Fibrotic response induced by angiotensin-II requires NAD(P)H oxidase-induced reactive oxygen species (ROS) in skeletal muscle cells

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Resumen

Fibrotic disorders are typified by excessive connective tissue and extracellular matrix (ECM) deposition that precludes normal healing processes in different tissues. Angiotensin-II (Ang-II) is involved in the fibrotic response. Several muscular dystrophies are characterized by extensive fibrosis. However, the exact role of Ang-II in skeletal muscle fibrosis is unknown. Here we show that myoblasts responded to Ang-II by increasing protein levels of connective tissue growth factor (CTGF/CCN2), collagen-III and fibronectin. These Ang-II-induced pro-fibrotic effects were mediated by AT-1 receptors. Remarkably, Ang-II induced reactive oxygen species (ROS) via a NAD(P)H oxidase-dependent mechanism, as shown by inhibition of ROS production via the NAD(P)H oxidase inhibitors diphenylene iodonium (DPI) and apocynin. This increase in ROS is critical for Ang-II-induced fibrotic effects, as indicated by the decrease in Ang-II-induced CTGF and fibronectin levels by DPI and apocynin. We also show that Ang-II-induced ROS production and fibrosis require PKC activity as indicated by the generic PKC inhibitor chelerythrine.

These results strongly suggest that the fibrotic response induced by Ang-II is mediated by AT-I receptor and requires NAD(P)H-induced ROS in skeletal muscle cells.

Palabras clave

Palabras clave de autor: Angiotensin-II; Fibrosis; NAD(P)H oxidase; Skeletal muscle; Reactive oxygen species (ROS); AT-1 receptor

KeyWords Plus: DUCHENNE MUSCULAR-DYSTROPHY; LEUKOCYTE NADPH OXIDASE; OXIDATIVE STRESS; RENAL FIBROSIS; CARDIAC FIBROSIS; EXPRESSION; PROTEOGLYCANS; P47(PHOX); DECORIN; PHOSPHORYLATION