[文章编号] 1007-3949(2011)19-03-0277-01 ·研究论文摘要·

Hydrogen-rich Saline Reduces Atherogenesis in Apolipoprotein E Knockout Mice Fed a High-fat Diet by Inhibiting the Non-HDL-mediated Arterial Inflammation and Promoting the Expression of Genes Involving Reverse Cholesterol Transport

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[**KEY WORDS**] Hydrogen; apoB-containing Lipoprotein; Inflammation; Atherosclerosis

Aim Hydrogen (dihydrogen, H_2) is an effective antioxidant to reduce oxidative stress and oxidative stress is implicated in atherogenesis. In this study we examined whether hydrogen-saturated saline can prevent atherosclerosis in apolipoprotein E knockout ($apoE^{-/-}$) mice fed either chow diet or high-fat diet, and characterized the underlying molecular mechanisms. **Methods and Results** The atherosclerotic lesion formation displayed by oil red O staining positive area was reduced significantly in either aortic root section or aortic arch en face in hydrogen administrated $apoE^{-/-}$ mice fed either chow diet or high-fat diet, compared to the control. Plasma analysis by enzymatic method showed that total cholesterol (TC) and non-high-density lipoprotein cholesterol (non-HDL-C) were remarkably decreased by treatment with hydrogen. Western blot analysis revealed a significant decrease of both plasma apolipoprotein B (apoB) level and hepatic expression of apoB after hydrogen treatment, suggesting hydrogen could downregulate the expression of the major protein constituent of non-HDL. In addition, spectrophotometric measurement showed that plasma levels of malondialdehyde (MDA) and serum amyloid A was decreased and paraoxonase-1 activity was increased in mice treated with hydrogen, suggesting plasma lipid oxidation and peroxidation was impaired by hydrogen treatment. Besides, the MDA content of the non-HDL, which separated by ultracentrifugation from the plasma of mice treated with and without hydrogen, was reduced by hydrogen, suggesting the oxidation of non-HDL was impaired by hydrogen. Moreover, we found hydrogen treatment significantly suppressed the production of tumor necrosis factor-α (TNF-α) and interleukin-6 in RAW264.7 macrophages after stimulation with the isolated non-HDL, suggesting hydrogen reduces atherogenesis by inhibiting non-high-density lipoprotein (HDL)-mediated inflammation. Furthermore, immunohistochemistry of aortic valve sections revealed that hydrogen attenuated lesion formation by suppressing the expression of several proinflammatory factors and decreasing vessel wall infiltration of macrophages, indicating hydrogen-treatment reduces arterial inflammation.

Besides, real-time PCR and western blot analysis disclosed that the expression of several transporter genes involved in the process of reverse cholesterol transport, including hepatic scavenger receptor class B type I (SR-BI), ATP-binding cassette (ABC) transporters ABCG8, ABCB4, ABCB11, and macrophage SR-BI, were all induced by hydrogen treatment. **Conclusion** These results revealed that administration of hydrogen-rich saline reduces atherogenesis in $apoE^{-/-}$ mice fed a high-fat diet by inhibiting the non-HDL-mediated arterial inflammation and promoting the expression of genes involving reverse cholesterol transport.

[基金项目] 山东省泰山学者工程专项基金(200867)

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(此文编辑 曾学清)