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Butorphanol attenuates inflammation via targeting NF-κB in septic rats with brain injury

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Abstract. – OBJECTIVE: To observe the therapeutic effect of butorphanol on brain tissue injury in rats with sepsis through the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. MATERIALS AND METHODS: Sprague-Dawley rats were divided into control group (n=20), sepsis model group [cecal ligation and perforation (CLP) group, n=20], and butorphanol treatment group (n=20). After successful modeling, the blood and brain tissues were collected from rats at 24 h. The content of serum brain injury indexes was detected. Hematoxylin-eosin (HE) staining assay and enzyme-linked immunosorbent assay (ELISA) were separately carried out to observe the pathological changes and measure the levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and myeloperoxidase (MPO) activity. The neurological function was scored in rats. Glial fibrillary acidic protein (GFAP), S100, and NF-κB signaling pathway genes and proteins in brain tissues were detected *via* quantitative Reverse Transcription-Polymerase Chain Reaction (qRT-PCR) and Western blotting.

RESULTS: CLP group showed remarkably increased levels of serum glucosuria (GLU), creatinine (CR), and Na^+ but an evidently reduced level of K^+ in comparison with the control group ($p<0.05$), while the treatment group displayed contrary trends. Histopathological observations showed that the rats in the CLP group suffered a brain injury, while those in the treatment group had mild pathological changes. The MPO in the CLP group was significantly increased compared with that in the control group ($p<0.05$). The levels of TNF-α and IL-6 were overtly higher in the CLP group than those in the control group, and these indexes in the treatment group were close to those in the control group. The messenger ribonucleic acid (mRNA) expression levels of S100, GFAP, Toll-like receptor 2 (TLR2), and NF-κB in CLP group were evidently higher than those in the control group and treatment group ($p<0.05$). The results of Western blotting revealed that the protein expression of NF-κB was significantly higher in CLP group than that in the control group, and it declined in the treatment group, which was close to that in the control group.

CONCLUSIONS: Butorphanol can reduce the content of inflammatory factors TNF-α, IL-1, and IL-6 through the NF-κB signaling pathway, thereby relieving the brain injury caused by sepsis.

Key Words:
Butorphanol, NF-κB signaling pathway, Rat, Sepsis, Brain injury.

Introduction

Sepsis is clinically manifested as infection and many common complications under stress conditions, including lung injury and brain injury[1]. Its essence is to release massive cytokines and inflammatory mediators to cause host autoimmune injury. Besides, sepsis is related to abnormal activation of multiple immune-related signaling pathways due to various epidemiological factors[2]. It is deemed to be a disease response syndrome combining two or more characteristics of systemic inflammation, and a severe bloodstream infection-induced infectious disease that can rapidly become life-threatening[3,4]. Moreover, sepsis is a deadly immunological disorder, and its pathophysiology is still poorly understood at present. It is mainly caused by the imbalance of inflammation, which is a huge burden on the medical system and society. Rapid advances have been achieved in the research of sepsis, but it remains the second

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leading cause of death from non-coronary heart diseases in the intensive care units and the tenth leading cause of death in high-income countries all over the world[5,6]. There are only a few specific treatments available due to its poorly-understood pathophysiology. Furthermore, sepsis leads to septic shock, multi-organ failure and death, and it is conducive to activating inflammation and pro-coagulant pathways[7,8]. Previous studies have proved that the roles of pro-inflammatory cytokines in the innate immune response are one of the most widely-studied aspects in the field of the pathophysiology of sepsis. Sepsis-induced white matter injury is a common brain injury that often leads to chronic neurological dysfunctions in premature infants, such as cerebral palsy and cognitive, behavioral, and attention deficits[9,10]. These chronic neurological dysfunctions result in fatal adverse consequences and bring heavy economic burdens around the world. However, successful interventions in the treatment of brain injury-related neurological diseases are lacking despite considerable time and efforts invested. Currently, hypothermia is a therapeutic strategy, but it leads to such adverse side effects as incomplete neuroprotection and abnormal neurodevelopment[11]. Therefore, it is urgent to explore new treatment methods to provide a basis for the prevention and treatment of sepsis and its complications.

