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Differential Angiotensin II Signaling in the Left and Right Atria

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The atria respond to various stimuli including pressure and volume overload as well as neuro-hormonal stimulation. Such stimulation can induce beneficial physiological reactions (modification of compliance, production of reactive substances) or pathological processes (atrial remodeling and arrhythmia). The left atrium is known to differ from the right for both reactions. Angiotensin II is a key mediator of cardiac hormonal response. We focused our attention on ATF3, an immediate early gene found at the receiving end of multiple stress and growth stimuli including angiotensin II. Angiotensin II injection (1.0 mg/Kg I.P.) induces ATF3 RNA and protein expression levels. We localized ATF3 protein to cardiomyocytes using immuno-histochemistry. Pre-treatment with an angiotensin receptor blocker (losartan) inhibits the response. Using ATF3 promoter constructs we demonstrate that ATF3 expression is regulated by angiotensin-receptor-mediated signaling at the transcriptional level in vitro (in a blood pressure independent manner). Whereas acute beta-adrenergic (isoproterenol 2.5mg/Kg) stimulus induces ATF3 expression in both atria and ventricles, acute exposure of mice to angiotensin II results in ATF3 expression only in the left atrium and ventricles but not in the right atrium. Conversely, continuous exposure (either 2 weeks osmotic pump or repeated injections) of mice to angiotensin II results in ATF3 expression specifically in the left atrium. The spatial regulation of ATF3 expression is probably post- receptor and may involve STAT3 signaling and helix-loop-helix protein inhibitors. The differential response to angiotensin II may explain differential responses of the right and left atria and since most pathological processes occur in the left atrium this may pose a potential target for altering atrial remodeling.