Int J Clin Exp Med 2019;12(3):2310-2317
www.ijcem.com /ISSN:1940-5901/IJCEM0081024

Original Article

Propofol inhibition of microglial inflammatory processes through the toll-like receptor 4-p38 mitogen-activated protein kinase signaling pathway

Sunren Sheng[2], Ruifeng Zeng[1], Peishun Qin[1], Yizhao Pan[1], Xuefei Ye[1]

Departments of [1]Anesthesiology, [2]Orthopaedics, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang, China

Received June 7, 2018; Accepted December 11, 2018; Epub March 15, 2019; Published March 30, 2019

Abstract: We investigated the effects of propofol on inflammatory processes induced by lipopolysaccharide (LPS)-treated microglia and elucidated the role of the toll-like receptor 4 (TLR4)-p38 mitogen-activated protein kinase (MAPK) pathway in such effects. First, BV-2 microglia were divided into control, propofol (30 μM), LPS (1 μg/mL), and LPS+ propofol (1 μg/mL LPS+ 30 μM propofol) groups. Then, enzyme-linked immunosorbent assay (ELISA) and MTT, polymerase chain reaction (PCR), and western blot assays were utilized to determine cell viability, inflammatory factors in the cell culture supernatant, and the expression of essential proteins in the TLR4-p38 MAPK inflammatory pathway. Microglial activation was significantly stronger in the LPS and LPS+ propofol groups than in the control and propofol groups ($P < 0.05$). The microglial cell viability was higher in the LPS+ propofol group than it was in the LPS group ($P < 0.05$). The interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α levels were higher in culture supernatant from the LPS and LPS+ propofol groups than they were in the control and propofol groups; the IL-1β, IL-6, and TNF-α levels were lower in the supernatant medium from the LPS+ propofol group than they were in the LPS group ($P < 0.05$). PCR and western blot results showed that microglial p38MAPK and TLR4 mRNA and protein expression was significantly higher in the LPS and LPS+ propofol groups than in the control and propofol groups ($P < 0.05$). Microglial p38 MAPK and TLR4 mRNA and protein expression was significantly lower in the LPS+ propofol group than in the LPS group ($P < 0.05$). Thus, our results indicated that propofol inhibits microglial activation and inflammatory reactions by possibly downregulating the TLR4-p38 MAPK signaling pathway.

Keywords: Inflammation, lipopolysaccharide, microglia, propofol, toll-like receptor 4

Introduction

Postoperative cognitive dysfunction (POCD), a central nervous system disorder, remains a common postoperative complication, especially in elderly patients. The most obvious clinical presentations of POCD are impairment of memory and the ability to concentrate. In addition, anxiety, reduced cognitive function, and personality changes may occur, potentially resulting in death in severely affected patients. Currently, our understanding of POCD is limited, and no effective measures have been identified to prevent it. Thus, POCD and its management constitute an ongoing challenge for clinical anesthesiologists [1].

The development and progression of POCD are closely related to inflammatory factor-mediated nerve inflammation and noninfectious nerve inflammation [2, 5]. Nerve inflammation, especially excessive activated microglial-induced nerve inflammation, is one of the most important factors contributing to the high incidence and underlying development of POCD [3, 4].

Microglia are the primary immune cells in the cerebrum. Any factor that disturbs brain homeostasis, such as pathogenic invasion or brain damage, can activate microglia [6]. The activation of microglia eliminates invading pathogens and induces inflammatory reactions, thereby serving a neuroprotective role in the brain [7]. However, microglial activation is also associated with cognitive deficits in disease states, with possible long-term impairment [8].

It is widely believed that medication- and surgery-induced stress disrupts cerebral homeostasis and provokes inflammatory reactions

Table 1. Primer sequences for RT-PCR analysis

Gene	Direction	Sequence
TLR4	Forward	CCAGGAAGGCTTCCACAAGAGC
TLR4	Reverse	ACAATTCCACCTGCTGCCTCAG
P38MAPK	Forward	CCGAGAGTTGCGTCTGCTGAAG
P38MAPK	Reverse	CGGTCAGCTTCTGGCACTTCAC
GAPDH	Forward	GAGTCAACGGATTTGGTCGT
GAPDH	Reverse	TTGATTTTGGAGGGATCTCG

that lead to molecular changes in signaling pathways that impair memory [9, 11]. Thus, excessive microglial-induced inflammatory reactions can damage neurons [10].

