THESIS TITLE : THE RENIN - ANGIOTENSIN SYSTEM AND THE DEVELOPMENT OF RENAL FUNCTION IN CONSCIOUS RATS.

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ABSTRACT

Many lines of evidence indicate that the renin-angiotensin system (RAS) not only plays important roles in blood pressure control and renal function, but also is a growth factor. This study tests the hypothesis that the RAS is important for growth and renal function development in conscious Sprague-Dawley rats. The animals were divided into 6 groups: untreated control (control) (n = 9), lifetime oral captopril (400 mg/L in drinking water) treatment from conception onward (lifetime) (n = 9), continuous oral captopril treatment from lactation period (lactation) (n = 10), continuous oral captopril treatment from post-lactation period (post-lactation) (n = 11), two-day treatment (short-term) (n = 13), and discontinuation after five-week captopril treatment from the conception onward (discontinuation) (n = 9). At 7-8 weeks of age, male Sprague-Dawley rats were implanted with femoral arterial, venous, and bladder catheters. Forty-eight hours later, arterial pressure was continuously measured in restrained, awake rats before, during, and after an intravenous infusion of isotonic saline (5% of body weight, 0.5 ml/min). Urine and blood samples were collected before and up to 90 minutes after saline infusion. Body, heart, and kidney weights decreased in all captopril treated rats. The body weight, not the heart and kidney weights, was linearly correlated to the treatment duration ($Y = -1.08X + 218.66$, $r = -0.92$, respectively; $P < 0.05$). While basal mean arterial pressure

declined in the same manner as the body weight, basal heart rate was not significantly different among the six groups. In addition, they displayed no significant mean arterial pressure and heart rate responses during saline infusion. On captopril discontinuation, the basal mean arterial pressure returned to the same level as the control (112.6 ± 2.7 vs. 114.6 ± 1.4 mm Hg, discontinuation vs. control, respectively; $P > 0.05$) whereas the body weight was partially recovered but remained significantly lower than the control (207.0 ± 4.9 vs. 221.2 ± 4.0 g, discontinuation vs. control, respectively; $P < 0.05$). While the heart weight did not differ from the control after drug discontinuation, the kidney weight was significantly increased (2.20 ± 0.15 vs. 1.86 ± 0.04 g, discontinuation vs. control, respectively; $P < 0.05$). Water diuresis and glomerular filtration rate of all continuous captopril treated groups were attenuated in response to acute saline load, but not correlated to the duration of RAS inhibition and the basal mean arterial pressure. There were no differences among groups. Natriuretic responses to saline load were significantly attenuated in a similar manner among the lifetime, the lactation, and the post-lactation, but not the short term. These changes of renal function persisted even after 2-3 weeks of captopril discontinuation. Fractional water and sodium excretion was almost similar among the six groups. In contrast to water and sodium, potassium excretion decreased only in the discontinuation. The present study indicates that the RAS is necessary for the growth and renal function development in the Sprague-Dawley rats. Continuous of RAS inhibition from the early life causes abnormalities in growth, blood pressure control, and renal glomerular function in adult rats, but the discontinuous treatment appears to be more deleterious.