Regulation of prostasin expression and its application for the treatment of salt-sensitive hypertension

Kenichiro Kitamura and Kimio Tomita
Department of Nephrology,
Kumamoto University Graduate School of Medical Sciences

Summary

Identification of gain-of-function mutation in epithelial sodium channel (ENaC) in Liddle's syndrome patients, a hereditary form of salt-sensitive hypertension, indicates the importance of the sodium reabsorption through the kidney in the pathogenesis of salt-sensitive hypertension. In 1997, Vallet et al isolated a channel-activating protease (CAP-1), a trypsin-like serine protease, from A6 cell line and demonstrated that co-expression of CAP-1 and ENaC in *Xenopus* oocytes increased ENaC activity. We isolated a serine protease prostasin, a mammalian CAP-1 homologue, from rat kidney cDNA library. We found that prostasin is expressed in CCD, OMCD, and IMCD in the kidney where the ENaC is also expressed and that co-expression of prostasin and ENaC increased the amiloride-sensitive sodium current in *Xenopus* oocytes. We also demonstrated that aldosterone increases sodium reabsorption through ENaC by increasing the expression of prostasin. These findings suggest the possibility that prostasin might be involved in the pathogenesis of the salt-sensitive hypertension.

In the current project, we determined the urinary prostasin excretion and blood pressure in Dahl salt-sensitive (DS) rats and salt-resistant (DR) rats, a rat model of salt-sensitive hypertension. We found that urinary prostasin excretion is increased in DS rats compared with DR rats at 7 weeks-old. We also investigated the effect of nafamostat mesilate (NM), a serine protease inhibitor, on prostasin expression and urinary sodium excretion to determine if inhibition of prostasin results in an increase in urinary sodium excretion through the inhibition of ENaC. We found that NM inhibits prostasin expression in the kidney as well as the urinary sodium excretion in rats.

These findings strongly suggest the possibility that prostasin might be involved in the pathogenesis of the salt-sensitive hypertension and indicate that NM or its derivatives might be a candidate of the new diuretics/anti-hypertensive drugs in the future.