

Involvement of altered tubuloglomerular feedback system in the renal injury during the development of salt-induced hypertension

¹Youichi Abe, ¹Akira Nishiyama, ²Tokunori Yamamoto, ³Toshiaki Tamaki, ⁴Hiroshi Iwao,
¹Shoji Kimura, ⁵Takatomi Shokoji

¹Dept. of Pharmacology and ⁵Second Dept. of Internal Medicine, Kagawa Medical University,

²Dept. of Urology, Nagoya University School of Medicine, ³Dept. of Pharmacology, The University of Tokushima School of Medicine, ⁴Dept. of Pharmacology, Osaka City University Medical School.

Summary

It has been suggested that tubuloglomerular feedback (TGF) mechanism plays a critical role in the progression of renal injury in salt-induced hypertension. Here, we conducted studies to visualize afferent arteriolar and efferent arteriolar responses to alterations in TGF activity directly in Dahl salt-sensitive (DS) rats. DS rats were maintained on high (H: 8.0% NaCl) or low (L: 0.3% NaCl) salt diet for 4 wk. An intravital tapered-tip lens-probe (pencil lens-probe) videomicroscopy with a charge-coupled device camera was used in anesthetized rats, and the superficial afferent and efferent arteriolar diameters were measured before and during the enhanced TGF activity induced by acetazolamide (ACZ). DS/H and DS/L rats were 148±9 and 102±5 mmHg, respectively. ACZ (2 mg/kg bolus and 4 mg/kg/h for 15 min, i.v.) decreased afferent arteriolar diameters with the magnitude of reductions in DS/H rats being significantly less than those in DS/L. Inhibition of the TGF response by furosemide (1 mg/kg bolus plus 4 mg/kg/h for 10 min, i.v.) following ACZ infusion revealed that the afferent arteriolar vasoconstriction caused by ACZ was reversed in these animals. Plasma Ang II levels were significantly reduced in DS/H rats compared with DS/L rats, but kidney Ang II contents and AT1 receptor levels were similar between these animals. Renal cortical expression of p22-phox and Nox-1, essential components of NAD(P)H oxidase, and thiobarbituric acid reactive substances (TBARS) contents as well as vascular superoxide production were significantly higher in DS/H rats than DS/L rats. AT1 receptor blockade with candesartan (10 mg/kg/day) and treatment of an antioxidant, Tempol (3mmol/L in drinking water), normalized vascular superoxide and renal TBARS levels, and ameliorated progressive sclerotic and proliferative glomerular changes in DS/H rats. These results provide direct evidence that the TGF responses were altered in DS rats. The present data also suggest that in DH rats, renal injury is accompanied by the production of reactive oxygen species induced by AT₁ receptor-mediated activation NAD(P)H oxidase.