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Dexmedetomidine alleviated lipopolysaccharide/D-galactosamine-induced acute liver injury in mice

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ABSTRACT

Dexmedetomidine (DEX), a highly selective α2-adrenergic receptor (α2-AR) agonist, is widely used as sedative in clinical. Its potential anti-inflammatory properties have been found in recent studies. The current study has investigated the profound effects of DEX on acute liver injury in mice. The mice were intraperitoneally injected lipopolysaccharide (LPS) and D-galactosamine (D-Gal) to induce acute liver injury, and vehicle or DEX were treated 30 min before or 2 h after LPS/D-Gal exposure. The results showed that pre-treatment with DEX inhibited the raising of plasma aminotransferases, reduced the damage of liver tissue, and improved the survival rate in mice exposed to LPS/D-Gal. Pre-treatment with DEX also inhibited the release of TNF-α and suppressed the phosphorylation of c-jun-N-terminal kinase (JNK) in mice exposed to LPS/D-Gal. In addition, pre-treatment with DEX down-regulated the expression of cleavage of caspase-3, decreased the activities of caspase-3, caspase-8, caspase-9, and consequently, reduced hepatocyte apoptosis. Interestingly, post-treatment with DEX also resulted in beneficial outcomes. The current study indicates that administration of DEX might provide protective benefits in inflammatory liver disease.

1. Introduction

Acute liver injury, results from infections, autoimmune factors, toxins and drugs, is a serious clinical condition highly associated with hepatic failure and even death [1–3]. Lipopolysaccharide (LPS), also known as endotoxin, locates in the outer membrane of Gram-negative bacteria [4]. LPS is one of the widely distributed toxins that induces strong inflammatory responses and plays crucial roles in the development of acute liver injury [5,6]. LPS selectively induces severe hepatic inflammation and liver injury in D-Galactosamine (D-Gal)-sensitized mice, which has been frequently used in experimental studies for the investigation of pathophysiological mechanisms of acute hepatitis and the development of pharmacological interventions [7–10].

Dexmedetomidine (DEX), a highly selective α2-adrenergic receptor (α2-AR) agonist, has been clinically used in patients with surgery or critical illness due to its anti-anxiety and analgesia effects [11]. Moreover, recent studies have found that treatment with DEX might provide anti-inflammatory benefits under some circumstance. For example, DEX inhibited the production of tumor necrosis factor-α (TNF-α) and interleukin 1β (IL-1β) in microglia exposed to LPS [12]. Besides, DEX reduced the level of TNF-α and monocyte chemotactic protein (MCP)-1 in LPS-challenged mice [13]. In critically ill patients, DEX significantly reduced the release of pro-inflammatory cytokines such as IL-6, IL-1β and TNF-α [14]. The data above indicate that DEX might play a crucial role in inflammatory response as a negative modulator.

In recent animal experiments, DEX has been reported to protect the organs from inflammation injury. It has been reported that treatment with DEX attenuated tissue injury in experimental animals with systemic inflammation induced by lethal dose of LPS or cecal ligation and puncture (CLP) [15,16]. Therefore, we speculated whether DEX could also provide protective effects on the progress of local inflammatory injury in liver. Thus, the purpose of the present study was to explore the potential beneficial effects of DEX on LPS/D-Gal-induced lethal hepatitis.

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2. Materials and methods

2.1. Regents

LPS (from Escherichia coli, 055: B5), D-Gal and DEX were purchased from Sigma (St. Louis, MO, USA). The assay kits for detecting plasma alanine amino transferase (ALT) and aspartate aminotransferase (AST) were the products of Nanjing Jiancheng Bioengineering Institute (Nanjing, China). Mouse TNF-α enzyme- linked immunosorbent assay (ELISA) kit was purchased from NeoBioscience Technology Company (Shenzhen, China). The colorimetric assay kits for detecting the caspase-3, -8, -9 and total protein extract kit were obtained from Beyotime Institute of Biotechnology (Jiangsu, China). The In Situ Cell Death Detection Kit was purchased from Roche (Indianapolis, USA). The rabbit anti-mouse c-jun-N-terminal kinase (JNK), phosphorylated JNK (p-JNK), cleaved caspase-3 and β-actin antibodies were obtained from Cell Signaling Technology (Danvers, MA, United States). The BCA protein assay kit, horseradish peroxidase-conjugated goat anti-rabbit antibody and enhanced chemiluminescence (ECL) reagents were the products of Pierce Biotechnology (Rockford, IL, USA).

2.2. Animals

6–8 weeks old Male BALB/c mice weighing 18–22 g were obtained from the Experimental Animal Center of Chongqing Medical University (Chongqing, China). All mice were reared in a specific pathogen-free facility with a regular 12 h light/dark cycle and free access to standard rodent chow and water ad libitum. All experimental procedures were approved by the University of Chongqing Medical Animal Care and Use Committee.

