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Early Treatment with Enalapril Aggravates Renal Injury in Postnatally Overfed Rats: Differential Modification of Enalapril in Lean and 'programmed' Obese Rats

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Deleterious long-term renal effects of a postnatal overnutrition have been addressed. We recently showed dysregulated renin angiotensin system (RAS) activity and a resulting renal impairment may play a role in the renal malprogramming induced by early postnatal overfeeding. In this study, we aimed to investigate the role of angiotensin II blockade on the renal pathophysiological changes of postnatally overfed rats. Male pups were assigned to either a small litter (Obese group; three pups per mother) or a normal litter (Lean group; ten pups per mother) during the first 21 days of life. These pups were randomized into four groups and treated with enalapril (Obese enalapril, OE; Lean enalapril, LE) or vehicle (Obese control, OC; Lean control, LC) between the ages of two and four weeks. All pups had their kidneys examined at one month of age. OC pups weighed more than those in the LC group between seven and 28 days of age ($p<0.05$). Enalapril decreased body weights between 22 and 28 days ($p<0.05$). Renal cell proliferation and apoptosis, glomerulosclerosis, and tubulointerstitial fibrosis were all increased by enalapril ($p<0.05$). Among the groups, renal cell proliferation was the lowest in OC rats whereas renal cell apoptosis was the highest in OE pups ($p<0.05$). Serum creatinine was also the highest in OE rats ($p<0.05$). In the kidneys of the Lean rats, enalapril increased renin, angiotensin II receptor type (AT) 2, and matrix metalloproteinase (MMP)-9, while decreasing AT 1, tissue inhibitor of MMP (TIMP)-1, and osteopontin expression. In contrast, enalapril decreased AT2 and MMP-9 and increased TIMP-1, osteopontin, and plasminogen activator inhibitor-1 expression in the Obese rat kidneys ($p< 0.05$). Taken together, early treatment with enalapril even after the nephrogenic period caused deleterious renal effects in both the Lean and Obese groups. It decreased body weights but did not prevent renal damage in postnatally overfed rats and even accelerated structural and functional anomalies in the kidneys of rats from the Lean group. These findings indicate that the renal changes following early postnatal overfeeding may be fundamentally different to those of normal postnatal growth after exposure to RAS inhibition. Angiotensin II may be a key player in the developmental renal programming following early postnatal overnutrition and inhibiting RAS during childhood may not be a beneficial intervention in patients with high body mass index.

Key Words: 안지오텐신 II, 성장과 발달, 과영양
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