DIRECT RENIN INHIBITION WITH ALISKIREN NORMALIZES BLOOD PRESSURE AND PROTEINURIA IN CYP1A1-REN2 TRANSGENIC RATS WITH INDUCIBLE ANG II-DEPENDENT MALIGNANT HYPERTENSION.

Catherine G. Howard and Kenneth D. Mitchell.
Department of Physiology, Tulane Hypertension and Renal Center of Excellence, Tulane University School of Medicine, New Orleans, LA.

In Cyp1a1-Ren2 transgenic rats [strain name: TGR(Cyp1a1Ren2)], the induction of the Cyp1a1 promoter by dietary administration of 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 and normalizes the elevated arterial blood pressure of hypertensive Cyp1-Ren2 transgenic rats, little information is available regarding the blood pressure and renal functional responses to direct inhibition of renin in this high circulating renin model of ANG II-dependent hypertension. The present study was performed to determine the effects of acute direct renin inhibition with aliskiren on blood pressure and renal hemodynamics in Cyp1a1-Ren2 transgenic rats with ANG II-dependent malignant hypertension. Male Cyp1a1-Ren2 rats (n=6) were fed a normal diet containing the aryl hydrocarbon, indole-3-carbinol (I3C; 0.3%, wt/wt), for 8-10 days to induce malignant hypertension. Mean arterial pressure (MAP) and renal hemodynamics were measured in pentobarbital-anesthetized male Cyp1a1-Ren2 rats during control conditions and following administration of the renin inhibitor, aliskiren (10 mg/kg, iv). Rats induced with I3C had higher MAP (196±4 vs. 135±5 mmHg, P<0.001) and lower renal plasma flow (RPF; 2.67±0.46 vs. 3.65±0.32 ml/min.g, P<0.05) than non-induced rats (n=6). There were no differences in glomerular filtration rate (GFR) between the two groups. Aliskiren administration decreased MAP (190±5 to 120±5 mmHg, P<0.01) and increased RPF (2.67±0.46 vs. 1.98±0.32 ml/min.g, P<0.05) in hypertensive but not in normotensive rats. GFR remained unaltered following aliskiren administration in both groups. Aliskiren did not alter MAP in the normotensive rats. The present data demonstrate that acute renin inhibition with aliskiren normalizes MAP and improves RPF in Cyp1a1-Ren2 transgenic rats with malignant hypertension. The normalization of MAP and the increased RPF following acute renin inhibition with aliskiren indicate that renin generated as a consequence of expression of the Ren2 gene is responsible for the
development of malignant hypertension and the associated reduced renal hemodynamic function in Cyp1a1-Ren2 transgenic rats.

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