2.3. Animal model and treatment

The mice were allocated into three sets. In each set, the mice were randomly assigned to one of the five groups: the control (CON) group, the mice received the vehicle (0.9% saline) only; the DEX group, the mice received DEX (200 μg/kg, Sigma, USA); the LPS/D-Gal group, the mice received LPS (10 μg/kg, Sigma, USA) combined with D-Gal (700 mg/kg, Sigma, USA); the DEX pretreated group, the mice treated with DEX (200 μg/kg) 30 min prior to LPS/D-Gal injection; the DEX post-treated group, the mice treated with DEX (200 μg/kg) 2 h after LPS/D-Gal injection. The dose of DEX was chosen based on previous reports and our preliminary experiment [13,17,18]. DEX, LPS and D-Gal were dissolved in 0.9% saline, and they were all injected intraperitoneally.

The first set of mice were randomly allocated into the five groups mentioned above (n = 8). The mice were euthanized at 1.5 h after LPS/D-Gal exposure for collecting the plasma samples to detect the level of TNF-α. The second set of mice were grouped as the first set above (n = 8) but euthanized at 6 h after LPS/D-Gal injection for obtaining the blood samples to detect the level of aminotransferases and harvesting the livers to evaluate the degree of liver damage. The third set of mice (n = 20) were designed to assess the survival rate. The observers recorded the survival of the mice every 6 h for at least three days. The cumulative survival curve was described by the Kaplan-Meier method.

2.4. Histological analysis

Fresh liver tissues were fixed in 4% paraformaldehyde, embedded in paraffin and cut into sections with a thickness of 5 mm. Hematoxylin & eosin were used to stain the sections which were then evaluated with a light microscope (Olympus, Japan). The degree of liver tissue damage was observed in 20 random fields per animal at 400× magnification (n = 4 per group) and assessed using a scoring method by a blinded pathologist. The detailed scoring standards were as follows: grade 0, no obvious injury observed; grade 1: mild injury including focal nuclear pyknosis and cytoplasmic vacuolation; grade 2: moderate to severe injury showing extensive nuclear pyknosis, cytoplasmic hypereosinophilia, and ambiguous boundary between cells, and grade 3: severe necrosis with hepatocyte disintegration, congestion, and neutrophil infiltration.

2.5. Detection of liver enzymes

The ALT and AST assay kits were used to determine the levels of ALT and AST. Briefly, added the plasma samples and the matrix fluid (ALT or AST) to the 96-well plates which were then incubated in the water bath at temperature of 37 °C for 30 min. Then, added 2-4-dinitrophenylhydrazine to the same plates which incubated again at the same temperature above for another 20 min. The last step was to add NaOH solution, and 5 min later the results were read at 490 nm.

2.6. Detection of TNF-α

ELISA kits (NeoBioscience) were used to detect the concentration of plasma TNF-α according to the instructions. In brief, Plasma samples (100 μL) were added to the plate containing specific antibody and incubated in the water bath at 37 °C for 90 min. Then, the wash buffer was added and the plate was washed five times. In the next step, the detection antibody solution was added and the plate was incubated at 37 °C for 60 min. The plate was washed five times and the working solution containing enzyme was subsequently added to the plate and then incubated at 37 °C for 30 min. After washing as above, added the TMB substrate solution and incubated protected from light for 15 min. At last, added the stop solution to end the reaction and the result were read at 450 nm.

2.7. Detection of caspase activities

The colorimetric assay kits (Beyotime) were used to detect the activities of caspase-3, -8 and -9 in liver samples following to the manufacturer's protocols. In brief, the liver homogenate was centrifuged at 4 °C for 15 min at 25,000*g*. Then transferred the supernatant to a new tube, and the protein concentrations were detected using the Bradford Protein Assay Kit (Beyotime). Then, added the reaction buffer to each sample, and the supernatants were respectively incubated with 10 μL chromogenic substrates (Ac-DEVD-ρNA, Ac-IETD-ρNA and Ac-LEHD-ρNA) for caspase-3, -8 and -9 for 90 min at 37 °C. The activities of caspases were read at 405 nm.

2.8. Terminal deoxynucleotidyl transferase-mediated nucleotide nick-end labeling (TUNEL) assay

In Situ Cell Death Detection Kit (Roche) was used to perform the TUNEL assay under the manufacturer's protocols. First, paraffin-embedded liver tissue sections were processed with deparaffinization and rehydration, the sections were in the process of 10 μg/mL protease K for 30 min. Then added the TUNEL reaction mixture on the samples and incubated at 37 °C in dark for 60 min. Subsequently, converter-POD was added to cover each sample for 30 min. Then, the samples were counterstained with hematoxylin slightly. At last, the sections were evaluated and the positive cells in 10 randomly selected field per animal (200×, n = 4 per group) were counted with a light microscope (Olympus, Japan).

