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Original Article

Dexmedetomidine on postoperative cognitive function in sleep-deprived rats

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Abstract: Objective: Dexmedetomidine is one of the most commonly used intravenous general anesthesia drugs in clinical practice. This study aimed to investigate the effect of dexmedetomidine on postoperative cognitive function in sleep-deprived rats. Methods: Forty rats were divided into control (Ctrl) group, sleep deprivation (SD) group, sleep deprivation + dexmedetomidine (SD + Dex) group and dexmedetomidine (Dex) group. SD model rats were trained for place navigation, and then rats were injected with lipopolysaccharide (LPS, 1 mg/kg) intraperitoneally as well as Dex (0.04 mg/kg) or normal saline (0.04 mg/kg) by caudal vein. Spatial reference memory was measured five days later, and the hippocampus was harvested to determine the content of inflammatory factors and NF-κB p-p65 protein expression. Results: Escape latency and original platform standing time were lengthened in SD group compared with Ctrl group ($P<0.05$). Content of inflammatory factors and p-p65 protein expression in the hippocampus increased significantly in SD group while declined in SD + Dex group (all $P<0.001$). Conclusion: Dexmedetomidine can alleviate cognitive dysfunction induced by preoperative sleep deprivation in rats and inhibit inflammatory response.

Keywords: Dexmedetomidine, sleep deprivation, cognitive dysfunction, memory, cytokines

Introduction

Sleep is vital in human life, and the maintenance of hormonal regulation and homeostasis during sleep is an important condition for health [1-3]. However, sleep problems caused by various factors seriously threaten human physical and mental health [4, 5]. If the sleeping time is less than five hours, significant damages will occur in the body's nine physiological systems [6] (Please make sure this is the right reference to be cited!). Moreover, persistent sleep deprivation leads to a significantly increased risk of cardiovascular disease and other systemic diseases and even an increased mortality [7]. Most patients have different degrees of sleep disorders before surgery due to worry and anxiety, which undoubtedly affects the degree of anesthesia during surgery, but also causes various degrees of damage to the cognitive function after surgery. It is generally acknowledged that patients' own condition, anesthesia process, surgical method and sleep quality are correlated with postoperative cognitive impairment [8]. The association between sleep insufficiency or poor sleep quality and postoperative cognitive dysfunction has received more and more attention [9]. However, the correlation between sleep disorders and postoperative cognitive dysfunction and the behind mechanisms remain to be elucidated.

Dexmedetomidine can reduce the ability of humans or animals to respond to the external environment, induce anesthesia, maintain anesthesia depth and regulate patients' awakening [10, 11]. It is one of the most commonly used intravenous general anesthesia drugs in clinical practice and is widely used in clinical anesthesia induction and maintenance as well as sedation in the intensive care unit. The main mechanism is that dexmedetomidine, as a highly effective and specific α2 adrenergic agonist and by binding to the presynaptic α adrenoreceptor in the locus ceruleus, can inhibit the release of adrenal hormone and reduce the stress response in the body [12, 13]. Dexmedetomidine inhibits sympathetic excitability, which offsets the decrease of arousal level caused by sleep insufficiency and has significant effects on postoperative cognitive function [14, 15].

NF-κB is a downstream factor in the TLR4 signaling pathway and can regulate the expressions of various pro-inflammatory factors [11]. NF-κB is an important transcription factor and is usually consisted of NF-κB family proteins p50 and p65 and their controlling proteins. NF-κB can stimulate the activation of tumor necrosis factor and other inflammatory factors to induce the expressions of a variety of genes, thus producing a variety of different cytokines to regulate the inflammatory response. After the activation of NF-κB, p65 protein is phosphorylated to p-p65 and enters into the nucleus; if the expression level of p-p65 increases, the inflammatory response is enhanced. Previous study found increased inflammatory responses in the hippocampus after 48 hours of sleep deprivation [16]. In recent years, more and more basic studies have shown that dexmedetomidine has a good anti-inflammatory effect, which can alleviate the inflammatory response in endotoxin-induced shock rats, inhibit the release of pro-inflammatory factors and the generation of oxygen free radicals, and reduce the mortality [17]. In this study, the content of NF-κB was measured to confirm the degree of inflammation, and to determine whether dexmedetomidine hydrochloride could control inflammation by inhibiting NF-κB, and the anti-inflammatory mechanism of dexmedetomidine.

