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Original Article

Protective Mechanism of NLRP3 Inflammatory Bodies Mediated by Dexmedetomidine on Renal Injury in Rats with Hemorrhagic Shock

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ABSTRACT

Objectives: to investigate the protective mechanism of NLRP3 inflammatory bodies mediated by Dexmedetomidine (DEX) on renal injury in rats with hemorrhagic shock. **Materials and Methods:** 18 healthy SD rats were divided into control (group A), model (group B) and right metomidine (group C) group. Group B and C were used to establish the model of hemorrhagic shock by improved Wiggers method. After successful modeling, the group B was injected intravenously with normal saline 5 μg kg^{-1} h^{-1}. The patients in group C were given DEX 5 μg kg^{-1}·h^{-1} intravenously. The mean arterial pressure of 60 min was recorded before shock, after shock and after resuscitation. Serum Creatinine (SCR) and BUN were measured by biochemical analyzer. The NLRP3, Caspase-1, IL-18 and IL-1 β in serum of rats were detected by ELISA method. The protein of NLRP3, Caspase-1 and Kim-1 were detected by Western blot. **Results:** The MAP after shock and resuscitation (30, 60 min) in the group B and C were reduced than group A. The indexes of SCR and BUN in the group B was increased than group A. The contents of serum NLRP3, Caspase-1, IL-18, IL-1 β and Kim-1 in the group B was increased than group A, while these in the group B was decreased than group A. The protein levels of NLRP3, Caspase-1 and Kim-1 in the group C was decreased than group B. **Conclusion:** DEX can reduce the renal injury induced by hemorrhagic shock in rats and has a protective effect on the kidney. The mechanism may be achieved by inhibiting the inflammatory bodies of NLRP3 and then reducing the expression of inflammatory factors and Kim-1.

Keywords: Dexmedetomidine, Nlrp3 Inflammatory Bodies, Hemorrhagic Shock, Renal Injury, Protective Mechanism.

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INTRODUCTION

Hemorrhagic shock is a common clinical emergency, which leads to insufficient tissue perfusion due to the sharp decrease of effective blood volume, which leads to multiple organ dysfunction.[1] Among them, the kidney is one of the most vulnerable organs during hemorrhagic shock and resuscitation and seriously affects the prognosis of patients.[2] Therefore, it is of great significance to study the mechanism of renal injury caused by hemorrhagic shock and to find effective therapeutic drugs. NLRP3 inflammatory bodies act as inflammatory response regulators in the kidney, promoting the secretion of inflammatory cytokines such as Interleukin (IL-1β) and interferon gamma Inducible protein-18 (IL-18) by activating caspase-1,[3] which triggers inflammation. Inhibition of NLRP3 inflammasome may play a nephroprotective role in a model of renal injury.[4] Dexmedetomidine (DEX) is a α2-adrenergic receptor agonist, which has been widely used in clinical anesthesia and analgesia. Dexmedetomidine has anti-inflammatory and anti-shock effects and has protective effects on endotoxemia and renal injury induced by ischemia reperfusion.[5] Whether it mediates the protective effect of NLRP3 inflammatory bodies on renal injury in hemorrhagic shock rats is still unknown. Therefore, this study aimed to explore the protective mechanism of NLRP3 inflammatory bodies mediated by DEX on renal injury in rats with hemorrhagic shock.

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MATERIALS AND METHODS

Experimental animal

18 SPF male rats, aged 13-15 weeks and weighing 220 g~250 g, were selected from Shanghai Shrek Experimental Animal Co., Ltd., license No. Wydw (Shanghai) 2014-0058. The room temperature is controlled at 22±2°C and the humidity is controlled at 40% 50%. Adapt to the environment and keep for a week.

