Urinary Kallikrein Excretion in Normal Man

RELATIONSHIPS TO SODIUM INTAKE AND SODIUM-RETAINING STEROIDS

By Harry S. Margolius, David Horwitz, Ronald G. Geller, R. Wayne Alexander, John R. Gill, Jr., John J. Pisano, and Harry R. Keiser

ABSTRACT

The urinary excretion of kallikrein, a renal enzyme that cleaves the potent vasodilator kinin, kallidin, from kininogen, was measured in normal volunteers by three different assays, one of which was a bioassay. When sodium intake was changed from ad libitum or 109 mEq/day to 9 mEq/day, daily kallikrein excretion increased progressively in every subject to a mean maximal value that was 271% of control by day 7; an increase in sodium intake to 259 mEq/day resulted in the return of kallikrein excretion to control values. Urinary excretion of amylase, a protein with a molecular weight similar to that of kallikrein, did not change when sodium intake was changed, but plasma renin activity and aldosterone excretion changed appropriately. In subjects on a constant-sodium (109 mEq/day), constant-potassium (100 mEq/day) diet, fludrocortisone, 0.5 mg/day for 10 days, increased kallikrein excretion to a mean maximal value that was 203% of control. In subjects on a diet containing 9 mEq sodium/day, elevated kallikrein excretion decreased during treatment with spironolactone, 400 mg/day. Rapid administration of water (1 or 2 liters in 30 minutes, orally) or rapid infusion of 2.4 liters of normal saline did not significantly alter urinary kallikrein excretion despite large changes in urine volume or sodium excretion. Thus, kallikrein excretion appears to be directly related to the effective level of circulating sodium-retaining steroid. The findings are consistent with a role for the kallikrein-kinin system in the renal response to sodium-retaining hormones.

KEY WORDS

spironolactone  low dietary sodium
renin  aldosterone  high dietary sodium
fludrocortisone

The presence of kallikrein in urine was recognized over 40 years ago (1). This enzyme acts on kininogen substrates to produce the potent vasodilator decapeptide, kallidin (lysyl-bradykinin) (2, 3). Kallikreins and kinins have been implicated in a variety of pathological events and physiological responses such as the carcinoid flush (4), hereditary angioedema (5), the normal physiological conversion from intrauterine to extrauterine life (6), and the dumping syndrome (7). More recently, we have shown that urinary kallikrein excretion can be either supranormal or subnormal in various forms of human and experimental hypertension (8-10). In normal rats, a low-sodium diet or administration of deoxycorticosterone increases kallikrein excretion, whereas adrenalectomy reduces it (11). Preliminary observations have suggested that a low-sodium diet also increases urinary kallikrein excretion in normal man (12). Other recent studies in man (13) and in dogs (14) have reported that kallikrein excretion correlates directly with urine volume or urinary sodium excretion.

The present investigation was undertaken to explore in detail the effects of sodium chloride and water intake and of sodium-retaining steroids on urinary kallikrein excretion in normal subjects.

Methods

A total of 27 normal volunteers, 17 men and 10 women, 18-55 years old were studied; all were Caucasian except for two black males. No subject was taking any drug prior to the study. All protocols were approved by the Clinical Research Committee, The Medical Board of The Clinical Center, and the Deputy Director for Science of the National Institutes of Health. Informed consent was obtained in writing from each volunteer for each study.

PROTOCOLS

Effects of Sodium Intake—Seven subjects (group 1) 19-29 years old (mean 22 years) were allowed an ad libitum sodium intake for 5 days, followed by a diet containing 9 mEq sodium/day. After 8 days, 250 mEq of sodium as salt in a shaker was added to their diet for 7-9 days. Six volunteers (group 2) 41-55 years old (mean 47 years) were given a diet containing 109 mEq sodium/day.
for 5 days, followed by a regimen similar to that for group 1 except that potassium intake was fixed at 100 mEq/day throughout the entire period of study. All subjects were given furosemide (Lasix) (40 mg/day, orally) for the first 3 days when their sodium intake was restricted to 9 mEq/day to accelerate sodium loss. An additional young subject was studied without furosemide.

