Nitric Oxide Inhibits Endothelin-1-Induced Cardiomyocyte Hypertrophy through cGMP-mediated Suppression of Extracellular-Signal Regulated Kinase Phosphorylation

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摘要

Abstract

Cardiac hypertrophy is a compensatory mechanism in response to a variety of cardiovascular diseases. Recently, reactive oxygen species and nitric oxide (NO) have been demonstrated to be involved in the pathogenesis of atherosclerosis; however, the role of these free radicals in the development of cardiac hypertrophy remains unclear. In this study, we investigate NO modulation of cellular signaling in endothelin-1 (ET-1)-induced cardiomyocyte hypertrophy in culture. ET-1 treatment of cardiomyocytes increased constitutive NO synthase activity and induced NO production via the stimulation of ET-receptor subtype ET(B). Using Northern blot analysis and chloramphenicol acetyltransferase assay, we found that NO suppressed the ET-1-induced increase in c-fos mRNA level and promoter activity. In contrast, ET-1 stimulation of c-fos expression was augmented by depletion of endogenous NO generation with the addition of NO scavenger PTIO into cardiomyocytes. Cells cotransfected with the dominant negative and positive mutants of signaling molecules revealed that the Ras/Raf/extracellular-signal regulated kinase (ERK) signaling pathway is involved in ET-induced c-fos gene expression. Furthermore, NO directly inhibited ET-1-induced ERK phosphorylation and activation in a cGMP-dependent manner, indicating that NO modulates ET-1-induced c-fos

expression via its inhibitory effect on ERK signaling pathway. The ET-1-stimulated activator protein-1 (AP-1) DNA binding activity and AP-1-mediated reporter activity were attenuated by NO. In addition, NO also significantly inhibited ET-1-stimulated promoter activity of hypertrophic marker gene beta-myosin heavy chain and the enhanced protein synthesis. Taken together, our findings provide the molecular basis of NO as a negative regulator in ET-1-induced cardiac hypertrophy.