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Effects of dexmedetomidine on sepsis-induced liver injury in rats

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Abstract. – OBJECTIVE: To explore the effect of dexmedetomidine (DEX) on sepsis-induced liver injury in rats and the mechanism of action, providing certain references for the prevention and treatment of sepsis-induced liver injury in clinical practice.

MATERIALS AND METHODS: A total of 60 male Sprague Dawley (SD) rats were randomly divided into 3 groups, namely sham operation group (Sham group, n=20), sepsis-induced liver injury group [lipopolysaccharides (LPS) group, n=20], and sepsis-induced liver injury + DEX group (LPS + DEX group, n=20) using a random number table. Rat models of sepsis-induced liver injury were established by intraperitoneal injection of LPS (10 mg/kg), and at the same time, DEX was intragastrically injected at a dose of 50 μg/kg. After 24 h, the survival analysis curves of each group of rats were plotted. Meanwhile, the levels of liver function indexes and oxidative stress markers were measured at 12 h in each group of rats. Hematoxylin-eosin (H&E) staining assay was carried out to detect the morphological changes of rat liver cells in each group. Terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-biotin nick end-labeling (TUNEL) staining assay was performed to detect the apoptosis level in rat liver tissues in each group. In addition, the expression level of Caspase 3 in three groups of rats was measured through immunohistochemical staining assay. Lastly, the effect of DEX on the protein expression of extracellular signal-regulated kinases 1/2 (ERK1/2) in liver tissues was detected via Western blotting.

RESULTS: DEX significantly improved liver dysfunction induced by LPS and raised the 24 h-survival rates of rats ($p<0.05$). Besides, H&E staining results showed that DEX clearly relieved the pathological damage of rat liver cells caused by LPS. In comparison with LPS group, LPS + DEX group displayed more neatly arranged liver cells, less degradation and necrosis, and evidently attenuated cellular edema. Immunohistochemistry results revealed that DEX significantly reversed the increase in Caspase 3 expression resulting from LPS. The results of the TUNEL staining assay showed that DEX clearly inhibited the apoptosis of rat liver cells induced by LPS. The results of Western blotting revealed that DEX notably reversed the decrease of phosphorylated ERK1/2 (p-ERK1/2) in rat liver tissues compared with LPS group.

CONCLUSIONS: DEX is able to markedly relieve LPS-induced liver injury in rats and the underlying mechanism may be related to the activation of the ERK1/2 signaling pathway.

Key Words:
Dexmedetomidine, Sepsis, Liver injury, ERK1/2.

Introduction

Lipopolysaccharides (LPS)-related liver injury is a leading cause of illness and death of patients with sepsis and other systemic and liver diseases[1,2]. Clinical studies[3,4] have revealed that the incidence rate of sepsis in acute or chronic hepatitis, hepatic fibrosis/cirrhosis, and hepatocellular carcinoma is as high as 75-95%. LPS is able to induce inflammation of the liver by activating hepatic macrophages (called Kupffer cells) and triggering inflammatory responses in the liver, eventually leading to liver failure[5,6].

Extracellular signal-regulated kinase-1/2 (ERK1/2), widely expressed in various cells such as cardiomyocytes, neurons, and hepatocytes, is directly activated by the phosphorylation of mitogen-activated protein kinase (MAPK) to promote

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the differentiation, pro-survival, and survival of cells[7]. Its activation or expression is promoted by multiple factors including various exogenous factors (such as curcumin and Asiatic acid) and endogenous factors (for example, lncRNA UCA1, lncRNA Gm2199, insulin, and adiponectin), thereby facilitating the proliferation of cells[8,9]. Besides, it is proved that after liver injury and hepatectomy, the activation of ERK1/2 in hepatocytes increases the proliferation and represses the apoptosis of hepatocytes[10]. Therefore, promoting the activation and expression of ERK1/2 in liver tissues is an effective way to ameliorate the sepsis-induced liver injury.

Dexmedetomidine (DEX) is an effective adrenergic receptor agonist, whose affinity for adrenergic receptors is 8 times that of quinindium (QND). It is predictable that DEX lowers hemodynamics (dose-related arterial blood pressure and heart rate decreases) and plasma catecholamine in postoperative patients[11,12]. The pharmacological roles of DEX in various diseases have been gradually revealed in recent years. However, currently there is no report on the effect of DEX on sepsis-induced liver injury. Therefore, the role and mechanism of DEX in the occurrence and development of sepsis-induced liver injury were observed and explored by establishing rat models of sepsis-induced liver injury using LPS plus DEX intervention.

