# THE MECHANISM BY WHICH DEXMEDETOMIDINE ALLEVIATES EARLY BRAIN INJURY IN RATS WITH SUBARACHNOID HEMORRHAGE BY DOWN-REGULATING THE EXPRESSION OF NLRP3 INFLAMMASOME

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***ABSTRACT***

***Objective****: To investigate the mechanism by which dexmedetomidine alleviates early brain injury in rats with subarachnoid hemorrhage by down-regulating the expression of NLRP3 inflammasome.*

***Method:*** *150 female SD rats were equally divided into 5 groups: healthy control group, model group, dexmedetomidine low-dose group, dexmedetomidine medium-dose group, and dexmedetomidine high-dose group. The submembrane hemorrhage was modeled, and the model group was given saline injection. Analysis was made on subarachnoid hemorrhage amount, brain water content, serum inflammatory factor levels, relative expression levels of NLRP3 and Caspase-1, microglia counts, and Bax, BCL-2, and TNFA expression levels of hippocampus in each group. The correlation between NLRP3 inflammasome and inflammatory factor levels was also analyzed.*

***Results:*** *The subarachnoid hemorrhage amount, brain water content, serum inflammatory factor levels, relative expression levels of NLRP3 and Caspase-1, microglia counts, and Bax, BCL-2, TNFA expression levels of hippocampus in each group were not statistically different before anesthesia ($P>0.05$), but showed statistical significance after anesthesia ($P<0.05$). With the increasing injection dose of dexmedetomidine, the levels of various inflammatory factors gradually decreased. Moreover, a positive correlation was shown between NLRP3 and IL-1β, TNF-α and IL-6 ($P<0.05$).*

***Conclusion:*** *Dexmedetomide can reduce the inflammatory response and NLRP3 level in rats by down-regulating the level of NLRP3 inflammasome, thereby lowering the degree of early brain injury in rats with subarachnoid hemorrhage.*

***Keywords:*** *Dexmedetomidine, NLRP3 inflammasome, subarachnoid hemorrhage, early brain injury.*

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## Introduction

Subarachnoid hemorrhage (SAH) refers to a hemorrhagic cerebrovascular disease caused by the rupture of blood vessels on the brain surface and basis cerebri, leading to direct blood flow into the subarachnoid space. Its incidence accounts for 6%-10% of acute cerebrovascular diseases[1, 2]. Clinically, patients often display severe headache, frequent vomiting, and positive meningeal irritation. With the continuous development and research progress of modern medical technology, NLRP3 inflammasome, as an important component of innate immunity, plays an important role in the body's immune response and disease development, which also plays a key role in the pathogenesis of subarachnoid hemorrhage. Therefore, research on NLRP3 inflammasome may provide a new target for the treatment of early brain injury in subarachnoid hemorrhage[3, 4]. Dexmedetomidine, one of the commonly used anesthetics in clinical practice, is a specific α2 adrenergic receptor agonist. Its affinity with α2 receptor is 8 times that of clonidine. Recent studies have also shown that[5], dexmedetomidine

has a protective effect on brain tissue in early brain injury of subarachnoid hemorrhage. Therefore, this study established a rat subarachnoid hemorrhage model to investigate the mechanism by which dexmedetomidine alleviates early brain injury in rats with subarachnoid hemorrhage by down-regulating the expression of NLRP3 inflammasome.

## Information and methods

### *General information*

150 SD rats, all female, were purchased from the Institute of Laboratory Animal Sciences, CAMS (Beijing HFK Bioscience Co., Ltd.). The breeding environment was room temperature; the relative humidity was controlled at about 50±5%, with 12 h light alternated with 12 h of darkness. The rats had free access to food and water and maintained normal activities. The experiment began after the rats adapted to the environment for a week. There was no statistical significance in the comparison between the age and weight of all rats ($P>0.05$).

### Method

### *Experimental grouping*

The above 150 rats were randomly divided into 5 groups, namely the healthy control group, the model group, the dexmedetomidine low-dose group, the dexmedetomidine medium-dose group and the dexmedetomidine high-dose group.

