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Rosiglitazone attenuates lipopolysaccharide-induced depressive-like behavior and cognitive deficits in mice

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Abstract

Previous studies have shown that neuroinflammation induced by lipopolysaccharide (LPS) cause depressive-like behavior and cognitive deficits in rodents. A number of studies have demonstrated that rosiglitazone, an agonist of peroxisome proliferator–activated receptor gamma (PPAR-γ), exerts neuroprotective effects in experimental models of neurological and psychiatric diseases. In this study, we aimed to evaluate the putative protective effects of rosiglitazone treatment on LPS-induced depressive-like behavior and cognitive deficits in mice. Animals were treated with rosiglitazone (5mg/kg, v.o.) one hour before LPS (0.5mg/kg, i.p.) administration. One day after LPS infusion, mice were submitted to the behavioral tests and, thereafter, biochemical determinations were performed. Rosiglitazone prevented an LPS-induced increase in the duration of immobility in tail suspension and forced swim tests, indicating an antidepressant-like effect. Rosiglitazone significantly prevented the decrease in spontaneous alternations induced by LPS in the Y-maze test. In the inhibitory avoidance task, LPS decreased the step-down latencies in the test session, which were ameliorated by rosilgitazone treatment. In the open field test, no changes in ambulation were observed. Rosiglitazone prevented LPS-induced increase in TNF-α and reduction of brain-derived neurotrophic factor (BDNF) levels in the hippocampus. Rosiglitazone also improved LPS-induced increase in lipid peroxidation and the reduction of glutathione levels in the hippocampus. Our findings suggest that rosiglitazone may possess neuroprotective effects against LPS-induced depressive-like behavior and cognitive deficits through attenuation of neuroinflammation, oxidative damage, and normalization of BDNF levels.

Introduction

Depression is a common and debilitating mental disease estimated to affect 350 million people of all ages across the world [1]. Core symptoms of depression include low mood, anhedonia, cognitive dysfunction, loss of interest, loss of energy, suicidal ideation and disturbed sleep or appetite [2]. Conventional treatment of depression is based on drugs that modulate monoaminergic transmission [3]. This traditional pharmacotherapy presents delayed onset of clinical action, provides a complete remission in only 50% of individuals and is associated with several side effects that make it difficult for patients adherence to the treatment [4]. Thus, there is a need to develop new highly effective and rapid-acting therapeutic strategies to treat depressive disorders.

Despite several pathophysiological hypotheses, the mechanisms underlying depression are not completely understood. However, previous studies have implicated an interaction between inflammation and depression [5,6]. Increased serum levels of pro-inflammatory cytokines have been demonstrated in depressed patients [7]. In mice, systemic administration of the bacterial endotoxin, lipopolysaccharide (LPS), has been shown to induce behavioral alterations such as depressive-like behavior and cognitive impairment [8,9]. LPS induces brain expression of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), promotes oxidative stress and decreases brain-derived neurotrophic factor (BDNF) levels [10,11]. These neurotoxic effects have been implicated in LPS-induced depressive-like behavior and memory impairments [12,13].

The ligand-activated peroxisome proliferator–activated receptor γ (PPAR-γ) is a member of the nuclear receptor superfamily that plays an important role in glucose homeostasis and lipid metabolism [14]. Rosiglitazone, a thiazolidinedione drug, is an agonist of PPAR-γ used for the treatment of type II diabetes [15]. Besides, rosiglitazone is known to exert neuroprotective effects in models of Alzheimer's disease, Parkinson's disease, Huntington's disease, epilepsy, stroke and traumatic brain injury [16,17]. Moreover, the antidepressant-like effect of rosilgitazone in mice has been demonstrated in an experimental model [18,19]. The neuroprotective effects of rosiglitazone have been attributed to attenuation of neuroinflammation and mitochondrial dysfunction [20].

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However, the mechanisms involved in the neuroprotective effects of rosiglitazone are not fully elucidated.

Therefore, we aimed to evaluate the efficacy of rosiglitazone in the behavioral alterations induced by LPS activation of the immune system. Besides, we evaluated whether rosiglitazone actions would be related to modulation of TNF-α expression, decrease in oxidative stress parameters and normalization of BDNF levels in the hippocampus of LPS treated mice.

