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Propofol alleviates intestinal ischemia/reperfusion injury in rats through p38 MAPK/NF-κB signaling pathway

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Abstract. – OBJECTIVE: The aim of this study was to investigate the influences of propofol on intestinal ischemia/reperfusion (I/R) injury in rats through the p38 mitogen-activated protein kinase (MAPK)/nuclear factor-kappa B (NF-κB) signaling pathway.

MATERIALS AND METHODS: The models of intestinal I/R injury were first successfully established. All rats were randomly divided into 4 groups, namely, S group, I/R group, P group and P + S group. Pathological-morphological changes, injury score and wet-to-dry weight ratio of intestinal tissues as well as oxidative stress indexes in each group of rats were detected. Enzyme-linked immunosorbent assay (ELISA) was applied to measure the levels of inflammatory factors such as creatine kinase-MB (CK-MB), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) in each group of rats. Furthermore, Western blotting (WB) assay was applied to determine the protein expression levels of p38 MAPK and NF-κB in different groups.

RESULTS: Intestinal tissue injury was the severest in I/R group, with the infiltration of massive inflammatory cells and oozing of blood (Figure 1A, I/R). Compared with those in I/R group, the infiltration of inflammatory cells and damage to intestinal villi were notably relieved in P group and P + S group, revealing that the intestinal mucosal injury was remarkably repaired in P group and P + S group (Figure 1A, P). Moreover, the intestinal tissue injury score was evidently higher in I/R group, P group and P + S group than that in S group ($p<0.05$). However, it was markedly lower in P group and P + S group than that in I/R group ($p<0.05$). I/R group, P group and P + S group exhibited significantly increased wet-to-dry weight ratio of intestinal tissues in comparison with S group ($p<0.05$). However, P group and P + S group exhibited distinctly lower wet-to-dry weight ratio of intestinal tissues than I/R group ($p<0.05$). The content of malondialdehyde (MDA) was reduced prominently, while that of superoxide dismutase (SOD) was elevated significantly in P group and P + S group in contrast with those in I/R group ($p<0.05$). On the contrary, P + S group displayed remarkably lower MDA content and higher SOD content than P group ($p<0.05$). The levels of CK-MB, TNF-α and IL-6 in the blood rose markedly in I/R group compared with those in S group ($p<0.05$). However, they declined evidently in P group and P + S group in contrast with those in I/R group ($p<0.05$). Besides, the protein expression level of phosphorylated p38 MAPK was significantly higher in I/R group, P group and P + S group than that in S group ($p<0.05$). However, no significant difference was observed in the protein expression of total p38 MAPK among the four groups ($p>0.05$). However, the protein expression level of phosphorylated p38 MAPK was distinctly down-regulated in P group and P + S group in comparison with that in I/R group ($p<0.05$). Finally, I/R group, P group and P + S group had a prominently higher protein expression level of NF-κB than S group ($p<0.05$). However, P group and P + S group exerted a significantly lower protein expression level of NF-κB than I/R group ($p<0.05$).

CONCLUSIONS: Propofol decreases the release of inflammatory factors and alleviates intestinal edema by inhibiting the p38 MAPK/NF-κB signaling pathway, thereby mitigating and treating the intestinal I/R injury in rats.

Key Words:
p38 MAPK/NF-κB signaling pathway, Propofol, Intestinal ischemia/reperfusion injury.

Introduction

Intestinal ischemia/reperfusion (I/R) is a pathological or physiological process caused by