Rats in each group were raised in separate cages, and except for the healthy control group, subarachnoid hemorrhage was modeled in the model group, dexmedetomidine low-dose group, dexmedetomidine medium-dose group, and dexmedetomidine high-dose group.

### *Subarachnoid hemorrhage modeling*

Each rat to be modeled was anesthetized with 5% chloral hydrate at a dose of 400 mg/kg during injection. After successful anesthesia, internal carotid artery puncture method was used for modeling. First, use an arterial clamp to clamp the proximal end of the common carotid artery and the internal carotid artery of the rat, and ligate the distal end of the artery at the same time, then cut a small opening in the external carotid artery, and loosen the common carotid artery clamp to create a successful model[6].

After the successful modeling, rats in the model group were given normal saline injection, and rats in the dexmedetomidine group were given high, medium and low doses of dexmedetomidine injection by intraperitoneal injection with injection volume of 5 mL.

### Observation indicators and methods

### *Comparative analysis of subarachnoid hemorrhage amount and brain water content in each group of rats*

According to method 1.2, rats in each group were continuously administered for 7 d and then sacrificed by cutting the neck. The brain of the rats was dissected and the intracranial subarachnoid hemorrhage and brain water content in each group were measured and analyzed.

The brain water content was determined as follows: accurately weigh the weight (wet weight) of the just dissected rat brain tissue, then put it in a constant temperature drying oven at 110°C to dry to constant weight, and then use the same electronic balance to accurately weigh the constant weight of the brain tissue (dry weight), brain water content (%) = (wet weight-dry weight)/wet weight × 100%[7].

### *Comparative analysis of serum inflammatory factor levels in each group of rats*

According to method 1.2, rats in each group were continuously administered for 7 days.

Before and after anesthesia, 2 mL of venous blood was taken from each group of rats, and centrifuged at 3000 r/min in a centrifuge at 4°C for 15 min to collect the supernatant. Rat serum inflammatory factors were determined by enzyme-linked immunosorbent assay (ELISA)[8]: Interleukin-Ibeta (IL-1β), Tumor necrosis factor-alpha (TNF-α), Interleukin-6 (IL-6) levels.

### *Comparative analysis of the expression levels of NLRP3, Caspase-1, Bax, BCL-2, TNFA in each group of rats*

According to method 1.2, rats in each group were continuously administered for 7 days, and 1 mL of cerebrospinal fluid of rats was taken before and after anesthesia.

The whole protein samples in the cerebrospinal fluid samples were extracted strictly according to the instructions of the whole protein extraction kit, followed by western blotting analysis. For the whole protein samples, detect the expression levels of NLRP3, Caspase-1, Bax, BCL-2, and TNFA in cerebrospinal fluid by enzyme-linked immunosorbent assay (ELISA).

***Comparative analysis of rat microglia counts in each group***

According to method 1.2, rats in each group were continuously administered for 7 days, and 2 mL of cerebrospinal fluid of rats was taken before and after anesthesia, filtered, washed with phosphate buffered saline to resuspend cells, centrifuged at 1000 r/min in a centrifuge at 4°C for 10 min to collect the supernatant and fluorescein isothiocyanate was added as a label[9]. It was left at room temperature for 20 min. 2 mL of phosphate buffered saline solution was added, centrifuged at 1000 r/min for 5 min to discard the supernatant, and resuspend the cells again. The number of microglia were counted by flow cytometry and fluorescence intensity.

***Correlation analysis between rat NLRP3 inflammasome and inflammatory factor levels***

Pearson test method was taken to analyze the correlation between NLRP3 inflammasome and inflammatory factor levels in rats, and the test level was $\alpha$=0.05.

***Statistical methods***

The data in this study were all processed by SPSS20.0 statistical analysis software (IBM, USA); measurement data were expressed as "mean±standard deviation" ($\bar{x}\pm s$), one-way analysis of variance or repeated measurement analysis of variance was used for comparison between groups. LSD-t test was used for pairwise comparison between groups; count data were expressed by percentage (%), $\chi^2$ was used for comparison between groups. P<0.05 indicates statistically significant difference.

