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Angiotensin II-induced pro-fibrotic effects require p38MAPK activity and transforming growth factor beta 1 expression in skeletal muscle cells.

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Abstract

Fibrotic disorders are typically characterised by excessive connective tissue and extracellular matrix (ECM) deposition that preclude the normal healing of different tissues. Several skeletal muscle dystrophies are characterised by extensive fibrosis. Among the factors involved in skeletal muscle fibrosis is angiotensin II (Ang-II), a key protein of the renin-angiotensin system (RAS). We previously demonstrated that myoblasts responded to Ang-II by increasing the ECM protein levels mediated by AT-1 receptors, implicating an Ang-II-induced reactive oxygen species (ROS) by a NAD(P)H oxidase-dependent mechanism. In this paper, we show that in myoblasts, Ang-II induced the increase of transforming growth factor beta 1 (TGF-β1) and connective tissue growth factor (CTGF) expression through its AT-1 receptor. This effect is dependent of the NAD(P)H oxidase (NOX)-induced ROS, as indicated by a decrease of the expression of both pro-fibrotic factors when the ROS production was inhibited via the NOX inhibitor apocynin. The increase in pro-fibrotic factors levels was paralleled by enhanced p38MAPK and ERK1/2 phosphorylation in response to Ang-II. However, only the p38MAPK activity was critical for the Ang-II-induced fibrotic effects, as indicated by the decrease in the Ang-II-induced TGF-β1 and CTGF expression and fibronectin levels by SB-203580, an inhibitor of the p38MAPK, but not by U0126, an inhibitor of ERK1/2 phosphorylation. Furthermore, we showed that the Ang-II-dependent p38MAPK activation, but not the ERK1/2 phosphorylation, was necessary for the NOX-derived ROS. In addition, we demonstrated that TGF-β1 expression was required for the Ang-II-induced pro-fibrotic effects evaluated by using SB-431542, an inhibitor of TGF-βRI kinase activity, and by knocking down TGF-β1 levels by shRNA technique. These results strongly suggest that the fibrotic response to Ang-II is mediated by the AT-1 receptor and requires the p38MAPK phosphorylation, NOX-induced ROS, and TGF-β1 expression increase mediated by Ang-II in skeletal muscle cells.