Methods

Subjects

Female adult Swiss albino mice (30–40 g) were kept on a 12-h light/dark cycle (lights on at 07.00 a.m.) at a temperature of 22 ± 1º C. Mice were obtained from the Central Animal Facility of the Universidade Federal de Mato Grosso. They were housed in plastic cages with tap water and commercial food ad libitum. All procedures were carried out according to the institutional policies on animal experimental handling, designed to minimize suffering and limit the number of animals used and were approved by local Ethical Committee for Animal Research (CEUA/UFMT, protocol number: 23108.098456/2015-93).

Reagents

Lipopolysaccharide from Escherichia coli (strain 055:B5), rosiglitazone, reduced glutathione and bovine serum albumin were purchased from Sigma (St. Louis, MO, USA). TNF-α immunoassay kits were purchased from BD Biosciences (BD Biosciences Laboratory Ltd. USA). The ELISA kit for the measurement of BDNF was purchased from Promega (Madison, WI, USA). All other chemicals were of analytical grade and were purchased from standard commercial suppliers.

Experimental design and treatments

Mice were treated with the vehicle (saline, 0.9%, p.o) or rosiglitazone (5mg/kg, p.o.). The dose of rosiglitazone used was chosen based on previous studies [19,21]. LPS was dissolved in sterile saline. One hour after rosiglitazone administration, mice were injected with saline or LPS (0.5 mg/kg, i.p.). The dose of LPS was chosen based on previous studies [10,22]. All solutions were freshly prepared on the day of injection and administered at a volume of 10ml/kg of body weight. Twenty-four hours after LPS or saline treatment, mice were submitted to behavioral tests. For biochemical analysis, mice were euthanized by decapitation, brains were rapidly removed, the hippocampi isolated and were used for neurochemical assays.

Forced swimming test (FST)

For the FST, mice were individually forced to swim in an open cylindrical container (diameter 10 cm, height 25 cm), containing 19 cm of water (depth) at 25 ±1°C; the total amount of time each animal remained immobile during a 6-min session was recorded (in seconds) as immobility time [23]. Each mouse was judged immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water. A decrease in the duration of immobility is indicative of an antidepressant-like effect [24].

Tail suspension test (TST)

The total duration of immobility induced by tail suspension was measured according to the method previously described [25]. Mice that were both acoustically and visually isolated were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time was recorded during a 6-min period. Mice were considered immobile only when they hung passively or stayed motionless. Conventional antidepressants decrease the immobility time in this test [25].

Open field test (OFT)

Measurement of locomotor activity in the OFT was performed as previously described [26]. The apparatus consisted of a wooden arena (30 × 30 × 15 cm) with the floor divided in nine equal squares. The experiments were conducted in a sound-attenuated room and light intensity in the centre of the apparatus was 110 lx. Mice were placed in the center of the open field and the number of squares crossed by each mouse with its four paws for 5 min was considered as indicative of locomotor activity. The arena floor was cleaned with a 70% ethanol solution between the trials.

Y-maze task

Spontaneous alternation, which is a measure of spatial working memory, was assessed in the Y-maze task. The Y-maze apparatus consisted of a three-arm horizontal maze with equal angles between all arms. Each arm was 30 cm length and 5 cm width, with walls 12 cm high and converged in an equilateral triangular central area. Each mouse was placed at the end of one arm and allowed to freely move through the maze for 8 min. The sequence and number of arm entries were recorded manually. Entry was considered to be completed when the hind paws of the mouse had been completely placed in the arm. An alternation was defined as entries in all three arms on consecutive occasions. The percentage of alternation was determined by dividing the total number of alternations by the total number of choices minus 2 multiplied by 100 as shown in the following equation: % Alternation = [(Number of alternations) / (Total arm entries − 2)] × 100. The number of arm entries serves as an indicator of locomotor activity [27]. The apparatus was cleaned with a 70% ethanol solution between each trial.

