Biochem Biophys Res Commun. 2011 Jul 22;411(1):143-9. doi: 10.1016/j.bbrc.2011.06.116. Epub 2011 Jun 23.

Molecular hydrogen inhibits lipopolysaccharide/interferon γ-induced nitric oxide production through modulation of signal transduction in macrophages

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PMID: 21723254 DOI: 10.1016/j.bbrc.2011.06.116

Abstract

Molecular hydrogen has been reported to be effective for a variety of disorders and its effects have been ascribed to the reduction of oxidative stress. However, we have recently demonstrated that hydrogen inhibits type I allergy through modulating intracellular signal transduction. In the present study, we examined the hydrogen effects on lipopolysaccharide/interferon γ LPS/IFNγ-induced nitric oxide (NO) production in murine macrophage RAW264 cells. Treatment with hydrogen reduced LPS/IFNγ-induced NO release, which was associated with a diminished induction of inducible isoform of nitric oxide synthase (iNOS). Hydrogen treatment inhibited LPS/IFNγ-induced phosphorylation of apoptosis signal-regulating kinase 1 (ASK1) and its downstream signaling molecules, p38 MAP kinase and JNK, as well as IκBα, but did not affect activation of NADPH oxidase and production of reactive oxygen species (ROS). As ROS is an upstream activator of ASK1, inhibition of ASK1 by hydrogen without suppressing ROS implies that a potential target molecule of hydrogen should be located at the receptor or immediately downstream of it. These results suggested a role for molecular hydrogen as a signal modulator. Finally, oral intake of hydrogen-rich water alleviated anti-type II collagen antibody-induced arthritis in mice, a model for human rheumatoid arthritis. Taken together, our studies indicate that hydrogen inhibits LPS/IFNγ-induced NO production through modulation of signal transduction in macrophages and ameliorates inflammatory arthritis in mice, providing the molecular basis for hydrogen effects on inflammation and a functional interaction between two gaseous signaling molecules, NO and molecular hydrogen.

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