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Tetrahydropyrimidines, ZL-5015 Alleviated Lipopolysaccharide (LPS)-Induced Acute Pneumonia in Rats by Activating the NRF-2/HO-1 Pathway

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Acute pneumonia is a severe inflammatory disease of the respiratory system. Drugs used to treat acute pneumonia often have strong side effects. Recent studies have shown that tetrahydropyrimidines, ZL-5015 has anti-inflammatory and antitumor effects. However, whether ZL-5015 can relieve symptoms of acute pneumonia is unclear.

Material/Methods: In this study, we used lipo-polysaccharide (LPS) to stimulate SD rats to simulate conditions of acute pneumonia. Diverse doses of ZL-5015 were used for treatment of these rats. After the rates were sacrificed, serum, lung tissue, and bronchoalveolar lavage fluid were collected for the next study. Hematoxylin-eosin (H&E) staining then was used to detect pathologic changes in lung tissues. Enzyme-linked immunosorbent assay was performed to assess levels of inflammatory factors in serum. Commercial kits were used to assess levels of reactive oxygen species (ROS) in bronchoalveolar lavage fluid.

Results: Treatment of ZL-5015 relieved stenosis of the alveolar space and pulmonary edema. Furthermore, levels of inflammatory factors (TNF-α, IL-1β and IL-18) in the lung tissues and serum were downregulated after treatment with ZL-5015. Production of ROS also was suppressed after application of ZL-5015. Moreover, inhibition of expression of NRF-2 and HO-1 was relieved after treatment with ZL-5015. The therapeutic effect of ZL-5015 showed a dose-response relationship.

Conclusions: ZL-5015 alleviated LPS-induced inflammatory injury and oxidative damage by activating the NRF-2/HO-1 pathway.

MeSH Keywords: Abnormalities, Drug-Induced • Acute Lung Injury • Guillain-Barre Syndrome

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Background

Acute pneumonia is an acute lower respiratory tract disease caused by environmental irritants. The main symptoms are dry cough, chest pain, fever, and shortness of breath [1,2]. Furthermore, severe pneumonia can lead to death, particularly in patients who are elderly or children [3,4]. In addition, lower respiratory tract infections caused by bacteria, viruses, and fungi can promote the occurrence and development of acute pneumonia [5,6]. In recent years, many studies have revealed the molecular mechanism of acute pneumonia. For example, some researchers have pointed out that lncRNA and miRNA play a critical role in occurrence and development of acute pneumonia [7–9]. However, there is still no effective therapy for alleviating damage caused by acute pneumonia. Therefore, it is urgent to find a drug that can effectively treat tissue damage caused by acute pneumonia.

Inflammation is a normal physiological response by the body to various stimuli, such as pathogens or autoantigens. Moreover, an inflammatory response usually induces severe damage in organs in the body. Dexamethasone and cyclophosphamide typically are usually for clinic treatment of inflammatory damage. However, when dexamethasone is used to alleviate inflammation and treat autoimmune diseases, it is associated with side effects and can aggravate physical damage [10]. Therefore, it is necessary to explore new anti-inflammatory drugs this indicatoin. Recently, some studies have shown that tetrahydropyrimidine derivatives have a wide range of biological activities, such as antimicrobial [11], anticancer [12], antitubercular [13], melanogenesis-inhibitory [14], and anti-inflammatory agents [15]. Another study revealed that the tetrahydropyrimidine derivative, ZL-5015 could inhibit production of IL-10, which is an anti-inflammatory cytokine, and therefore, alleviate damage induced by inflammation [16]. Whether ZL-5015 canalleviate lung damage caused by acute pneumonia is unclear.

Lipopolysaccharide (LPS) is a biologically active component in the cell wall of Gram-negative bacteria, which can induce occurrence and development of inflammation [9,17,18]. In this study, we used LPS to induce acute pneumonia in SD rats, and then explored whether ZL-5015 could alleviate inflammatory damage, oxidative stress, and apoptosis of tissue cells caused by acute pneumonia in rats. Our results were intended to identify the effect of tetrahydropyrimidine derivative, ZL-5015 on injury induced by acute pneumonia.