Propofol, a sedative widely used as an intravenous anesthetic, has beneficial effects on the cardiovascular [15], respiratory [16], and urinary systems [17]. Its neuroprotective effects have also been widely investigated [18]. Our previous studies have shown that propofol has significant anti-inflammatory activity [12]. Other studies, such as those conducted by Gui Bo et al. on cell models, have demonstrated that propofol inhibits the release of inflammatory factors from activated microglia and the expression of toll-like receptor 4 (TLR4) protein [13]. In addition, van Eldik et al. revealed that p38α mitogen-activated protein kinase (MAPK) signaling is the primary functional mechanism for neurodegeneration and the secretion of large amounts of tumor necrosis factor (TNF)-α after excessive microglial activation by lipopolysaccharides (LPSs) [14].

We hypothesized that propofol may inhibit microglial overactivation through the downregulation of the TLR4-p38 MAPK signaling pathway, thereby exerting a neuroprotective effect.

Materials and methods

Cell culture and treatments

Mouse BV-2 microglial cells (CAS, China) were inoculated in Dulbecco's modified Eagle's medium/Ham's nutrient mixture F-12 (DMEM/F12; Gibco, USA) culture medium containing 10% fetal bovine serum (Gibco), 10 IU/mL penicillin (Invitrogen, USA), and 100 μg/mL streptomycin (Invitrogen), and grown in an incubator at 37°C and 5% CO_2. Propofol was obtained from Sigma-Aldrich (USA). When the cells reached 70-80% confluence, 0.25% trypsin digestion was used to passage or harvest the cells for experiments.

The experimental cells were divided into five groups: (1) the control group (cells were incubated in serum-free DMEM/F12 culture medium for 24 h); (2) the LPS group (cells were treated with 1 μg/mL LPS for 24 h); (3) the propofol group (cells were treated with 30 μM propofol for 24 h); (4) the LPS+ propofol group (cells were pretreated with 1 μg/mL LPS for 1 h, followed by the addition of 30 μM propofol for 24 h); (5) the dimethyl sulfoxide (DMSO) group (cells were treated with DMSO at a final concentration of 0.1% for 24 h).

After completion of their respective treatments, the cell culture media and the cells were centrifuged at 5000 rpm for 15 min and the collected pellets were stored at -80°C until use.

Morphological observation

After treatment, the cells were observed using a binocular inverted light microscope (Nikon TS100, Japan), and their morphological changes were recorded.

Cell viability

A homogeneous cell suspension was placed into a 96-well plate (5×10^3 cells/well). After adhering to the plate, the cells were treated as described earlier in "Cell culture and treatments". An MTT (Sigma-Aldrich) colorimetric method was utilized to determine the viability of each group of BV-2 microglial cells after 24 h. The following formula was used: Viability (%) = $(OD_{\text{treatment group}} - OD_{\text{blank group}})/(OD_{\text{control group}} - OD_{\text{blank group}}) \times 100$, where OD is optical density.

ELISA

After 24 h of treatment, the culture medium for each group of cells was centrifuged, and interleukin (IL)-1β, IL-6, and TNF-α levels in the supernatant were measured using an enzyme-linked immunosorbent assay (ELISA) kit (R&D systems, USA).

RT-qPCR

Total RNA was extracted from each group of cells after 24 h of treatment. Using glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as an internal reference, we performed a reverse transcription polymerase chain reaction (RT-PCR) analysis to determine the mRNA expression of p38 MAPK and TLR4 in microglia from each treatment group.

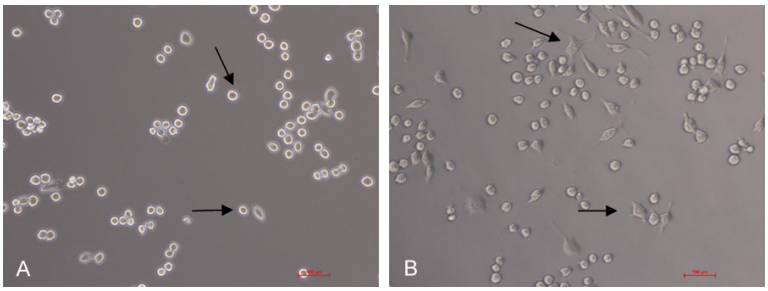

Figure 1. Morphological changes in BV-2 cells in the control (A) and LPS (B) groups. Magnification, 100 ×.

