Uric acid activates extracellular signal-regulated kinases and thereafter endothelin-1 expression in rat cardiac fibroblasts.

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摘要

Abstract

BACKGROUND: The association between hyperuricemia and cardiovascular diseases has long been recognized. Elevated levels of uric acid may have a causal role in hypertension and cardiovascular diseases. However, the direct effect of uric acid on cardiac cells remains unclear. Therefore, this study was aimed to examine the effect of uric acid in rat cardiac fibroblasts and to identify the putative underlying signaling pathways. METHODS: Cultured rat cardiac fibroblasts were stimulated with uric acid; cell proliferation and endothelin-1 (ET-1) gene expression were examined. The effect of uric acid on NADPH oxidase activity, reactive oxygen species (ROS) formation, and extracellular signal-regulated kinases (ERK) phosphorylation were tested to elucidate the intracellular mechanism of uric acid in ET-1 gene expression. RESULTS: Uric acid-increased cell proliferation and ET-1 gene expression. Uric acid also increased NADPH oxidase activity, ROS formation, ERK phosphorylation, and activator protein-1 (AP-1)-mediated reporter activity. Antioxidants suppressed uric acid-induced ET-1 gene expression, and ERK phosphorylation, and AP-1 reporter activities. Mutational analysis of the ET-1 gene promoter showed that AP-1 binding site was an important cis-element in uric acid-induced ET-1 gene expression. CONCLUSIONS: These results suggest that uric acid-induced ET-1 gene expression, partially by the activation of ERK pathway via ROS generation in cardiac fibroblasts

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