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ORIGINAL ARTICLE

Tempol and perindopril protect against lipopolysaccharide-induced cognition impairment and amyloidogenesis by modulating brain-derived neurotropic factor, neuroinflammation and oxido-nitrosative stress

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Abstract We aim to evaluate the protective role of the central angiotensin-converting enzyme (ACE) inhibitor perindopril, compared with the standard reactive oxygen species (ROS) scavenger tempol, against lipopolysaccharide (LPS)-induced cognition impairment and amyloidogenesis in a simulation to Alzheimer's disease (AD). Mice were allocated into a control group, an LPS control group (0.8 mg/kg, i.p., once), a tempol (100 mg/kg/day, p.o., 7 days) treatment group, and two perindopril (0.5 and 1 mg/kg/day, p.o., 7 days) treatment groups. A behavioral study was conducted to evaluate spatial and nonspatial memory in mice, followed by a biochemical study involving assessment of brain levels of Aβ and BDNF as Alzheimer and neuroplasticity markers; tumor necrosis factor-alpha (TNF-α), nitric oxide end-products (NOx), neuronal nitric oxide synthase (nNOS), and inducible nitric oxide synthase (iNOS) as inflammatory markers; and superoxide dismutase (SOD), malondialdehyde (MDA), glutathione reduced (GSH), and nitrotyrosine (NT) as oxido-nitrosative stress markers. Finally, histopathological examination of cerebral cortex, hippocampus, and cerebellum sections was performed using both routine and special staining. Tempol and perindopril improved spatial and nonspatial memory in mice without affecting locomotor activity; decreased brain Aβ deposition and BDNF depletion; decreased brain TNF-α, NOx, nNOS, iNOS, MDA, and NT levels; and increased brain SOD and GSH contents, parallel to confirmatory histopathological findings. Tempol and perindopril may be promising agents against AD progression via suppression of Aβ deposition and BDNF decline, suppression of TNF-α production, support of brain antioxidant status, and amelioration of oxido-nitrosative stress and NT production.

Keywords Amyloidogenesis · Brain-derived neurotropic factor · Neuroinflammation · Oxido-nitrosative stress · Perindopril · Tempol

Highlights
- Administration of LPS to mice in a single i.p. dose causes AD simulation.
- Tempol and perindopril may be protected against experimental AD progression.
- Both agents act through inhibition of Aβ deposition and BDNF decline.
- Both agents also suppress brain TNF-α production and oxido-nitrosative stress.

About the current study
We are interested in investigating beneficial effects of drugs interfering with the renin-angiotensin system on noncardiovascular disorders, including respiratory, musculoskeletal, immunological, and CNS disorders. I have just coauthored a manuscript in the *European Journal of Pharmacology* concerning the effect of angiotensin-converting enzyme inhibition by ramipril on experimental rheumatoid arthritis (doi:10.1016/j.ejphar.2015.08.026), another one in *Pharmacological Reports* concerning the role of angiotensin receptor blockade by telmisartan on the progression of bronchial asthma (doi:10.1016/j.pharep.2015.02.010), and a third one in *Saudi Pharmaceutical Journal* concerning the hepatoprotective role of ACE inhibition by lisinopril (doi:10.1016/j.jsps.2015.04.004).
In the present investigation, we evaluated the protective effect of perindopril, a centrally acting angiotensin-converting enzyme inhibitor, compared with tempol, a well-known superoxide scavenger, on LPS-induced cognition impairment and amyloidogenesis in mice in a simulation to Alzheimer disease. We focused on mechanisms not studied before regarding the effect of tempol or perindopril on this model, including particularly the role of brain-derived neurotropic factor, nitrotyrosine production, and cerebellar amyloidogenesis.

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Introduction

Alzheimer's disease (AD), the most common form of dementia, is a severe neurodegenerative disorder with massive and permanent loss of memory and ultimately complete intellectual incapability (Araujo et al. 2014; Dhikav et al. 2014). Five years ago, 35.6 million people worldwide suffered from dementia, with the numbers doubled every 20 years (Prince et al. 2013).

The neurodegenerative process in the course of AD is associated with the deposition of beta amyloid (Aβ) plaques, a process termed amyloidogenesis (Kugaevskaya 2011; Zhang et al. 2015). Experimentally, lipopolysaccharide (LPS) administration to normal or transgenic rodents causes amyloidogenesis and ultimate cognition impairment in a simulation to AD (Arai et al. 2001; Sheng et al. 2003; El-Sayed and Bayan 2015). Amyloidogenesis, in turn, increases brain levels of tumor necrosis factor alpha (TNF-α), while the latter was reported to cause death of human cortical neurons (Barichello et al. 2009; Packer and Hoffman-Goetz 2015). Aβ was also reported to be included in the activation of free radical generation through the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, resulting in increased production of reactive oxygen species (ROS), malondialdehyde (MDA), and nitrotyrosine (NT; Hardy and Selkoe 2002; Han et al. 2015; Mota et al. 2015). ROS is also released through catalysis from extracellular iron and copper ions attached to Aβ (Collingwood et al. 2008; Graham et al. 2014). Immunologically, microglial cells recognize and attack Aβ plaques, starting a circle of ROS formation and cytokine production (Gallagher et al. 2012). Alternatively, the brain-derived neurotropic factor (BDNF) is a neuroprotective protein encoded by BDNF gene and claimed to suppress Aβ toxicity (Mattson 2000). Oxido-nitrosative stress was reported to suppress BDNF expression (Eraldemir et al. 2015; Psotta et al. 2015).

Oxidative stress could be not only a result of Aβ deposition but also a starting factor for the progression of brain neuroinflammation and amyloidogenesis (Pearson et al. 2015; Abdel Moneim 2015). Tempol, 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl, was selected in the current study based on its ability to catalyze the detoxification of ROS, particularly superoxide (Wilcox and Pearlman 2008; Mizera et al. 2015). Interestingly, tempol was reported by Yamada et al. (2003) to be a cell-permeable ROS scavenger. Although tempol is not applied clinically up to now, it seems a promising agent for the management of a variety of ailments. Tempol administration was recently reported to prevent chronic sleep deprivation-induced cognition impairment in experimental rats via its ability to improve hippocampus levels of antioxidant enzymes (Alzoubi et al. 2016). Being a membrane-permeable ROS scavenger and superoxide dismutase (SOD)-mimetic, tempol was reported by many authors to improve redox homeostasis in different animal models (Chatterjee et al. 2000; Aksu et al. 2014; Dornas et al. 2015; Lewis et al. 2015). According to the results of Silswal et al. (2015), the antioxidant effect of tempol may be partially attributed to activation of peroxisome proliferator activated receptor-α (PPAR-α) receptors.

Angiotensin II produced from the activated renin-angiotensin system (RAS) was reported to mediate pro-oxidant and pro-inflammatory effects, at least by stimulating NADPH oxidase and uncoupling endothelial nitric oxide synthase (Benigni et al. 2010; de Cavanagh et al. 2010). The brain is now known to have its own RAS (von Bohlen und Halbach and Albrecht 2006; Claflin and Grobe 2015), reported to play a role in amyloidogenesis (Zhu et al. 2011). We have recently reported that interference with the renin-angiotensin system may have beneficial outcomes in different animal models, namely experimental bronchial asthma (Abdel-Fattah et al. 2015), hepatotoxicity (Mohammed et al. 2015), and rheumatoid arthritis (Fahmy Wahba et al. 2015), based on modulation of oxidative stress and immuno-inflammatory progression. Accordingly, the centrally acting angiotensin-converting enzyme (ACE) inhibitor perindopril was selected in the current study. The drug was previously reported to have good central antioxidant and anti-inflammatory activities (Marchesi et al. 2008; Mashhoody et al. 2014). Perindopril was recently reported to attenuate LPS-induced amyloidogenesis and cognition impairment in spontaneously hypertensive rats (Goel et al. 2015). According to Jawaid et al. (2015), ACE inhibitors might protect experimental rats against scopolamine-induced memory impairment, with the centrally acting member perindopril being significantly better than other members of the class, namely enalapril and ramipril. Interestingly, Yang et al. (2014) concluded that perindopril could protect experimental mice against d-galactose/aluminum trichloride-induced neurotoxicity via inhibition of neuronal apoptosis in the hippocampus.

Based on the aforementioned background, the current investigation was carried out to elucidate the possible beneficial effects of tempol and perindopril on LPS-induced AD simulation in mice. A preliminary compound behavioral study was performed to evaluate cognition impairment, followed by a biochemical study to explore the underlying mechanisms of cognition impairment. This was finally confirmed by a multipanel histopathological study.

Material and methods

Animals

Adult 12-week-old male albino mice of the BALB/c strain, weighing 22–25 g, were purchased from the animal house of

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the National Research Center. Mice were kept in the laboratory animal center of the Faculty of Pharmacy, Beni-Suef University under a controlled temperature (22–23 °C), on 12-h light/dark cycles, and were supplied with standard chow and tap water ad libitum. The study was carried out according to the guidelines of the Ethics Committee, Faculty of Pharmacy, Beni-Suef University, which followed the recommendations of the National Institutes of Health Guide for Care and Use of Laboratory Animals (publication no. 85–23, revised 1985).

Drugs, chemicals, and reagent kits

Tempol, LPS, thiobarbituric acid (TBA), 1,1,3,3-tetramethoxypropane (MDA standard), 5,5′-dithio-bis-(2-nitrobenzoic acid) (DTNB), and glutathione reduced (GSH) standard were purchased from Sigma Chemicals Co. (USA). Perindopril was obtained from Servier Pharmaceutical Co. (Egypt). Murine Aβ and BDNF ELISA kits were obtained from MyBioSource Co. and Kamiya BioMedical Co. (USA), respectively. Murine TNF-α ELISA kit was obtained from RayBiotec Co. (USA). Murine neuronal nitric oxide synthase (nNOS) and inducible nitric oxide synthase (iNOS) ELISA kits were obtained from Cloude-Clone Co. (USA) and ShangHai Crystal Day Biotech Co. (China), respectively. Nitrate/nitrite assay ELISA kit was obtained from Assay Designs Co. (USA). Murine SOD and NT ELISA kits were obtained from Trevigen Co. (USA) and Uscn Life Science Co. (China). All other chemicals, solvents, and reagents used were obtained from certified sources and were of analytical grade.