Preoperative sleep deprivation can affect the prognosis of patients and act on the cognitive ability by activating oxidative stress response, changing neurotransmitters in the brain and inhibiting long-term potentiation [18]. In this study, the sleep deprivation rat model was used to investigate the internal relations between sleep deprivation and postoperative cognitive dysfunction and the effect of dexmedetomidine hydrochloride on postoperative cognition in sleep-deprived rats.

Materials and methods

Animals and grouping

Forty male Sprague-Dawley rats of clean grade weighing 200-250 g were purchased (Permission number: SCXK (Su) 2009-0002) and fed for 1 week to adapt to the environment. The rats were randomly divided into control group (Ctrl group), sleep deprivation group (SD group), sleep deprivation + dexmedetomidine group (SD + Dex group) and dexmedetomidine group (Dex group), with 10 rats in each group. Sleep-deprived rat models in SD group and SD + Dex group were established by multi-platform method in a water tank. This study was approved by the Ethics Committee of Hunan Children's Hospital. All animal experiments were carried out in accordance with the relevant guidelines for the care and use of laboratory animals.

All rats were deprived of sleep for 8 h a day, for 5 days, and then trained for place navigation by Morris water maze test. After training, all rats were intraperitoneally injected with 1 mg/kg lipopolysaccharide (LPS, sigma, 0111:B4) to simulate the inflammatory response caused by surgery. Meanwhile, 0.04 mg/kg dexmedetomidine (Jiangsu Hengrui Pharmaceutical Co., Ltd., China) were injected once a day via the caudal vein in SD + Dex group and Dex group, and 0.04 mg/kg normal saline was injected once a day via the caudal vein in Ctrl group and SD group. Spatial reference memory was measured five days later. Finally, all rats were intraperitoneally injected with 50 mg/kg pentobarbital sodium and sacrificed by rapid cervical dislocation (heartbeat stopped, pupil dilated), then the hippocampus was harvested.

Establishment of sleep deprivation model

The water tank was 150 cm in diameter and 65 cm in height, with an internally installed small platform of 4.5 cm in diameter, and was filled with water; the platform rose 1 cm above the water surface. Rats were placed on the platform, and the diameter of the platform was small enough. Therefore, when the rats fell asleep, they fell into the water due to muscle relaxation and woke up. As a result, they could not sleep freely, thereby achieving sleep deprivation. The rats were deprived of sleep for 8 h per day, for 5 days [19].

Morris water maze to measure learning and memory ability of the rats

Rats facing the sidewall of the tank were put into the water from 4 quadrants (randomly), with an interval of 30 s. The maximum detection time of the software was set as 60 s and the standing time was set as 5 s (as the standard for finding the platform). If rats stayed on the platform for 5 s, the recording was stopped, and the time of rats swimming in the water recorded by the software was recorded as escape latency. If rats still not found the plat-

Table 1. Comparison of the escape latency

Group	Ctrl (n=10)	SD (n=10)	SD + Dex (n=10)	Dex (n=10)
Day 1	35.40±2.34	50.20±4.23	40.40±3.20	38.20±2.32
Day 2	36.01±0.67	46.88±1.12	39.56±1.88	37.78±2.45
Day 3	34.88±3.04	42.57±2.01***	38.01±2.45$^{**,\#\#\#}$	35.98±0.89$^{\#\#\#}$
Day 4	34.32±1.45	35.78±1.34***	39.56±2.21$^{**,\#\#\#}$	35.01±1.23$^{\#\#\#}$
Day 5	33.21±1.34	32.98±2.24***	33.56±1.12$^{***,\#\#\#}$	33.33±2.01$^{*,\#\#\#}$

