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ANGIOTENSIN II ACTIVATES MYOSTATIN EXPRESSION IN CULTURED RAT NEONATAL CARDIOMYOCYTES VIA INSULIN-LIKE GROWTH FACTOR-1 AND THROUGH P38 MAP KINASE PATHWAY

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BACKGROUND: Angiotensin II (AngII) plays a critical role in cardiac remodeling and promotes cardiac myocyte hypertrophy. Myostatin, a negative regulator of muscle growth, is increased in hypertrophied and infarcted hearts. The direct effect of AngII on cardiac myocyte myostatin expression has not been previously investigated. We hypothesized that myostatin may act as a cardiac chalone for AngII.

METHODS AND RESULTS: AngII-induced myostatin protein expression in cultured rat neonatal cardiomyocytes was dose-dependent. AngII at 10 nM showed the maximal effect to enhance myostatin protein expression in cardiomyocytes. AngII significantly increased the insulin-like growth factor-1 (IGF-1) secretion from myocytes. IGF-1 significantly increased myostatin protein and mRNA expression in a time- and dose-dependent manner. Addition of losartan or IGF-1 monoclonal antibody 30 min before AngII stimulation significantly blocked the increase of myostatin protein by AngII. Addition of losartan 30 minutes before IGF-1 stimulation did not affect the myostatin protein expression induced by IGF-1. The IGF-1-induced increase of myostatin protein was almost completely attenuated after the addition of p38 mitogen-activated protein (MAP) kinase inhibitor, SB203580, and p38 siRNA 30 minutes before IGF-1 stimulation. Gel shifting assay showed a significant increase of DNA-protein binding activity of myocyte enhance factor 2 **(**MEF2) after IGF-1 treatment, and SB203580 and IGF-1 monoclonal antibody abolished the DNA-protein binding activity induced by IGF-1. IGF-1 or AngII alone significantly increased myocyte protein synthesis. Co-stimulation with myostatin and IGF-1 significantly inhibited the protein synthesis induced by IGF-1. Co-stimulation with myostatin and AngII also significantly attenuated the protein synthesis by AngII.

CONCLUSION: AngII enhances myostatin expression in cultured rat neonatal cardiomyocytes. The AngII-induced myostatin expression is mediated by IGF-1 at least in part through p38 MAP kinase and MEF2 pathways.

Key words: myostain, angiotensin II, cardiomyocyte