Experimental grouping

According to 0 the modified Wiggers method,[6] the rat model of hemorrhagic shock was established. Rats were anesthetized by intraperitoneal injection of pentobarbital sodium at the dose of 45 mg/kg^{-1} and the rats were treated with heparinization (heparin saline, dose: 0.5 U/g). According to the standard of Mean Arterial Pressure (MAP) 30-40 mmHg after blood loss, 60 min was maintained to make the animals reach irreversible shock. After maintaining the shock state for 60 min, the right metomidine group was given right metomidine through the femoral vein (rate: 5 μg kg^{-1} h^{-1}), while the control group and model group were given the same amount of normal saline.

Drugs, reagents and instruments

DEX (manufacturer: Sichuan Guorui Pharmaceutical Co., Ltd., dose: 2 mL: 200 μg 10), Heparin Sodium (manufacturer: Dongying Tiandong Pharmaceutical Co., Ltd., approval No.: 20058187), ELISA (manufacturer: ThermoFisherScientific), Westenblot instrument (manufacturer: Bio-Rad), biochemical Analyzer (manufacturer: BeckmanCoulter), biochemical Analyzer (HITACHI7180).

Experimental method

Observation of mean arterial pressure in rats with hemorrhagic shock

Mean arterial pressure was measured by BC7500CRP hematology analyzer before shock, after shock and 30 days after resuscitation at 60 min.

Detection by biochemical analyzer

In the experiment, after 2 hr of administration of DEX, the blood was collected through the femoral vein and placed at 4°C for 2 hr. After that, the serum was isolated by centrifugation at the rate of 5 min 2000 r·min^{-1}. At the same time, the rats were killed and the kidneys were removed by bloodletting of the femoral artery. The kidney sample was treated with a tissue homogenizer in ice water into 10% saline homogenate. Then, using TGL-16 high-speed table centrifugation and 15 min 3000 r·min^{-1}, the supernatant was separated for subsequent use. Using SCR and BUN protein kits to determine.

ELISA

At the end of the experiment, the rats in each group were killed and the blood was collected. The blood was placed at room temperature for static coagulation and then at 4°C, the serum was collected after centrifugation after 3000 r stop mineling for 10 min. The enzyme labeling instrument was preheated to 37°C. The standard substances (NLRP3, Caspase-1, IL-18, IL-1 β, Kim-1) were diluted according to the dilution ratio provided in the experimental manual. The serum sample to be tested was added to the sample diluent 40 μL and then added to the enzyme plate. Put the enzyme plate into the enzyme meter and incubate according to the recommended time in the experimental manual. Wash the enzyme plate with detergent and then pat dry. The substrate solution was added and incubated in an enzyme-labeled instrument. The chromogenic agent was added and then incubated in the enzyme labeling instrument. The terminating solution was added and then the absorbance of each hole was determined by enzyme labeling instrument. According to the experimental results, the expression levels of NLRP3, Caspase-1, IL-18, IL-1 β and Kim-1 in serum of rats in each group were calculated.

Western Blot

50 mg was extracted from renal tissue and Ripa 200 μL lysate was added to the lysate to fully lyse the cells. The protein was quantified according to the working solution prepared according to BCA kit. The supernatant was separated by SDS- polyacrylamide gel electrophoresis and transferred to PVDF membrane. 10 m 15% skimmed milk powder was sealed at room temperature for 2 hr or incubated overnight at 4°C. After the PVDF membrane was incubated in an anti-RhoA treatment at 4°C, TBST washed off the first antibody that binds to the membrane and the corresponding second antibody was added to incubate for 1 hr at room temperature for 2 hr. Coloration by ECL chemiluminescence.

Table 1: Changes of MAP in rats of each group mmHg, *x*±s, *n*=6).

