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**Dissertations-Kurzfassung**

**Overexpression of the human angiotensin II type I receptor in neonatal cardiac myocytes directly promotes hypertrophic responses to angiotensin II in vitro**

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The Renin Angiotensin System (RAS) plays an important role in the control of blood pressure and cardiac growth and function through its vasoactive peptide Angiotensin II (Ang II). Most of its known actions are transmitted via AT1 receptors which are localized on blood vessels as well as on the heart. Furthermore, both cardiac myocytes and non-myocytes possess these receptors. Therefore, it is difficult to dissect the complex pattern of Ang II actions on the heart, which could include cardiac myocyte hypertrophy due to wall stress by increased blood pressure, due to direct growth effects on myocytes and due to increased release of growth factors from cardiac non-myocytes. To address the hypothesis that Ang II can induce cardiac hypertrophy apart from high blood pressure via direct actions on cardiac myocytes we developed transgenic rats overexpressing the human AT1 receptor gene specifically in cardiac myocytes. The overexpressed transgenic AT1 receptors augmented cardiac hypertrophy induced by other stimuli, but did not initiate hypertrophic growth in vivo.

Since compensatory mechanisms could be developed in vivo the aim of the present study was to investigate the AT1 receptor function in neonatal ventricular myocytes and to target the issue whether the AT1 receptors on ventricular myocytes are coupled to cell hypertrophy. Therefore we established a cell culture system for very pure neonatal cardiac myocytes and for co-culture of cardiac myocytes/non-myocytes (ratio 3:1). The experiments were performed on both transgenic (high AT1 receptor density) and non-transgenic (low AT1 receptor density). Three parameters were utilized to test hypertrophic response, namely cell area, the rate of protein synthesis and ANP release, as well as the expression of  $\alpha$ -sarcomeric actin. Cells were stimulated with vehicle, Ang II, AT1 receptor antagonist CV-11974, AT2 receptor antagonist PD-123319, Ang II+CV-11974, Ang II+PD-123319, respectively. The results from SD culture confirmed the those previous studies which demonstrated that the hypertrophic response of cardiac myocytes to Ang II requires the participation of non-myocytes. However, TGR myocytes displayed hypertrophy and remodeling in the absence of non-myocytes when treated with Ang II. This was indicated by significantly enlarged and widened cells, increases of [ $^3$ H] leucine incorporation and ANP expression, and up-regulated  $\alpha$ -sarcomeric actin. Moreover, CV-11974 suppressed these changes and PD-123319 had no influence on them. Furthermore, the up-regulation of  $\alpha$ -sarcomeric actin in nontreated TGR myocytes was observed, which is an important parameter for hypertrophic growth, whereas, apart from this, no significant differences were displayed between nonstimulated TGR and SD myocytes regarding growth and morphology.

The present investigation demonstrates that the overexpressed AT1 receptor causes the up-regulation of  $\alpha$ -sarcomeric actin. Though overexpressed AT1 receptor is not sufficient to trigger a hypertrophic response, it can enhance it. Ang II stimulation can induce cardiac myocyte hypertrophy directly through AT1 receptor on myocytes. Therefore, the hypertrophic response requires both overexpressed AT1 receptors and high activity of the RAS. The study provides a useful model to elucidate the mechanisms of actions of Ang II.