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Molecular hydrogen stabilizes atherosclerotic plaque in low-density lipoprotein receptor-knockout mice

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Abstract

Hydrogen (H(2)) attenuates the development of atherosclerosis in mouse models. We aimed to examine the effects of H(2) on atherosclerotic plaque stability. Low-density lipoprotein receptor-knockout (LDLR(-/-)) mice fed an atherogenic diet were dosed daily with H(2) and/or simvastatin. In vitro studies were carried out in an oxidized-LDL (ox-LDL)-stimulated macrophage-derived foam cell model treated with or without H(2). H(2) or simvastatin significantly enhanced plaque stability by increasing levels of collagen, as well as reducing macrophage and lipid levels in plaques. The decreased numbers of dendritic cells and increased numbers of regulatory T cells in plaques further supported the stabilizing effect of H(2) or simvastatin. Moreover, H(2) treatment decreased serum ox-LDL level and apoptosis in plaques with concomitant inhibition of endoplasmic reticulum stress (ERS) and reduction of reactive oxygen species (ROS) accumulation in the aorta. In vitro, like the ERS inhibitor 4-phenylbutyric acid, H(2) inhibited ox-LDL- or tunicamycin (an ERS inducer)-induced ERS response and cell apoptosis. In addition, like the ROS scavenger N-acetylcysteine, H(2) inhibited ox-LDL- or Cu(2+) (an ROS inducer)-induced reduction in cell viability and increase in cellular ROS. Also, H(2) increased Nrf2 (NF-E2-related factor-2, an important factor in antioxidant signaling) activation and Nrf2 small interfering RNA abolished the protective effect of H(2) on ox-LDL-induced cellular ROS production. The inhibitory effects of H(2) on the apoptosis of macrophage-derived foam cells, which take effect by suppressing the activation of the ERS pathway and by activating the Nrf2 antioxidant pathway, might lead to an improvement in atherosclerotic plaque stability.

Keywords: Endoplasmic reticulum stress; Free radicals; Hydrogen; Macrophage apoptosis; NF-E2-related factor-2; Plaque stability.

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