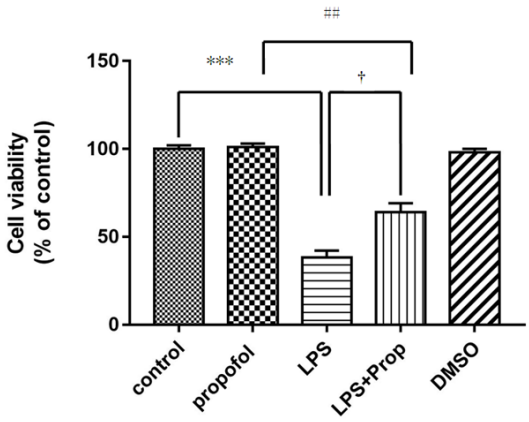

Figure 2. Comparison of BV-2 microglial viability in control, propofol, LPS, and LPS+propofol groups. ***P < 0.001 vs control group, ##P < 0.01 vs propofol group, †P < 0.05 vs LPS group.

The PCR reaction conditions were as follows: denaturation at 95°C for 4 min, denaturation at 95°C for 30 s, annealing at 55°C for 60 s, elongation at 72°C for 60 s for 42 cycles, followed by elongation at 72°C for 5 min. The RT-PCR results are presented as CT, with $2^{-\Delta\Delta CT}$ representing the relative expression of the target gene, which was calculated using the following formula: $2^{-\Delta\Delta CT}$ = (expression of the target gene in each group of BV2 microglial cells)/(expression of the target gene in the control group).

The sequences of the PCR primers for the target genes and internal reference GAPDH are shown in **Table 1**.

Western blot

After 24 h of treatment, western blots of each group of cells were used to measure p38 MAPK and TLR4 protein expression, and the Bradford assay was used to determine the total protein concentration. A 10-μL sample of protein was subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and electroblotted onto a polyvinylidene difluoride membrane. The membrane was blocked with nonfat milk powder and incubated with mouse anti-TLR4 (1:500 dilution) and mouse anti-p38 MAPK (1:250 dilution) primary antibodies overnight at 4°C. Then, secondary antibodies were added (1:1000 dilution). After incubation for 2 h at room temperature, an enhanced chemiluminescence reagent was added, and the membrane was exposed to an X-ray film [13]. A Quantity 1 image analysis system (Bio-Rad, USA) was used to determine the grayscale value of p38 MAPK and TLR4 protein bands for each treatment group.

Statistical analysis

All data are presented as the mean ± standard error of the mean (SEM). GraphPad Prism 7.0 (GraphPad Software, USA) and SPSS 20.0 statistical software (SPSS, USA) were used for data analysis and processing. The homogeneity of variance test was used for comparing the means of the sample groups. One-way analysis of variance (ANOVA) was used for comparison of data between groups. The least significant difference method was used for pairwise comparisons of data between homoscedastic groups. Dunnett's T3 test was used for comparing data between heteroscedastic groups. Differences with P < 0.05 were considered statistically significant. Differences with P < 0.01 were considered highly statistically significant.

Results

LPS enlarges microglial cells and thickens synapses

Cells in the control group were round or elliptical. Cell bodies had a relatively regular shape, and no obvious thickening of synapses was observed (**Figure 1A**). In the LPS group, activation of some microglia was observed, with obvious enlargement of the cell body, thickening of synapses and extension of large processes in all four directions, which was consistent with the morphological characteristics of activated microglia (**Figure 1B**).