Effects of Fludrocortisone.—Four normal subjects 19–20 years old were given a diet containing 109 mEq sodium/day and 100 mEq potassium/day for 21 or 22 days. After a 5- or 6-day control period, each subject was given fludrocortisone (Florinef) tablets (0.5 mg, orally) each morning for 9 or 10 days. A subsequent 6-day control period followed fludrocortisone administration.

Effects of Spironolactone.—Two normal men 19 and 22 years old were allowed an ad libitum sodium intake for 5 days, followed by a diet containing 9 mEq sodium/day. Furosemide (40 mg/day, orally) was given for the first 3 days when their sodium intake was restricted to 9 mEq/day; after 5 additional days on the low-sodium diet, spironolactone (400 mg/day, orally) was given for 7 or 9 days. A 7- or 8-day period on a sodium intake of 9 mEq/day followed spironolactone administration.

Twenty-four-hour urine samples were collected during each of these protocols for measurement of kallikrein, sodium, potassium, creatinine, amylase, and aldosterone excretion. Serum sodium, potassium, chloride, and CO₂ were measured at 2-4-day intervals. Plasma for determination of renin activity was drawn at noon after the subjects had stood for 4 hours on the last day of each dietary regimen. Supine and standing blood pressures were measured four times a day, and the subjects were weighed each morning.

Effects of Saline Infusion.—Seven normal women 19–23 years old who had no history of urinary tract abnormality or disease were given a diet containing 59 mEq sodium/day for 3 days. After an overnight fast, an intravenous infusion of 5% dextrose (3 ml/min) was begun. Urine was collected through an indwelling bladder catheter. When urine flow had stabilized approximately 50 minutes after the start of the infusion, urine was collected for 20-minute periods and the bladder was washed with water and air at the end of each period. After four control periods, normal saline was infused (15 ml/min) for 160 minutes. All infusates contained inulin and para-aminohippurate. Urine volume, urinary kallikrein and sodium excretion, and the clearances of inulin and para-aminohippurate were determined for each period. The mean values for the last four periods of saline infusion are presented. No subject was studied more than once, and urine cultures before, at the time of, and several days after study were obtained.

Effects of Dietary Water.—Four normal subjects 18–21 years old were allowed an ad libitum sodium intake, but their water intake was fixed at 1 liter/day. After 3 days, 1 or 2 liters of added water was drunk between 8:00 and 8:30 A.M. Twenty-four-hour urine samples were collected for determination of kallikrein excretion at each of the three water intake levels in all subjects. The study was repeated in two of the subjects.

**ANALYTICAL PROCEDURES**

Three different techniques were used to measure kallikrein.

**Radiochemical Assay.**—The principal assay for kallikrein was the radiochemical esterolytic method of Beaven et al. (15). Urine was collected for 24 hours under 30 ml of toluene, and a sample was stored under toluene at 4°C. Within 2 weeks after collection, 3 ml of each sample was desalted using Sephadex G-25 (fine) and a centrifugal filter holder as previously described (15). The esterolytic activity of the urine filtrate was then determined using α,-p-tosyl-L-arginine-[³H]-methyl ester ([³H]-TAME) (Biochemical and Nuclear Corp.) as the substrate to provide a measure of kallikrein, the only alkaline TAME esterase in human urine (15,16). The incubation mixture contained 0.047 μM of [³H]-TAME (0.01 ml, approximate specific activity 200 mcm/m mole), 0.01-0.03 ml of the filtrate urine, and 0.04 ml of 0.2M Tris-HCl buffer (pH 8.0) for a total volume of 0.06-0.08 ml. The original method (15) was modified (17) to achieve the separation of [³H]-methanol from unhydrolyzed [³H]-TAME by a technique less laborious than ion exchange chromatography with Bio-rex 70. Incubations were carried out in 1.5 ml polypropylene capless flasks (Eppendorf) which, at zero time, were placed in glass counting vials containing 10 ml of scintillation fluid (20 ml of Liquiflor-480 ml of toluene) and 0.05 ml of an aqueous "stop" solution (ten parts of 0.01M nonradioactive TAME in 50% N.N-dimethylformamide and one part of glacial acetic acid). After incubation for 30 minutes at room temperature, the reaction was stopped by shaking for 10-15 seconds. The unhydrolyzed [³H]-TAME was retained in the aqueous phase, but the [³H]-methanol was extracted into the organic phase which contained the scintillation fluid. These modifications did not affect background counts, the standard curve, or assay values. Then, as in the original method, the vials were counted in a Packard Tri-Carb scintillation spectrometer with 29% efficiency. Standard curves of esterase activity were constructed using a purified human urinary kallikrein² (16). Each urine sample was assayed in duplicate. A standard curve and recoveries from random urine samples were measured daily. Data were not corrected for recovery, since daily random urine recoveries ranged from 95% to 105%; this range is in keeping with previously reported results obtained using this assay (8, 9, 11, 15, 17). Results were expressed in terms of esterase units excreted per unit time by multiplying esterase units per milliliter by urine volume per time period. One esterase unit is defined as that amount of kallikrein which hydrolyzes one micromole of TAME per minute at pH 8.0 and 30°C in a titrimetric assay (16).