The therapeutic means of sepsis now mainly focus on the antagonistic treatment of early inflammatory factors, with unsatisfactory efficacy[12]. Therefore, finding a new generation of drugs with ideal therapeutic effects is extremely urgent. However, the etiology and pathogenesis of sepsis are complex, and there are no specific or effective prevention strategies for sepsis and no suitable treatment options. During the treatment, multiple signaling pathways participate in the inflammatory response and tissue damage. Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a widely distributed transcription factor, can control many biological processes including inflammation and apoptosis[13]. In cells, NF-κB p65 is most common, and plays a key role in tumor necrosis factor-alpha (TNF-α)-induced apoptosis[14] and can notably inhibit TNF-α and protect the body from TNF-α toxic persecution[15]. NF-κB activation-related regulatory mechanisms include nuclear localization, signal export, phosphorylation, and proteolytic processing. The dysregulation of NF-κB signal transduction is a potential cause of various diseases[16]. Therefore, it is important to understand the relationships of NF-κB with various downstream signaling molecules. NF-κB, as a switch or sensor, triggers inflammatory responses to various stimuli and activates genes. Many factors can activate nuclear transcription factors, giving rise to the activation of NF-κB[17]. Disordered NF-κB becomes a driving force for diseases. Butorphanol is a new anti-inflammatory analgesic drug[18], which is rarely applied in the treatment of sepsis-induced brain injury in rats, currently. In addition, the mechanism of action remains unclear, and further research is needed for verification. Therefore, it was put forward in this study that butorphanol can treat brain tissue injury in rats with sepsis through the NF-κB pathway.

In the present study, it was proposed that butorphanol exerted a therapeutic effect on brain injury in rats with sepsis through the NF-κB signaling pathway. The therapeutic effect of butorphanol on brain injury in rats with sepsis was revealed using typical animal models of sepsis and was based on the biochemical indicators determined. The changes in NF-κB pathway genes and proteins in tissues were detected *via* quantitative Reverse Transcription-Polymerase Chain Reaction (qRT-PCR) and Western blotting, which provided experimental evidence for subsequent research and development of new drugs.

Materials and Methods

Animal Model Establishment and Sample Collection and Processing

Establishment of rat models of sepsis [cecal ligation and perforation (CLP)]: Sprague-Dawley (SD) rats weighing about 280 g and aged about 12 weeks old fasted for 12 h before surgery. This study was approved by the Animal Ethics Committee of Jining Medical University Animal Center. Then, they were anesthetized *via* intraperitoneal injection with 2% pentobarbital sodium. Next, the abdomen was disinfected routinely, and an incision about 2 cm was made. After finding the cecum in the abdominal cavity, the mesentery between the distal cecum and large intestine was separated. Thereafter, the distal cecum was half-ligated, a puncture was made in the middle using a needle, the abdomen was sutured, and the cecum was placed back in the abdominal cavity. Besides, the normal control group (n=20) was set, in which the rats were subjected to the same procedures in CLP modeling except ligation and puncture. Then, the butorphanol treatment group (20 μg/kg, n=20) was set up. After modeling, the

blood was collected from rats in the treatment group and centrifuged, and the serum was collected and stored at -80°C for the detection of the serum biochemical indicators. Next, the rats were anesthetized with pentobarbital sodium, and two samples of appropriate number of tissues were taken, with one placed in fixation solution for subsequent hematoxylin-eosin (HE) staining assay (Boster, Wuhan, China), and one stored at -80°C for measurement of gene, enzyme activity, and protein expression levels.

Detection of Brain Injury Indicators

Previous studies have manifested that blood glucose level and ion concentration are changed in case of brain injury. To predict the brain injury in advance in clinical practice, the indicators including GLU, CR, K^+, and Na^+ were examined. The serum stored in a low-temperature refrigerator was taken out, thawed in gradients, centrifuged, and dispensed in centrifuge tubes. The change in content was detected using an automatic biochemical analyzer with running procedure set.