Experimental design

Mice were randomly divided into five groups, namely a normal control group, an LPS control group, a tempol treatment group, and two perindopril treatment groups. Tempol and perindopril were administered as solutions in normal saline via the i.p. route on a daily basis for seven consecutive days, where tempol was given in a dose of 100 mg/kg/day (Hahn et al. 1992) and perindopril was given in doses of 0.5 and 1 mg/kg/day (Hou et al. 2008; El-Sayed et al. 2009; Yamada et al. 2010).

The doses of test agents were selected based on pilot trials guided with the published literature. Doses of perindopril were particularly critical and were carefully selected to ensure there would be no hypotensive effect sufficient to cause vascular dementia secondary to cerebral hypoperfusion (Washida et al. 2010; Kennelly and Collins 2012). Doses of 0.5 and 1 mg/kg of perindopril were reported to be safe and even to improve cognition of mice in different experimental models (Yamada et al. 2010; Wiesmann et al. 2013; Yang et al. 2013). In support, Lu et al. (2008) showed that administration of perindopril to ApoE knockout mice in a dose of 1.5 mg/kg/day for 20 weeks did not cause significant lowering of blood pressure.

One hour after the last drug dose, the test phase of all the behavioral studies was carried out, and 24 h later animals were sacrificed with brain tissues withdrawn as indicated.

Alzheimer simulation induction

Induction of brain neuroinflammation and amyloidogenesis, in a simulation to AD, was performed by a single i.p. dose of LPS (0.8 mg/kg) dissolved in 1 % Tween 80 solution in normal saline. Such dose in experimental mice was reported to cause memory impairment (Arai et al. 2001; El-Sayed and Bayan 2015) and amyloidogenesis (El-Sayed et al. 2009; Maher et al. 2014). Test agents were administered on a daily basis for seven consecutive days starting from the day of LPS injection (2 h after LPS administration).

Behavioral study

On the day of the behavioral experiments, mice were transported to the experimental facility (Behavioral Lab, Faculty of Pharmacy, Beni-Suef University). Morris maze and Y-maze tests were performed to evaluate spatial memory, while novel object recognition test was performed to evaluate nonspatial memory in experimental mice. The sequence of behavioral training and test phases is illustrated in Fig. 1.

The Morris maze test

This was used to evaluate spatial memory in mice according to the method described by Vorhees and Williams (2006). The maze apparatus was a metal cage 122 cm in diameter with black sides, 50 cm high, containing water with a temperature of 19–22 °C which was turned turbid using milk. The area inside the maze was divided into four quadrants, where a platform (mice target), 10–12 cm in diameter, was submerged under water at 1-cm depth in one quadrant. Each animal was exposed to three training trials with different three starting points (in the three quadrants not containing the platform) every day for 5 days. On the day of the test (probe trial), the platform was removed and each animal was placed on the position that was facing the fourth quadrant and the total time that the animal spent in the fourth quadrant (Q4 time) was calculated through 1 min. The animal had better memory when it spent a higher duration in the fourth quadrant.

A learning curve during the training days was prepared through daily assessment of Q4 values to evaluate gradual loss of learning and memory in the mice. Additionally, swimming speed was calculated to evaluate locomotor activity in mice.

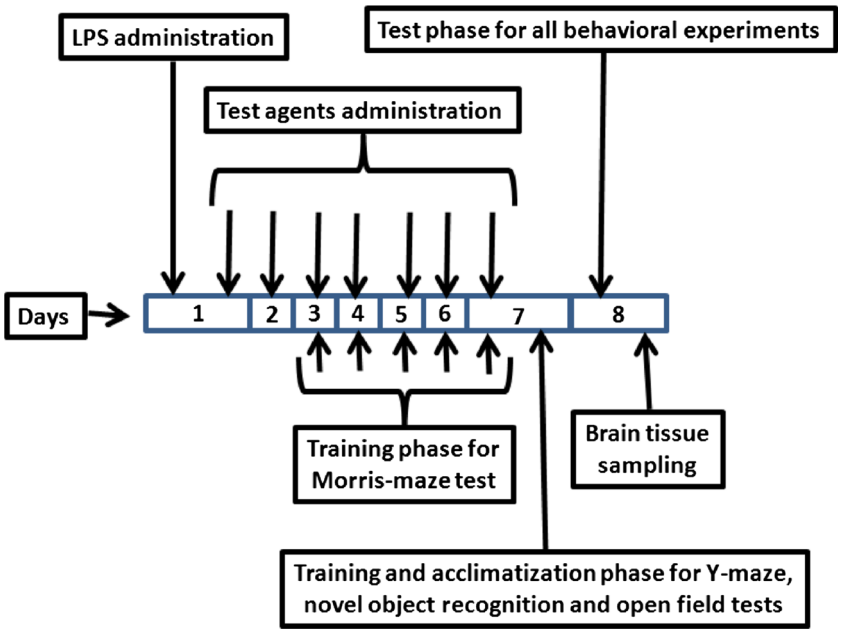

Fig. 1 A schematic diagram showing schedules of LPS and test agents administration, training and test phases, as well as sampling

The Y-maze test

It was used to evaluate spatial memory in mice to assess spontaneous alternation behavior according to the method described by Sarter et al. (1988). The apparatus was a 3-arm Y-shaped maze made of black-painted wood, where each arm was 25 cm long, 14 cm high, and 5 cm wide and adjusted at equal angles. Each mouse was placed in the center of the Y-maze and allowed to explore during an 8-min session without any re-enforcers such as food, water, or electrical stimuli. The series of arm entries were recorded visually and an arm entry was considered to be completed as long as the hind paws of the mouse were completely placed in the arm. The alternation behavior (actual alternations) was defined as the consecutive entry into three arms. The maximum number of alternations was thus the total number of arms entered minus 2, and the percentage of alternation behavior, known as spontaneous alternation percentage (SAP), was calculated as (actual alternations/maximum alternations) × 100 %. The animal had better memory when it had a higher alternation ratio.

The novel object recognition test

It was used to evaluate nonspatial memory in mice according to the method described by Leger et al. (2013). The apparatus was made of a black-painted wooden box, 30 cm × 30 cm × 30 cm. In the first day, each mouse was allowed to explore the empty apparatus as a familiarization phase for 4 min; then, it was allowed to explore two similar objects for another 4 min. On the second day, the mouse was subjected to the test phase, where one of the two similar objects was replaced by a novel one and the animal was allowed to explore the objects for four minutes. A discrimination ratio (DR) was calculated for each mouse, being equal to the number of attempts to the novel object/total number of attempts to the both objects. The animal had better memory when it achieved a higher DR.

The open field test

This test was performed to confirm that results of behavioral tests are not affected by changes in mice locomotor activity, as open field test was extensively applied to evaluate locomotor behavior (Kafkafi et al. 2003; Onaolapo et al. 2015). The study was performed according to method described by Cunha and Masur (1978). Briefly, mice were placed for 3 min in an open field of wooden box (80 × 80 × 40 cm) with red walls and white floor divided into 16 equal squares 4 × 4 by black lines. Latency is the time in seconds taken from dropping the animal in the center of the field until it decides to move. Ambulation frequency is the number of squares crossed by the animal. Grooming frequency is the number of face washings and scratching with the hind limbs. Rearing frequency is the number of times the animal stood stretched on hind limbs.

Sampling

Twenty-four hours after the last dose of test agent administration, animals were sacrificed by decapitation and the brains were removed rapidly on ice-cold saline. Three brains of each group were kept in 10 % formalin solution in normal saline for histopathological examination, and the other brains were homogenized in cold saline using a tissue homogenizer (yellow line, DI18 basic, Germany) and centrifuged at 4000 rpm at 4 °C for 15 min using a cooling centrifuge (Sigma 3-30 k,

USA). The supernatant was withdrawn and kept at −80 °C in a deep freezer (Als Angelantoni Life Science, Italy) for the time of assay of Aβ, BDNF, TNF-α, nNOS, iNOS, NOx, SOD, NT, MDA, and GSH levels.

Biochemical estimations

Amyloidogenesis and neuroplasticity markers

The levels of the Alzheimer marker Aβ and the neuroplasticity marker BDNF in brain tissue were measured using ELISA diagnostic kits as described by manufacturer's instructions according to the principles described by Verges et al. (2011) and Trajkovska et al. (2007), respectively.

Inflammatory markers

The levels of TNF-α in brain tissue were measured using ELISA diagnostic kits as described by manufacturer's instructions according to George et al. (1999) and Wang et al. (2007). Brain tissue NOx was measured using ELISA diagnostic kit as described by Sun et al. (2003) and Tsikas (2007). The levels of nNOS and iNOS in brain tissue were measured using ELISA diagnostic kits as described by Hevel and Marletta (1994).

Oxido-nitrosative markers

Brain tissue SOD was measured using ELISA diagnostic kits as described by Robak and Gryglewski (1988). Brain tissue MDA and GSH levels were assessed colorimetrically according to the principles of Ohkawa et al. (1979) and Ellman (1959), respectively. Brain tissue NT was measured using ELISA diagnostic kits as described by ter Steege et al. (1998).

Histopathological study

After hardening for at least 7 days, tissue specimens were taken from the brain involving cerebral cortex, cerebellum, and hippocampus and processed according to the technique described by Bancroft and Gamble (2008). Briefly, specimens were washed in running water for 1 h, dehydrated in graded concentrations of ethyl alcohol (50, 70, 75, and 100 %; 2 h each), then cleared in xylene. After complete clearance, the specimens were embedded in melted paraffin wax and dried in an oven at 70 °C for 4–6 h. Paraffin blocks were exposed to microtomy to prepare 5-μm sections, which were stained by either the routine hematoxylin and eosin (H&E) stain for examination of brain tissue degeneration and neuronal plasticity, or the Congo red special stain for Aβ plaque deposition.