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acute mesenteric ischemia, traumatic shock and surgery[1,2]. Intestinal I/R injury can lead to multiple organ failure and systemic inflammatory response syndrome, so it is likely to cause the death of patients[3,4]. The restoration of blood flow and oxygen supply during reperfusion can save time for rescue. However, reperfusion will give rise to cell injury, also known as reperfusion injury, and even severer ischemic injury. Excessive injury mainly includes the release of inflammatory cytokines, formation of oxygen free radicals, and infiltration of neutrophils in damaged tissues[5-7]. I/R can not only increase intestinal permeability, but also induce mucosal barrier dysfunction[8,9]. Impaired intestinal mucosal barrier may increase intestinal epithelial permeability[10,11]. Therefore, reversing the increase of intestinal epithelial permeability is conducive to preventing and ameliorating intestinal I/R that can also trigger small intestinal bacterial overgrowth[4]. As a result, intestinal mucosal barrier safeguarding the body against the invasion of pathogenic microorganisms should be protected, so as to avoid I/R injury. Current studies have shown that oxidative stress plays a critical role in intestinal I/R injury[12]. Excess reactive oxygen species (ROS) are produced in damaged tissues and cells, which activate multiple signaling pathways, promote inflammatory responses and impair the intestinal mucosal barrier function in the process of intestinal I/R injury[12,13].

The p38 mitogen-activated protein kinase (MAPK) signaling pathway mediates inflammatory responses, apoptosis and differentiation under stress, including I/R injury[14-16]. In the case of stress, however, intra-cellular p38 can migrate into the nucleus to participate in regulating the expressions of transcription factors under the control of phosphorylation[17,18]. A growing number of studies have demonstrated that interfering in the functions of p38 MAPK may reduce the degree of tissue injury in disease models, including intestinal injury models[19,20]. The nuclear factor-kappa B (NF-κB) signaling pathway is an important pathway that modulates the expressions of inflammatory factors in cells, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β) and IL-6[21]. Activated TLR4-MD2-CD14 complex can control the MyD88 signaling pathway to activate a series of cascades. Meanwhile, it can activate the IκB kinase complex to control the phosphorylation of NF-κB p65 subunit[22,23], eventually decreasing the release of inflammatory factors.

Propofol is a kind of anesthetic agent that can be commonly used in clinical practice. Recent studies have indicated that propofol has various effects, such as anti-inflammatory effect. Hence, the effects of propofol on intestinal I/R injury in rats through the p38 MAPK/NF-κB signaling pathway were explored in this study. All our findings might help to provide a theoretical basis for the treatment of intestinal ischemia.

Materials and Methods

Materials

A total of 40 healthy male Sprague-Dawley rats (220-250 g) were provided by Xi'an Jiaotong University (Xi'an, China). Propofol was purchased from Sigma (St. Louis, MO, USA), and SB203580 was bought from Absin Bioscience Inc. (Shanghai, China). Enzyme-linked immunosorbent assay (ELISA) kits for superoxide dismutase (SOD), malondialdehyde (MDA), creatine kinase-MB (CK-MB), TNF-α and IL-6 were offered by Sigma-Aldrich (St. Louis, MO, USA). Anti-Bcl-2 and anti-Bax rabbit polyclonal antibodies for Western blotting (WB) were purchased from Abcam (Cambridge, MA, USA). The WB protein detection kit and chemiluminescence assay kit were provided by KPL (Middlesex County, MA, USA).

Methods

Establishment of Rat Model of I/R Injury

This investigation was approved by the Animal Ethics Committee of Xi'an Jiaotong University Animal Center. At 1 week before use, the rats were adaptively fed *ad libitum* with standard diets in a temperature-controlled room with a 12-h light/dark cycle. They were given free access to food and water. Subsequently, the rats were deprived of food but not water for 12 h and prepared into the I/R injury model. The rat model of intestinal I/R injury was successfully established as follows[11]. Rats were intraperitoneally injected with pentobarbital sodium (50 mg per kilogram of body weight) for anesthesia, and a 2 cm-long incision was then made on the medioventral line. The superior mesenteric artery (SMA) was separated and clipped using a non-traumatic vascular clamp for 45 min. Next, the clamp was removed gently for reperfusion.

After that, the rats were sacrificed to obtain 5 cm of jejunum, and blood samples were collected from the abdominal aorta for analysis. All experimental rats were randomly divided into 4 groups, with 10 rats in each group. (1) Rats in S group were treated by sham operation, without blocking the SMA, and administered by gavage. (2) 45 min of intestinal ischemia and 90 min of reperfusion were performed for rats in I/R group, followed by administration by gavage. (3) In P group, 50 mg/kg propofol was injected into the left femoral vein using a venous pump at 1 h before ischemia, and the remaining manipulations were the same as those in I/R group. (4) At 1 h before ischemia, 50 mg/kg propofol was injected into the left femoral vein by means of the venous pump in P + S group. 4 h later, the rats were injected with p38 MAPK inhibitor SB203580 (15 μg/kg), and the remaining manipulations were identical to those in I/R group. At 2 h after perfusion, rats in all the 4 groups were killed. Intestinal tissues and blood samples were collected for subsequent experiments.