2.9. Western blot (WB) analysis

The liver tissue was homogenized on ice and centrifuged at 14,000*g* at 4 °C for 15 min. Then collected the supernatant and BCA protein assay kit was used to determine the total protein concentration. Liver proteins (40 μg) were separated on 12% SDS-PAGE polyacrylamide

gels, and then electro-transferred to nitrocellulose membrane. Next, put the membranes into blocking solution (5% defatted milk powder dissolved in Tween-Tris-buffered saline) incubating at room temperature for 2 h to block the non-specific protein. Then the membranes were incubated with the primary antibody at 4 °C overnight. Next day, membranes were taken to the room temperature for 30 min, then washed three times (15 min each time) with Tween-Tris buffered saline buffer before added the secondary antibody intubating at room temperature for 2 h. At last, ECL chemiluminescence system was used to visualize the antibody binding.

2.10. Statistical analysis

All data recorded were presented as means ± SD. One-way ANOVA with the Tukey's post hoc test was used to compare differences between groups. The Kaplan-Meier curve and log-rank test were used to analysis the survival statistics. A p value < 0.05 was decided statistical significance.

3. Results

3.1. DEX pretreated alleviated LPS/D-Gal-induced acute liver injury

The level of plasma ALT and AST elevated after LPS/D-Gal exposure, which were significantly suppressed in mice pre-treated with DEX (Fig. 1A and B). Correspondingly, LPS/D-Gal-induced liver congestion and destruction of liver structure were ameliorated by the pretreatment with DEX (Fig. 2A and B). In addition, the survival rate of the mice from DEX pretreated group was significantly higher than that of LPS/D-Gal-exposed mice (Fig. 3). These results indicated that DEX pretreatment attenuated the LPS/D-Gal-induced acute liver injury.

3.2. DEX pretreated inhibited LPS/D-Gal-induced elevation of TNF-α and phosphorylation of JNK

TNF-α is an important pro-inflammatory cytokine took part in the progression of liver injury induced by LPS/D-Gal [19,20]. As shown in Fig. 4, DEX pretreatment suppressed the plasma levels of TNF-α induced by LPS/D-Gal. In addition, WB analysis implied that DEX pretreatment suppressed the level of phosphorylated JNK induced by LPS/D-Gal (Fig. 5A and B). All these results indicated that DEX pretreatment could inhibit the production of TNF-α induced by LPS/D-Gal and suppress the related pro-apoptotic signal.

3.3. DEX pretreated alleviated LPS/D-Gal-induced hepatocyte apoptosis

As shown in Fig. 6, pretreatment with DEX significantly decreased the level of cleaved caspase-3 (which is considered a reliable marker for cells that are dying, or have died by apoptosis [21].) in LPS/D-Gal-exposed mice. In addition, DEX pretreatment suppressed the activities of caspase-3, -8 and -9 upregulated by LPS/D-Gal (Fig. 7A–C). Consistently, the TUNEL assay suggested that DEX pretreatment decreased the number of positive cells in LPS/D-Gal-exposed mice (Fig. 8). These results showed that DEX pretreatment could suppress LPS/D-Gal-induced hepatocyte apoptosis.

3.4. The protective effect of DEX posttreatment on LPS/D-Gal-induced acute liver injury

Similarly, DEX post-treatment also inhibited the elevation of ALT (Fig. 9A), improved the survival rate (Fig. 9B), alleviated hepatic histological changes (Fig. 9C and D), and suppressed the activities of caspase-3 (Fig. 9E). These results showed that DEX may have therapeutic benefits in LPS/D-Gal-induced liver injury.

4. Discussion

DEX has been widely used as a sedative during surgery or in the ICU [22]. Interestingly, recent studies have also found that DEX might have anti-inflammatory properties both in vitro and in vivo [12–15,23–25]. In the current study, we investigated the effect of DEX on inflammatory responses and mortality in LPS/D-Gal-induced acute liver injury. It was found that DEX suppressed the elevation of plasma ALT and AST, ameliorated destruction of liver structure, reduced the death of hepatocyte, and improved the survival rate of the LPS/D-Gal-exposed mice. All these results suggested that DEX might have potential protective effects in LPS/D-Gal-induced acute liver injury.