Material and Methods

Establishment of an acute pneumonia rat model

Three-week-old SD rats were obtained from the Shanghai Lingchang Biotechnology Company (Shanghai, China). The compound, ZL-5015, was synthesized by the one-step method from diethyl acetylenedicarboxylate, cyclohexylamine and formaldehyde in our laboratory as described in previous reports [19,20]. The rats were divided into six groups of 10 rats each: control, LPS, LPS+ZL-5015 25 mg/kg, LPS+ZL-5015 50 mg/kg, LPS+ZL-5015 100 mg/kg, and LPS+ribavirin 50 mg/kg group. The rats in the LPS group were injected intraperitoneally with 4 mg/kg LPS. Rats in the control group were injected with normal saline. Rats in the ZL-5015-treated groups were injected intraperitoneally with the respective concentrations of ZL-5015 (25 mg/kg, 50 mg/kg, and 100 mg/kg). The ZL-5015 was injected 2 hours before the LPS and the rates were treated with LPS for 24 hours. Given that the ribavirin relieves inflammation-induced lung damage [21,22], it was used as the positive control drug in this study. Rats in the ribavirin group were injected with ribavirin (50 mg/kg) before being treated withi LPS. All the rats were anesthetized by intraperitoneal injection of sodium pentobarbital (Sigma-Aldrich, Germany) and then sacrificed after stimulation with LPS. Then blood samples were collected and serum was extract from them. Five rats were selected from each group and their lungs of these rats were irrigated with saline and the corresponding bronchoalveolar lavage fluid (BALF) was collected for the next experiment. The left lungs of the other rats in each group were used to determine the wet-to-dry ratio to reflect the severity of pulmonary edema.

Partial tissues from the right lungs were fixed with 4% formaldehyde solution for H&E staining. The rest of the right lung tissue was collected for Western blot analysis. All of the samples were preserved in the –80°C refrigerator.

Hematoxylin-eosin staining

H&E staining was performed for histopathological observation of lung tissue. Lung tissue was embedded with paraffin and then cut into 5-μm sections. These sections were subsequently stained with hematoxylin and eosin. Finally, the sections were photographed under a microscope (Olympus, Japan).

Detection of wet-to-dry ratio

Left lung weight was measured when the rats were sacrificed. After that, the lung tissues were dried at 80°C for 48 hr and the lungs were weighed again. A high wet-to dry-ratio often reflects severe pulmonary edema.

ELISA assays

Levels of inflammatory factors and pulmonary surfactant in serum of rats were determined with Enzyme-linked immunosorbent (ELISA) assays. The rats (Abcam, ab100785) tumor necrosis factor (TNF)-α ELISA kit, rats (Abcam, ab100768) interleukin

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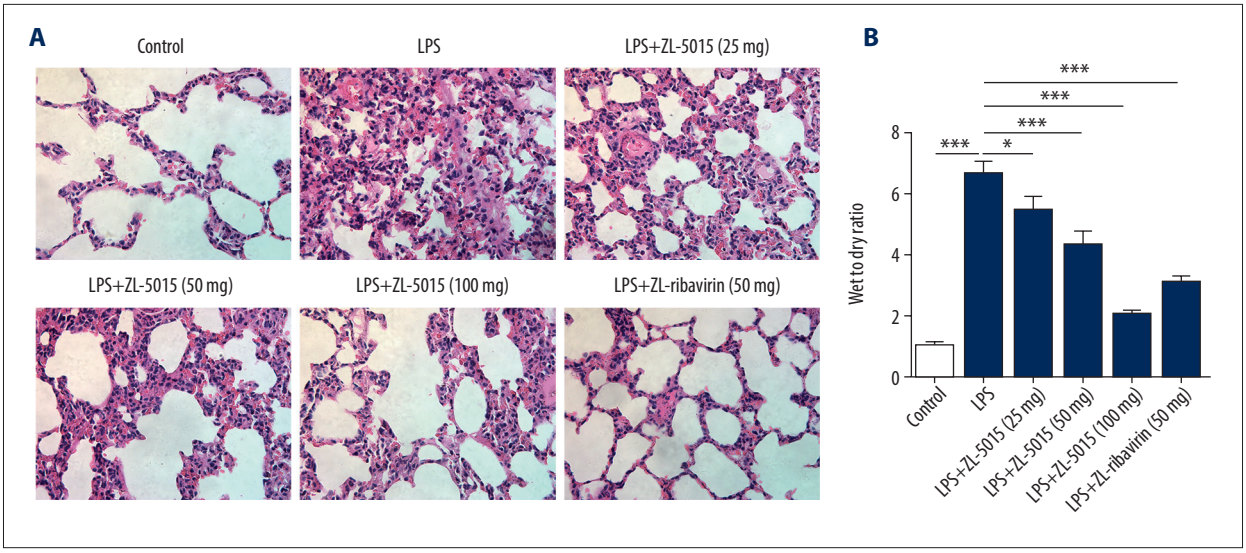

