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ORIGINAL ARTICLE

Berberine ameliorates lipopolysaccharide-induced learning and memory deficit in the rat: insights into underlying molecular mechanisms

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Abstract

Systemic lipopolysaccharide (LPS) triggers neuroinflammation with consequent development of behavioral and cognitive deficits. Neuroinflammation plays a crucial role in the pathogenesis of neurodegenerative disorders including Alzheimer's disease (AD). Berberine is an isoquinoline alkaloid in Berberis genus with antioxidant and anti-inflammatory property and protective effects in neurodegenerative disorders. In this research, beneficial effect of this alkaloid against LPS-induced cognitive decline was assessed in the adult male rats. LPS was intraperitoneally administered at a dose of 1 mg/kg to induce neuroinflammation and berberine was given via gavage at doses of 10 or 50 mg/kg, one h after LPS, for 7 days. Treatment of LPS group with berberine at a dose of 50 mg/kg (but not at a dose of 10 mg/kg) improved spatial recognition memory in Y maze, performance in novel object recognition task (NORT), and prevented learning and memory dysfunction in passive avoidance tasks. Furthermore, berberine lowered hippocampal activity of acetylcholinesterase (AChE), malondialdehyde (MDA), protein carbonyl, activity of caspase 3, and DNA fragmentation and improved antioxidant capacity through enhancing glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase, and glutathione (GSH). Besides, berberine attenuated inflammation-related indices, as was evident by lower levels of nuclear factor-kappa B (NF-κB), toll-like receptor 4 (TLR4), tumor necrosis factor α (TNFα), and interleukin 6 (IL-6). Berberine also appropriately restored hippocampal 3-nitrotyrosine (3-NT), cyclooxygenase 2 (Cox 2), glial fibrillary acidic protein (GFAP), sirtuin 1, and mitogen-activated protein kinase (p38 MAPK) with no significant alteration of brain-derived neurotrophic factor (BDNF). In summary, berberine could partially ameliorate LPS-induced cognitive deficits via partial suppression of apoptotic cascade, neuroinflammation, oxido-nitrosative stress, AChE, MAPK, and restoration of sirtuin 1.

Keywords Berberine · Lipopolysaccharide · Learning and memory · Apoptosis · Oxidative stress · Neuroinflammation

Abbreviations

3-NT	3-nitrotyrosine
AChE	acetylcholinesterase
AD	Alzheimer's disease
BDNF	brain-derived neurotrophic factor
Cox 2	cyclooxygenase 2
GFAP	glial fibrillary acidic protein
GSH	glutathione
GPx	glutathione peroxidase
IL-6	interleukin 6
LPS	lipopolysaccharide
MDA	malondialdehyde
MAPK	mitogen-activated protein kinase
NF-κB	nuclear factor-kappa B
NORT	novel object recognition task
RNS	reactive nitrogen species
ROS	reactive oxygen species
Sirt 1	sirtuin 1
SOD	superoxide dismutase
TLR4	toll-like receptor 4
TNFα	tumor necrosis factor α

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Introduction

Neuroinflammation is a substantial hallmark of neurodegenerative disorders including Alzheimer's disease (AD) and Parkinson's disease (Fischer and Maier 2015). Neuroinflammation and mitochondrial dysfunction in neurodegenerative diseases are also associated with oxidative stress due to extreme production and release of reactive oxygen (ROS) and nitrogen (RNS) species with subsequent neuronal damage (Fischer and Maier 2015; Islam 2017). Lipopolysaccharide (LPS) is a constituent of the cell wall of Gram-negative bacteria that is routinely used to develop neuroinflammation (Mayer 1998; Pardon 2015). Systemic LPS is associated with microglial activation (Mayer 1998) and enhances release of various inflammatory mediators/cytokines (Qiao et al. 2011). Systemic LPS also induces behavioral alterations such as cognitive deficit and dementia (Zakaria et al. 2017). Early prevention of neuroinflammation and management of oxidative stress could lower incidence of some neurological disorders (Cayero-Otero et al. 2018; Morris et al. 2018).

Berberine is an organic compound isolated from various medicinal herbs such as *Berberis vulgaris* with multi-faceted defensive capability (Jiang et al. 2015). Berberine agonist has shown neuroprotective effect against dysfunction of learning and memory in traumatic brain injury via modulation of Sirt 1/p38 MAPK expression (Wang and Zhang 2018) and it is capable to exert neuroprotective effect against heavy metals-induced neurotoxicity and Alzheimer's-like disease in rats (Hussien et al. 2018). In addition, berberine has conferred neuroprotection in a model of focal cerebral ischemia through down-regulation of pro-inflammatory and up-regulation of anti-inflammatory cytokines (Maleki et al. 2018). Moreover, berberine could ameliorate ethanol-induced oxidative stress and memory decline in rats (Patil et al. 2015) and alleviate mercury chloride-induced neurotoxicity due to its anti-inflammatory and anti-apoptotic activity and augmentation of antioxidant capacity (Abdel Moneim 2015). In addition, berberine could attenuate LPS-induced inflammation and apoptosis in β-cells, partly mediated through p65 NF-κB pathway (Wang 2013) and is able to up-regulate BDNF expression in hippocampus following exogenous corticosterone (Shen et al. 2016). Therefore, this study was undertaken to investigate whether berberine could ameliorate LPS-induced learning and memory deficit in the rat and unravel some of its modes of action.