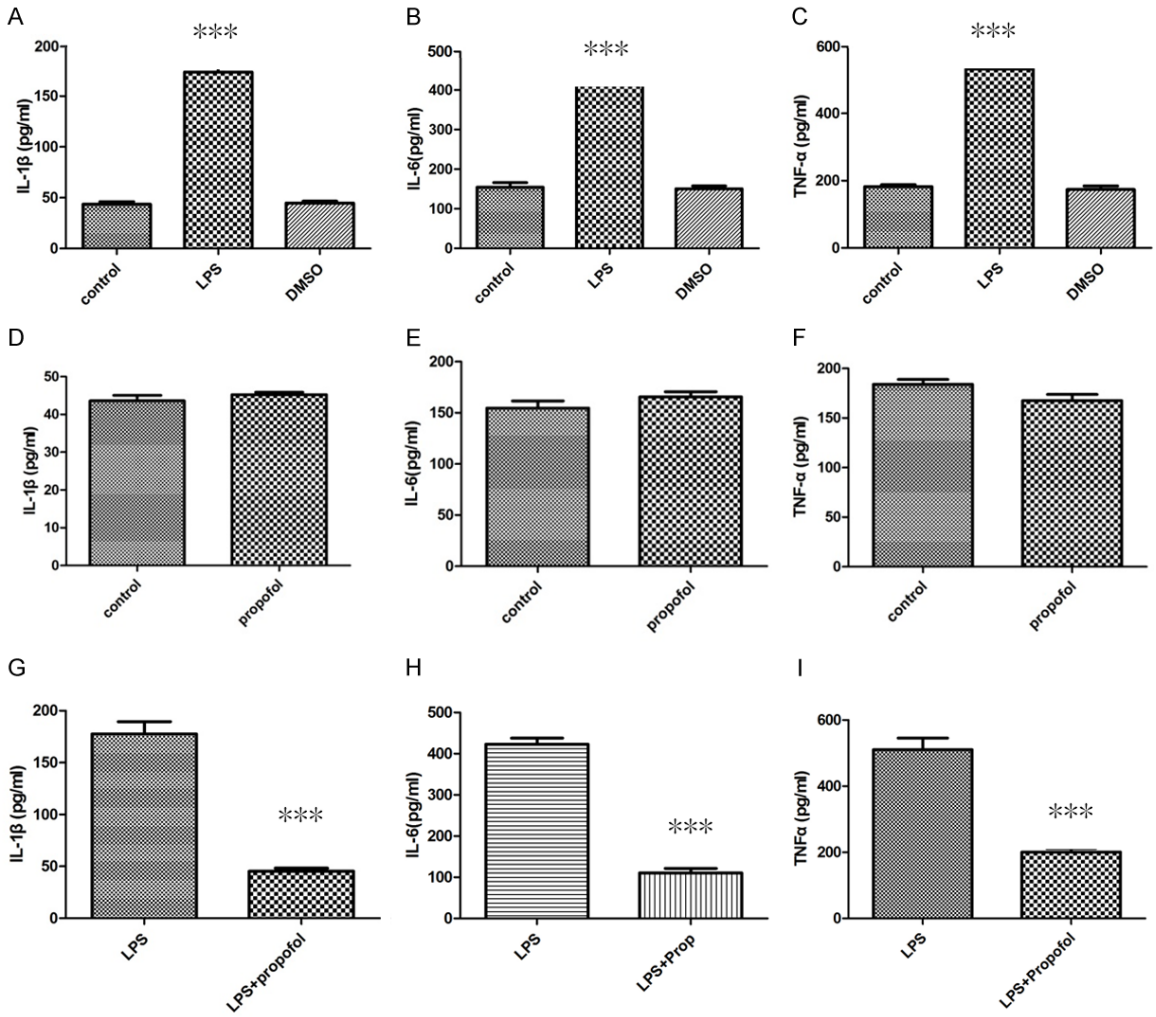

Figure 3. Comparison of IL-1β, IL-6, and TNF-α content in the culture supernatant from the control, LPS, DMSO (A, B, C), propofol (D, E, F), and LPS+propofol groups(G, H, I). ***$P < 0.001$, n = 8.

Propofol improves viability of LPS-treated M1 microglial cells

We investigated the effect of propofol on the viability of M1-activated microglial cells by using an MTT assay to determine cell viability in each treatment group. We found that microglial cell viability in the LPS and LPS+ propofol groups was lower than in the control and propofol groups, respectively ($P < 0.001$, $P < 0.01$). Microglial cell viability in the LPS+ propofol group was higher than that in the LPS group ($P < 0.05$; **Figure 2**). Cell lysate from each treatment group was subjected to western blotting.

LPS stimulates the release of large amounts of inflammatory factors

We verified that LPS stimulates microglial activation by using ELISA to measure the levels of inflammatory factors in the culture supernatant. We found that IL-1β, IL-6, and TNF-α levels in the supernatant of the LPS group were higher than then they were in the control and DMSO groups ($P < 0.001$). There were no significant differences in the levels of these cytokines between the control and DMSO groups ($P > 0.05$; **Figure 3A-C**).

Propofol has no effect on inflammatory factors released by quiescent microglia cells

We determined the effect of propofol on inflammatory factors released by quiescent microglia by using ELISA to detect the release of inflammatory factors into the supernatant medium. ANOVA revealed no significant differences in the levels of IL-1β, IL-6, and TNF-α between the supernatants of the control and propofol groups ($P > 0.05$; **Figure 3D-F**).

