THE EFFECT OF SODIUM AND POTASSIUM LOADING ON URINARY KALLIKREIN-LIKE ACTIVITY IN YOUNG PATIENTS WITH BORDERLINE HYPERTENSION

KATSUYUKI ANDO, M.D., YASUSHI ITO, M.D.
HIROSHI NODA, M.D. AND TOSHIRO FUJITA, M.D.

We studied the effects of a potassium supplement on urinary kallikrein excretion in a setting of high sodium intake after sodium deprivation with diuretics in young patients with borderline hypertension. Eleven patients, who took the potassium supplementation during the high sodium diet period, showed lower increments in mean blood pressure with salt loading than 12 patients without the potassium supplementation. In the non-potassium-supplemented patients, urinary kallikrein was increased significantly when plasma renin activity (PRA), plasma aldosterone concentration (PAC), and urinary aldosterone were increased during the diuretic treatment. It was decreased significantly when the other hormones were decreased during the sodium load. During the high sodium diet period, PRA, PAC and urinary aldosterone were greater in the potassium-supplemented patients than in the non-potassium-supplemented ones, but urinary kallikrein excretion was not higher when potassium was supplemented. Thus, the present results did not support the theory that the kallikrein-kinin system may be involved in the natriuretic and antihypertensive effects of potassium. In addition, these findings suggest that some kallikrein-modulating factor(s) may counteract the increased urinary kallikrein excretion with the augmented renin-angiotensin-aldosterone system during salt loading with potassium supplementation.

URINARY kallikrein, chemically identical with renal kallikrein, converts kininogen to kallidin,¹ which promotes natriuresis and diuresis due to renal vasodilation.² Therefore, it has been suggested that the renal kallikrein-kinin system may be involved in the regulation of electrolytes and water metabolism. When dietary sodium intake is altered, urinary kallikrein may change in the similar direction to aldosterone concentration.³⁻⁶ The association between the

increase in urinary and/or plasma aldosterone and that in urinary kallikrein was found in patients with primary aldosteronism^{3,6,7} and Bartter's syndrome,⁸ and in normal subjects during low sodium intake⁵ or high potassium intake.⁹ In addition, the rate of kallikrein secretion in suspensions of rat renal cortical cells was enhanced by aldosterone and was reduced by spironolactone.¹⁰ Moreover, the localization of kallikrein at aldosterone-sensitive sites of sodium reabsorption in the kidney lends credence to the hypothesis that aldosterone is a kallikrein-stimulating hormone.^{11,12} In addition, the kallikrein-kinin and renin-angiotensin systems are interdependently related, since kallikrein can activate renin *in vitro*,¹³ and angiotensin I-converting enzyme acts as kininase II.¹⁴

Key Words:

Sodium,
Potassium,
Kallikrein,
Borderline hypertension,
Renin-angiotensin-aldosterone system

(Received January 8, 1985; accepted June 25, 1985)

Department of Internal Medicine, Institute of Clinical Medicine, University of Tsukuba, Ibaraki 305, Japan
Mailing address: Toshiro Fujita, M.D., Department of Internal Medicine, Institute of Clinical Medicine,
University of Tsukuba, Ibaraki 305, Japan

TABLE I CHANGES IN BLOOD PRESSURE (BP), BODY WEIGHT, AND URINARY ELECTROLYTES

	Control	Diuretic-Treatment	Sodium-Load
Mean BP (mmHg)			
Group I	98.1 ± 3.1	93.8 ± 2.9	99.0 ± 3.0
Group II	100.4 ± 2.6	98.0 ± 2.0	96.5 ± 2.9
Systolic BP (mmHg)			
Group I	137.2 ± 3.2	131.1 ± 3.2	135.9 ± 3.1
Group II	137.7 ± 3.3	131.6 ± 3.2	132.6 ± 3.3
Diastolic BP (mmHg)			
Group I	78.5 ± 4.2	75.2 ± 3.4	80.6 ± 3.8
Group II	81.8 ± 3.7	81.2 ± 3.5	78.4 ± 3.9
Body Weight (Kg)			
Group I	70.7 ± 4.4	69.9 ± 4.5	70.5 ± 4.5
Group II	66.8 ± 2.6	66.1 ± 2.6	66.8 ± 2.6
Urinary Sodium (mEq/day)			
Group I	213 ± 17	222 ± 19	355 ± 18
Group II	231 ± 21	218 ± 21	371 ± 28
Urinary Potassium (mEq/day)			
Group I	51 ± 4	52 ± 3	52 ± 5
Group II	59 ± 6	54 ± 4	151 ± 8*

* $p < 0.01$, vs. Group I.

