17 beta-estradiol downregulates angiotensin II-induced endothelin-1 gene expression in rat aortic smooth muscle cells

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摘要

Abstract

It is well documented that 17-estradiol (E2) exerts a cardiovascular protective effect. A possible role of E2 in the regulation of endothelin-1 (ET-1) production has been reported. However, the complex mechanisms by which E2 inhibits ET-1 expression are not completely understood. The aims of this study were to examine whether E2 may alter angiotensin II (Ang II)-induced cell proliferation and ET-1 gene expression and to identify the putative underlying signaling pathways in rat aortic smooth muscle cells. Cultured rat aortic smooth muscle cells were preincubated with E2, then stimulated with Ang II, and [3H]thymidine incorporation and ET-1 gene expression were examined. The effect of E2 on Ang-II-induced extracellular signal-regulated kinase (ERK) phosphorylation was tested to elucidate the intracellular mechanism of E2 in proliferation and ET-1 gene expression. Ang II increased DNA synthesis which was inhibited with E2 (1-100 nM). E2, but not 17-estradiol, inhibited the Ang-II-induced ET-1 gene expression as revealed by Northern blotting and promoter activity assay. This effect was prevented by coincubation with the estrogen receptor antagonist ICI 182,780 (1 μM). E2 also inhibited Ang-II-increased intracellular reactive oxygen species (ROS) as measured by a redox-sensitive fluorescent dye, 2',7'-dichlorofluorescin diacetate, and ERK phosphorylation. Furthermore, E2 and antioxidants, such as N-acetylcysteine and diphenylene iodonium, decreased Ang-II-induced cell proliferation, ET-1 promoter activity, ET-1 mRNA, ERK phosphorylation, and activator protein-1-mediated reporter activity. In summary, our results suggest that E2 inhibits Ang-II-induced cell proliferation and ET-1 gene expression, partially by interfering with the ERK pathway via attenuation of ROS generation. Thus, this study provides important new insight regarding the molecular pathways that may contribute to the proposed beneficial effects of estrogen on the cardiovascular system.

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