Involvement of reactive oxygen species in urotensin II-induced proliferation of cardiac fibroblasts

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摘要

Abstract

Urotensin II, a cyclic dodecapeptide, has recently been demonstrated to play an important role in cardiac remodeling and fibrosis. Cardiac fibroblast is the cell type known to proliferate during cardiac fibrosis and to produce the excess matrix proteins characteristic of cardiac remodeling. However, the effect of urotensin II on cardiac fibroblast proliferation and the intracellular mechanisms remain to be clarified. Cultured neonatal rat cardiac fibroblasts were stimulated with urotensin II, cell proliferation and the reactive oxygen species generation were examined. We also examined the effects of antioxidant pretreatment on urotensin II-induced cell proliferation, extracellular signal-regulated kinase phosphorylation, and the tyrosine phosphorylation of epidermal growth factor receptor, to elucidate the redox-sensitive pathway in urotensin II-induced cell proliferation. Urotensin II-increased cell proliferation and intracellular reactive oxygen species levels which were inhibited by antioxidants N-acetylcysteine, and the flavin inhibitor diphenyleneiodonium. Urotensin II potently activated the tyrosine phosphorylation of epidermal growth factor receptors and extracellular signal-regulated kinase. Pretreatment of cells with U0126, an inhibitor of the upstream activator of mitogen-activated protein kinase kinase, or with AG1478, a selective epidermal growth factor receptor kinase inhibitor, reduced the urotensin II-increased extracellular signal-regulated kinase phosphorylation. Antioxidants, U0126, and AG1478, all significantly inhibited urotensin II-increased cell proliferation in cardiac fibroblasts. Our data suggest that the redox-sensitive intracellular signaling pathway plays a role in urotensin II-induced proliferation in rat cardiac fibroblasts.

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