Detection of Pathological-Morphological Changes and Injury Score of Intestinal Tissues in each Group of Rats

Intestinal tissues in each group were separately fixed in 5% paraformaldehyde solution, soaked for 24 h and sliced into 5 μm-thick sections. Next, the sections were subjected to hematoxylin and eosin (HE) staining (Boster, Wuhan, China). Pathological-morphological changes in intestinal tissues were observed under a light microscope. Moreover, Chiu's score was applied to analyze intestinal tissues in each group.

Detection of Wet-To-Dry Weight Ratio of Intestinal Tissues in Each Group of Rats

Intestinal tissues of each group of rats were cleansed with normal saline and weighed after removing water droplets on the surface, which was regarded as wet weight. Meanwhile, dry weight was measured by drying the intestinal tissues in a drying oven at 80°C for 24 h. The wet-to-dry weight ratio of intestinal tissues was finally calculated.

Determination of Oxidative Stress Indexes in Each Group of Rats

Intestinal tissues of rats were taken out from liquid nitrogen tanks and prepared into tissue homogenates by normal saline in ice bath at 4°C. After 15 min of centrifugation, the supernatant was obtained to determine the activity of SOD and the content of MDA in accordance with the instructions.

Examination of Inflammatory Factors CK-MB, TNF-α and IL-6 in Each Group of Rats Via ELISA

4 mL of blood was first drawn from every rat and centrifuged at 4°C and 3,000 r/min for 15 min. Only the supernatant was stored at -60°C for use. Inflammatory factors CK-MB, TNF-α and IL-6 in the serum were tested in sequence according to the kit instructions.

Measurement of Protein Expression Levels of p38 MAPK and NF-κB in Different Groups Via WB

Total proteins were extracted from intestinal tissues in each group. The concentration of extracted protein was detected by the bicinchoninic acid (BCA) method (Pierce, Rockford, IL, USA). After that, protein samples were examined as per the procedures of the WB assay, and chemiluminescence apparatus was used for luminescence after pre-processing. Protein expressions were finally calculated.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 18.0 software package (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. Experimental data were presented as mean ± standard deviation ($\bar{x} \pm s$) and analyzed by univariate analysis of variance. $^{*}p<0.05$, $^{\#}p<0.05$, $^{\&}p<0.05$, $^{***}p<0.01$, $^{\#}p<0.01$ and $^{\&}p<0.01$ suggested statistically significant differences.

Results

Effects of Propofol on Pathological Changes in Intestinal Tissues of Rats

The intestinal tissue injury was the severest in I/R group, with the infiltration of massive inflammatory cells and oozing of blood. Compared with those in I/R group, the infiltration of inflammatory cells and damage to intestinal villi were notably relieved in P group, revealing that the intestinal mucosal injury of rats was remarkably repaired in P group. In addition, intestinal mucosal injury was further restored, and the damage to intestinal villi and infiltration of inflammatory cells were markedly improved in P

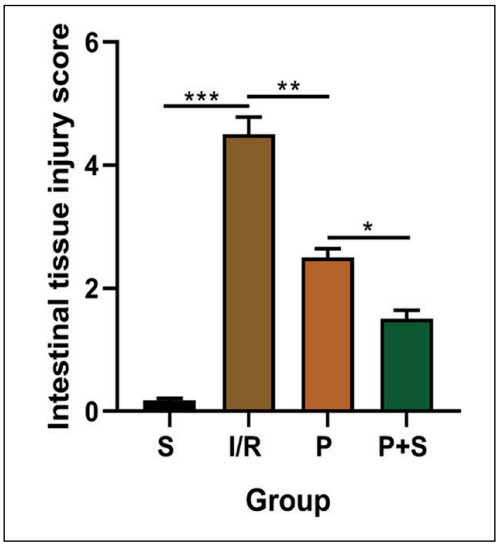

Figure 1. Intestinal tissue injury scores in each group of rats. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