Figure 1. Treatment with ZL-5015 relieved LPS-induced pulmonary edema in rats. (**A**) Representative images of H&E staining (200×) in rat lung tissue. (**B**) values for wet-to-dry ratios in the different groups. * P<0.05, ** P<0.01, ***P<0.001.

(IL)-1β ELISA kit, rats (Abcam, ab213909) IL-18 ELISA kit, rats (Yubo company, Shanghai, China) surfactant protein A (SP-A) ELISA kit and rats (Yubo company, Shanghai, China) surfactant protein A (SP-D) ELISA kit were used to determine levels of TNF-α, IL-1β, IL-18, SP-A and SP-D in the serum of rats. In addition, levels of inducible nitric oxide synthase (iNOS) in serum were detected with commercial kits (Lanpai company, Shanghai, China). All the assays were performed according to the manufacturers' operating instructions.

Detection of ROS

Levels of reactive oxygen species (ROS) in the bronchoalveolar lavage fluid were determined with commercial kits (Jining company, Shanghai, China). All the assays were performed according to the manufacturer's instructions.

Western blotting

Total protein was extracted with RIPA buffer (Beyotime, China). Then the concentrations in the samples were determined with BCA (Beyotime, China) methods. Next, the protein samples were separated with 10% SDS-PAGE gel (Beyotime, China). After that, the proteins were transferred to the PVDF membrane (Millipore, United States). Then, the membranes were blocked with a 5% skim milk powder solution (BD Bioscience, Regilait, France). After that, the membranes were incubated overnight with primary antibodies at 4°C. The primary antibodies used in this study were TNF-α (Abcam, ab34674), IL-1β (Abcam, ab200478), IL-18 (Abcam, ab71495), NRF-2 (Abcam, ab137550), HO-1 (Abcam, ab137749) and GAPDH (Abcam, ab181602). On Day 2, the membranes were washed with PBST three times. The membranes were then incubated with the second antibody for 2 hours. Finally, bands were developed with enhanced chemiluminescence reagents (Millipore, United States).

Statistical analysis

Data in this study were analyzed with the Graphpad Prism 7.0 (GraphPad Software Inc., United States). The Student's *t* test was performed to compare differences between the groups. P<0.05 was considered statistically significant. All the data in this study are presented as mean±SD. All of the experiments in this study were repeated three times.

Results

Treatment with ZL-5015 relieved LPS-induced injury to lungs and pulmonary edema. H&E staining was performed to investigate pathological changes in lung tissues. As shown in Figure 1A, comparison with the control group showed that the space in the alveoli was narrowed after stimulation with LPS. Moreover, the space in the alveoli was gradually amplified with upregulation of doses of ZL-5015. Furthermore, the wet-to-dry ratio of lung tissues also increased after stimulation with LPS. In contrast, wet-to-dry ratios were downregulated after treatment with ZL-5015. As the doses of ZL-5015 increased, the values in the wet-to-dry ratio further declined (Figure 1B).