Materials and methods

Experimental design

Adult male albino Wistar rats (185–220 g; 8–10 weeks) were obtained from Pasteur's Institute of Tehran (Iran). The animals had free access to tap water and standard rat chow and were maintained in vivarium with controlled humidity and temperature (22–24 °C) and under 12-h light-dark cycle. All behavioral experiments were conducted during the light phase of the cycle (between 10:00 a.m. and 05:00 p.m.) in a sound-attenuated and air-conditioned room. The animals were transferred to laboratory 60 min before conductance of tests for adequate adaptation. All experimental methods involving animals and their care were consistent with NIH guidelines for the care and use of laboratory animals. The research was also approved by Ethics Committee of Shahed University in 2016 (Certificate No. IR.Shahed.REC.1395.129).

The rats ($n = 40$) were assigned in random to the following equal-sized groups, i.e. control, berberine 50-treated control, LPS, berberine 10-, and berberine 50-treated LPS. To develop neuroinflammation, LPS from *Escherichia coli* (SigmaAldrich, USA; 0111:B4 serotype) was freshly dissolved in cold 0.9% saline solution and intraperitoneally administered at a dose of 1 mg/kg (Li et al. 2017). Systemic administration of LPS is generally used to produce neuroinflammation in rodents (Czerniawski et al. 2015; Henry et al. 2008). Animals in the control and LPS groups were given the vehicle Kolliphor® EL using gavage. Berberine hydrochloride (Santa Cruz Biotechnology, Inc., USA) was orally given at doses of 10 or 50 mg/kg/day, 60 min after LPS, for 7 days. We administered berberine 60 min after LPS and behavioral tests were performed 2 h after berberine. This administration timing was according to LPS and berberine pharmacokinetics. In this respect, it has been shown that cytokines release including TNFa occurs within 1 h after LPS challenge (Patrignani et al. 2010). For berberine, after its oral administration, a time range of 2–24 h is needed for attaining its maximum concentration at the tissue level (Tan et al. 2013). However, time to the maximum concentration in different tissues is various. In other words, we should await at least 2 h to have initiation of beneficial effect of berberine. Furthermore, dose of berberine (50 mg/kg) was chosen on the basis of its effect in prevention of dopaminergic neuronal loss and hippocampal apoptosis in a mouse model of Parkinson's disease (Kim et al. 2014) and its effect in amelioration of oxidative stress and astrogliosis in the hippocampus of diabetic rats (Moghaddam et al. 2014). Behavioral experiments were conducted 2 h after berberine administration by trained experimenters unaware of interventions. Behavioral tests consisting of Y-maze (on day 2), novel object recognition (on day 3), and passive avoidance tasks (on days 4–7) were done at week 1. Conductance of behavioral tests on different days following LPS challenge was in accordance with earlier reports (Gu et al. 2015; Mirahmadi et al. 2018; Vasconcelos et al. 2014; Zarezadeh et al. 2017).

Y-maze task

This test is a reliable and non-invasive task for assessment of short-time recognitive working memory in rodents by

measurement of spontaneous alternation. The maze was made of black-painted Plexiglas and consisted of three arms and an equilateral triangular central area. The animals in this task were tested according to the protocol described before (Nitta et al. 2002; Roghani et al. 2006). In short, each rat was positioned at the end of one arm and allowed to pass freely for 8 min. Arm entries was serially recorded. Alternation was taken as consecutive entries into the three arms on overlapping triplets. Finally, the value (total correct alternating sequence/total alternating sequence × 100) was calculated to assess the spatial recognition ability of animals in addition to evaluation of their locomotor activity. All arms were cleaned using 10% ethanol to exclude the possible effect of odorous cues on animal's performance between sessions,

Novel object recognition task (NORT)

This task evaluates novel object recognition memory by the differences in the exploration time of novel and familiar objects and is considered a valuable measure of cognition in rodents (Antunes and Biala 2012). Our rules for this task have been mentioned in an earlier research (Stuart et al. 2013). Concisely, each rat received two consecutive 5 min object exploration trials parted by a 4 h inter-trial interval. The objects used here had never been seen by the animals prior to testing. Rats explored two similar objects (two red plastic cubic boxes with a dimension of 6x6x6 cm) during the first (familiarization) trial, and one of the objects was replaced with a novel one (a blue metallic cylinder with a diameter of 6 cm and a height of 6 cm) in the second testing session. Object placement was counterbalanced within each experimental group for avoidance of possible biases due to a preference that rodents may have for an object or its position. Exploration of objects, defined as chewing, licking, sniffing, or approximating vibrissae at ≤1 cm from the object was obtained and discrimination ratio was determined from the formula: (t [novel]-t [familiar]) / (t [novel] + t [familiar]) *100. The working area and objects were cleaned with 10% ethanol between trials.

Passive avoidance test

The passive avoidance task evaluates the conditioned learning and memory ability of rodents and performed as previously reported (Baluchnejadmojarad et al. 2017). Concisely, rats tested in a shuttle box consisting of two chambers, i.e. illuminated and dark, interconnected by a door and with grid floor. On the first and second days, animals were adapted to device for 5 min. On the third day, rats performed acquisition trial in the shuttle box. After a 5 min period, the light was turned on and door was elevated and the latency to enter the dark chamber was recorded as initial latency. When the rat entered the dark chamber, the door was lowered and the animal received an electric foot shock (1 mA, 1 s). After 1 day, the test was repeated. The animal was placed in the illuminated chamber and the time required to enter the dark chamber was recorded as step-through latency with cut-off set at 150 s.

