ALPHA CALCITONIN GENE-RELATED PEPTIDE PLAYS A PROTECTIVE ROLE IN BOTH AN ACUTE AND SUSTAINED MODEL OF HYPERTENSION, A MECHANISM WHICH MAY BE LINKED TO THE LOSS OF ENDOTHELIAL NITRIC OXIDE SYNTHASE (ENOS) AS THE HYPERTENSION PROGRESSES

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doi:10.1136/heartjnl-2013-304019.204

Calcitonin gene-related peptide (CGRP) is a sensory nerve-derived neuropeptide, and its potent microvascular vasodilator activities have been suggested to be protective in a range of murine models of hypertension using the genetically mutant mouse. The aim of this study was to learn of the influence of αCGRP on vascular mechanisms in the acute angiotensin-II (Ang II) murine model of hypertension, and then assess whether αCGRP remains involved at the vascular level in an established model of Ang II induced hypertension. Hypertension was established in C57BL/6 wildtype (WT) and αCGRP knockout (KO) mice using the osmotic minipump with Ang II (1.1 mg/kg/day for 14 days, 0.9mg/kg/day for 28 days) or vehicle (saline) as described previously. Blood pressure was recorded by tail-cuff plethysmography until days 14 or 28. Vascular hypertrophy was assessed by histology and mRNA expression was measured by RT-qPCR. Data were analysed using ANOVA plus Bonferroni’s test. CGRP does not play a role in blood pressure regulation under normotensive conditions in WT and αCGRP KO mice. Systolic pressure significantly increased after 14 days Ang II in WT (129±3.84) and αCGRP KOs (140±7.23, p<0.001), this being significantly enhanced in the αCGRP KOs (p<0.001). This exacerbated hypertensive response was still apparent at day 28 (204±9.8, p<0.01). The hypertensive response in the WT at day 14 was accompanied by an elevation of αCGRP mRNA expression in the aorta. This expression was progressively more upregulated by day 28 (p<0.01). Nitric oxide (NO) is an important cellular signalling molecule, and its endothelial source eNOS plays a role in vascular homeostasis, with a shift in the redox state resulting in diminished eNOS bioavailability and the onset of oxidative stress and vascular damage. At day 14 aortic eNOS mRNA was downregulated in the aorta of hypertensive subjects. This was accompanied by vascular remodelling, characterised by increased collagen expression, antioxidant markers (SOD and GPX) and markers of oxidative stress (NOX-2). This remodelling and mRNA expression was exacerbated in Ang II-treated αCGRP KOs (p<0.5, p<0.001). At day 28, this eNOS mRNA expression was diminished further, vascular hypertrophy was progressively worse, and antioxidant expression was no longer visible in the αCGRP KOs, suggesting a progressed and possibly irreversible hypertensive state. This study provides evidence suggesting a non-acute protective role for αCGRP in the Ang II model of hypertension. Mechanisms by which αCGRP is protective still remain to be elucidated, however eNOS and antioxidant signalling pathways may be involved, whereby αCGRP expression is enhanced to compensate for a lack of eNOS signalling in the onset and progression of hypertension and vascular damage. S-J Smillie is funded by the BHF and an IMB capacity building grant.

REFERENCE