P-49

Hypoxanthine Induces Cholesterol Accumulation in Hepatocytes and Incites Atherosclerosis in Apoliprotein E Deficient Cells and Mice

Hye-Myung Ryu, You-Jin Kim, Eun-Joo Oh, Se-Hyun Oh, Ji-Young Choi
Jang-Hee Cho, Chan-Duck Kim, Sun-Hee Park, Yong-Lim Kim

Division of Nephrology and Department of Internal Medicine, Kyungpook National University Hospital

Background: Reactive oxygen species (ROS) generation during purine metabolism is associated with xanthine oxidase and uric acid. However, the direct effect of hypoxanthine on ROS generation and atherosclerosis has not been evaluated. Smoking and heavy drinking are associated with elevated levels of hypoxanthine. In this study, we investigated the role of hypoxanthine on cholesterol synthesis and atherosclerosis development, particularly in apolipoprotein E (APOE)-deficient mice.

Methods and Results: The effect of hypoxanthine on the regulation of cholesterol synthesis and atherosclerosis were evaluated in cultured HepG2 cells and Apoe knockout (KO) mice. In HepG2 cells, hypoxanthine increased intracellular ROS production. Hypoxanthine increased cholesterol accumulation and decreased APOE and ATP-binding cassette transporter A1 (ABCA1) mRNA and protein expression in HepG2 cells. Furthermore, H2O2 also increased cholesterol accumulation and decreased APOE and ABCA1 expression. This effect was partially reversible by pre-treatment with the antioxidant N-acetyl cysteine. Hypoxanthine and APOE knockdown using APOE-siRNA synergistically induced cholesterol accumulation and reduced APOE and ABCA1 expression. Hypoxanthine markedly increased serum cholesterol levels and the atherosclerotic plaque area in Apoe KO mice.

Conclusions: Hypoxanthine induces cholesterol accumulation in hepatic cells through alterations in enzymes that control lipid transport and induces atherosclerosis in APOE-deficient cells and mice. These effects are partially mediated through ROS produced in response to hypoxanthine.

Key Words: Atherosclerosis, apoE, Hypoxanthine