**Bioassay.**—Samples of urine were also assayed for biologically active kallikrein by bioassay with a guinea pig ileum (18, 19). This bioassay utilizes either heated plasma or a purified human kininogen³ as substrate (9-12). Again, purified human urinary kallikrein was used as the standard. Specificity of this procedure was established by noting that: (1) neither the substrate nor the kallikrein sample alone contracted the tissue, (2) the

¹ Kindly supplied by Dr. Jack V. Pierce, Hypertension-Endocrine Branch, National Heart and Lung Institute, National Institutes of Health, Bethesda, Maryland.

² Kindly supplied by Dr. Jack V. Pierce, Hypertension-Endocrine Branch, National Heart and Lung Institute, National Institutes of Health, Bethesda, Maryland.
characteristically slow response of the ileum observed following mixing of the substrate and the kallikrein sample was always abolished by the addition of carboxypeptidase B which specifically destroys kinins but none of the other substances known to contract the ileum, and (3) pancreatic trypsin inhibitor, an inhibitor of urinary kallikrein, blocked the formation of ileum-contracting substance.

Colorimetric Assay.— Samples of urine from four subjects on different sodium intakes were also assayed for kallikrein esterase activity by a previously described modification (15) of the TAMe colorimetric assay of Roberts (20). Analysis of these samples for kallikrein by the colorimetric assay agreed with results obtained by radiochemical assay (Table 2), and the radiochemical assay results agreed with the bioassay results (Fig. 1). Results in Tables 2-5 were obtained with the radiochemical assay, but repeated comparisons with the bioassay showed good agreement.

Aldosterone excretion rate was measured by the double-isotope derivative method of Kliman and Peterson (21). Amylase excretion was measured by the method of O’Neal and Gochman (22). Plasma renin activity was measured by the method of Boucher et al. (23).

TABLE 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>Dietary sodium intake</th>
<th>Radiochemical assay</th>
<th>Colorimetric assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.C. (normal)</td>
<td>Ad libitum</td>
<td>0.072</td>
<td>0.076</td>
</tr>
<tr>
<td></td>
<td>9 mEq/day</td>
<td>0.225</td>
<td>0.276</td>
</tr>
<tr>
<td></td>
<td>259 mEq/day</td>
<td>0.105</td>
<td>0.135</td>
</tr>
<tr>
<td>R.J. (normal)</td>
<td>Ad libitum</td>
<td>0.107</td>
<td>0.110</td>
</tr>
<tr>
<td></td>
<td>9 mEq/day</td>
<td>0.393</td>
<td>0.360</td>
</tr>
<tr>
<td>J.G. (hypertensive)</td>
<td>Ad libitum</td>
<td>0.075</td>
<td>0.080</td>
</tr>
<tr>
<td></td>
<td>9 mEq/day</td>
<td>0.073</td>
<td>0.071</td>
</tr>
<tr>
<td></td>
<td>259 mEq/day</td>
<td>0.085</td>
<td>0.089</td>
</tr>
<tr>
<td>C.N. (hypertensive)</td>
<td>Ad libitum</td>
<td>0.016</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>9 mEq/day</td>
<td>0.020</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>259 mEq/day</td>
<td>0.039</td>
<td>0.040</td>
</tr>
</tbody>
</table>

E.U. = esterase unit. Kallikrein was measured as E.U. per milliliter of urine; the concentrations given in this table are ten times normal, since samples of urine had to be concentrated 10:1 to perform the less-sensitive colorimetric assay.