Determination of oxido-nitrosative stress, neuroinflammation, apoptosis, GFAP, sirtuin 1, BDNF, and p38 MAPK

Seven days after first LPS injection, hippocampal tissue ($n = 6$ from each group) was isolated from deeply anesthetized rats under diethyl ether, rinsed with ice-cold phosphate-buffered saline (pH 7.4) and 5% homogenate was prepared in ice-cold Tris–HCl buffer (150 mM, pH 7.4) having protease inhibitor cocktail from SigmaAldrich (USA). After centrifuging the homogenate, the supernatant was separated for further experiments.

Part of cognitive deficit in neuroinflammation is attributed to alterations of acetylcholinesterase activity (AChE) (Tyagi et al. 2010). AChE activity was assessed in accordance with degradation of acetylthiocholine iodide into a product that could bind to 5,5-dithiobis-2-nitrobenzoic acid with development of a yellow color (Ellman et al. 1961). The reaction was followed for 5 min at 412 nm and enzyme activity was shown as mmole of substrate/min/g protein.

LPS challenge leads to enhanced lipid peroxidation in brain tissue (Al-Amin et al. 2018). Tissue quantity of malondialdehyde (MDA) as a reliable biomarker of lipid peroxidation and oxidative stress was determined by thiobarbituric acid method and final result was shown as nmole/mg of protein with tetraethoxypropane as its standard (Wang et al. 2005).

Protein carbonyl quantity as another biomarker of oxidative stress and as a valid parameter of protein oxidation was measured according to a previous report (Levine et al. 1990; Shagirtha and Pari 2011). In summary, homogenate was re-centrifuged at 10,000 g for 20 min to separate cytosolic fraction and this fraction was mixed with trichloroacetic acid at equal ratios. Afterwards, dinitrophenyl hydrazine was added and it was kept for 60 min at room temperature. Pellet was washed 3 times with a mixture of ethanol-ethyl acetate and the pellet was dissolved using guanidine hydrochloride and absorbance was obtained at 366 nm.

Superoxide dismutase (SOD) activity was measured as indicated before (Wang et al. 2005). In brief, supernatant was incubated with xanthine and xanthine oxidase in potassium phosphate buffer for 40 min, and nitroblue tetrazolium was added. Blue formazan production was followed at 550 nm.

Determination of catalase activity as an enzyme responsible for degradation of hydrogen peroxide was done in accordance with Claiborne's method (Claiborne 1985). In summary, H_2O_2 was added to a mixture of potassium phosphate buffer and supernatant and its rate of decomposition was followed at 240 nm.

Measurement of glutathione peroxidase (GPx) activity with protective potential against oxidative damage was done according to an earlier method by Paglia and Valentine with minor modification (Paglia and Valentine 1967). In this test, absorbance change in the presence of H_2O_2, reduced glutathione, NADPH, sodium azide, and glutathione reductase was followed at 365 nm.

Glutathione (GSH) content as a non-enzymatic antioxidant defensive system was measured as indicated before (Ellman 1959; Raoufi et al. 2015; Sedlak and Lindsay 1968). In this test, the supernatant was re-centrifuged in the presence of 5% TCA. To obtained supernatant, phosphate buffer (pH 8.4), 5′5 dithiobis (2-nitrobenzoic acid) (DTNB) and distilled water was added and the absorbance was read at 412 nm.

Bradford method using Coomassie brilliant blue G-250 was applied for determination of total protein content with BSA as its standard (Bradford 1976).

Since LPS exposure also causes enhanced apoptosis in brain tissue (Lykhmus et al. 2017), we measured caspase 3 activity as an apoptotic pathway element based on hydrolysis of the p-nitroaniline (pNA) and according to an earlier investigation (Movsesyan et al. 2002). In summary, 20 μl of tissue homogenate was incubated with assay buffer containing 50 nmol/l HEPES, pH 7.4, 0.2% CHAPS, 20% sucrose, 2 mmole/l EDTA, 10 mmole/l dithiothreitol, and 50 μmole/l of chromogenic pNA specific apopain substrate (Z-Asp-IH-Val-Asp-pNA) at 37 °C. The quantity of chromogenic pNA formed was measured at a wavelength of 450 nm and the obtained values were shown as optical density (OD). In addition, intensity of DNA fragmentation as a consistent indicator of apoptotic process was also measured using Cell Death Detection ELISA kit (Roche Diagnostics, Germany).

LPS challenge is associated with enhanced expression and/or release of inflammatory mediators such as nuclear factor-κB (NF-κB p65), tumor necrosis factor α (TNFα), toll-like receptor 4 (TLR4), and interleukin 6 (IL-6) in addition to reduction of brain-derived neurotrophic factor (BDNF) in the hippocampus (Vasconcelos et al. 2014). Besides, systemic LPS elevates glial fibrillary acidic protein (GFAP) as a specific biomarker of astrocytes and mitogen-activated protein kinase (MAPK) (Fan et al. 2013) in addition to disturbance in sirtuin 1 expression (Liu et al. 2016). Hippocampal level of NF-κB p65, TNFα, TLR4, IL-6, 3-nitrotyrosine (3-NT) as a biomarker of nitrosative stress, GFAP, cyclooxygenase 2 (Cox2) as an inflammatory biomarker, BDNF, p38 MAPK, and sirtuin 1 was determined using enzyme-linked immunosorbent assay (for NF-κB p65 and 3-NT from Abcam (USA), for TLR4, IL-6, Cox2, and GFAP from Cloud-Clone Corp. (USA), for sirtuin 1, BDNF and p38 MAPK from MyBioSource, Inc. (USA), and for TNFα from SigmaAldrich (USA)). The absorbance of microwells was read at 450 nm by Synergy HT microplate reader (BioTek, USA) and values were reported as their concentration (*w*/*v*) or as fold changes versus control group.

