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Propofol attenuates inflammatory response and apoptosis to protect D-galactosamine/lipopolysaccharide induced acute liver injury via regulating TLR4/NF-κB/NLRP3 pathway

Zhaojian Zhang[a], Liang Tian[a], Kai Jiang[b,*]

[a] Department of Anaesthesiology, The First People's Hospital of Lianyungang, 222000, China
[b] Department of Hepatobiliary and Pancreatic Surgery & Minimally Invasive Surgery, Zhejiang Provincial People's Hospital, Hangzhou 310058, China

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ABSTRACT

Objective: Propofol has been reported to be protective against liver injury due to its anti-inflammatory, anti-oxidative and anti-apoptotic activities. The purpose of this study was to examine the protective effects of propofol on D-galactosamine/lipopolysaccharide (D-GalN/LPS) induced acute liver injury.
Methods: Mice were given an intraperitoneal injection of propofol before D-GalN/LPS treatment. Liver injury was confirmed by serum biochemical analysis and liver histopathological analysis. Relevant molecular events were determined by ELISA, western blot, and test kits. Cell apoptosis were evaluated by TUNEL assay.
Results: The results showed that propofol significantly prevented D-GalN/LPS-induced liver damage by preventing associated increases of serum alanine transaminase (ALT) and aspartate transaminase (AST) and restoring liver histopathological changes. Propofol markedly inhibited the production of inflammatory cytokines and oxidative stress-related factors. Propofol markedly reduced hepatocyte apoptosis, decreased Bax, Bad, cleaved caspase-3 and increased Bcl-2 expression. Besides, NLRP3 inflammasome and TLR4/NF-κB pathway were inactivated under the treatment of propofol according to the expression of pathways-related proteins.
Conclusion: Taken together, propofol contributed to liver protection against D-GalN/LPS-induced liver injury in mice by inhibiting inflammation, oxidative stress and hepatocyte apoptosis through regulating TLR4/NF-κB/NLRP3 pathway.

1. Introduction

Liver disease is one of the most common diseases that affect human health worldwide. Acute liver injury is a complicated inflammatory disease caused by various etiologies, including heat stroke, antibiotics abuse and viral hepatitis [1–3]. D-galactosamine (D-GalN)/lipopolysaccharide (LPS)-induced acute liver injury is a representative animal model widely used to screen hepatoprotective drugs and to elucidate the mechanism of liver injury [4,5]. LPS is a main structural and functional composition of the outer membrane of Gram-negative bacterial [6]. The stimulation of LPS promote the release of proinflammatory cytokines from hepatic macrophages, leading to liver injury. D-GalN, an amino sugar that specific metabolized from liver, can directly deplete uridine triphosphate in liver cells, prevent the regeneration of organelles, and cause functional obstacle of liver cells [5]. Besides, D-GalN is able to sensitize toxic effect of LPS on hepatocytes and results in fulminant hepatic failure within a few hours [7].

Propofol (2, 6-dissopropyl phenol), one of the widely used intravenous general anesthesia clinical drugs, has rapidly awakening effect, continuous infusion, and has no accumulation. Recent years, propofol is considered to have positive effects on organ protection, such as kidney and liver [8–10]. Amounts of evidence have revealed a protective role of propofol in liver injury not only in clinical but also in experiments. Compared to other anesthetics, propofol has a comparable minor effect on liver function after an elective posterolateral thoracotomy or after living-donor liver transplantation [11,12]. Besides, Ge et al. showed protective effects of propofol against liver transplantation-induced graft-liver injury [10]. Wei et al. reported that propofol protected hepatic ischemia/reperfusion injury [13]. However, whether propofol is also protective for the amelioration of liver injury resulted from D-GalN/LPS remains unclear.

In this study, we investigated whether propofol played a positive role in protecting liver against D-GalN/LPS induced acute liver injury, and how propofol exerted its protective function. We found that

* Corresponding author at: Zhejiang Provincial People's Hospital, No. 158 Shangtang Road, Xiacheng District, Hangzhou 310058, China.
E-mail address: jiangk147@163.com (K. Jiang).

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propofol remarkably restored the liver function in D-GalN/LPS induced of mice, attenuated the stimulation of proinflammatory cytokines and oxidative stress, and inhibited hepatic cells apoptosis. Besides, propofol is possibly involved with the modulation of the TLR4/NF-κB signaling pathway in the protection of liver injury. The data in our study indicated the protective role of propofol in D-GalN/LPS induced acute liver injury and revealed the potential mechanism of propofol which were related to inflammation, oxidative and apoptosis via modulating TLR4/NF-κB signaling pathway.

2. Materials and methods

2.1. Experimental animals and design

Male C57BL/6 mice (8–12 weeks of age) were purchased from Shanghai Laboratory Animal Center (Shanghai, China). The mice were housed in a controlled environment (21 ± 2 °C, 12 h light/dark cycle) for at least one week to adapt to the environment before experiments. All animal experiments were performed in accordance with the National Institutes of Health guide for the Care and Use of Laboratory Animals. This study was approved by the Animal Experiment Ethics Committee of Zhejiang Provincial People's Hospital.