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lyzer. Inulin and para-aminohippurate clearances were determined as previously described (24). The data were analyzed using a standard Student's t-test except for paired analysis of data in Table 4.

Results

Effects of Sodium Intake.—The constancy of kallikrein excretion in subjects on a diet containing 109 mEq sodium/day or in those on ad libitum sodium intake can be noted in Table 2. Kallikrein excretion increased in every subject when sodium intake was low (9 mEq/day) (Table 2, Fig. 1). Mean kallikrein excretion, 12.2 ± 1.1 (SE) esterase units (E.U.)/day on the fourth day of the ad libitum diet or the diet containing 109 mEq sodium/day, did not change on the first day on a sodium intake of 9 mEq/day, but it had increased by day 3 to 21.5 ± 2.0 E.U./day (P < 0.001) and reached 33.0 ± 2.5 E.U./day (P < 0.001) by day 7. Kallikrein excretion in group 1 was similar to that in group 2. On the diet containing 259 mEq sodium/day, kallikrein excretion gradually decreased over 7-9 days to values that were not significantly different from those observed when sodium intake was ad libitum or 109 mEq/day (Table 2).

Table 3 compares urinary sodium excretion, plasma renin activity, and aldosterone excretion rate with kallikrein excretion on the fourth control day, the seventh day of the diet containing 9 mEq/day, and the seventh day of the diet containing 259 mEq sodium/day.

In the one additional subject who did not receive furosemide, kallikrein excretion ranged from 12.4 to 13.1 E.U./day during a sodium intake of 109 mEq/day. On days 7-9 on the diet containing 9 mEq sodium/day kallikrein excretion ranged from 12.2 ± 1.1 to 13.1 ± 1.0 E.U./day.

### Table 3

<table>
<thead>
<tr>
<th>Urinary Sodium Excretion, Plasma Renin Activity, Aldosterone Excretion Rate, and Kallikrein Excretion in Normal Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>U_{\text{Na}} (mEq/day)</td>
</tr>
<tr>
<td>PRA (ng/ml hour *)</td>
</tr>
<tr>
<td>Aldo (\mu g/day)</td>
</tr>
<tr>
<td>Kallikrein (E.U./day)</td>
</tr>
</tbody>
</table>

All values are means ± s.e. for 13 normal subjects. U_{\text{Na}} = urinary sodium excretion, PRA = plasma renin activity, Aldo = aldosterone excretion rate, and Kallikrein (E.U./day) = esterase units in a 24-hour collection of urine.

* Differ from values on control diet (ad libitum sodium or 109 mEq Na/day) or diet containing 259 mEq Na/day, P < 0.001.
Urinary amylase excretion (normal range 1,000 to 6,000 Somogyi units (S.U.)/day) in five group 1 subjects on an ad libitum sodium intake was 2,211 ± 557 S.U./day; on day 7 of the diet containing 9 mEq sodium/day, it was 1,970 ± 230 S.U./day, and on day 9 of the diet containing 259 mEq sodium/day it was 2,045 ± 308 S.U./day. These changes were not significant (P > 0.05).

Effects of Fludrocortisone.—In four normal subjects on 109 mEq sodium/day, urinary kallikrein excretion was 14.1 ± 3.2 E.U./day (days 5 and 6). Kallikrein excretion increased significantly (P < 0.025) when fludrocortisone was administered to 28.6 ± 7.3 E.U./day (days 9 and 10) and decreased to 13.5 ± 4.0 E.U./day (days 5 and 6) after fludrocortisone was stopped (Table 4). Weight gain with fludrocortisone averaged 0.9 kg, and weight loss averaged 2.2 kg after fludrocortisone was stopped. Values for urinary sodium excretions during days 9 and 10 of fludrocortisone administration were similar to control values, since "escape" had occurred earlier. Kallikrein excretion did not change for at least 3–4 days after the start of treatment with fludrocortisone except in subject M.A. who showed a 100% increase in kallikrein excretion on the first day of fludrocortisone administration. The rate and the magnitude of change in kallikrein excretion ranged from an increase of 100% on day 1 of fludrocortisone administration (M.A.) to an increase of 63% on days 8–10 (J.S.).

