European Journal of Pharmacology 747 (2015) 45–51

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Pulmonary, gastrointestinal and urogenital pharmacology

Citral inhibits lipopolysaccharide-induced acute lung injury by activating PPAR-γ

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ARTICLE INFO

Article history:
Received 22 August 2014
Received in revised form
17 September 2014
Accepted 22 September 2014
Available online 2 October 2014

Keywords:
Citral
LPS
Acute lung injury
NF-κB
PPAR-γ

Chemical compound studied in this article:
Citral (PubChem CID: 24893046)

ABSTRACT

Citral, a component of lemongrass oil, has been reported to have many pharmacological activities such as anti-bacterial and anti-inflammatory effects. However, the effects of citral on acute lung injury (ALI) and the molecular mechanisms have not been reported. The aim of this study was to detect the effects of citral on lipopolysaccharide (LPS)-induced acute lung injury and investigate the molecular mechanisms. LPS-induced acute lung injury model was used to detect the anti-inflammatory effect of citral in vivo. The alveolar macrophages were used to investigate the molecular mechanism of citral in vitro. The results showed that pretreatment with citral remarkably attenuated pulmonary edema, histological severities, TNF-α, IL-6 and IL-1β production in LPS-induced ALI in vivo. In vitro, citral inhibited LPS-induced TNF-α, IL-6 and IL-1β production in alveolar macrophages. LPS-induced NF-κB activation was also inhibited by citral. Furthermore, we found that citral activated PPAR-γ and the anti-inflammatory effects of citral can be reversed by PPAR-γ antagonist GW9662. In conclusion, this is the first to demonstrate that critral protects LPS-induced ALI in mice. The anti-inflammatory mechanism of citral is associated with activating PPAR-γ, thereby inhibiting LPS-induced inflammatory response.

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1. Introduction

Acute lung injury (ALI) and its severe form, acute respiratory distress syndrome (ARDS), are characterized by overwhelming lung inflammation (Kimmel and Still, 1999). They often result in multi-organ failure with high mortality in critically ill patients (Lew et al., 2003). LPS has been reported to be an important risk factor of ALI (Atabai and Matthay, 2002; Rubenfeld et al., 2005). Alveolar macrophages play a critical role in lung inflammation (Martin et al., 1984; Thepen et al., 1994). LPS activates macrophages could induce inflammatory cytokines production (Dentener et al., 1993). These cytokines amplify the inflammatory responses and lung injury (Joh et al., 2012). Peroxisome proliferators-activated receptor gamma (PPAR-γ), belongs to the nuclear receptor superfamily, has essential roles in adipogenesis and glucose homeostasis (Kawai et al., 2010; Kim and Ahn, 2004). Recently, it has been implicated as a regulator of inflammatory responses (Jiang et al., 1998; Pascual et al., 2005).

Citral, a major active compound lemongrass oil, has been reported to have antibacterial, anti-cancer and anti-inflammatory effects (Bachiega and Sforcin, 2011; Katsukawa et al., 2010; Zarai et al., 2011). Citral was found to inhibit cytokines production in LPS-stimulated murine peritoneal macrophages (Bachiega and Sforcin, 2011). Studies showed that citral inhibited COX-2 expression in LPS-stimulated U937 cells (Katsukawa et al., 2010). Futhermore, crital was found to have a protective effect on focal segmental glomerulosclerosis in mice (Yang et al., 2013). However, the anti-inflammatory effect of citral on LPS-induced ALI remains unclear. The objective of this work was to detect the anti-inflammatory effects of citral on LPS-induced ALI and to elucidate the potential anti-inflammatory mechanism.

2. Materials and methods

2.1. Reagents

Citral and LPS (Escherichia coli 055:B5) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). Mouse TNF-α, IL-6 and IL-1β enzyme-linked immunosorbent assay (ELISA) kits were purchased from Biolegend (CA, USA). Antibodies against NF-κB, IκBα, PPAR-γ, and horseradish peroxidase-conjugated (HRP) secondary antibodies were purchased from Santa Cruz Biotechnology (Autogen, Bioclear, UK). All other chemicals were of reagent grade.