Note: Compared with Ctrl group, *P<0.05, **P<0.01, ***P<0.001; compared with SD group, $^{\#\#\#}$P<0.001. Ctrl: control; SD: sleep deprivation; SD + Dex: sleep deprivation + dexmedetomidine; Dex: dexmedetomidine.

form within 60 s, the escape latency was recorded as 60 s. The test was performed for 5 days, 4 times a day, and the mean value was used to calculate the escape latency of rats.

Crossing platform times test: After the escape latency was tested, the platform was removed; the rats were put into the water from the contralateral quadrant of the original platform; times of crossing the original platform within 60 s were recorded.

Cytokines detection

The hippocampus was detected by ELISA according to the instruction of the kit (Xitang Biotechnology Co., Ltd., China). The changes of serum factors, tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β) and interleukin 6 (IL-6; Xitang Biotechnology Co., Ltd., China), were determined. The mean value was obtained.

Protein content detection by Western blot

The hippocampus was obtained to extract and quantify proteins. After the protein was boiled, the total protein of all samples was separated by SDS-PAGE. The protein was transferred to polyvinylidene fluoride membrane by wet method. The membrane was sealed with 50 g/L skim milk/tris buffered saline tween for 30 min. The membrane was incubated with rat NF-κB p65 (1:1,000, Beyotime Biotechnology Co., Ltd., China), NF-κB p-p65 (1:1,000, Beyotime Biotechnology Co., Ltd., China) and β-actin monoclonal antibody (1:1,000, Abmart) at 4°C overnight; the membrane was washed with 1× phosphate buffered saline-tween three times, each time for 10 min, and the washing liquid was renewed per time. The membrane was incubated with horse radish peroxidase-labeled rabbit anti-rat secondary antibody (1:10,000, Beyotime Biotechnology Co., Ltd., China) at room temperature for 1 h; after washed with 1× tris buffered saline tween, the membrane was reacted by ECL chemiluminescence method and exposed. The β-actin protein was used as the control.

Statistical analysis

SPSS 22.0 software was employed to carry out the statistical analysis. The measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± sd). The measurement data among groups were compared by one-way analysis of variance. Pairwise comparison was performed by SNKq test. A *P* value of less than 0.05 indicated a significant difference.

Results

Dexmedetomidine shortened the escape latency of rats with preoperative sleep deprivation

After sleep deprivation, the escape latency was lengthened in SD group compared with Ctrl group, and the escape latency was significantly shorter in SD + Dex group than that in SD group (both P<0.001); the escape latency was improved in Dex group as compared to Ctrl group (P<0.05, **Table 1** and **Figure 1**).

Dexmedetomidine increased the crossing platform times of rats with preoperative sleep deprivation

The crossing platform times were less in SD group than in Ctrl group and increased in SD + Dex group compared with SD group (both P<0.01). Swimming trajectories decreased significantly in SD group. Swimming trajectories increased significantly in SD + Dex group compared with SD group (**Figure 2**).

Dexmedetomidine decreased the inflammatory factors levels of rats with preoperative sleep deprivation

IL-1β, IL-6 and TNF-α levels in the hippocampus increased significantly in SD group compared with Ctrl group; IL-1β, IL-6 and TNF-α levels in the hippocampus decreased in SD + Dex group compared with SD group (both P<0.01). There