## Results

***Comparative analysis of subarachnoid hemorrhage amount and brain water content in each group of rats***

Before anesthesia, subarachnoid hemorrhage amount and brain water content in each group of rats were not statistically different (P>0.05); after anesthesia, the subarachnoid hemorrhage amount and brain water content were both lower, the dexmedetomidine group had lower subarachnoid hemorrhage amount and brain water content than the model group.

With the increasing injection dose of dexmedetomidine, the subarachnoid hemorrhage amount and brain water content become smaller and smaller (P<0.05) (Table 1).

| Group | Before anesthesia | | After anesthesia | |
|---|---|---|---|---|
| | Subarachnoid hemorrhage amount (mL) | Water content (mL) | Subarachnoid hemorrhage amount (mL) | Water content (mL) |
| Healthy control group (n=30) | 4.23±1.43 | 3.69±1.04 | 0.22±0.01 | 0.68±0.24 |
| Model group (n=30) | 4.16±1.02 | 3.65±1.02 | 3.92±1.03 | 4.19±2.01 |
| Dexmedetomidine low-dose group (n=30) | 3.88±0.92 | 3.54±0.92 | 2.55±0.83 | 3.14±1.92 |
| Dexmedetomidine medium-dose group (n=30) | 4.32±1.02 | 3.59±0.88 | 1.91±0.77 | 2.29±0.72 |
| Dexmedetomidine high-dose group (n=30) | 3.94±1.17 | 3.39±0.54 | 1.07±0.54 | 1.21±0.65 |
| *F* value | 1.023 | 0.923 | 24.234 | 15.021 |
| *P* value | 0.672 | 0.921 | 0.001 | 0.001 |

**Table 1:** Comparative analysis of subarachnoid hemorrhage amount and brain water content in each group of rats ($\bar{x}\pm s$).

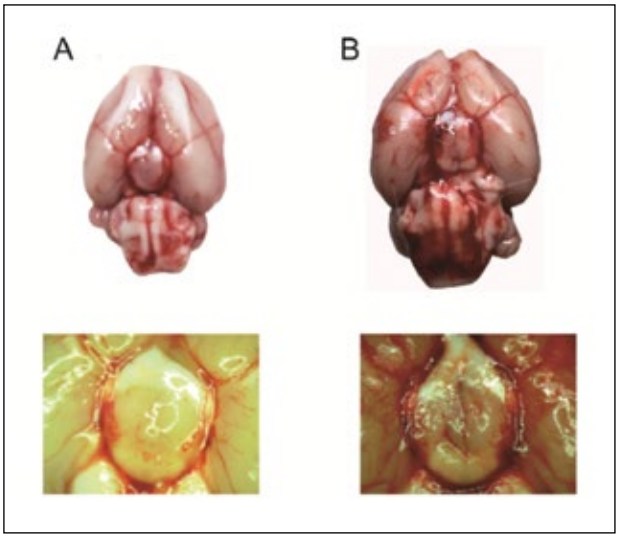


**Figure 1:** Photo of rat skull base; A: is the model control group; B: is the dexmedetomidine group.

***Comparative analysis of serum inflammatory factor levels in each group of rats***

Before anesthesia, the serum levels of inflammatory factors IL-1β, TNF-α and IL-6 in each group were not statistically different (P>0.05); after anesthesia, serum levels of inflammatory factors IL-1β, TNF-α and IL-6 were lower, and dexmedetomidine group had lower serum levels of inflammatory factors IL-1β, TNF-α and IL-6 than the model group.

