Antiapoptotic effect of Angiotensin-II type-1 receptor blockade in renal tubular cells of hyperoxalouric rats

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Hyperoxaluria is a cause of renal stone disease and tubulointerstitial (TI) damage. Oxalate accumulates in the renal proximal tubules as the crystalline form and leads to continuous inflammation. Renal tubular cells produce various cytokines of inflammatory response, including angiotensin-II. The renin-angiotensin system has an important role in the development of TI damage in several models of chronic TI injury. Angiotensin II type 1 (AT1) receptor stimulation can trigger the TI damage via apoptosis. In this study, we investigated the protective effect of losartan as an AT1 receptor antagonist by evaluating the changes in the expression of apoptosis-regulatory genes contribute to the progressive damage in hyperoxaluric rats.

Wistar rats were divided into 3 groups; (1)control, (2)ethylene glycol(EG), (3)EG+ losartan(los). For 4 weeks EG as a precursor for oxalates was administered to groups 2 and 3 continuously in drinking water and losartan was administered daily in group 3 by gavage. Urine and blood samples were collected for biochemical determination. Serum creatinine and urine oxalate and creatinine were determined by enzymatic methods. Urine albumin and pH were calculated by dipstick urine test. At the end of experimental period, kidney perfused tissue samples were removed for histologic examination. Bcl-2, bax, caspase(cas)-3 and TGF-β1 antibodies were used for immunohistochemistry. Apoptosis was determined by TUNEL method.

At the end of the experiment in urinary oxalate levels were slightly elevated in the groups 2 and 3. There were no significant changes in urinary pH or urinary albumine levels. Reduced urinary creatinine levels were seen in the EG group whereas enhanced urine creatinine levels in group3. At the EG treated group TGF-β1cells immune positivity markedly was increased at the interstitial regions and the tubules. In the EG+los group, TGF-β1 immunostaining was weaker at the glomerulus, tubulus and interstitial regions, TGF-β1 expression was seen especially at the juxta glomerulus apparatus (Fig 1a). Bax expression markedly increased in the renal tubules of EG group compared to the controls, and reduced in the EG+los group (Fig 1b). In the EG+los group the intensity of immunoreactivity of Bcl-2 was increased in glomerules. The group EG had the increased cas-3 expression especially at the tubuloepithelial cells compared with the other treated and control group ($p<0,01$). In the EG+Los group the numbers and distribution of cas-3 immunoreactive cells were significantly decreased compared to the EG group ($p<0,01$)(Fig 2a). Apoptotic cells were observed rarely at the control group were significantly increased in the cortex and medulla of the EG treated group ($p<0.01$) compared the other groups (Fig 1c). Decreased apoptotic cell number was observed in the EG+los compared to the EG group ($p<0.01$) (Fig 2b).

Our findings suggest that losartan would provide a benefical effect against tubulointerstital lesions and decreases renal tubular apoptosis caused by hyperoxaluria.