D-GalN and LPS were dissolved in sterile 0.9% normal saline according to the product protocol. The mice were received D-GalN (300 mg/kg; Sigma, St. Louis, MO, USA) and LPS (50 μg/kg; Sigma, St. Louis, MO, USA) via intraperitoneal injection to induce acute liver injury. Mice were divided into four groups (n = 8 in each group): Normal group; Saline group, received 0.9% normal saline; D-GalN/LPS group, intraperitoneally injected with D-GalN/LPS; D-GalN/LPS + propofol group, intraperitoneally injected with D-GalN/LPS, followed by 60 mg/kg propofol 2 h prior to D-GalN/LPS exposure. Mice were sacrificed 24 h after D-GalN/LPS injection. Liver and blood samples were collected for future analysis.

2.2. Serum biochemical parameters and oxidative stress factors

Blood samples were centrifuged at 3000 rpm for 15 min at 4 °C to gain serum. Activity of serum alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), malondialdehyde (MDA), glutathione-peroxidase (GSH-px), superoxide dismutase (SOD) and reactive oxygen species (ROS) were determined using corresponding test kits (Nanjing Jiancheng Institute of Biotechnology, Nanjing, China)

2.3. Histopathology evaluation

Hematoxylin and eosin (H&E) staining was carried out to determine the degree of liver injury. Liver specimens were dissected and fixed immediately in 4% paraformaldehyde after rats were sacrificed. Liver samples were then embedded in paraffin, cut into sections of 4 μm thick and stained with H&E. The images were observed by the microscope (Olympus, BX51T-PHD-J11, Tokyo, Japan). Histological severity of liver injury was scored by Suzuki's criteria on a scale from 0 to 4 as reported previously [14].

2.4. Western blot

Proteins were extracted from liver tissue in lysis buffer with protease inhibitor. The protein concentration was detected with a BCA kit, and the same amount of protein was subjected to 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis, electrotransferred onto a polyvinylidene fluoride membrane (Bio-Rad, Hercules, CA), and blocked with 5% skimmed milk for 2 h. Membranes were incubated with the primary antibodies against NLRP3, ASC, caspase-1, Bax, Bcl-2, Bad, Cleaved caspase 3, Caspase 3, TLR4 (Abcam, Cambridge, MA, USA), Myd88 (Santa Cruz Biotechnology, CA, USA), IκB-α, p65 (Cell Signaling Technology Inc., Beverly, MA, USA) and GAPDH (Abcam) overnight at 4 °C, followed by incubation with a secondary horseradish peroxidase-conjugated antibody (Santa Cruz Biotechnology) at room temperature for 1 h. The bands were visualized using a chemiluminescence (ECL) Western blotting detection kit (Thermo, USA).

2.5. Cytokine assay

Liver was mixed with 0.9% normal saline, homogenized, and then centrifuged to obtain supernatant. The levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6 and IL-18 in supernatant were detected by their own ELISA assay kits (Beyotime, Nanjing, China) following the protocols of manufacturer.

2.6. TUNEL assay

Terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL; Roche, Basal, Swiss Basel) was applied for detection of hepatocyte apoptosis in liver. In brief, paraffin sections of 4 μm-thickness were deparaffinized, and treated with 0.1% TritonX-100 for 8 min. After washing with PBS twice, sections were incubated with TUNEL reaction mixture at room temperature for 1 h, followed by an incubation with DAPI for 10 min. TUNEL-positive cells were observed in the fluorescence microscope (Olympus, Japan).

2.7. Statistical analysis

Statistical analysis were performed using GraphPad Prism 5 (Graphpad Software, Inc., San Diego, CA) and SPSS version 20.0 (SPSS Inc., Chicago, IL). Data were presented as mean ± SD. The differences between different groups analyzed by one-way analysis of variance followed by Tukey post hoc comparisons were considered as statistically significant when p value < 0.05.

3. Results

3.1. Propofol protects mice against acute liver injury induced by D-GalN/LPS

We first evaluated the effect of propofol on acute liver injury induced by D-GalN/LPS. Serum ALT and AST levels were determined as a measure of hepatic function. As shown in Fig. 1A–B, both of ALT and AST levels were significantly increased in the D-GalN/LPS group compared to those in normal group and saline group. In contrast, the serum ALT and AST levels were distinctly decreased in D-GalN/LPS + propofol group. Besides, histological changes were observed in Fig. 1C. The results revealed that liver exhibited normal hepatic architectures in normal group and saline group, while liver showed severe inflammatory cell infiltration, hepatocytes necrosis and vacuolation in D-GalN/LPS group. The administration of propofol relieved the liver architecture by histology and Suzuki scoring. These results demonstrated that propofol exhibited hepatoprotective effects on D-GalN/LPS-induced acute liver injury.