Step-down inhibitory avoidance (IA) task

The step-down inhibitory avoidance apparatus consisted of a 50-cm × 25-cm × 25-cm acrylic box with the front and superior wall made of transparent acrylic. The apparatus floor consisted of a grid of parallel stainless-steel bars of 1 mm diameter spaced 1 cm apart. A 22x5-cm wide, 2-cm high acrylic platform was placed in the left end of the box floor. Mice were placed on the platform facing the left corner of the training box, and their latency to step down on the grid with all four paws was measured. Mice were submitted to the IA task using a protocol similar to that described previously [28]. During the training session, immediately after stepping down on the grid, the animals received a scrambled foot shock (0.5 mA for 2 s) and were then removed from the box. Test sessions were performed 24 h after the training. Test sessions were procedurally identical to training session except that no foot shock was given and the step-down latency (maximum 180 s) was used as a measure of retention. The measure of memory retention of this test consists of delay of the latency to step-down in test session when compared to the training session.

Non-protein thiol groups (NPSH) determination

Hippocampi were dissected and homogenized (1:10 w/v) in phosphate buffer (50 mM, pH 7.4). Homogenates were centrifuged at 1000g for 10 min at 4º C to discard nuclei and cell debris. NPSH was determined as previously described [29] with slight modifications. NPSH compounds were measured in an aliquot (60 µl) of hippocampal

homogenates after protein precipitation with one volume of 10 % trichloroacetic acid. After centrifugation (10,000g for 10 min at 4º C), samples were added to 800 mM phosphate buffer, pH 7.4, and 500 µM 5,50-dithiobis-2-nitrobenzoic acid. Color development resulting from the reaction between 5,50-dithio-bis-2-nitrobenzoic acid and thiols reached a maximum in 5 min and it was stable for more than 30 min. Absorbance was read at 412 nm after 10 min. A standard curve of reduced glutathione (GSH) was used to calculate NPSH concentrations in samples and the results were expressed as nmol NPSH/mg protein.

Determination of thiobarbituric acid reactive substances (TBARS)

Thiobarbituric acid reactive substances were determined in tissue homogenates as previously described [30], in which malondialdehyde (MDA), a product of lipid peroxidation, reacts with TBA to form a colored complex. In brief, an aliquot (100µl) of tissue homogenates supernatant was collected and incubated at 100º C for 60 min in acid medium containing 0.45 % sodium dodecyl sulfate and 0.6 % TBA. After centrifugation (10,000g for 10 min at 20ºC), the reaction product was determined at 532 nm using 1,1,3,3-tetramethoxypropane as the standard, and the results were expressed as nmol MDA/mg protein.

Estimation of TNF-α and BDNF levels

The hippocampi were homogenized in ten volumes of phosphate-buffered saline (PBS) buffer with protease and phosphatase inhibitors (Sigma–Aldrich) and centrifuged at 4,000 rpm for 20 min. The concentration of TNF-α and BDNF in 50µl samples was determined by the Enzyme-Linked Immunosorbent Assay (ELISA), according to the manufacturer's instructions. The sample values were then read from the standard curve. TNF-α and BDNF levels were expressed in pg/g tissue and ng/g tissue, respectively.

Measurement of protein content

Protein content was evaluated by the method of Lowry [31]. Bovine serum albumin was used as standard.

Statistical analysis

Data were expressed as mean ± S.E.M. Comparisons among groups were performed by one-way analysis of variance (ANOVA) followed by Newman-Keuls's post hoc test when appropriate. Data obtained in IA task were expressed as medians and interquartile range and were analysed by the Kruskal–Wallis test. Comparisons between groups were determined by Mann–Whitney *U* tests (two-tailed). P values of less than 0.05 were regarded as statistically significant.

Results

Rosiglitazone prevents LPS-induced depressive-like behavior

One-way ANOVA revealed the main effect in the duration of immobility time in the TST [$F(3,24)=11.76$, $P<0.01$]. Post-hoc analysis indicated that LPS administration promoted a significant increase in the duration of immobility in the TST as compared to control group ($P<0.01$) and this effect was prevented by rosiglitazone treatment ($P<0.05$) (Figure 1A). In the FST, one-way ANOVA also revealed statistically significant alteration in the duration of immobility [$F(3,31)=6.85$, $P<0.01$] (Figure 1B). Newman-Keuls post-hoc test revealed that LPS administration increased immobility duration as compared to the control group ($P<0.01$). Rosiglitazone treatment prevented the increase in immobility time induced by LPS injection ($P<0.01$) in the FST.