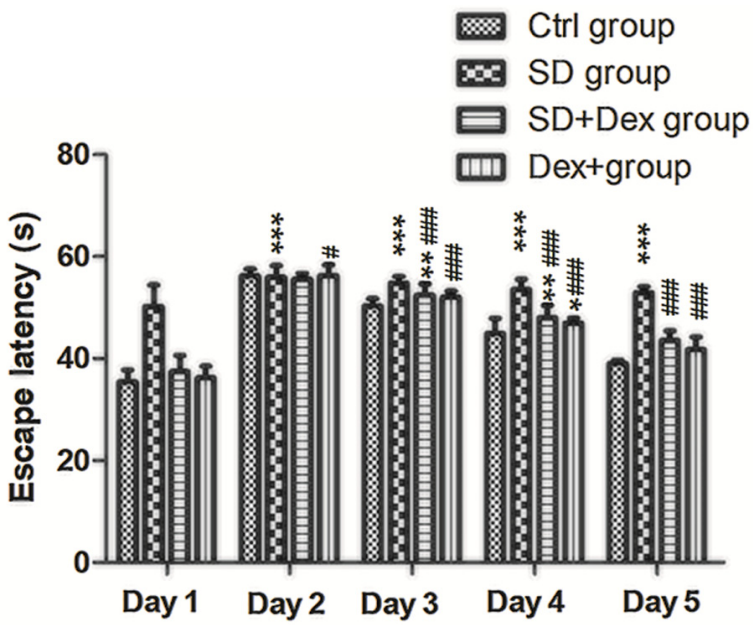

Figure 1. Comparison of the escape latency. Compared with Ctrl group, *P<0.05, **P<0.01, ***P<0.001; compared with SD group, #P<0.05, ###P<0.001. Ctrl: control; SD: sleep deprivation; SD + Dex: sleep deprivation + dexmedetomidine; Dex: dexmedetomidine.

were no significant differences between Dex group and Ctrl group (P>0.05, **Figure 3**).

Dexmedetomidine decreased p-p65 protein expression of rats with preoperative sleep deprivation

p-p65 protein expression in the hippocampus was significantly higher in SD group than in Ctrl group, and p-p65 protein expression in the hippocampus was significantly lower in SD + Dex group than in SD group (both P<0.01). There was no significant difference in p65 protein expression among these groups (P>0.05, **Figure 4**).

Discussion

Sleep disorders caused by preoperative anxiety are not uncommon in clinical practice, and sleep deprivation rat models established by modified multi-platform method in a water tank can simulate insomnia caused by preoperative anxiety in clinical patients [20]. Ali et al. has proved that sleep deprivation increases the slow wave on electroencephalogram, indicating that sleep deprivation significantly inhibits the electrical activity in the cerebral cortex of SD rats [21].

Experimental rats were trained for forming memory about the place of a hidden platform by Morris water maze test which was mainly used to study the learning, memory and spatial exploration abilities of animals [22, 23]. In this study, dexmedetomidine shortened the escape latency and increased the crossing platform times of rats with sleep deprivation. The potential mechanism was that postoperative cognitive dysfunction in sleep-deprived rats was closely related to the inflammatory response in the hippocampus.

Sleep deprivation will lead to internal environmental disorders and significantly increase stress response and the secretion of inflammatory factors [24]. Dexmedetomidine, a α2-adrenergic receptor agonist, can effectively inhibit the release of epinephrine in the presynaptic membrane [25]. The release of inflammatory factors decreased significantly as the stress response reduced [26]. Yamakita et al. has indicated that dexmedetomidine could reduce the internal stress response and inflammatory response [27]. In this study, we also found that the levels of inflammatory factors in the hippocampus were lower in SD + Dex group than that in SD group. A meta-analysis conducted by Zhou et al. showed that dexmedetomidine could effectively improve postoperative cognitive dysfunction and reduce the incidence of postoperative cognitive dysfunction in elderly patients, making dexmedetomidine great potentials for clinical application [28]. Yamanaka D et al. reported a direct effect of dexmedetomidine on the release of pro-inflammatory factors in lipopolysaccharide-induced hippocampal microglial cells [29], which was consistent with our results.

Surgery can stimulate the binding of ligand of injury-related molecules with their receptors, thereby activating the signaling pathway related to bone marrow-derived macrophage nuclear factor NF-κB, and promoting the synthesis and release of pro-inflammatory factors [30].

