No. 0728

Molecular Mechanisms by which Prostasin Stimulates Aldosterone Production by Adrenal Glands

Kenichiro Kitamura and Kimio Tomita

Department of Nephrology, Kumamoto University, Graduate School of Medical Sciences

Summary

Previously we demonstrated that a serine protease prostasin increases the activity of epithelial sodium channel (ENaC) when the two are coexpressed in Xenopus oocytes. We also found that aldosterone increases the expression of prostasin in the kidney and that urinary prostasin is increased in primary aldosteronism patients. These findings strongly suggest that the possibility that prostasin might be one of the candidate factors involved in the development of salt-sensitive hypertension. In 2003, Dr. Julie Chao's lab reported that intravenous injection of adenovirus carrying human prostasin cDNA through a rat tail vein resulted in an elevation of blood pressure and plasma aldosterone concentration. However, the precise mechanisms by which overexpression of prostasin increases plasma aldosterone concentration remain undetermined.

In the current studies, we demonstrated that enzymatically active recombinant prostasin significantly increased the mRNA expression of CYP11B2 (aldosterone synthase) as well as the secretion of aldosterone into the culture medium in H295R cells (a human cell line from adrenocortical adenoma). Prostasin increased the mRNA expression of CYP11B2 6 hr after treatment and reached maximum induction at 24 hr, then returned to the basal levels at 48 hr. Induction of CYP11B2 by prostasin was dose-dependent within the range from 0 to 400 μg/mL. Luciferase assay using 1.5 kbp promoter region of human CYP11B2 revealed that prostasin enhances the transcriptional activity of CYP11B2 in H295R cells. A protease-dead mutant of prostasin had no effect on the expression of CYP11B2, suggesting that proteolytic activity of prostasin is required for the activation of CYP11B2. Continuous intravenous infusion of active recombinant prostasin into male Wister rats resulted in an increase in CYP11B2 expression in the adrenal glands and an elevation of plasma aldosterone concentration. Furthermore, we demonstrated a significant positive correlation between serum prostasin concentration and plasma aldosterone concentration in healthy volunteer and patients with essential hypertension.

Our current findings suggest that prostasin stimulates aldosterone production in the adrenal gland through its proteolytic activity and that there may be a positive feedback between prostasin and aldosterone. Recently, aldosterone-mediated organ damage has been demonstrated by a number of basic and clinical studies. Therefore, a prostasin inhibitor might serve as an organ protection drug through the suppression of aldosterone production.