Kallikrein-Kinin System and Blood Pressure Sensitivity to Salt

Paolo Madeddu, Maria Vittoria Varoni, Maria Piera Demontis, Julie Chao, Jo Anne Simson, Nicola Glorioso, Vittorio Anania

Abstract We evaluated the blood pressure response to chronic salt loading in a rat strain inbred for low urinary kallikrein excretion. Low-kallikrein rats showed greater systolic blood pressure values (130±1 versus 114±2 mm Hg in controls, P<0.05) at 9 weeks of age. Systolic blood pressure was increased after 10 days of dietary sodium loading in the low-kallikrein group and remained unchanged in controls (153±1 versus 112±2 mm Hg, P<0.01). In addition, blood pressure sensitivity to salt was tested in low-kallikrein rats receiving a chronic infusion of rat glandular kallikrein (1.7 µg/day per 100 g body weight, IV) or vehicle. Systolic blood pressure of vehicle-treated rats was increased by salt loading (from 138±1 to 158±2, 153±1, and 145±2 mm Hg at 5, 10, and 15 days, respectively, P<0.01), while it remained unchanged in the kallikrein-treated group (from 136±2 to 146±3, 140±2, and 134±2 mm Hg at 5, 10, and 15 days, respectively, P=NS). Urinary kallikrein excretion was increased by kallikrein infusion (from 13.6±1.4 to 17.8±2.1 nanokatals per 24 hours, P<0.01). Plasma immunoreactive kallikrein levels were higher in the kallikrein-treated group (66±4±4 versus 57.7±1.4 ng/mL in vehicle-treated rats, P<0.01). On normal sodium diet, the ratio of kidney weight to body weight was lower in low-kallikrein rats (329±5 versus 370±8 mg/100 g body weight in controls, P<0.01). This difference was associated with an increased number of glomeruli per square area and increased width of Bowman’s space. These results indicate that kallikrein replacement prevents the exaggerated blood pressure increase observed in rats with a genetically determined defect in urinary kallikrein excretion. Histological abnormalities are present at different levels in the nephron, and they may be functionally related to the altered cardiovascular and renal phenotype of this strain. (Hypertension. 1997;29[part 2]:471-477.)

Key Words • sodium • kinins • blood pressure

Cosegregation of a sequence variation of the kallikrein gene with high blood pressure phenotype in inbred strains derived from the spontaneously hypertensive rat and the normotensive Brown Norway rat suggests that this gene may have the capacity to affect blood pressure.1 This hypothesis is supported by the observation that kinins, which are derived from the enzymatic action of kallikrein on kininogen, cause vasodilation, diuresis, and natriuresis. Urinary kallikrein excretion is reduced in genetic hypertension. In particular, the low-kallikrein phenotype has been used as a marker of salt sensitivity in normotensive subjects as well as in essential hypertensive patients.2,3 These studies also suggest that depressed activity of the renal kallikrein-kinin system could contribute in the pathogenesis of salt-dependent hypertension.

Recently, a strain was developed in our laboratory, by breeding rats from a Wistar stock according to urinary kallikrein phenotype, exclusively.4 This breeding approach represents an important difference compared with other experimental models of genetic hypertension in which urinary kallikrein excretion has been found to be decreased.5,7 Indeed, the low-kallikrein phenotype could be secondary to the increase in blood pressure in the latter strains. We found that application of dietary sodium load-

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All procedures complied with the standards for the care and use of animals as stated in Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, National Academy of Science, Bethesda, Md).

Experiment 1: Effect of High Sodium Intake on SBP of Low-Kallikrein Rats

Rats had free access to rat chow (sodium, 0.12 mmol per gram chow) until the ninth week of age. At this stage, both controls...
and the low-kallikrein group (n=8 males each) were assigned to a high (0.84 mmol per gram chow) sodium diet for the following 20 days. SBP, HR, and BW were measured every 5 days. SBP and HR were obtained by the tail-cuff plethysmography method (Recorder 8002, Ugo Basile, Biological Research Apparatus) in unanesthetized rats prewarmed for 10 minutes at 37°C in a thermostatically controlled heating cabinet. Each pressure value was obtained by averaging 8 to 10 individual readings.

