A potentially protective role for CGRP and its receptor components in angiotensin-II induced hypertension?

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Sensory nerves contain and release the potent vasodilator calcitonin gene-related peptide, CGRP. This peptide is considered to play a positive role in wound healing and protects in neuro-vascular conditions and vascular related stress (Brain & Grant 2004). However, the protective mechanisms are less well understood. The purpose of this study was to determine the role of CGRP and its receptor in angiotensin II (Ang II) induced hypertension and vascular inflammation.

Age and sex matched C57BL/6 wildtype (WT) and CGRP knockout (KO) mice, aged 8 weeks, were used. The animals were anaesthetised using isoflurane (4%) and osmotic minipumps, filled with either angiotensin II (Ang II, 1.1 mg/kg/day for 14 days) or vehicle (saline), were implanted. Post surgery, pain relief was provided with buprenorphine (50µg/kg s.c.). Blood pressure was monitored via tail cuff plethysmography, and vascular hypertrophy assessed via histological and molecular techniques (RT-qPCR). The CGRP receptor components were also studied by looking at mRNA expression by RT-qPCR. At baseline there was no significant difference in systolic pressure in WT (119.3±0.53, n=8) and CGRP KO (120.2±0.53, n=8) mice. Following 14 days of Ang II infusion, systolic pressure was significantly increased in both WT and KO mice (p<0.001). However, at both days 7 and 14, hypertension was significantly increased in the CGRP KO mice compared to their WT counterparts (p<0.001). Vascular hypertrophy was observed in the aortas of the hypertensive as compared to normotensive animals, characterised by increased smooth muscle cell proliferation and collagen deposition. Total width (µm) and area (µm²) was significantly increased in the CGRP KO infused with Ang II in comparison to WT (p<0.001). Immunohistochemical analysis of VCAM-1 in the aorta showed increased expression in the hypertensive animals, that was significantly increased in the CGRP KO compared to WT mice (p<0.001). These trends also mirrored mRNA expression levels in both the aorta (p<0.001) and the kidney (p<0.05). Analysis of plasma inflammatory cytokine concentrations showed elevated levels of IL-1β, 6 and 12 in the CGRP Ang II treated KO’s compared to controls (p<0.01 and 0.001). IL-6 was significantly increased in the hypertensive CGRP KO compared to hypertensive WT (p<0.01). Heterodimerization of CLR with RAMP1 and also possibly RAMP3 forms functional CGRP receptors at the cell surface. CLR mRNA expression was shown to be upregulated in the aorta of the Ang II groups, regardless of genotype (p<0.05). In addition, increased mRNA expression of RAMP1 was observed in the kidney in CGRP KOs only. RAMP3 expression was not significantly altered. We conclude that CGRP KO mice are more susceptible to Ang II-induced hypertension and vascular injury. This data provides evidence to suggest a potentially protective role for CGRP in Ang II induced hypertension in terms of both blood pressure regulation and vascular inflammation, which may in turn be a novel target for the treatment of the vascular inflammation aspects. However the precise mechanisms via which CGRP exerts the protection are at present unknown.

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