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Dexmedetomidine Alleviates Neuroinflammation-Induced Cognitive Impairment by Modulating the NLRP3 Inflammasome Activation Pathway

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Objective: Neuroinflammation-induced cognitive dysfunction (NICD) relies on symptomatic treatment, with no causative treatment strategies available yet. Therefore, comprehensive investigations on the pathogenesis of NICD are crucial for the development of novel and effective therapeutic drugs. Hence, we aimed to elucidate the impact of Dexmedetomidine (Dex) in modulating nucleotide-binding domain, leucine-rich repeat-containing family, pyrin domain-containing-3 (NLRP3) inflammatory vesicles for improving cognitive dysfunction.

Methods: The study employed both cellular and animal models. The HT22 cells were utilized to assess the impact of Dex on Lipopolysaccharide (LPS)-induced neuroinflammation. Cell viability was examined using an 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, and changes in mitochondrial membrane potential were evaluated using the JC-1 kit. Furthermore, the expression levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and NLRP3 were analyzed using Enzyme-Linked Immunosorbnent Assay (ELISA) and qPCR techniques. Additionally, NICD was induced in mice using LPS, and cognitive functions were assessed through the Morris water maze experiment. The expression levels of inflammatory markers in the hippocampal tissues of the mice were evaluated using the qPCR method.

Results: The Dex treatment was found to restore the LPS-induced reduction in HT22 cell viability ($p < 0.05$), as well as significantly reduced the cellular levels of TNF-α, IL-1β, IL-6, and NLRP3 ($p < 0.05$). Furthermore, Dex treatment restored the mitochondrial membrane potential of HT22 cells ($p < 0.05$). Additionally, we observed that Dex treatment significantly improved the declining cognitive ability of NICD mice ($p < 0.05$).

Conclusion: Dex can protect the learning and memory capabilities of cognitively impaired mice by inhibiting the expression of NLRP3 inflammatory vesicles as well as inflammatory factors.

Keywords: cognitive impairment; dexmedetomidine; NLRP3; inflammatory vesicles

Introduction

The chronic inflammatory response in the brain has been found to serve as an important pathological feature of cognitive dysfunction [1]. Furthermore, microglia with cognitive dysfunction induced by neuroinflammation have shown excessive activation along with an accumulation of degenerated neurons. It is generally recognized that microglia play a dual regulatory role in cognitive dysfunction. Under normal conditions, microglia can effectively clear metabolites and toxic substances, acting as a "scavenger". However, when stimulated by inflammation, microglia rapidly undergo activation, changing their morphology, and migrating to the site of the lesion to remove damaged nerve cells, thereby playing an immune defense function [2]. Furthermore, microglia release trophic factors to support the growth of nearby neurons. However, when microglia are "continuously activated", they release large amounts of inflammatory factors, leading to neuronal death and contributing to a variety of central nervous system disorders, including cognitive impairment [3]. It has been reported in the literature that due to the lack of blood-brain barrier, peripheral inflammation induced by intraperitoneal injection of Lipopolysaccharide (LPS) can infiltrate the periventricular area of the brain, activating microglia and resulting in neuroinflammation and cognitive dysfunction [4]. Neuroinflammation-induced cognitive dysfunction (NICD) is primarily mediated by a large number of inflammatory factors, with nucleotide-binding domain, leucine-

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rich repeat-containing family, pyrin domain-containing-3 (NLRP3) inflammatory vesicles being closely associated with the activation of inflammatory signaling pathways [5].

The NLRP3 inflammasome primarily consists of receptor proteins, regulatory proteins, and effector proteins. The NLRP3 inflammasome's receptor proteins are predominantly composed of NOD structural domains, C-terminal LRR structural domains, and N-terminal PYD structural domains. The regulatory proteins consist of apoptosis-associated speckled proteins, while effector proteins include pre-Caspase-1 [6,7]. The activation of the NLRP3 inflammasome requires initial signals such as ligands for different toll-like receptors (TLRs) and second signals such as extracellular adenosine triphosphate (ATP) and mitochondrial DNA. Several studies have found that targeting or inhibiting NLRP3 inflammatory vesicles significantly improved cognitive dysfunction in mouse models [8,9]. Meanwhile, the activation of NLRP3 inflammatory vesicles has been reported in activated microglia [10]. NLRP3 inflammatory vesicles are involved in cognitive dysfunction. The emtROS/NLRP3 inflammatory vesicle/interleukin (IL)-1β signaling pathway has been implicated in postoperative cognitive dysfunction triggered by anesthetics [11,12]. Additionally, NLRP3 is correlated with the isoflurane-induced microglia inflammatory response and cognitive dysfunction.