Statistical analysis

All data are presented as means ± S.E.M. Statistical software SigmaPlot (version 12) was used for data analysis. After verification of parametric distribution of data using Kolmogorov-Smirnov statistical test, we applied one-way ANOVA and multiple comparison Tukey *post-hoc* tests. In all computations, significance level was taken at $p < 0.05$.

Results

Behavioral findings

Figure 1a displays performance of animals in Y-maze task that evaluates single-trial short-term working spatial recognition memory in rodents. Obtained data showed that alternation percentage in LPS ($p < 0.001$) and LPS + berberine 10 ($p < 0.01$) groups was significantly lower versus control. In addition, berberine administration to LPS group at a dose of 50 mg/kg significantly elevated alternation score in comparison with LPS group ($p < 0.05$). Moreover, control+berberine 50 group showed no significant change when compared to control. In the meantime, total number of entries was counted for this maze as an indicator of animal's locomotor activity. Findings showed that there exists no significant differences between the groups regarding this parameter (data not presented).

We also take advantage of NORT test to assess recognition memory capability in tested animals. Our findings revealed that there exists a significant decrease in discrimination ratio in LPS ($p < 0.001$) and LPS + berberine 10 ($p < 0.01$) groups as compared to control group and no such difference was obtained for LPS + berberine 50 group. Meanwhile, discrimination ratio in LPS + berberine 50 group was significantly more as compared to LPS-challenged rats ($p < 0.05$) (Fig. 1b). Again, no significant alteration was obtained in control+berberine 50 group versus control.

We used passive avoidance test to assess conditional learning and memory ability of tested animals through evaluation of retention and recall, as indicated by initial and step-through latencies (Fig. 1c). Regarding initial latency, no statistically significant difference was noted amongst the experimental groups. On the contrary, LPS ($p < 0.001$) and LPS + berberine 10 ($p < 0.01$) groups had a significant reduction of step-through latency as compared to control. In addition, LPS + berberine 50 did not show a significant reduction of step-through latence versus control group. Meanwhile, berberine treatment of LPS group at a dose of 50 mg/kg significantly elevated this latency ($p < 0.05$). Besides, control+berberine 50 group did not show a significant alteration of this parameter relative to control.

