Resuscitation 83 (2012) 907–912

Contents lists available at SciVerse ScienceDirect

Resuscitation

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

BML-111, a lipoxin receptor agonist, protects haemorrhagic shock-induced acute lung injury in rats☆

Jie Gong, Si Guo, Hong-Bin Li, Shi-Ying Yuan, You Shang*, Shang-Long Yao*

Department of Anesthesiology and Critical Care, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

ARTICLE INFO

Article history:
Received 28 October 2011
Received in revised form 5 December 2011
Accepted 26 December 2011

Keywords:
Haemorrhagic shock
Acute lung injury
Resolution
Lipoxin
NF-κB

ABSTRACT

Objectives: The main pathogenesis of acute lung injury induced by haemorrhagic shock is inflammation. BML-111, a lipoxinA_4-receptor agonist, promotes acute inflammatory resolution. We sought to elucidate whether BML-111 protects haemorrhagic shock-induced acute lung injury in rats.
Methods: Thirty two adult male rats were randomized to sham group (sham), haemorrhagic shock/resuscitation (HS), HS plus BML-111 (BML-111), and HS plus BML-111 and BOC-2 (BOC-2). Haemorrhagic shock was induced by blood drawing, and then resuscitation was obtained by infusion of shed blood and two-fold volume saline.
Results: Histological findings, as well as assays of neutrophilic infiltration (myeloperoxidase activity, ICAM-1 expression), inflammatory cytokines and pro-inflammatory factor (IκB-α and NF-κB p65) confirmed that haemorrhagic shock induced acute lung injury. BML-111 significantly mitigated acute lung injury induced by haemorrhagic shock. However, BOC-2, an antagonist of the lipoxinA_4-receptor, partially reversed the protective effect of BML-111 on the haemorrhagic shock-induced the acute lung injury.
Conclusion: BML-111 protects haemorrhagic shock-induced acute lung injury in rats.

1. Introduction

Haemorrhagic shock promotes the development of systemic inflammatory response syndrome (SIRS) that eventually results in multiple organ dysfunction syndrome, including acute lung injury.[1] The precise pathogenesis of these phenomena has not yet been fully understood. The widely recognized mechanism is inflammatory cascades caused by ischaemia and reperfusion.[2] Haemorrhagic shock increased the pro-inflammatory factors, neutrophilic accumulation, and resulted in the severe lung injury.[3,4] Thus, control and prevention of SIRS in haemorrhagic shock would be a new and effective therapeutic approach.

Lipoxins (LXs) are biosynthesized from arachidonic acid via lipoxygenase. Lipoxin A_4 (LXA_4) is one of the principle LXs. LXA_4 and analogues, have been demonstrated in many disease models, including dorsal air pouch,[5] ischaemia/reperfusion injury,[6,7] and LPS-induced acute lung injury.[8] LXA_4 receptor, a G-protein coupled receptor, is termed as formyl peptide receptor 2 (FPR-2). LXs are rapidly degradated, thereby more stable analogues were biosynthesized.[9,10]

BML-111 is a commercially stable FPR-2 agonist, and even more potent compared with the original LXA_4 molecule.[11] BML-111 displayed the pro-resolving and anti-inflammatory effects in carbon tetrachloride-induced liver injury[12] and zymosan-induced arthritis.[13] However, whether BML-111 could exert protective effects in haemorrhagic shock/resuscitation remained unknown. To elucidate further, we thus carried out present study with the hypothesis that BML-111 protects haemorrhagic shock-induced acute lung injury in rats.

2. Methods

2.1. Animal preparation

Thirty two male Sprague-Dawley rats (200–250 g) were purchased from Shi lai ke jing da Company (Hunan, China). All animal experiments were approved by the Animal Care and Use Committee of Tongji Medical College of Huazhong University of Science and Technology.

Rats were randomly divided into 4 groups ($n = 8$ in each group): sham group (sham), haemorrhagic shock/resuscitation (HS), HS plus BML-111 (BML-111), and HS plus BML-111 and BOC-2 (BOC-2).

☆ "A Spanish translated version of the summary of this article appears as Appendix in the final online version at doi:10.1016/j.resuscitation.2011.12.035".

* Corresponding authors at: Department of Anesthesiology and Critical Care, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1277, Jiefang Avenue, Wuhan, Zip Code: 430022, China.
E-mail addresses: shang_you@yahoo.cn (Y. Shang), ysltian@163.com (S.-L. Yao).

0300-9572/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.resuscitation.2011.12.035

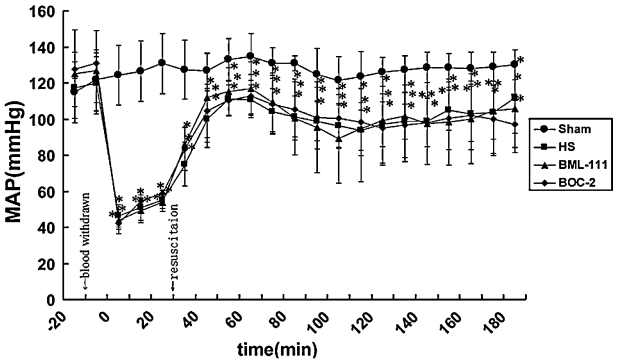

Fig. 1. MAP during the haemorrhagic shock and resuscitation. Data are means ± SD. $^{*}p < 0.05$ vs. the sham group.