3.2. Propofol protects mice against acute liver injury by regulating NLRP3-mediated inflammatory response

Due to the severe inflammatory cell infiltration in D-GalN/LPS-stimulated liver injury found in liver tissue, inflammatory response is supposed to be involved. Thus we investigated the role of propofol in D-GalN/LPS-induced inflammatory injury of liver. Nucleotide-binding domain and leucine-rich repeat protein 3 (NLRP3) inflammasome is related to various inflammatory disorders [15]. Here, we detected the activity of NLRP3 inflammasome including NLRP3, apoptosis associated speck like protein containing a CARD (ASC), and caspase-1. As shown in Fig. 2A, the protein expressions of NLRP3, ASC and caspase-1

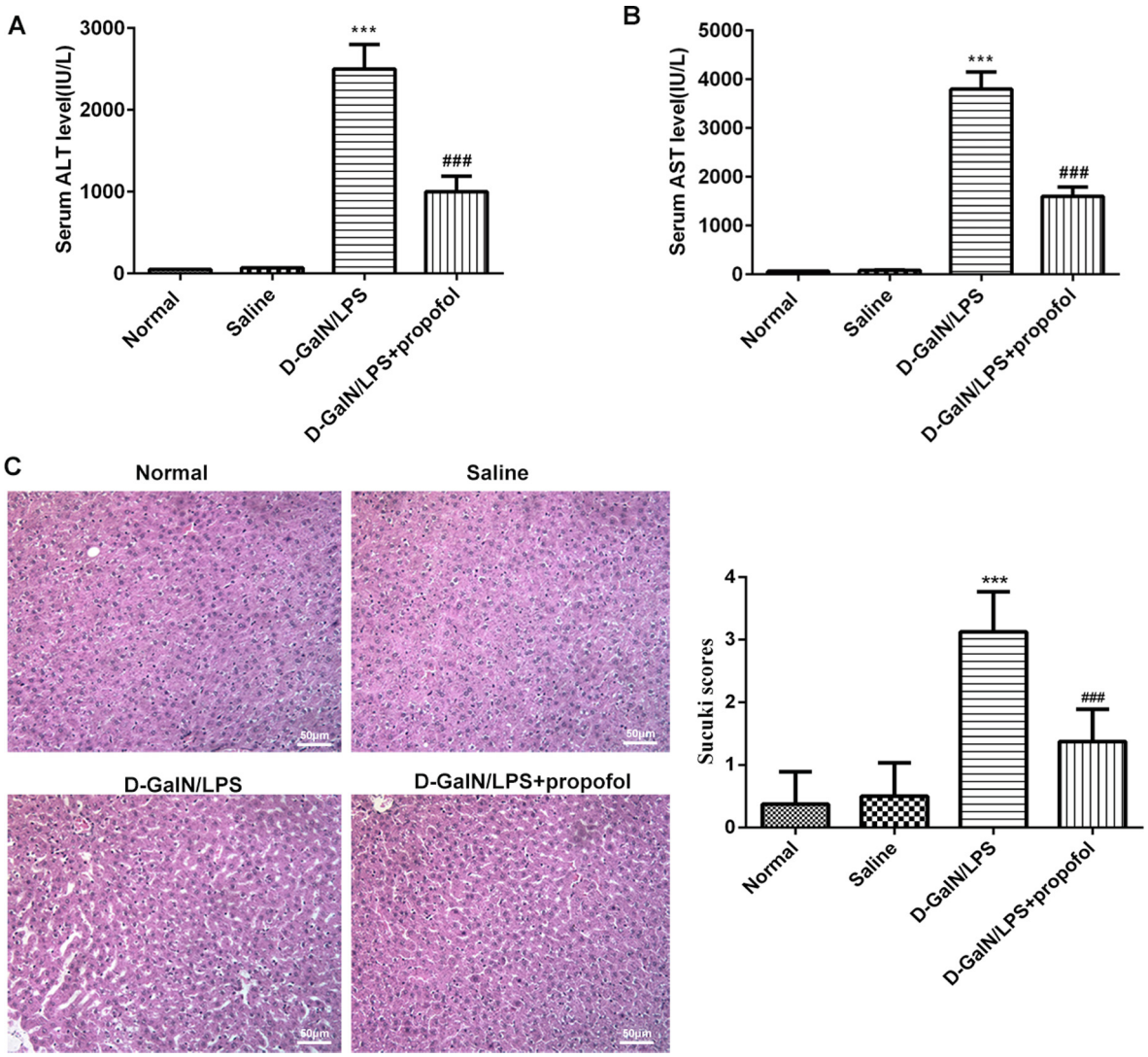

Fig. 1. The effect of propofol on liver injury in D-GalN/LPS-induced mice. Male C57BL/6 mice were inflicted with D-GalN/LPS to cause acute liver injury. Propofol was intraperitoneally injected into mice 2 h prior to exposure to D-GalN/LPS. Serum alanine transaminase (ALT) and aspartate transaminase (AST) were measured to examine the changes of liver function (A-B). Hematoxylin and eosin (H&E) staining was performed to examine the histopathological changes of liver, and histological severity of liver injury was scored by Suzuki's criteria (C). Results were performed for at least 3 times. ***$p < 0.001$ vs Normal group; ###$p < 0.001$ vs D-GalN/LPS group.

were significantly upregulated in D-GalN/LPS-induced mice, while the administration of propofol significantly decreased the activity of NLRP3 inflammasome. Meanwhile, propofol also inhibited the production of inflammatory cytokines such as TNF-α, IL-18, IL-6 and IL-1β which was elevated after the stimulation of D-GalN/LPS (Fig. 2B–E).