Rosiglitazone prevents LPS-induced cognitive deficits

Spatial working memory, as evaluated by the Y-maze test, revealed that LPS-treated mice presented a significant reduction in the percentage of correct alternations as compared to the control group $F(3,27)=5.73$, $P<0.01$] (Figure 2). Whereas, administration of rosiglitazone significantly prevented the alterations induced by LPS injection ($P< 0.01$) (Figure 2).

Long-term memory was evaluated in the IA task. There were no significant differences in the step-down latencies during the training session across all groups ($P=0.67$) (Figure 3). LPS administration significantly decrease the step-down latency when compared to the control group in the test session ($P<0.05$) (Figure 3), suggesting that LPS treatment promoted an impairment of aversive memory. The administration of rosiglitazone significantly prevented the LPS induced a decrease in the latency to step-down in the test session ($P< 0.05$) (Figure 3).

Effects of rosiglitazone or LPS on locomotors activity

No significant difference was found among groups in the number of crossings in the OFT [$F(3,31)=0.35$, $P=0.78$] (Figure 4). These data indicated that treatment with rosiglitazone or LPS did not alter locomotor activity.

Effects of rosiglitazone on TNF-α levels in the hippocampus

LPS injection promoted an increase in hippocampal levels of TNF-α as compared to control group [$F(3,26)=27.58$, $P<0.01$]. Rosiglitazone treatment significantly prevented the LPS-induced increase in TNF-α levels ($P<0.01$) (Figure 5).

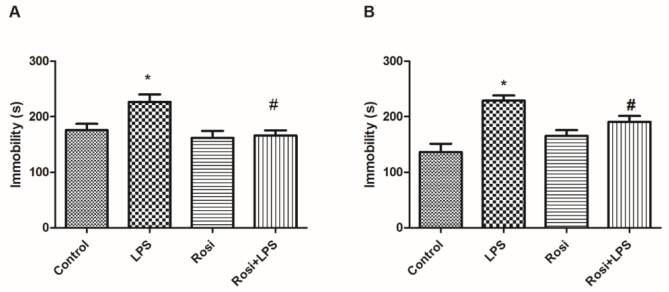

Figure 1. Effect of rosiglitazone treatment on behavioral alterations in the FST and TST promoted by Lipopolysaccharide (LPS) in mice. Mice (n=7-9 mice/group) were treated with vehicle (saline 0.9%, v.o., Control group) or rosiglitazone (5 mg/kg, v.o., rosi group) 60 min before LPS administration (0.5 mg/kg, i.p.). After 24h of LPS injection, mice were subjected to behavioral test immobility time in the FST (A) and TST(B) The values represent mean ± SEM. * means significantly different from control group. # means significantly different from LPS group. P<0.05 (ANOVA followed by Newman-Keuls)

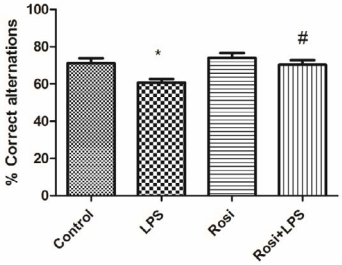

Figure 2. Effect of rosiglitazone treatment on behavioral alterations promoted by Lipopolysaccharide (LPS) in the Y-maze Test. The values represent mean ± SEM (n=7-8 mice/group). * means significantly different from the control group. # means significantly different from the LPS group. P<0.05 (ANOVA followed by Newman-Keuls)

Effects of rosiglitazone on oxidative stress parameters in the hippocampus

Figures 6A and 6B show the effects of rosiglitazone on LPS-induced alterations on oxidative stress parameters. LPS administration promoted a decrease in hippocampal GSH levels [$F(3,27)=4.52$, $P<0.05$] in comparison to control group, while rosiglitazone treatment prevented this effect ($P<0.05$) (Figure 6A). ANOVA demonstrated significant alterations in the MDA levels among the groups [$F(3,27)=4.56$, $P<0.05$]. Post-hoc analysis demonstrated that LPS injection induced an increase in the MDA levels in comparison to the control group ($P<0.05$) and that rosiglitazone treatment prevented this elevation ($P<0.01$) (Figure 6B).

