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MOLECULAR MECHANISM OF ENDOTHELIN-1-INDUCED CARDIOMYOCYTE HYPERTROPHY

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BACKGROUND/AIMS: Recently, reactive oxygen species (ROS) 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 investigated ROS and NO modulation of cellular signaling in the endothelin-1 (ET-1)-induced cardiomyocyte hypertrophy.

METHODS: Cultured neonatal rat cardiomyocytes were stimulated with ET-1, and β-myosin heavy chain (β-MHC) expression, H^3-leucine incorporation, and sarcomere assembly were examined. We also examined the effect of antioxidants and NO donor on ET-1-induced cardiomyocyte hypertrophy and mitogen-activated protein kinase (MAPK) phosphorylation to elucidate the hypertrophic signaling pathway.

RESULTS: We demonstrated that: a) ET-1 treatment of cardiomyocytes increases intracellular ROS generation via Ras pathway, which modulates ET-1-induced *c-fos* and β-MHC gene expression; b) antioxidants inhibit all four components of hypertrophic response, i.e., the induction of immediate-early gene, expression of fetal gene, and increased protein synthesis and sarcomere assembly; c) ET-1 increases NOS activity and NO formation via ET_B receptor stimulation in cardiomyocytes; d) ET-1-induced *c-fos* and β-MHC gene expression are inhibited by NO via the ERK signaling pathway in a cGMP-dependent manner; and e) NO inhibits ET-1-stimulated protein synthesis and sarcomere organization in cardiomyocytes.

DISCUSSION/CONCLUSIONS: Our findings provide the molecular mechanism of ROS and NO, acting as positive and negative regulators, respectively, in ET-1-induced cardiac hypertrophy and may offer clinical implications for the therapeutic potential of antioxidant and NO donor treatment against the transition from compensatory hypertrophy to intractable heart failure.

Key words: Reactive oxygen species, Nitric oxide, Cardiomyocyte hypertrophy