Role of mitogen-activated protein kinase pathway in reactive oxygen species-mediated endothelin-1-induced beta-myosin heavy chain gene expression and cardiomyocyte hyptertrophy

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摘要

Abstract

Endothelin-1 (ET-1) has been found to increase cardiac beta- myosin heavy chain (beta-MyHC) gene expression and induce hypertrophy in cardiomyocytes. ET-1 has been demonstrated to increase intracellular reactive oxygen species (ROS) in cardiomyocytes. The exact molecular mechanism by which ROS regulate ET-1-induced beta-MyHC gene expression and hypertrophy in cardiomyocytes, however, has not yet been fully described. We aim to elucidate the molecular regulatory mechanism of ROS on ET-1- induced beta-MyHC gene expression and hypertrophic signaling in neonatal rat cardiomyocytes. Following stimulation with ET-1, cultured neonatal rat cardiomyocytes were examined for H-3-leucine incorporation and beta-MyHC promoter activities. The effects of antioxidant pretreatment on ET-1- mduced cardiac hypertrophy and mitogen-activated protein kinase (MAPKs) phosphorylation were studied to elucidate the redox- sensitive pathway in cardiomyocyte hypertrophy and beta-MyHC gene expression. ET-1 increased H- 3-leucine incorporation and beta-MyHC promoter activities, which were blocked by the specific ETA receptor antagonist BQ-485. Antioxidants significantly reduced ET-1-induced H-3-leucine incorporation , beta-MyHC gene promoter activities and MAPK (extracellular signal-regulated kinase. p38, and c-Jun NH2-terminal kinase) phosphorylation. Both PD98059 and SB 203580 inhibited ET-1- increased H-3-leucine incorporation and beta-MyHC promoter activities. Co-transfection of the dominant negative mutant of Ras, Raf, and MEK1 decreased the ET-1-induced beta-MyHC promoter activities, suggesting that the Ras-Raf-MAPK pathway is required for ET-1 action. Truncation analysis of the beta-MyHC gene promoter showed that the activator protein-2 (AP-2)/specificity protein-1 (SP-1) binding site(s) were(was) important cis-element(s) in ET-1-induced beta- MyHC gene expression. Moreover, ET-1-induced AP-2 and SP-1 binding activities were also inhibited by antioxidant. These data demonstrate the involvement of ROS in ET-1-induced hypertrophic responses and beta-MyHC expression. ROS mediate ET-1-induced activation of MAPK pathways, which

culminates in hypertrophic responses and beta-MyHC expression..

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