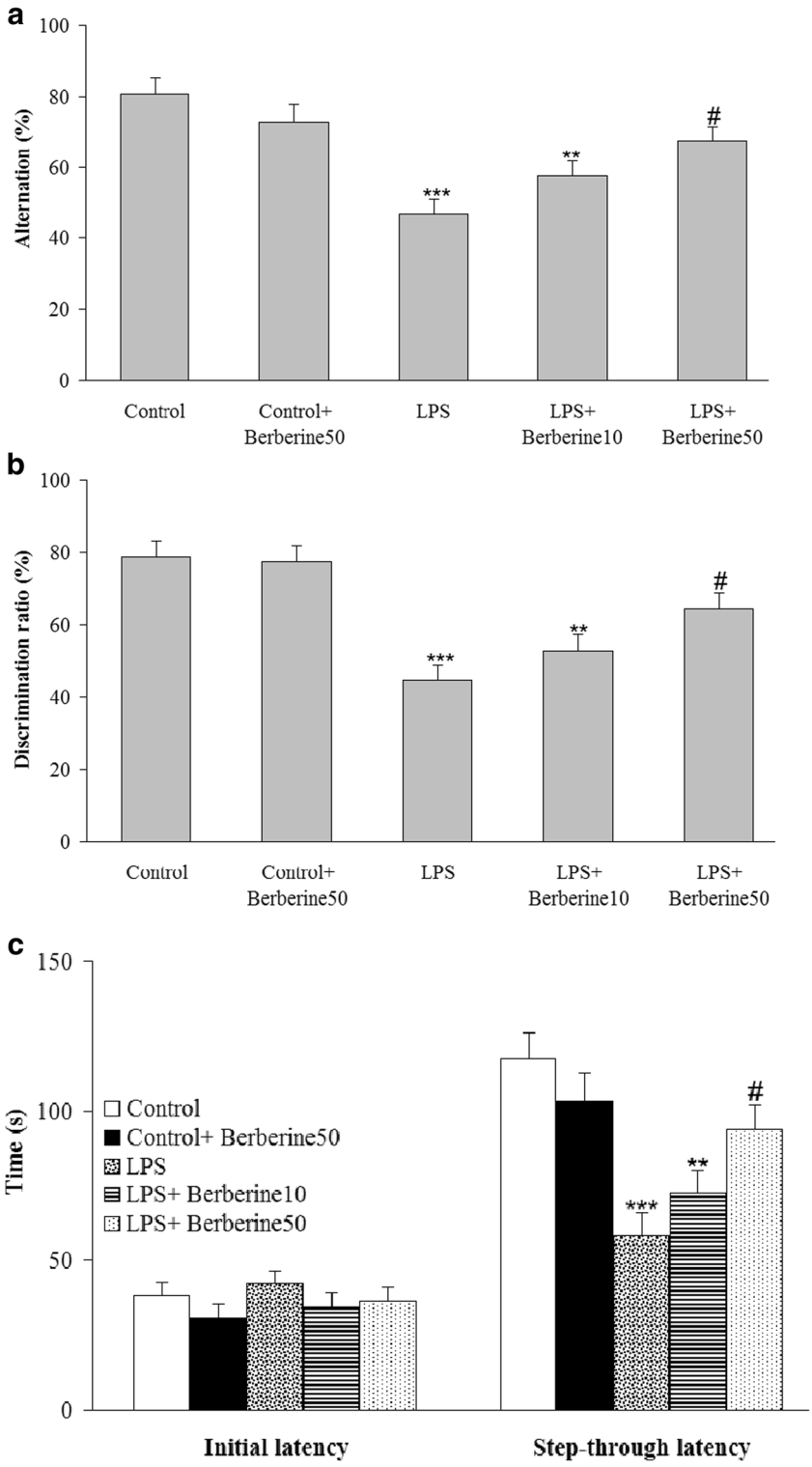

Fig. 1 Alternation behavior in Y-maze test (**a**), performance of animals in novel object recognition task (as shown by discrimination ratio) (**b**), and initial and step-through latencies in passive avoidance test (**c**). ** $p < 0.01$, *** $p < 0.001$ (as compared to control); # $p < 0.05$ (as compared to LPS)

Hippocampal level and/or activity of AChE, oxidative stress- and apoptosis-related biomarkers

Related data are presented in Table 1. In this respect, activity of AChE was significantly greater in LPS ($p < 0.001$) and LPS + berberine 10 ($p < 0.001$) groups and no such significant elevation was obtained for LPS + berberine 50 group as compared to control group. In addition, LPS + berberine 50 group exhibited a significantly lower activity of AChE when compared to LPS ($p < 0.05$). Likewise, LPS group had a significantly greater content of MDA ($p < 0.001$), protein carbonyl ($p < 0.001$), caspase 3 activity ($p < 0.001$), DNA

Table 1 Hippocampal level and/or activity of AChE, oxido-nitrosative stress- and apoptosis-related biomarkers

	Control	Control + Berberine 50	LPS	LPS + Berberine 10	LPS + Berberine 50
AChE (mmole/min/g) n = 6/group	60.1 ± 5.2	62.7 ± 5.1	100.6 ± 6.4***	98.8 ± 5.9***	74.9 ± 5.4#
MDA (nmole/mg) n = 6/group	6.35 ± 0.43	5.32 ± 0.45	9.74 ± 0.57***	8.61 ± 0.52*	7.65 ± 0.47#
Protein carbonyl (nmole/mg) n = 6/group	4.17 ± 0.31	3.94 ± 0.35	6.91 ± 0.39***	6.08 ± 0.43*	4.83 ± 0.37##
SOD (unit/mg) n = 6/group	10.9 ± 0.47	10.1 ± 0.54	6.1 ± 0.51***	6.5 ± 0.49***	8.4 ± 0.56*#
Catalase (unit/mg/min) n = 6/group	11.32 ± 0.53	11.83 ± 0.62	6.71 ± 0.68***	7.62 ± 0.65**	9.86 ± 0.67#
GPx (unit/mg) n = 6/group	3.91 ± 0.26	3.67 ± 0.29	1.92 ± 0.27***	2.37 ± 0.32**	3.29 ± 0.24#
GSH (nmole/mg) n = 6/group	5.47 ± 0.31	5.76 ± 0.34	2.83 ± 0.27***	3.58 ± 0.32**	4.85 ± 0.29##
Caspase 3 (OD) n = 6/group	0.31 ± 0.02	0.35 ± 0.02	0.58 ± 0.03***	0.54 ± 0.03***	0.43 ± 0.03**#
DNA fragmentation (OD) n = 5/group	0.31 ± 0.03	0.38 ± 0.03	0.88 ± 0.05***	0.78 ± 0.05***	0.56 ± 0.05*#

All data are presented as mean ± S.E.M.

* p < 0.05, ** p < 0.01, *** p < 0.001 (versus Control); # $p < 0.05$, ## $p < 0.01$ (versus LPS)

fragmentation (p < 0.001) and lower level or activity of SOD (p < 0.001), catalase (p < 0.001), GPx (p < 0.001), and GSH (p < 0.001) as compared to control. On the contrary, berberine administration at a dose of 50 mg/kg, but not at a dose of 10 mg/kg, to LPS group significantly reversed inappropriate deviations regarding MDA ($p < 0.05$), protein carbonyl ($p < 0.01$), SOD (p < 0.05), catalase (p < 0.05), GPx (p < 0.05), GSH (p < 0.01), caspase 3 activity (p < 0.05), and DNA fragmentation (p < 0.05) versus LPS-injected rats. In addition, berberine at a dose of 10 mg/kg did not produce a significant change in LPS group.