3.3. Propofol protects mice against acute liver injury by suppressing oxidative stress

To evaluate the effect of propofol on the liver antioxidant capacity, the markers of liver injury by oxidative stress containing ROS, MDA, LDH, GSH-px and SOD were evaluated. As shown in Fig. 3A–E, the activity of ROS, MDA, LDH, GSH-px was increased, and the activity of SOD was decreased in D-GalN/LPS group, compared to the normal or saline group. Administration of propofol lead to a considerable statistical antioxidative effect as indicated by the significant decrement in the levels of ROS, MDA, LDH, GSH-px, and by the significant augment in the level of SOD. These results indicated that propofol exhibited an obvious inhibition of oxidative stress in D-GalN/LPS-induced liver injury.

3.4. Propofol protects mice against acute liver injury by inhibiting hepatocyte apoptosis

Hepatocyte apoptosis is a critical event in the early stage of acute liver injury [16]. Thus whether propofol administration could protect mice against hepatocyte apoptosis was further evaluated. The results from TUNEL assay in Fig. 4A showed that normal mice exhibited seldom hepatocyte apoptosis, while the cell number of hepatocyte apoptosis was dramatically increased in D-GalN/LPS-induced mice, and that propofol administration significantly decreased hepatocyte apoptosis. Besides, apoptosis-related proteins were detected to support anti-apoptosis activity of propofol as propofol administration significantly promoted the expression of Bcl-2, and inhibited the expression of Bax and Bad, and cleaved caspase-3 (Figure B-C). These results indicated that propofol could protect mice against hepatocyte apoptosis.

3.5. Propofol inhibits TLR4/NF-κB signaling pathway activation in D-GalN/LPS induced acute liver injury

To understand the potential mechanism that how propofol exerted

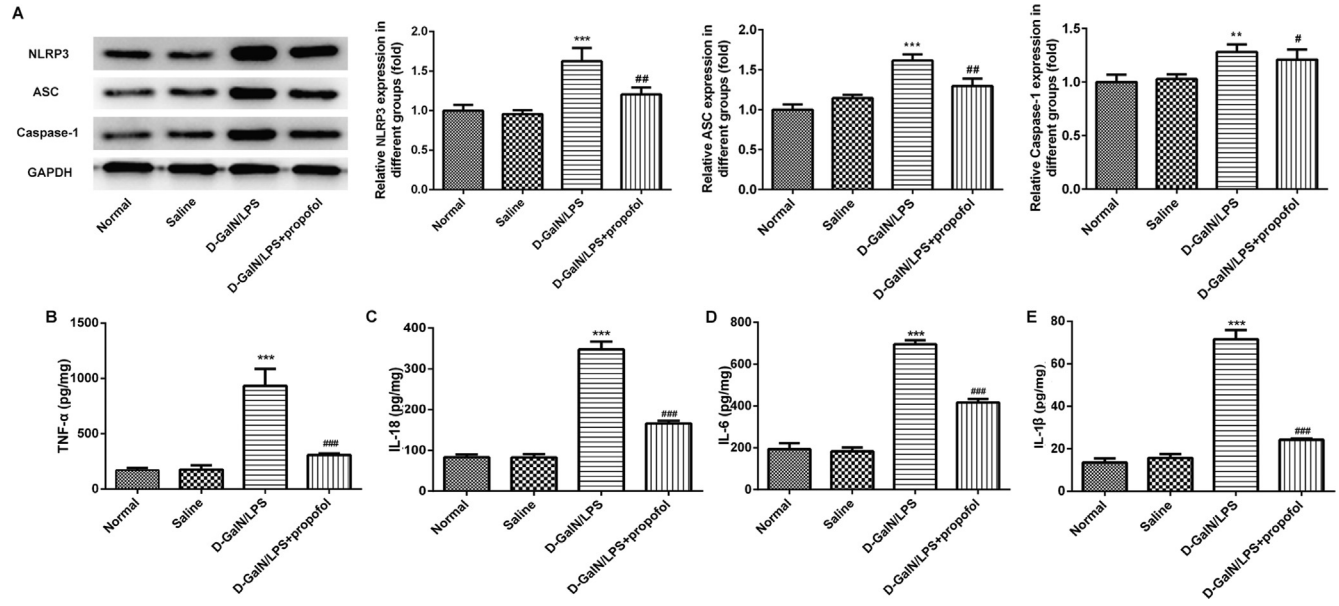

Fig. 2. The effect of propofol on inflammation in D-GalN/LPS-induced liver injury. Nucleotide-binding domain and leucine-rich repeat protein 3 (NLRP3) inflammasome-related proteins NLRP3, apoptosis associated speck like protein containing a CARD (ASC), and caspase-1 were examined by western blot (A). The level of inflammatory cytokines: tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6 and IL-18, were determined by ELISA kits (B-E). Results were performed for at least 3 times. ***$p < 0.001$ vs Normal group; #, ##, ###$p < 0.05$, 0.01, and 0.001 vs D-GaIN/LPS group.