+ S group in comparison with P group. The statistical analysis of the Chiu's score for intestinal injury in each group was displayed in Figure 1. The intestinal tissue injury score was evidently higher in I/R group, P group and P + S group than S group ($p<0.05$). However, it was markedly lower in P group and P + S group than that in I/R group ($p<0.05$). P + S group had a significantly decreased intestinal tissue injury score compared with P group ($p<0.05$). It can be seen that propofol can repair intestinal I/R injury in rats, which may be related to the inhibition of p38 MAPK signaling pathway.

Effects of Propofol on Oxidative Stress Indexes in Intestinal Tissues of Each Group of Rats

The influences of propofol on oxidative stress indexes MDA and SOD in the serum of rats with intestinal I/R injury were shown in Table I and Figure 2. The concentration of MDA increased significantly, but that of SOD decreased overtly in I/R group in comparison with those in S group ($p<0.05$) (Table I). Besides, the content of MDA was reduced prominently, while that of SOD was elevated remarkably in P group and P + S group in contrast with those in I/R group ($p<0.05$). On the contrary, P + S group displayed remarkably lower MDA content and notably higher SOD content than P group ($p<0.05$). These results suggest that propofol and MAPK inhibitor have certain inhibitory effects on oxidative stress indexes in the serum of rats with intestinal I/R injury.

Effects of Propofol on Intestinal Inflammatory Factors CK-MB, TNF-α and IL-6 in Each Group of Rats

According to the results of the influences of propofol on inflammatory factors CK-MB, TNF-α and IL-6 in the blood of rats with intestinal I/R injury (Table II), the levels of CK-MB, TNF-α and IL-6 rose markedly in I/R group compared with those in S group ($p<0.05$). However, they declined evidently in P group and P + S group in contrast with those in I/R group ($p<0.05$). P + S group exhibited overtly lower levels of CK-MB, TNF-α and IL-6 in the blood than P group ($p<0.05$). These findings imply that propofol and MAPK inhibitor are able to decrease inflammatory factors in the serum of rats with intestinal I/R injury, thus ameliorating the symptoms of intestinal ischemia to some extent.

Effect of Propofol on Wet-To-Dry Weight Ratio of Intestinal Tissues of Rats

As shown in Figure 3, I/R group, P group and P + S group exhibited a significantly increased wet-to-dry weight ratio of intestinal tissues in comparison with S group ($p<0.05$). P group and P + S group had a distinctly lower wet-to-dry weight ratio of intestinal tissues than I/R group ($p<0.05$). P + S group displayed an apparently reduced wet-to-dry weight ratio of intestinal tissues compared with P group ($p<0.05$). The results of Chiu's score and wet-to-dry weight ratio of intestinal tissues reflected that the rat model of intestinal I/R injury was successfully established. Meanwhile, it can be seen that propofol and MAPK inhibitor can alleviate the edema in rats with intestinal I/R injury.

Table I. Effects of propofol on oxidative stress indexes in intestinal tissues of each group of rats (n = 10, ($\bar{x} \pm s$).

Group	MDA (μmol/mL)	SOD (U/mg)
S	21.22 ± 2.50	432.15 ± 20.13
I/R	70.43 ± 5.13[a]	183.32 ± 16.25[a]
P	38.29 ± 4.18[ab]	281.13 ± 19.13[b]
P + S	30.55 ± 3.61[bc]	335.29 ± 22.60[bc]

Note: [a]$p<0.05$ *vs*. S group, [b]$p<0.05$ *vs*. I/R group, [c]$p<0.05$ *vs*. P group.