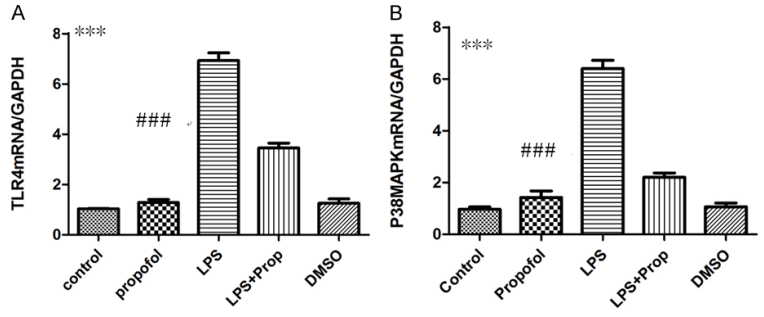

Figure 4. Effect of propofol on TLR4 (A), p38 MAPK (B) mRNA levels in activated BV-2 microglia. ***P < 0.001 vs control group; ###P < 0.001 vs LPS group; ##P < 0.01 vs LPS group.

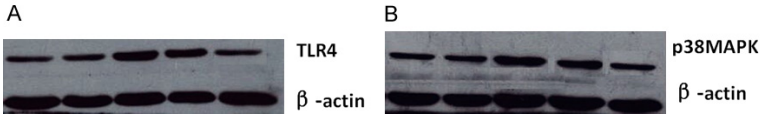

Figure 5. Effect of propofol on TLR4 (A), p38 MAPK (B) protein expressions on in activated BV-2 microglia.

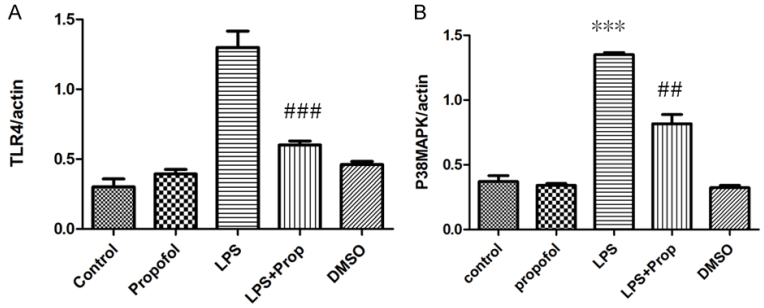

Figure 6. Effect of propofol on TLR4 (A), p38 MAPK (B) protein levels in activated BV-2 microglia. ***P < 0.001 vs control group; ###P < 0.001 vs LPS group; ##P < 0.01 vs LPS group.

Propofol significantly inhibits the release of inflammatory factors from activated microglial cells

We determined the effect of propofol on inflammatory factors released by activated microglial cells by using ELISA to measure the levels of inflammatory factors in the culture supernatants of the LPS and LPS+ propofol groups. We found that the levels of IL-1β, IL-6, and TNF-α in the supernatant medium of the LPS+ propofol group were significantly lower than in that of the LPS group (P < 0.05; **Figure 3G-I**).

Propofol significantly inhibits TLR4 and p38MAPK mRNA expression in activated microglial cells

Reverse transcription quantitative polymerase chain reaction (RT-qPCR) was used to determine the mRNA expression of the signaling pathway components TLR4 and p38 MAPK following propofol treatment in activated microglia. We found that *p38MAPK* and *TLR4* mRNA expression in the microglia of the LPS and LPS+ propofol groups was higher than it was in the control and propofol groups (P < 0.001). Moreover, *p38MAPK* and *TLR4* mRNA expression in the microglia of the LPS+ propofol group was lower than it was in the LPS group (P < 0.001; **Figure 4A** and **4B**).

Propofol significantly inhibits TLR4 and p38 MAPK protein expression in activated microglial cells

Western blot was used to determine the protein expression of the signaling pathway components TLR4 and p38 MAPK following propofol treatment in activated microglia. We found that p38 MAPK and TLR4 protein expression in microglia in the LPS and LPS+ propofol groups was higher than it was in the control and propofol groups (P < 0.001). Protein expression of p38 MAPK and TLR4 in microglia of the LPS+ propofol group was lower than it was in the LPS group (P < 0.01 and P < 0.001, respectively) (**Figures 5** and **6**).

Discussion

Upon activation, microglia produce inflammatory factors such as IL-1β, TNFα, IL-1, and IL-6. While IL-1β is necessary for normal learning and memory, excessively high levels of IL-1β can negatively affect cognitive function [19, 20]. When IL-1β acts synergistically with other inflammatory factors such as TNFα and IL-6, the risk of cognitive dysfunction increases [21].