Dexmedetomidine (Dex) is the dextro isomer of medetomidine, producing a sedative effect similar to natural sleep through selective agonism of α2-adrenergic receptors in the nucleus accumbens (NAc) of the central nervous system [13]. Additionally, Dex exhibits analgesic, antisympathetic excitation, and hemodynamic stabilization effects. Importantly, it does not inhibit respiration nor interfere with brain electrophysiological activities. Consequently, it can significantly reduce the dosage of anesthesia drugs during the perioperative period, thereby reducing the occurrence of adverse reactions [14,15]. Hence, Dex is widely used across many perioperative processes.

This study intends to experimentally elucidate the significant effects of Dex intervention in NICD. This study seeks to investigate the molecular mechanism of Dex intervention in NICD, particularly focusing on the activation of the NLRP3 inflammatory vesicle pathway. We hope to identify new biomarkers of cognitive dysfunction, thereby providing a new therapeutic idea and theoretical basis for the clinical prevention and treatment of cognitive dysfunction.

Materials and Methods

MTT Assay for HT22 Cell Viability

The HT22 cells (CL0619, Procell, Wuhan, China) were obtained after being authenticated through STR profiling and mycoplasma testing. The cells were seeded into 96-well plates and their survival rate was assessed using an MTT assay (M1020, Solarbio, Beijing, China). Following stimulation with 200 ng/mL of LPS, the cells were treated with varying concentrations of Dex (1, 10, 50, 100, and 500 μg/mL) for 8 hours. After this, they were centrifuged, and the supernatant was carefully aspirated. In the next step, the cells were resuspended in 90 μL of fresh culture medium followed by the addition of 10 μL of MTT solution and incubation for 4 hours. Afterward, the supernatant was removed and 110 μL of Formazan solution was added to each well. The cell culture plate was then gently shaken for 10 minutes to completely dissolve the crystals. Finally, the absorbance value at 490 nm was assessed using a microplate reader (SpectraMax PLUS 384, Molecular Devices, San Jose, CA, USA).

Enzyme-Linked Immunosorbnent Assay (ELISA) for Inflammation-Related Factors

The expression levels of cytokines in HT22 cells were determined utilizing corresponding ELISA kits, including tumor necrosis factor (TNF)-α (PT512, Beyotime, Shanghai, China), IL-1β (PI301, Beyotime, Shanghai, China), IL-6 (PI326, Beyotime, Shanghai, China), and NLRP3 (ab279417, Abcam, Shanghai, China). For this purpose, the cell culture's supernatant of different treatment groups was collected followed by centrifugation at 1000 $\times$g for 20 minutes. After this, 100 μL of the sample was added to the plate, covered with a membrane, and incubated at 37 °C for 1 hour. Subsequently, 100 μL of Assay Solution A was added to each well followed by incubation at 37 °C for 1 hour. Following removal from the liquid, they were washed with 350 μL of washing solution. In the next step, 100 μL of Detection Solution B was added, covered again with a membrane, and incubated at 37 °C for 30 minutes. After washing, 90 μL of 3,3′,5,5′-tetramethylbenzidine (TMB) substrate solution was added followed by incubation at 37 °C to develop the color. Finally, 50 μL of termination solution was applied to terminate the reaction, and the optical density (OD) at 450 nm was determined using a microplate reader (SpectraMax PLUS 384, Molecular Devices, San Jose, CA, USA).

Detection of Mitochondrial Membrane Potential

The cellular mitochondrial membrane potential was assessed using the Mitochondrial Membrane Potential Assay Kit (JC-1) (C2006, Beyotime, Shanghai, China) [16]. For this purpose, the HT22 cells were cultured in 6-well plates. One milliliter of JC-1 staining working solution was added and underwent thorough mixing. They were then incubated at 37 °C for 20 minutes in a cell incubator. After this, the supernatant was eliminated, and the cells were washed twice with JC-1 staining buffer. Subsequently, two milliliters of cell culture solutions were added, and the samples were observed employing a fluorescence microscope (CX23, Olympus, Tokyo, Japan).

