The Hypertrophic Heart Rat (HHR) exhibits enhanced myocardial PI3-K mediated signalling in the neonate, but not in the adult

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Hypertrophy of the heart represents a significant cardiovascular risk, independent of blood pressure. There is growing appreciation that adult cardiovascular disease states may be 'programmed' in early life, though the influence of perinatal growth on the development of adult cardiac hypertrophy has not been established. We have previously identified a genetic locus (*Lvm-1*) in the spontaneously hypertensive rat (SHR) associated with heart size but not blood pressure, and developed the Hypertrophic Heart Rat (HHR) as a normotensive model of adult primary cardiac hypertrophy (Harrap *et al.*, 2002). As phenotypic characterization revealed neonatal cardiac growth restriction relative to the control Normal Heart Rat (NHR), this study compared the expression and activation of selected intermediates of growth signalling pathways in young and adult HHR and NHR.

Neonatal (post-natal day 2, n =7) and adult (12 week old, n = 10) male NHR/HHR were anaesthetized with halothane inhalation, and hearts excised and immediately placed in liquid nitrogen. Ventricles were homogenized at 4°C in a HEPES/sucrose buffer using an Ultra-Turrax tissue grinder, with samples centrifuged at 3,000g for 5 minutes at 4˚C to recover the cytosolic fraction. Equal amounts of protein were subsequently loaded onto polyacrylamide gels (10%) for SDS-PAGE/Western blot analysis (quantified as relative expression units).

Marked hypertrophy was observed in adult HHR hearts, however, no changes in the phosphorylation status of Akt (1.14 ± 0.09 *vs* 1.00 ± 0.05, HHR *vs* NHR, p = ns), GSK3β (1.14 ± 0.12 *vs* 1.00 ± 0.12, p = ns) or ERK1/2 (1.03 ± 0.04 *vs* 1.00 ± 0.04, p = ns) were observed (*vs* NHR). Total calcineurin expression was similarly unchanged (1.19 ± 0.10 *vs* 1.00 ± 0.10, p = ns). In contrast to the adult, neonatal HHR hearts were smaller than NHR controls. This was associated with an increase in Akt phosphorylation (2.31 ± 0.53 *vs* 0.99 ± 0.07, p = 0.029), and a decrease in phosphorylation of both GSK3β (0.46 ± 0.06 *vs* 1.00 ± 0.17, $p < 0.01$) and ERK1/2 (0.82 ± 0.04 *vs* 1.00 ± 0.05, $p < 0.01$). Calcineurin expression was unchanged (0.98 ± 0.09 *vs* 1.00 ± 0.05, p = ns).

These differential activities are consistent with augmented PI3-K mediated 'physiological' growth signalling in the neonatal HHR. These findings indicate that where there is a genetic pre-disposition for hypertrophy, transient growth signalling perturbation in the neonate is observed and may represent an important modeling event in determining the occurrence of adult hypertrophy.

Harrap SB, Danes VR, Ellis JA, Griffiths CD, Jones EF, Delbridge LM (2002). *Physiological Genomics*, **9:** 43-8.