011; Sastre et al. 2006; Wilkins and Swerdlow 2016). Few studies investigated the effect of moderate training on the hippocampal levels of inflammatory cytokines in LPS-induced learning and memory impairment. Wu et al. reported that treadmill exercise (V = 10 m/min, 60 min/day for 5 weeks) did not change the LPS-stimulated hippocampal cytokine expressions (TNF-α and IL-1β). However, exercise improved neurogenesis and learning and memory impairment through restoring brain-derived neurotrophic factor (BDNF) signaling pathway (Wu et al. 2007). In LPS-induced neural toxicity and low-grade inflammation, the protective effect of exercise might be mediated through activation of the PI3K-AKT pathway, inhibition of doublecortin expression, increase of the BDNF, tyrosine receptor kinase B, and neuronal nuclei expression and cell proliferation, synaptic plasticity and neurogenesis in the hippocampal dentate gyrus (Wu, Chen et al. 2007, Kim, Sung et al. 2015, Jung and Kim 2017).

Oxidative damage plays an important role in many diseases of the nervous system (Kim et al. 2015a). Our results indicated that LPS increased the levels of MDA and decreased thiol contents, SOD and CAT activity in both cortical and hippocampal tissues. Scientific findings have shown that LPS triggers oxidative stress by stimulating the production of oxygen species (Tyagi et al. 2008). It was indicated that LPS injection increased MDA levels and decreased the activity of glutathione peroxidase, SOD and CAT (Kacem et al. 2015; Kheir-Eldin et al. 2001).

Regular physical activity plays a role in regulating the oxidant/antioxidant balance (Farzanegi et al. 2013). Mild and moderate intensity aerobic exercise stimulated the antioxidant system against free radicals. In fact, adaptation to exercise with the appropriate intensity can reduce oxidative stress markers and makes people more resistant to oxidative damage (Baradaran et al. 2013). In our study, moderate exercise decreased MDA concentrations and increased thiol contents and activity of SOD and CAT in both the hippocampal and cortical tissues of the LPS + MT group compared to the LPS group. We showed that moderate exercise, like an effective antioxidant, can play an important role in the alleviation of LPS-induced learning and memory impairment. To best of our knowledge, there were not any studies that investigated the effect of moderate training on stress oxidative markers in LPS-induced learning and memory. It had been indicated that moderate treadmill exercise (V = 15 m/min, 50 min/day for 8 weeks) can improve cognitive impairment by improve the oxidative state of the hippocampus in the aged rat (Yu et al. 2013). Physical activity might ameliorate the neurodegenerative effects of oxidative stress and inflammation in neural tissue through reduction of activated microglia and astrocytes number and expression of pro-inflammatory cytokines as well as increase antioxidant activity (Stigger et al. 2018).

In the current study, LPS increased the NO metabolite concentrations in both hippocampal and cortical tissues. In physiological concentration, NO as an important signaling molecule plays an essential role in learning and memory processes (Saffarzadeh et al. 2010); while in overproduction of NO, it reacts with oxygen species including superoxide to produce peroxynitrite which lead to lipid peroxidation, protein

oxidation and oxidation of thiols and apoptosis (Beheshti et al. 2017). Similar to our results, some studies reported that LPS-induced learning and memory impairment through the overproduction of NO metabolite in brain (Anaeigoudari et al. 2015; Bargi et al. 2017). In addition, moderate training decreased the NO metabolite concentrations in the LPS + MT group compared to the LPS group, but these differences were not significant. The effect of moderate training on NO metabolite in LPS-induced learning and memory had been not evaluated in previous studies. Therefore, the effect of moderate training on different isoforms of NOS in LPS-induced learning and memory should be investigated in future studies.

Taken together, in this study the biochemical results of LPS and LPS + MT groups were approved by behavioral findings. So LPS might lead to behavioral and memory impairments by induction of neuroinflammation and oxidative damage, while moderate training prevented LPS-induced behavioral impairments by attenuating the hippocampal cytokine levels and brain oxidative damage. But, there were not complete associations between behavioral and biochemical results of MT group. In this study, moderate training non-significantly improved the results of behavioral tests compared to control group. Therefore, exercise might not significantly improve normal and physiological values of memory (Roig et al. 2013), but our results and previous studies evidence have shown its preventive and therapeutic non-pharmacological effects in neuroinflammatory and neurodegenerative disorders. Although it is suggested that exercise might increase both ROS and antioxidant enzyme (Radak et al. 2017). In the present study, exercise increased the hippocampal IL-1β and MDA levels and decreased thiol contents and SOD activity in both hippocampal and cortical tissues of MT group compared to control group. As our limitation, we did not measured hippocampal neurotrophins or histological changes to more elaborate these changes. Moreover, there are few studies investigated exercise effects in normal condition, as in one study the behavioral results were the same as our findings in MT group (Wu et al. 2007). In addition, inflammation and LPS injection might induces sickness behavior in animals. Our results did not show decline in motor activity and animals' weight loss (data was not showed), but as another limitation of this study all parameters of animals behavioral assessment were not evaluated. Therefore, the above mentioned questions should be replied in future studies.

Conclusion

In conclusion, the results of the current study indicated that LPS administration impairs learning and memory by induction the behavioral impairment and increase in the levels of inflammatory cytokines and oxidative stress markers of the brain. Moreover, our findings showed that moderate exercise improved LPS-induced learning and memory impairments, hippocampal cytokine levels and brain tissues oxidative damage. However, exercise might not significantly improve learning and memory in normal animals.

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Compliance with ethical standards

Conflict of interests The authors declare no conflicts of interests in this study.

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