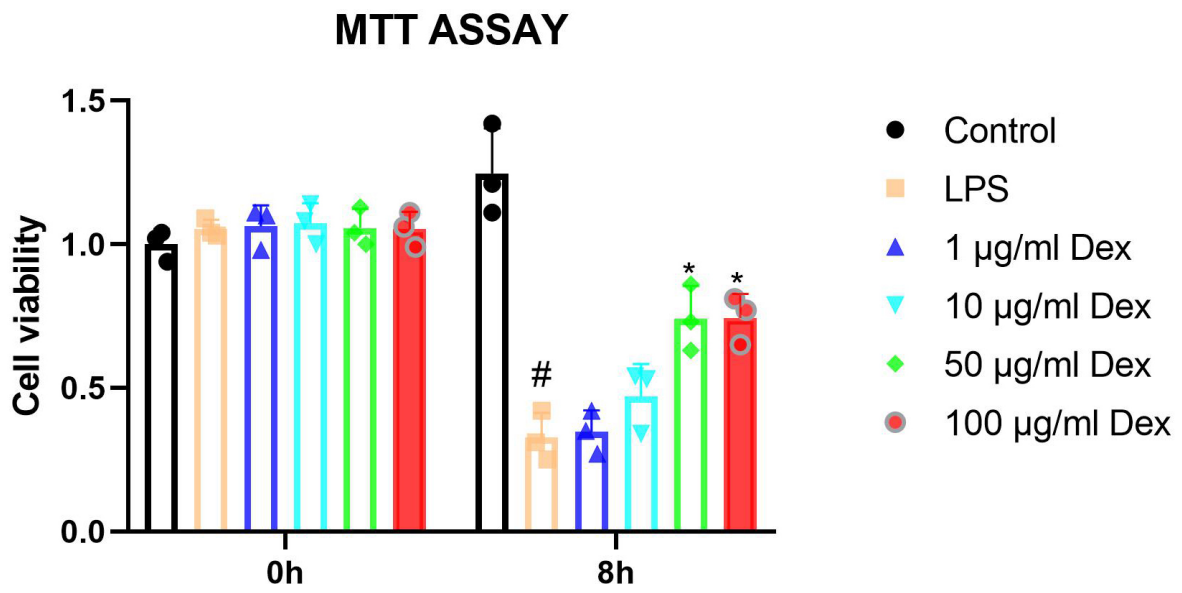

Fig. 1. The impact of Dexmedetomidine (Dex) treatment on Lipopolysaccharide (LPS)-induced reduction in HT22 cell viability. $^{\#}p < 0.05$ compared to the 8-hour control group. $^{*}p < 0.05$ compared to the 8-hour LPS group. n = 3.

Establishment of NICD Mouse Model and Drug Administration

Male C57BL/6 mice of SPF grade (n = 30), aged 6 months and weighing 24–26 g, were provided by Chongqing Ensweil Biotechnology Co., Ltd. (Chongqing, China). Following the establishment of the mouse model of cognitive dysfunction, the mice were randomly divided into three groups, with 10 animals in each group: the control group (mice without any treatment), the LPS group (mice treated with 15 mg/kg of LPS), and Dex + LPS group (LPS mice treated with 50 μg/kg of Dex). The mice that exhibited memory impairment were exposed to drug treatments for three consecutive days, with each administration occurring once a day. Following the final administration, the escape latency, the number of the mice crossing the cryptic platform, and other relevant indexes were assessed. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine, China (20220108).

Water Maze Experiment

The Morris water maze (XR-XM101, XinRuan Science and Technology Company, Shanghai, China) approach was used to assess the acquisition training, probing, and alignment training in the mice. The water maze consisted of a cylindrical black pool, 1.5 m in diameter and 50 cm in height, submerged with a 10-cm-diameter removable solid platform 2 cm below the middle partition in the first quadrant. The water temperature in the system was maintained at 19–21 °C. The mice were placed in the water of each quadrant facing towards the wall, four times per day for a period of 120 seconds. This training was continued for four days, and the data were recorded. However, the recording was stopped automatically when the mice found the platform within 120 seconds, where they were allowed to stay on the platform for an additional 20 seconds. Moreover, those who did not find the platform, were directed towards the platform using the guiding rod with in the designated 120 seconds. On the fifth day of the observation, the platform was displaced, and the mice were placed diagonally in the water, facing the wall of the pool. The length of time the mice climbed to the platform or reached (the pre-set training time) as well as the time spent searching for the platform (the latency to escape) were calculated [17,18]. After the experiment, the mice were anesthetized with 1% pentobarbital sodium (50 mg/kg) (P-010-1ML, Merck, Kenilworth, NJ, USA) and were euthanized by cervical dislocation, and their hippocampal tissues were surgically collected for subsequent analysis. Furthermore, blood samples were collected utilizing the eyeball removal method followed by centrifugation at 3000 rpm for 10 minutes at 4 °C. The upper layer of serum was stored at –80 °C for subsequent experimentations.

Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR)

Total RNA was extracted from the hippocampal tissue and subsequently converted into cDNA. The expression levels of *TNF-α*, *IL-1β*, *IL-6*, and *NLRP3* mRNA were determined using qRT-PCR performed in a fluorescence qPCR instrument. The relative expression levels of the target genes were assessed using the $2^{-\Delta\Delta Ct}$ method, with *GAPDH* as an internal reference [19]. The primers used in qRT-PCR were as follows: *TNF-α*-F, 5′-CTGTGAAGGGAATGGGTGTT-3′; *TNF-α*-R, 5′-GGTCACTGTCCCAGCATCTT-3′; *IL-1β*-F, CATGT-

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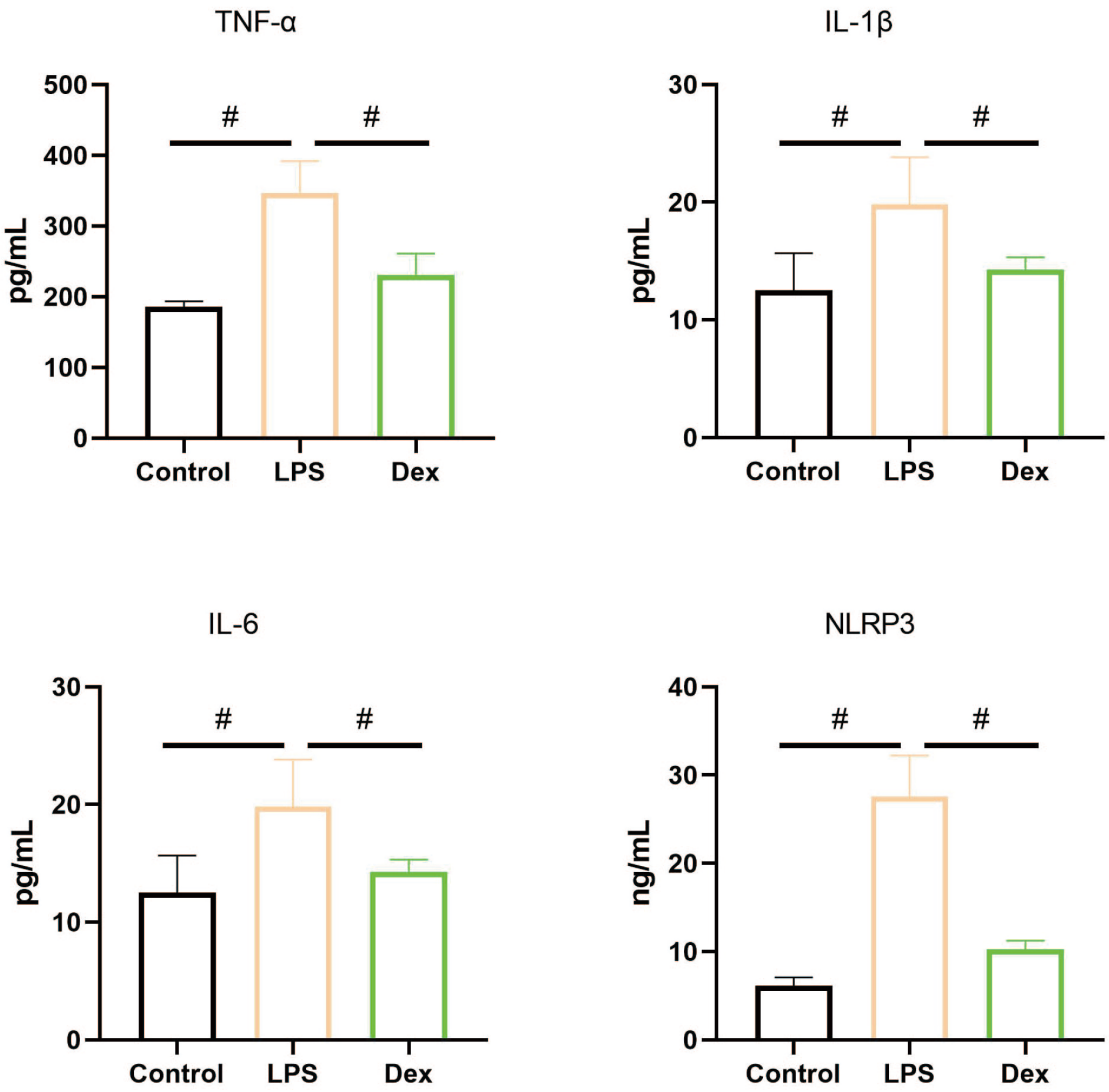

Fig. 2. The expression levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and nucleotide-binding domain, leucine-rich repeat-containing family, pyrin domain-containing-3 (NLRP3). $^{\#}p < 0.05$. n = 3.