Fig.1. Effects of potassium supplement on changes in mean blood pressure from the diuretic-treatment period to high-sodium period for Group I (left panel) and Group II (right panel) are indicated on the right side of the figure. Note that increase in mean BP with salt loading in Group II was significantly lower ($p < 0.05$) than in Group I.

In our previous study, the potassium supplement prevented the rise in blood pressure (BP) with sodium load in both patients with essential hypertension¹⁵ and young patients with borderline hypertension¹⁶ as a result of the natriuretic action of potassium. We found that renin-angiotensin-aldosterone (R-A-A) system was

enhanced, probably because of volume depletion, when potassium was supplemented during the high sodium diet period. Since the R-A-A system is stimulated with the potassium supplementation during salt loading, it could be speculated that urinary kallikrein is increased during the potassium supplement, which may in turn promote natriuresis and exert antihypertensive action despite the augmented R-A-A system. Thus, in order to examine the relationship between urinary kallikrein and the R-A-A system and to clarify whether the kallikrein-kinin system may play any role in the antihypertensive action of potassium, we studied the effects of potassium supplementation with sodium load on urinary kallikrein excretion in young borderline hypertensive patients.

MATERIALS AND METHODS

Subjects

Twenty-three young (less than 35 years of age) male patients with borderline hypertension were studied. Patients were considered to have borderline hypertension if their diastolic pressure at times exceeded but at other times was lower than 90 mmHg in a minimum of three pressure measurements taken in the outpatient depart-

TABLE II HORMONAL FINDINGS DURING THREE EXPERIMENTSL PERIODS

	Control	Diuretic-Treatment	Sodium-Load
<i>PRA (ng/ml/hr)</i>			
Group I	2.31 ± 0.27	6.06 ± 0.52	1.07 ± 0.14
Difference		3.75 ± 0.36	-4.99 ± 0.45
Group II	2.20 ± 0.23	5.93 ± 0.98	2.71 ± 0.21**
Difference		3.73 ± 0.66	-3.22 ± 0.47**
<i>PAC (pg/ml)</i>			
Group I	92.0 ± 12.6	207.6 ± 14.1	65.7 ± 10.9
Difference		115.6 ± 19.1	-141.9 ± 16.9
Group II	82.8 ± 11.6	249.7 ± 27.2	121.9 ± 23.7*
Difference		166.8 ± 22.1	-127.7 ± 16.1
<i>Urinary Aldosterone (μg/day)</i>			
Group I	12.3 ± 2.4	44.0 ± 8.4	6.2 ± 1.0
Difference		31.7 ± 7.2	-37.8 ± 9.5
Group II	8.5 ± 1.8	34.0 ± 3.6	16.9 ± 2.3***
Difference		22.9 ± 3.2	-17.1 ± 4.3**
<i>Urinary Kallikrein (units/day)</i>			
Group I	1.52 ± 0.17	2.82 ± 0.47	1.43 ± 0.18
Difference		1.31 ± 0.37	-1.39 ± 0.34
Group II	1.42 ± 0.20	2.41 ± 0.37	1.72 ± 0.26
Difference		0.99 ± 0.26	-0.69 ± 0.30

During the control and diuretic-treatment period, plasma renin activity (PRA), plasma aldosterone concentration (PAC), urinary aldosterone, and urinary kallikrein did not differ between the two groups. However, with salt loads, PRA, PAC, and urinary aldosterone were greater in Group II than in Group I, although urinary kallikrein was not significantly different.

p* < 0.05, vs. Group I. *p* < 0.01, vs. Group I. ****p* < 0.001, vs. Group I.

ment in one year.^{17,18} None had been given antihypertensive therapy. Each patient underwent a medical history and physical examination. Laboratory examinations including urinalysis, serum electrolytes, serum creatinine, plasma renin activity (PRA), plasma catecholamines, electrocardiogram, and chest radiogram were performed. The study subjects had no evidence of target organ damage, nor evidence of a secondary cause of hypertension. All patients were informed of the nature of the study and provided written consent.