Treatment with ZL-5015 alleviated LPS-induced reduced expression of pulmonary surfactant proteins in lung tissue

Higher levels of inducible nitric oxide synthase (iNOS) was the symbol of the acute pneumonia which was caused with diverse

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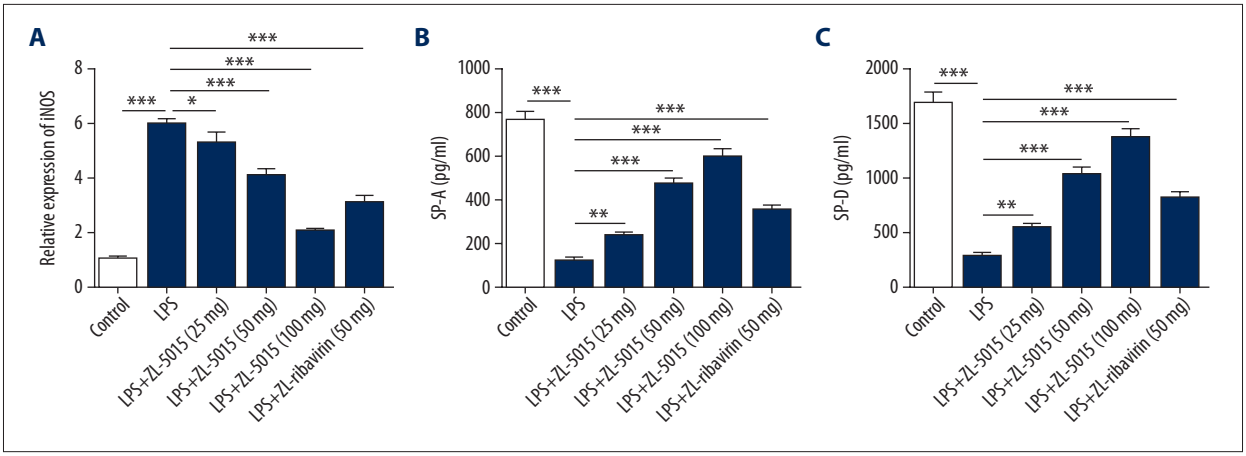

Figure 2. Treatment of ZL-5015 rescued the expression of SP-A and SP-D in the serum of rats. (**A**) Levels of iNOS in serum of rats were determined with commercial kits. (**B, C**) Levels of SP-A and SP-D in serum of rats were determined with ELISA. * P<0.05, **P<0.01, ***P<0.001.

