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Inhalation of hydrogen gas attenuates brain injury in mice with cecal ligation and puncture via inhibiting neuroinflammation, oxidative stress and neuronal apoptosis

Lingling Liu [1], Keliang Xie [2], Hongguang Chen [3], Xiaoqing Dong [4], Yuan Li [5], Yang Yu [6], Guolin Wang [7], Yonghao Yu [8]

Affiliations

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Abstract

During the development of sepsis, the complication in central nervous system (CNS), appearing early and frequently relative to other systems, can obviously increase the mortality of sepsis. Moreover, sepsis survivors also accompany long-term cognitive dysfunction, while the ultimate causes and effective therapeutic strategies of brain injury in sepsis are still not fully clear. We designed this study to investigate the effects of 2% hydrogen gas (H2) on brain injury in a mouse model of sepsis. Male ICR mice were underwent cecal ligation and puncture (CLP) or sham operation. 2% H2 was inhaled for 60min beginning at both 1 and 6h after sham or CLP operation, respectively. H2 concentration in arterial blood, venous blood and brain tissue was detected after H2 inhalation separately. The survival rate was observed and recorded within 7 days after sham or CLP operation. The histopathologic changes and neuronal apoptosis were observed in hippocampus by Nissl staining and TUNEL assay. The permeability of brain-blood barrier (BBB), brain water content, inflammatory cytokines, activities of antioxidant enzymes (SOD and CAT) and oxidative products (MDA and 8-iso-PGF2α) in serum and hippocampus were detected at 24h after sham or CLP operation. The expressions of nucleus and total nuclear factor erythroid 2-related factor 2 (Nrf2) and cytoplasmic heme oxygenase-1(HO-1) in hippocampus were measured at 24h after sham or CLP operation. We assessed their cognitive function via Y-maze and Fear Conditioning test on day 3, 5, 7 and 14 after operation. H2 treatment markedly improved the survival rate and cognitive dysfunction of septic mice. CLP mice showed obvious brain injury characterized by aggravated pathological damage, BBB disruption and brain edema at 24h after CLP operation, which was markedly alleviated by 2% H2 treatment. Furthermore, we found that the beneficial effects of H2 on brain injury in septic mice were linked to the decreased levels of inflammatory cytokines and oxidative products and the increased activities of antioxidant enzymes in serum and hippocampus. In addition, 2% H2 inhalation promoted the expression and transposition of Nrf2 and the expression of HO-1 to mitigate brain injury in sepsis. Thus, the inhalation of hydrogen gas may be a promising therapeutic strategy to relieve brain injury in sepsis.

Keywords: Cognitive function; Hydrogen gas; Inflammatory cytokines; Nrf2; Oxidative stress; Sepsis.

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