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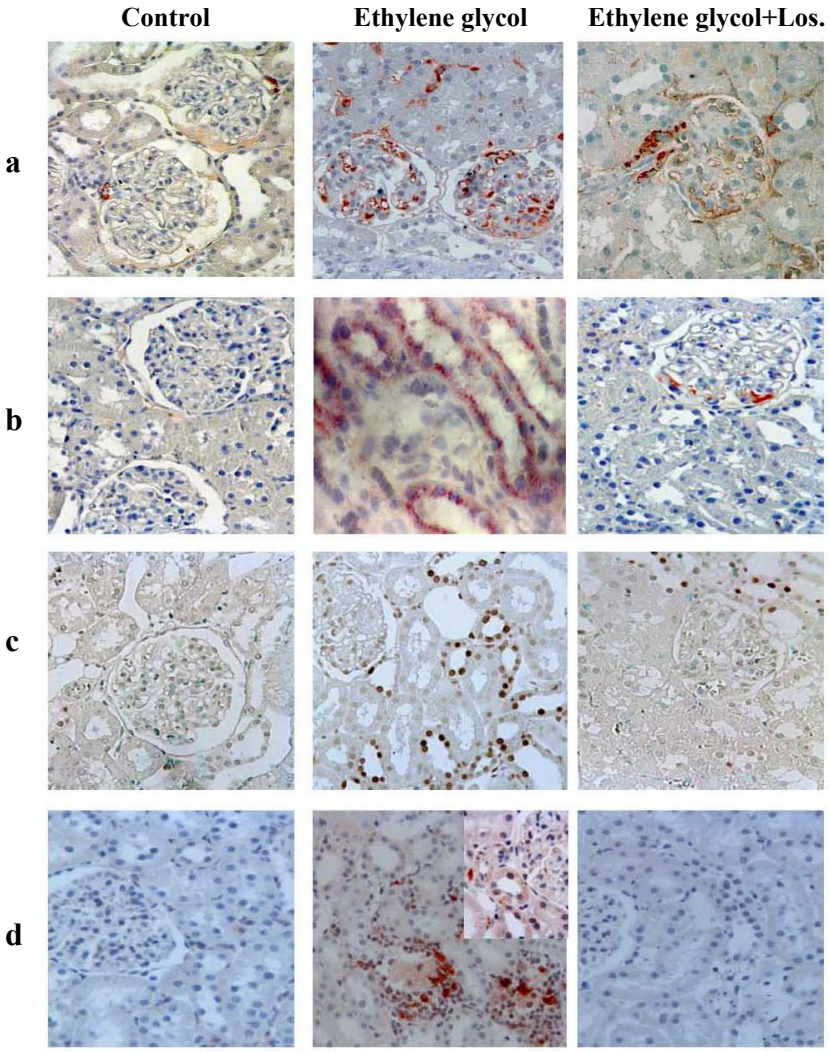

Figure 1: a)TGF-β1 ;TGF-β1 expression is increased in tubules, glomeruli and interstitial area of EG group whereas decreased in the losartan treated EG group. **b)** Bax; Bax immunoreactivity was stronger at EG goups glomeruli and tubules than the control group. At losartan treated EG group the immunoreactivity at glomerules and tubules was less stronger than the EG group **c)** TUNEL. A number of labelled nuclei of the apoptotic cells are seen in renal tubules in EG group, apoptotic cells are markedly decreased in EG+los group. **d)** Cas-3; Cas-3 expression is increased in renal tubules of EG group whereas decreased in the losartan treated EG group. Immunostaining: Strept-Bio-Perox/ Counterstain:Hematoxylene

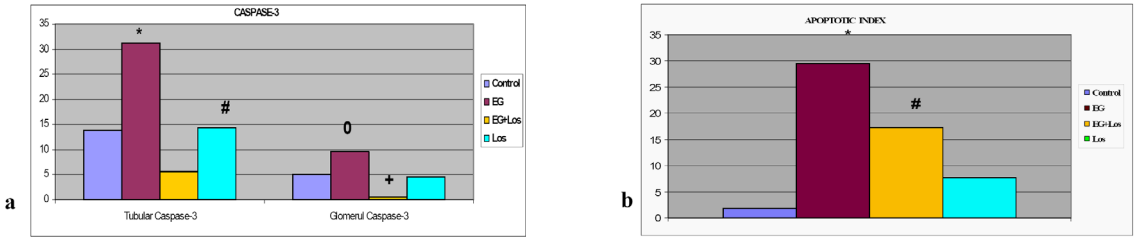

Figure 2: a) Caspase-3 immunopositive cell distrubution in all groups.(*:p<0.01 vs other groups, #p<0.01 vs EG,Contr,Los , 0:p<0.01 Cont, +:p<0.01 vs other groups).**b)** Apoptotic index (*p< 0.01, vs other groups, #p< 0.01 vs EG)

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