When stimulated by LPS combined with D-Gal, the inflammatory cells were activated and the inflammatory factors were produced, which considered to be the early reactions in vivo [19,26]. TNF-α, a representative inflammatory cytokine [27], plays a significant role in the development of LPS/D-Gal-induced liver injury. In the current study, we found that LPS/D-Gal-induced production of TNF-α was suppressed by the pretreatment with DEX. Consistent with our results, Tanikuchi [24] also found that DEX could lower the elevated concentration of TNF-α and IL-6 stimulated by LPS. DEX also inhibited the elevation of proinflammatory cytokines, which are a part of the innate immune response in sepsis patients [25]. Taken together, the anti-

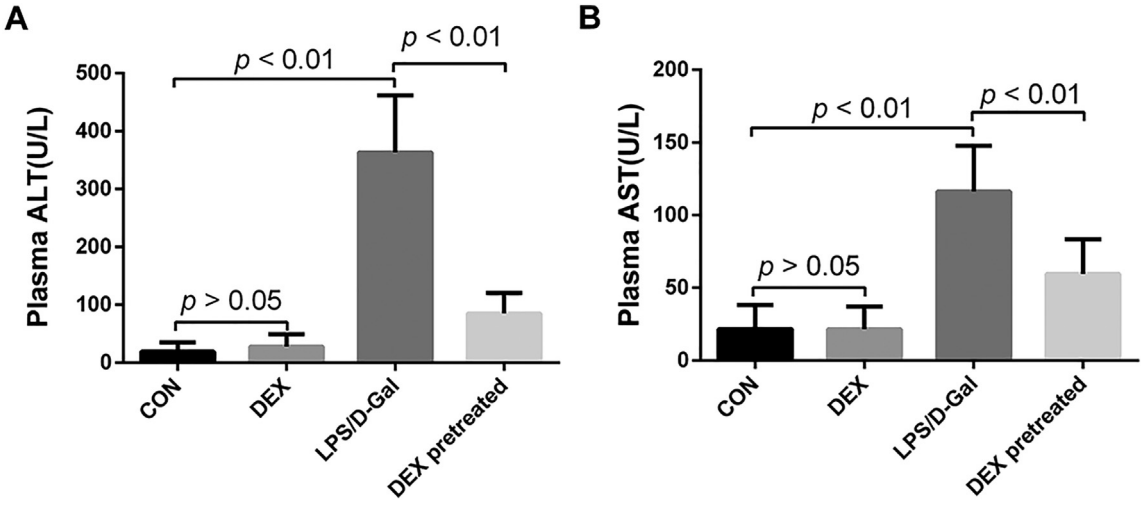

Fig. 1. Pretreatment with DEX inhibited LPS/D-Gal-induced elevation of ALT and AST. The levels of (A) ALT and (B) AST in plasma were detected and compared. Data were presented as the means ± SD (n = 8 per group).

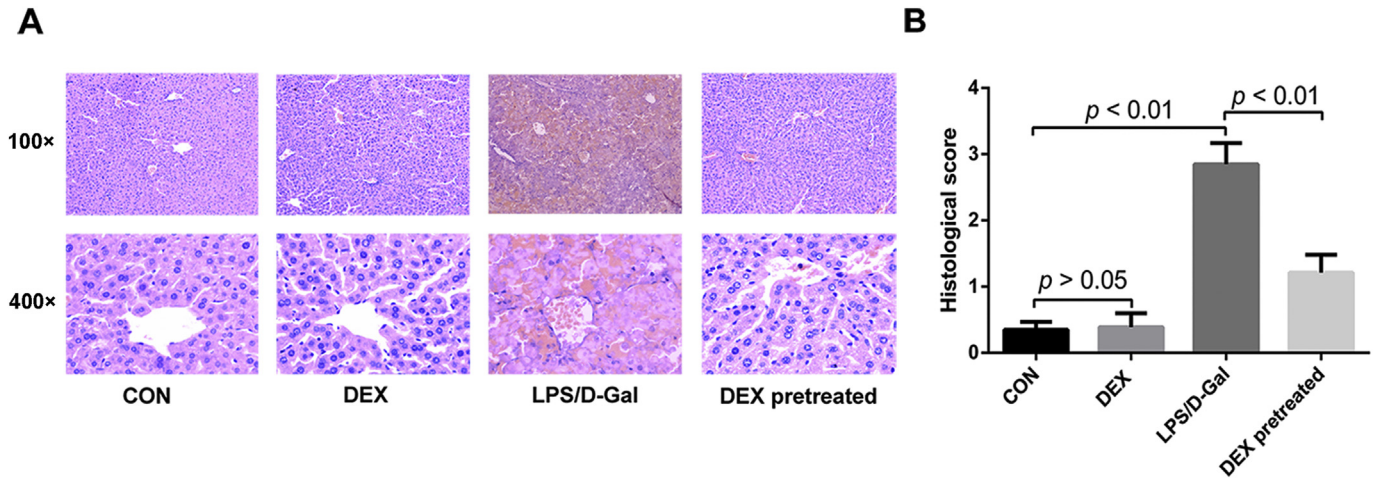

Fig. 2. Pretreatment with DEX alleviated histological liver abnormalities in LPS/D-Gal-challenged mice. (A) Liver sections were stained with hematoxylin/eosin for morphological assessment. (Original magnification: 100× and 400×). (B) The degree of liver tissue damage was observed in 20 random fields per animal at 400 × magnification (n = 4 per group) and assessed using the scoring standard. Data were expressed as the means ± SD, n = 4.