Protocol

The subjects were studied on an outpatient basis. After four screening visits during two months, they were admitted to the trial. Each patient participated in three consecutive studies: measurement was performed during a regular customary diet¹⁶ (control period), after sodium deprivation with the administration of the diuretic, mefruside, 25 mg/day, for one week (diuretic-treatment period), and subsequently

after 180 mEq sodium chloride (NaCl) were added each day as a 10 mEq-salt tablets for one week (high-sodium period). During the high-sodium diet, in Group I, twelve of 23 borderline hypertensive patients received their customary diet plus 180 mEq/day of NaCl. In Group II, eleven of 23 patients received their customary diet plus NaCl plus 96 mEq/day of potassium chloride.

At every visit throughout the trial, 24-hour urine samples were measured under toluene for aldosterone, kallikrein, sodium, potassium, and creatinine levels. Each fasting subject had been supine and had an indwelling catheter inserted in an arm vein. At least 30 minutes after insertion of the catheter, but not before the patients were subjectively relaxed and had a stable pulse rate, blood for the determination of PRA and plasma aldosterone concentration (PAC) was drawn. Then, BP was measured repeatedly at least four times and mean BP, calculated for every reading as diastolic pressure plus one third of pulse pressure, was used for statistical comparison. Body weight was recorded at every visit.

Fig. 2. Plasma renin activity (PRA), plasma aldosterone concentration (PAC), urinary aldosterone, and urinary kallikrein in Group I (open column) and Group II (shaded column) during a customary diet (Control), during the administration of 25 mg/day mefruside for one week (Diuretic-Treatment), and during dietary supplementation with 180 mEq/day sodium chloride (Sodium-Load). * $p < 0.05$, vs. Group I; ** $p < 0.01$, vs. Group I.

Laboratory Procedures

A urine collection was judged to be adequate when the variation of daily urinary creatinine level was lower than 20%. Sodium and potassium concentrations in the urine were determined by flame photometry, utilizing lithium as an internal standard. PRA, PAC, and urinary aldosterone were measured by radioimmunoassay, as previously reported.¹⁹ Urinary kallikrein-like activity was measured using a fluorogenic peptide substrate, prolyl-phenyl-alanyl-arginine-4-methylcoumaryl-7-amide, and kallikrein activity

was expressed in terms of units (μ moles of 7-amide-4-methylcoumarin liberated per minute), as previously reported.²⁰⁻²²

We measured kallikrein activity initially in dialyzed and desalted urine by the fluorogenic method, because urinary kallikrein activity determined by esterase assay could be effected by non-kallikrein esterase and kallikrein inhibitors. For dialysis, urine samples were dialyzed at 4°C against 10 l of distilled water for 24 hours. Desalting was performed by passing 1 ml of urine through hydrated Sephadex G-25 fine using a column, 1.0 $\times$ 7.5 cm. The kallikrein activity in the untreated urine was significantly correlated to those in both the dialyzed urine ($n = 14$, $r = 0.987$, $p < 0.001$) and the desalted urine ($n = 19$, $r = 0.956$, $p < 0.001$). Therefore, the kallikrein activity was measured in raw urine in the present study. Recently, it was warned that urinary cations might modify the kallikrein activity.²³ However, the urine sample was greatly (1/26) diluted in the assay buffer in the present method, so that the ionic composition of the reaction mixture was only slightly altered by any variation in urinary composition. Moreover, it has been demonstrated that esterase activity correlated highly ($r > 0.9$) with both kininogenase activity and kallikrein by direct radioimmunoassay in the urine of human and rat.²⁴

Statistical Analysis

Data are expressed as the mean $\pm$ standard error of the mean. Statistical analysis was performed using two-tailed Student's t test (paired for within group and unpaired for between group comparison). The null hypothesis was rejected for $p < 0.05$.