Studies have shown that IL-1β plays an essential role in cognitive dysfunction by interfering with the long-term function of the hippocampus [22-25], an important brain region involved in

memory [26]. IL-1β directly or indirectly stabilizes protein synthesis required for long-term plasticity and memory by interacting with microglia. Microglia and inflammatory factors work to inhibit neuronal development in the hippocampus, thus impairing memory [27]. In our study, large amounts of pro-inflammatory factors were released after the LPS-induced activation of microglia. This effect was significantly mitigated by propofol stimulation.

The anti-inflammatory effects of propofol have gained considerable attention. Studies have shown that propofol exerts a neuroprotective effect during the acute inflammation phase of neurological and cardiovascular diseases [30, 31]. Animal studies have also shown that propofol inhibits cytokine release during sepsis and reduces neutrophil-mediated inflammation during acute lung injury [32-34]. Clinical studies have shown that propofol reduces *in vitro* circulating cardiac reperfusion injury and pulmonary failure by mitigating free radical release and inhibiting the inflammation process [35, 36].

Our data showed that 30 μM of propofol significantly inhibited excessive M1 activation of microglia and reduced the release of inflammatory factors to induce a protective effect and prevent cell death, which was consistent with the results of the abovementioned studies [30-36]. We noted that the dose used (30 μM) is considered a clinically relevant concentration of propofol in BV microglia [29], as human studies have demonstrated that the concentration range of propofol at the site of action (i.e., brain) is 2-6 μg/mL, which corresponds to 11-33 μM [28].

With regard to the functional mechanism underlying inhibition of excessive microglial activation by propofol, we found that LPS-induced activation of microglia was accompanied by an increase in TLR4 and p38 MAPK expression. In contrast, LPS-induced microglial activation after propofol treatment was accompanied by a decrease in TLR4 and p38 MAPK expression. Thus, propofol inhibition of excessive microglial activation may occur via the TLR4-p38 MAPK signaling pathway. Consistent with our results, a study by Yi Wang showed that within a short time after surgery in aging rats, TLR4 expression significantly increases and short-term deficits in memory and learning occurs [37]. His study found that the development of cognitive dysfunction is most significant on postoperative day 1, which coincides with the peak expression of TLR4, IL-1β, and TNFα. With the passage of time, cognitive deficits gradually recover, accompanied by a return to baseline levels of TLR4, IL-1β, and TNFα. A study by van Eldik et al. revealed that the p38α MAPK signaling is the primary functional mechanism for secretion of large amounts of TNF-α and for neurodegeneration following excessive microglial activation by LPS [14]. In addition, they found that TLR4 activates microglial cells, which then secrete large amounts of IL-1β and TNFα. However, the addition of the p38α MAPK inhibitor MW01-2-069A-SRM significantly inhibits the microglial release of inflammatory factors [38]. Additional studies on different subunits of p38 MAPK have shown that p38α MAPK plays an important role in LPS-stimulated microglial secretion of pro-inflammatory factors, whereas the role of p38β MAPK is very limited [39]. This indicates that the functional mechanism underlying propofol inhibition of microglial activation warrants further investigation at the subunit level.

Taken together, the findings of the present study indicate that clinically relevant concentrations of propofol can significantly inhibit excessive activated microglia-induced inflammatory reactions, thereby having a protective effect on cell viability. Moreover, our findings suggest that propofol's effects are exerted primarily through the TLR4-p38 MAPK signaling pathway.

Acknowledgements

This work was supported by a grant from the Zhejiang medical and health science and technology project (grant number 2016KYA140).

Disclosure of conflict of interest

None.

Address correspondence to: Xuefei Ye, Department of Anesthesiology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang, China. E-mail: yexuefei016@163.com

References

[1] Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS; ISPOCD Group. Long-term consequences of postoperative cognitive dysfunction. Anesthesiology 2009; 110: 548-55.

