ENHANCED URINARY ANGIOTENSINOGEN EXCRETION IN CYP1A1-REN2 TRANSGENIC RATS WITH INDUCIBLE ANG II-DEPENDENT MALIGNANT HYPERTENSION.

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Previous studies have demonstrated that ANG II-infusion in normal rats results in paradoxical increases in renal expression of angiotensinogen mRNA and protein. In addition, the urinary excretion of angiotensinogen is significantly increased in ANG II-infused hypertensive rats, which is associated with an augmentation of intrarenal ANG II levels. These findings suggest that urinary angiotensinogen excretion rates provide an index of intrarenal ANG II levels in ANG II-dependent hypertensive states. However, little information is available regarding the urinary excretion of angiotensinogen in ANG II-dependent malignant hypertension. The present study was performed to determine if urinary angiotensinogen excretion is increased in Cyp1a1-Ren2 transgenic rats [strain name: TGR(Cyp1aRen2)] with inducible ANG II-dependent malignant hypertension. Adult male Cyp1a1-Ren2 rats (n=6) were fed a normal diet containing 0.3% indole-3-carbinol (I3C) for 10 days to induce ANG II-dependent malignant hypertension. Rats induced with I3C exhibited pronounced increases in systolic blood pressure (SBP) (208±7 vs. 127±3 mmHg, P<0.001), marked proteinuria (29.4±3.6 vs. 5.0±0.4 mg/day, P<0.01), and augmented urinary angiotensinogen excretion (996±186 vs. 199±19 mg/day, P<0.05). Chronic administration of the AT$_1$ receptor antagonist, candesartan (25 mg/L in drinking water, n=6), prevented the I3C-induced increases in SBP (125±5, P<0.001), proteinuria (7.3±1.5 mg/day, p<0.001) and urinary angiotensinogen excretion (488±51 mg/day, P<0.05). The present findings confirm that AT$_1$ receptor activation contributes to the increase in SBP and proteinuria in Cyp1a1-Ren2 transgenic rats with ANG II-dependent malignant hypertension. These data also demonstrate that the urinary excretion of angiotensinogen is markedly augmented in ANG II-dependent malignant hypertension. Such increased urinary angiotensinogen excretion likely reflects an AT$_1$ receptor-mediated stimulation of intrarenal angiotensinogen production which may contribute to augmented intrarenal ANG II levels and, thereby, to the increased blood pressure in Cyp1a1-Ren2 transgenic rats with inducible ANG II-dependent malignant hypertension.
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