17 beta-estradiol inhibits cyclic strain-induced endothelin-1 gene expression within vascular endothelial cells

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摘要

Abstract

It has been well documented previously that 17beta-estradiol (E-2) exerts a protective effect on cardiovascular tissue. The possible role of E-2 in the regulation of endothelin (ET)-1 production has been previously reported, although the complex mechanisms by which E-2 inhibits ET-1 expression are not completely understood. The aims of this study were to examine whether E-2 was able to alter strain-induced ET-1 gene expression and also to identify the putative underlying signaling pathways that exist within endothelial cells. For cultured endothelial cells, E-2 (1-100 nM), but not 17 alpha-estradiol, inhibited the level of strain-induced ET-1 gene expression and also peptide secretion. This inhibitory effect elicited by E-2 was able to be prevented by the coincubation of endothelial cells with the estrogen receptor antagonist ICI-182,780 (1 muM). E-2 also inhibited strain-enhanced NADPH oxidase activity and intracellular reactive oxygen species (ROS) generation as measured by the redox-sensitive fluorescent dye 2',7'-dichlorofluorescin diacetate and the level of extracellular signal-regulated kinase (ERK) phosphorylation. Furthermore, the presence of E-2 and antioxidants such as N-acetylcysteine and diphenylene iodonium were able to elicit a decrease in the level of strain-induced ET-1 secretion, ET-1 promoter activity, ET-1 mRNA, ERK phosphorylation, and activator protein-1 binding activity. In summary, we demonstrated, for the first time, that E-2 inhibits strain-induced ET-1 gene expression, partially by interfering with the ERK pathway via the attenuation of strain-induced ROS generation. Thus this study delivers 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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