CYP1A1-REN2 TRANSGENIC RATS WITH ANG II-DEPENDENT MALIGNANT HYPERTENSION EXHIBIT MAINTAINED KIDNEY ANGIOTENSINOGEN mRNA EXPRESSION AND ELEVATED PRORENIN RECEPTOR LEVELS.


Department of Physiology, Tulane Hypertension and Renal Center of Excellence, Tulane University School of Medicine, New Orleans, LA.

The Cyp1a1-Ren2 transgenic [TGR(Cyp1a1Ren2)] rat, an inducible model of Ang II-dependent hypertension by activation of the inserted mouse Ren2 gene with dietary administration of the aryl hydrocarbon, indole-3-carbinol (I3C), exhibits increased Ang II content in kidney cortex and medulla due in part to internalization mediated by AT_{1}R, as well as potentially de novo intrarenal Ang II formation. We have suggested that coordinated actions among angiotensinogen (AGT)-derived from proximal tubules and renin and prorenin receptors –(P)RR present in collecting ducts (CD) may help to explain increased intrarenal Ang II de novo formation in Ang II-dependent hypertension. In this study, we examined the gene expression of AGT, as well as (P)RR and renin in the CD from renal tissues of TGR(Cyp1a1Ren2) rats (n=4) fed a normal diet containing 0.3% I3C for ten-days to induce ANG II-dependent malignant hypertension in an attempt to correlate them with the elevated intrarenal Ang II levels. AGT mRNA levels measured by qRT-PCR were not significantly different between hypertensive Cyp1a1-Ren2 rats and non-induced normotensive rats (n=4) (AGT=0.75±0.15 AU vs. 1.00±0.1 AU). Although, transcript levels of the mouse Ren2 renin were undetectable and those of the endogenous rat renin gene (Ren 1c) were significantly lower in kidney medulla of hypertensive rats, kidney medulla renin contents were similar to those in non-induced control rats (3067±414 vs. 3398±420 μg ANG l/hr/g). Kidney cortex renin content was significantly elevated in the hypertensive rats (659±36 vs. 470±35 μg ANG l/hr/g, P<0.01). Importantly, (P)RR mRNA and protein levels were significantly higher in renal medullary tissues of hypertensive Cyp1a1-Ren2 rats than in control rats [(mRNA: 3.7±0.3 vs. 1.9±0.1AU)(protein: 0.03±0.0 vs. 0.01 vs. 0.0 DU)]. These data indicate that the elevated intrarenal ANG II levels observed in Cyp1a1-Ren2 rats with malignant hypertension are associated with maintained kidney medullary renin content and AGT mRNA levels, elevated kidney cortex renin content and increased medullary (P)RR mRNA and protein levels. Such maintained intrarenal AGT generation and medullary renin content
together with the increased cortical renin content and elevated kidney medullary (P)RR levels likely contribute to the elevated intrarenal ANG II levels and, thereby, to the development of malignant hypertension in Cyp1a1-Ren2 transgenic rats.

This study was supported by the Tulane COBRE in Hypertension and Renal Biology (NCRR 2P20RR017659-06), and NHLBI grant HL26371.