With the increasing injection dose of dexmedetomidine, serum levels of inflammatory factors IL-1β, TNF-α and IL-6 become lower and lower (P<0.05) (Table 2).

| Group | Before anesthesia | | | After anesthesia | | |
|---|---|---|---|---|---|---|
| | IL-1β (pg/mL) | TNF-α (μmoL/L) | IL-6 (pg/mL) | IL-1β (pg/mL) | TNF-α (μmoL/L) | IL-6 (pg/mL) |
| Healthy control group (n=30) | 49.23±8.12 | 32.44±4.12 | 42.12±6.93 | 10.94±2.23 | 8.18±2.32 | 13.23±3.23 |
| Model group (n=30) | 50.12±5.32 | 33.09±5.52 | 40.92±5.92 | 41.29±6.34 | 29.04±5.12 | 38.42±5.23 |
| Dexmedetomidine low-dose group (n=30) | 49.82±6.02 | 32.98±6.02 | 41.15±4.92 | 30.54±4.23 | 22.19±3.23 | 29.10±4.82 |
| Dexmedetomidine medium-dose group (n=30) | 49.51±5.66 | 34.01±3.45 | 42.11±8.23 | 23.39±4.11 | 15.23±2.01 | 22.67±2.64 |
| Dexmedetomidine high-dose group (n=30) | 49.01±7.92 | 33.92±5.23 | 41.91±3.39 | 15.39±3.09 | 9.53±1.32 | 15.83±3.84 |
| *F* value | 1934 | 1.233 | 1.012 | 2.234 | 19232 | 3.834 |
| *P* value | 0.543 | 0.823 | 0.512 | 0.001 | 0.002 | 0.001 |

**Table 2:** Comparative analysis of serum inflammatory factor levels in each group of rats ($\bar{x}\pm s$).

### *Comparative analysis of relative expression levels of NLRP3 and Caspase-1 in each group of rats*

Before anesthesia, the relative expression levels of NLRP3 and Caspase-1 in each group were not statistically different (P>0.05); after anesthesia, the relative expression levels of NLRP3 and Caspase-1 were lower, and the dexmedetomidine group had lower relative expression levels of NLRP3 and Caspase-1 than the model group.

With the increasing injection dose of dexmedetomidine, the relative expression levels of NLRP3 and Caspase-1 become lower and lower (P<0.05) (Table 3).

| Group | Before anesthesia | | After anesthesia | |
|---|---|---|---|---|
| | NLRP3 (pg/mL) | Caspase-1 (pg/mL) | NLRP3 (pg/mL) | Caspase-1 (pg/mL) |
| Healthy control group (n=30) | 50.23±7.34 | 30.12±3.44 | 14.32±5.23 | 17.89±3.12 |
| Model group (n=30) | 49.94±5.12 | 31.46±5.63 | 42.09±4.57 | 26.73±5.23 |
| Dexmedetomidine low-dose group (n=30) | 50.82±6.03 | 32.94±4.01 | 34.12±4.12 | 22.45±3.95 |
| Dexmedetomidine medium-dose group (n=30) | 51.12±4.85 | 31.00±5.23 | 28.95±7.23 | 20.94±4.12 |
| Dexmedetomidine high-dose group (n=30) | 48.92±7.84 | 30.12±3.92 | 17.79±5.12 | 18.73±2.09 |
| *F* value | 1.234 | 1994 | 2.435 | 3.345 |
| *P* value | 0.653 | 0.523 | 0.001 | 0.001 |

**Table 3:** Comparative analysis of relative expression levels of NLRP3 and Caspase-1 in each group of rats ($\bar{x}\pm s$).

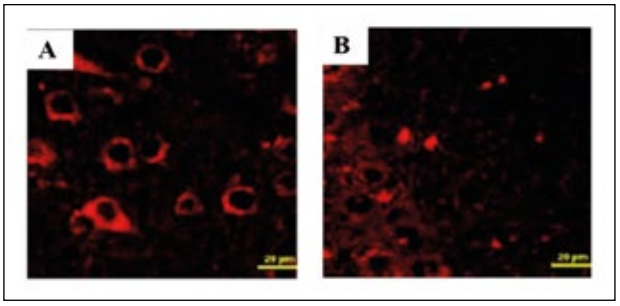


**Figure 2:** PCo-localization of NLRP3 in the cortex and hippocampus of rat brain tissue (×600).
*Where, Figure A shows the rat brain tissue cortex; Figure B shows the hippocampus of the brain tissue.*

### *Comparative analysis of rat microglia counts in each group*

Before anesthesia, the microglia count of rats in each group were not statistically different (P>0.05); after anesthesia, the microglia counts were lower, and the dexmedetomidine group had higher microglia counts than the model group.