![Figure 2](http://circres.ahajournals.org/)

**Figure 2**

Effect of spironolactone on the increase in kallikrein excretion, sodium excretion (U_{NaCl}), weight (Wt.), plasma renin activity (PRA), and aldosterone excretion (ALDO Ex.) in two normal subjects. Note the decrease in urinary kallikrein excretion despite the continued low-sodium intake and additional sodium loss. E.U. = esterase unit; AD LIB = ad libitum sodium intake, LASIX = furosemide.
TABLE 4
Effect of Fludrocortisone on Urinary Kallikrein Excretion in Normal Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Sex</th>
<th>Control (E.U./day)</th>
<th>Fludrocortisone (E.U./day)</th>
<th>Control (E.U./day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.S.</td>
<td>18</td>
<td>F</td>
<td>8.4</td>
<td>13.7</td>
<td>7.3</td>
</tr>
<tr>
<td>T.H.</td>
<td>20</td>
<td>M</td>
<td>22.8</td>
<td>48.7</td>
<td>25.3</td>
</tr>
<tr>
<td>M.A.</td>
<td>20</td>
<td>M</td>
<td>14.3</td>
<td>25.0</td>
<td>11.8</td>
</tr>
<tr>
<td>D.B.</td>
<td>20</td>
<td>M</td>
<td>10.8</td>
<td>27.0</td>
<td>9.6</td>
</tr>
<tr>
<td>MEAN</td>
<td></td>
<td></td>
<td>14.1</td>
<td>28.6</td>
<td>13.5</td>
</tr>
<tr>
<td>± SE</td>
<td></td>
<td></td>
<td>3.2</td>
<td>7.3</td>
<td>4.0</td>
</tr>
</tbody>
</table>

| P       |     |     | < 0.025            | < 0.025                  |                     |

Fludrocortisone was administered in a dose of 0.5 mg/day. E.U. = esterase unit.

Effects of Spironolactone.—In two normal subjects, K.R. and S.L., urinary kallikrein excretion increased from 8.4 and 15.5 E.U./day, respectively, on the last day of ad libitum sodium intake to 23.6 and 38.5 E.U./day, respectively, after 8 days on a diet containing 9 mEq sodium/day (Fig. 2). Administration of spironolactone (400 mg/day) during a continued low-sodium intake increased sodium excretion and decreased body weight 3.2 kg (K.R.) and 2.3 kg (S.L.); urinary kallikrein excretion decreased to 12.3 and 19.1 E.U./day, respectively, after 7-9 days. With cessation of spironolactone administration and continued low-sodium intake, kallikrein excretion increased to a maximum of 36.8 E.U./day in K.R. and 81.6 E.U./day in S.L. Plasma renin activity and aldosterone excretion were elevated throughout the period of the diet containing 9 mEq sodium/day.

Effects of Saline Infusion.—Saline infusion increased urinary sodium excretion from 107 ± 12 µEq/min to 359 ± 51 µEq/min but did not change kallikrein excretion (Table 5).

Effects of Dietary Water.—In six control observations in four normal volunteers, urinary kallikrein excretion averaged 8.3 ± 1.2 E.U./day and urine volume was 1,154 ± 119 ml/day. Kallikrein excretion was 10.3 ± 1.1 E.U./day during the 24 hours after an additional 1 liter of dietary water had been consumed and urine volume was 1,979 ± 363 ml/day. Kallikrein excretion was 9.4 ± 2.0 E.U./day after an additional 2 liters of dietary water had been consumed and urine volume was 3,163 ± 184 ml/day. These changes in kallikrein excretion were not significantly different.

Urinary Kallikrein and Sodium Excretion.—In 59 24-hour urine collections from 48 normal subjects (27 normal volunteers and laboratory personnel) on an ad libitum sodium intake, there was no correlation between urinary kallikrein excretion and urinary sodium excretion (r = 0.047, P > 0.1).