Experiment 2: Effect of Chronic Intravenous Administration of Rat Glandular Kallikrein on the Blood Pressure Response to High Salt Intake in Low-Kallikrein Rats

RUK was purified from pooled urine according to the established method, and its purity was assessed with polyacrylamide gel electrophoresis and Western blot analysis.8

Low-kallikrein rats had free access to rat chow (sodium, 0.12 mmol per gram chow) until the 10th week of age. At this stage, they were randomly allocated to two groups (n=10 males each). Group 1 (controls) received an intravenous infusion of vehicle (normal saline, 60 μL/day) for 4 weeks, and group 2 received RUK (17 μg in 60 μL saline/d per 100 g BW). In preliminary experiments, this dose of RUK did not affect the SBP of low-kallikrein rats fed a normal sodium diet. Infusions were performed by the use of Alzet osmotic pumps (Alza Co) connected linearly through both poles, having well-delineated cortex as well as outer and inner medulla, was analyzed from each animal. For linear measurements (diameters), an ocular micrometer was calibrated against a stage micrometer, and conversion factors were calculated for low (×4 objective) and medium (×10 objective) magnifications.

Cortical width (from capsule to arcuate arteries) was measured at low magnification along at least five (usually more) different perpendiculers to the cortex, going around the circumference of the cortex from pole to pole in each kidney section examined. These measurements were averaged for each sample, and the averages of the three samples in each group were then averaged for the group mean. The diameters of renal corpuscles and glomeruli were measured at medium magnification in a randomized way as follows. A cortical field was found randomly, and the ocular micrometer was set perpendicular to the cortical curvature. The two nearest renal corpuscles with either vascular or urinary poles were chosen and moved under the micrometer, and their maximum outer diameter (renal corpuscle) and width of vascular tuft (glomerulus) were measured. Then at least five subsequent fields were analyzed in a similar fashion. The measurements within each sample were averaged, and the mean of these averages formed a group mean.

For the glomerular counts, a square ocular grid, measuring 0.8 mm per side at medium magnification, was positioned over a cortical field so that a corner touched the capsule. Again, the fields were chosen randomly, at least six fields per kidney section. All glomeruli that were completely within the grid were counted, as well as those touching or intersecting the upper and lower demarcation lines of the grid. Those touching or intersecting the right and bottom lines of the grid were not counted. The counts within each sample were averaged, and the mean of these sample averages was calculated as the group mean.

For immunohistochemistry studies, renal sections (5 μm) were cut and incubated overnight at 22°C with rabbit antiserum raised against purified RUK diluted in phosphate-buffered saline, according to the established method. This polyclonal antibody has been shown to be highly specific for kallikrein, but it also shows a low level (10%) cross-reactivity for esterase A, a related enzyme.

Analytical Procedures

UV was determined gravimetrically. Ucr was determined by flame photometry. Ucr was measured by an automatic analyzer (Hitachi 704). Uall was determined by an amidoxylic assay modified by addition of inhibitors of esterase A in the incubation buffer. It was expressed in katal (kat) per milliliter of urine, where 1 kat represents the enzyme activity able to cleave 1 mol substrate per second. To calculate urinary excretion, Ucr, and Uall were multiplied by UV. Kallikrein levels in plasma were determined by a highly sensitive and specific radioimmunoassay for rat glandular kallikrein and expressed as nanograms per milliliter.
Statistical Analysis

All data are expressed as mean±SEM. Multivariate repeated measures ANOVA was performed to test for interaction between time and grouping factor. Univariate ANOVA then was used to test for differences among groups and over time. Differences within or between groups were determined using paired or unpaired Student's t test, respectively, with the Bonferroni multiple-comparison adjustment. A probability (P) less than 0.05 was used as the criterion of significance. Mathematical and statistical analyses were performed with a STATVIEW II package (Brain Power) on an Apple Macintosh IIcx computer.