2.2. Animals

All animal experiments were performed in accordance with the Health's Guide for the Care and Use of Laboratory Animals published by the US National Institute of Health. Male BALB/c mice

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http://dx.doi.org/10.1016/j.ejphar.2014.09.040
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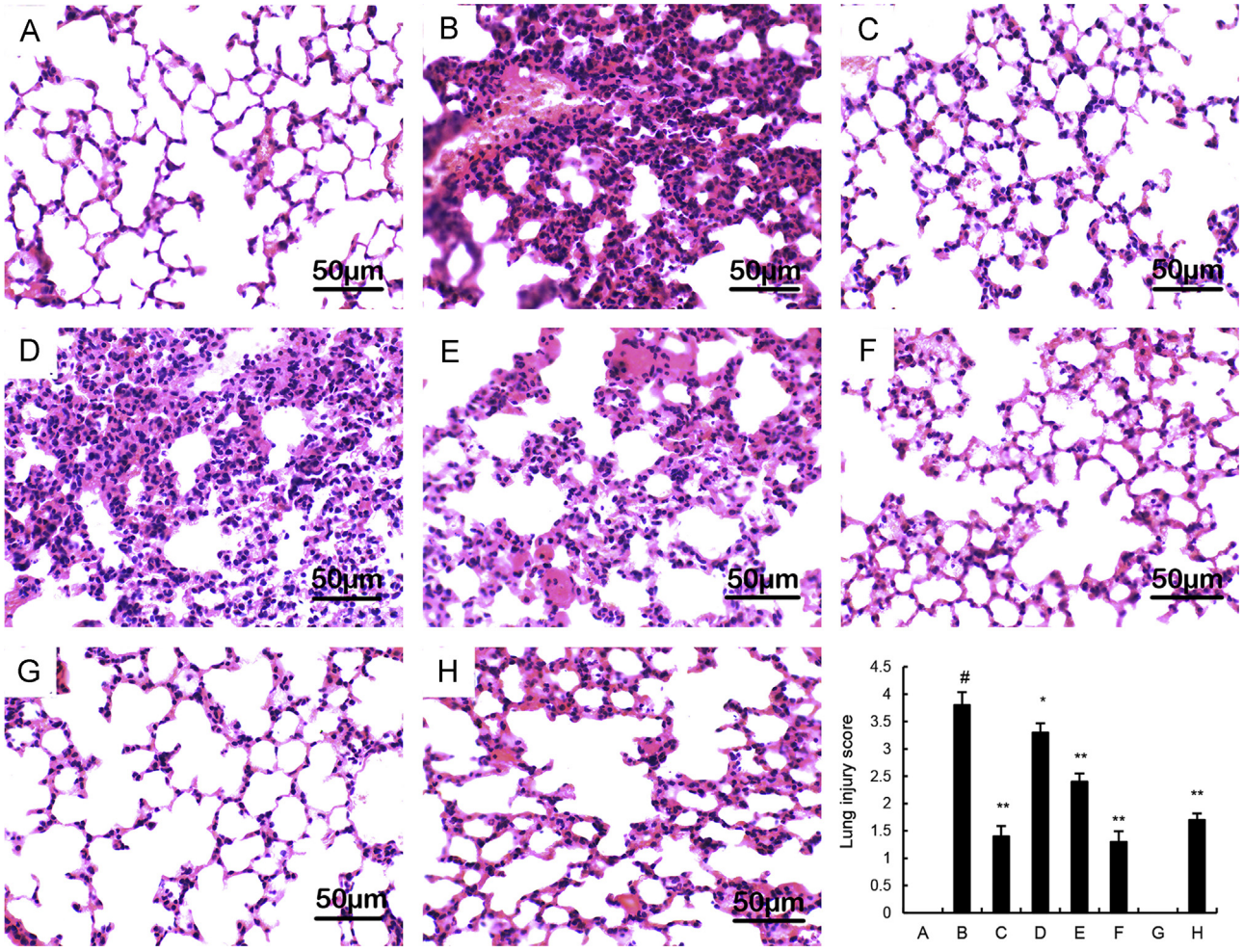

Fig. 1. Effects of citral on histopathological changes in lung tissues in LPS-induced ALI mice. Representative histological changes of lung obtained from mice of different groups. A: control group, B: LPS group, C: DEX+LPS group, D: citral (10 mg/kg)+LPS group, E: citral (20 mg/kg)+LPS group, F: citral (40 mg/kg)+LPS group, G: citral (40 mg/kg) alone group, and H: LPS+ citral (40 mg/kg) group (Hematoxylin and eosin staining, magnification 200 ×).