Group	Before shock	After shock	Resuscitation	
			30 min	60 min
A	108.25±5.62	110.26±6.62	111.38±5.21	113.16±5.62
B	106.33±6.02	33.25±3.42[a]	31.27±3.25[a]	30.21±4.21[a]
C	106.25±7.36	34.50±1.36[ab]	38.36±2.52[ab]	36.20±2.44[ab]
F	0.19	610.33	803.49	697.01
P	0.829	<0.001	<0.001	<0.001

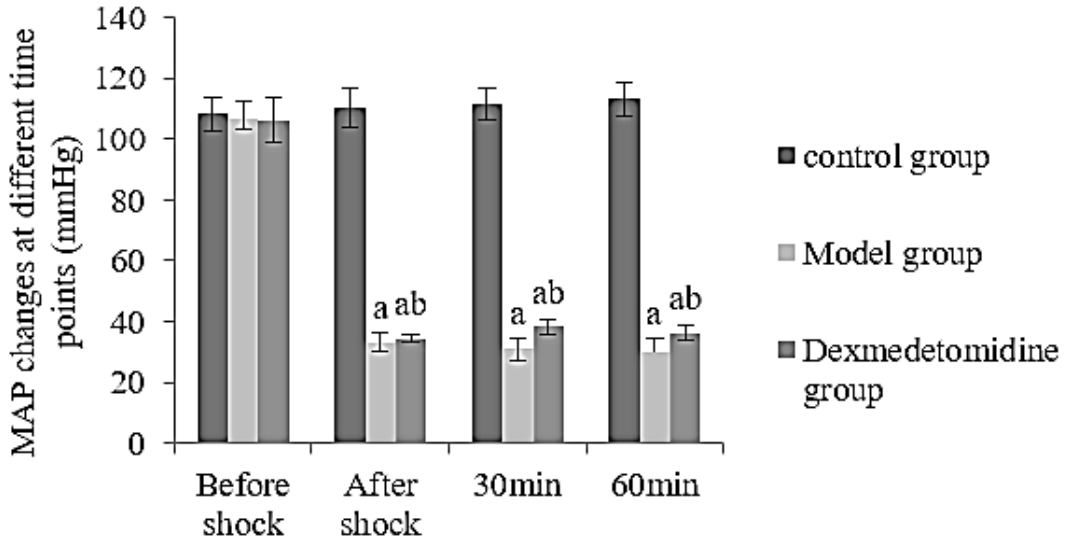

Figure 1: MAP changes at different time points in rats.

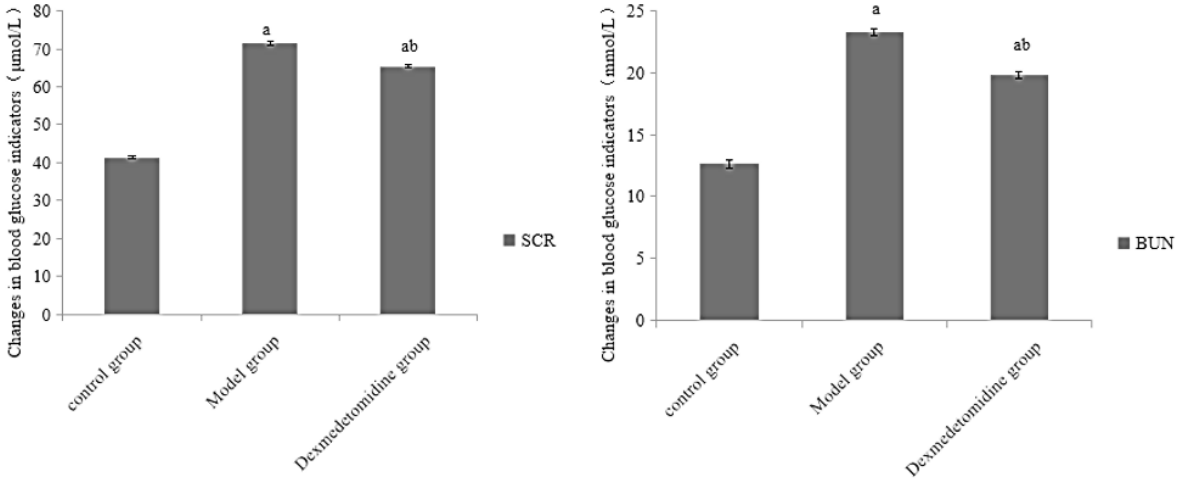

Figure 2: Changes in SCR and BUN indicators.