Results

Experiment 1: Effect of High Sodium Intake on SBP of Low-Kallikrein Rats

UKall V was significantly reduced in the low-kallikrein group at 9 weeks of age (112±11 versus 22±23 nkat/24 hours, P<0.01). No group difference was detected in basal BW (266±9 versus 256±5 g in controls, P=NS). The BW gain of the low-kallikrein rats fed a high-sodium diet was greater than that of controls (80±4 versus 51±3 g, respectively; P<0.05). The low-kallikrein group showed higher SBP levels on normal sodium diet (130±1 versus 114±2 mm Hg in controls, P<0.05). SBP was further increased by 23 mm Hg after 10 days of dietary sodium loading in the low-kallikrein group, while it remained unchanged in controls (153±1 versus 112±2 mm Hg, P<0.01). A group difference in SBP was also observed at 20 days (155±1 versus 113±3 mm Hg in controls, P<0.01).

Experiment 2: Effect of Chronic Intravenous Administration of RUK on the Blood Pressure Response to High Salt Intake in Low-Kallikrein Rats

As indicated in Fig 1, no group difference was detected regarding SBP, HR, and BW under basal conditions (day -4) as well as 4 days after the beginning of RUK or vehicle infusions. Application of sodium loading increased the SBP of the vehicle-treated rats, while it did not affect that of RUK-treated rats. Indeed, a modest increase was observed only at day 5 in the latter group, but this change did not reach statistical significance (P=0.08, NS). A group difference in SBP levels was detected 10 days after the start of sodium loading, and it was maintained after the rats had returned to a normal sodium diet. Though the SBP of RUK-treated rats was brought below basal levels at days 20 and 25, these differences did not reach statistical significance (P=0.08, NS). In vehicle-treated rats, SBP returned to basal levels after 20 days on the high-sodium diet, and it changed no further when the diet was returned to normal. At this stage, the MBP levels of RUK-treated rats were lower than those of controls (105±2 versus 120±2 mm Hg, respectively, P<0.05). No between-group difference was detected over all the durations of the study as far as HR and BW values were concerned.

As shown in Table 1, high sodium intake increased UV and UN,V in both groups, while Uc,V was reduced. These changes were similar between groups. No group difference was detected regarding the cumulative intake of food and water as well as the cumulative UV and UN,V during the first 5 days of the high-sodium diet (data not shown)

Ukall V was increased after 4 days of RUK infusion (from 13.6±4.1 to 17.8±2.1 nkat/24 hours, P<0.01). No further change was observed after 20 days of sodium loading in this group (17.5±2.3 nkat/24 hours). Ukal V remained unchanged in vehicle-treated rats (from 13.2±0.9 to 14.3±1.1 and 14.8±1.7 nkat/24 hours, P=NS).

At the end of the experiments, plasma immunoreactive kallikrein levels were higher in low-kallikrein rats given RUK (66.4±4.4 versus 57.7±2.4 ng/mL in controls, P<0.05).

The ratio of heart weight to BW was significantly lower in low-kallikrein rats given RUK infusion (30±8 versus 321±4 mg/100 g BW in controls, P<0.01), whereas the ratio of kidney weight to BW was similar (335±47 versus 333±7 mg/100 BW in controls, P=NS).

Experiment 3: Comparison of Histological Parameters of Kidney Sections From Normal (Controls) and Low-Kallikrein Rats on Normal Sodium Diet

The ratio of kidney weight to BW was lower in low-kallikrein rats than in controls (329±47 and 370±7 mg/100 g BW, respectively, P<0.01). Initial observations of stained histological sections of the kidneys from the two groups of animals suggested that the renal corpuscles in the low-kallikrein group may have been more "swollen" than those in the control group (Fig 2A and 2B, left panels). This was verified by performing morphometric analyses. As shown in Table 2, the difference between the groups was largely in the width of Bowman's space (urinary space) enclosed by the parietal and visceral layers of Bowman's capsule. The width of the urinary space in low-

