CHRONIC DIRECT RENIN INHIBITION WITH ALISKIREN PREVENTS THE DEVELOPMENT OF HYPERTENSION IN CYP1A1-REN2 TRANSGENIC RATS WITH INDUCIBLE ANG II-DEPENDENT HYPERTENSION

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In Cyp1a1-Ren2 transgenic rats [strain name: TGR(Cyp1a1Ren2)], the induction of the Cyp1a1 promoter by dietary administration of the aryl hydrocarbon, indole-3-carbinol (I3C), drives hepatic expression of the Ren2 renin gene and results in the development of angiotensin (ANG) II-dependent hypertension. Although AT1 receptor blockade prevents the development of hypertension in this model little information is available regarding the blood pressure and renal functional responses to direct renin inhibition in this high circulating renin model of hypertension. The present study was performed to determine the effects of chronic direct renin inhibition on blood pressure and renal hemodynamics in Cyp1a1-Ren2 transgenic rats with slowly progressive ANG II-dependent hypertension. Male Cyp1a1-Ren2 rats (n=6) were fed a normal diet containing 0.15% I3C for 16 days to induce slowly progressive ANG II-dependent hypertension. Conscious systolic blood pressure (SBP) was measured daily using tail-cuff plethysmography. The rats were then anesthetized with pentobarbital sodium and surgically prepared for the measurement of mean arterial pressure (MAP) and renal hemodynamic and excretory function. In rats induced with I3C, SBP increased by day 3 (130±7 to 160±5 mmHg, P<0.01) and continued to increase to 191±6 mmHg (P<0.001) by day 16. In a separate group of rats (n=6), chronic administration of the direct renin inhibitor, aliskiren (30 mg/kg/day, sc), prevented the development of hypertension (113±5 vs. 114±5 mmHg, NS). Rats treated with aliskiren exhibited significantly lower MAP (138±4 vs. 201±6 mmHg, P<0.001), renal vascular resistance (23±4 vs. 38±3 mmHg/ml/min.g, P<0.01), urine flow (17.6±1.5 vs. 25.1±3 μL/min, P<0.05), and urinary sodium excretion (1.11±0.32 vs. 2.35±0.28 μEq/min, P<0.05), and higher renal plasma flow (4.22±0.23 vs. 2.56±0.21 ml/min.g, P<0.01) and glomerular filtration rate (1.19±0.07 vs. 0.78±0.08 ml/min.g, P<0.01), compared with induced rats not treated chronically with aliskiren. The present findings demonstrate that acute direct renin inhibition with aliskiren prevents the development of ANG II-dependent hypertension and the associated decrease in renal hemodynamic and excretory function in Cyp1a1-Ren2 transgenic rats with slowly progressive ANG II-dependent hypertension. The data also show that renin generated as a consequence of expression of the Ren2 gene is responsible for the development of slowly progressive ANG II-dependent hypertension and the associated derangements in renal hemodynamics and excretory function in Cyp1a1-Ren2 transgenic rats.

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