Materials and Methods

Grouping and Treatment of Experimental Animals

A total of 60 male Sprague Dawley (SD) rats weighing (285.61 ± 10.66) g and aged 12-14 weeks old were divided into three groups, namely sham operation group (Sham group, n=20), sepsis-induced liver injury group (LPS group, n=20), and sepsis-induced liver injury + DEX group (LPS + DEX, n=20) using a random number table. This research was approved by the Animal Ethics Committee of Jining Medical University. No statistically significant differences were found in basic data such as age and body weight among the three groups of rats. Rats in LPS + DEX group were intragastrically injected with DEX at a dose of 50 μg/kg. After 3 days, rats in each group were intraperitoneally injected with LPS at a dose of 10 mg/kg. After 12 h, rats were sacrificed and the liver was taken out and stored at –80°C for later use.

Terminal Deoxynucleotidyl Transferase-Mediated Deoxyuridine Triphosphate-Biotin Nick End Labeling (TUNEL) Staining Assay

Liver tissue sections cut were baked in an oven at 60°C for 30 min, deparaffinized with xylene (5 min/3 times), and dehydrated with 100%, 95% and 70% ethanol each for 3 times. Then, the sections were incubated with protein kinase K for 0.5 h, rinsed with phosphate-buffered saline (PBS), and reacted with terminal deoxynucleotidyl transferase and luciferase-labeled deoxyuridine triphosphate at 37°C for 1 h. Thereafter, horseradish peroxidase (HRP)-labeled specific antibody was added and incubated an incubator at 37°C for 1 h. After that, diaminobenzidine (DAB) was added as a substrate and reacted at room temperature for 10 min. Lastly, cell nuclei were stained with hematoxylin, photographed using a light microscope, and counted.

Western Blotting

Rat liver tissues from each group were thoroughly grounded in lysis buffer, followed by ultrasonic lysis. Next, the lysis solution was centrifuged and the supernatant was sucked off and dispensed into Eppendorf (EP) tubes. Thereafter, protein concentration was measured by bicinchoninic acid (BCA; Beyotime, Shanghai, China) method and ultraviolet spectrometry, while the proteins of all samples were adjusted to an equal concentration, dispensed, and stored in a refrigerator at –80°C. Subsequently, the total proteins were extracted for dodecyl sulfate, sodium salt-polyacrylamide gel electrophoresis (SDS-PAGE). After that, the proteins in the gel were transferred onto a cellulose acetate polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA) and incubated with primary antibody at 4°C overnight, and then, goat anti-rabbit secondary antibody in a dark place for 1 h. Protein bands were scanned and quantified using an Odyssey membrane scanner and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used to correct the level of protein to be tested.

Hematoxylin-Eosin (H&E) Staining Assay

The liver obtained from each group was placed in 10% formalin overnight, dehydrated, and embedded in paraffin blocks. Next, all liver tissues were sectioned into thin pieces (5 μm in thickness), fixed on a glass slide, dried, and stained. According to the instructions, the sections were soaked in xylene, gradient concentrations of eth-

anol and hematoxylin, respectively, followed by mounting with resin. After that, they were dried, observed, and photographed using the light microscope. Lastly, the morphology of hepatocytes and stroma was observed.

Immunohistochemical Staining Assay

After being baked in the oven at 60°C for 30 min, the cut liver tissue sections were deparaffinized with xylene (5 min/3 times), and dehydrated with 100%, 95%, and 70% ethanol each for 3 times. Next, the sections were added with 3% methanol peroxide to inhibit endogenous peroxidase activity and blocked with goat serum for 1 h. Thereafter, they were incubated with Caspase 3 antibody [diluted at 1:200, Abcam, Cambridge, MA, USA (PBS)] at 4°C overnight, and washed with PBS on a shaker for 4 times, followed by addition of secondary antibody. After that, diaminobenzidine was added for color development. Thereafter, 6 samples were randomly selected from each group and 5 fields of view were randomly selected from each selected sample for photographing using the light microscope (200´ and 400´).

Detection of Oxidative Stress Marker Molecules

To evaluate the level of oxidative stress in three groups of liver tissues, the activity of superoxide dismutase (SOD) and malondialdehyde (MDA) was examined using an oxidative stress-related kit (Beyotime, Shanghai, China) according to standard operating procedures on the official website.

