Enalapril Increases Fibrosis, Osteopontin and Tissue Inhibitor of Metalloproteinase (TIMP)-2 Expression in the Neonatal Rat Kidney

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The renin-angiotensin system plays an important role in renal growth and development: exposure of the neonate to angiotensin converting enzyme (ACE) inhibitor increases mortality and results in growth retardation and abnormal renal development including tubular atrophy and increased interstitial extracellular matrix. We have demonstrated that ACE inhibition in the developing kidney also decreases TGFβ1 and TGFβ type I receptor expression (Pediatr Nephrol 18:865-871, 2003). This study was designed to investigate the modulating effect of ACE inhibition to the mechanism of renal fibrosis and expression of its control cytokines in the normal neonatal rat kidney. Newborn rat pups were treated with enalapril (30 mg/kg/d) or vehile for 7d, and to detect evidence of renal fibrosis, Masson-Trichrome (MT) stain, immunehistochemical stain and western blotting of α Smooth muscle actin (SMA) & collagen type I were performed. Addition to this, immunehistochemical stain and western blotting were used to detect the changes of osteopontin, matrix metalloproteinase (MMP)-2, and TIMP-2.

Enalapril treatment resulted in 24% mortality by day7, reduced body weight, decreased glomerular diameter and caused tubular dilatation ($p<0.05$). In MT stain, interstitial volume of renal cortex was increased, and collagen type I & SMA were increased by enalapril on immunehistochemical stain ($p<0.05$). Osteopontin and TIMP-2 expressions were increased also by enalapril on immunehistochemical stain and western blotting ($p<0.05$), but MMP-2 expressions revealed no changes between groups.

These results indicate that ACE inhibition in normal neonatal rat increases renal fibrosis (SMA and collagen) and it might depend on increased expression of osteopontin and TIMP-2.