Neurological Scores of Rats in Each Group

Before the rats were sacrificed in each group, the neurological function was scored according to the six-point score method, with the specific scoring rubric shown in Table I. The rats with the highest and lowest scores were discarded. During experiments, the rats with other clinical symptoms were also discarded, and the rats were supplemented in a random manner.

Determination of Inflammatory Factor Content Via Enzyme-Linked Immunosorbent Assay (ELISA)

The serum inflammatory factors are important indicators in brain injury and capable of indicating the degree of injury repair. The serum samples previously collected and cryopreserved at -80°C were taken out, slowly thawed at 4°C and centrifuged at low speed, and the supernatant was collected. ELISA (Novus, Littleton, CO, USA) kits and all reagents were buffered at room temperature for 30 min, and the standard solution was prepared, followed by incubation, the addition of biotin-labeled antibody, incubation, and washing. Subsequently, the changes in all indexes were detected according to the instructions based on the actual conditions. Lastly, a microplate reader was used to read the absorbance of the inflammatory factors in each group.

Observation of Brain Tissue Changes in the Two Groups Through HE Staining Assay

The isolated brain tissues fixed in the tissue fixation solution were taken out, washed with running water for 36 h, fixed, dehydrated using an automatic dehydrator, and embedded with paraffin using a section automatic embedding machine. Next, the sections were deparaffinized, hydrated with 95%, 90%, 80%, 75%, and 50% ethanol, respectively, permeabilized, dipped, and embedded in paraffin. The embedded blocks were made into pathological sections (about 5 μm in thickness). Lastly, dried thin sections were stained with hematoxylin for 20 min, separated with hydrochloric acid and ethanol solution for 30 s, stained with eosin for 12 min, separated with 90% ethanol for 45 s, mounted, and observed under a light microscope.

Detection of Myeloperoxidase (MPO) Activity in Brain Tissues

The activity of MPO was determined to observe the infiltration of neutrophils in brain tissues. The brain tissues stored at -80°C were carefully taken out and put onto the ice. Then, the tissues were added with the lysis solution and subjected to low-temperature homogenization, followed by centrifugation. Next, the supernatant was collected, and the MPO activity in the brain

Table I. Specific scoring rubric.

Score	Behavior
0	Autonomous walking
1	Rotation to the contralateral side of the lesion
2	Rotation to the contralateral side of the lesion when the rat tail was grabbed
3	Contralateral stress resistance decrease
4	Flexion of the whole body to the contralateral side
5	No neurological deficit

Table II. Primer sequences of all indexes in RT-PCR.

Target gene	Primer sequence (5'-3')
GAPDH	F: 5′-TGACTTCAACAGCGACACCCA-3′ R: 5′-CACCCTGTTGCTGTAGCCAAA-3′
S100	F: 5′-GGTGGTCATATGACAAAACTTGAAGAG-3′ R: 5′-GGTGGTACTAGTGCATCTCCCGTGATTT-3’
GFAP	F: 5'-AGAATTCGACGAGGACGACAAGGAGAGGA-3' R: 5'-ACTCGAGTCACATCACATCCTTGTGCTC-3'
TLR2	F: 5′-CTGAACCAGGGCATACCTGT-3′ R: 5′-GAGAAGTCCATGTCCGCAAT-3′
NF-κB	F: 5′-CTGAACCAGGGCATACCTGT-3′ R: 5′-GAGAAGTCCATGTCCGCAAT-3′

homogenate was determined by spectrophotometry. The results were expressed as mg.