Statistical method

SPSS22.0 software (IBM, USA) was used for processing. The measurement data are represented by Mean±Standard Deviation (x±s). One-way Analysis of Variance (one-way ANOVA) is used for comparison between groups and SNK-q method is used for pairwise comparison. The difference is statistically significant. Compared with the group A, $^{a}p<0.05$; compared with the group B, $^{b}p<0.05$.

RESULTS

Changes of MAP in rats

The MAP of shock and resuscitation (30, 60 min) in the group B and C were reduced than group A (Table 1, Figure 1).

Changes of SCR and BUN indexes

The indexes of SCR and BUN in the group B was increased than group A, while the indexes of SCR and BUN in the group C was decreased (Table 2 and Figure 2).

The levels of NLRP3, Caspase-1, IL-18, IL-1 β and Kim-1 in the rats

Compared with the control group, the levels of NLRP3, Caspase-1, IL-18, IL-1 β and Kim-1 in the group B was increased than group A, while these in the group C was decreased than group B (Table 3, Figure 3).

Protein levels of NLRP3, Caspase-1 and Kim-1 in kidney tissue of rats

The protein levels of NLRP3, Caspase-1 and Kim-1 in the group B was increased than group A, while these in the group C was decreased (Table 4 and Figure 4).

DISCUSSION

Hemorrhagic shock causes complex physiological and pathological processes and the degree of shock varies with the amount of blood loss.[7] During hemorrhagic shock, insufficient systemic blood flow will lead to cell hypoxia and organ dysfunction, affect energy metabolism, cause calcium overload caused by a large number of oxygen free radicals and cause membrane phospholipid decomposition and lipid peroxidation.[8] DEX is a α 2 receptor agonist, which has the functions of sedation, analgesia, hemodynamic stability and anti-stress response.[9] Some studies have found that,[10] DEX can inhibit the production of inflammatory factors, reduce the inflammatory response and block the activation of apoptosis signal pathway, thus protecting the kidney, lung, brain and other important organs. DEX can reduce the levels of TNF-α, IL-1 β and IL-6 in serum

