Roles of the Renal Kallikrein-Kinin System in Salt-Sensitive Hypertension

To the Editor:

We read with great interest the review article “Dietary Sodium and Blood Pressure” by Dr Daniel W. Jones in Hypertension,1 which gives an excellent overview of the present status of the relationship between sodium intake and blood pressure increase. It is, however, a pity that this review did not mention the roles of the renal kallikrein-kinin system in the kidney.

On the basis of ample evidence, we believe that the renal kallikrein-kinin system plays an important role in the excretion of “extra sodium,”2 as follows:

1. The renal kallikrein-kinin system has a unique localization. After the tubulo-glomerular feedback system has completed its role at the macula densa, the distal connecting tubule cells secrete renal kallikrein, whereas the adjacent collecting tubule cells secrete its substrate (low molecular weight kininogen). Bradykinin B2 receptors, tubular-specific kinin-degradation enzymes, and kallistatin (a specific inhibitor of tissue kallikrein) are located or secreted along the cortical and medullary collecting ducts, downstream to the connecting tubules.

2. The role of the renal kallikrein-kinin system in the kidney has been clarified, using mutant kininogen-deficient (Brown Norway Katholiek, BN-Ka) rats, which cannot generate urinary kinin. The mutant BN-Ka rats show neither apparent physiological disorders nor increases in systemic blood pressure compared with that of normal BN-Kitasato rats and of rats of other strains, as long as they have a normal NaCl content in their diet. Nevertheless, a dietary NaCl content of only 2%, which does not affect blood pressure in normal rats, increases it to 170 mm Hg in BN-Ka rats, as measured by tail-cuff plethysmography. Sodium accumulates particularly in cells, such as erythrocytes, and in body fluid, such as cerebrospinal fluid. Importantly, sodium accumulation in the cells increases arteriolar sensitivity to angiotensin II (10-fold) and norepinephrine (30-fold).2 Clearly, then, a dysfunctional renal kallikrein-kinin system makes rats salt-sensitive. This may answer the author’s question1: “What are the mechanisms involved in the dietary sodium/blood pressure relationship?”

3. Renal kallikrein secretion is accelerated by potassium in sliced kidney and in vivo and also by ATP-sensitive potassium channel blockers, such as glibenclamide.

4. Do hypertensive patients excrete less urinary kallikrein? Most hypertensive animal models were reported to show reduced levels of urinary kallikrein. In humans, it was reported in 1971 that the urinary kallikrein level of patients with essential hypertension is less than that of normotensive subjects, but racial difference may have since confused the picture. However, blacks were reported to excrete less potassium in their urine than do whites.3 Total potassium excretion may reflect potassium intake. As mentioned above, potassium intake accelerates the release of renal kallikrein, so that blacks, with their lower potassium intake, may excrete less urinary kallikrein. Thus, in clinical studies, intake levels of both sodium and potassium must be controlled. In this context, measurement of urinary kallikrein levels may be “a practical method for determining salt sensitivity”1 in humans, as long as sodium and potassium intake is controlled.

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Response

I concur with Drs Katori and Majima that it is important to understand the mechanisms for sodium handling in the kidney and that it would be useful to have a clinically reliable test for salt sensitivity. Along with others, I will watch this line of research with interest as it evolves.

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