its protective role in D-GalN/LPS-induced acute liver injury, the activity of TLR4/NF-κB signaling was detected by western blot. The results (Fig. 5) showed that stimulation of D-GalN/LPS significantly activated TLR4/NF-κB signaling as the protein expressions of TLR4, Myd88 dramatically increased and IκB-α were decreased in D-GalN/LPS-induced mice. However, these alternation was changed by administration of propofol, and propofol significantly decreased the activity of TLR4/NF-κB signaling pathway. Besides, nuclear translocation of the NF-κB subunit p65 was assessed. D-GalN/LPS promoted the translocation of NF-κB p65 from cytosol into the nucleus, while propofol blocked the translocation of p65 into the nucleus, resulting in an inhibition of TLR4/NF-κB signaling activity.

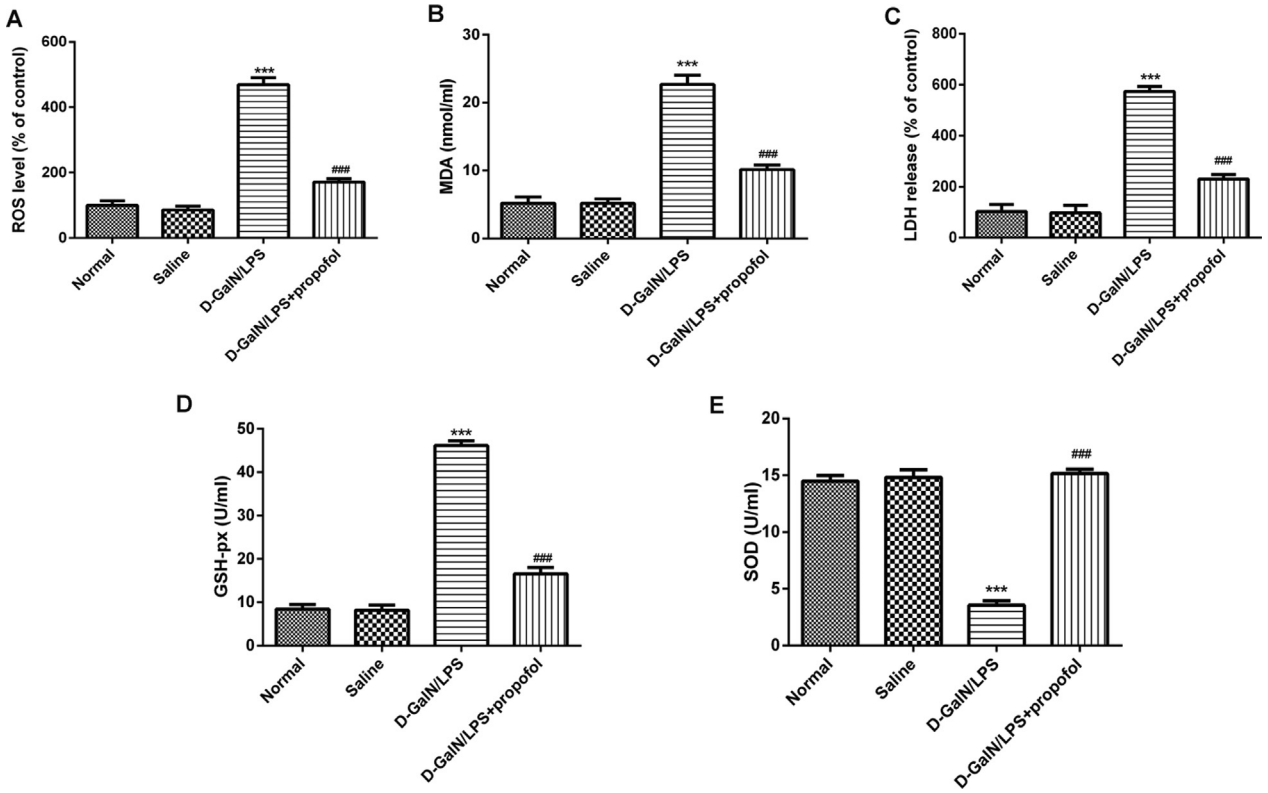

Fig. 3. The effect of propofol on oxidative stress in D-GalN/LPS-induced liver injury. The oxidative stress factors: lactate dehydrogenase (LDH), malondialdehyde (MDA), glutathione-peroxidase (GSH-px), superoxide dismutase (SOD) and reactive oxygen species (ROS) in serum of different groups of mice were analyzed according to their corresponding test kits (A-E). Results were performed for at least 3 times. ***$p < 0.001$ vs Normal group; ###$p < 0.001$ vs D-GaIN/LPS group.

