Effect of the Protease Inhibitor Aprotinin on Renal Hemodynamics in the Pig

MANFRED MAIER, MICHAEL STARLINGER,* ZYDI ZHEGU, HEMANTA RANA, AND BERND R. BINDER

SUMMARY  Aprotinin, the serine protease inhibitor that also inhibits glandular (urinary) kallikrein, or vehicle was infused into the aorta above the renal arteries of anesthetized pigs. Renal hemodynamic and functional parameters were followed over time and during hemorrhagic hypotension. Both renal cortical blood flow and glomerular filtration rate were maintained in vehicle-treated animals at mean arterial pressures as low as 70 mm Hg. As long as renal cortical blood flow and glomerular filtration rate were maintained during the progressive hypotension, urinary excretion rate of kallikrein (as defined by kinin-generating activity) was increased. In contrast, all aprotinin-treated animals had a decreased excretion rate, and the renal cortical blood flow declined with the mean arterial pressure during hemorrhage. The pattern of glomerular filtration rate and plasma renin activity was comparable in both aprotinin-treated and vehicle-treated hemorrhaged animals. Our findings suggest that the endogenous renal kallikrein-kinin system is required for functional renal vasodilatation to maintain renal cortical blood flow during hemorrhage and is therefore directly or indirectly responsible for adjustment of preglomerular resistance. (Hypertension 7: 32–38, 1985)

KEY WORDS  renal hemodynamics  hemorrhage  kallikrein  renin  aprotinin

THE regulation of the renal circulation depends on resistance changes that result from the constriction or relaxation, or both, of vascular smooth muscle, whether mediated by neural, humoral, or physical factors. A special feature of the mechanisms that regulate local hemodynamics in several organs — especially the kidney — is the ability to maintain relative constancy of blood flow despite major changes in perfusion pressure. Because the changes in renal vascular resistance that accompany these variations in perfusion pressure are demonstrable in innervated and denervated kidneys and in isolated, blood-perfused kidneys, this phenomenon is thought to be mediated by events intrinsic to the kidney and has been termed autoregulation of renal blood flow.2,3

Several factors, such as the renin-angiotensin system,2 the prostaglandins,4 and the kallikrein-kinin system,3 appear to influence renal vascular resistance. There is considerable evidence that angiotensin II controls the glomerular filtration rate (GFR) through an efferent arteriolar constricting mechanism,7,8,17 thereby maintaining effective filtration pressure at reduced arterial pressure. Despite increased formation of vasoconstrictory angiotensin II, the afferent arterioles dilate in response to reduced arterial pressure,11 apparently through activation of a vasodilatory mechanism.7,9 The maintenance of efferent arteriolar resistance along with afferent arteriolar vasodilatation provides an effective means for regulating renal blood flow as well as GFR when renal artery pressure is lowered.7

Because of the complexity of the several intrarenal systems and their interactions15–17 this vasodilator mechanism has not been defined. In a previous study on hemorrhagic hypotension in pigs we found increased excretion of urinary kallikrein within the arterial pressure range of 100 to 70 mm Hg, which corresponded to the relative maintenance of renal cortical

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Dr. Zhegu is a grantee of the government of Albania in Tirana, Albania.


Supported in part by Grants 124 and 189 from the mayor of the city of Vienna.

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Received January 6, 1984; revision accepted August 1, 1984.
blood flow (RCBF) and GFR. This finding suggested to us that the renal kallikrein-kinin system might be involved in maintenance of local renal blood flow during hemorrhagic hypotension.19 Urinary kallikrein has been demonstrated to be synthesized by the kidney30 and by renal cortical cells in suspension,21 and its excretion into the urine is thought to reflect its intrarenal activity. This serine protease, by limited proteolytic action, liberates the peptide sequence bradykinin (BK) or lysyl-bradykinin (Lys-BK) from its protein substrates, kininogens.22 Among the numerous effects of kinins, dilatation of arterioles and a subsequent increase in blood flow seem to be the most prominent.5,6 The present study was designed to establish that the maintenance of RCBF during hemorrhage (probably mediated by an activated kallikrein-kinin system) can be abolished by administration of the protease inhibitor aprotinin, which also inhibits kallikrein.