GTGCTGAAGGCTCTC; *IL-1β*-R, AGTGTCGGCGTATCACCTTT; *IL-6*-F, GGGCTGCTCCTGGTGATGACTT; *IL-6*-R, CGATGTGCTTAATGAGAGCTTCGG; *NLRP3*-F, 5′-AGTGGATAGGTTTGCTGGGATA-3′; *NLRP3*-R, 5′-CTGGGTGTAGCGTCTGTTGAG-3′; *GAPDH*-F, 5′-GAAGGTGAAGGTCGGAGTC-3′; *GAPDH*-F, 5′-GAAGATGGTGATGGGATTTC-3′.

Statistical Analysis

Statistical analyses were conducted using GraphPad Prism (version 9.0, GraphPad Software, San Diego, CA, USA). The data were expressed as the mean ± standard deviation ($\bar{x} \pm$ SD). Statistical comparison between the two groups was conducted utilizing an independent sample *t*-test. Moreover, analysis of variance (ANOVA) was employed for comparisons involving multiple groups followed by Tukey's test to examine intergroup differences. A *p*-value < 0.05 was defined as statistically significant.

Results

Dex Can Restore LPS-Induced Reduction in HT22 Cell Viability

MTT assay revealed a significantly reduced HT22 cell viability in the LPS group compared to the control group. However, cell viability was significantly increased in the Dex-treated group following treatment with different concentrations of Dex (50 μg/mL and 100 μg/mL). The impact of Dex treatment on HT22 cell viability is shown in Fig. 1. These observations indicate that Dex can restore the reduction in HT22 cell viability induced by LPS. However, a 50 μg/mL concentration of Dex was used in the subsequent experimentation.