Detection of Related Gene Expression Via Quantitative Real Time Polymerase Chain Reaction (qRT-PCR)

Firstly, the brain tissue homogenate was taken from each group of rats, and the total ribonucleic acids (RNAs) were extracted using a TRIzol (Invitrogen, Carlsbad, CA, USA) kit. The ultraviolet spectrophotometry and agarose gel electrophoresis were used to detect the concentration, purity, and integrity of RNAs. After meeting the criteria for the assay, messenger RNAs (mRNAs) were reversely transcribed into complementary deoxyribonucleic acids (cDNAs) and stored in a refrigerator at -80°C. Secondly, 20 μL amplification system (2 μL cDNA, 10 μL qPCR mix, 2 μL primer and 6 μL ddH_2O) was prepared for primer amplification with 40 cycles. The primer sequences of the target genes and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) internal reference were designed according to the sequences on GenBank. The expression levels of the target genes were detected through qRT-PCR. The specific primer sequences are shown in Table II. The relative expression levels of the related genes in brain tissues in each group of rats were calculated by the $2^{-\Delta\Delta Ct}$ method. Ct of each model had a linear relation with the logarithm of the initial copy number of the model, i.e., the more the copy number, the smaller the Ct.

Western Blotting

The left hemisphere brain tissues were sampled and quick-frozen at -80°C. Then, the frozen samples were weighed and broken on ice. Next, the samples were added with protease inhibitor and modified the radioimmunoprecipitation assay (RIPA) buffer (Beyotime, Shanghai, China) and incubated in the refrigerator until the tissues were fully lysed to release the tissue proteins. Thereafter, the mixture was centrifuged, and the supernatant was collected. The determination of the protein concentration was conducted according to the instructions of the bicinchoninic acid (BCA) kit (Pierce, Rockford, IL, USA), followed by the calculation of the concentration of each protein. The proteins were loaded, separated in 12% gel and transferred onto a polyvinylidene difluoride (PVDF) membrane (Roche, Basel, Switzerland). After that, the membrane was blocked with 5% skim milk at room temperature for 1.5 h and incubated with primary antibody and secondary antibody (1:1000) for Western blotting. A gel imaging system was utilized for development and imaging. GAPDH was used to correct the levels of the proteins to be tested. Lastly, the gray value of the protein bands was analyzed. The experiment was repeated three times.

Statistical Analysis

All original experimental data recorded were processed by Statistical Product and Service Solutions (SPSS) 20.0 (IBM Corp., Armonk, IL, USA) software and subjected to multiple comparisons. The obtained experimental results were expressed by the mean ± standard deviation ($\bar{\chi}$ ± SD). $p<0.05$ suggested that the difference was statistically significant. Each assay was repeated at least three times. GraphPad Prism 7.0 (La Jolla, CA, USA) was used for the histogram.

Results

Results of Serum Brain Injury Indexes Detected

Indicators [glucosuria (GLU), creatinine (CR), K^+ and Na^+] were detected in this study to predict

Table III. Change in GLU, CR, K+, and Na+ content.

Group	K+ (mmol/L)	GLU (U/L)	Na+ (mmol/L)	CR (μmol/L)
Control group	28.28±5.32	8.62±2.28	100.89±2.37	25.45±3.45
CLP group	10.14±1.75[a]	18.53±1.54[a]	215.66±6.23[a]	89.36±5.14[a]
Treatment group	22.67±2.6[b]	11.34±3.87[b]	126.48±5.89[b]	38.78±4.29[b]

Note: CLP group shows clearly elevated GLU, CR, and Na+ content but overtly decreased K+ content ($p<0.05$). [a]$p<0.05$ *vs.* control group, [b]$p<0.05$ *vs.* CLP group.

Table IV. Serum TNF-α, IL-1, and IL-6 levels.

Group	TNF-α (fmol/mL)	IL-6 (mg/L)	IL-1 (mg/L)
Control group	14.38±3.24	25.37±6.15	30.12±5.23
CLP group	43.11±2.43[a]	84.26±4.62[a]	89.45±6.21[a]
Treatment group	20.56±3.56[b]	32.15±3.47[b]	35.24±5.26[b]

Note: The levels of IL-1, IL-6, and TNF-α are increased in CLP group ($p<0.05$) but decline in treatment group ($p<0.05$). [a]$p<0.05$ *vs.* control group, [b]$p<0.05$ *vs.* CLP group.

brain injury in advance in clinical practice. The results (Table III) showed that CLP group exhibited overtly increased GLU, CR, and Na^+ content but evidently lowered K^+ content, while the treatment group had an opposite change in the content ($p<0.05$), suggesting that the disease is relieved.