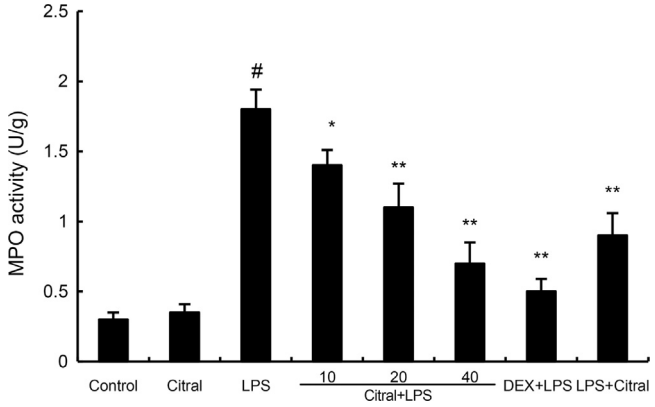

Fig. 2. Effects of citral on MPO activity in lung tissues of LPS-induced ALI. The values presented are the mean ± S.E.M. ($n=12$ in each group). $P^{\#} < 0.01$ vs. control group, $P^{*} < 0.05$, $P^{**} < 0.01$ vs. LPS group.

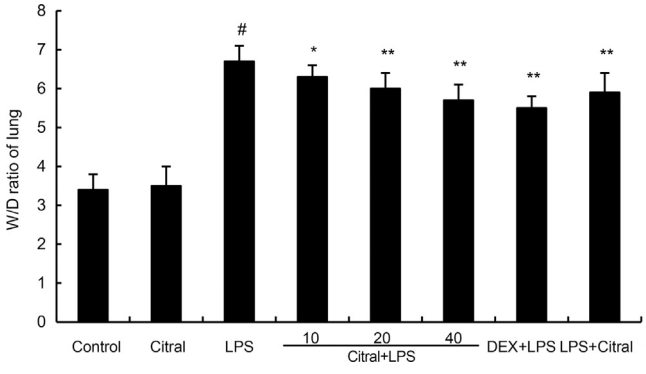

Fig. 3. Effects of citral on the lung W/D ratio of LPS-induced ALI mice. The values presented are the means ± S.E.M. ($n=12$ in each group). $P^{\#} < 0.01$ vs. control group, $P^{*} < 0.05$, $P^{**} < 0.01$ vs. LPS group.

(18–20 g) were purchased from the Center of Experimental Animals of Harbin Medical University (Harbin, China). The mice were kept in the animal house and received food and water ad libitum. Laboratory temperature was 24 ± 1 °C, and relative humidity was 40–80%.

2.3. Experimental design and grouping

Ninety-six mice were randomly divided into eight groups and each group contained 12 mice: normal control, Citral (40 mg/kg) alone, LPS, Citral (10, 20 and 40 mg/kg)+LPS, DEX+LPS group and LPS+Citral (40 mg/kg) group. The doses used in this study were based on our preliminary experiment (data not shown). We found that citral at doses of 40 mg/kg has better effects on LPS-induced ALI and the effect is similar to the doses of 60 mg/kg and 80 mg/kg. Thus, we chose the doses of 40 mg/kg, 20 mg/kg, and 10 mg/kg in this study. 10 mg citral was first dissolved in 100 μl DMSO and then dissolved in PBS or RPMI 1640 to the concentration used in this study. Citral (10, 20 and 40 mg/kg) and DEX (5 mg/kg) dissolved in 50 μl

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