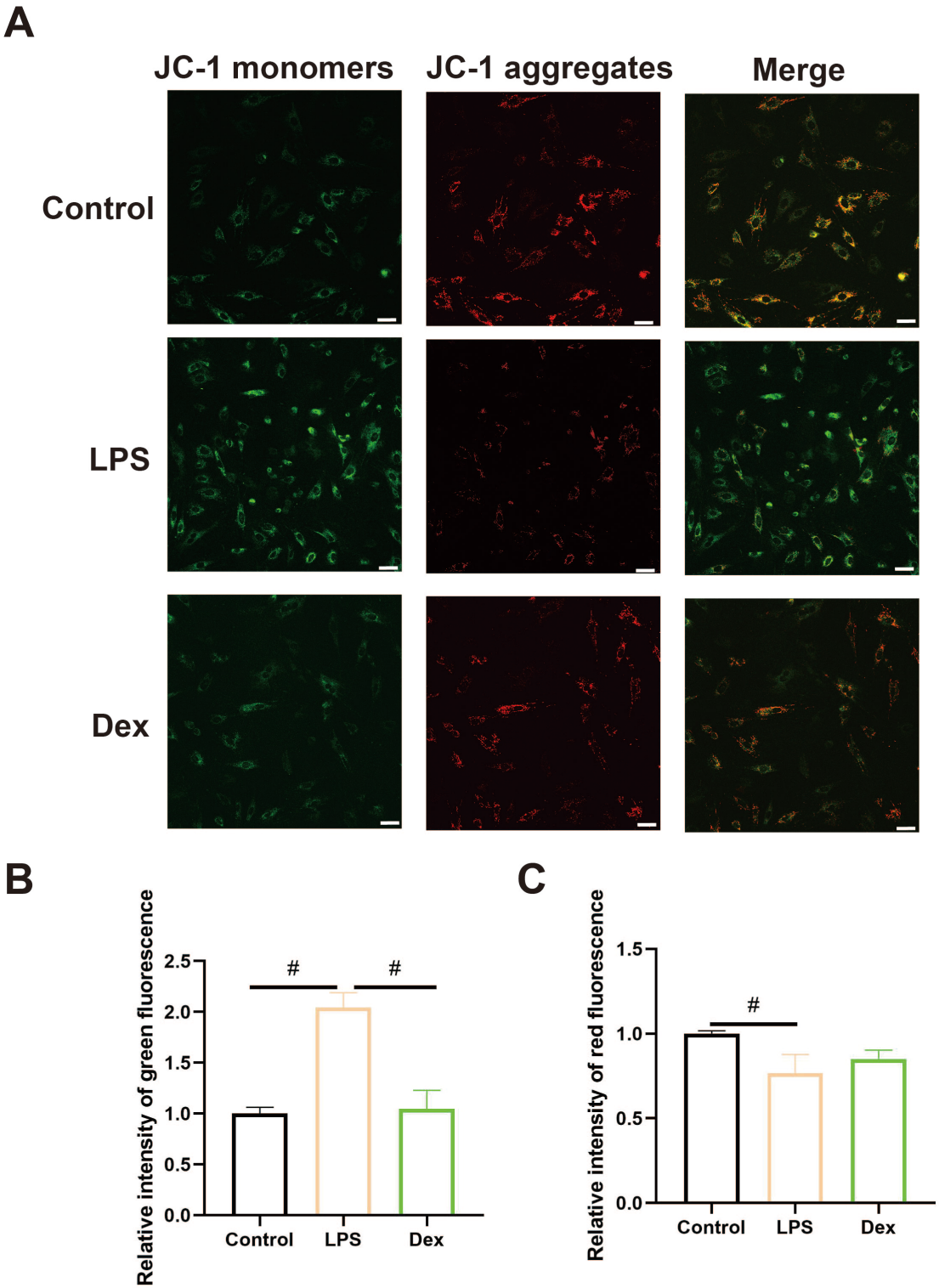

Fig. 3. Dex restores mitochondrial membrane potential in HT22 cells. (A) Fluorescence staining results of mitochondrial membrane potential detection kit (JC-1). Scale bar = 100 μm. (B,C) Relative intensity of both green and red fluorescence. $^{\#}p < 0.05$. n = 3.

Dex Reduces the Expression of Inflammatory Factors as well as NLRP3

We analyzed the expression levels of TNF-α, IL-1β, IL-6, and NLRP3 in the cells using ELISA. It was found that following LPS treatment, the levels of TNF-α, IL-1β, IL-6, and NLRP3 were significantly elevated. In contrast, their levels were found to be significantly reduced in the Dex-treated group compared to the LPS group (Fig. 2).

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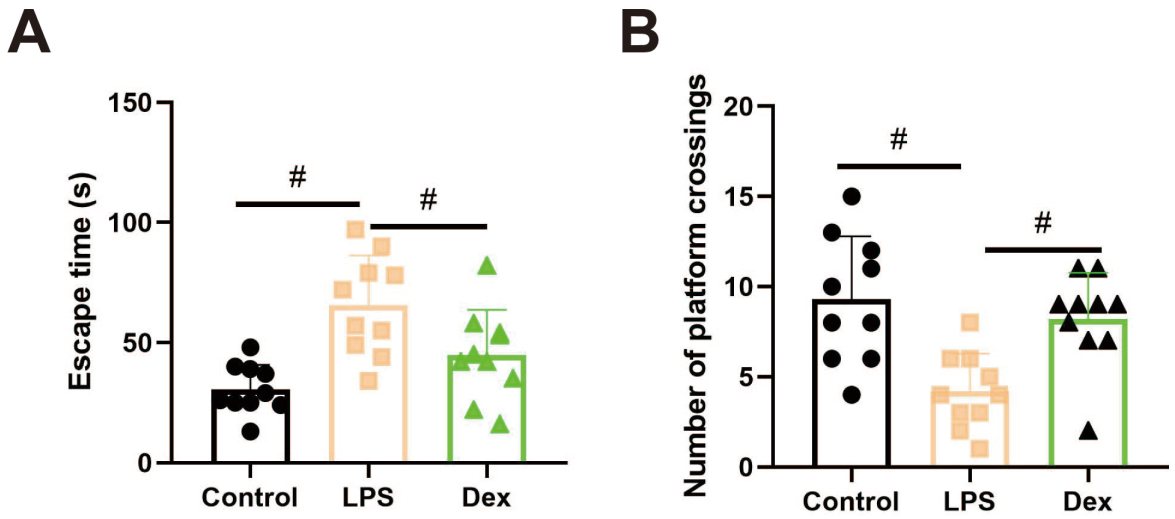

Fig. 4. Water maze experiment to detect cognitive function in mice. (A) Escape latency of mice. (B) Number of times mice entered the platform. $^{\#}p < 0.05$. n = 10.

Dex Restores Mitochondrial Membrane Potential in HT22 Cells

We used the Mitochondrial Membrane Potential Assay Kit (JC-1) to detect cellular mitochondrial membrane potential (Fig. 3). We observed that the levels of green fluorescence were significantly higher in the LPS-treated group compared to the control group. However, the levels of red fluorescence were significantly lower in the LPS-treated group than in the control group. This suggests that LPS treatment resulted in a decrease in the cellular mitochondrial membrane potential. Conversely, the levels of green fluorescence were significantly lower in the Dex group compared to the LPS group, while the levels of red fluorescence were slightly higher than in the LPS group. These findings demonstrate that Dex can effectively restore the mitochondrial membrane potential of HT22 cells.