Materials and Methods

Experimental Protocol

Experiments were carried out on 28 pigs (4 groups of 7 animals each, weighing 24–31 kg) fed a normal diet (approximately 40–60 mEq sodium per day). Anesthesia was induced with sodium thiopental (Pentothal, 30 mg/kg, i.v.). An endotracheal tube was inserted and the animals were allowed to breathe spontaneously a halothane-O₂/N₂O mixture (0.7%, 29.3%, 70% respectively). The electrocardiogram was continuously recorded. Catheters (5F, pigtail) were inserted through the left femoral artery into the left ventricle, into the left femoral artery, into the left femoral vein, and into the right femoral artery (polyethylene catheters: ID 1.5 mm, OD 2 mm). The tip of the latter was placed above the renal arteries, and the correct position of this catheter was checked after each experiment. The catheter from the left femoral artery was connected to a Statham transducer (Statham Instruments, Inc., Oxnard, CA) for continuous recording of the mean arterial blood pressure (MAP; Gould Brush polygraph, Gould Medicals GesmbH, Düsseldorf, FRG). Polyethylene catheters (ID 0.9 mm) also were inserted through a small suprapubic incision into both ureters and 5-minute combined urine samples were collected by means of a fraction collector; the dead space in both catheters was less than 150 ml. Care was taken to ensure free urine flow from both ureters and to avoid blood contamination. The surgical procedure was followed by a 60-minute stabilization period.

Experimental Groups

Hemorrhagic Hypotension with Infusion of Aprotinin or Vehicle

After the stabilization period two groups of seven animals each received a continuous infusion of either aprotinin or vehicle. Aprotinin (Trasylol, Bayer AG, Leverkusen, FRG) was dissolved in 50 ml of 0.9% NaCl (final concentration 3 × 10^6 kallikrein inhibitor units or 0.064 mmol in 50 ml), and the freshly prepared solution or the vehicle alone was infused through the right femoral artery catheter into the aorta above the renal arteries at a constant rate of 0.8 ml/min (approximately 1,700 kallikrein inhibitor units/kg/min or 0.036 μmol/kg/min) by means of a Harvard pump (Harvard Apparatus Co., Inc., Millis, MA). Sixty minutes (control period) after the infusions were started hypovolemia was induced by continuous bleeding from the carotid artery at a rate of 1 ml/kg/min until the death of the animals (30–60 minutes). Mean arterial pressure was allowed to stabilize at 100, 90, 80, 70, and 60 mm Hg (time interval 5–12 minutes) for 2 to 3 minutes to obtain blood samples and to inject microspheres as outlined in Measurements.

Infusion of Aprotinin or Vehicle Without Hemorrhagic Hypotension

After the stabilization period two groups of seven animals each were infused with aprotinin or vehicle for 120 minutes as described in the previous section, except that hemorrhagic hypotension was not induced. The infusions were then stopped and after an additional 20 minutes (total experimental time 140 minutes) the animals were sacrificed.

Measurements

Twenty minutes before the stabilization period ended 0.5 ml 3H-inulin (dissolved in isotonic saline to approximately 5.5 × 10^6 dpm; the Radiochemical Centre, Amersham Buckinghamshire, England) was given as a single bolus injection into the left femoral vein. The first blood sample was taken and urine fractionation was started at the end of the stabilization period. Thereafter the infusion of either aprotinin or vehicle was started and 5-ml samples from the left femoral vein were taken every 20 minutes. In hemorrhaged animals the first blood sample was taken and urine fractionation was begun after 60-minute infusion of either aprotinin or vehicle (end of control period) and at every 10 mm Hg decrease of MAP during bleeding. Plasma was obtained and sodium (Eppendorf flame photometer, Eppendorf Gerätebau, Hamburg, FRG), 3H-inulin (Beckman liquid scintillation counter LS 7500; Beckman Instruments, Inc., Irvine, CA), and plasma renin activity were determined as indicated. Urine volume was measured and concentrations of sodium, 3H-inulin, and urinary kallikrein were determined. From these data excretion rates of Na⁺ and urinary kallikrein as well as values for GFR could be calculated. Plasma renin activity (PRA) was measured by radioimmunoassay of angiotensin I generated after incubation of 0.1 ml of plasma sample for 1 hour at 37 °C with an assay kit from New England Nuclear (Boston, MA).23