Neurological Score in Each Group of Rats

In the CLP group, some rats could not walk, with flexion of the whole body to the contralateral side ($p<0.01$). The rats in the control group had no abnormality. The rats in the treatment group had a similar situation to those in the control group. The specific scores are shown in Figure 1.

Serum TNF-α, Interleukin-1 (IL-1), and IL-6 Levels

The levels of IL-1, IL-6, and TNF-α were increased in the CLP group ($p<0.05$) but declined in the treatment group ($p<0.05$) (Table IV).

MPO Activity in Brain Tissues Measured

Compared with that in the control group, the MPO activity was elevated in both the CLP group and treatment group ($p<0.05$), but the content in the treatment group was close to that in the control group ($p>0.05$), and CLP group exhibited evidently raised content in comparison with the control group ($p<0.05$) (Figure 2).

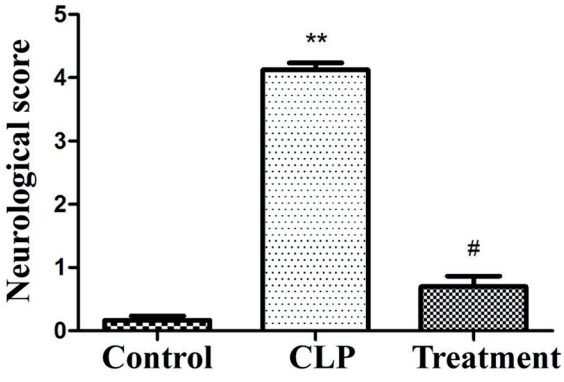

Figure 1. Neurological score. Some rats in CLP group cannot walk, with flexion of the whole body to the contralateral side, the rats in control group are normal ($p<0.05$), and the rats in the treatment group are similar to those in the control group. **$p<0.01$ *vs.* control group, #$p<0.05$ *vs.* CLP group.

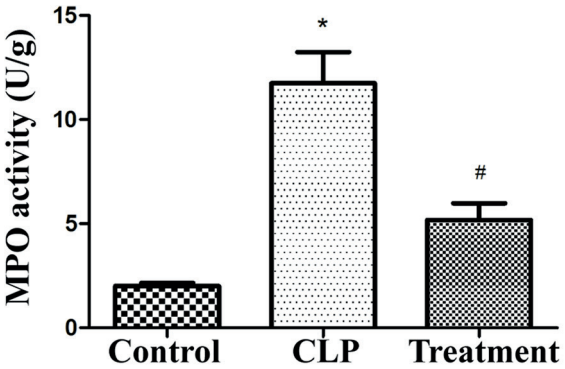

Figure 2. Change in MPO activity in tissues. Compared with that in control group, the MPO activity is elevated in both CLP group and treatment group ($p<0.05$), but the content in the treatment group is close to that in the control group ($p>0.05$). *$p<0.05$, #$p<0.05$.

