

Endothelin-1 and calcitonin gene-related peptide are both involved in hypertension; evidence from 2 experimental models of hypertension

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Introduction: recently we provided in vivo evidence that the vasodilator calcitonin gene-related peptide (CGRP) can selectively terminate the potent and long lasting vasoconstriction caused by binding of endothelin-1 (ET-1) to ET_A-receptors in various vascular beds (Meens et al; Hypertension; July 2011). We hypothesize the participation of both ET-1 and CGRP in hypertension. This concept was tested in 2 experimental models of hypertension: the spontaneously hypertensive rat (SHR) and the Cyp1a1-Ren-2 transgenic rat (TGR).

Animals and methods: in 4 weeks old TGR high blood pressure was induced by dietary addition of 0.3% indole-3-carbinole (I3C) for 4 weeks (iTGR). I3C activates the Cyp1A1 promoter of the mouse Ren-2 gene. Control TGR (cTGR) received a standard diet. Two days after implantation of an indwelling catheter mean arterial pressure (MAP) was recorded in 8 weeks old TGR. Similarly MAP was recorded in age-matched SHR and normotensive Wistar Kyoto (WKY) rats. Next, rats were sacrificed and cardiac and renal tissue was collected to monitor ET-1 and CGRP content via radio immuno assay. Also renal gene expression of pre-pro-ET-1, endothelin converting enzyme (ECE-1), neutral endopeptidase (NEP), the ET_A- and ET_B- receptor and the CGRP-receptor components receptor activity modifying protein 1 (RAMP-1) and calcitonin receptor-like receptor (CRLR) was measured in TGR.

Results: after I3C stimulation, blood pressure markedly increased in iTGR, reaching a MAP of 200 mmHg. In 8 weeks old SHR MAP was increased by 40 mmHg compared to WKY. Cardiac as well as renal ET-1 and CGRP levels were significantly increased in iTGR compared to cTGR. In 8 weeks old SHR both cardiac and renal ET-1 content as well as renal CGRP content markedly increased compared to age-matched WKY. In contrast cardiac CGRP levels were lower in SHR than in WKY. Compared to cTGR renal expression of the ET_B- receptor was significantly decreased and RAMP-1 expression was significantly increased in iTGR. No differences in the expression of pre-pro-ET-1, ECE-1, NEP, ET_A-receptor and CRLR between iTGR and cTGR were observed.

Conclusion: these data indicate the potential involvement of ET-1 and CGRP in 2 models of experimental hypertension and it is for the first time that we demonstrate the involvement of both peptides in the transgenic Cyp1a1-Ren-2 model of inducible hypertension. Finally, while ET-1 content was increased in both models, CGRP content appeared to be locally and differentially regulated.

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