Analysis of Liver Function

At 12 h, peripheral blood was collected from each group of rats and added with citrate for anticoagulation. Blood samples were centrifuged at 3,000 rpm for 15 min to obtain the serum. Lastly, an automatic analyzer was employed to measure the alanine aminotransferase (ALT) level (Beyotime, Shanghai, China).

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Armonk, NY, USA) software was used to analyze all data. Measurement data were expressed as mean ± standard deviation and the *t*-test was applied for data comparison between two groups. $p<0.05$ suggested that the difference was statistically significant.

Results

Effect of DEX on the Survival Rate of Rats in Each Group

The survival rate of rats within 24 h was first examined in each group. It was found that the 24 h-survival rate in LPS + DEX group was evidently higher than that in LPS group ($p<0.05$) (Figure 1), indicating that DEX is capable of significantly improving the survival rate of septic rats.

Influence of DEX on Liver Function in Each Group of Rats

The fully automatic blood biochemical analyzer was utilized to evaluate liver function after 12 h of LPS stimulation in each group of rats. Results (Figure 2) showed that the ALT content in rat peripheral blood was significantly higher in LPS group than that in LPA + DEX group ($p<0.05$), suggesting that DEX can effectively improve liver function in rats.

Role of DEX in Pathological Liver Injury in Septic Rats

The pathological changes in liver tissues of each group of rats were assessed *via* H&E staining assay. It was discovered that in comparison with Sham group, LPS group exhibited a significant hepatocyte apoptosis and necrosis, nucleus pyknosis, hepatocyte edema, and ballooning degeneration in rat liver tissues, while the above pathological injuries were clearly alleviated in liver tissues of rats in LPS + DEX group (Figure 3).

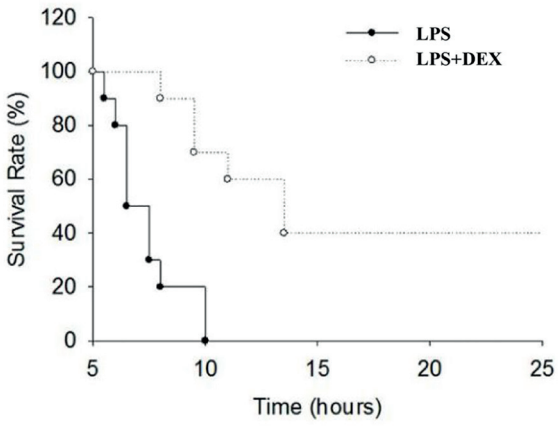

Figure 1. Effect of DEX on the survival rate of rats in LPS group and LPS + DEX group

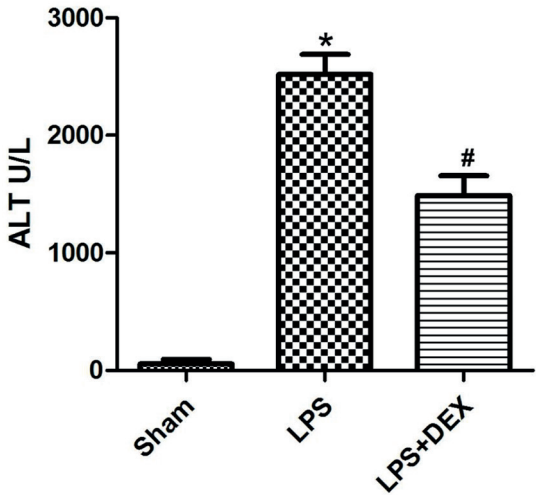

Figure 2. Influence of DEX on rat liver function in Sham group, LPS group and LPS + DEX group**.** *: There is a statistically significant difference (p<0.05) *vs.* Sham group, #: There is a statistically significant difference (p<0.05) *vs.* LPS group.

Levels of Oxidative Stress Markers in Rat Liver Tissues in Each Group

The levels of oxidative stress markers pro-oxidation proteins myeloperoxidase (MPO) and malondialdehyde (MDA), and the antioxidant protein glutathione peroxidase (GSH-Px) were measured in fresh liver tissues in each group of rats using the oxidative stress kit. Results (Figure 4) revealed that compared with those in LPS group, the content and activity of MPO and MDA in LPS + DEX group were overtly decreased, while the activity of GSH-Px was significantly increased (p<0.05), implying that DEX exerts a certain antioxidant effect on the liver.