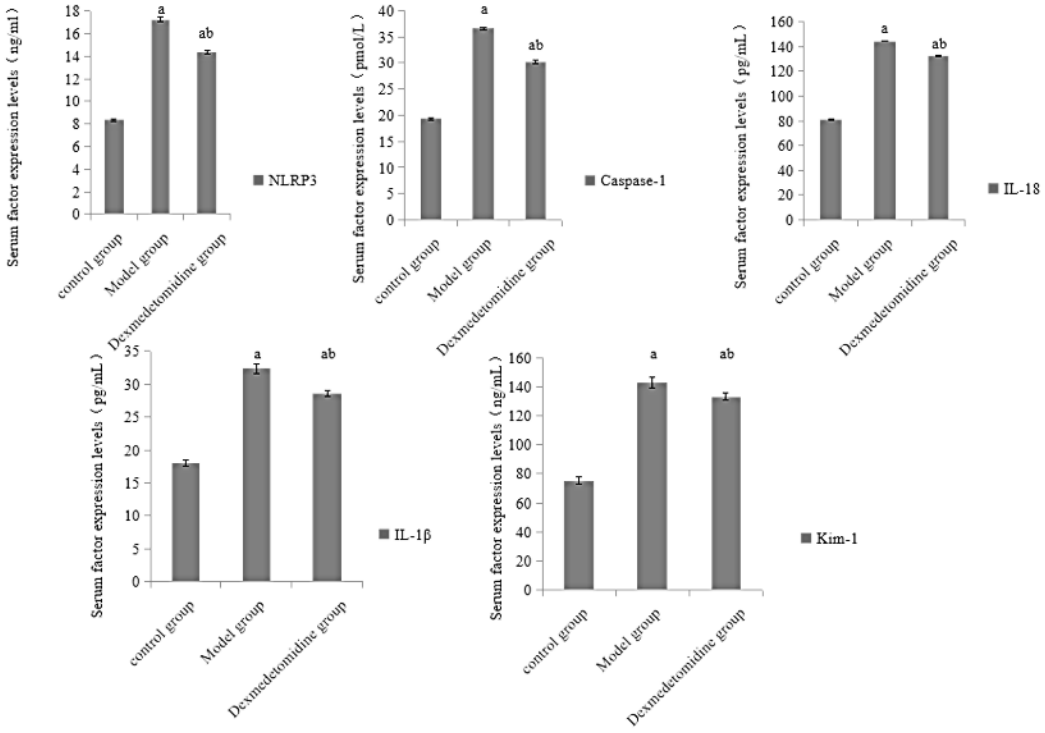

Figure 3: NLRP3, Caspase-1, IL-18, IL-1 β and Kim-1 expression in the rats.

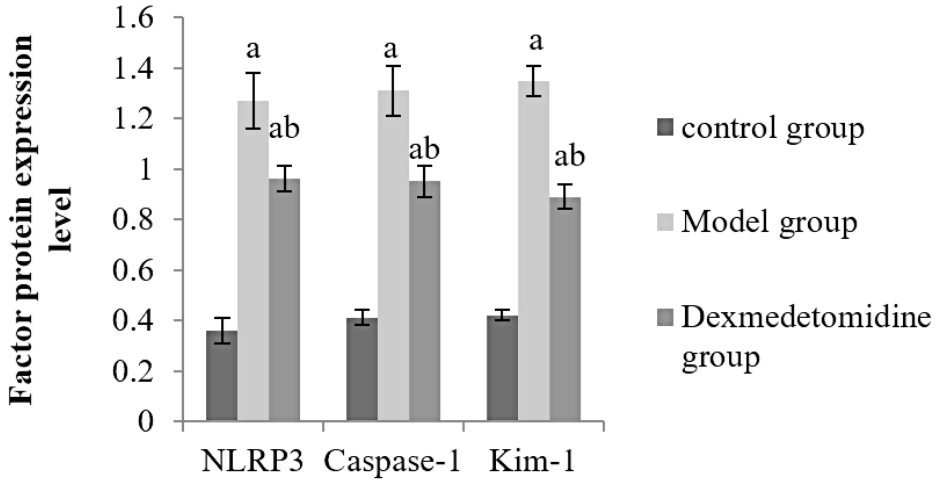

Figure 4: Expression levels of NLRP3, Caspase-1 and Kim-1 proteins in each group of rats.

Table 2: Changes of SCR and BUN indexes (*x*±s, *n*=6).

Group	SCR(μmol/L)	BUN(mmol/L)
A	41.28±0.36	12.66±0.33
B	71.36±0.52[a]	23.25±0.26[a]
C	65.36±0.41[ab]	19.86±0.29[ab]
F	8030.20	2020.11
P	<0.001	<0.001

Table 3: The levels of NLRP3, Caspase-1, IL-18, IL-1 β and Kim-1 in the rats (*x*±s, *n*=6).

Group	NLRP3 (ng/mL)	Caspase-1 (pmol/L)	IL-18 (pg/mL)	IL-1β (pg/mL)	Kim-1 (ng/mL)
A	8.36±0.11	19.38±0.24	81.52±1.27	17.96±0.45	75.39±2.33
B	17.27±0.22[a]	36.56±0.31[a]	144.56±1.33[a]	32.38±0.75[a]	142.86±3.54[a]
C	14.35±0.21[ab]	30.21±0.27[ab]	132.82±1.31[ab]	28.57±0.41[ab]	133.39±2.56[ab]
F	3550.51	5994.23	3968.43	1077.013	979.75
P	<0.001	<0.001	<0.001	<0.001	<0.001

Table 4: Protein levels of NLRP3, Caspase-1 and Kim-1 in kidney tissue of rats (*x*±s, *n*=6).

