flow in the high-K diet group were mirrored by the changes in urinary vasopressin excretion. Indeed, when analyzed by a regression analysis, there was a significant correlation between the two parameters ($r = 0.800$). It is possible that changes in urine flow, along with the increased solute excretion, could alter the excretion of vasopressin. It has been demonstrated that, at physiological concentrations, vasopressin is freely filterable at the glomerulus[7]. Furthermore, Kimura et al.[8] have shown that vasopressin is reabsorbed and/or metabolized in the proximal nephron and is secreted into the distal nephron. It is conceivable that the increased urine flow could result in a decrease in the removal of vasopressin (by reabsorption and/or metabolism) from the proximal nephron, thus increasing the delivery of vasopressin to the distal nephron and presumably into the urine. It is unlikely that in the present study glomerular filtration rate increased enough to account for the elevation in vasopressin excretion.

In summary, the present study indicates that an increased potassium intake can increase both the plasma vasopressin concentration and the urinary vasopressin excretion of rats. The exact mechanisms involved in these changes, however, are not clear.

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Effects of kallidinogenase on urinary kallikrein excretion and plasma prostanoid concentrations in patients with essential hypertension

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Summary. The effects of kallidinogenase on urinary kallikrein excretion, plasma immunoreactive prostanoids and platelet aggregation were investigated in patients with essential hypertension. Urinary kallikrein excretion and plasma 6-keto $PGF_{1\alpha}$ concentration were significantly decreased in these patients. Significant decreases in blood pressure, as well as significant increases of urinary kallikrein excretion and plasma 6-keto $PGF_{1\alpha}$ concentration after kallidinogenase administration were also observed.
Key words. Kallidinogenase; kallikrein; 6-keto $PGF_{1\alpha}$; thromboxane B_2; platelet aggregation; essential hypertension.

Many reports have suggested that the kallikrein-kinin system is of pathogenic significance in human hypertensive disease[1,2,3]. The authors studied, in patients over an 8-week period, the role of kallikrein, prostacyclin and thromboxane A_2 in essential hypertension, and the effects of kallidinogenase on these parameters as well as blood pressure.

Materials and methods. Twelve patients (10 males, 2 females, mean age 43.2) with essential hypertension but not on medication were selected for this study after their informed consent was obtained. The average, casual blood pressure on sitting during outpatient visits on more than 2 occasions was greater than 160/90 mmHg in all patients. Each patient was given a sufficient work-up to exclude any known cause of hypertension. All patients were considered to be mildly or moderately hypertensive and corresponded to stage I or II of the WHO classification (1962). After a 2-week control period, each patient was given, orally and over an 8-week-period, 450 kallikrein units (KU)/day of kallidinogenase prepared from hog pancreas by Sanwa Chem. Lab. Twenty-four hour urine and venous blood were collected on the morning previous to, and at 2 and 4 weeks after kallidinogenase administration, respectively. Urinary kallikrein was measured by radioimmunoassay[4]. Plasma 6-keto $PGF_{1\alpha}$ and thromboxane B_2 were measured by radioimmunoassay according to Jaffe and Granström et al.[5,6], using antiserum prepared by New England Nuclear. Platelet aggregation was measured with the addition of ADP, collagen or ristocetin by aggregometer. Statistical significance of difference was determined by Wilcoxon's signed ranks test for matched pairs and Wilcoxon's rank sum U test for unpaired data, respectively. The correlation was determined by Spearman rank correlation coefficient test. Statistical significance was taken as $p < 0.05$.

Results. As shown in table 1, mean urinary kallikrein excretion was 62.8 ± 9.8 µg/day in patients with essential hypertension, while that in normal subjects was 122.0 ± 6.9 µg/day. There was a significant difference between them ($p < 0.001$). The mean concentration of plasma 6-keto $PGF_{1\alpha}$ in patients with essential hypertension was 145.2 ± 17.8 pg/ml, against 304 ± 24.7 pg/ml in normal subjects. There was a significant decrease of 6-keto $PGF_{1\alpha}$ in patients with essential hypertension with $p < 0.001$. On the other hand, there was no significant difference of plasma thromboxane B_2 concentration between patients with essential hypertension and normal subjects.

The mean systolic and diastolic blood pressure before the administration of kallidinogenase was 172.6 ± 3.2 mmHg and 94 ± 4.6 mmHg, respectively. These decreased to 160.6 ± 2.9 mmHg (6.9%, $p < 0.01$) and 88.6 ± 3.3 mmHg (5.7%, $p < 0.23$) after 4 weeks and to 155.9 ± 3.4 mmHg (9.7%, $p < 0.01$) and 81.5 ± 3.8 mmHg (13.3%, $p < 0.01$) after 8 weeks of kallidinogenase administration, respectively. The mean blood pressure was 120.2 ± 3.5 mmHg before administration and significantly decreased to 113.6 ± 2.4 mmHg (5.5%, $p < 0.05$) after 4 weeks and 106.3 ± 3.3 mmHg (11.6%, $p < 0.01$) after 8 weeks.