Data presentation and statistical analysis

All data are expressed as means ± standard error of the mean (SEM). Statistical analysis was done using Statistical Package for Social Sciences (SPSS) computer software (version 22). One-way analysis of variance (ANOVA) test was used to elucidate significance among group means, followed by Tukey's post hoc test to compare mean values pairwise. Differences were considered significant at $p < 0.05$.

Results

Behavioral study

Morris maze test

Lipopolysaccharide administration to mice significantly decreased Q4 time in Morris maze test compared with normal mice. This reduction was significantly corrected in all treatment groups, being all restored back to normal levels, where no significant difference was reported among treatment groups (Fig. 2). The time course learning curve (Fig. 3) shows significant prolongation of the time taken by LPS control mice to reach the visible platform in Q4, as compared with normal control mice, starting from day 4 of the training phase. Alternatively, this time was significantly shortened in all treatment groups, being restored back to normal levels. The higher dose of perindopril was significantly better than tempol or the lower dose of perindopril, while tempol effect was not

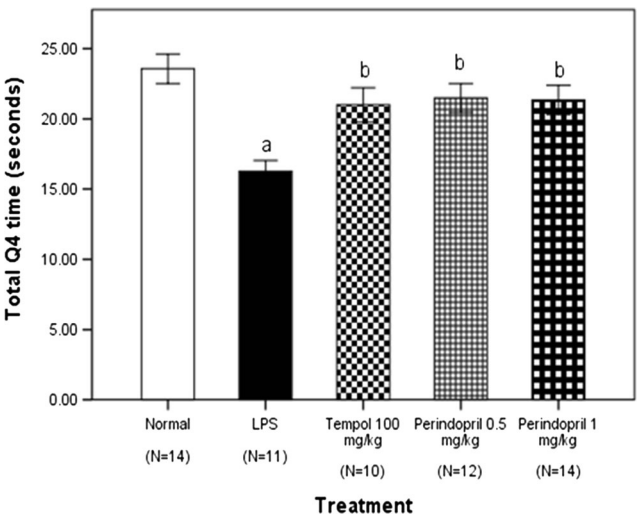

Fig. 2 A graphical presentation of Q4 time in Morris maze (water maze) test, where LPS stands for lipopolysaccharide, Q4 stands for time spent in the fourth quadrant, F value = 6.486, *df* value between groups = 4, *df* value within groups = 56, total *df* value = 60. [a]Significantly different from normal control value; [b]significantly different from LPS control value

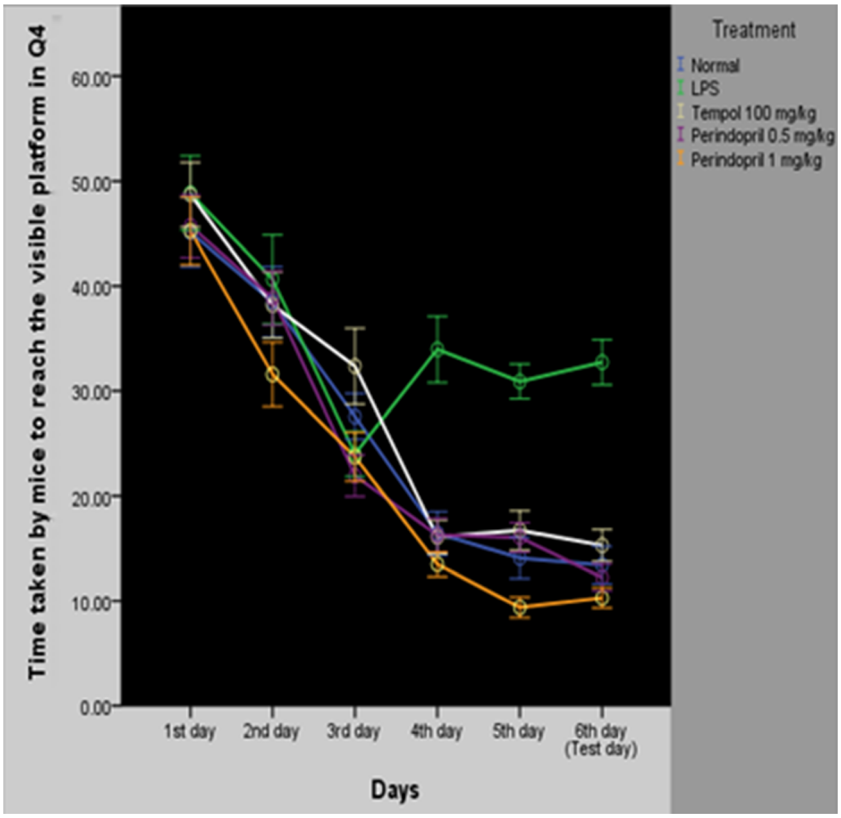

Fig. 3 A time course learning curve for Morris maze test

significantly different from that of the lower dose of perindopril regarding the time required to reach the visible platform in Q4.

Alternatively, the swimming speed was not affected by either LPS or test agent administration (Table 1).

Y-maze test

In Y-maze test, SAP value was significantly decreased in LPS-intoxicated mice, and was significantly corrected in all treatment groups, being restored back to normal level only in the tempol treatment group (Fig. 4).

Novel object recognition test

In novel object recognition test, LPS-treated animals showed significantly lower DR values compared with normal control mice, where the value was significantly corrected, being restored back to normal level, in all treatment groups (Fig. 5).

Open field test

Locomotor activity in mice was not significantly affected either by LPS administration or by treatments with test agents. This was evident from the observed values of latency time and frequencies of ambulation, grooming, and rearing (Table 1).

Biochemical estimations

Amyloidogenesis and neuroplasticity markers

Administration of LPS to mice significantly increased brain tissue level of Aβ compared with normal control values. Treatment of mice with tempol or perindopril in both dose levels significantly decreased Aβ levels but not back to normal levels. The lower dose level of perindopril showed significantly lower improvement of Aβ levels compared with tempol, while the higher dose level of perindopril showed a tissue Aβ level not significantly different from that of tempol treatment group (Fig. 6).

Side by side, brain tissue BDNF level was significantly decreased in LPS group, and this decrease was significantly corrected in tempol treatment and perindopril treatment in the higher, but not the lower, dose level (Fig. 7).

Inflammatory markers

Mice exposed to LPS administration showed significantly higher brain tissue levels of TNF-α, nNOS, iNOS, and NOx, as compared with normal control mice.

Brain tissue TNF-α level was significantly reduced in all treatment groups, being restored back to normal level only in mice treated with the higher dose level of perindopril, as

Table 1 Effect of tempol and perindopril on locomotor activity in mice with lipopolysaccharide (LPS)-induced cognition impairment

Group parameter		Statistical data	Normal control	LPS control	Tempol (100 mg/kg)	Perindopril (0.5 mg/kg)	Perindopril (1 mg/kg)
Open field test	Latency time (s)	$P < 0.05$. Total $df = 75$ F = 0.667	1.44 ($N = 18$) ± 0.12	1.62 ($N = 16$) ± 0.15	1.31 ($N = 13$) ± 0.12	1.42 ($N = 14$) ± 0.13	1.46 ($N = 15$) ± 0.13
	Ambulation frequency	$P < 0.05$. Total $df = 69$ F = 2.386	35.94 ($N = 16$) ± 2.05	35.07 ($N = 14$) ± 2.80	35.20 ($N = 10$) ± 3.52	42.29 ($N = 14$) ± 4.19	46.87 ($N = 16$) ± 4.27
	Grooming frequency	$P < 0.05$. Total $df = 69$ F = 0.514	3.33 ($N = 15$) ± 0.23	3.14 ($N = 14$) ± 0.31	3.38 ($N = 13$) ± 0.29	3.14 ($N = 14$) ± 0.29	2.86 ($N = 14$) ± 0.27
	Rearing frequency	$P < 0.05$. Total $df = 58$ $F = 0.602$	10.50 ($N = 14$) ± 1.11	11.27 ($N = 11$) ± 1.20	12.18 ($N = 11$) ± 1.40	13.50 ($N = 11$) ± 1.18	12.42 ($N = 12$) ± 1.24
Morris maze test	Swimming speed (m/s)	$P < 0.05$. Total $df = 60$ $F = 1.767$	0.250 ($N = 14$) ± 0.007	0.234 ($N = 11$) ± 0.005	0.245 ($N = 10$) ± 0.006	0.244 ($N = 12$) ± 0.005	0.255 ($N = 14$) ± 0.006

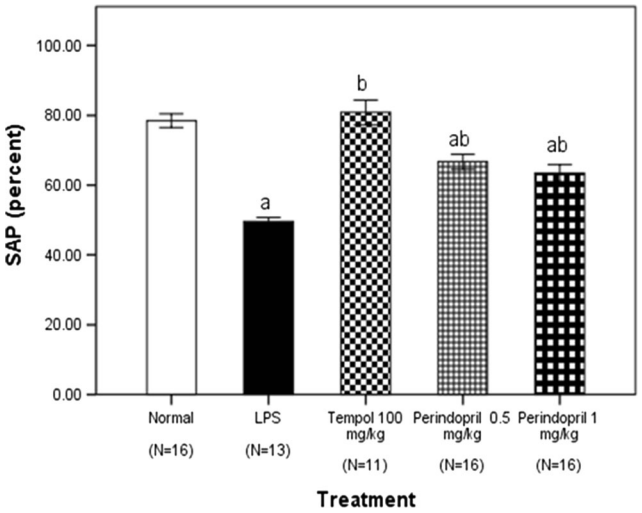

Fig. 4 A graphical presentation of SAP value in Y-maze test, where LPS stands for lipopolysaccharide, SAP stands for spontaneous alternation percentage, F value = 27.442, df value between groups = 4, df value within groups = 67, total df value = 71. [a]Significantly different from normal control value; [b]significantly different from LPS control value

compared with LPS group. Effect of the higher dose of perindopril was significantly better than that of the lower dose (Fig. 8).