Effects of rosiglitazone on BDNF levels in the hippocampus

LPS administration significantly reduced the hippocampal BDNF level as compared to the control group [$F(3,26)=11.43$, $P<0.01$]. Rosiglitazone treatment significantly prevented the reduction in the BDNF level in the hippocampus induced by LPS ($P<0.01$) (Figure 7).

Discussion

It has been shown that cytokines produced during activation of the immune system affect the behavior of humans and rodents. In the present study, we aimed to evaluate if activation of PPAR-γ would attenuate the behavioral and neurochemical alterations promoted by immune system activation following LPS administration in mice. Here, we observed that PPAR-γ agonist, rosiglitazone, ameliorated depressive-like behavior and memory impairments induced by systemic LPS administration. Of note, rosiglitazone attenuated LPS-induced

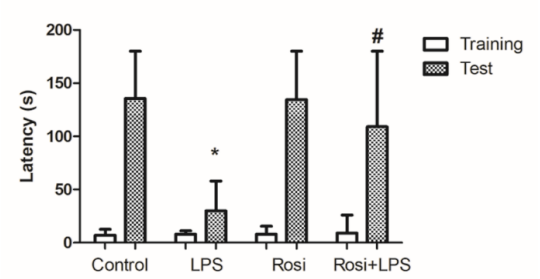

Figure 3. Effect of rosiglitazone treatment on behavioral alterations promoted by Lipopolysaccharide (LPS) in the Inhibitory Avoidance Task. The values represent median and interquartile ranges of latencies to step-down in the training and test sessions (n=10-12 mice/group). * means significantly different from control group during the test session. # means significantly different from LPS group during the test session. P<0.05 (Kruskal-Wallis test)

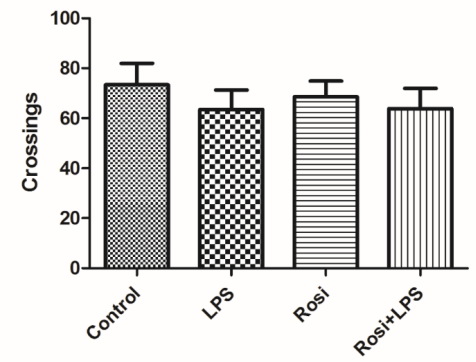

Figure 4. Effect of rosiglitazone treatment in the OFT in mice challenged with LPS. The values represent mean ± SEM. N = 8 mice/group. (One-way ANOVA)

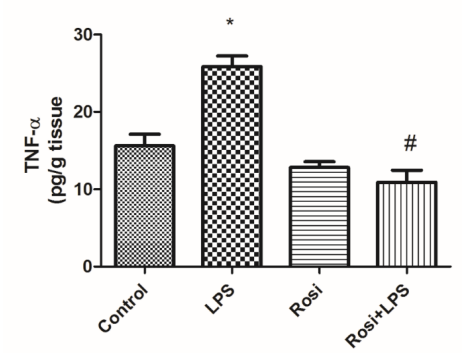

Figure 5. Effect of rosiglitazone treatment on lipopolysaccharide (LPS)-induced increase in hippocampal levels of t*umor necrosis* factor-α (TNF-α). The values represent mean ± SEM (n=7-8 mice/group). * means significantly different from control group. # means significantly different from LPS group. P<0.05 (ANOVA followed by Newman-Keuls)