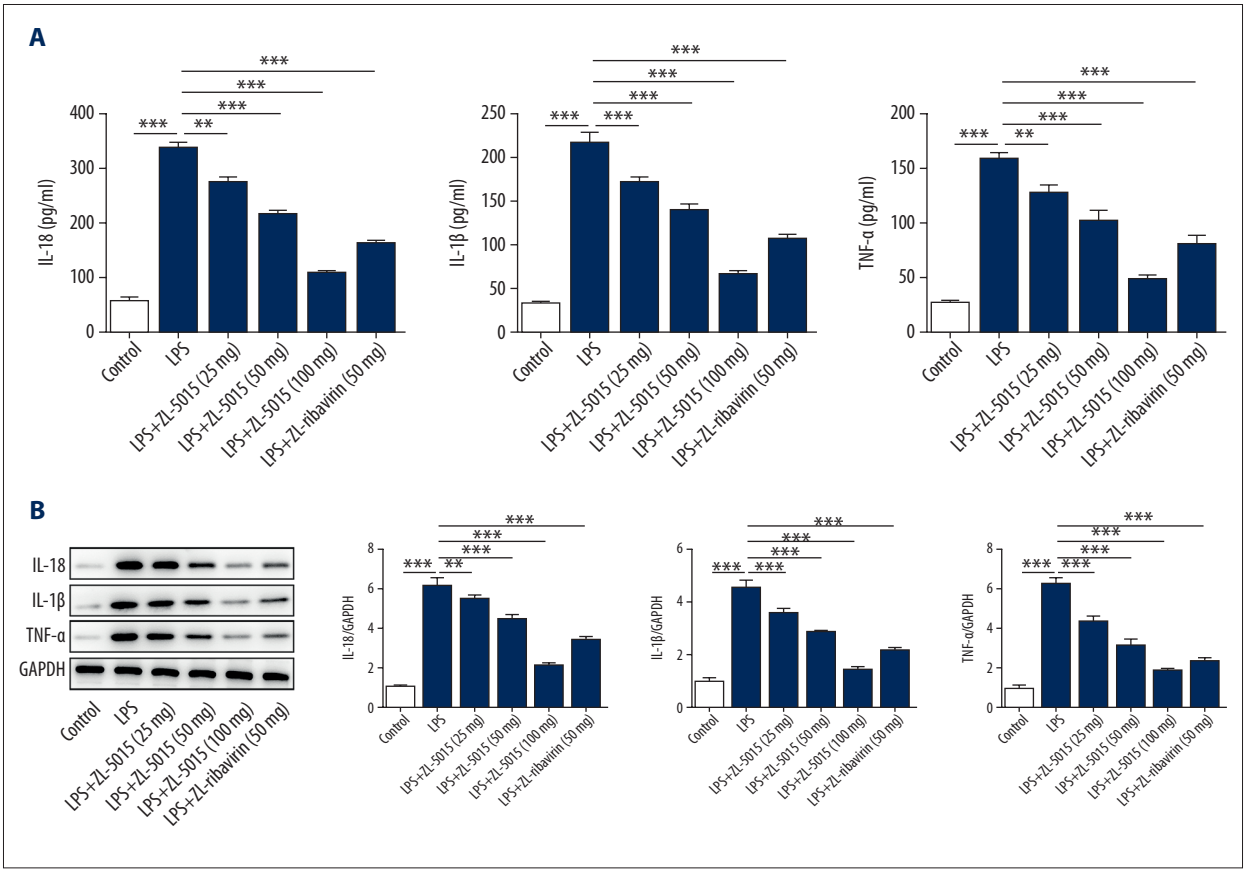

Figure 3. Treatment of ZL-5015 alleviated the LPS induced inflammatory damage of rats. (**A**) Levels of TNF-α, IL-1β, and IL-18 in serum of rats were determined with ELISA. (**B**) Expression of TNF-α, IL-1β, and IL-18 in lung tissues was detected with Western blotting. * P<0.05, * *P<0.01, *** P<0.001.

reasons [23,24]. Therefore, we detected the levels of iNOS in the serum. According to the results (Figure 2A), we found that the levels of iNOS were increasing after the stimulation of LPS. However, the expression of iNOS was downregulated after the treatment of ZL-5015. And the expression of iNOS was further suppressed with the increasing dose of ZL-5015. In addition, the surfactant protein A (SP-A) and surfactant protein D (SP-D) were the critical component of lung surfactant,

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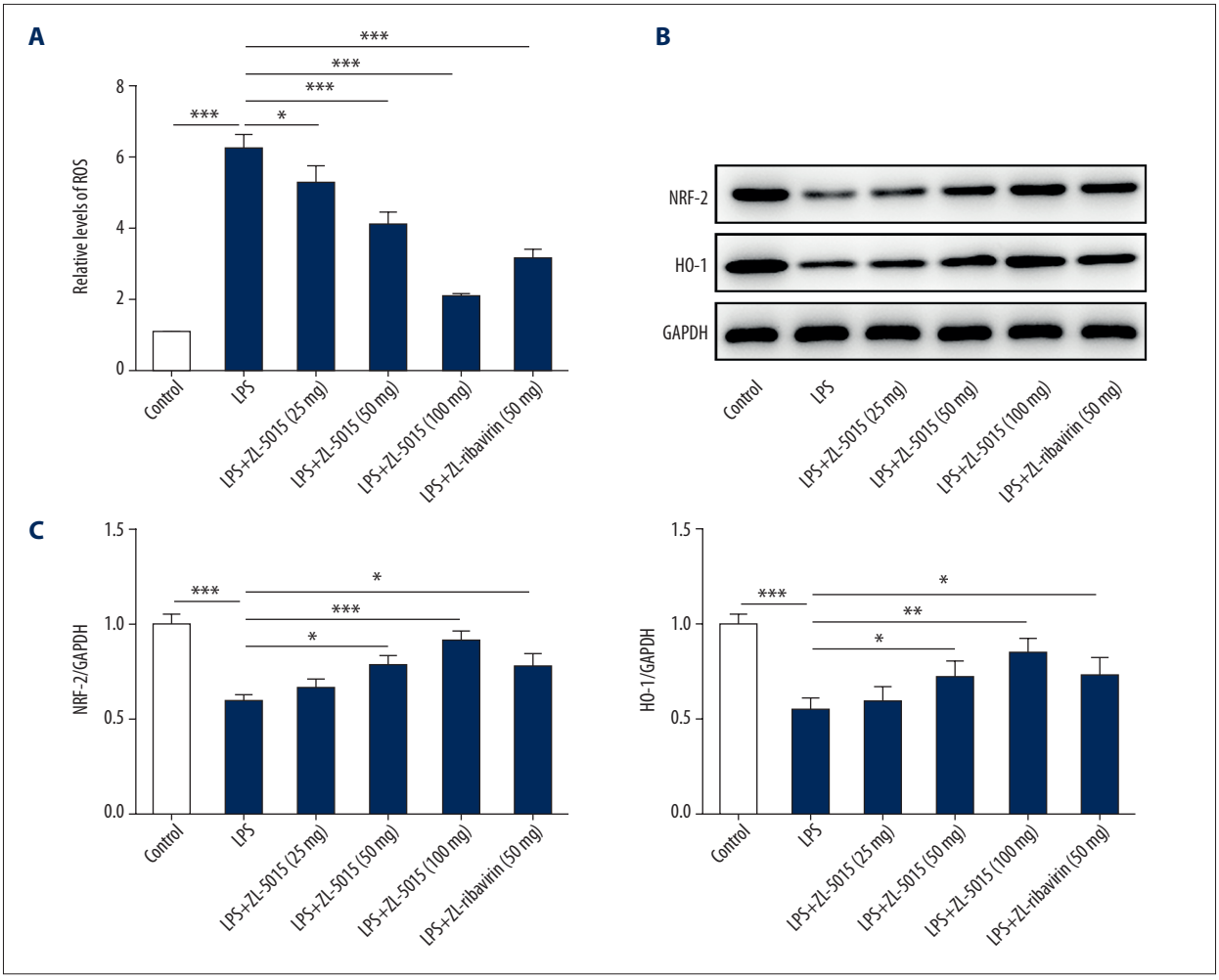

