REDUCED DISTAL NEPHRON SODIUM REABSORPTION IN CYP1A1-REN2 TRANSGENIC RATS WITH INDUCIBLE ANG II-DEPENDENT MALIGNANT HYPERTENSION.

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In addition to its well documented stimulatory actions on proximal tubular sodium reabsorption, ANG II also exerts a direct stimulatory action on distal nephron salt and water reabsorption in normotensive states. However, the ANG II-dependence of distal nephron sodium reabsorption in ANG II-dependent forms of hypertension remains uncertain; in particular, in ANG II-dependent malignant hypertension. The present study was performed to determine whether ANG II exerts a stimulatory action on distal nephron sodium reabsorption in Cyp1a1-Ren2 transgenic rats [strain name: TGR(Cyp1a1-Ren2)] with inducible ANG II-dependent malignant hypertension. Adult male Cyp1a1-Ren2 transgenic 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. To assess distal nephron sodium reabsorptive function, we compared sodium excretion before and after blockade of the two main distal nephron sodium transporters by intravenous administration of amiloride (AMIL; 5 mg/kg of body weight) plus bendrofulmethiazide (BFTZ; 12 mg/kg of body weight) in pentobarbital sodium-anesthetized (50 mg/kg, IP) Cyp1a1-Ren2 transgenic rats. Cyp1a1-Ren2 transgenic rats induced with 0.3% I3C exhibited a substantially elevated mean arterial pressure (MAP) (185±5 vs. 135±5 mmHg, P<0.001) compared with non-induced normotensive rats (n=6). Administration of AMIL+BFTZ increased urinary sodium excretion in both the hypertensive rats (4.5±1.0 vs. 1.5±0.5 μEq/min, P<0.05) and in the non-induced control rats (9.5±2.5 vs. 1.2±0.5 μEq/min, P<0.01). However, the magnitude of the increase in sodium excretion elicited by AMIL+BFTZ was substantially greater in the hypertensive rats (P<0.01). Distal nephron sodium delivery was higher in the non-induced control rats than in the hypertensive rats (9±2 vs. 4±2 μEq/min, P<0.01). Similarly, absolute distal nephron sodium reabsorption and fractional reabsorption of distal nephron sodium delivery were markedly lower in the hypertensive rats than in the normotensive control rats (2±0.5 vs. 7.5±2.0 μEq/min and 65±7 vs. 90±2 %, respectively, P<0.01 in both cases). These findings demonstrate that distal nephron sodium delivery is markedly decreased in Cyp1a1-Ren2 rats...
with malignant ANG II-dependent malignant hypertension suggesting that segments proximal to
the distal nephron have increased sodium reabsorptive rates. The data also show that distal
sodium reabsorptive function is substantially decreased in these transgenic rats. Such impaired
distal nephron sodium reabsorptive function suggests that ANG II-dependent stimulation of
distal nephron sodium reabsorption does not contribute substantively to the hypertension in
Cyp1a1-Ren2 transgenic rats with ANG II-dependent malignant hypertension.

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