The mechanism of the activation of sodium channel by serine protease and the cloning of rat prostasin

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Summary

Abnormal renal physiology plays a central role in virtually all sustained hypertensive states. In Japan, the population of salt-sensitive hypertension is relatively high. There are several mechanisms in the kidney to reabsorb Na from the luminal fluid, for examples, Na co-transporter systems in the proximal tubule, Na/K/2Cl co-transporter in the loop of Henle, Na/Cl co-transporter and Na channel in the distal nephron. Recent report has given strong impact on the pathogenesis of essential hypertension. Liddle syndrome, in which patients develop a form of genetic hypertension, has been shown to have mutations within the cytoplasmic COOH terminal of the β-and γ-subunits of the epithelial Na channel lead to a hyperactivity of the channel. In patients with essential hypertension, however, significant relation has not detected. Recently, a new Na channel activator, channel-activating protease(CAP1), has been cloned from a *Xenopus* kidney epithelial cell line. We investigated the mechanism of the activation of Na channel by serine protease using trypsin, and cloned the rat prostasin.

RKRR sequence of γ-subunit is essential for the activation of Na channel by trypsin. We have cloned a 342-residue protein belonging to the serine protease family. A major mRNA expression is highly expressed in kidney, stomach, intestine, skin, prostate, and lung, all epithelial tissues that express epithelial Na channel mRNA. Coexpression of rat prostasin together with the α β γ epithelial Na channel subunits led to a 2 –fold increase in the amiloride-sensitive Na current.

Our data suggest that prostasin, a serine protease, stimulates Na channel. Further studies are necessary to clarify whether prostasin and other Na regulatory hormone systems are closely linked or not.