All treatment groups showed significantly lower nNOS activity in brain tissue compared with LPS group. Only the higher dose level of perindopril could significantly restore nNOS activity back to normal level. The effect of the higher dose level of perindopril was significantly better than the effect of tempol or that of the lower dose level of perindopril regarding brain tissue nNOS (Fig. 9).

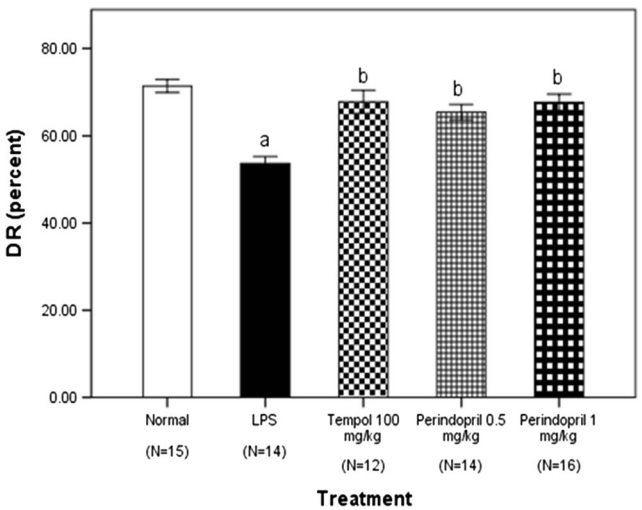

Fig. 5 A graphical presentation of DR value in novel object recognition test, where DR stands for discrimination ratio, LPS stands for lipopolysaccharide, F value = 13.289, df value between groups = 4, df value within groups = 67, total df value = 71. [a]Significantly different from normal control value; [b]significantly different from LPS control value

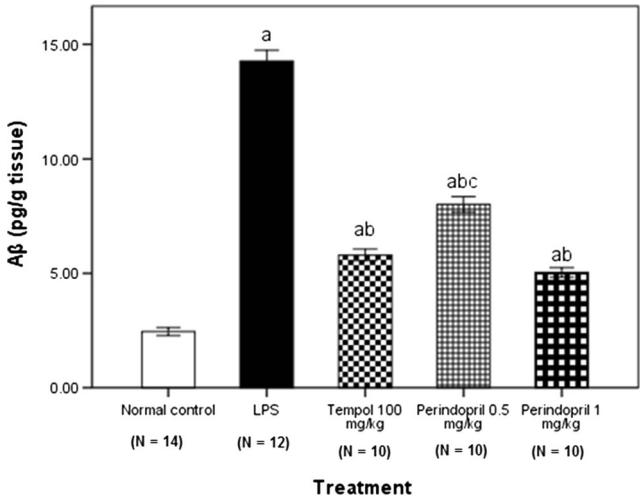

Fig. 6 A graphical presentations of brain tissue $A\beta_{1-42}$ level in different groups, where Aβ stands for amyloid beta, *F* value = 228.297, *df* value between groups = 4, *df* value within groups = 51, total *df* value = 55. [a]Significantly different from normal control value; [b]significantly different from LPS control value; [c]significantly different from tempol treatment value at $p < 0.05$

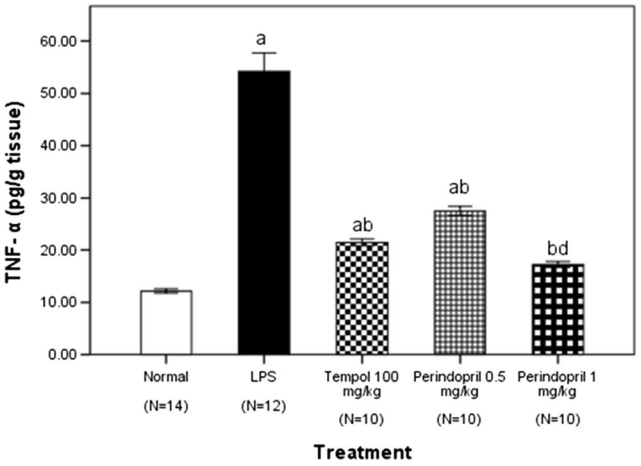

Fig. 8 A graphical presentations of brain tissue TNF-α level in different groups, where TNF-α stands for tumor necrosis factor alpha, *F* value = 96.218, *df* value between groups = 4, *df* value within groups = 39, total *df* value = 43. [a]Significantly different from normal control value; [b]significantly different from LPS control value; [d]significantly different from perindopril (0.5 mg/kg/day) treatment value at $p < 0.05$

Brain tissue iNOS activity was significantly improved in all treatment groups, but not restored back to normal levels. The effects of tempol and the higher dose level of perindopril were significantly better than that of the lower dose level of perindopril (Fig. 10).

Brain tissue NOx level was significantly reduced in all treatment groups compared with LPS group, where the effect of the higher dose level of perindopril was significantly better than the effect of tempol or that of the lower dose level of perindopril (Fig. 11).

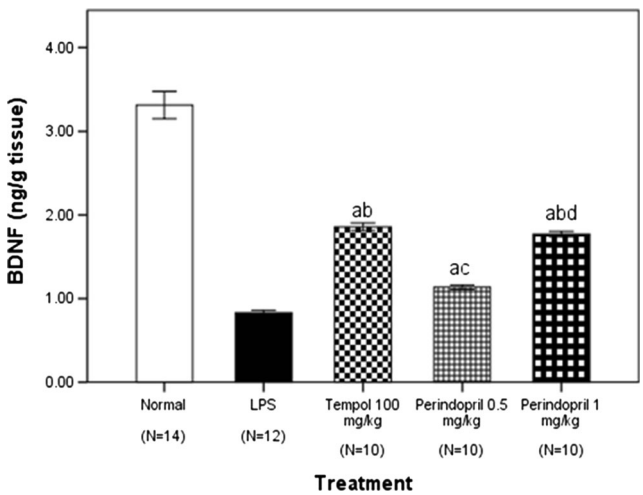

Fig. 7 A graphical presentations of brain tissue BDNF level in different groups, where BDNF stands for brain-derived neurotropic factor, *F* value = 110.804, *df* value between groups = 4, *df* value within groups = 51, total *df* value = 55. [a]Significantly different from normal control value; [b]significantly different from LPS control value; [c]significantly different from tempol treatment value; [d]significantly different from perindopril (0.5 mg/kg/day) treatment value at $p < 0.05$

Oxidative stress markers

Mice injected with LPS showed significantly lower brain tissue levels of SOD and GSH, coupled with significantly higher NT and MDA levels as compared with normal mice.

Brain tissue SOD activity was significantly improved in all treatment groups. The effect of the higher dose level of perindopril was significantly better than the effect of either tempol or the lower dose level of perindopril (Fig. 12).

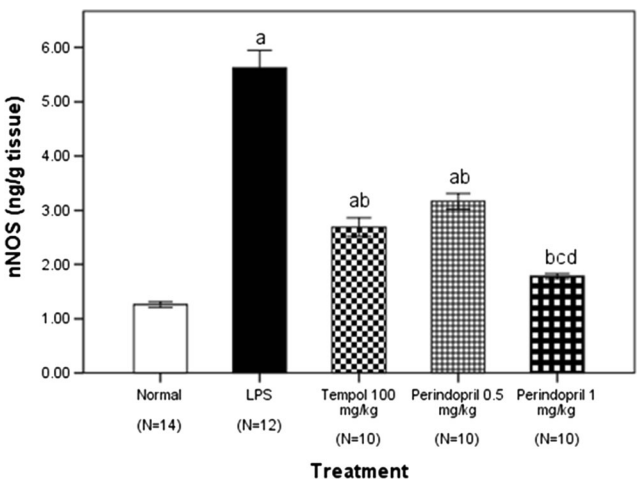

Fig. 9 A graphical presentations of brain tissue nNOS level in different groups, where nNOS stands for neuronal nitric oxide synthase, *F* value = 95.947, *df* value between groups = 4, *df* value within groups = 51, total *df* value = 55. [a]Significantly different from normal control value; [b]significantly different from LPS control value; [c]significantly different from tempol treatment value; [d]significantly different from perindopril (0.5 mg/kg/day) treatment value at $p < 0.05$

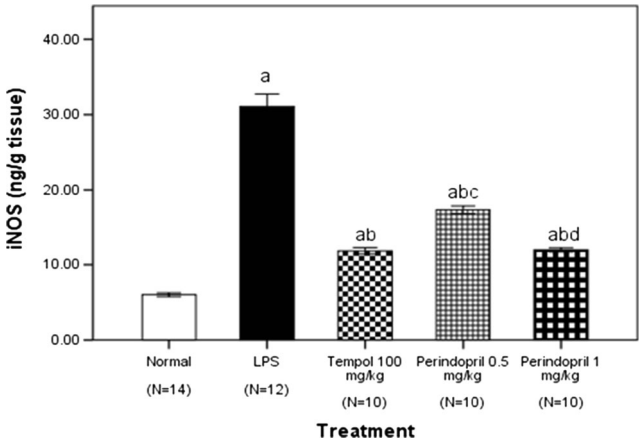

Fig. 10 A graphical presentations of brain tissue iNOS level in different groups, where iNOS stands for inducible nitric oxide synthase, *F* value = 135.288, *df* value between groups = 4, *df* value within groups = 51, total *df* value = 55. [a]Significantly different from normal control value; [b]significantly different from LPS control value; [c]significantly different from tempol treatment value; [d]significantly different from perindopril (0.5 mg/kg/day) treatment value at $p < 0.05$

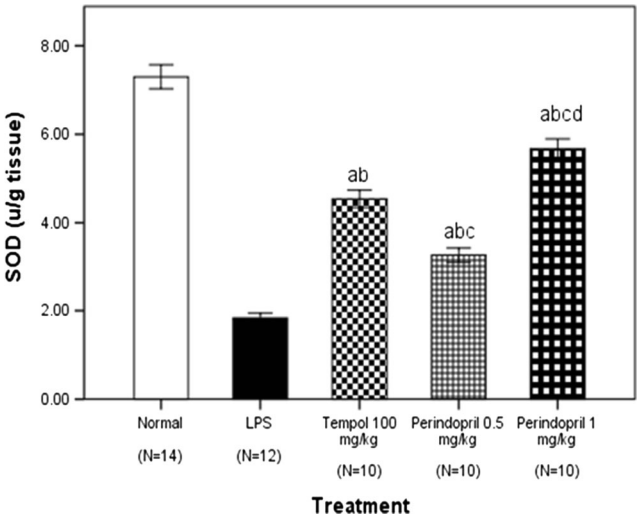

Fig. 12 A graphical presentations of brain tissue SOD level in different groups, where SOD stands for superoxide dismutase, *F* value = 114.189, *df* value between groups = 4, *df* value within groups = 51, total *df* value = 55. [a]Significantly different from normal control value; [b]significantly different from LPS control value; [c]significantly different from tempol treatment value; [d]significantly different from perindopril (0.5 mg/kg/day) treatment value at $p < 0.05$

Brain tissue NT level was also significantly improved in all treatment groups but the effect of the higher dose level of perindopril or that of tempol was significantly better than the effect of the lower dose level of perindopril (Fig. 13).