2.2. Haemorrhagic shock-resuscitation protocols

All rats were anaesthetized with 2% sodium pentobarbital (80 mg/kg, intraperitoneally). After anaesthesia, BOC-2 group received BOC-2 (50 μg/kg, intraperitoneally). 10 min later, rats were cannulated into the left common carotid artery and right jugular vein. The catheters were filled with isotonic sodium chloride solution containing heparin (100 U/ml) and the left common carotid artery was connected to a pressure transducer. A digital blood pressure was recorded by monitor (Hewlett-Packard Development Company, L.P. USA). The right jugular vein was used for resuscitation. After surgical procedures, rats were stabilized for 15 min. And then, monitor blood pressure for 5 min before haemorrhagic shock.

Each animal's estimated blood volume was calculated using the formula: [estimated blood volume (ml) = weight (g) × 0.06 (ml/g) + 0.77].[14] The rats were haemorrhaged 35% of calculated total blood volume via common carotid artery for 10 min. Haemorrhagic shock sustained for 30 min. In BML-111 group and BOC-2 group, BML-111 (1 mg/kg, intraperitoneally) was given at the beginning of resuscitation. Rats were resuscitated by infusion of shed blood and two-fold volume saline. Resuscitation was completed in 30 min. Rats in the sham group underwent all surgical procedures, but they were not subjected to haemorrhage and resuscitation.

After 2 h, rats were sacrificed and lung tissues were harvested for storage at −80°C.

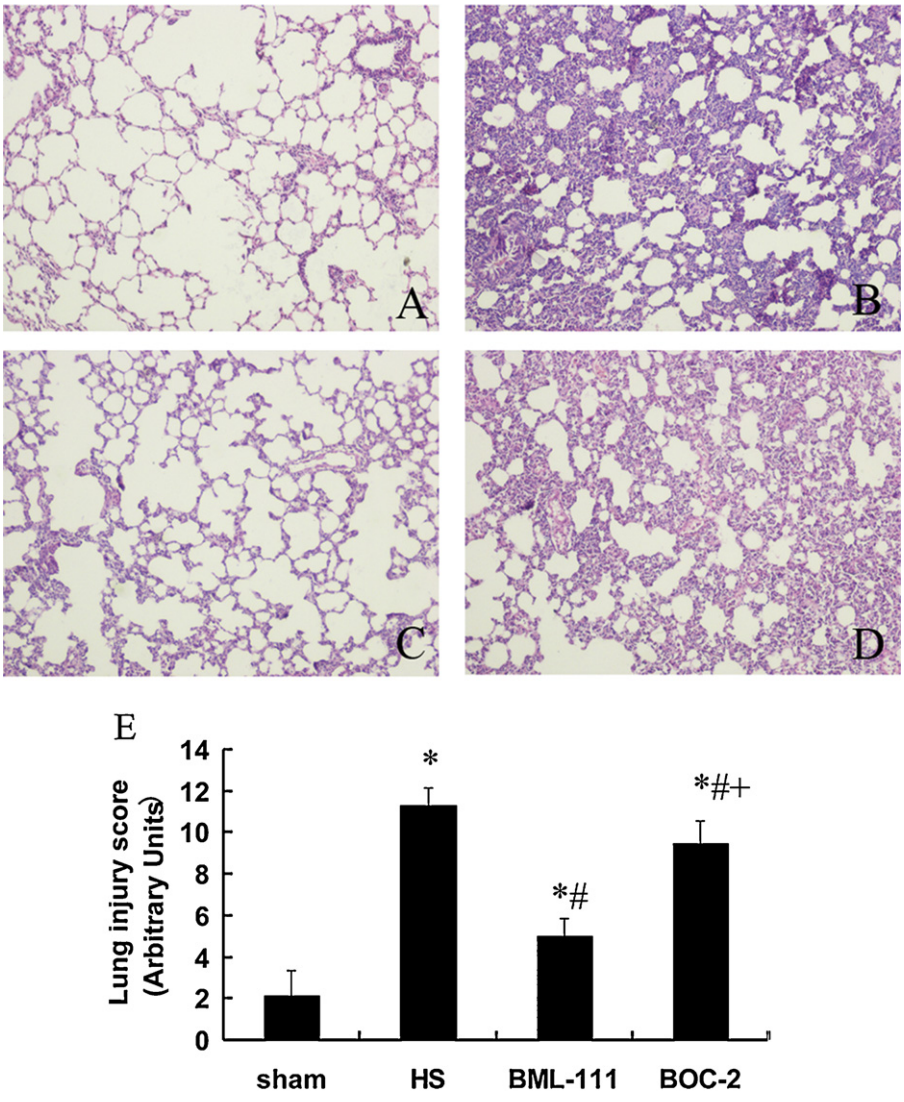

Fig. 2. BML-111 mitigated the lung injury induced by haemorrhagic shock. (A) The sham group. (B) The HS group. (C) The BML-111 group. (D) The BOC-2 group. (E) Lung injury score. Data are means ± SD. $^{*}p < 0.05$ vs. the sham group. $^{\#}p < 0.05$ vs. the HS group. $^{+}p < 0.05$ vs. the BML-111 group.