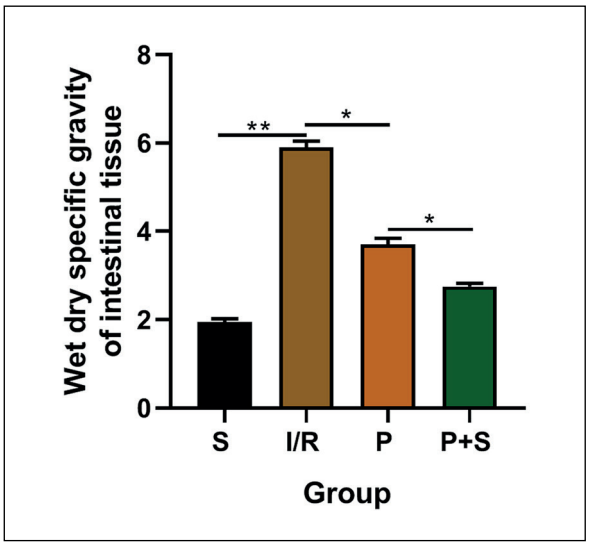

Figure 2. Oxidative stress indexes in intestinal tissues of each group of rats, *p<0.05 *vs.* S group, #p<0.05 *vs.* I/R group, &p<0.05 *vs.* P group.

Effect of Propofol on the Protein Expression Level of p38 MAPK in Intestinal Tissues of Rats

The protein expression level of p38 MAPK in intestinal tissues in each group was detected *via* WB assay (Figure 4A and 4B). The results showed that the protein expression level of phosphorylated p38 MAPK was significantly higher in I/R group, P group and P + S group than that in S group (p<0.05). However, no statistically significant difference was observed in the protein expression of total p38 MAPK among the four groups (p>0.05). However, the protein expression level of phosphorylated p38 MAPK was distinctly down regulated in P group and P + S group in comparison with that in I/R group (p<0.05). Meanwhile, it also declined remarkably in P + S group compared with that in P group (p<0.05). All these findings demonstrate that propofol is capable of repressing the protein expression of phosphorylated p38 MAPK in rats with intestinal I/R injury.

Effect of Propofol on the Protein Expression Level of NF-κB in Intestinal Tissues of Rats

The protein expression level of NF-κB in the intestinal tissues in each group was determined through WB assay (Figure 5A and 5B). I/R group, P group and P + S group had a prominently higher protein expression level of NF-κB than S group (p<0.05). However, P group and P + S group exhibited a clearly lower protein expression level of NF-κB than I/R group (p<0.05). Additionally, the protein expression level of NF-κB decreased significantly in P + S group compared with that in P group (p<0.05). This illustrates that propofol can inhibit the protein expression of NF-κB in rats with intestinal I/R injury. Therefore, propofol has some therapeutic effects on rats with intestinal I/R injury by repressing the p38 MAPK/NF-κB signaling pathway.

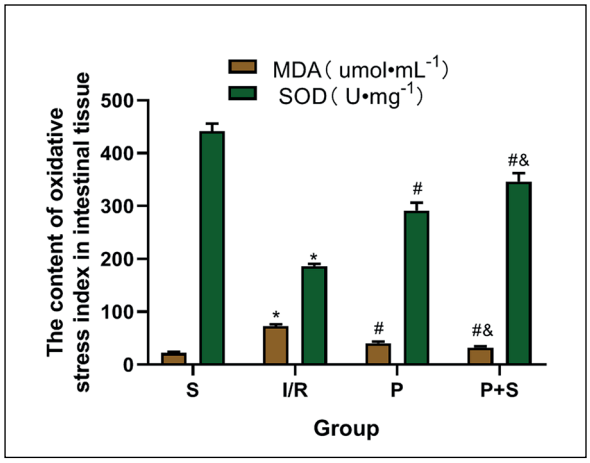

Figure 3. Effect of propofol on wet-to-dry weight ratio of intestinal tissues of rats. *p<0.05: a significant difference among different groups.

Table II. Effects of propofol on inflammatory factors CK-MB, TNF-α and IL-6 in the serum of each group of rats (n = 10, ($\bar{x}$ ± s).