Brain tissue MDA level was significantly corrected in all treatment groups, with the effect of the higher dose level of perindopril being significantly better than the effect of tempol or of the lower dose level of perindopril (Fig. 14).

Brain tissue store of GSH was significantly increased in all treatment groups compared with LPS group, again with the effect of the higher dose level of perindopril being significantly better than that of tempol or of the lower dose level of perindopril (Fig. 15).

Histopathological study

Routine H&E stain

Cerebral cortex, hippocampus, and cerebellum sections obtained from normal control mice showed histologically intact neurons and normal histological architecture,

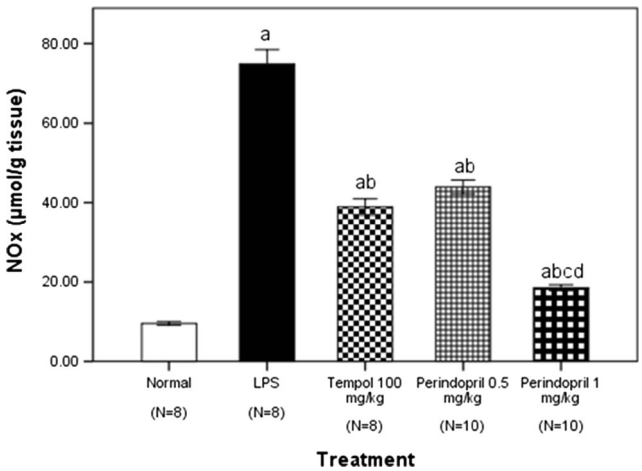

Fig. 11 A graphical presentations of brain tissue NOx level in different groups, where NOx stands for nitric oxide end products, *F* value = 158.089, *df* value between groups = 4, *df* value within groups = 39, total *df* value = 43. [a]Significantly different from normal control value; [b]significantly different from LPS control value; [c]significantly different from tempol treatment value; [d]significantly different from perindopril (0.5 mg/kg/day) treatment value at $p < 0.05$

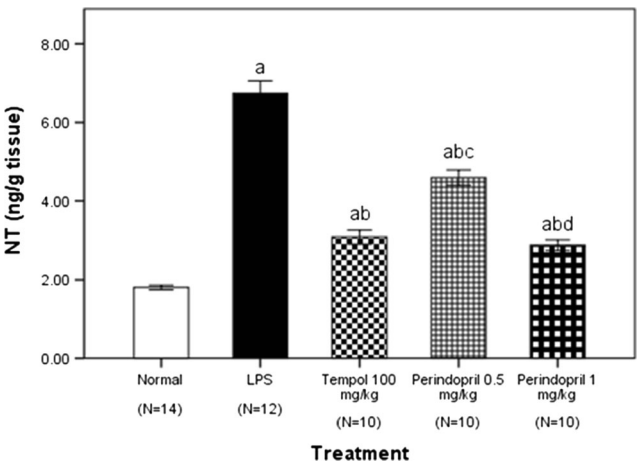

Fig. 13 A graphical presentations of brain tissue NT level in different groups, where NT stands for nitrotyrosine, *F* value = 107.740, *df* value between groups = 4, *df* value within groups = 51, total *df* value = 55. [a]Significantly different from normal control value; [b]significantly different from LPS control value; [c]significantly different from tempol treatment value; [d]significantly different from perindopril (0.1 mg/kg/day) treatment value at $p < 0.05$

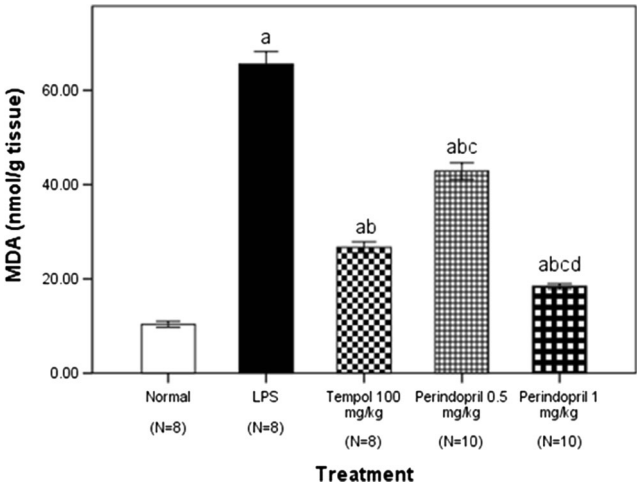

Fig. 14 A graphical presentations of brain tissue MDA level in different groups, where MDA stands for malondialdehyde, *F* value = 190.236, *df* value between groups = 4, *df* value within groups = 39, total *df* value = 43. [a]Significantly different from normal control value; [b]significantly different from LPS control value; [c]significantly different from tempol treatment value; [d]significantly different from perindopril (0.5 mg/kg/day) treatment value at $p < 0.05$

while sections obtained from LPS control mice showed many eosinophilic deposits, degenerated neurons, Hirano bodies and hemorrhagic regions. Alternatively, cerebral cortex, hippocampus, and cerebellum sections obtained from tempol-treated mice showed more or less normal neuronal integrity with nearly absence of abnormal deposits or hemorrhagic lesions. Cerebral cortex, hippocampus, and cerebellum sections obtained from LPS-intoxicated mice treated with the lower dose level of perindopril showed few degenerated neurons with only few Hirano bodies. Treatment with the higher dose level of perindopril nearly normalized cerebral cortical, hippocampal, and cerebellar sections evidenced by nearly normalized neuronal integrity and brain tissue architecture except for just a few neuronal degenerations and some Hirano bodies (Figs. 16, 17, and 18).

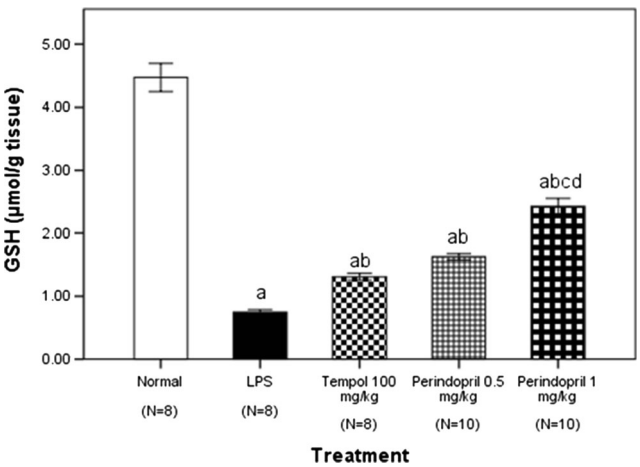

Fig. 15 A graphical presentations of brain tissue GSH level in different groups, where GSH stands for glutathione reduced, *F* value = 142.863, *df* value between groups = 4, *df* value within groups = 39, total *df* value = 43. [a]Significantly different from normal control value; [b]significantly different from LPS control value; [c]significantly different from tempol treatment value; [d]significantly different from perindopril (0.5 mg/kg/day) treatment value at $p < 0.05$

Special Congo red stain

Normal sections obtained from cerebral cortex, hippocampus or cerebellum did not show any amyloid deposits with Congo red stain, while LPS sections from the same regions showed massive amounts of stained amyloid deposits. Sections obtained from tempol-treated mice showed little or no amyloid deposits. Treatment of mice with the lower dose level of perindopril showed a low level of amyloid deposition, while this level was massively declined with the higher dose level (Figs. 19, 20, and 21).

Discussion

The present investigation aims at elucidating mechanistically the possible protective effects of tempol and perindopril against LPS-induced AD in mice. Our results revealed that LPS caused memory impairment (Figs. 2, 4, and 5), coming in agreement with El-Sayed and Bayan (2015) and Wu et al. (2015a). In this model, LPS seems to impair learning capability in experimental mice, not only memory. Control mice showed good learning behavior in the training trials and the test day toward the visible platform in Morris maze test. Alternatively, mice in the LPS group seem to lose their ability to learn after the third day (Fig. 3). It seems that this is the time where significant effects of LPS on the brain become evident. Interestingly, LPS showed no significant changes regarding the open field test or the swimming speed in Morris maze test (Table 1), indicating no effect on locomotor activity, again in agreement with previous studies (Xu et al. 2014; Zhao et al. 2015a, b).