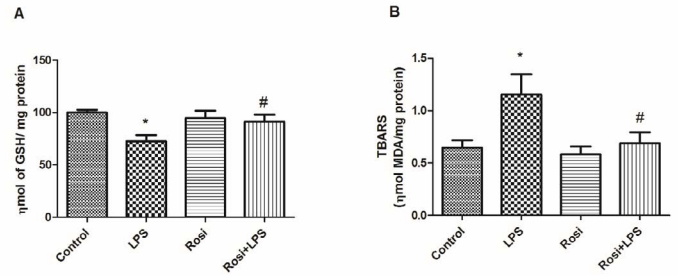

Figure 6. Effect of rosiglitazone treatment on LPS induced oxidative stress in the hippocampus: (A) reduced glutathione (GSH) levels and (B) thiobarbituric acid reactive substances (TBARS) content. The values represent mean ± SEM. N=7-9 mice per group. * means significantly different from control group. # means significantly different from the LPS group. P<0.05 (ANOVA followed by Newman-Keuls)

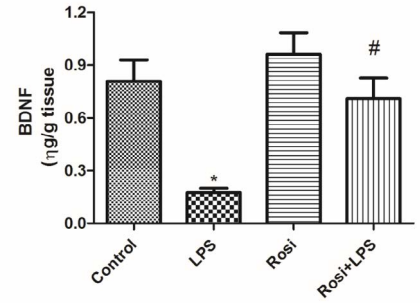

Figure 7. Effect of rosiglitazone treatment on lipopolysaccharide (LPS)-induced decrease in hippocampal levels of brain-derived neurotrophic factor (BDNF) in mice. The values represent mean ± SEM (n=7-8 mice/group). * means significantly different from control group. # means significantly different from the LPS group. P<0.05 (ANOVA followed by Newman-Keuls)

increase in TNF-α level, oxidative stress and restored the decrease in BDNF levels.

Neuroinflammation has been intimately associated with depression pathogenesis [32]. In preclinical studies, the cytokine inducer LPS has been demonstrated to promote behavioral alterations in mice, some of which, resemble depressive symptoms in humans [33]. Using two validated depression tests in rodents, the FST and the TST, we observed that LPS administration increased immobility time indicating an increase in depressive-like behavior, which is in agreement with previous studies [34,35]. Apart from the classical depressive symptoms, evidence indicates that depressed patients also display cognitive impairment [36]. In this vein, elevated levels of pro-inflammatory cytokines in the brain,

besides exacerbating depressive-like behavior, have been shown to result in cognitive deficits in rodents [37]. In the current study, working memory and long-term memory were evaluated in the Y-maze and IA tasks, respectively. In the Y-maze test, LPS injection induced a decrease in the percentage of correct alternations indicating an impairment of spatial working memory. This is in agreement with previous studies that have demonstrated that LPS injection can impair mice and rat's performance in the Y-maze task [38-40]. In the IA task, LPS induced a decrease in the latency to step-down in the test session that indicates an impairment of IA learning. Since the test session was conducted 24h after the training session, it may represent a long-term memory impairment. In addition, it has been demonstrated that LPS can impair long-term memory in other behavioral tests such as the step-through and water maze tasks [41,42].

In this study, rosiglitazone prevented depressive-like behavior in the TST and FST induced by systemic LPS administration. In agreement with our results, it has been demonstrated that pioglitazone, another PPAR-γ agonist, improved the depressive-like behavior induced by central administration of LPS [43]. Moreover, rosiglitazone has been shown to exert antidepressant-like effects in other rodent models of depression. Zhao and cols [19] have demonstrated that rosiglitazone treatment attenuated depressive-like behavior induced by unpredictable chronic mild stress [19]. Besides, rosiglitazone ameliorated chronic restraint stress or neuropathic pain induced depressive-like behavior [44,45]. Interestingly, PPAR-γ agonists treatment alone or in combination with conventional treatments have been shown to improve depressive scores in human patients [46]. Beyond preventing LPS-induced depressive-like behavior, we observed that rosiglitazone also attenuated LPS-induced memory impairments in the Y-maze and IA tasks. In agreement with our results, previous reports have shown that PPAR-γ agonists improved the cognitive deficits in the Morris water maze and passive avoidance induced by Aβ42 [47], 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Kumar et al. 2009) or streptozotocin [48]. Furthermore, rosiglitazone has been shown to prevent LPS-induced spatial memory impairment [49]. In this referred study, memory evaluation was performed at four weeks after LPS injection, a period after the cessation of the depressive symptoms [49]. Importantly, as there was no significant statistical difference in the number of crossings in the OFT, the behavioral alterations promoted by LPS and the protective effects of rosiglitazone in our findings cannot be related to alterations in locomotor activity of the mice.