Results of TUNEL Staining of Rat Liver Tissues in Each Group

To explore the effect of DEX on the apoptosis of rat liver tissues, the TUNEL staining assay was conducted to evaluate the apoptosis level in rat liver tissues in each group. It was found that the apoptosis level in rat liver tissues was (1.23±0.22), (15.39±1.02), and (7.09±0.92) in the three groups, showing a statistically significant difference (p<0.05) (Figure 5).

Expression of Caspase 3 in Liver Tissues in Each Group of Rats

The immunostaining technique was also used to measure the expression level of Caspase 3 in each group of rat liver tissues. The results showed that compared with that in Sham group, the expression level of Caspase 3 in rat liver tissues was notably elevated in LPS group (p<0.05), but evidently declined in LPS + DEX group (p<0.05) (Figure 6).

Impact of DEX on the ERK1/2 MAPK Signaling Pathway

The effect of DEX pretreatment on the expression of the ERK1/2/MAPK signaling pathway-related proteins in liver tissues of rats with sepsis-induced liver injury was determined *via* Western blotting. It was found that (Figure 7) the level of phosphorylated ERK1/2 (p-ERK1/2) in rat liver tissues in LPS group was remarkably lower than that in Sham group, while after intervention with DEX, the inhibition of p-ERK1/2 in liver tissues of rats with the sepsis-induced liver injury was clearly reversed (p<0.05).

Discussion

Sepsis is a highly fatal disease, but now, there are no effective treatments[13]. The latest definition of sepsis in February 2016 i.e., a life-threatening organ dysfunction (OD) caused by the dysregulation of the body in response to infection, emphasizes that OD is a vital risk factor for poor prognosis of sepsis and that OD should be treated in time before infection control[14]. The liver is one of the organs most vulnerable to sepsis. Previous studies[15] have manifested that about 40% patients with

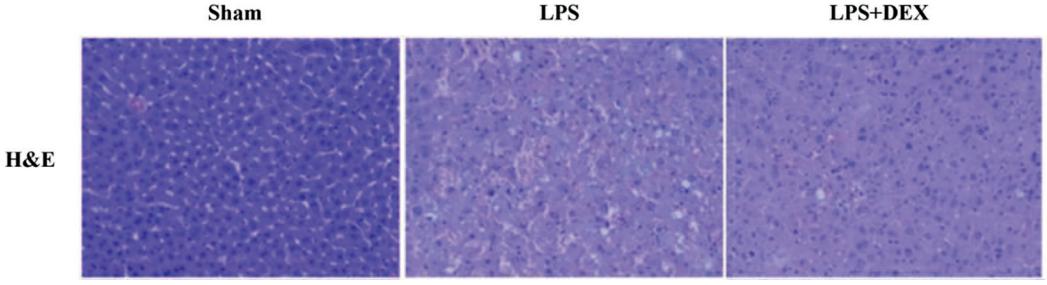

Figure 3. Role of DEX in pathological liver injury in septic rats in Sham group, LPS group and LPS + DEX group (magnification: 100×**)**.

