Angiotensin II induces endothelin-1 gene expression via extracellular signal-regulated kinase pathway in rat aortic smooth muscle cells

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摘要

Abstract

Angiotensin II (Ang II) increases vascular endothelin-1 (ET-1) tissue levels, which in turn mediate a major part of Ang II-stimulated vascular growth and hypertension in vivo. Ang II also stimulates reactive oxygen species (ROS) generation in vascular smooth muscle cells (SMCs). However, whether ROS are involved in Ang II-induced ET-1 gene expression and the related intracellular mechanisms in vascular SMCs remains to be determined. Methods: Cultured rat aortic SMCs were stimulated with Ang II, [3H]thymidine incorporation and the ET-1 gene expression was examined. Antioxidants pretreatment on Ang II-induced extracellular signal-regulated kinase (ERK) phosphorylation were performed to elucidate the redox-sensitive pathway in proliferation and ET-1 gene expression. Results: Ang II-increased DNA synthesis was inhibited by AT1 receptor antagonist (olmesartan) and ETA receptor antagonist (BQ485). ET-1 gene was induced with Ang II as revealed by Northern blotting and promoter activity assay. Ang II-increased intracellular ROS levels were inhibited by olmesartan and antioxidants. Antioxidants suppressed Ang II-induced ET-1 gene expression and ERK phosphorylation. An ERK inhibitor U0126 fully inhibited Ang II-induced ET-1 expression. Co-transfection of dominant negative mutant of Ras, Raf and MEK1 attenuated the Ang II-increased ET-1 promoter activity, suggesting that the Ras-Raf-ERK pathway is required for Ang II-induced ET-1 gene. Truncation and mutational analysis of the ET-1 gene promoter showed that activator protein-1 (AP-1) binding site was an important cis-element in Ang II-induced ET-1 gene expression. Moreover, Ang II- or H2O2-induced AP-1 reporter activities were also inhibited by antioxidants. Conclusions: Our data suggest that ROS are involved in Ang II-induced proliferation and the redox-sensitive ERK pathway plays a role in ET-1 gene expression in rat aortic SMCs.

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