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The Effect of Aberrant ENaC Activation on Salt-Sensitive Hypertension and Blood Pressure Circadian Rhythm in Chronic Kidney Disease.

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Summary

Background: Chronic kidney disease (CKD) causes the salt-sensitivity and disrupted circadian rhythm of blood pressure. Epithelial sodium channel (ENaC) in the renal collecting duct plays pivotal roles in the regulation of sodium homeostasis and blood pressure. The proteolytic cleavage of ENaCγ by extracellular serine proteases (SPs) is important process for the full activation of this channel. In the setting of CKD with proteinuria, circulating SPs filtered through injured glomerular filtration barrier could activate ENaC, leading to Na retention and hypertension independently of aldosterone. Several SPs such as plasmin, prostasin and uPA are suggested to be involved in this process. In this study, we evaluated the effects of aberrant ENaC activation by SPs on the salt-sensitive hypertension and alterd circadian rhythm of blood pressure in the proteinuric CKD. Furthermore, we elucidated the antihypertensive effect of SP inhibitors.

Methods: Five-week-old Dahl salt-sensitive (DS) rats were divided into normal salt diet (NS), high salt diet (HS) and HS+SP inhibitor (camostat mesilate, CM). After systolic BP measurement and 24h urine collection were performed for 5 weeks, rats were sacrificed. Urinary SPs excretion and ENaCγ activation were evaluated by zymography and western blotting. The antihypertensive effects of plasmin inhibitors (tranexamic acid and YO-2) ware elucidated. Urinary excretion of SPs in the proteinuric CKD patients were also studied.

Results: HS diet induced severe hypertension, marked proteinuria and urinary SPs activation as well as the proteolytic activation of urinary exosomal ENaCγ. The treatment with CM and YO-2, but not tranexamic acid, significantly suppressed these changes and mitigated glomerular injuries. Urinary SPs activation was also observed in the proteinuric CKD patients.

Conclusions: Our current study indicates that urinary SPs including plasmin are associated with the pathogenesis of salt-sensitive hypertension and glomerular injury in CKD with proteinuria, and serine protease inhibition could be a novel therapeutic strategy for CKD.