With the increasing injection dose of dexmedetomidine, the microglia count become smaller and smaller (P<0.05) (Table 4).

| Group | Before anesthesia | After anesthesia |
|---|---|---|
| Healthy control group (n=30) | 165.34±34.54 | 133.23±45.34 |
| Model group (n=30) | 159.34±39.03 | 90.23±23.12 |
| Dexmedetomidine low-dose group (n=30) | 166.34±54.12 | 122.67±43.02 |
| Dexmedetomidine medium-dose group (n=30) | 163.93±49.03 | 119.53±56.63 |
| Dexmedetomidine high-dose group (n=30) | 162.54±51.13 | 108.32±43.01 |
| *F* value | 1.002 | 54.772 |
| *P* value | 0.823 | 0.001 |

**Table 4:** Comparative analysis of rat microglia counts in each group ($\bar{x}\pm s$, $\times 10^5$).

### *Comparison of Bax, BCL-2 and TNFA expression in hippocampus of rats in each group*

Before anesthesia, the expression levels of Bax, BCL-2, and TNFA in hippocampus of each group were not statistically different (P>0.05); after anesthesia, the expression levels of Bax, BCL-2, and TNFA in the hippocampus were higher. With the increasing injection dose of dexmedetomidine, the expression levels of Bax, BCL-2 and TNFA in hippocampus become lower and lower (P<0.05) (Table 5).

| Group | Before anesthesia | | | After anesthesia | | |
|---|---|---|---|---|---|---|
| | Bax (pg/mL) | BCL-2 (pg/mL) | TNFA (pg/mL) | Bax (pg/mL) | BCL-2 (pg/mL) | TNFA (pg/mL) |
| Healthy control group (n=30) | 5.20±0.56 | 8.53±2.12 | 1.32±0.43 | 5.76±1.93 | 27.65±2.65 | 1.87±0.54 |
| Model group (n=30) | 5.02±1.34 | 8.02±0.95 | 0.95±0.12 | 30.54±4.52 | 12.72±4.89 | 9.10±1.45 |
| Dexmedetomidine low-dose group (n=30) | 4.89±0.65 | 8.12±1.53 | 1.29±0.32 | 31.65±6.73 | 15.64±2.04 | 9.78±1.23 |
| Dexmedetomidine medium-dose group (n=30) | 4.81±1.03 | 8.43±1.21 | 1.43±0.41 | 24.54±4.19 | 18.49±3.45 | 6.93±0.89 |
| Dexmedetomidine high-dose group (n=30) | 5.04±0.54 | 7.94±0.75 | 1.22±0.34 | 21.75±3.43 | 19.53±2.43 | 5.23±0.93 |
| *t* value | 1.114 | 0.934 | 1.132 | 12.545 | 9.034 | 11.535 |
| *P* value | 0.183 | 0.223 | 0.123 | 0.001 | 0.001 | 0.003 |

**Table 5:** Comparison of Bax, BCL-2 and TNFA expression in hippocampus of rats in each group ($\bar{x}\pm s, \times 10^5$).

### *Correlation analysis between rat NLRP3 inflammasome and inflammatory factor levels*

The level of NLRP3 inflammasome has a positive correlation with inflammatory factors IL-1β (r=0.654, P=0.005), TNF-α (r=0.552, P=0.002) and IL-6 (r=0.582, P=0.004) (Table 6).

| Inflammatory factor | NLRP3 inflammasome level | |
|---|---|---|
| | r | *P* vlaue |
| IL-1β | 0.654 | 0.005 |
| TNF-α | 0.552 | 0.002 |
| IL-6 | 0.582 | 0.004 |

**Table 6:** Correlation analysis between rat NLRP3 inflammasome and inflammatory factor levels.

## Discussion

Subarachnoid hemorrhage refers to a brain injury disease in which sudden rupture of cerebral blood vessels causes blood flow to the subarachnoid space, which poses a great threat to the patient's physical and mental health[10]. However, clinically, the pathogenesis of subarachnoid hemorrhage has not yet been clarified. At present, research on the disease is mainly to establish rat subarachnoid hemorrhage models and simulate the pathological and physiological changes in patients with subarachnoid hemorrhage[11].

