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Identification of Serine Proteases that Promote the Organ Injuries in the Salt-Sensitive Hypertension

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Summary

The increasing number of dialysis patients and high prevalence of chronic kidney disease (CKD) are major social problems in Japan and other developing countries. Although renin-angiotensin system (RAS) inhibitors are widely used to treat CKD, it is still difficult to stop the progression of CKD. Hypertension, especially salt-sensitive hypertension, is one of important factor to exaggerate CKD. Aldosterone increases sodium reabsorption via the activation of epithelial sodium channel in the distal nephron, resulting in the salt-sensitive hypertension. In addition, emerging evidence has suggested that aldosterone has direct deleterious effects on the kidney independently of its hemodynamic effects. We have previously studied the physiological and pathophysiological roles of serine proteases in the sodium homeostasis and kidney injuries. The current study was conducted to investigate the roles of serine proteases and the beneficial effects of serine protease inhibitor in kidney injuries with salt-sensitive hypertension caused by aldosterone and salt. We observed a serine protease that was activated by aldosterone/salt in rat kidney lysate, and identify it as plasmin with liquid chromatography-tandem mass spectrometry. Eplerenone, a selective aldosterone receptor blocker, suppressed the activation of plasmin and attenuated kidney injuries, suggesting that the interaction of aldosterone and mineralocorticoid receptor is necessary for the induction of plasmin. Plasmin increased pro-fibrotic and inflammatory gene expressions in rat renal fibroblast cells. A synthetic serine protease inhibitor (SPI) inhibited the protease activity of plasmin in vitro and suppressed cell injury markers induced by plasmin in the fibroblast cells. Furthermore, SPI ameliorated glomerulosclerosis and interstitial fibrosis in the kidney of aldosterone/salt-treated rats. Our findings indicate that serine protease plasmin has important roles in kidney injuries caused by salt-sensitive hypertension, and that serine protease inhibitor could provide a new strategy for the treatment chronic kidney diseases with hypertension in humans.