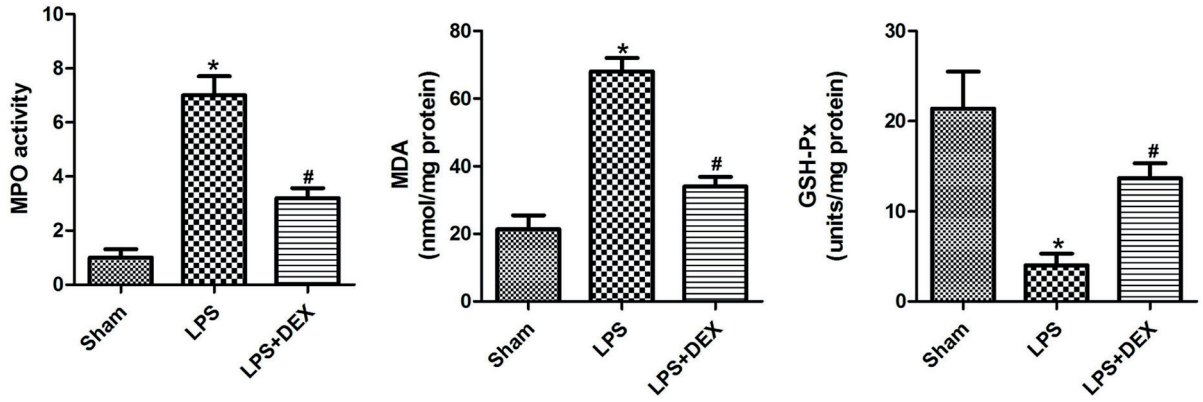

Figure 4. Levels of oxidative stress markers in rat liver tissues in Sham group, LPS group and LPS + DEX group. *: There is a statistically significant difference (p<0.05) *vs.* Sham group, #: There is a statistically significant difference (p<0.05) *vs.* LPS group.

severe sepsis suffer liver injury and the recovery of liver function is considered to be a critical factor for patient survival. The current research[16] has revealed that the pathogenesis of sepsis-induced liver injury mainly includes: 1) microcirculation and microvascular abnormalities, 2) autonomic dysfunction, 3) metabolic abnormality, 4) mitochondrial dysfunction, 5) cell death, and 6) inflammatory cell and factor activation.

Apoptosis (also known as programmed cell death) refers to the programmed death of cells controlled by genes to maintain homeostasis under physiological or pathological conditions[17]. Apoptosis of hepatocytes is a major pathophysiological change in early acute liver injury. Considering the rapid progression and variable course of acute liver injury, establishing a therapeutic window is necessary to improve the prognosis in patients with acute liver injury[18,19]. Research has also found that targeting hepatocyte apoptosis can effectively relieve sepsis-induced liver dysfunction. For instance, baicalein suppresses the NF-κB signaling pathway and apoptosis to ameliorate LPS-induced acute liver failure in mice[20]. Moreover, Paeonol exerts anti-oxidant, anti-inflammatory, and anti-apoptotic effects on LPS-induced acute liver failure in mice[21]. Furthermore, hepatocyte apoptosis is caused by various stimulating factors including increased oxidative stress and activated inflammation. These factors interact with each other during the occurrence of acute liver injury, ultimately accelerating the progression of the disease. Studies have revealed that the continuous inhibition of the ERK1/2/MAPK signaling pathway is one of the main mechanisms leading to hepatocyte apoptosis in rats with sepsis-induced liver injury. Besides, one work[22] showed that the ERK1/2/MAPK signaling pathway is repressed before hepatocyte apoptosis. Therefore, activating the ERK1/2 signaling pathway is an important mean for the treatment of the sepsis-induced liver injury.

In recent years, several pharmacological effects of DEX, a common sedative used in ICU

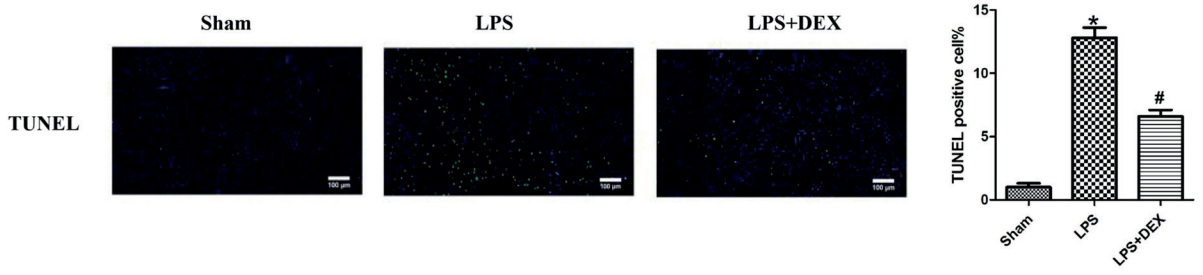

Figure 5. Apoptosis level in rat liver tissues in Sham group, LPS group and LPS + DEX group. *: There is a statistically significant difference (p<0.05) *vs.* Sham group, #: There is a statistically significant difference (p<0.05) *vs.* LPS group (magnification: 100×).

