Shock. 2016 Feb;45(2):228-37. doi: 10.1097/SHK.0000000000000503.

HYDROGEN-RICH MEDIUM AMELIORATES LIPOPOLYSACCHARIDE-INDUCED BARRIER DYSFUNCTION VIA RHOA-MDIA1 SIGNALING IN CACO-2 CELLS

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PMID: 26529665 DOI: 10.1097/SHK.0000000000000503

Abstract

Gastrointestinal barrier dysfunction is associated with the severity and prognosis of sepsis. Hydrogen gas (H2) can ameliorate multiple organ damage in septic animals. Ras homolog gene family member A (RhoA) and mammalian diaphanous-related formin 1 (mDia1) are important to regulate tight junction (TJ) and adherens junction (AJ), both of which determine the integrity of the intestinal barrier. This study was aimed to investigate whether H2 could modulate lipopolysaccharide (LPS)-stimulated dysfunction of the intestinal barrier and whether RhoA-mDia1 signaling is involved. Caco-2 cells were exposed to different concentrations of LPS (1 μg/mL-1 mg/mL). The permeability of the intestinal barrier was evaluated by transepithelial resistance (TER) and fluorescein-isothiocyanate-dextran flux. Expression and distribution of occludin and E-cadherin were analyzed by Western blot and immunofluorescence. RhoA activity was measured by G-Lisa assay, and mDia1 expression was assessed by Western blot. LPS (100 μg/mL) decreased TER and increased fluorescein-isothiocyanate-dextran flux, which were alleviated by H2-rich medium. Also, H2 down-regulated LPS-induced oxidative stress. Moreover, H2 improved the down-regulated expression and redistribution of occludin and E-cadherin caused by LPS. Additionally, H2 alleviated LPS-caused RhoA activation, and the beneficial effects of H2 on barrier were counteracted by RhoA agonist CN03. Rho inhibitor C3 exoenzyme mitigated LPS-induced barrier breakdown. Furthermore, H2-rich medium increased mDia1 expression, and mDia1 knockdown abolished protections of H2 on barrier permeability. mDia1 knockdown eliminated H2-induced benefits for occludin and E-cadherin. These findings suggest that H2 improves LPS-induced hyperpermeability of the intestinal barrier and disruptions of TJ and AJ by moderating RhoA-mDia1 signaling.

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