Figure 4. Treatment of ZL-5015 relieved the LPS induced oxidative damage of rats. (**A**) Levels of ROS in bronchoalveolar lavage fluid were detected with commercial kits. (**B**) Protein bands of NRF-2 and HO-1 in lung tissues of rats. (**C**) Expression of NRF-2 and HO-1 in lung tissues of rats was determined with Western blotting. * P<0.05, ** P<0.01, *** P<0.001.

and the results (Figure 2B, 2C) showed the downregulation of SP-A and SP-D could lead to the aggravation of inflammation in lung tissues [25]. In this study, we found that the levels of SP-A and SP-D was decreasing after the stimulation of LPS. Moreover, the expression of SP-A and SP-D in the serum was gradually declined when these rats were treated with the lower and higher doses of ZL-5015.

ZL-5015 therapy relieved the LPS induced inflammatory response in the lung tissues

In the next study, levels of inflammatory factors (TNF-α, IL-1β and IL-18) in the serum of rats were determined with the ELISA assays. And the results (Figure 3A) showed that stimulation of LPS lead to the upregulation of these inflammatory factors. Moreover, the treatment of ZL-5015 suppressed the expression of TNF-α, IL-1β and IL-18 in the serum of these rats. Furthermore, the expression of TNF-α, IL-1β and IL-18 in the lung tissues was determined with the western-blotting assays. As shown in Figure 3B, the expression of TNF-α, IL-1β and IL-18 was promoted after the stimulation of LPS. The levels of these proteins in lung tissues were decreasing when these rats were treated with diverse doses of ZL-5015. And high doses of ZL-5015 could more effectively inhibit the expression of these inflammatory factors.

Treatment of ZL-5015 alleviated the LPS induced oxidative damage of lung tissues

Finally, ROS levels in bronchoalveolar lavage fluid were measured with commercial kits. As shown in Figure 4A, the ROS levels were enhanced after stimulation with LPS. However, higher levels of ROS gradually decreased as doses of ZL-5015 increased. On the other hand, some studies revealed that lower levels of NRF-2 and HO-1 were associated with inflammation, oxidative stress, and production of ROS, and activation

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of the NRF-2/HO-1 pathway relieved inflammatory injury and oxidative damage [26–28]. Therefore, we detected expression of NRF-2 and HO-1 in lung tissues of the rats. We also found that stimulation with LPS suppressed expression of NRF-2 and HO-1. Moreover, application of ZL-5015 reduced expression of NRF-2 and HO-1 in the lung tissues of the rats. Treatment with higher dose of ZL-5015 further promoted expression of NRF-2 and HO-1 (Figure 4B, 4C).