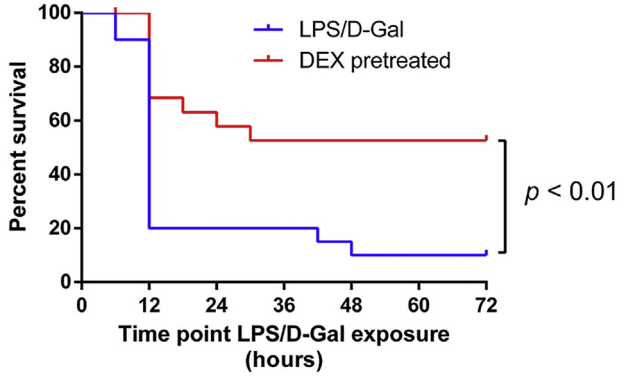

Fig. 3. Pretreatment with DEX improved the survival rate of LPS/D-Gal exposed mice. The survival of the mice in four groups was monitored every 6 h for at least 7 days, and the cumulative survival curve was presented as a Kaplan-Meier survival curves. The survival curve in group CON and group DEX were not shown for no death.

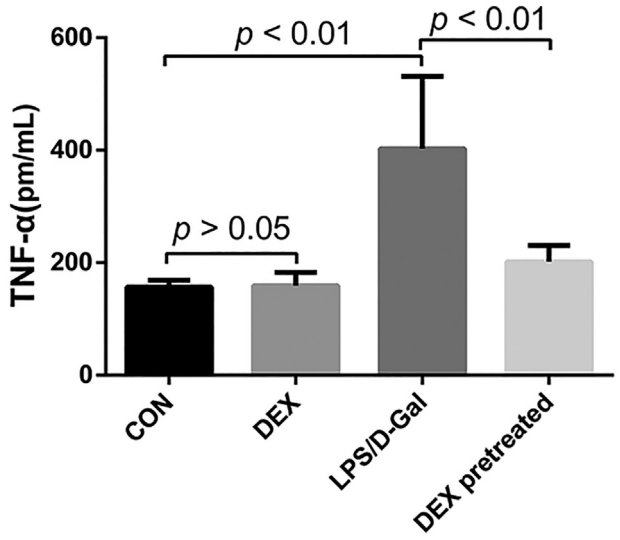

Fig. 4. Pretreatment with DEX suppressed production of TNF-α in LPS/D-Gal-exposure mice. The concentration of TNF-α in the plasma were detected by ELISA. Results were presented as the means ± SD.

inflammatory properties of DEX might be at least partially contributing to its beneficial effects on LPS/D-Gal-induced acute liver injury.

TNF-α is one of the major detrimental factors that involved in the development of acute liver injury induced by LPS/D-Gal as well as other etiology [28,29]. In addition to its pro-inflammatory effects, TNF-α also has strong pro-apoptotic activities [30–32]. The mitogen-activated protein kinase (MAPK) is one the major pathway down streaming TNF-α and the members of MAPK family have profound regulatory roles in the induction of apoptosis [33]. In general, ERK functions as a pro-survival factor, whereas JNK and p38 enhance apoptosis [33,34]. And a recent study found that JNK, but not p38, plays vital roles in signaling LPS/D-Gal-induced apoptosis [35]. In the present study, LPS/D-Gal-induced phosphorylation of JNK was suppressed by DEX, suggesting that the JNK-mediated pro-apoptotic signaling was inhibited.

TNF-α signaling finally leads to the cleavage and activation of caspase cascade, the principal mediators of the apoptotic cell death [36,37]. In the current study, pretreatment with DEX suppressed the elevation of cleaved caspase-3, inhibited the activities of caspase-3, -8, -9, reduced the count of TUNEL-positive cells, indicating that DEX protected hepatocytes from LPS/D-Gal-induced apoptosis. In agreement with our findings, several researches have shown that DEX attenuated anesthetics-induced neuroapoptosis [38–40]. It has also been reported that DEX lighten the apoptosis of lung induced by intestinal ischemia reperfusion [41]. In addition, DEX could attenuate apoptosis induced by high glucose in human retinal epithelial cells [42]. Therefore, the attenuated hepatocytes apoptosis might be a crucial event associated with the alleviated liver injury treated with DEX.