NLRP3 inflammasome can regulate Caspase-1-dependent programmed cell death, and further induce cell death under inflammatory and stress pathological conditions[12]. Dexmedetomidine is often used as an adjuvant drug in combination with sedatives and analgesics, which can significantly facilitate recovery after anesthesia, reduce postoperative nausea and fatigue, reduce the dosage of sedatives without prolonging the recovery time. In recent years, studies have found that, dexmedetomidine can reduce the degree of brain injury in subarachnoid hemorrhage[13]. The results of this study showed, that compared to the model group, the relative expression levels of NLRP3 and Caspase-1 in rats in the dexmedetomidine group were lower after anesthesia, and the inflammatory factor levels were relatively low. With the increasing injection dose of dexmedetomidine, the relative expression levels of NLRP3 and Caspase-1 became lower and lower, with significant reduction in subarachnoid hemorrhage amount and brain water content. Therefore, the application of dexmedetomidine can down-regulate the level of NLRP3 inflammasome, thereby reducing the degree of early brain injury in rats with subarachnoid hemorrhage.

NLRP3 inflammasome is mainly involved in the occurrence and development of various diseases in the body. First, when dangerous signals such as pathogens and inflammatory factors appear, NLRP3 inflammasomes will be activated, then NLRP3 inflammasomes will undergo oligomerization, and related reactive proteins will be recruited at the same time[14-16]. The resident immune cells in the brain are microglia, which are also the main receptors of NLRP3 inflammasome. That is to say, when the external environment changes to a certain degree, microglia will produce various cytokines and chemokines to provide peripheral immune cells needed for the diseased area[17]. In addition, occurrence of subarachnoid hemorrhage will cause dysregulation of normal brain tissues such as the hippocampus, finally leading to the body's neurological dysfunction[18].

Dexmedetomidine is a drug for alleviating subarachnoid hemorrhage, which mainly protects the brain tissue and nervous system to alleviate the symptoms of subarachnoid hemorrhage, further reduce the patient's subarachnoid hemorrhage amount and cerebral edema water content, thereby effectively protecting the normal physiological function of hippocampus. In addition, with the increasing dexmedetomidine injection dose, the level of inflammation in rats is significantly reduced[19, 20].

In summary, dexmedetomidine can reduce the subarachnoid hemorrhage amount and brain water content in subarachnoid hemorrhage model rats, which shows a certain regular change with

the increasing dose. Therefore, dexmedetomide can reduce the inflammatory response and NLRP3 level of rats by down-regulating the level of NLRP3 inflammasome, thereby lowering the degree of early brain injury in rats with subarachnoid hemorrhage.