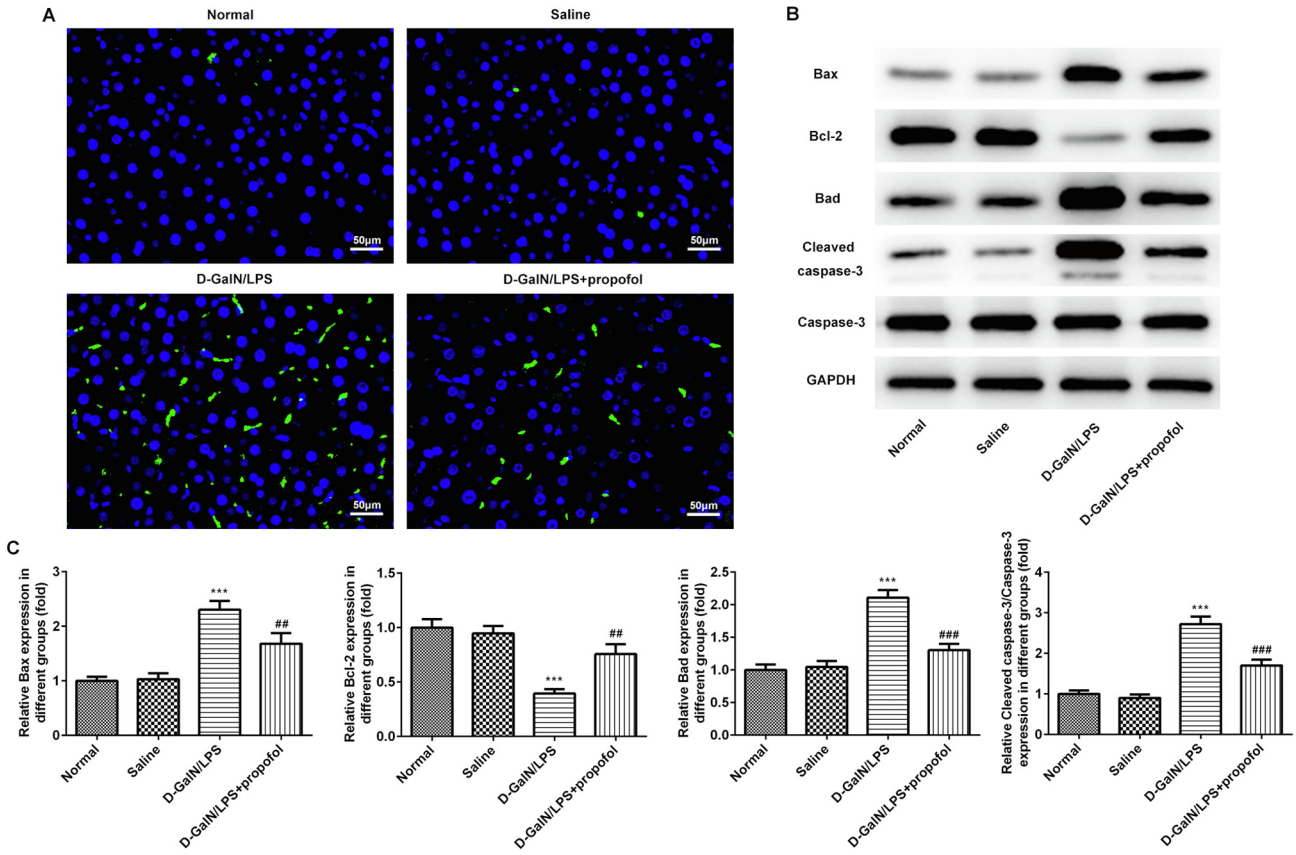

Fig. 4. The effect of propofol on hepatocyte apoptosis in D-GalN/LPS-induced liver injury. TUNEL assay were applied for the detection of hepatocyte apoptosis in liver (A). Apoptosis-related proteins: Bax, Bcl-2, Bad, Cleaved caspase-3, and caspase-3, were analyzed using western blot (B), and relative protein content was quantified (C). Results were performed for at least 3 times. ***p < 0.001 vs Normal group; ##, ###p < 0.01, 0.001 vs D-GalN/LPS group.

4. Discussion

Acute liver injury D-GalN/LPS-induced liver damage is a well-accepted animal model for acute injury to research underlying mechanisms and screen potential drugs [17]. Excessive production of inflammatory cytokines, oxidative stress, and hepatocyte apoptosis were deeply involved in acute liver injury, and not a few potential drugs that have anti-inflammatory and anti-oxidant activities were demonstrated to be effective for the treatment of D-GalN/LPS-induced liver injury [17–19]. According to previous studies, propofol has been reported to be anti-inflammatory through inhibition of inflammatory substance expression such as TNF-α and IL-1β and suppression of NF-κB activation [20]. Besides, propofol was demonstrated to be protective in liver injury induced by orthotopic liver transplantation and ischemia/reperfusion [10,13]. Nevertheless, there is no report presenting the influence of propofol on acute liver injury induced by D-GalN/LPS. Therefore, the effect of propofol on acute liver injury was investigated in the present study. Our results provided substantial evidence of liver protective role of propofol through suppressing inflammatory injury, oxidative stress, and hepatocyte apoptosis. Besides, the present study suggested that propofol possess potent protective activity in acute liver injury partly through inhibiting NLRP3 inflammasome and TLR4/NF-κB signaling pathway.

