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A ROLE FOR THE GLUCOCORTICOID RECEPTOR IN CARDIAC REMODELLING?

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Variation in the glucocorticoid receptor (GR) associates with relative glucocorticoid resistance, hypertension and increased cardiovascular disease risk in humans. Mice heterozygous for the glucocorticoid receptor (GR+/−) are similarly glucocorticoid resistant with raised circulating glucocorticoid levels and elevated blood pressure; susceptibility to heart disease is uncharacterised. Here we describe the cardiac phenotype of adult male GR+/− mice and show evidence of impaired cardiac remodelling in response to pharmacological challenge.

Heart weight (% body weight) is unchanged in 12 week old GR +/− mice (WT:0.57±0.03%, GR+/−:0.61±0.03%), but cardiomyocyte cross-sectional area is reduced (WT:240±21 μm^2, GR+/−:193 ±9.0 μm^2, $p<0.05$), and cardiac nuclei density is increased (nuclei/field; WT:67±1, GR+/−:74±2, $p<0.05$), suggesting GR+/− mice have more but smaller cardiomyocytes than WT. Whilst histological analysis does not reveal differences in fibrosis, cardiac levels of mRNA encoding connective tissue growth factor are reduced in GR+/− mice (WT:100±12%, GR+/−:65±4%, $p<0.05$) implying subtle alterations in pro-fibrotic signalling. Echocardiography demonstrates comparable cardiac function in 10 week old GR+/− and WT mice.

Intriguingly, preliminary data show cardiac hypertrophy in response to angiotensin II infusion (100 ngkg-1 min-1 by osmotic mini-pump) is attenuated in GR+/− mice (heart weight/tibia length Vehicle: WT 7.47±0.326 mg/mm, GR+/−7.29 mg/mm; AngII: WT 8.66±0.249 mg/mm, GR+/−8.07±0.217 mg/mm, $p<0.05$ (AngII treatment)).

These data show that GR deficiency alters the size and number of cardiomyocytes and that, whilst adult GR+/− mice match WT cardiac function under basal conditions, cardiac remodelling following pathological challenge is attenuated. Further characterisation of the GR+/− cardiac phenotype may provide critical insights into how GR variation in humans increases risk of heart disease.