## References


1) Xu W., Li T., Gao L., et al., Apelin-13/APJ system attenuates early brain injury via suppression of endoplasmic reticulum stress-associated TXNIP/NLRP3 inflammasome activation and oxidative stress in a AMPK-dependent manner after subarachnoid hemorrhage in rats, J Neuroinflammation, 2019, 16(1), 247.
2) Yao Y., Hu X., Feng X., et al., Dexmedetomidine alleviates lipopolysaccharide-induced acute kidney injury by inhibiting the NLRP3 inflammasome activation via regulating the TLR4/NOX4/NF-κB pathway, J Cell Biochem, 2019, 120(10), 18509-18523.
3) Cheng F., Yan F.F., Liu Y.P., et al., Dexmedetomidine inhibits the NF-κB pathway and NLRP3 inflammasome to attenuate papain-induced osteoarthritis in rats, Pharm Biol, 2019, 57(1), 649-659.
4) Yang T., Feng X., Zhao Y., et al., Dexmedetomidine enhances autophagy via α2-AR/AMPK/mTOR pathway to inhibit the activation of NLRP3 inflammasome and subsequently alleviates lipopolysaccharide-induced acute kidney injury, Front Pharmacol, 2020, 11, 790.
5) Zheng B., Zhang S., Ying Y., et al., Administration of dexmedetomidine inhibited NLRP3 inflammasome and microglial cell activities in hippocampus of traumatic brain injury rats, Biosci Rep, 2018, 38(5), BSR20180892.
6) Lv M., Zeng H., He Y., et al., Dexmedetomidine promotes liver regeneration in mice after 70% partial hepatectomy by suppressing NLRP3 inflammasome not TLR4/NFκB, Int Immunopharmacol, 2018, 54, 46-51.
7) Li H., Zhang X., Chen M., et al., Dexmedetomidine inhibits inflammation in microglia cells under stimulation of LPS and ATP by c-Fos/NLRP3/caspase-1 cascades, EXCLI J, 2018, 17, 302-311.
8) Song H.L., Zhang S.B., Therapeutic effect of dexmedetomidine on intracerebral hemorrhage via regulating NLRP3, Eur Rev Med Pharmacol Sci, 2019, 23(6), 2612-2619.
9) Peng J., Zhang P., Zheng H., et al., Dexmedetomidine reduces hippocampal microglia inflammatory response induced by surgical injury through inhibiting NLRP3, Chin J Traumatol, 2019, 22(3), 161-165.
10) Gao J., Wei L., Xu G., et al., Effects of dexmedetomidine vs sufentanil during percutaneous tracheostomy for traumatic brain injury patients: A prospective randomized controlled trial, Medicine (Baltimore), 2019, 98(35), e17012.
11) Li F., Wang X., Zhang Z., et al., Dexmedetomidine attenuates neuroinflammatory-induced apoptosis after traumatic brain injury via Nrf2 signaling pathway, Ann Clin Transl Neurol, 2019, 6(9), 1825-1835.
12) Ding M., Chen Y., Luan H, et al., Dexmedetomidine reduces inflammation in traumatic brain injury by regulating the inflammatory responses of macrophages and splenocytes, Exp Ther Med, 2019, 18(3), 2323-2331.
13) Zhu Y., Li S., Liu J., et al., Role of JNK signaling pathway in dexmedetomidine post-conditioning-induced reduction of the inflammatory response and autophagy effect of focal cerebral ischemia reperfusion injury in rats, Inflammation, 2019, 42(6), 2181-2191.
14) Zhai M., Liu C., Li Y., et al., Dexmedetomidine inhibits neuronal apoptosis by inducing Sigma-1 receptor signaling in cerebral ischemia-reperfusion injury, Aging (Albany NY), 2019, 11(21), 9556-9568.
15) Chen L., Cao J., Cao D., et al., Protective effect of dexmedetomidine against diabetic hyperglycemia-exacerbated cerebral ischemia/reperfusion injury: An in vivo and in vitro study, Life Sci, 2019, 235, 116553.
16) Sun D., Wang J., Liu X., et al., Dexmedetomidine attenuates endoplasmic reticulum stress-induced apoptosis and improves neuronal function after traumatic brain injury in mice, Brain Res, 2020, 1732, 146682.
17) Dardalas I., Stamoula E., Rigopoulos P, et al., Dexmedetomidine effects in different experimental sepsis in vivo models, Eur J Pharmacol, 2019, 856, 172401.
18) Ren C., Gao J., Xu G.J, et al., The nimodipine-sparing effect of perioperative dexmedetomidine infusion during aneurysmal subarachnoid hemorrhage: a prospective, randomized, controlled trial, Front Pharmacol, 2019, 10, 858.
19) He Y., Yang Z., Li J, et al., Dexmedetomidine reduces the inflammation and apoptosis of doxorubicin-induced myocardial cells, Exp Mol Pathol, 2020, 113, 104371.
20) Wang Y.G., Liu C.Z., Li Y.Z., et al., Cotreatments with Dex and Na2SeO3 further improved antioxidant and anti-inflammatory protection of myocardial cells from I/R injury compared to their individual treatments, Free Radic Res, 2020, 54(1), 76-90.


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