It is well known that NLRP3 inflammasome and TLR4/NF-κB pathways are involved in D-GalN/LPS-induced inflammatory response and thus is implicated in the pathogenesis of acute liver injury [21,22]. NLRP3 inflammasome plays an important role in the modulation of inflammation response by producing pro-inflammatory cytokines [23]. Once activated, NLRP3 recruits the adapter ASC, which in turn recruits procaspase-1, resulting in the maturation and release of biologically active IL-1β and IL-18 [24]. In the present study, we observed a decreased secretion of IL-1β and IL-18, and a restored inflammatory response in mice after the administration of propofol, compared to D-GalN/LPS-stimulated mice. In addition, TLR4/NF-κB is a classical signailing pathway that participates in the regulation of inflammation [25]. NF-κB p65 is normally in the resting state in the cytoplasm. Upon TLR4 is activated by the stimulation of LPS, p65 is separated from its inhibitory protein IκB-α, and transferred into the nucleus, promoting the production of pro-inflammatory cytokines [26,27]. In our study, an increased expression of TLR4, Myd88, p65 (nucleus), and decreased expression of IκB-α and p65 (cytoplasm) were detected in the stimulation of D-GalN/LPS, indicating that TLR4//NF-κB signaling was activated in D-GalN/LPS-induced acute liver injury. While the treatment of propofol significantly reduced the activity of TLR4//NF-κB signaling. Emerging bodies of evidence have indicated that NLRP3 inflammasome also participate in TLR4/NF-κB signaling pathway-mediated inflammatory response [28–30]. As report goes, Knockdown of has_circ_0068087 inhibited high glucose-induced excessive inflammatory factors, TNF-α, IL-6, and IL-1β, from HUVECs by suppression of the TLR4/NF-κB/NLRP3 inflammasome signaling pathway [29]. Isorhynchophylline inhibited LPS-induced oxidative stress and inflammation through suppressing TLR4/NF-κB/NLRP3 inflammasome pathway [30]. Thus, inhibition of TLR4/NF-κB/NLRP3 inflammasome pathway might be an effective approach to alleviating inflammation-related diseases. In the present study, inflammatory factors, TNF-α, IL-18, IL-6 and IL-1β, were significantly increased after the stimulation of D-GalN/LPS, which were then reversed by the treatment of propofol. Besides, inflammation-related oxidative stress was also relieved by the treatment of propofol, compared to D-GalN/LPS-induced mice, as decreased levels of ROS, MDA, LDH, GSH-px and increased SOD level were observed under the treatment of propofol. Oxidative stress is one of the main factors that contribute to liver injury, which is closely connected