SBP (mmHg) HR (beats/min) BW (grams)

![Graphs showing SBP, HR, and BW values](image-url)
TABLE 1. Effect of High Sodium Intake in Rats Given Urinary Kallikrein Infusion or Vehicle

<table>
<thead>
<tr>
<th>Parameter and Group</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-4</td>
</tr>
<tr>
<td>UV, mL/24 h</td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>24±1</td>
</tr>
<tr>
<td>Kallikrein</td>
<td>26±1</td>
</tr>
<tr>
<td>U_kall, mmol/24 h</td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>2.5±0.5</td>
</tr>
<tr>
<td>Kallikrein</td>
<td>2.2±0.3</td>
</tr>
<tr>
<td>U_kall, mg/24 h</td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>23.5±2.7</td>
</tr>
<tr>
<td>Kallikrein</td>
<td>23.9±1.8</td>
</tr>
</tbody>
</table>

Values represent mean±SEM. Rats were given rat urinary kallikrein or vehicle intravenously from day -4, and they were fed a high-sodium diet from day 0.

*p<.05 vs day -4.

Kallikrein rats was about double that of the normal group. The method of acquisition of the data precludes this difference resulting from tissue processing, sectioning, or orientation artifact. The data obtained also indicate that although the cortical widths of kidneys from both groups are similar, the number of renal corpuscles (and glomeruli) per unit square area is significantly lower in the low-kallikrein group (Fig 2A and 2B, right panels). Other differences (not analyzed morphometrically) were observed in portions of the distal tubule: (1) the nuclei in the macula densa of the low-kallikrein group appeared not to be as closely packed as those of controls (compare Fig 2A and 2B, right panels), and (2) the late distal tubule (connecting tubule/cortical collecting duct), which is the site of most of the true kidney kallikrein, appeared to be longer and more distended in the control group than in the low-kallikrein group (see Fig 3A and 3B).

Fig 3 shows the results of immunohistochemistry studies. A greater intensity of staining was detected in the late distal tubule (arrows) in sections obtained from normal-kallikrein rats. Lighter staining in proximal tubules probably indicates the presence of another member of the kallikrein gene family that cross-reacts with the polyclonal antiserum.9,12 In the sections obtained from low-kallikrein rats, the intensity of staining was much stronger. The section obtained from the low-kallikrein rat shows a larger share of renal corpuscles than the control (Fig 3B).
rats, the staining appeared to be greater in the proximal tubules, while the late distal tubules exhibited little or no staining.

### Discussion

On a normal sodium diet, the SBP of low-kallikrein rats exceeded by 16 mm Hg that of normal kallikrein rats, a difference that is consistent with the number observed previously in the same strain and in Wistar rats in which blockade of bradykinin B$_2$-receptors was achieved by subcutaneous injection of the antagonist icatibant (at the dose of 300 nmol/kg BW per day) since the second day of life. This mild difference is also consistent with the predicted contribution of the kallikrein gene to the overall blood pressure variability. Environmental factors, such as excessive salt intake, may lead to hypertension in subjects with genetic susceptibility. Among various putative genetic markers, low urinary excretion of kallikrein reportedly predicts in which subjects an increase in blood pressure response to chronic dietary sodium loading in a rat strain inbred for the low-kallikrein phenotype.

Preliminary studies suggest that kallikrein administration reduces blood pressure in salt-sensitive but not in salt-resistant hypertensives. In addition, long-term infusion of RUK, at a dose that does not affect systemic blood pressure, reduces renal injury in hypertensive salt-sensitive Dahl rats, as reflected by attenuation of glomerulosclerotic lesions and tubular damage and by a reduction in proteinuria.

In our study, infusion of RUK prevented the increase in SBP induced by a high-salt diet in low-kallikrein rats. Immunoreactive tissue kallikrein levels in plasma were increased by 14% in RUK-treated low-kallikrein rats. Since circulating levels were not measured in normal-kallikrein rats, we cannot say if circulating immunoreactive kallikrein differs between strains and if RUK infusion normalized the plasma levels of low-kallikrein rats. Thus, it is not possible to conclude that the blood pressure response to RUK is related to its effect on plasma kallikrein.