In agreement with our results too (Figs. 6, 7, 19, 20, and 21), Jaeger et al. (2009) reported that LPS administration to experimental animals enhanced brain amyloidogenesis (Maher et al. 2014), while Kirsten et al. (2015) reported that LPS administration to rodents downregulated brain BDNF. LPS administration

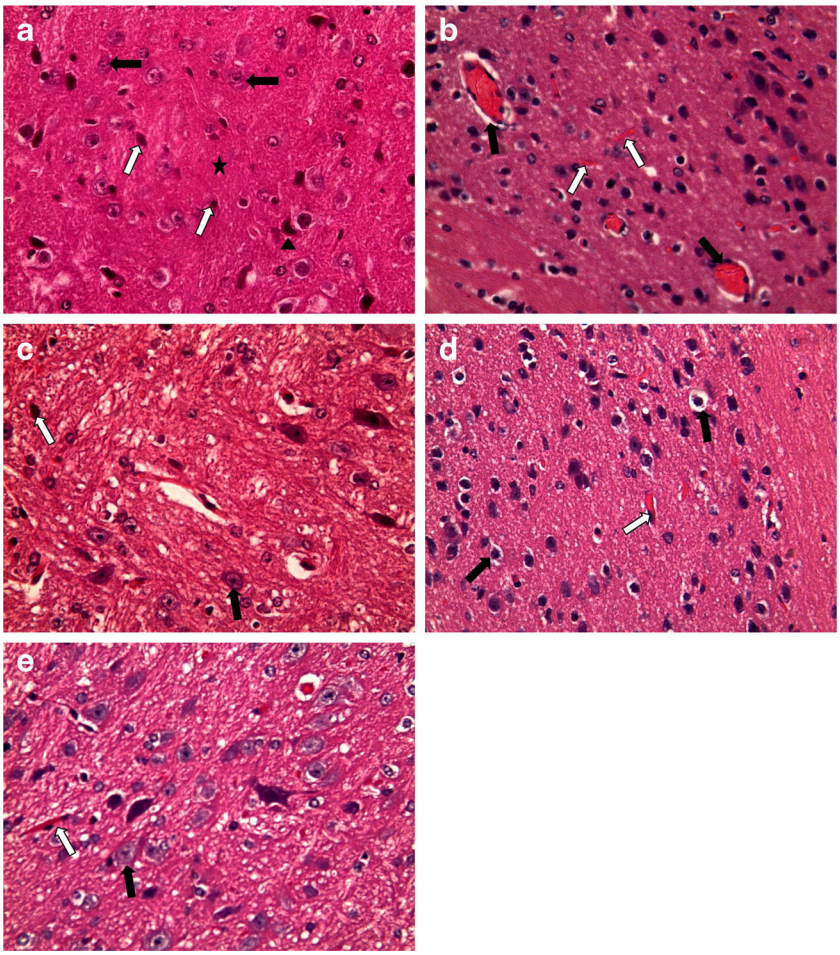

Fig. 16 Photomicrographs of cerebral cortex sections, stained with routine H&E stain (×400), obtained from different groups. Normal control section (**a**) shows histologically intact neurons (*black arrows*) embedded in a framework of neuroglial cells (*white arrows*). Note intensely stained "dark" neurons (*arrowheads*), following manipulation of the unfixed brain. Both neurons and glial cells synapse through neurobil (astrix). LPS control section (**b**) shows many neurons with abnormal cellular deposits (*black arrows*) with many Hirano bodies (*white arrows*). Tempol (100 mg/kg/day) treatment section (**c**) shows normal neurons with vesicular nucleus and prominent nucleolus (*black arrow*) and glial cells (*white arrow*). Perindopril (0.5 mg/kg/day) treatment section (**d**) shows some degenerated neurons with vacuolated cytoplasm and pyknotic nuclei (*black arrows*). Hirano bodies can be also observed. Perindopril (1 mg/kg/day) treatment section (**e**) shows that many neurons are normal with basophilic cytoplasm, vesicular nucleus, and prominent nucleolus (*black arrow*). Hirano bodies can be also observed (*white arrow*)

enhanced immunological inflammation evidenced by upregulation of brain TNF-α (Fig. 8), which was also reported to play a mechanistic role in the pathogenesis of AD (Bhaskar et al. 2014). Excessive NOx production emerged by nNOS and iNOS overexpression was also evident (Fig. 11), again supported by with previous investigations showing excessive NOx production as a result of amyloidogenesis (Li et al. 2010; Choi et al. 2015). Alternatively, excessive NOx production was reported to enhance AD progression through enhanced neuronal degeneration (Malinski 2007; Hu and Zhu 2014). Similarly, brain tissue oxidative stress, evidenced by increased levels of MDA and NT coupled with decreased levels of GSH and SOD (Figs. 12, 13, 14, and 15), was considered, at least partially, as a result of Aβ deposition (Kim et al. 2015) and also as a pathogenic factor enhancing neurodegeneration (Dubinina et al. 2015).

Although most studies on AD focused on the involvement of cerebral cortex and hippocampus, the cerebellum seems to be involved too. In the current study, amyloidogenesis was evident in cerebellum in addition to cerebral cortex and hippocampus (Fig. 21). Previous investigations supported our findings showing

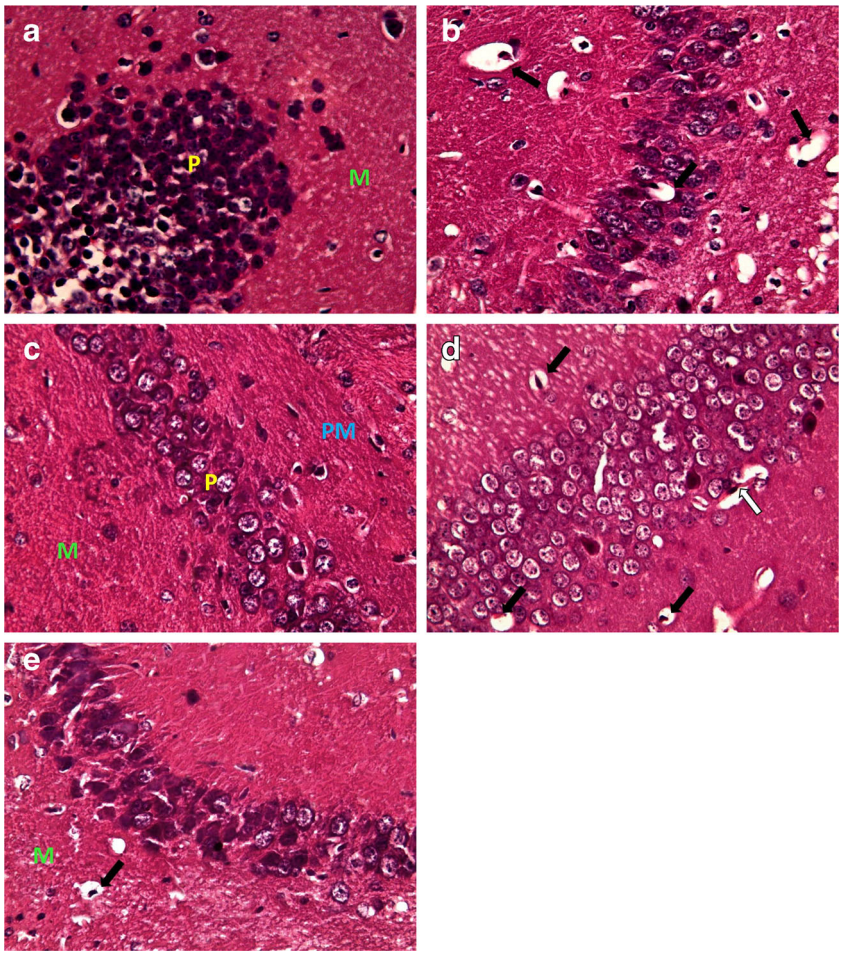

Fig. 17 Photomicrographs of hippocampus sections, stained with routine H&E stain (×400), obtained from different groups. Normal control section (**a**) shows hippocampus formed of three layers; molecular (*M*), pyramidal (*P*), and polymorphic (not seen). LPS control section (**b**) shows many degenerated neurons with vacuolated cytoplasm and pyknotic nuclei (*black arrows*) in all layers. Tempol (100 mg/kg/day) treatment section (**c**) shows that most of neurons are normal in molecular (*M*), pyramidal (*P*), and polymorphic (*PM*) layers. Perindopril (0.5 mg/kg/day) treatment section (**d**) shows few degenerated neurons with vacuolated cytoplasm and pyknotic nuclei (*black arrows*) in all layers. Hirano bodies can be also observed (*white arrow*). Perindopril (1 mg/kg/day) treatment section (**e**) shows molecular layer (*M*) with degenerated cells with pyknotic nuclei (*black arrow*)

amyloidogenesis in mouse cerebellum in different models of AD (Brugg et al. 1995; Hu et al. 2000; Deng et al. 2014). Clinically, Baldaçara et al. (2011) concluded that the cerebellum may provide useful information related to AD prognosis. Interestingly, a number of recent investigations revealed the role of cerebellum in cognition and spatial memory (Rochefort et al. 2013; Tan et al. 2015; Weier et al. 2015).

Our behavioral study revealed that tempol or perindopril significantly improved spatial and nonspatial memory without affecting locomotor activity as evident from the results of open field test and swimming speed (Table 1). Biochemically, both agents significantly improved brain levels of Aβ (Fig. 6). Histopathological findings strongly supported behavioral and biochemical findings (Figs. 16, 17, 18, 19, 20, and 21).

Attractively, administration of test agents resulted in more or less complete protection against LPS-induced cognitive impairment. However, test agents caused only partial protection regarding amyloidogenesis and other biochemical markers. There seems to be a threshold level of amyloidegenesis that must be reached to cause significant impairment of cognition. Otherwise, this asymmetry may be merely attributed to statistical factors.

