Increased angiotensin AT_2 receptor expression is associated with neonatal cardiac growth restriction in a genetic model of adult cardiac hypertrophy

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Angiotensin II has important trophic and inotropic actions on the heart via AT_1 and AT_2 receptor subtypes. Receptor expression is known to be developmentally regulated,[1] yet the roles of the receptors in relation to cardiomyocyte growth and function during early development are poorly understood. The goal of this study was to determine whether there is disturbed balance of cardiac angiotensin receptor expression in the neonate of the Hypertrophic Heart Rat (HHR), a model in which normotensive cardiac hypertrophy has been demonstrated at maturity.[2] Links between altered receptor expression, neonatal myocardial growth and evidence of defective ionic homeostasis were examined. HHR and control strain Normal Heart Rat (NHR) neonates were sacrificed by decapitation at postnatal days 1, 2, and 3 and ventricle weights were determined. Ventricular mRNA expression levels of AT_{1A} and AT_2 were measured in 2 day neonates by real-time RT-PCR (Rotor-Gene 3000, Corbett Research). At post-natal day 2, HHR ventricles weighed approximately 25% less than NHR ventricles (26.09 ± 0.68 mg vs 34.44 ± 0.70 mg, $p < 0.05$, n = 10/8). This difference was also significant when ventricular weights were normalised to body weight (4.36 ± 0.19 mg/g vs 5.01 ± 0.08 mg/g, $p < 0.05$). This growth phenotype was associated with an up-regulation of AT_2 receptor and a concomitant down-regulation of AT_{1A} receptor expression. Additionally, there was a down-regulation of sodium-calcium exchanger (NCX1.1) and sodium-hydrogen exchanger (NHE-1) mRNA in the HHR neonates. These findings suggest that early suppression of ventricular growth may be associated with the later development of cardiac and cardiomyocyte hypertrophy seen in mature HHR. This neonatal growth state is characterised by high ventricular AT_2 expression and indication of altered myocyte Ca^{2+} and pH homeostasis.

(1) Harrap SB, Danes VR, Ellis JA, Griffiths CD, Jones EF, Delbridge LMD. Physiological Genomics. 2002; 9: 43-48.
(2) Bastien NR, Ciuffo GM, Saavedra JM, Lambert C. Regulatory Peptides. 1996; 63: 9-16.