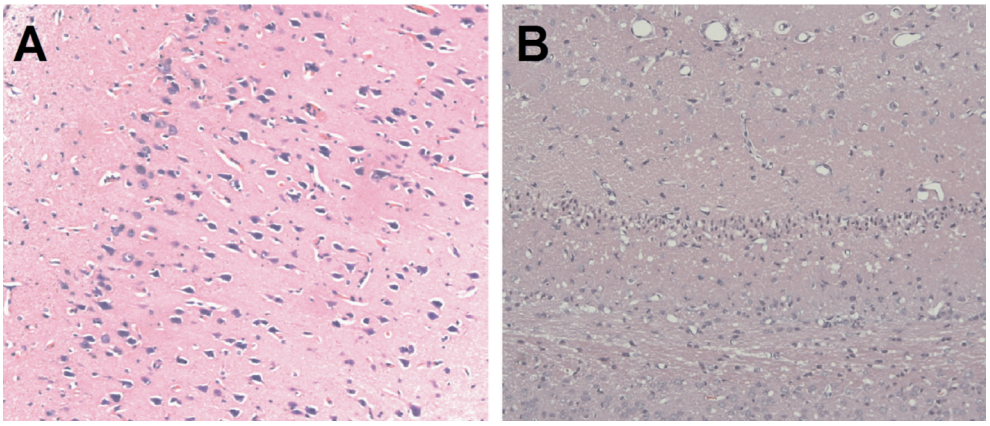

Figure 3. Morphological observations of brain tissues. Treatment group has complete basic structure, clear boundary, normal neuron morphology, clear cytoplasm, and uniform and clear cortical nucleus in brain tissues (***A,*** 10×), while CLP group exhibits abnormal and disordered neuron structure and destroyed basic structure (***B,*** 10×).

Changes in Brain Tissues in CLP and Treatment Groups Observed Via HE Staining

HE staining results (Figure 3) revealed that the treatment group had complete basic structure, clear boundary, normal neuron morphology, clear cytoplasm, and uniform and clear cortical nucleus in brain tissues (Figure 3A), while CLP group exhibited abnormal and disordered neuron structure and destroyed basic structure, with vacuoles (Figure 3B).

QRT-PCR Results of Related Genes in Brain Tissues

The mRNA levels of glial fibrillary acidic protein (GFAP), S100, Toll-like receptor 2 (TLR2), and NF-κB were significantly higher in CLP group than those in the control group ($p<0.05$), while they were notably lower in the treatment group than those in the CLP group but higher than those in control group ($p>0.05$) (Figure 4).

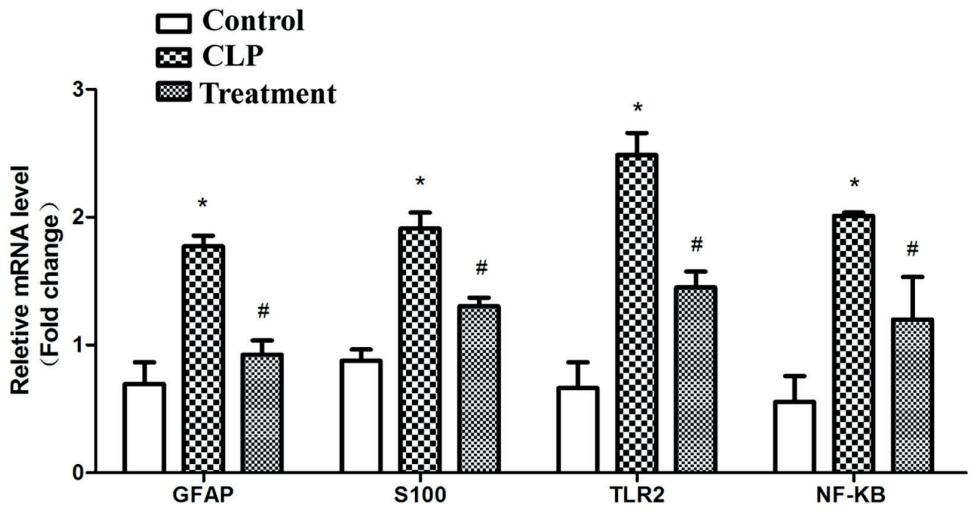

Figure 4. QRT-PCR results of related genes in brain tissues. CLP group displays clearly elevated mRNA levels of GFAP, S100, TLR2, and NF-κB in comparison with the control group ($p<0.05$), while these mRNA levels in the treatment group are notably lower than those in the CLP group but higher than those in the control group ($p>0.05$). *$p<0.05$, $^{\#}p<0.05$.