Group	NLRP3	Caspase-1	Kim-1
A	0.36±0.05	0.41±0.03	0.42±0.02
B	1.27±0.11[a]	1.31±0.10[a]	1.35±0.06[a]
C	0.96±0.05[ab]	0.95±0.06[ab]	0.89±0.05[ab]
F	225.30	254.73	598.80
P	<0.001	<0.001	<0.001

and pancreatic tissue of septic mice, thus reducing pancreatic inflammation. DEX attenuates renal injury induced by sepsis by inhibiting TLR4/MyD88/NF- κ B/iNOS signal pathway.[11] However, the effect and mechanism of it on renal injury in rats with hemorrhagic shock are not clear.

NLRP3 is a protein found to be involved in immune response and pro-inflammatory response, which is associated with the occurrence and development of a variety of diseases; including kidney disease.[12] Many factors such as ischemia-reperfusion injury and oxidative stress can trigger the activation of NLRP3 inflammatory bodies. After activation, NLRP3 inflammatory body promotes the self-cleavage of Caspase-1 precursor molecules, produces active Caspase-1 and promotes the activation of IL-1β and IL-18, resulting in multiple organ damage after shock. Research found[13] than in the mouse model of renal ischemia-reperfusion injury, the expression of NLRP3 and Apoptosis-associated Spot-like protein (ASC) increased. Animals with NLRP3, ASC and Caspase-1 defects were not affected by kidney inflammation. Knockout of NLRP3 gene decreased the expression of Caspase-1, ASC, IL-1 β and IL-18 and reversed renal injury.[14] Caspase-1 is a cysteine protease of the caspase family. In the kidney, the activity of Caspase-1 is related to a variety of disease states, including renal inflammation, ischemia-reperfusion injury and so on. Song Chundong *et al.*,[15] found that Caspase-1 inhibits cell death in renal tissue expression and reduces renal injury. IL-18 is a pro-inflammatory cytokine involved in the regulation of inflammatory and immune responses. In renal disease, overexpression of IL-18 can cause inflammation, fibrosis and cell damage and aggravate renal injury. Some studies have shown that[16,17] Overexpression of IL-1 beta in the kidney as a proinflammatory cytokine also causes inflammation, cell damage and fibrosis, exacerbating kidney disease. Kim-1 is usually increased when renal tubular epithelial cells are damaged. Kim-1 is considered to be a marker for early diagnosis of kidney disease and chronic kidney disease. The contents of NLRP3, Caspase-1, IL-18, IL-1 β and Kim-1 in the serum of the group C was decreased than group B and these proteins in the kidney tissue of the group C also was decreased than group B. It is suggested that DEX can reduce the contents of NLRP3, Caspase-1, IL-18, IL-1 β and Kim-1 in serum and the expression of NLRP3, Caspase-1 and Kim-1 in kidney, reduce the release of inflammatory factors, reduce inflammatory reaction and protect kidney.

CONCLUSION

To sum up, Dexmedetomidine can reduce the renal injury induced by hemorrhagic shock in rats and has a protective effect on the kidney. Its mechanism may be achieved by inhibiting the

inflammatory bodies of NLRP3 and then reducing the expression of inflammatory factors and Kim-1. However, this study was only carried out in model animals and the specific mechanism of dexmedetomidine inhibiting NLRP3 inflammatory bodies needs to be further studied.

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ABBREVIATIONS

DEX: Dexmedetomidine; **SCR:** Serum creatinine; **IL-18:** Inducible protein-18; **NLRP3:** Nod like receptor family pyrin domain containing 3.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This paper has received research ethics approval from Jiangsu Provincial People's Hospital.

SUMMARY

The study investigates the protective effects of Dexmedetomidine (DEX) on renal injury in rats subjected to hemorrhagic shock. The research focuses on the NLRP3 inflammasome, a critical regulator of the inflammatory response. The study found that DEX significantly reduced renal injury by inhibiting the activation of NLRP3, Caspase-1, IL-18, IL-1β and Kim-1, which are associated with inflammation and kidney damage. These findings suggest that DEX protects against renal injury in hemorrhagic shock by suppressing the NLRP3 inflammasome and reducing the expression of inflammatory factors. This study highlights the potential therapeutic role of DEX in managing renal injuries associated with hemorrhagic shock.

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