It has been well-documented that JNK plays crucial roles in mediating the pro-apoptotic activities of TNF-α. The activation of JNK is usually associated with the cleavage of caspase cascade and the activation of apoptosis program in hepatocytes [43,44]. In addition, several studies with genetic or pharmacological approaches have confirmed that JNK is a pivotal regulator controlling the fate of hepatocytes in LPS/D-Gal-exposed mice [45,46]. A recent study showed that dexmedetomidine attenuated dendritic cell apoptosis by inhibiting the activation of JNK [47]. In the current study, LPS/D-Gal-induced phosphorylation of JNK was suppressed by DEX. Therefore, DEX may reduce hepatocyte apoptosis by inhibiting JNK-mediated pro-apoptotic signaling.

In clinical patients, dexmedetomidine is usually administered via continuous intravenous drip. However, a single intraperitoneal injection of DEX might be a common and convenient approach in experimental studies [48]. In addition, it seems impractical that administer a pharmacological reagent before the exposure to the injurious factors

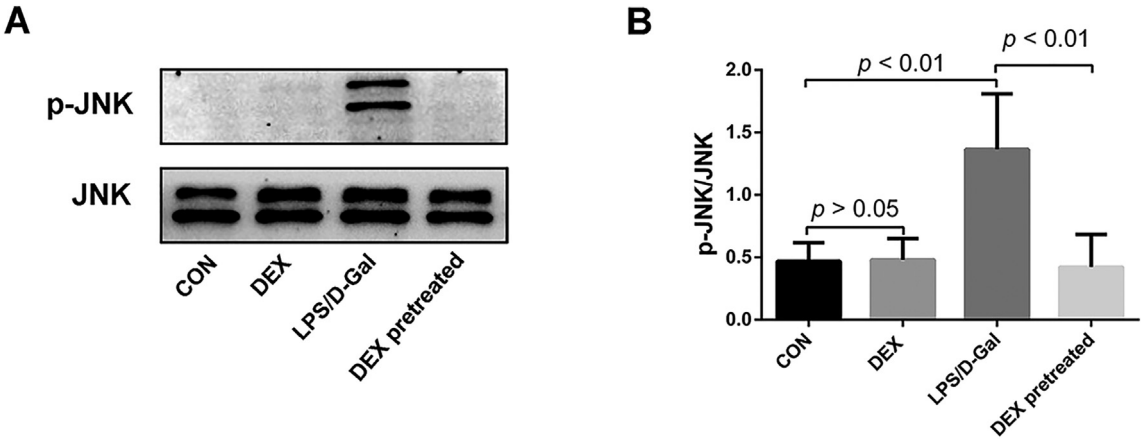

Fig. 5. Pretreatment with DEX decreased the level of phosphorylated JNK. The level of phosphorylated JNK (p-JNK) and total JNK (JNK) in liver tissues were detected by immunoblot analysis. (A) The blots were scanned by densitometry, and (B) data are depicted as relative intensity units. Data were expressed as the means ± SD, n = 4.

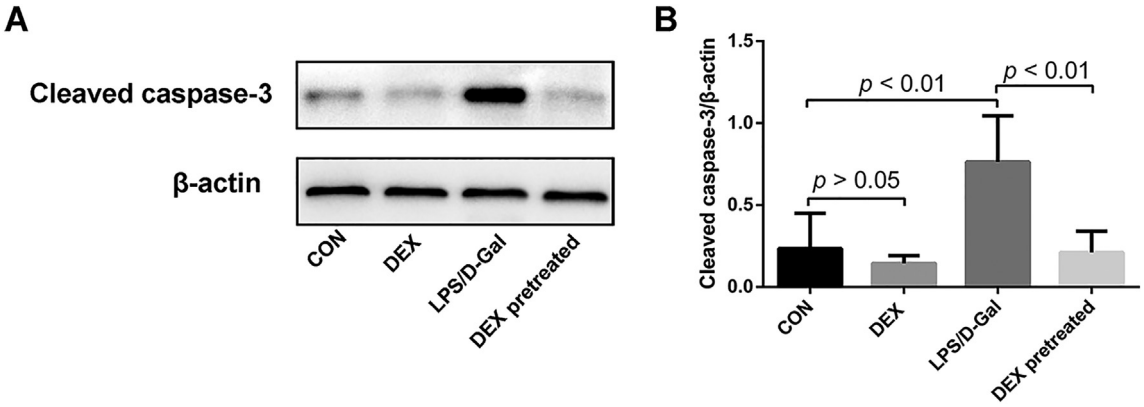

Fig. 6. Pretreatment with DEX suppressed the up-regulation of cleaved caspase-3 induced by LPS/D-Gal. (A) The levels of cleaved caspase-3 in the liver were determined by immunoblot analysis. The bands of cleaved caspase-3 and β-actin are indicated by arrows. (B) The blots were scanned by densitometry and data are presented as relative intensity units. Data were expressed as the means ± SD, n = 4.