We found that RUK infusion normalized the elevated ratio of heart weight to BW found in this strain. Uehara et al. found that infusion of RUK alone was ineffective in lowering blood pressure and in preventing the increase in heart weight in salt-sensitive hypertensive Dahl rats. However, RUK infusion potentiated the antihypertensive and antihypertrophic effects of cilazapril, an angiotensin-converting enzyme inhibitor. Since the dose of RUK used in the present study was ≈4× higher than that used by Uehara et al. (1.7 and 0.4 μg/d, respectively), the antihypertrophic effect of RUK may be dose related and dependent on the concomitant reduction in the hemodynamic load to the heart. Another important difference is that in the study by Uehara et al., treatment with RUK was performed in rats whose SBP and heart weight values (190 mm Hg and 390 mg/100 g BW, respectively) indicate more severe hypertension and greater heart hypertrophy than in our salt-loaded low-kallikrein rats (158 mm Hg and 321 mg/100 g BW, respectively). Therefore, diversity in the severity and duration of hypertension could affect the protection exerted by RUK. Recent studies have suggested that modulation of the endogenous kallikrein-kinin system is instrumental for cardiovascular protective mechanisms, namely by interfering with myocardial and vascular smooth muscle cell proliferation. Thus, regression of myocardial hypertrophy following RUK infusion could be attributable not only to the reduced hemodynamic load but also to a direct effect of RUK and its enzymatic products on the heart.

In association with an enhanced blood pressure sensitivity to salt, the low-kallikrein rats showed a decreased urinary excretion of sodium during salt loading. Similar results were reported in reninogen-deficient Brown Norway Katholie rats, which genetically lack the ability to generate kinins. Thus, we hypothesized that the enhanced blood pressure sensitivity to salt in low-kallikrein rats (whose alteration is limited to kidney) is due to sodium retention and total fluid volume expansion. The possibility that alterations in renal filtration and/or tubular handling of sodium are present in this strain is supported by previous findings showing that salt loading causes positive sodium balance, a reduced ratio of U$_{NaV}$ to U$_{NaL}$, decreased excretion of creatinine, and increased BW. Hence, correction of the exaggerated blood pressure response to sodium loading by RUK might be attributed to the effects of kinins on renal filtration and/or tubular sodium handling. We did not measure plasma or urinary kinins in low-kallikrein rats under basal conditions or during RUK infusion; however, Uehara et al. showed that urinary excretion of bradykinin increased twofold by RUK at a dose lower than that used by us. Our results indicate that renal function was not affected by RUK infusion during the first 5 days of high sodium intake. This does not exclude a diuretic and natriuretic effect of RUK during the following days of sodium loading, since UV and U$_{NaV}$ were not measured thereafter. Another possibility is that the blood pressure effect of RUK in salt-loaded rats is due to a direct effect of kinins on vascular tone. To define the role of bradykinin in the action of RUK, it would be necessary to evaluate whether its antihypertensive effect in salt-loaded rats is abolished with the bradykinin B$_2$-receptor antagonist icatibant. In preliminary experiments, we found that the acute intravenous injection of 50 nmol icatibant does not alter the MBP of RUK-treated low-kallikrein rats (P.M., unpublished observations, 1996). However, chronic blockade of the B$_2$-receptor appears to be a more appropriate approach to elucidate this issue.