Hippocampal 3-NT, sirtuin 1, GFAP, BDNF, p38 MAPK, and inflammation-related findings

With respect to inflammation-related biochemical variables as shown in Table 2, hippocampal level of NF-κB p65 ($p < 0.001$), TLR4 (p < 0.001), TNFα (p < 0.001), and IL-6 (p < 0.001) noticeably and significantly raised in LPS and LPS + berberine 10 groups as compared to control. Meanwhile, hippocampal level of NF-κB p65 ($p < 0.05$), TLR4 ($p < 0.01$), and TNFα (p < 0.05) was significantly greater in LPS + berberine 50 group when compared to control group. On the other hand, treatment of LPS group with berberine at a dose of 50 mg/kg, but not at a dose of 10 mg/kg, significantly and appropriately reversed back NF-kB ($p < 0.001$), TLR4 ($p < 0.01$), TNFα ($p < 0.05$), and IL-6 ($p < 0.01$) as compared to LPS group.

Figure 2 displays biochemical findings for hippocampal level of 3-NT as a specific marker of nitrosative stress, Cox2 as an inflammatory biomarker, GFAP as a consistent and valid indicator of astrocyte activity and astrogliosis, the protective protein sirtuin 1, BDNF, and p38 MAPK in different groups. In this respect, hippocampal level of 3-NT, Cox2, GFAP, and MAPK was significantly greater ($p < 0.01$–0.001) and level of Sirtuin 1 was significantly lower (p < 0.01–0.01) in LPS and LPS + berberine 10 groups as compared to control. In addition, berberine treatment of LPS group at a dose of 50 mg/kg significantly decreased 3-NT (p < 0.01), Cox 2 (p < 0.01), GFAP ($p < 0.05$), p38 MAPK (p < 0.05), and also significantly up-regulated sirtuin 1 (p < 0.01) with no significant change of BDNF in comparison with vehicle-treated LPS-challenged group. In addition, berberine at a dose of 10 mg/kg did not induce a significant beneficial change.

Discussion

The findings of this research demonstrated that berberine dose-dependently and partially prevents LPS-induced learning and memory dysfunctions as evidenced by better performance of animals in Y-maze, novel object recognition, and passive avoidance tests and its protective/reversal effect is

Table 2 Hippocampal level of inflammation-related biomarkers

	Control	Control + Berberine 50	LPS	LPS + Berberine 10	LPS + Berberine 50
NF-kB (ng/ml) $n = 5$/group	4.61 ± 0.58	5.47 ± 0.56	12.09 ± 0.75***	10.67 ± 0.72***	7.58 ± 0.61*###
TLR4 (ng/ml) n = 5/group	2.86 ± 0.34	3.47 ± 0.38	7.64 ± 0.45***	6.97 ± 0.46***	5.12 ± 0.41**##
TNFα (pg/ml) n = 5/group	89.5 ± 12.8	103.6 ± 14.5	251.7 ± 16.8***	225.3 ± 18.3***	168.7 ± 16.4*#
IL-6 (pg/ml) n = 5/group	46.1 ± 4.5	42.7 ± 5.3	97.6 ± 6.2***	89.1 ± 5.5***	65.3 ± 4.9##

All data are presented as mean ± S.E.M.

* p < 0.05, ** p < 0.01, *** $p < 0.001$ (versus Control); # p < 0.05, ## p < 0.01, ### p < 0.001 (versus LPS)