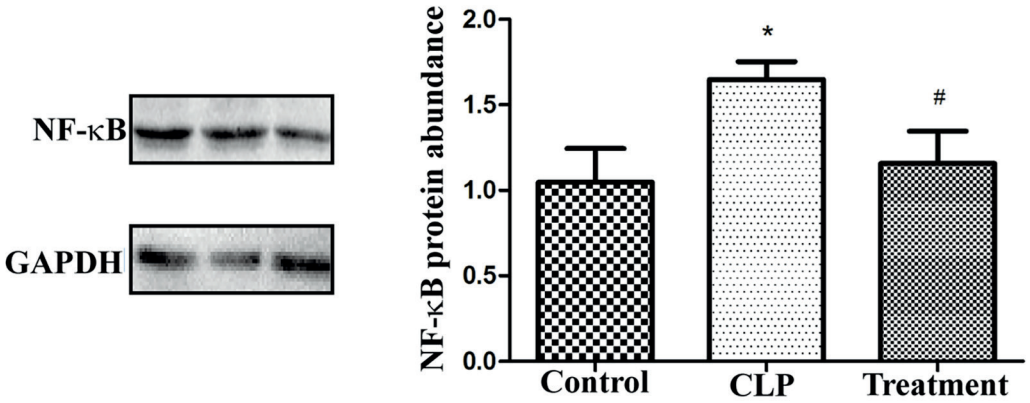

Figure 5. Detection results of signaling pathway protein. CLP group exhibits an evident increase in the NF-κB protein content in comparison with control group ($p<0.05$), while the treatment group shows an opposite trend. $^{*}p<0.05$, $^{\#}p<0.05$.

Detection Results of Inflammatory Pathway Protein in Brain Tissues

The results (Figure 5) showed that, compared with that in control group, the NF-κB protein content in CLP group was significantly increased ($p<0.05$), while the content in the treatment group was significantly decreased, but higher than that in the control group ($p>0.05$).

Discussion

With the deepening of research on sepsis, the progression of sepsis gradually becomes clear. The clinicopathological processes of sepsis mainly include cytokine storm, inflammatory mediator decrease, intestinal bacterial translocation, endotoxemia, and interaction between the coagulation system and inflammation[19,20]. Sepsis is often accompanied by damage to tissues and organs, which is one of the reasons for the high mortality rate. Sepsis leads to brain injury, thus resulting in chronic neurological dysfunction (including cerebral and cognitive palsy and other deficits)[10] that can cause fatal consequences. However, as to the treatment of brain injury-related neurological diseases, there is still a lack of successful interventions. Therefore, new treatment methods are urgently needed to provide a basis for the prevention and treatment of sepsis and its complications. In this study, the rat models of sepsis were established to study the therapeutic effect of butorphanol and the specific mechanism of action. Besides, to predict the development of brain injury in advance in clinic, the indicators GLU, CR, K^+, and Na^+ were detected in this study, and the results showed that the CLP group had overtly increased GLU, CR, and Na^+ content and evidently lowered K^+ content, while the treatment group exhibited opposite tendencies, indicating that the disease is attenuated. Since chronic neurological dysfunction, including cerebral palsy and cognitive and other defects, may occur in case of brain injury, we scored the neurological function in rats. The results revealed that some rats in CLP group were unable to walk, with flexion of the whole body to the contralateral side, the rats in the normal group showed no abnormality ($p<0.05$), and the rats in the treatment group had a similar status to those in the control group. A study has shown that curcumin reduces neurological deficit score, cerebral infarct size, and neuronal damage in rats with permanent focal brain damage, decreases brain water content in rats with permanent focal cerebral ischemia, and lowers the activity of MPO, suggesting that curcumin inhibits the inflammatory response caused by ischemia[21]. In addition, the results showed that the MPO activity was increased in both CLP group and treatment group compared with that in the control group ($p<0.05$), while the treatment group displayed the content close to that in the control group. Moreover, HE staining results revealed that in the treatment group, the basic structure of brain tissues was intact, the boundary was clear, the neuron morphology was normal, the cytoplasm was clear, and the cortical nucleus was uniform and clear, while in the CLP group, the neuron structure was abnormal and disordered, and the basic structure was destroyed, which are consistent with the findings of Sinnecker et al[22]. The above results imply that sepsis can lead to brain tissue injury, and butor-

phanol can resist the progression of such an injury. However, further research was needed for its specific mechanism. Therefore, the gene and protein experiments were carried out in this study for verification.