A trophic role of the kallikrein-kinin system in postnatal renal development is suggested by the observation that early, lifelong blockade of bradykinin receptors suppresses renal growth and reduces U$_{cr}$ excretion. Consistent with this possibility is our observation that the functional alterations reported above in the low-kal-

### Table 2. Comparison of Histological Parameters of Kidney Sections From Normal (Controls) and Low-Kallikrein Rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Rats</th>
<th>Low-Kallikrein Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical width, mm</td>
<td>1.62±0.01</td>
<td>1.55±0.08</td>
</tr>
<tr>
<td>Number of glomeruli, n/mm$^2$</td>
<td>108±4.0</td>
<td>72±0.3$^*$</td>
</tr>
<tr>
<td>Diameter (μm)</td>
<td>97±1.2</td>
<td>112.2±0.6$^*$</td>
</tr>
<tr>
<td>Glomeruli</td>
<td>87±1.2</td>
<td>95±0.3$^*$</td>
</tr>
<tr>
<td>Bowman’s spaces</td>
<td>9.9±0.6</td>
<td>18.4±0.3$^*$</td>
</tr>
</tbody>
</table>

Data (mean±SEM) derived from histological sections of kidneys obtained from three rats per group. Details of measurements and counts in the "Methods" section.

*P<.05 versus control rats.
A general consensus exists regarding localization of kallikrein in the connecting tubule segment of the distal tubule. Serious problems with localizing kallikrein-like enzymes relate to the antigenic similarity of the members of the kallikrein gene family of serine proteinases. Hence, polyclonal antibodies to a member of the kallikrein gene family may also bind to related antigens if they are present. For instance, staining of polyclonal an-

likrein rats were associated with a lower ratio of kidney weight to BW and reduction of the number of glomeruli per unit of area. On other hand, the low-kallikrein strain might be particularly susceptible to develop renal damage as a consequence of modest elevations in blood pressure levels. The increase in the width of Bowman’s space (urinary space) could be attributable to greater filtration pressure in this strain.

Fig 3. Kidney sections stained with polyclonal antibody to rat kallikrein. (×120 magnification). Control animal (A) illustrating the intensity of staining in the late distal tubule (arrow). Lighter staining in proximal tubules probably indicates the presence of another member of the kallikrein gene family that cross-reacts with polyclonal antiserum. Low-kallikrein rat (B) illustrating that the staining in proximal tubules appears greater than in controls, but the late distal tubules (arrow) exhibit little or no staining.
tibodies against RUK at the level of the proximal tubule has been demonstrated to be due to another kallikrein gene family member such as esterase A. Therefore, the light staining detected in proximal tubules of normal rats using polyclonal antibodies may be attributable to the latter enzyme. In the sections obtained from low-kallikrein rats, the late distal tubules exhibit little or no staining, thus suggesting reduced production of the enzyme at the level where true kallikrein is synthesized. The other finding, that proximal tubule staining appeared to be greater, might be explained by enhanced production of a tissue kallikrein-related enzyme in the low-kallikrein strain. Though it is not clear how this enzyme functions in kidney physiology, esterase A shares substrate specificity with kallikrein and generates kinins from kininogen. Therefore, one might speculate that an increase in esterase A could compensate at least in part for the deficient production of true kallikrein.

Another possible explanation of our immunohistochemical results may be that staining in the proximal tubule of low-kallikrein rats is related to glomerular filtration of circulating tissue kallikrein and consequent reabsorption by epithelial cells. On the basis of its molecular weight and isoelectric point and on the results of clearance studies using radiolabeled kallikrein in the rat, it is unlikely that circulating kallikrein is normally filtered at the glomerulus. However, it could cross the glomerular membrane in chronic renal failure models, as suggested by the observation of reabsorption droplets in the proximal tubule, a site of the nephron where true tissue kallikrein is not detected in either human or rat normal kidneys. Should the latter hypothesis be confirmed, urinary kallikrein levels could overestimate the real amount of enzyme synthesized within the kidney of low-kallikrein rats. Studies using two different monoclonal antibodies, each specific for kallikrein and esterase A, are necessary to elucidate this issue.

The major conclusions that can be drawn from our results are that an inherited low urinary kallikrein phenotype does result in an increased blood pressure sensitivity to salt that can be corrected by chronic replacement with rat tissue kallikrein. In addition, histological abnormalities have been detected at different levels in the nephron that may be functionally related to the altered cardiovascular and renal phenotype.

Acknowledgments

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