Dex Can Restore Cognitive Function in NICD Mice

Subsequently, we conducted further validation analysis *in vivo* using a mouse model. We evaluated the cognitive functions, the expression of inflammatory factors, and the spatial learning and memory in each group of mice. It was observed that the learning ability of mice was significantly impaired within the LPS-treated group compared to the control group, as evidenced by a significant increase in escape latency. However, the escape latency of mice in the Dex-treated group was significantly reduced (Fig. 4A). Furthermore, we found that mice in the Dex-treated group entered the platform more often (Fig. 4B). These results suggest that Dex can improve the declining cognitive ability of NICD mice.

The expression levels of *TNF-α*, *IL-1β*, *IL-6*, and *NLRP3* in the hippocampal tissues of mice were assessed using qPCR and were found similar to the results observed at the cellular level study. Moreover, the levels of *TNF-α*, *IL-1β*, *IL-6*, and *NLRP3* were significantly increased in the LPS-treated group. Conversely, their levels were significantly reduced in the Dex-treated group compared to the LPS group (Fig. 5).

Discussion

This study aimed to investigate the therapeutic effects of Dex in NICD and to provide insights into its mechanisms in regulating NLRP3 inflammatory vesicles. Chronic neuroinflammatory responses are recognized as an important pathological feature of cognitive dysfunction [20,21]. Microglia play a key role in neuroinflammation, and their persistent activation may lead to the release of excessive inflammatory factors, causing neuron damage and triggering cognitive dysfunction. In this study, we explored the therapeutic potential of Dex in alleviating NICD and elucidated its underlying mechanism involving the inflammasome pathway. Our findings demonstrate that Dex effectively restored the LPS-induced reduction in HT22 cell viability, decreased the expression levels of inflammatory factors (TNF-α, IL-1β, IL-6), and mitigated NLRP3 activation, both *in vitro* and *in vivo*.

NLRP3 inflammatory vesicles, recognized as a key component of the inflammatory signaling pathway, have attracted significant attention due to their regulatory role in cognitive dysfunction. Certain drugs targeting NLRP3 have achieved some efficacy in the treatment of cognitive dysfunction. For example, in db/db mice, aspalathinamine improved their learning and memory functions and significantly inhibited the activation of hippocampal NLRP3 inflammatory vesicles [22]. Aspalathin A ameliorated cognitive dysfunction and reduced neuroinflammatory responses in erythrocyanine-induced rats by exerting antioxidant effects and inhibiting the NLRP3/caspase-1 signaling