Discussion
In normal subjects, a sustained reduction in sodium intake to 9 mEq/day, with and without a diuretic, caused a progressive increase in the urinary excretion of kallikrein but did not change the urinary excretion of amylase, a similar-sized protein. Although the changes in kallikrein excretion were associated with a regimen which tended to decrease body sodium and the volume of extracellular fluid, changes in sodium balance per se did not appear to be the stimulus to kallikrein excretion. Treatment with fludrocortisone during a sodium intake of 109 mEq/day, a regimen which tended to increase body sodium and the volume of extracellular fluid, also increased kallikrein excretion (Table 4); usually, the time required for the change in excretion was the same as that observed in the studies of the response to a diet containing 9 mEq sodium/day. The increase in urinary kallikrein excretion did not appear to be linked to plasma renin activity, since both sodium restriction and treatment with fludrocortisone affected kallikrein excretion in a similar fashion even though they had opposite effects on plasma renin activity. The two experimental regimens of sodium restriction and fludrocortisone administration did not appear to be the stimulus to kallikrein excretion.
have in common an increase in circulating sodium-retaining steroid which could in some way determine kallikrein excretion. In support of this hypothesis is the observation that in subjects whose kallikrein excretion had been increased by a low-sodium diet, treatment with an aldosterone antagonist, spironolactone, produced additional sodium loss but a decrease in kallikrein excretion in face of an increase in circulating aldosterone (Fig. 2). This latter observation suggests that kallikrein excretion is determined in part by the effective level of circulating sodium-retaining steroid, presumably as a consequence of steroid-cellular interaction. Also consistent with the notion of an important effect of aldosterone on urinary kallikrein excretion is the finding that the range of sodium intake (9 to 109 mEq/day) which accounted for most of the change in aldosterone excretion in normal subjects (Table 3) also accounted for most of the change in kallikrein excretion. Sodium intake in the range from 109 to 259 mEq/day appeared to have little effect on the excretion of either aldosterone or kallikrein (Tables 2 and 3). In previous studies from this laboratory (11), rats showed changes in urinary kallikrein excretion in response to high- and low-sodium intakes that qualitatively resembled those reported in this paper for man. Also, in the rat, deoxycorticosterone, a sodium-retaining steroid, increased kallikrein excretion and adrenalectomy decreased it. Thus, the results of the present study in man and the earlier study in rats provide considerable evidence for the hypothesis that sodium-retaining steroids in some way determine kallikrein excretion. What relationship, if any, changes in urinary kallikrein have to the control of sodium metabolism is not apparent from these studies. Our results, however, differ from the results and conclusions of others (13, 14).

Adetuyibi and Mills (13) have reported that urinary kallikrein excretion, determined by a colorimetric method, is positively correlated with sodium excretion in random, 24-hour collections of urine from normal human subjects on an ad libitum salt intake with a range of sodium excretion from 100 to 350 mEq/day. Also, Marin-Grez et al. (14) have reported that a liter of normal saline, given orally to dogs, is associated with a higher urinary kallikrein excretion than is a liter of water. We cannot explain these findings, since in the present study kallikrein excretion showed no relation to sodium excretion in 48 normal subjects on an ad libitum sodium intake; sodium excretion exceeded 100 mEq/day in the majority of these subjects. Furthermore, there was no difference in kallikrein excretion when sodium intake was controlled at either 109 or 259 mEq/day (Table 2). In addition, rapid intravenous infusion of 2.4 liters of normal saline was without effect on kallikrein excretion (Table 5). This observation is consistent with the other observation that a change in aldosterone, whether produced by manipulation of dietary sodium or by administration of a sodium-retaining steroid, does not produce an immediate change in kallikrein excretion but requires more than a day.

Other studies (13) have reported that 1 liter of ingested water increases urinary kallikrein excretion. Although earlier studies (25) did not show a correlation between kallikrein excretion and urine volume, it is possible that abrupt changes in urine flow could be associated with transient changes in kallikrein excretion, the so-called washout phenomenon. However, in studies designed to double or triple urine volume by adjustments in oral fluid intake, no change in urinary kallikrein was observed.

Kallikrein has been identified in plasma as well as in sweat, salivary glands, pancreas, and kidney (26–29). Its function in these tissues remains to be elucidated. Kallikreins in urine or renal tissue are distinct from those derived from plasma (30, 31). The source of urinary kallikrein appears to be the kidney, since kallikrein synthesized by rat kidney slices from radioactive amino acid precursors is indistinguishable from kallikrein isolated from rat kidney or urine.* Determination of the relationship of urinary kallikrein excretion to renal kallikrein activity, the localization of the enzyme within the kidney, and the evaluation of its importance in the function of the kidney are subjects for future study.

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References


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