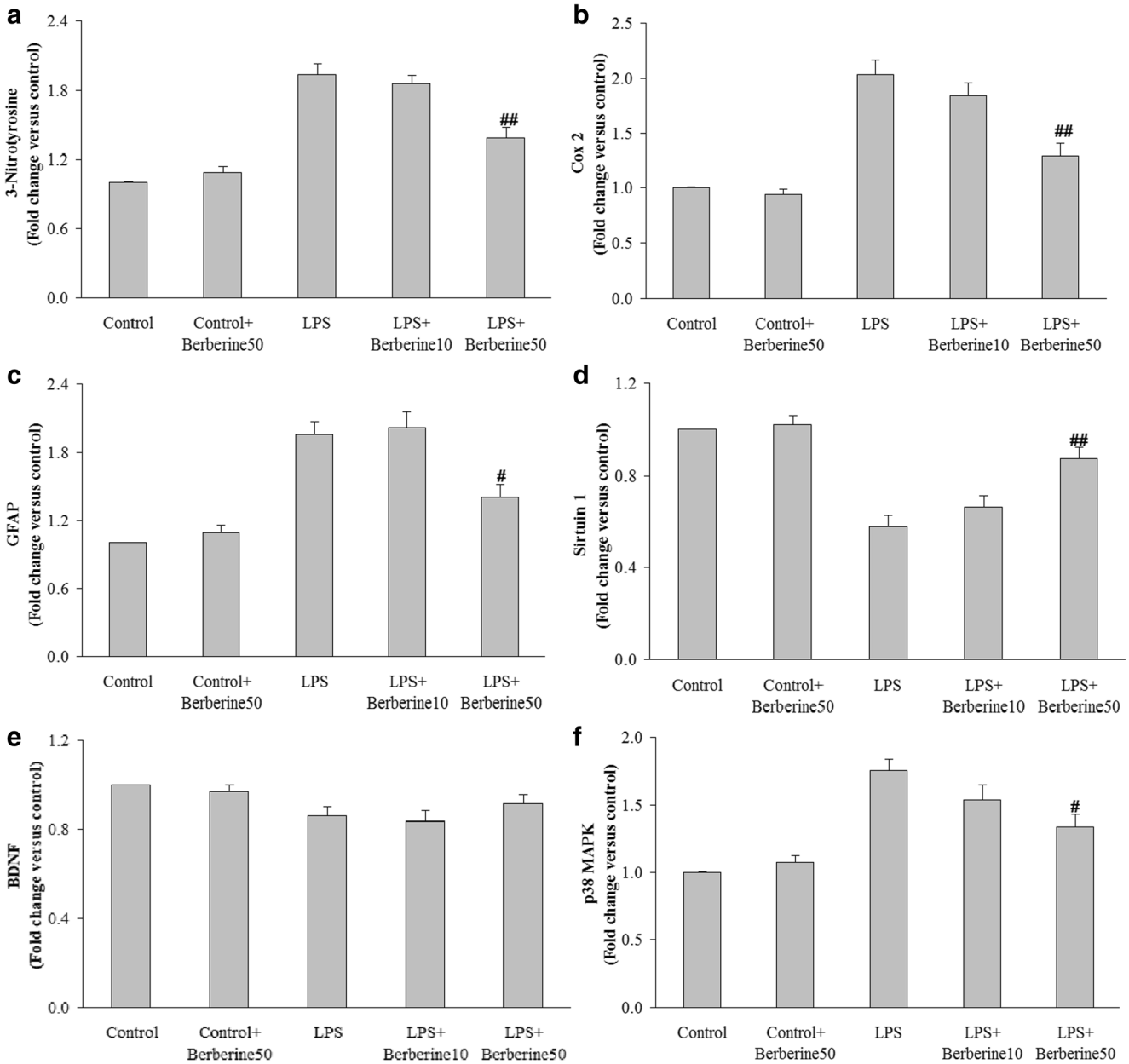

Fig. 2 Hippocampal level of 3-nitrotyrosine (**a**), Cox2 (**b**), GFAP (**c**), sirtuin 1 (**d**), BDNF (**e**), and p38-MAPK (**f**) shown as fold changes versus control group in different groups. # $p < 0.05$, ## $p < 0.01$ (relative to LPS)

somewhat ascribed to its hippocampal mitigation of apoptotic cascade, inflammation, oxidative and nitrosative stress, inhibition of AChE and p38 MAPK, and restoration of sirtuin 1.

Experimental evidence indicates that berberine satisfactorily exerts neuroprotective effect in models of various brain disorders (Aski et al. 2018; Hussien et al. 2018; Wang and Zhang 2018) and its neuroprotective effect in rodents is somewhat mediated through mitigation of apoptosis, inflammation, and oxidative stress processes (Sedaghat et al. 2017; Wang and Zhang 2018). Patients with sepsis or septic shock may experience cognitive impairment of varying nature and severity (Gotz et al. 2014; Widmann and Heneka 2014). In addition, sepsis-associated encephalopathy could bring about permanent neurocognitive impairments and functional deficits, even after recovery of the patients. Sepsis could potentially increase liability to development of neurodegenerative disorders with further worsening of cognitive ability and even elevating risk of dementia in later life (Widmann and Heneka 2014). On this foundation, our present research mimicked a septic condition using systemic challenge of LPS and functional deficits were assessed with the aid of different cognitive tasks. Similar to our findings, earlier researches have also shown that LPS derived from *E. coli* leads to learning and memory deficits in passive avoidance task, as shown by lower capability of mice for retention and recall with no significant change of acquisition competence that is partly due to activation of TLR4 signaling cascade (Zhang et al. 2018).

Spontaneous alternation behavior as assessed by performance of animals in Y maze was impaired following systemic LPS in our study that is also reported by other research teams (Chowdhury et al. 2017; Wang et al. 2018c) and is somehow attributed to neuroinflammation, deposition of amyloids β, and enhanced level of hyperphosphorylated tau proteins in the hippocampus and cortex (Wang et al. 2018c) in addition to development of oxidative stress and BDNF down-regulation (Chowdhury et al. 2017). Moreover, LPS exposure also impairs cognitive performance in novel object recognition (Fruhauf et al. 2015) that was also proven in this study. In this respect, it has shown that LPS challenge leads to lower overall exploration on introduction of a novel object that may be due to lower motivation as well as cognitive impairment itself (Haba et al. 2012). Furthermore, part of LPS-induced cognitive deficits is attributed to reduction of the number of excitatory synapses in the hippocampus and cerebral cortex with subsequent impairment of synaptic functions (Moraes et al. 2015).

As mentioned before, part of cognitive decline in neurodegenerative disorders such as AD is as a result of occurrence of brain inflammation (Ownby 2010). Scientific evidence indicate that activation of immune system due to systemic infection usually leads to neuroinflammation and ensuing neuropsychiatric symptoms in animal models and humans (Jangra et al. 2016; Notter et al. 2018). LPS exposure triggers brain generation of pro-inflammatory mediators like NF-κB in mice (Gu et al. 2015), IL-6 in mice (Chowdhury et al. 2017), TNF-α in BV2 microglial cells (Lee et al. 2013), TLR4 and Cox 2 in rats (Mirahmadi et al. 2018) that also occurred in this research. Conversely, berberine treatment at a dose of 50 mg/kg beneficially and significantly mitigated neuroinflammation-related factors. In support of these findings, Wang and Zhang in 2018 showed that part of neuroprotective effect of berberine agonist against learning and memory deficits in traumatic brain injury is through suppression of inflammation, oxidative stress and apoptosis and at a molecular level via appropriate modulation of Sirt1/p38 MAPK signaling (Wang and Zhang 2018). In addition, neuroprotective effect of oral berberine against learning and memory deficits in diffuse axonal injury has been ascribed to its suppression of TNF, interleukin-1β and monocyte chemoattractant protein-1, and nuclear factor-κB (Wang et al. 2018a).