Group	CK-MB (U/L)	TNF-α (ng/L)	IL-6 (ng/L)
S	1022.35 ± 100.78	53.20 ± 3.53	100.30 ± 9.32
I/R	3635.72 ± 278.35[a]	172.21 ± 12.51[a]	387.32 ± 19.34[a]
P	2005.13 ± 186.23[b]	110.26 ± 10.31[b]	215.65 ± 13.71[b]
P + S	1765.39 ± 190.36[bc]	84.51 ± 8.58[bc]	175.97 ± 13.93[bc]

Note: [a]p<0.05 *vs*. S group, [b]p<0.05 *vs*. I/R group, [c]p<0.05 *vs*. P group.

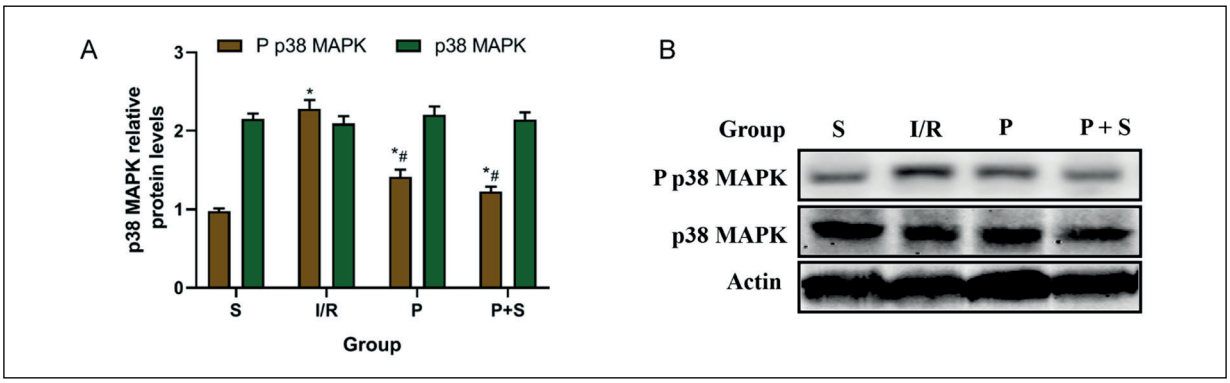

Figure 4. Effect of propofol on protein expression level of p38 MAPK in intestinal tissues of rats. *p<0.05 *vs.* S group, $^{\#}p$<0.05 *vs.* I/R group.

Discussion

Intestinal I/R injury is a very intractable clinical problem characterized by trauma, infection and shock. Meanwhile, intestinal I/R may increase the mortality rate[4]. Intestinal I/R destroys the barrier function of intestinal mucosa to induce intestinal bacterial infection, and even endotoxemia, systemic inflammatory response syndrome and multiple organ dysfunction in the body in severe cases[24]. Recent studies have discovered that the rationale for intestinal I/R in the injury of other organs is that bacterial and viral infections and endotoxin can lead to hemorrhage, ROS overproduction, mitochondrial dysfunction and energy failure, chemotaxis and recruitment of neutrophils and other leukocytes as well as cell death. All of these processes involve the regulation and control of genes[25]. Hence, exploring the pathogenesis of intestinal I/R and applying its treatment methods have become an urgent issue to be resolved, which also requires special attention from researchers. Intestinal I/R-related diseases may result in the release of inflammatory factors, such as IL-6, IFN and TNF-α, and the formation of ROS[21]. Chemokines can recruit neutrophils to the site of inflammation and secret MMPs to degrade the extracellular matrix. Moreover, released inflammatory factors activate the p38 MAPK and NF-κB signaling pathways[26]. Multiple studies have revealed that reducing the level of p38 MAPK may relieve tissue injury in disease models, including the intestinal injury model. According to the literature, propofol possesses anesthetic and anti-inflammatory effects[27]. In the present study, it was found that propofol modulated intestinal I/R in rats by the p38 MAPK/NF-κB signaling pathway.