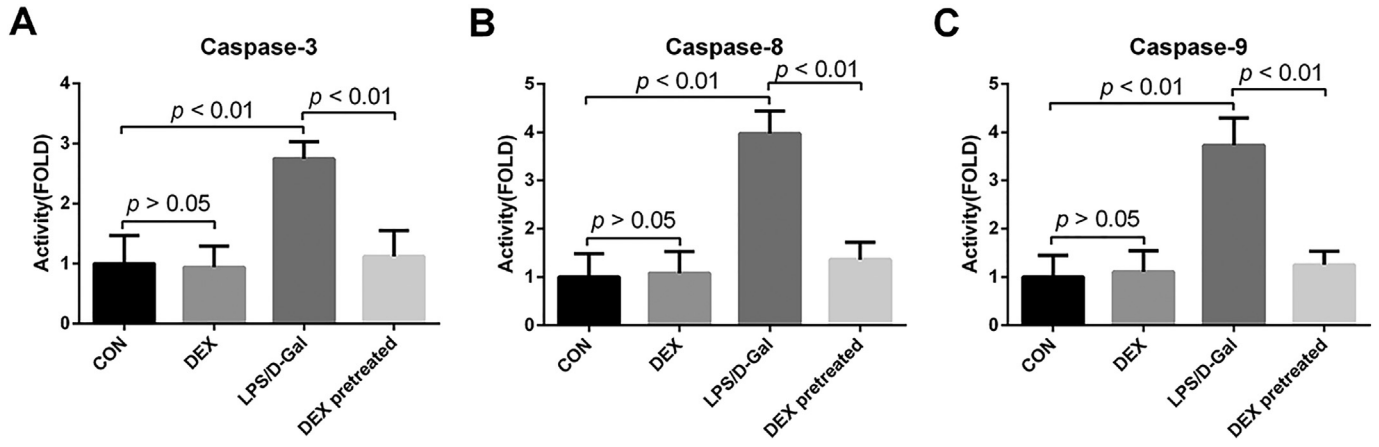

Fig. 7. Pretreatment with DEX inhibited LPS/D-Gal-induced activation of caspases. Hepatic caspase-3 (A), caspase-8 (B) and caspase-9 (C) activities were determined. Data are expressed as the means ± SD.

under most clinical situations. Most interestingly, the present study also found that post-treatment with DEX (when TNF-α has already produced to its peak level) inhibited the raising of ALT, reduced the damage of liver tissue, improved the survival rate. These data implied that post-treatment with DEX might mainly work on the downstream of TNF-α signaling pathway, which implies the promising potential of DEX in clinical therapy.

In conclusion, the current study found that DEX could provide protective effects on LPS/Dal-induced liver injury. These effects were related to the suppression of TNF-α production and the inhibition of JNK activation. In addition to TNF-α-induced apoptosis, the excessive production of harmful inflammatory mediators, such as matrix metalloproteinases, and the uncontrolled formation of neutrophil extracellular traps are also critical factors involved in the development of

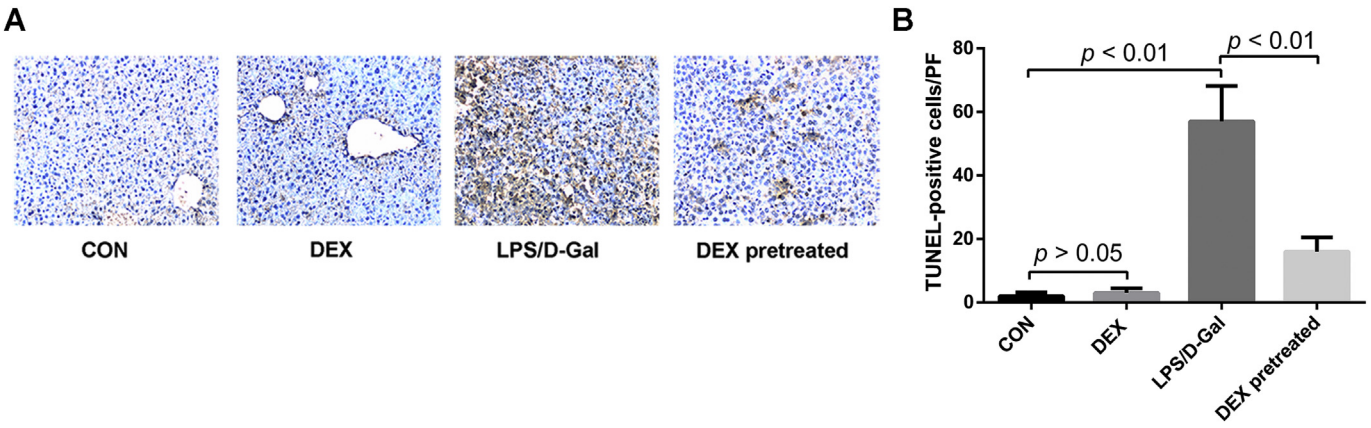

Fig. 8. Pretreatment with DEX suppressed hepatocyte apoptosis in LPS/D-Gal exposed mice. The apoptotic cells were determined by a TUNEL assay, and the TUNEL-positive cells showed a dark-brown nucleus. (A) Representative liver sections of each group are shown (original magnification 200 ×). (B) The positive cells in 10 randomly selected field per animal were counted with a light microscope. Data were expressed as the means ± SD. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

