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Identification of Serine Proteases That are Involved in Podocyte Injuries in Salt-Sensitive Hypertension and Its Application for Anti-Proteinuria Treatment

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Summary

Background: We previously reported that an orally active synthetic serine protease (SP) inhibitor, camostat mesylate (CM), suppressed epithelial sodium channel (ENaC) activation by SPs and exerted an antihypertensive effect in Dahl salt-sensitive (DS) rats. Furthermore, CM significantly attenuated proteinuria even before it exerted BP lowering effect, suggesting that some SPs are involved in glomerular injuries independently of BP. Recently, it was reported that plasminogen filtered through damaged glomeruli was activated to plasmin by uPA on the surface of podocytes, and that plasmin could directly cause podocyte injuries. We conducted this study to identify SPs which could be associated with glomerular injuries and to explore therapeutic effects of SP inhibition on glomerular injuries in salt-sensitive hypertension.

Methods: Four-week-old male DS rats were divided into following three groups: control group (0.3% NaCl), high-salt (HS) group (8% NaCl diet), and HS＋CM group (HS＋0.1%CM diet). After systolic BP measurement and 24h urine collection were performed, rats were sacrificed at day 7. SP activities were evaluated by zymography.

Results: HS group did not develop hypertension and obvious renal histological changes but displayed significant proteinuria at day 7, which was attenuated in HS+CM (Urinary TP (mg/day); control 4.09±1.17, HS 42.01±3.72, HS+CM 14.31±7.63). CM did not mitigate glomerular hyperfiltration reflected by increased creatinine clearance (Ccr) with salt loading (Ccr (ml/h); control 0.3±0.1, HS 0.8±0.1, HS+CM 0.8±0.2). Urinary plasmin activation was induced by HS, which was substantially inhibited by CM. Furthermore, CM also suppressed albuminuria as early as at day 1-2 even when any apparent activation of SPs was not detected in urine.

Conclusions: Our current study indicates that plasmin and other unknown SPs would be involved in the pathogenesis of glomerular injuries, suggesting that SP inhibition could be a new strategy for the treatment of renal injuries in salt-sensitive hypertension.