RESULTS

Eleven borderline hypertensive patients (Group II), aged 23 ± 4 (mean $\pm$ standard deviation) years, were given potassium supplement during the high-sodium diet period, while 12 hypertensives (Group I), aged 24 ± 5 years, did not. At the outset of the study, BP (systolic, diastolic, mean) or body weight did not differ significantly between the groups (Table I). Creatinine clearance was also not significantly different between Group I (122.2 ± 8.0 ml/min) and II (112.8 ± 8.5 ml/min). As shown in Table II, PRA, PAC, urinary aldosterone, or urinary kallikrein were not significantly different in the two groups during the control period.

Urinary sodium and potassium excretion values are shown in Table I. There was no significant difference in urinary sodium in Group II compared to Group I either before or during the administration of diuretics. During the salt loading, urinary sodium increased equally in both groups. Although urinary potassium was not significantly different between the two groups during the control or diuretic-treated periods, it was greater ($p < 0.01$) in Group II than in Group I during the high-sodium period, because of the potassium supplement in Group II. These changes in urinary sodium and potassium excretion indicate good compliance with therapy.

Changes in BP

With the diuretic treatment, BP was decreased to the same extent in both groups (Table I). Salt load significantly ($p < 0.05$) increased mean BP from 93.8 ± 2.9 mmHg to 99.0 ± 3.0 mmHg in Group I. In contrast, mean BP was not increased with the high sodium intake (from 98.0 ± 2.0 to 96.5 ± 2.9 mmHg; N.S.), when potassium was supplemented (Group II). As shown in Fig. 1, the change in mean BP with sodium load was significantly ($p < 0.05$) less in Group II ($-1.6 \pm 2.0\%$) than in Group I ($5.8 \pm 2.4\%$).

Changes in PRA, PAC, Urinary Aldosterone, and Urinary Kallikrein

PRA, PAC, urinary aldosterone, and urinary kallikrein changed in the same direction with alteration in sodium balance; all these hormones increased by the diuretic treatment, and decreased by salt loading (Table II, Fig. 2). With the high sodium intake following sodium deprivation with the diuretic treatment, PRA (both groups; $p < 0.001$, paired *t* test), PAC (both groups; $p < 0.001$), urinary aldosterone (Group I; $p < 0.01$, Group II; $p < 0.2$) and urinary kallikrein (Group I; $p < 0.001$, Group II; $p < 0.05$) were significantly decreased in both groups. However, during the salt loading, Group II showed greater PRA (Group I; 1.07 ± 0.14 ng/ml/hr, Group II; 2.71 ± 0.21 ng/ml/hr, $p < 0.01$), PAC (Group I; 65.7 ± 10.9 pg/ml, Group II; 121.9 ± 23.7 pg/ml, $p < 0.05$), and urinary aldosterone (Group I; 6.2 ± 1.0 μ g/day, Group II; 16.9 ± 2.3 μ g/day, $p < 0.001$) than Group I, while there was no significant difference in urinary kallikrein between Group I (1.43 ± 0.18 units/day) and Group II (1.72 ± 0.26 units/day).

DISCUSSION

Results obtained in the present study indicates that there was no significant difference in urinary kallikrein during the high sodium intake between potassium-supplemented patients (Group II) and non-potassium-supplemented ones (Group I). Thus, the present results do not support the speculation that the kallikrein-kinin system may be involved in the natriuretic and antihypertensive effects of potassium, although the potassium supplement prevented sodium-induced BP rise, as previously reported.^{15,16,25}

On the other hand, we found that PRA, PAC, urinary aldosterone, and urinary kallikrein changed together in the same direction in Group I patients who had the sodium load alone after sodium depletion with diuretics. This observation is consistent with the results of many previous reports,³⁻¹⁰ suggesting the concept that aldosterone may be one of major factors for regulating the production of kallikrein in the kidney. However, during the high sodium diet period, urinary kallikrein did not differ between the groups, in spite of higher PRA, PAC, and urinary aldosterone in Group II than in Group I.