[2] Wan Y, Xu J, Ma D, Zeng Y, Cibelli M, Maze M. Postoperative impairment of cognitive function in rats: a possible role for cytokine-mediated inflammation in the hippocampus. Anesthesiology 2007; 106: 436-43.
[3] Haseneder R, Kochs E and Jungwirth B. Postoperative cognitive dysfunction. Possible neuronal mechanisms and practical consequences for clinical routine. Anaesthesist 2012; 61: 437-443.
[4] Schlachetzki JC, Hull M. Microglial activation in Alzheimer's disease. Curr Alzheimer Res 2009; 6: 554-563.
[5] Rosczyk HA, Sparkman NL and Johnson RW. Neuroinflammation and cognitive function in aged mice following minor surgery. Exp Gerontol 2008; 43: 840-846.
[6] Shao J, Liu T, Xie QR, Zhang T, Yu H, Wang B, Ying W, Mruk DD, Silvestrini B, Cheng CY, Xia W. Adjudin attenuates lipopolysaccharide (LPS)- and ischemia-induced microglial activation. J Neuroimmunol 2012; 254: 83-90.
[7] Kamer AR, Galoyan SM, Haile M, Kline R, Boutajangout A, Li YS, Bekker A. Meloxicam improves object recognition memory and modulates glial activation after splenectomy in mice. Eur J Anaesthesiol 2012; 29: 332-337.
[8] Griffin R, Nally R, Nolan Y, McCartney Y, Linden J, Lynch MA. The age-related attenuation in long-term potentiation is associated with microglial activation. J Neurochem 2006; 99: 1263-1272.
[9] Vereker E, Campbell V, Roche E, McEntee E, Lynch MA. Lipopolysaccharide inhibits long term potentiation in the rat dentate gyrus by activating caspase-1. J Biol Chem 2000; 275: 26252-26258.
[10] Cai ZY, Yan Y and Chen R. Minocycline reduces astrocytic reactivation and neuroinflammation in the hippocampus of a vascular cognitive impairment rat model. Neurosci Bull 2010; 26: 28-36.
[11] Coburn M, Fahlenkamp A, Zoremba N and Schaelte G. Postoperative cognitive dysfunction: Incidence and prophylaxis. Anaesthesist 2010; 59: 177-184; quiz 185.
[12] Ye X, Lian Q, Eckenhoff MF, Eckenhoff RG, Pan JZ. Differential general anesthetic effects on microglial cytokine expression. PLoS One 2013; 8: e52887.
[13] Gui B, Su M, Chen J, Jin L, Wan R, Qian Y. Neuroprotective effects of pretreatment with propofol in LPS-induced BV-2 microglia cells: role of TLR4 and GSK-3β. Inflammation 2012; 35: 1632-40.
[14] Xing B, Bachstetter AD, Van Eldik LJ. Microglial p38α MAPK is critical for LPS-induced neuron degeneration, through a mechanism involving TNFα. Mol Neurodegener 2011; 6: 84.
[15] Zhu M, Wen M, Sun X, Chen W, Chen J, Miao C. Propofol protects against high glucose-induced endothelial apoptosis and dysfunction in human umbilical vein endothelial cells. Anesth Analg 2015; 120: 781-9.
[16] Yang P, Yang N, Zhang X, Xu X. The significance and mechanism of propofol on treatment of ischemia reperfusion induced lung injury in rats. Cell Biochem Biophys 2014; 70: 1527-32.
[17] Yoo YC, Yoo KJ, Lim BJ, Jun JH, Shim JK, Kwak YL. Propofol attenuates renal ischemia-reperfusion injury aggravated by hyperglycemia. J Surg Res 2013; 183: 783-91.
[18] Chen J, Chen W, Zhu M, Zhu Y, Xu P, Miao C. Angiotensin II-induced mouse hippocampal neuronal HT22 cell apoptosis was inhibited by propofol: role of neuronal nitric oxide synthase and metallothinonein-3. Neuroscience 2015; 305: 117-27.
[19] Rachal Pugh C, Fleshner M, Watkins LR, Maier SF, Rudy JW. The immune system and memory consolidation: a role for the cytokine IL-1beta. Neurosci Biobehav Rev 2001; 25: 29-41.
[20] Chen J, Buchanan JB, Sparkman NL, Godbout JP, Freund GG, Johnson RW. Neuroinflammation and disruption in working memory in aged mice after acute stimulation of the peripheral innate immune system. Brain Behav Immun 2008; 22: 301-311.
[21] Allan SM, Tyrrell PJ, Rothwell NJ. Interleukin-1 and neuronal injury. Nat Rev Immunol 2005; 5: 629-640.
[22] Pugh CR, Kumagawa K, Fleshner M, Watkins LR, Maier SF, Rudy JW. Selective effects of peripheral lipopolysaccharide administration on contextual and auditory-cue fear conditioning. Brain Behav Immun 1998; 12: 212-229.
[23] Barrientos RM, Higgins EA, Sprunger DB, Watkins LR, Rudy JW, Maier SF. Memory for context is impaired by a post context exposure injection of interleukin-1 beta into dorsal hippocampus. Behav Brain Res 2002; 134: 291-298.
[24] Cunningham AJ, Murray CA, O'Neill LA, Lynch MA, O'Connor JJ. Interleukin-1 (IL-1) and tumor necrosis factor (TNF) inhibit long-term potentiation in the rat dentate gyrus in vitro. Neurosci Lett 1996; 203: 17-20.
[25] Vereker E, Campbell V, Roche E, McEntee E, Lynch MA. Lipopolysaccharide inhibits long term potentiation in the rat dentate gyrus by activating caspase-1. J Biol Chem 2000; 275: 26252-26258.
[26] Morris RG. Synaptic plasticity and learning: selective impairment of learning rats and blockade of long-term potentiation in vivo by the N-methyl-D-aspartate receptor antagonist AP5. J Neurosci 1989; 9: 3040-3057.