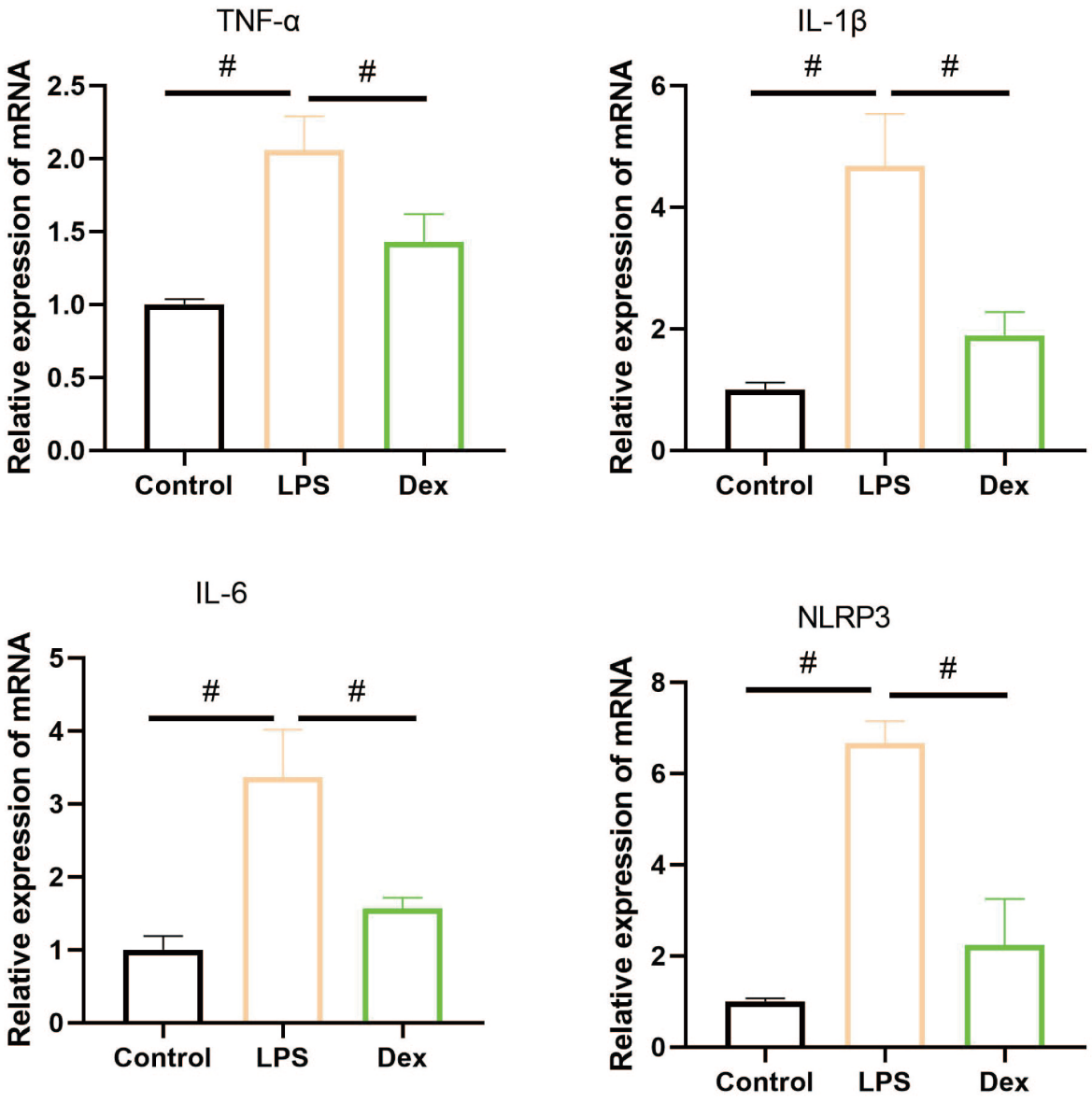

Fig. 5. Expression levels of *TNF-α*, *IL-1β*, *IL-6* and *NLRP3*. $^{\#}p < 0.05$. n = 3.

pathway. Baicalin alleviated microglial inflammatory responses and cognitive dysfunction by inhibiting the activation of NLRP3 inflammatory vesicles and the TL4/NF-κB signaling pathway [23,24]. Our results corroborate previous studies highlighting the involvement of NLRP3 inflammasome activation in NICD pathogenesis. Importantly, Dex treatment was associated with a significant reduction in NLRP3 expression, suggesting its regulatory effect on the inflammasome pathway. Activation of inflammatory vesicles could mediate inflammatory responses through multiple signaling pathways, thereby affecting normal neuronal function. Therefore, targeting NLRP3 might be a potential strategy for treating cognitive dysfunction.

Dex, as a drug, induces sedation by agonizing α2-adrenergic receptors within the central nervous system, and it shows both analgesic and anti-inflammatory effects. Dex was found to restore LPS-induced reduction in cell viability, and decrease the expression of inflammatory factors (e.g., TNF-α, IL-1β, IL-6) and NLRP3, while also restoring mitochondrial membrane potential. These findings suggest that Dex could serve as a neuroprotective agent by inhibiting neuroinflammation and suppressing the activation of NLRP3 inflammatory vesicles [25]. Dex has been widely used in perioperative anesthesia management in previous studies, and its role in improving cognitive function has been reported, primarily focusing on cognitive improvement after anesthetics [15,26]. Our study extends the therapeutic potential of Dex beyond its traditional applications, demonstrating its neuroprotective effects in NICD. Importantly, our findings suggest that Dex exerts its neuroprotective effects, at least in part, by modulating the activation of the NLRP3 inflammasome.

One limitation of this study is the lack of comparisons to other treatment groups, emphasizing further evidence to

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argue for the superiority of Dex over other treatments. Furthermore, the effects of Dex on other inflammatory pathways have not been thoroughly observed, thus implying future studies could explore its role in modulating other crucial factors in neuroinflammation.

Conclusion

Dex protects the learning and memory capabilities of cognitively impaired mice by exerting its anti-inflammatory effects, which involve the inhibition of NLRP3 inflammatory vesicle expression and inflammatory factors. These findings provide novel possibilities for the treatment of neuroinflammation-induced cognitive dysfunction.

Availability of Data and Materials

All experimental data included in this study can be obtained by contacting the corresponding authors if needed.

Author Contributions

SJT and BJM contributed to the design and implementation of the research. RC, YZ, JT, JSZ, XL, LHW, BL, TCC, YC and SML contributed to the analysis of the results and the writing of the manuscript. RC, YZ, SJT and BJM conceived the original and supervised the project. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All procedures were approved by the Ethics Committee of the First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine (approval number: 20220108).

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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