The mean urinary kallikrein excretion significantly increased from 62.8 ± 9.8 µg/day to 105.1 ± 14.9 µg/day after 4 weeks and to 119.3 ± 16.0 µg/day after 8 weeks of kallidinogenase in patients with essential hypertension (both, $p < 0.01$); it reached the same excretion level in normal subjects as shown in the table.

There was a significant negative correlation between mean blood pressure and urinary kallikrein excretion in patients with essential hypertension ($r = -0.514$, $p < 0.01$).

The mean plasma concentration of 6-keto $PGF_{1\alpha}$ in patients with essential hypertension was 145.2 ± 17.8 pg/ml before kallidino-

Effects of kallidinogenase on urinary kallikrein excretion, plasma 6-keto $PGF_{1\alpha}$ and thromboxane B_2 concentration

	U kal V/cr (μg/day)	6-keto $PGF_{1\alpha}$ (pg/ml)	TXB_2 (pg/ml)
Normal subjects	122 ± 6.9 (47)	304 ± 24.7 (37)	150.2 ± 20.3 (42)
EH: Before	62.8 ± 9.8 (12)***	145.2 ± 17.8 (11)***	140.0 ± 9.3 (11)
EH: After 4 weeks	105.1 ± 14.9 (12)(**)	229.0 ± 28.4 (11)(*)	164.0 ± 16.9 (11)
EH: After 8 weeks	119.3 ± 16.0 (12)(**)	252.3 ± 29.2 (11)(*)	126.4 ± 21.1 (11)

EH: Patients with essential hypertension. UkalV/cr: Urinary kallikrein excretion/creatinine excretion. () indicates number of subjects studied. *** $p < 0.001$ compared to normal subjects. (**) $p < 0.01$, (*) $p < 0.05$ compared to EH: Before.

genase administration, while those after 4 and 8 weeks of the administration were 229.0 ± 28.4 pg/ml and 252.3 ± 29.2 pg/ml, respectively. There was significant increase in concentration of plasma 6-keto $PGF_{1\alpha}$ after kallidinogenase administration (both, $p < 0.05$). No significant changes in plasma thromboxane B_2 concentration were found at 4 and 8 weeks after treatment. A tendency of inhibition of platelet aggregation by collagen was noted at 8 weeks after kallidinogenase administration (33.6 ± 13.0%, $p < 0.056$). There was no significant inhibition of platelet aggregation by ADP or restocetin.

Discussion. Margolius et al.[7], using an esterolytic assay, confirmed that in patients with essential hypertension, kallikrein excretion was significantly less than in the control population. Abe et al.[8] reported that the basal level of urinary excretion of kallikrein and PGE was lower in essential hypertension than in normal subjects and that the release of renal kallikrein and PGE after furosemide administration was also suppressed in essential hypertension patients compared with that in normal subjects. Decreased generation of prostacyclin has been reported with atherosclerosis[9] or ischemic heart disease[10]. However, there have been conflicting reports as to the concentration of prostacyclin in patients with essential hypertension. Uehara et al.[11] reported that plasma concentrations of 6-keto $PGF_{1\alpha}$ were significantly lower in patients with essential hypertension than in normotensive subjects. Grose et al.[12] demonstrated that urinary 6-keto-$PGF_{1\alpha}$ concentrations were significantly suppressed in patients with essential hypertension. In contrast, increased vascular prostacyclin synthesis in spontaneously hypertensive rats[13] and enhanced plasma 6-keto $PGF_{1\alpha}$ concentrations in patients with essential hypertension[14] have been reported. Kallikreins are serine proteinases which release kinins from plasma substrates called kininogens. Two main classes of kallikreins have been described: plasma kallikreins and glandular kallikreins[15,16]. Also, two main forms of kallikrein substrate have been identified in plasma: low and high molecular weight kininogen[15]. Plsama kallikrein releases kinins (bradykinin) only from high molecular weight kininogen. The plasma kallikrein system differs from the glandular kallikrein system not only in its biochemical and immunological characteristics, but also in its functions. Glandular kallikreins release kallidin (lysbradykinin) from low and high molecular weight kininogen. Kallidinogenases (glandular kallikreins) are found in the urine, kidney, salivary and sweat glands, pancreas, and intestines.

Kallidinogenase has been used widely for the treatment of essential hypertension. It is postulated that kinins which are liberated from the kininogens of plasma globulin by the action of kallikrein give rise to dilation of blood vessels with a resultant increase in blood flow both by their direct action on smooth muscle[17] and by indirect action through activation of phospholipase A_2 and formation of endogenous prostacyclin[18]. In our present studies, urinary kallikrein excretion and plasma 6-keto $PGF_{1\alpha}$ concentration were significantly decreased in patients with essential hypertension. Moreover, there were significant mild lowering effects of blood pressure in patients with essential hypertension with significant increases of urinary kallikrein excretion and plasma 6-keto $PGF_{1\alpha}$ concentration after kallidinogenase administration.

Thus, there was a suppression of kallikrein-kinin-prostaglandin system in patients with essential hypertension, a mild lowering effect of blood pressure with the increment of urinary kallikrein excretion and plasma 6-keto $PGF_{1\alpha}$ and a tendency toward inhibition of platelet aggregation through the kallikrein-kinin-prostaglandin system by the administration of kallidinogenase.

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