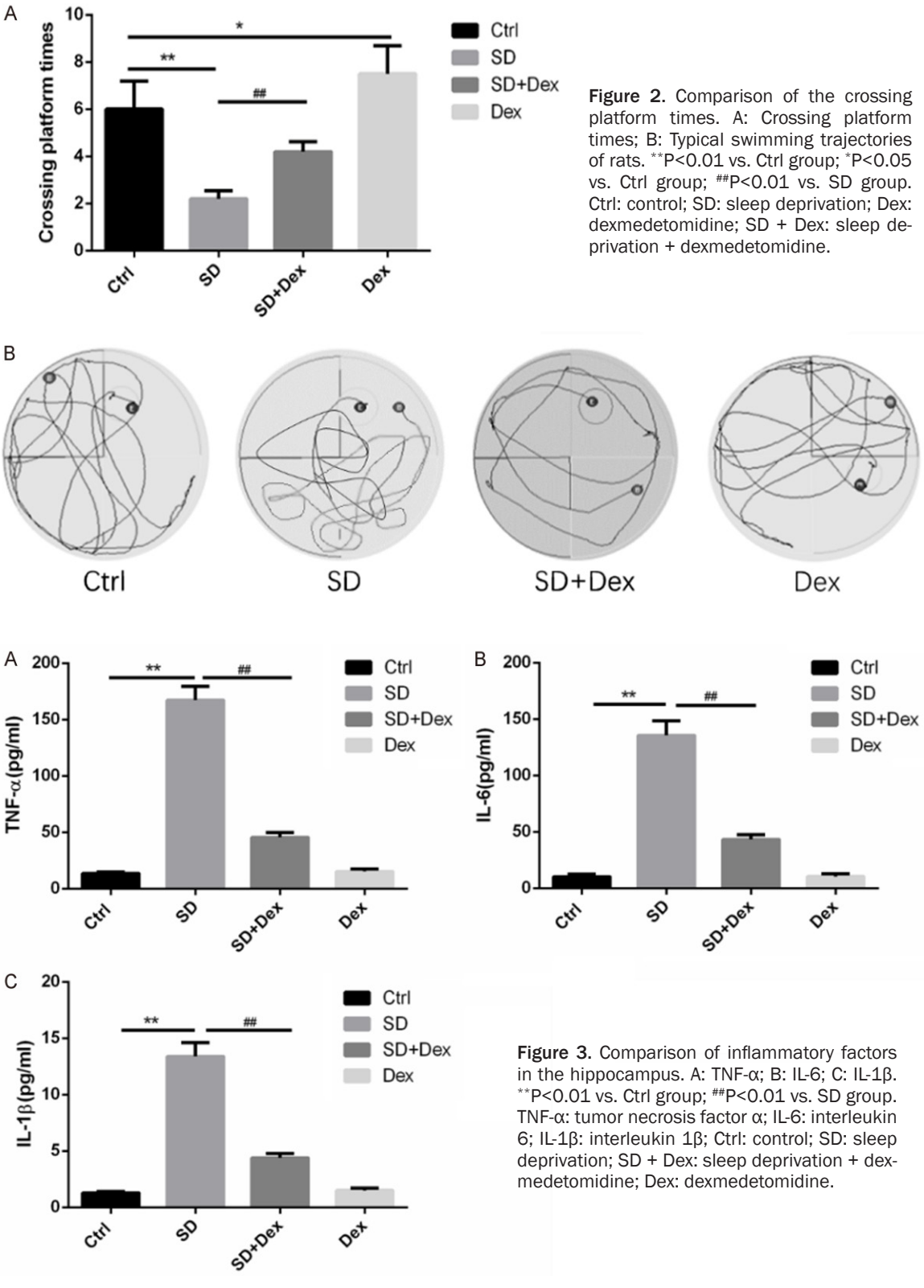

Figure 2. Comparison of the crossing platform times. A: Crossing platform times; B: Typical swimming trajectories of rats. **P<0.01 vs. Ctrl group; *P<0.05 vs. Ctrl group; ##P<0.01 vs. SD group. Ctrl: control; SD: sleep deprivation; Dex: dexmedetomidine; SD + Dex: sleep deprivation + dexmedetomidine.