Sepsis, whose clinical pathological changes mainly include increased inflammatory cytokines, intestinal endotoxemia, and interaction with inflammation, releases inflammatory factors such as TNF-α, IL-1, and IL-6 to activate the downstream critical anti-inflammatory transcription factors like NF-κB[23,24]. It was found in this study that the levels detected *via* ELISA such as IL-6 and TNF-α were increased in the CLP group, further aggravating the inflammatory response. TNF-α is indispensable in the development of inflammation in rats with sepsis, and IL-6 also triggers the excessive production of other inflammatory mediators[25]. The results are in line with the findings of predecessors. Damage to tissues and organs is always detected in the case of sepsis, which is one of the reasons for the high mortality rate of sepsis. NF-κB, a transcription factor, promotes the increase of TNF-α and the expression of inflammatory cytokines. It was discovered in this study that the inflammatory factor levels were lowered after treatment with butorphanol (p<0.05). The expression level of S100 is increased in inflammatory diseases, moreover, some pro-inflammatory cytokines and anti-inflammatory cytokines show increased expression levels in sepsis. These cytokines display diagnostic value and correlations with death in sepsis, suggesting that S100 is of great significance for the development of sepsis[26]. Glial cells such as astrocytes and microglia are mediators of neuronal inflammation, which produce pro-inflammatory cytokines that are toxic to the central nervous system after activation by exogenous or endogenous ligands[27]. GFAP is a specific astrocyte marker, whose specific increase quickly activates microglia and astrocytes[28]. The results of this study showed that the mRNA levels of GFAP and S100 were evidently increased in the CLP group (p<0.05) but clearly lowered in the treatment group, which is consistent with the above findings.

The TLR2-NF-κB signaling pathway triggers the expression of pro-inflammatory mediators and induces inflammatory responses[29], leading to expanded cerebral infarction and aggravated brain injury[30]. Studies have shown that in rats with permanent focal cerebral ischemia, TLR2 gene and protein expressions are up-regulated, and the level of NF-κB p65 is elevated, indicating that the TLR2-NF-κB signaling pathway regulates the inflammatory responses and aggravates brain injury[31]. In addition, the TLR2-NF-κB signaling pathway may be the therapeutic target of the inflammatory cascade in the treatment of ischemic stroke. This study showed that the mRNA content of TLR2 and NF-κB was significantly elevated in CLP group (p<0.05), but notably decreased in the treatment group, suggesting that butorphanol mediates inflammatory responses by inhibiting the TLR2-NF-κB signaling pathway. Moreover, the expression levels of the inflammatory cytokines are lower in the ischemia-induced experimental stroke mice lacking TLR2/4[32], indicating that TLR2/4 may be an upstream target of inflammatory cytokines. The protein detection results showed that the NF-κB protein content was significantly increased in the CLP group (p<0.05), but overtly declined in the treatment group, which is in line with the above findings. The above results imply that butorphanol suppresses the excessive production of inflammatory factors such as IL-6 to prevent further influence on brain injury. This may be related to the inhibitory effect of butorphanol on the NF-κB pathway. Butorphanol may protect against CLP-induced brain injury.

Conclusions

This study shows that butorphanol represses the destructive effect of NF-κB pathway on brain tissues in rats with sepsis, thereby inhibiting the expression activity of the inflammatory factors like TNF-α and IL-6 and the further progression of inflammation in septic rats, and ultimately affecting the progression of sepsis-induced brain injury. This study provides a new theoretical and experimental basis for the prevention and treatment of sepsis and its complications.

Conflict of interest

The authors declare no conflicts of interest.

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