In addition to inducing neuroinflammation, LPS challenge in mice is also associated with oxidative and nitrosative stress that play pivotal roles in cognition-related disorders (Ali et al. 2016; Wang et al. 2018b). We reached similar findings, as revealed by elevated hippocampal level of MDA, 3-NT, and protein carbonyl and weakened antioxidant capacity consisting of SOD, catalase, GPx, and GSH following systemic LPS. Development of neuroinflammation in parallel to oxidative stress could perpetuate a vicious circle that finally causes behavioral dysfunction (Li et al. 2017). Conversely, berberine at a dose of 50 mg/kg, but not at a dose of 10 mg/kg, alleviated intensity of hippocampal oxido-nitrosative stress following systemic LPS and was also able to reinforce antioxidant defensive system. In agreement with these findings, anti-oxidative property of berberine in brain tissue in different models of neurotoxicity has been reported before (Hussien et al. 2018; Maleki et al. 2018; Patil et al. 2015; Sedaghat et al. 2017). An earlier research also showed that berberine is capable to attenuate oxidative/nitrosative stress in kidney tissue following cisplatin nephrotoxicity, as demonstrated by lower levels of 4-hydroxynonenal and 3-NT (Domitrovic et al. 2013),

In this research, systemic challenge of LPS increased hippocampal activity of caspase 3 and DNA fragmentation as valid variables of apoptosis in addition to enhancing p38 MAPK. Similar findings have been reported indicating that LPS exposure in rats induces apoptotic cell death in some brain regions like the hippocampus that is coupled to stimulation of p38 MAPK signaling (Nolan et al. 2003). Conversely, we showed that berberine (50 mg/kg) alleviates hippocampal intensity of apoptosis following LPS exposure. Our findings are supported by earlier reports regarding anti-apoptotic potential of this alkaloid (Wang et al. 2018a; Wang and Zhang 2018).

Central cholinergic system plays an important role in cognition (Sohanaki et al. 2016) and its impairment is associated with learning and memory disturbance in neuroinflammatory settings (Silverman et al. 2014; Tyagi et al. 2010). Nevertheless, there are contrasting reports on direction of alterations of this system after LPS exposure, some indicating its up-regulation (Chowdhury et al. 2017; Khajevand-Khazaei et al. 2018) and some showing its down-regulation (Abdel-Salam et al. 2013; Lykhmus et al. 2016) that the former is similar to our study. Conversely, berberine 50-treated LPS group had a lower activity of hippocampal AChE. AChE inhibitory activity of berberine has been reported before (Hussien et al. 2018). LPS exposure also accompanies lower expression of the protective agent sirtiuin 1 in the hippocampus (Liu et al. 2016). It has shown that stimulation of sirtuin 1/nuclear factor-erythroid 2-related factor 2 (Nrf2) pathway might alleviate LPS-induced oxidative injury and agents with such potential could confer neuroprotection (Shah et al. 2017). In our research, administration of berberine (50 mg/kg) to LPS-challenged group significantly minimized hippocampal drop of sirtuin 1 and this is probably responsible for a portion of its protective effect. Previous researchers have shown that berberine could up-regulate sirtuin 1 in liver (Lin et al. 2017) and myocardial (Yu et al. 2016) tissues under stressful conditions.

BDNF is involved in many functional aspects of neurons including synaptic plasticity, neurogenesis, and neuronal survival in addition to its role in some features of cognitive disorders (Leal et al. 2017; Tanila 2017). Considering our results, we did not find out a significant reduction of hippocampal BDNF following LPS challenge and berberine treatment did not significantly increase its level. To justify our unexpected finding with respect to BDNF, Zhu et al. 2014 demonstrated that chronic LPS exposure in the rat produces cognitive abnormality without affecting hippocampal expression of BDNF (Zhu et al. 2014).

Hippocampal level of GFAP as a biomarker of astrogliosis increases after a challenge of LPS (Andrade et al. 2017; Carvalho et al. 2016). Elevated expression of GFAP evidently suggests presence of overactive astrocytes and associated astrogliosis (Ahshin-Majd et al. 2016; Zarezadeh et al. 2017). In our study, berberine administration at a dose of 50 mg/kg to LPS group alleviated GFAP level, indirectly showing a lower hippocampal level of astrogliosis. Consistent with our obtained data, it has been shown that berberine could protect against secondary injury in mice with traumatic brain injury, partly through down-regulation of brain GFAP (Huang et al. 2018).

One of the drawbacks of this research study was the issue that it was not possible to conduct all behavioral tests on the same day and/or within a narrower time span and for this reason, our biochemical parameters measured on day 7 may not be well-related to some cognitive variables.

Collectively, the natural alkaloid berberine could ameliorate LPS-induced cognitive deficits in the rat through partial inhibition of apoptotic cascade, neuroinflammation, oxido-nitrosative stress, AChE, and MAPK and prevention of sirtuin 1 reduction. Berberine may be recommended as a prophylactic and/or adjunct medication for neurodegenerative diseases related to oxidative stress and inflammation and to diminish cognitive deficits in septic conditions.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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