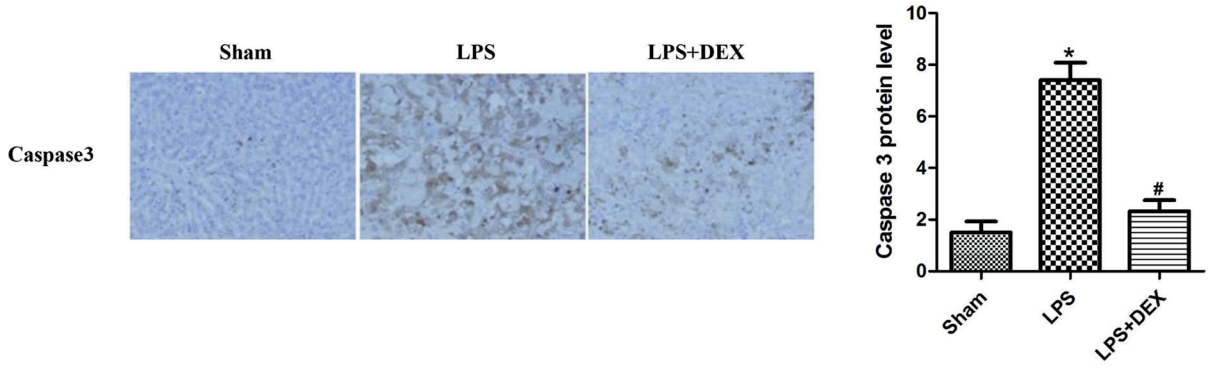

Figure 6. Expression level of Caspase 3 in rat liver tissues in Sham group, LPS group and LPS + DEX group. *: There is a statistically significant difference ($p<0.05$) *vs.* Sham group, #: There is a statistically significant difference ($p<0.05$) *vs.* LPS group (magnification: 100×).

in clinical practice, have been revealed. For example, DEX effectively decreases the inflammatory response to myocardial surgery under mini-cardiopulmonary bypass[23]. Perioperative DEX reduces the incidence rate and severity of acute kidney injury following valvular heart surgery[24]. DEX exerts a key protective effect on perioperative hemodynamic homeostasis in hypertensive cerebral hemorrhage patients in the perioperative period[25]. In addition, DEX has certain protective effects on the liver and remote organs against hepatic ischemia reperfusion injury in rats[26]. In this study, it was discovered for the first time that DEX significantly improved liver function in rats with sepsis-induced liver injury, lowered the ALT level in peripheral blood of rats, and improved the short-term survival of rats. Besides, DEX had an important regulatory effect on oxidative stress, namely, it up-regulated the level of GSH-Px, an anti-oxidase, inhibited the levels of MPO and MDA, peroxidases, thereby reducing the level of oxidative stress in rat liver tissues. Moreover, DEX reduced the LPS-induced apoptosis level of rat hepatocytes and repressed the protein expression level of the pro-apoptotic gene Caspase 3. Finally, it was discovered that the protective effect of DEX on the liver might be related to the activation of p-ERK1/2 triggered by it.

Conclusions

We revealed for the first time that DEX represses the oxidative stress and phosphorylation of hepatocytes by activating p-ERK1/2, thereby mitigating sepsis-induced liver injury.

Conflict of Interests

The Authors declare that they have no conflict of interests.

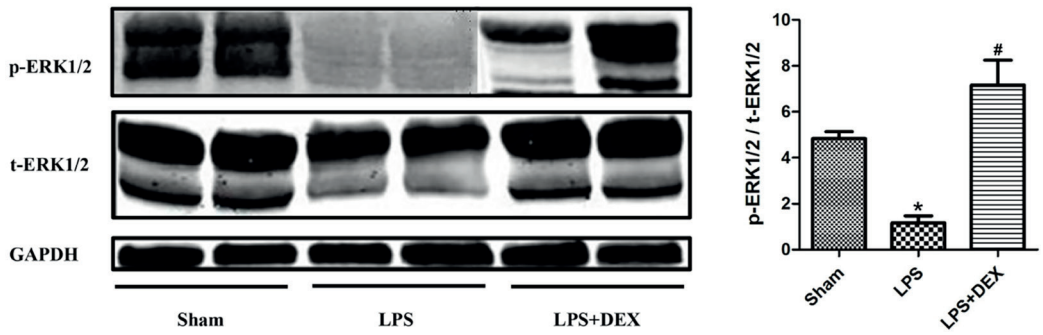

Figure 7. Protein expression level of ERK1/2 in rat live tissues in Sham group, LPS group and LPS + DEX group. *: There is a statistically significant difference ($p<0.05$) *vs.* Sham group, #: There is a statistically significant difference ($p<0.05$) *vs.* LPS group.

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