Contrary to our data, Horwitz et al.⁹ reported that potassium supplement stimulated both urinary aldosterone and kallikrein. However, this study was performed by the different protocol from the present study; the subjects received 110 mEq/day of NaCl throughout the experiment. In the present study, potassium was supplemented with high sodium intake (the average was 363 mEq/day) after the diuretic treatment. As suggested by Mills,²⁶ urinary kallikrein may be influenced by the alteration of sodium intake. Thus, the different results of the effect of potassium supplement on urinary kallikrein between the two studies could be explained by the different sodium intake. In addition, study subjects differed in age, race, or BP.

In our previous study,²⁰ urinary kallikrein excretion was higher in young borderline hypertensive patients with high PRA than in ones with normal PRA, but there was no significant correlation between urinary kallikrein and urinary aldosterone in borderline hypertensive patients. Also, there have been some reports that urinary kallikrein was dissociated from the R-A-A system. In animal study,²⁷ intrarenal infusion of aldosterone did not alter urinary kallikrein excretion. Urinary kallikrein did not change

during the administration of spironolactone.²⁸ Furthermore, Lawton et al. reported that there were some hypertensive patients who had the abnormal response of urinary kallikrein to salt restriction: they were associated with the decrease in urinary kallikrein excretion despite the increase in urinary and plasma aldosterone and PRA.²⁹ Thus, kallikrein-modulating factor(s) other than aldosterone should be considered.

To account for the discrepancy between urinary kallikrein and the R-A-A system, one might speculate that renal function may be different between Group I and II, since urinary kallikrein was reduced in hypertensive patients with mild renal insufficiency when compared with patients with normal renal function.³ However, the evidence does not support such a speculation, since creatinine clearance did not significantly differ between Group I and II.

Some investigators have demonstrated that expansion of extracellular fluid volume might augment the renal kallikrein-kinin system, leading to the concept that this system is a part of the effector mechanism for natriuresis induced by volume expansion.³⁰⁻³² It should be noted that kallikrein excretion was not increased during the first few days of mineralocorticoid administration. Thereafter, it was increased gradually, probably due to progressive volume expansion with early sodium retention rather than due to the effect of the hormone, per se.³³ Supporting this concept, studies in rats showed that a fluid load of either 5% glucose or 1% saline produced a comparable rise in urine volume and urinary kallikrein, despite the markedly different urinary sodium excretion value.³⁴ The similar finding was reported in oral sodium-loaded rabbits.³⁵

Thus, it is possible that the difference in extracellular fluid volume between Group I and II during the period of high sodium diet may result in the present discrepancy between urinary kallikrein and the R-A-A system, since the potassium supplementation prevented volume expansion with salt loading, via natriuresis.^{15,25} In Group I, extracellular fluid volume was expanded during salt loading and the R-A-A system was suppressed with sodium retention, whereas in Group II, the R-A-A system was relatively elevated with the lesser volume expansion via increased sodium excretion. This finding suggests relative volume depletion in Group II when compared to Group I, since Group II had greater PRA than did Group I, in spite of the renin-lowering effect of potassium.^{36,37} As a

result, urinary kallikrein during sodium load did not significantly differ in the groups, because of kallikrein-stimulating independent effects of aldosterone and volume expansion. Some investigators have reported that urinary kallikrein excretion changed directly with the alteration of sodium intake in man³⁸ and animals,³⁹ but others found no effect of sodium load on urinary kallikrein.⁴⁰⁻⁴² These seemingly discrepant results in the previous studies could be explained by the possibility that volume expansion may offset the kallikrein-lowering effect induced by the reduced aldosterone concentration.

There is increasing evidence that urinary kallikrein is directly related to renal perfusion.⁴³⁻⁴⁵ In animal studies with renal artery constriction, the amount of urinary kallikrein in the urine was correlated highly with renal artery pressure distal to the region of the constriction.⁴⁵ Thus, Mills²⁶ has postulated that one of the important kallikrein-regulating components may be the direct pressure of the renal artery. Since BP was increased by salt loading in Group I, renal artery pressure must be elevated. In contrast, BP did not change in Group II. According to the above Mills' hypothesis, it is suggested that the less increased renal artery pressure due to lesser extracellular volume expansion may decrease urinary kallikrein excretion during salt loading with potassium supplement and thus, counteract the increase in urinary kallikrein associated with the augmented R-A-A system.

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