Little research results are available regarding the effect of tempol on AD, but Rama Rao et al. (2013) revealed that tempol could suppress expression of the matrix proteins thrombospondins in cultured astrocytes, while Han et al. (2015) reported that tempol could decrease cerebral amyloid angiopathy and Aβ deposition in mice through ROS scavenging. Regarding perindopril, Hou et al. (2008); Yamada et al. (2010), and Dong et al. (2011) reported that it could improve impaired cognition induced by intracerebroventricular injection of Aβ in mice, while Yang et al. (2013) reported that perindopril could protect mice against d-galactosamine/aluminum chloride-induced AD. Local RAS was reported to be present in different tissues including

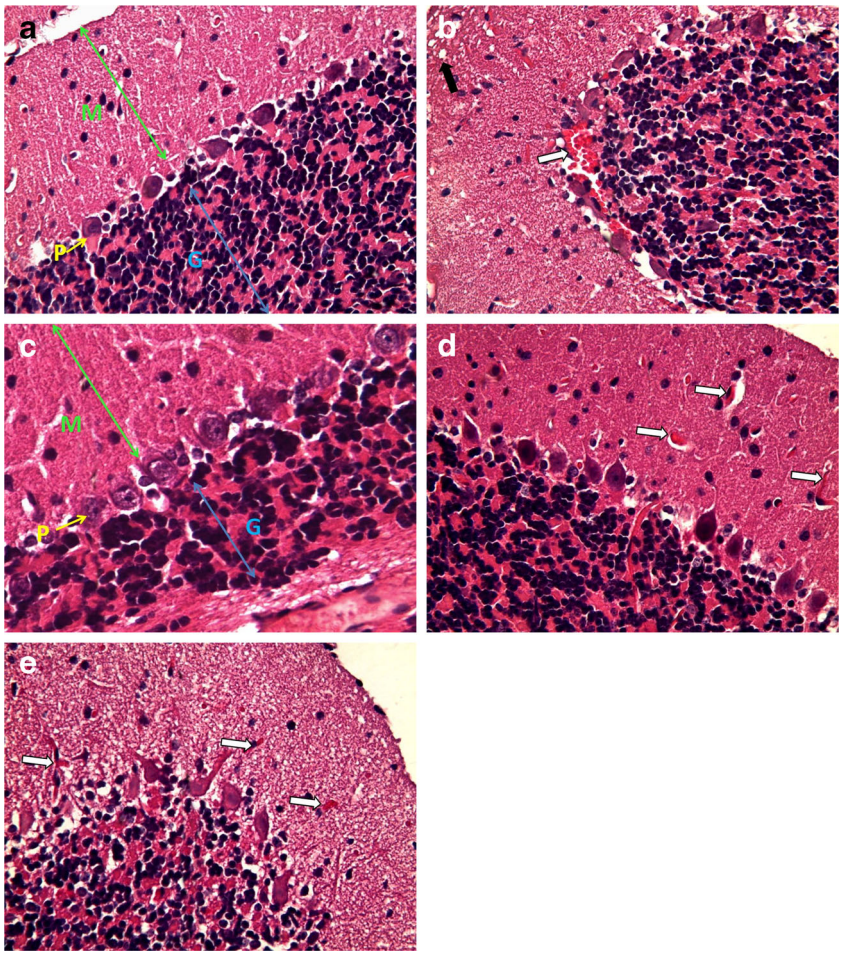

Fig. 18 Photomicrographs of cerebellum sections, stained with routine H&E stain (×400), obtained from different groups. Normal control section (**a**). The cerebellar cortex contains three well-defined layers, which are, from inside to outside, the granular layer (*G*), the Purkinje cell layer (*P*), and the molecular layer (*M*). LPS control section (**b**) shows molecular layer with spongiform changes (*black arrow*) and many Hirano bodies, with hemorrhage within Purkinje cell layer (*white arrow*). Tempol (100 mg/kg/day) treatment section (**c**) shows normal neurons of molecular (*M*), Purkinje (*P*), and granular (*G*) layers of cortex. Perindopril (0.5 mg/kg/day) treatment section (**d**) shows no detected abnormality except for Hirano bodies can be observed (*white arrows*). Perindopril (1 mg/kg/day) treatment section (**e**) shows no abnormality detected except for Hirano bodies can be observed (*white arrows*)

nervous system (McKinley et al. 2003; Paul et al. 2006). Mateos et al. (2011) reported that upregulation of brain RAS is strongly linked with neuronal dysregulation and AD progression.

It is clear from our results that tempol and perindopril significantly improved brain tissue BDNF levels (Fig. 7). This offers an interesting neuroprotective mechanism for both agents. Although this result is not supported by any previous investigations regarding the effects of tempol or perindopril on experimentally-induced AD, Tsai et al. (2012) showed that upregulation of BDNF by antioxidants had a neuroprotective potential in a rat model of status epilepticus. According to the results obtained by Xiong et al. (2015), long-term exercise could improve spatial memory in mice through an increase in BDNF-positive cells in the hippocampus and cerebral cortex. In another study, BDNF upregulation was found to counteract cognitive deficits induced by ethanol in mice through enhancement of hippocampus neurogenesis (Stragier et al. 2015). Side by side, exposure of developing rat brains to anesthesia was reported to yield memory deficiency through epigenetic inhibition of BDNF expression (Wu et al. 2015b).

Concerning our results, tempol and perindopril could suppress brain tissue TNF-α production, indicating anti-inflammatory and immunomodulatory potential (Fig. 8). TNF-α production is a major contributing factor in AD progression (Bhaskar et al. 2014). Kang et al. (2014) reported a strong link between genetic TNF-α overproduction and AD incidence, while Wang (2015) investigated the link between TNF-α polymorphism and AD progression. Similarly, Cantarella et al. (2015) reported that neutralization of TNFSF10, a proapoptotic cytokine similar to TNF-α, may suppress AD progression.

Tempol and perindopril could also decrease NOx production and consequently NT formation, which was explained by suppression of nNOS and iNOS activities (Figs. 9, 10, 11, and 13). Although NOx overproduction

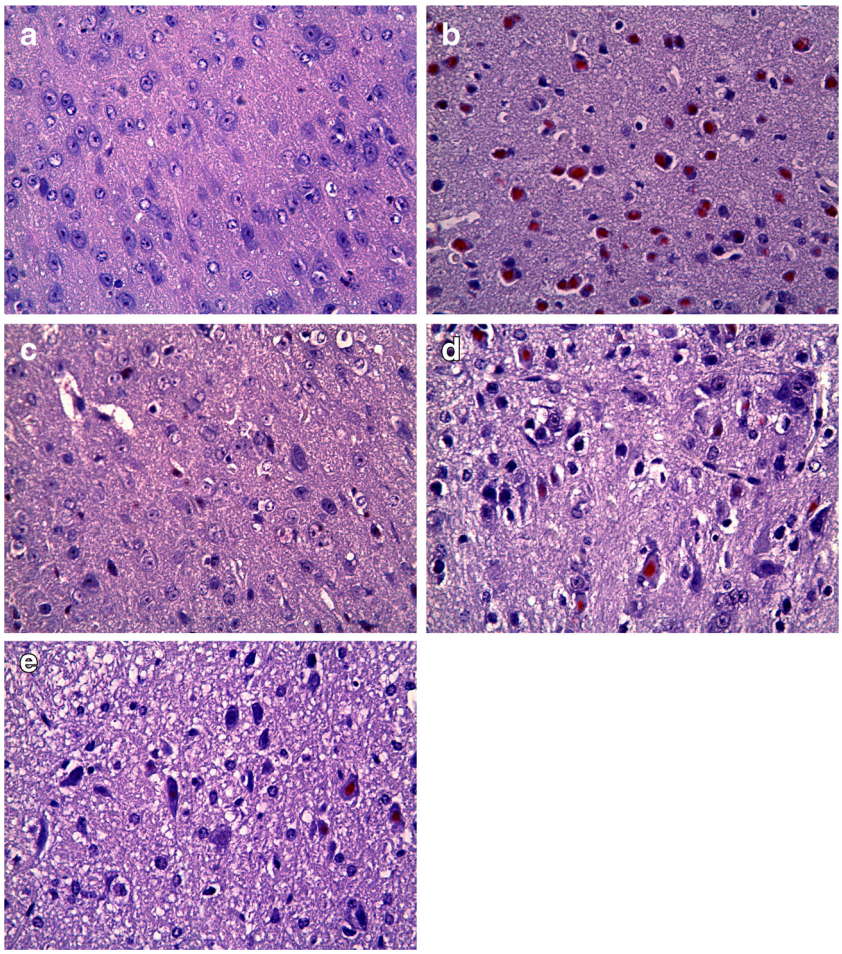

Fig. 19 Photomicrographs of cerebral cortex sections, stained with Congo red (×400), obtained from different groups. Normal control section (**a**) shows no abnormal amyloid deposits. LPS control section (**b**) shows excessive orange-red-stained amyloid deposits. Tempol (100 mg/kg/day) treatment section (**c**) shows little or no amyloid deposition. Perindopril (0.5 mg/kg/day) treatment section (**d**) shows few scattered amyloid deposits. Perindopril (1 mg/kg/day) treatment section (**e**) shows very few deposits of amyloid plaques

and NOS upregulation was reported to occur as a result of intracerebroventricular injection of Aβ in experimental animals (Cetin et al. 2013), NOx overproduction was reported by many authors to stimulate neuronal degeneration (Díaz et al. 2014; Jiang et al. 2014). Guix et al. (2012) reported that nitrosative stress may increase Aβ deposition in brain, while Eraldemir et al. (2015) reported that nitrosative stress could progress AD via suppression of BDNF. This comes in agreement with our results concerning the effect of tempol or perindopril on Aβ and BDNF (Figs. 6 and 7).

