Shock. 2015 May;43(5):504-11. doi: 10.1097/SHK.0000000000000316.

Combination therapy with nitric oxide and molecular hydrogen in a murine model of acute lung injury

Huiying Liu [1], Xiaojun Liang, Dadong Wang, Hongquan Zhang, Lingling Liu, Hongguang Chen, Yuan Li, Qing Duan, Keliang Xie

Affiliations

PMID: 25643010 DOI: 10.1097/SHK.0000000000000316

Abstract

Acute lung injury (ALI) is still a leading cause of morbidity and mortality in critically ill patients. Inhaled nitric oxide (NO) has been reported to ameliorate ALI. However, reactive nitrogen species produced by NO can cause lung injury. Because hydrogen gas (H2) is reported to eliminate peroxynitrite, it is expected to reduce the adverse effects of NO. Moreover, we have found that H2 inhalation can attenuate lung injury. Therefore, we hypothesized that combination therapy with NO and H2 might afford more potent therapeutic strategies for ALI. In the present study, a mouse model of ALI was induced by intratracheal administration of lipopolysaccharide (LPS). The animals were treated with inhaled NO (20 ppm), H2 (2%), or NO + H2, starting 5 min after LPS administration for 3 h. We found that LPS-challenged mice exhibited significant lung injury characterized by the deterioration of histopathology and histologic scores, wet-to-dry weight ratio, and oxygenation index (ratio of oxygen tension to inspired oxygen fraction [Pao2/Fio2]), as well as total protein in the bronchoalveolar lavage fluid (BALF), which was attenuated by NO or H2 treatment alone. Combination therapy with NO and H2 had a more beneficial effect with significant interaction between the two. While the nitrotyrosine level in lung tissue was prominent after NO inhalation alone, it was significantly eliminated after breathing a mixture of NO with H2. Furthermore, NO or H2 treatment alone markedly attenuated LPS-induced lung neutrophil recruitment and inflammation, as evidenced by downregulation of lung myeloperoxidase activity, total cells, and polymorphonuclear neutrophils in BALF, as well as proinflammatory cytokines (tumor necrosis factor α, interleukins 1β and 6, and high-mobility group box 1) and chemokines (keratinocyte-derived chemokine, macrophage inflammatory proteins 1α and 2, and monocyte chemoattractant protein 1) in BALF. Combination therapy with NO and H2 had a more beneficial effect against lung inflammatory response. Moreover, combination therapy with NO and H2 could more effectively inhibit LPS-induced pulmonary early and late nuclear factor κB activation as well as pulmonary cell apoptosis. In addition, combination treatment with inhaled NO and H2 could also significantly attenuate lung injury in polymicrobial sepsis. Combination therapy with subthreshold concentrations of NO and H2 still had a significantly beneficial effect against lung injury induced by LPS and polymicrobial sepsis. Collectively, these results demonstrate that combination therapy with NO and H2 provides enhanced therapeutic efficacy for ALI.

Related information

LinkOut – more resources

Full Text Sources

Ovid Technologies, Inc.

Wolters Kluwer

Other Literature Sources

The Lens - Patent Citations

Research Materials

NCI CPTC Antibody Characterization Program