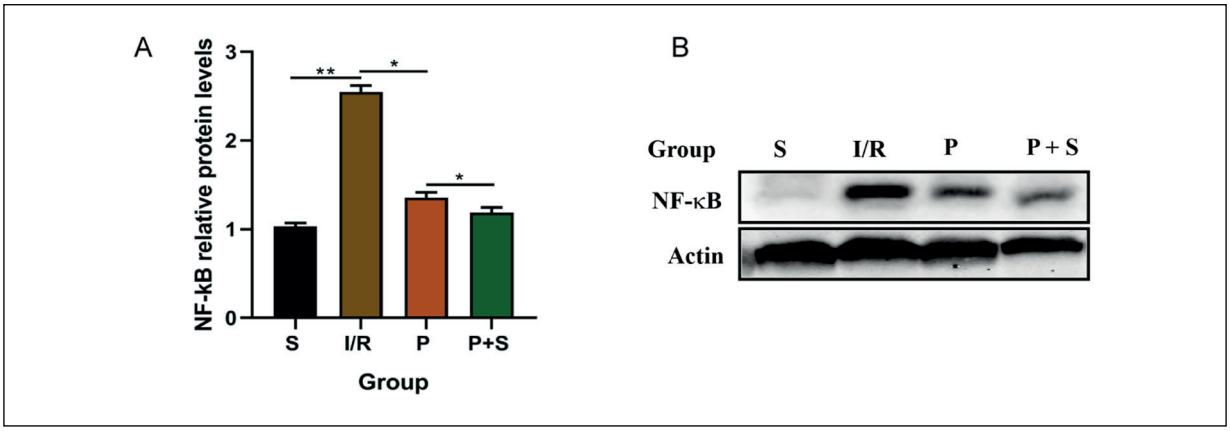

Figure 5. Effect of propofol on protein expression level of NF-κB in intestinal tissues of rats. *p<0.05 *vs.* S group, $^{\#}p$<0.05 *vs.* I/R group.

In this research, intestinal tissue injury and Chiu's score were evaluated first. It was demonstrated that I/R group had the most serious tissue injury, including the infiltration of inflammatory cells and blood oozing. Remarkably repaired intestinal mucosal injury of rats and apparently milder infiltration of inflammatory cells and damage to intestinal villi were observed in P group compared with those in I/R group. The results of Chiu's score and wet-to-dry weight ratio of intestinal tissues elucidated that the rat model of intestinal I/R injury was successfully established. Meanwhile, propofol and MAPK inhibitor alleviated the edema in rats with intestinal I/R injury. It can be seen that propofol is able to repair intestinal I/R injury in rats, which may be correlated with the inhibition of the p38 MAPK signaling pathway. Intestinal I/R injury has been confirmed strongly associated with the release of oxidative stress indexes and inflammatory factors[12-16]. It was manifested in this research that the content of MDA was prominently lower, while that of SOD was clearly higher in P group and P + S group than those in I/R group. However, the opposite results of MDA and SOD were observed between P + S group and P group. Furthermore, the levels of CK-MB, TNF-α and IL-6 in the blood declined markedly in P + S group in contrast with those in P group. All these results suggest that propofol and MAPK inhibitor have certain inhibitory effects on oxidative stress indexes and inflammatory factors in the serum of rats with intestinal I/R injury, thereby relieving the symptoms of intestinal ischemia to some extent. In addition, WB assay was utilized to examine the expressions of related proteins to verify whether propofol regulated inflammatory factors *via* the p38 MAPK/NF-κB signaling pathway. Based on the results, I/R group, P group and P + S group had a markedly elevated protein expression level of phosphorylated p38 MAPK compared with S group. However, there was no statistically significant difference in the protein expression of total p38 MAPK among the four groups. The protein expression level of NF-κB was reduced notably in P group and P + S group in comparison with that in I/R group. Similarly, the same trend was observed between P + S group and P group. The above findings elaborate that propofol is capable of repressing the protein expression of phosphorylated p38 MAPK in rats with intestinal I/R injury and attenuating the release of inflammatory factors. As a result, propofol can repress the p38 MAPK/NF-κB signaling pathway to exert some therapeutic effects on rats with intestinal I/R injury.

Conclusions

The novelty of this study was that propofol decreases the release of inflammatory factors by inhibiting the p38 MAPK/NF-κB signaling pathway, thereby mitigating and treating intestinal I/R injury in rats.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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