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Enalapril Induces Dysregulation of Angiogenesis-related Genes and Loss of Microvasculature in the Neonatal Rat Kidney

Hyung Eun Yim, Kee Hwan Yoo, Eun Soo Bae, Young Sook Hong, Joo Won Lee

Korea University College of Medicine, Department of Pediatrics

Background: We aimed to investigate the effect of angiotensin II inhibition on the expression of angiogenesis-related genes and microvascular endothelial cells in neonatal rat kidney.

Methods: Newborn rat pups were treated with enalapril (30 mg/kg/d) or vehicle for 7 days after birth. The grade of tubular injury and glomerular maturity was determined by hematoxylin and eosin stain. Intrarenal expressions of angiopoietin-1, angiopoietin-2, Tie-2, and thrombospondin-1 were investigated with Western blots and immunohistochemical staining at postnatal day 8. For determination of capillary density, the endothelial cell marker aminopeptidase P (JG-12) was also assessed.

Results: Enalapril-treated rats demonstrated a higher score of tubular injury and a lower grade of glomerular maturity ($p<0.05$). In the enalapril-treated group, angiopoietin-2, Tie-2 and thrombospondin-1 protein expression were significantly increased whereas angiopoietin-1 expression was decreased, as compared to the control group ($p<0.05$). Immunohistochemical staining of kidney sections for JG-12 showed a dense capillary network in cortex and medulla from control rats; however, enalapril-treated kidney showed a reduced endothelial immunostaining ($p<0.05$). The number of JG12-positive endothelial cells showed a positive correlation with the grade of glomerular maturation ($r= 0.948$, $p<0.001$) and a negative correlation with the tubular alteration grade ($r= -0.842$, $p<0.05$).

Conclusion: Our findings suggest that enalapril treatment can induce the dysregulation of angiopoietin system and thrombospondin-1 genes and the loss of renal microvasculature, which may be relevant to the pathogenesis of structural deterioration caused by angiotensin II inhibition in the neonatal rat kidney.

Key Words: Angiogenic proteins, Capillary endothelial cells, Angiotensin