Figure 3. Comparison of inflammatory factors in the hippocampus. A: TNF-α; B: IL-6; C: IL-1β. **P<0.01 vs. Ctrl group; ##P<0.01 vs. SD group. TNF-α: tumor necrosis factor α; IL-6: interleukin 6; IL-1β: interleukin 1β; Ctrl: control; SD: sleep deprivation; SD + Dex: sleep deprivation + dexmedetomidine; Dex: dexmedetomidine.

TNF-α released by activated macrophages can further damage the blood-brain barrier, leading to the entry of bone marrow-derived macrophages into the brain parenchyma under the

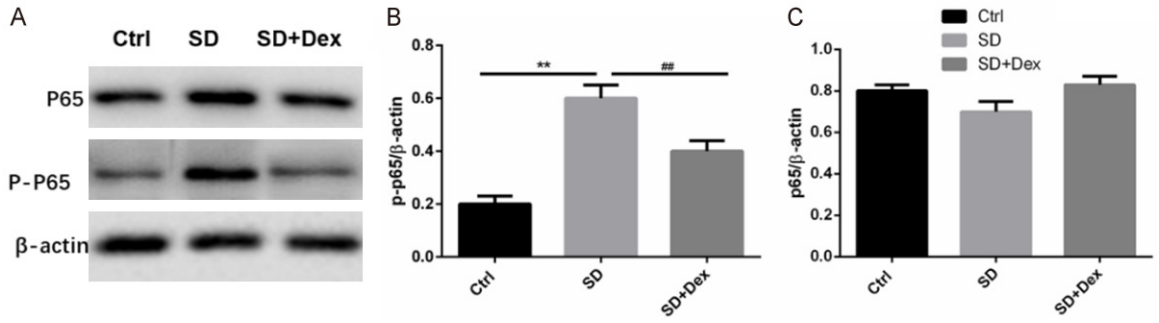

Figure 4. Comparison of p-p65 protein expression in the hippocampus. A: Typical protein bands; B: Relative expression level of p-p65; C: Relative expression level of p-65. **P<0.01 vs. Ctrl group; $^{\#\#}$P<0.01 vs. SD group. Ctrl: control; SD: sleep deprivation; SD + Dex: sleep deprivation + dexmedetomidine; Dex: dexmedetomidine.

action of chemokine MCP-1 [31]. Especially in the hippocampus, peripheral macrophages release a large number of pro-inflammatory factors, which lead to impaired long-term potentiation, thereby reducing learning and memory functions [32]. However, dexmedetomidine can also improve the inflammatory response, and thus improve the postoperative cognitive dysfunction [18, 19]. In this study, after surgical stimulation using LPS, the levels of inflammatory factors IL-1β, IL-6 and TNF-α in the hippocampus of rats increased, and the expression of p-p65 protein in the hippocampus was significantly elevated; dexmedetomidine inhibited the increase of inflammatory factors and the phosphorylation level of p65. These results suggested that dexmedetomidine might reduce the level of inflammatory factors in the hippocampus through the NF-κB signaling pathway, thereby alleviating the cognitive dysfunction induced by preoperative sleep deprivation in rats.

Dexmedetomidine can reduce the cognitive dysfunction induced by preoperative sleep deprivation in rats, which may be because it can inhibit inflammatory response and NF-κB. However, we did not explore the relevant signaling pathway in this study. Further exploration of the behind mechanisms is still needed in the future so as to provide a theoretical basis for clinical treatment.

Disclosure of conflict of interest

None.

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