Regarding oxido-nitrosative stress markers, tempol and perindopril significantly decreased MDA production and increased GSH stores compared with LPS control values, indicating amelioration of oxidative stress (Figs. 14 and 15). Both agents could enhance endogenous antioxidant defense capacity evidenced by significantly increased brain tissue SOD activity. As mentioned above, oxidative and nitrosative stress play significant pathogenic roles in neuronal damage and AD progression, and this may explain, at least partly, the protective effect of tempol and perindopril in AD (Dubinina et al. 2015). Brain exposure to oxidative stress was reported to precipitate Aβ formation as a compensatory response (Nunomura et al. 2006; Abdel Moneim 2015). Support of antioxidant status was claimed by many authors to suppress AD progression in different models (Braidy et al. 2015; Leirós et al. 2015; Persichilli et al. 2015). Different pathways may explain the correlation between oxidative stress and cognition impairment evident in the current study. Lipid peroxidation caused by ROS yields a peroxidation product termed 4-hydroxnonenal, which differentially affects β- and γ-secretase activities, causing elevation of Aβ42/Aβ40 ratio, in the direction of harmful amyloidogenesis (Arimon et al. 2015). Recently, oxysterol, produced from the interaction of cholesterol with ROS, is considered a key factor in the pathogenesis of AD via enhancement of amyloidogenesis

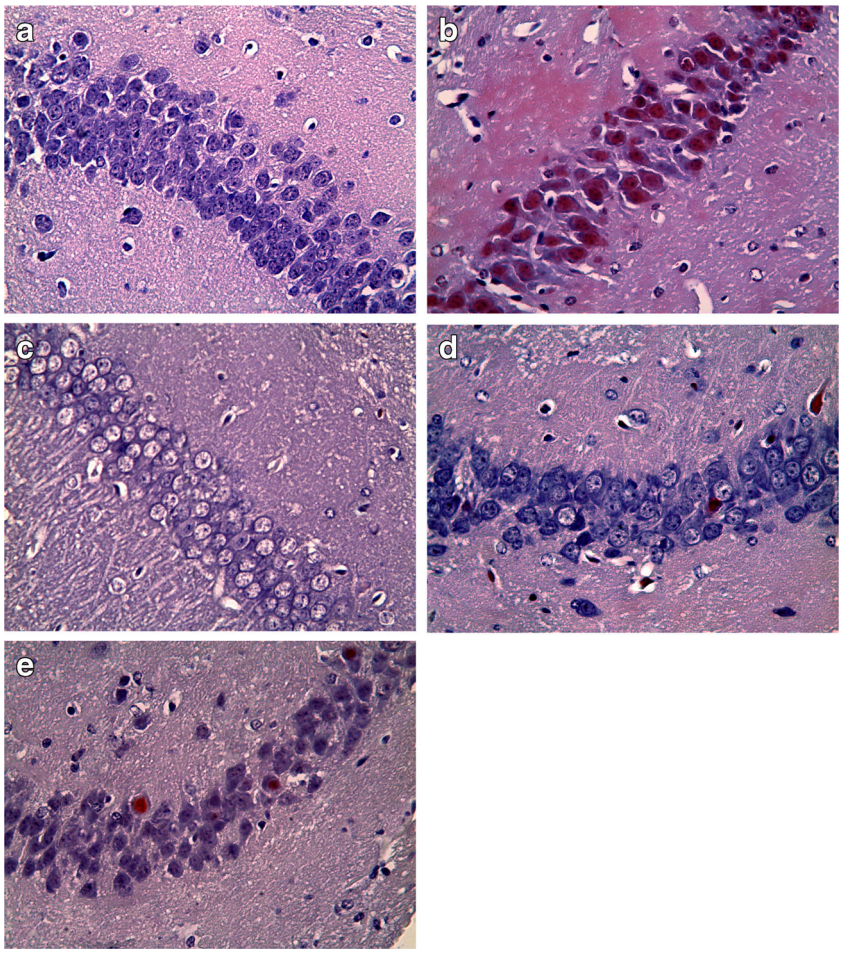

Fig. 20 Photomicrographs of hippocampus, stained with Congo red (×400), obtained from different groups. Normal control section (**a**) shows that amyloid deposits are not evident. LPS control section (**b**) shows excessive amyloid deposits. Tempol (100 mg/kg/day) treatment section (**c**) shows nearly absence of amyloid deposits. Perindopril (0.5 mg/kg/day) treatment section (**d**) shows few scattered amyloid deposits. Perindopril (1 mg/kg/day) treatment section (**e**) shows a very low level of amyloid deposition

(Gamba et al. 2015). Side by side, tempol, owing to its potent antioxidant effect, was reported to suppress pathological glutamate release which precedes neuronal damage (Dohare et al. 2014). This is particularly important when we know that exogenous glutamate was reported earlier to enhance amyloidogenesis in rat hippocampus (Rogers 2015). This further explains the effect of the ROS scavenger tempol regarding amyloidogenesis evident in the current study.

Nitrotyrosine is a very important marker of oxido-nitrosative stress as it is a product of tyrosine nitration by peroxynitrite and other reactive nitrogen species (RNS), while peroxynitrite is the product of interaction between nitrite and hydrogen peroxide (Beckman and Koppenol 1996; Pacher et al. 2007). Peroxynitrite and other RNS are particularly causative factors of neuronal loss and hence suppression of their production may be of particular value in the progression of brain neuronal damage (Tajes et al. 2013; Awooda and Lutfi 2015). Amelioration of NT production by tempol or perindopril in the current study is attractively important (Fig. 13). Although this result is not supported by any previous investigation regarding the effects of tempol or perindopril on NT production in animal models of LPS-induced neuroinflammation, the effects of test agents on NT and RNS production may offer another protective mechanism for test agents. Attractively, NT itself was reported to play a key role in the pathogenesis of AD via nitrotyrosination of the γ-secretase catalytic site, shifting towards harmful amyloidogenesis (Guix et al. 2012).

Several signaling pathways were reported to link oxidative stress with neurodegeneration, of which the most prominent are mitogen-activated protein kinase (MAPK) and NADPH oxidase (Rowan et al. 2004). Oxidative stress causes activation of MAPK and NADPH oxidase mostly through hydrogen peroxide and other ROS (Cao et al. 2014). The activated MAPK in particular was reported to play a role in neuroinflammation, neurodegeneration, and Aβ

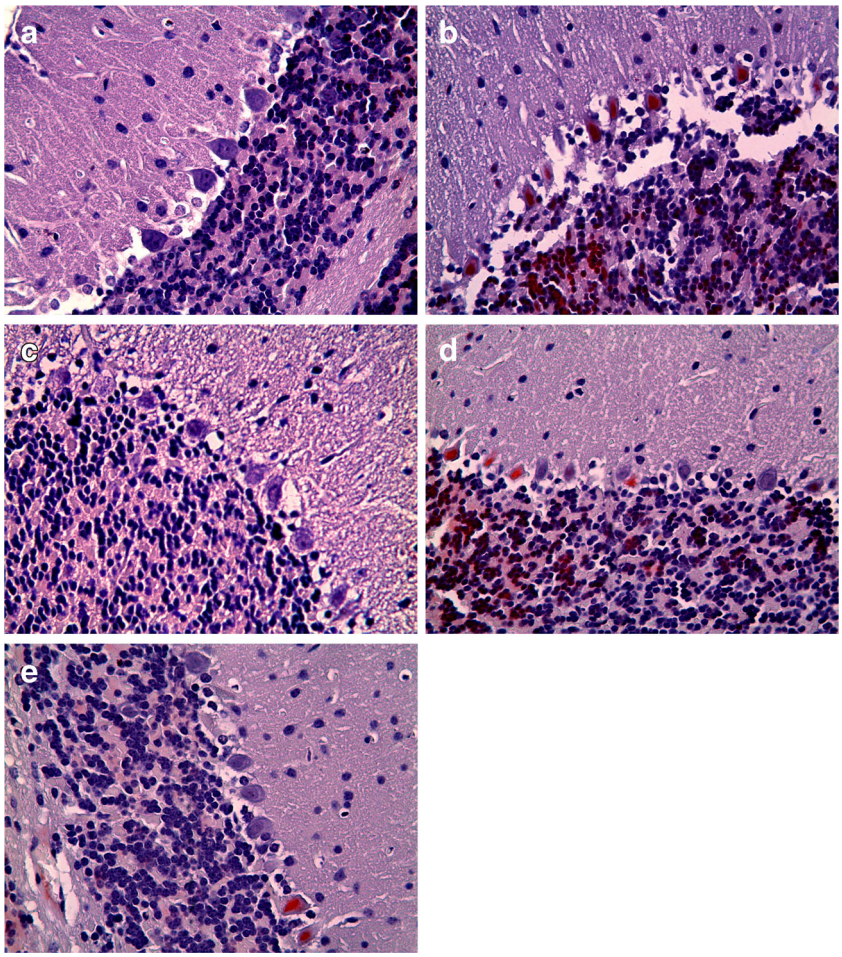

Fig. 21 Photomicrographs of cerebellum sections, stained with Congo red (×400), obtained from different groups. Normal control section (**a**) shows absence of stained amyloid deposits. LPS control section (**b**) shows massive deposition of amyloid plaques. Tempol (100 mg/kg/day) treatment section (**c**) shows more or less absence of amyloid deposits. Perindopril (0.5 mg/kg/day) treatment section (**d**) shows limited amyloid deposition. Perindopril (1 mg/kg/day) treatment section (**e**) shows very few amyloid depositions

internalization in cortical neurons in the early stages of AD (Liu et al. 2014; Bellaver et al. 2015; Yang et al. 2015). Moreover, MAPK was reported to play an important role in tau phosphorylation during the course of AD progression (Giraldo et al. 2014). Side by side, Li et al. (2015) concluded that MAPK down-regulation could protect rats against Aβ-induced cognition impairment. On the other hand, NADPH oxidase stimulated by oxidative stress was reported to play a role in neurobehavioral impairment in mice (Yuan et al. 2015). The reverse is also true, as NADPH oxidase activation triggers oxidative stress via superoxide anion production (Chen et al. 2012; Zhang et al. 2012). This is a further guide to explain the neuroprotective effects of the SOD mimetic tempol and the NADPH oxidase indirect inhibitor perindopril.

In conclusion, tempol and perindopril are promising agents against amyloidogenesis and cognition impairment. The protective mechanisms may include suppression of BDNF decline, suppression of TNF-α production, support of brain antioxidant status, and amelioration of oxido-nitrosative stress and NT production.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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