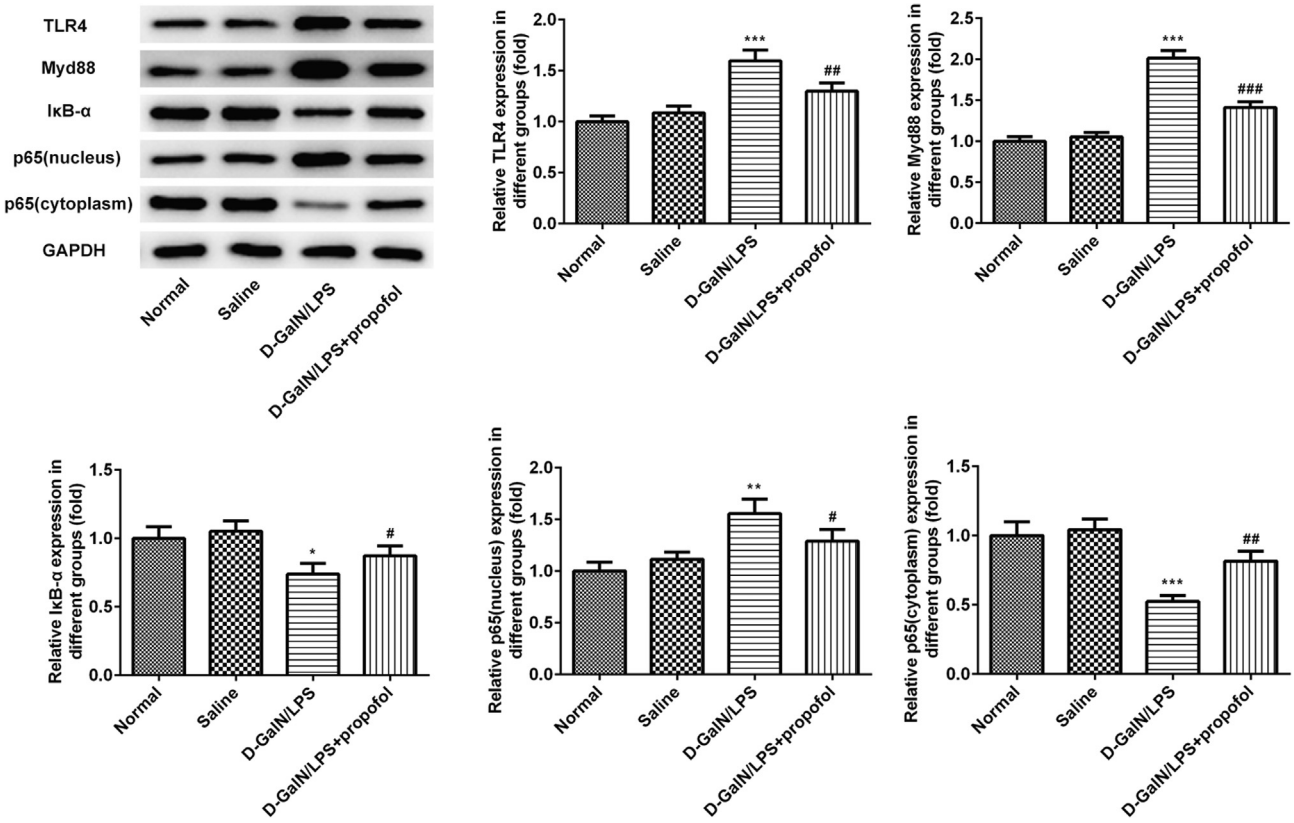

Fig. 5. The effect of propofol on TLR4/NF-κB pathway in D-GalN/LPS-induced liver injury. The activity of TLR4/NF-κB signaling was determined by detecting protein expression of TLR4/NF-κB pathway-related proteins: TLR4, Myd88, IκB-α, and NF-κB p65 using western blot, and the relative protein content was quantified. Results were performed for at least 3 times. *, **, ***p < 0.05, 0.01, and 0.001 vs Normal group; #, ##, ###p < 0.05, 0.01, and 0.001 vs D-GaIN/LPS group.

to a decrease of antioxidant defense [31]. Propofol has been reported to promote the antioxidant capacity of various antioxidants and alleviates heart, renal and liver ischaemia-reperfusion injury [32–34]. Further investigation disclosed that propofol might exert its antioxidant activity through Nrf2 activation [10]. Besides, propofol could induce the production of antioxidant enzymes in the liver and decrease oxidative stress, thus maintaining oxidative-antioxidative balance in Parkinson's diseases [35]. These results are in agreement with what we showed in our study, indicating that propofol has a potential antioxidant capacity to enhance the resistance to oxidative stress in D-GaIN/LPS-induced liver injury. From the above results, we verified that propofol could inhibit TLR4/NF-κB/NLRP3 inflammasome pathway to alleviate the occurrence and the development of inflammation and oxidative stress, which enhanced the resistance to D-GalN/LPS-induced liver injury.

Additionally, we further investigated the mechanisms underlying propofol-mediated protection against acute liver injury, which might be implicated with its anti-apoptotic properties. As shown in previous studies, propofol could inhibit LPS-mediated cell apoptosis in BEAS-2B cells and attenuate TNF-α-induced cell apoptosis in HT22 cells, thus relieving acute respiratory distress syndrome and cognitive dysfunction, respectively [36,37]. As the apoptosis of hepatocytes was observed in liver injury induced by D-GalN/LPS [18], we next investigated whether propofol could exert its anti-apoptotic ability in liver injury to inhibit the apoptosis of hepatocytes. The results showed that propofol significantly reduced the apoptotic cells in liver tissues according to the TUNEL assay. Bcl-2 family proteins include two different types that modulate apoptosis. Bax and Bad are pro-apoptotic proteins, while Bcl-2 is anti-apoptotic protein. Caspase-3 is regarded as one of the most important downstream effector protease in the classical nuclear changes associated with apoptosis [38]. It is the primary terminal cleavage and will result in hepatocyte apoptosis and eventually cause liver injury [39]. Here, the levels of Bax, Bad, and cleaved caspase-3 were markedly increased, and the level of Bcl-2 was decreased in mice stimulated by D-GalN/LPS. These alterations were attenuated by the treatment of propofol, indicating that propofol significantly decreased the elevated hepatocyte apoptosis induced by D-GalN/LPS.

5. Conclusion

Taken together, the present study reveals protective effects of propofol on the D-GalN/LPS inflicted acute liver injury in mice. It is demonstrated that propofol ameliorated the degree of histological injury, down-regulated the hepatocyte apoptosis, inflammation, and oxidative stress through inhibiting the activity of TLR4/NF-κB/NLRP3 inflammasome pathway. These results provide is a promising drug for the prevention and treatment of liver damage, and propofol is potential to serve as a hepatoprotective agent for the therapy of acute liver injury.

Acknowledgments

Not applicable.

Declaration of Competing Interest

Authors declare that there is no potential interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.105974.

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