Discussion

Acute pneumonia is a common disease of the lower respiratory tract [29]. Some studies have suggested that occurrence and development of pneumonia are related to increased levels of pro-inflammatory factors (TNF-α, IL-1β and IL-6). These pro-inflammatory factors may further activate the immune system to induce development of an inflammatory response [30,31]. Severe inflammation often induces injury to lung function by damaging cells in lung tissue. Therefore, development of new drugs to treat acute pneumonia is important.

Furthermore, pulmonary edema is a disease associated with lung ventilation and ventilation disorders. It is caused by a large amount of fluid in tissues in the lungs, which cannot be absorbed by pulmonary lymph and veins [32]. Moreover, some studies have revealed that pulmonary edema is caused by the acute pneumonia [33,34]. The wet-to dry-ratio inf lung tissues is used to assess the severity of pulmonary edema. An increase in the values of the ratio indicates aggravation of pulmonary edema, and a decrease implies remission of symptoms of pulmonary edema. In our study, we found that values in the wet-to-dry ratio of lung tissue were promoted after stimulation with LPS. However, treatment with ZL-5015 suppressed increased in the wet-to-dry ratio. Application of ZL-5015 also relieved alveolar stenosis induced by LPS. These results indicated that ZL-5015 relieved pulmonary edema and damage to lung tissues that was caused by LPS.

In addition, iNOS was a crucial marker of pneumonia. Some studies have revealed that expression of iNOS is enhanced during development of diverse types of pneumonia [35,36]. In this study, we found that application of ZL-5015 alleviated with LPS-induced higher levels of iNOS. On the other hand, SP-A and SP-D are pulmonary surfactant proteins, and lower levels of them lead to aggravation of acute pneumonia [25]. We found that expression of SP-A and SP-D in rats was inhibited after stimulation with LPS. However, levels of SP-A and SP-D were reduced after treatment with ZL-5015. These results suggest that treatment with ZL-5015 alleviated symptoms of acute pneumonia by regulating expression of pulmonary surfactant proteins.

This study also revealed that higher levels of TNF-α were associated with development of respiratory tract inflammation [37]. In addition, aberrant expression of inflammatory factors (IL-1β, IL-6 and IL-18) may aggravate symptoms of pneumonia [38,39]. In this study, we revealed that stimulation with LPS can induce upregulation of levels of TNF-α, IL-1β and IL-18 in the serum and lung tissues of rats. However, expression of these inflammatory factors was suppressed after treatment with ZL-5015. Expression of TNF-α, IL-1β, and IL-18 was further suppressed with increasing doses of ZL-5015. All these results imply that ZL-5015 can relieve inflammatory damage by inhibiting expression of inflammatory factors (TNF-α, IL-1β, and IL-18).

Oxidative stress induced by pneumonia can also result in injury to lung tissues [40,41]. In our research, we found that treatment with ZL-5015 repressed production of ROS induced by LPS. Furthermore, the NRF-2/HO-1 pathway also was associated with oxidative damage to many tissues. Another study revealed that activation of the NRF-2/HO-1 pathway relieved oxidative stress and, therefore, alleviated acute pancreatitis in mice [42]. Activation of the NRF-2/HO-1 pathway may also suppress production of ROS in astrocytes [27]. In our study, we found that expression of NRF-2 and HO-1 in lung tissues was inhibited after stimulation with LPS. Levels of NRF-2 and HO-1 gradually recovered after treatment with increasing doses of ZL-5015. These results indicate that ZL-5015 alleviated LPS-induced oxidative stress by activating the NRF-2/HO-1 pathway.

Conclusions

We assessed the effect of the tetrahydropyrimidines ZL-5015 on LPS-induced acute pneumonia in rats. The results of our study show that ZL-5015 relieved LPS-induced inflammation and oxidative stress by inhibiting expression of inflammatory factors (TNF-α, IL-1β and IL-18) and activating the NRF-2/HO-1 pathway. ZL-5015 may represent a new target for development of clinical treatment for acute pneumonia.

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