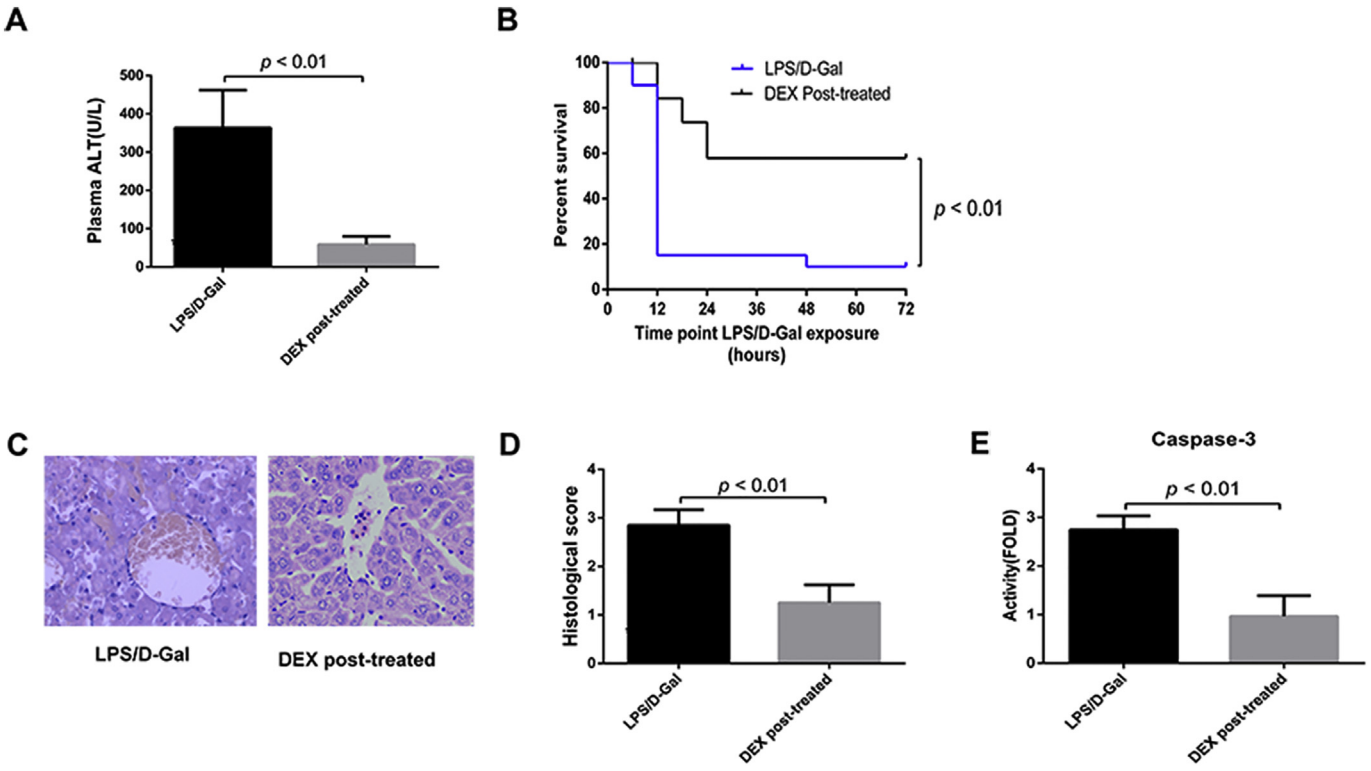

Fig. 9. Posttreatment with DEX alleviated LPS/D-Gal-induced acute liver injury. The levels of (A) ALT in plasma was detected and compared. (B) The survival of the mice in two groups were monitored every 6 h for at least 7 days, and the cumulative survival curve was presented as a Kaplan-Meier survival curves. (C) Liver sections were stained with hematoxylin/eosin for morphological assessment. (Original magnification: 400×). (D) The degree of liver tissue damage was observed in 20 random fields per animal at 400 × magnification (n = 4 per group) and assessed using the scoring standard. (E) Hepatic caspase-3 activity was determined and compared. Data were expressed as the means ± SD, n = 4.

liver injury [49,50], the potential effects of DEX on these detrimental events remain to be further investigated. Taken together, although the detailed mechanisms underlying the hepatoprotective effects of DEX remains to be studied, the current study implies that DEX may have potential value for pharmacological interventions in inflammatory liver injury.

Disclosure of interest

The authors declare that there are not any conflicts of interest concerning this article.

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