Clinical studies demonstrated that depressed patients display elevated levels of TNF-α which may be related to the development of depressive symptoms and cognitive decline observed in these patients [7,50,51]. In accordance to this, preclinical studies demonstrated that TNF-α administration to rodents exacerbate depressive-like behavior and blockade of TNF-α receptors exerts antidepressant and pro-cognitive effects [50,52,53]. In our findings, rosiglitazone prevented the LPS-induced increase in TNF-α level in the hippocampus. In a similar manner, previous studies associated rosiglitazone neuroprotective effects to the attenuation in the increase in TNF-α level in the rodent models of neuropsychiatric disorders [54,55]. Increased levels of TNF-α may be caused by activation of NF-κB in microglia [56]. In fact, it has been demonstrated that PPAR-γ activation may exert anti-inflammatory actions through inhibition of NF-κB signalling, which may prevent the expression of pro-inflammatory cytokine [43,57]. Taken together, it may be suggested that antidepressant-like effects of rosilgitazone is related to reduction of TNF-α levels in LPS treated mice.

LPS induced the expression of pro-inflammatory cytokines and activation of microglia may promote an increase in the production of reactive oxygen (ROS) species [58]. This may cause deleterious effects to the brain since it is highly vulnerable to oxidative damage [59]. This vulnerability arises from a high production of ROS due to its elevated aerobic metabolic activity, lower antioxidant defences and high content of polyunsaturated fatty acids, which may undergo peroxidation [59]. In the present study, we observed that LPS administration induced an increase in MDA levels and a decrease in GSH levels in the hippocampus. These alterations may contribute to LPS induced behavioral alterations as compounds with antioxidant actions have been shown to prevent LPS induced depressive-like behavior [10,11,60] or memory impairments [61-63]. In our study, rosiglitazone treatment ameliorated LPS-induced reduction of antioxidant status in the hippocampus. Our results are in line with previous reports, which demonstrated that the neuroprotective effects of PPAR-γ agonists might be related to the prevention of increased MDA levels and reduction of GSH levels in the brain [64-66]. In humans, the increased levels of MDA and decreased levels of GSH have been associated with depressive symptoms and cognitive decline [67-69]. In this way, rosiglitazone prevention of depressive-like behavior and cognitive deficits may be related to the reduction of LPS induced oxidative stress.

Growing pieces of evidence suggest that neurogenesis and neuronal plasticity are compromised in major depression [70]. Lower BDNF levels have been observed in people with depression [71] and it is known that antidepressant treatment increases BDNF level in depressed patients [72-74]. Furthermore, BDNF is required for memory consolidation [75], and that cognitive deficits found in depressive disorders may be related to the decrease in BDNF levels [76]. In rodents, neuroinflammation caused by LPS exposure has been shown to decrease hippocampal BDNF expression [77]. Moreover, the decrease in BDNF levels has been implicated in the depressive-like behavior and memory deficits observed after LPS administration in rodents [78-80]. Here, we observed that rosiglitazone administration prevented LPS-induced decrease in BDNF levels in the hippocampus. This is in agreement with a recent study where pioglitazone prevented the alterations in CREB/BDNF signalling pathway induced by central administration of LPS [43]. Besides, rosiglitazone has been shown to prevent the decrease in BDNF levels in the neuropathic pain model of depression [45] and to increase the expression of BDNF in a diabetes model of cognitive deficits [81].

Conclusions

In conclusion, these findings demonstrated that rosiglitazone treatment ameliorated LPS-induced depressive-like behavior and memory impairment in mice. Rosiglitazone attenuated LPS-induced neuroinflammation and oxidative stress in mice brain. Besides, rosiglitazone treatment prevented the reduction of BDNF levels in the hippocampus. Taking together, these findings demonstrate a potential role of rosiglitazone in the treatment of depressive and cognitive deficits following neuroinflammation.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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