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Renin Angiotensin System and Kidney Growth

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The renin-angiotensin system plays an important role in renal growth and development : exposure of the neonate to ACE inhibitor increases mortality and results in growth retardation and abnormal renal development. Renin-angiotensin system (RAS) of neonate is also activated than that of adult. ANG II is necessary for normal embryonic and postnatal kidney development. In vitro, ANG II stimulates renal cell growth - increases DNA synthesis in tubular epithelial cells, increases rapid cell division in LLCPK1 cells, and stimulates renal proximal tubular cell hypertrophy and proliferation. We have demonstrated that ACE inhibition in the developing kidney reduces the renal expression of TGF-β1 and EGF, which may account for renal growth impairment (Pediatr Res 42:588-592, 1997). This study was designed to investigate the relationship between this growth impairment, and 1) apoptosis, cell proliferation, bcl-2 and clusterin expression, 2) expression of developmentally regulated growth factor receptors. Newborn rat pups were treated with enalapril (30 mg/kg/d) or vehicle for 7 d, and kidneys were removed for Masson-trichrome stain, semiquantitative RT-PCR, immunohistochemistry and western blotting of bcl-2, clusterin, PDGF (AA, BB), PDGF receptors (PDGFR-α, β), TGFβ1 and TGFβ receptors (type I and type II). Distribution of apoptosis was determined by modified TUNEL technique and PCNA for cell proliferation was stained by immunohistochemistry. Enalapril treatment resulted in increased mortality by day 7 and reduced body weight ($p<0.05$ versus vehicle group). Enalapril increased renal apoptosis and decreased PCNA positive proliferating cells especially in cortical tubular epithelial cells ($p<0.05$). Renal bcl-2 and clusterin mRNA expression was increased ($p<0.05$), but bcl-2 and clusterin protein expression was decreased by enalapril treatment. Also, by immunohistochemistry and western blotting, enalapril decreased renal PDGF-AA, PDGF-BB, PDGFR-α, PDGFR-β, TGFβ1 and TGFβ type I receptor protein expressions ($p<0.05$). TGFβ type I receptor mRNA expression by RT-PCR were decreased by enalapril treatment ($p<0.05$). These results indicate that ACE inhibition in the developing kidney - 1) increases apoptosis and decreases cell proliferation, 2) decrease bcl-2 and clusterin protein expression, 3) decreases PDGF, PDGFR, TGFβ1 and TGFβ type I receptor expressions, which may account for renal growth impairment.