[27] Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. Science 2003; 302: 1760-1765.
[28] Zhang J, Xia Y, Xu Z, Deng X. Propofol suppressed hypoxia/reoxygenation-induced apoptosis in HBVSMC by regulation of the expression of Bcl-2, Bax, Caspase3, Kir6.1, and p-JNK. Oxid Med Cell Longev 2016; 2016: 1518738.
[29] Zhou CH, Zhu YZ, Zhao PP, Xu CM, Zhang MX, Huang H, Li J, Liu L, Wu YQ. Propofol inhibits lipopolysaccharide-induced inflammatory responses in spinal astrocytes via the toll-like receptor 4/MyD88-dependent nuclear factor-kappaB, extracellular signal-regulated protein kinases1/2, and p38 mitogen-activated protein kinase pathways. Anesth Analg 2015; 120: 1361-8.
[30] Marik PE. Propofol: an immunomodulating agent. Pharmacotherapy 2005; 25: 28S-33S.
[31] Yang SC, Chung PJ, Ho CM, Kuo CY, Hung MF, Huang YT, Chang WY, Chang YW, Chan KH, Hwang TL. Propofol inhibits superoxide production, elastase release, and chemotaxis in formyl peptide-activated human neutrophils by blocking formyl peptide receptor 1. J Immunol 2013; 190: 6511-6519.
[32] Taniguchi T, Yamamoto K, Ohmoto N, Ohta K, Kobayashi T. Effects of propofol on hemodynamic and inflammatory responses to endotoxemia in rats. Crit Care Med 2000; 28: 1101-1106.
[33] Taniguchi T, Kanakura H, Yamamoto K. Effects of posttreatment with propofol on mortality and cytokine responses to endotoxin-induced shock in rats. Crit Care Med 2002; 30: 904-907.
[34] Chen HI, Hsieh NK, Kao SJ, Su CF. Protective effects of propofol on acute lung injury induced by oleic acid in conscious rats. Crit Care Med 2008; 36: 1214-1221.
[35] Corcoran TB, Engel A, Sakamoto H, O'Callaghan-Enright S, O'Donnell A, Heffron JA, Shorten G. The effects of propofol on lipid peroxidation and inflammatory response in elective coronary artery bypass grafting. J Cardiothorac Vasc Anesth 2004; 18: 592-604.
[36] An K, Shu H, Huang W, Huang X, Xu M, Yang L, Xu K, Wang C. Effects of propofol on pulmonary inflammatory response and dysfunction induced by cardiopulmonary bypass. Anaesthesia 2008; 63: 1187-1192.
[37] Wang Y, He H, Li D, Zhu W, Duan K, Le Y, Liao Y, Ou Y. The role of the TLR4 signaling pathway in cognitive deficits following surgery in aged rats. Mol Med Rep 2013; 7: 1137-1142.
[38] Bachstetter AD, Xing B, de Almeida L, Dimayuga ER, Watterson DM, Van Eldik LJ. Microglial p38α MAPK is a key regulator of proinflammatory cytokine up-regulation induced by toll-like receptor (TLR) ligands or beta-amyloid (Aβ). J Neuroinflammation 2011; 8: 79.
[39] Xing B, Bachstetter AD, Van Eldik LJ. Deficiency in p38β MAPK fails to inhibit cytokine production or protect neurons against inflammatory insult in in vitro and in vivo mouse models. PLoS One 2013; 8: e56852.