ANGIOTENSIN-II TYPE 1 RECEPTOR (AT1) AND NOX2 MEDIATE TCF/LEF AND CREB DEPENDENT WISP1 INDUCTION AND CARDIOMYOCYTE HYPERTROPHY

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Angiotensin-II (Ang-II) plays a key role in myocardial hypertrophy, remodeling and failure. We investigated whether Ang-II-induced cardiomyocyte hypertrophy is dependent on WNT1 inducible signaling pathway protein 1 (WISP1), a pro growth factor. Ang-II induced hypertrophy and WISP1 expression in neonatal rat cardiomyocytes (NRCM), effects that were significantly inhibited by pre-treatment with the AT1 antagonist losartan and by WISP1 knockdown. Further, Ang-II induced WISP1 was superoxide-dependent, and inhibited by DPI, an inhibitor of NADPH oxidases, and by knockdown of NOX2. AT1 physically associated with NOX2 both in vitro and in vivo, and Ang-II increased this interaction in vivo. Ang-II induced WISP1 expression via superoxide/Akt/GSK3β/β-catenin/TCF/LEF and by Akt-dependent CREB activation. Further, Ang-II also activated CREB via superoxide-mediated p38MAPK and ERK activation. Continuous infusion of Ang-II for 7 days induced myocardial hypertrophy in rats, and was associated with increased Akt, phospho-Akt, p-p38 MAPK, p-ERK1/2, and WISP1 expression. These results demonstrate that Ang-II induced cardiomyocyte hypertrophy is mediated through AT1, NOX2 and the induction of WISP1, and may involve the direct interaction of AT1 with NOX2. Thus targeting both WISP1 and NOX2 may have a therapeutic potential in improving cardiomyocyte survival and growth following myocardial injury and remodeling.

This work was supported by Veterans Affairs Office of Research and Development Biomedical Laboratory Research and Development Service Award 1I01BX000246 and the NHLBI Grant HL-86787.