Urinary kallikrein was determined as kinin-generating activity. The kinin generated was bioassayed on a guinea pig terminal ileum segment suspended in Tyrode's solution made 5 × 10⁻⁷ M with atropine and aerated with a constant stream of compressed air.34 Urine samples (5–100 μl) were incubated at 37 °C for 5 minutes with 100 to 500 μl of heat-inactivated pig plasma in a final volume of 600 μl. Before incubation...
the reaction mixture was brought to a pH of 7 to 8 by adding divalent cation-free Tyrode's solution fortified with 2.5% sodium bicarbonate. After incubation the mixtures were assayed immediately for kinin content, which was quantitated by comparison with the contractile response of the ileum to a synthetic BK standard (Sigma Chemical Co., St. Louis, MO). The smooth muscle preparation was standardized after every fifth sample with at least four doses of synthetic BK and was used only if it responded to 2 ng BK/ml of organ bath fluid and gave a linear dose response up to 50 ng BK/ml. Kinin formation was directly proportional to both the duration of incubation (0–60 minutes) and the amount of urine sample. Pig plasma was obtained and heated for 2 hours at 59 to 60 °C to eliminate plasma kininase and spontaneous kinin-generating activity. The kallikrein substrate concentration in these preparations was usually between 20 to 45 μg/ml. As 98.3% to 101.7% of BK standards incubated at 37 °C for 5 minutes with urine samples obtained at five different time points from each experiment could be recovered, no inhibitors of kininases were used in the bioassay. Only substrate-dependent activities were found, which were expressed as μg BK equivalents.

To determine whether or not aprotinin-treated animals excreted free kallikrein inhibitor in their urine, the following experiments were conducted. 10 μl purified pig urinary kallikrein was incubated with 200 μl heat-inactivated plasma for 5 minutes at 37 °C with or without preincubation with 100 μl pig urine for 5 minutes at 37 °C. The enzyme activity could be completely recovered after incubation with urine samples, which indicates the absence of free kallikrein-inhibitor capacity in the urine of aprotinin-treated pigs.

Renal cortical blood flow was evaluated in all pigs by means of 15 μ radio-active-labeled microspheres (3M Company, St. Paul, MN) as previously described. The RCBF was determined at the end of the control period and at 100, 90, 80, 70, and 60 mm Hg during bleeding experiments and is given in milliliters per kilogram body weight. The PRA continuously increased throughout the experiments (Table 1). The PRA did not increase but was still significantly elevated.

**Results**

**Infusion of Aprotinin or Vehicle Without Hemorrhagic Hypotension**

During infusion of 0.9% saline the values for parameters obtained at the end of the stabilization period remained stable throughout the experiments (Table 1). In contrast, infusion of aprotinin in control animals was followed by a reduction of RCBF and an increase in renal resistance. Although these changes were not significant, the resulting decrease in GFR and FF obtained during the first 20 minutes of aprotinin infusion reached significance but returned to control values thereafter (Figure 1). Urinary sodium excretion, MAP, and urine flow did not change significantly as shown in Table 1. While PRA was significantly elevated within the first 60 minutes of aprotinin infusion, the excretion rate of urinary kallikrein (as defined by kinin-generating activity) decreased. After the infusion of aprotinin was stopped all values for the parameters measured returned toward control levels except for urinary kallikrein and urine flow, which were significantly elevated (Table 1). The PRA did not increase but was still significantly elevated.

**Infusion of Vehicle During Hemorrhagic Hypotension**

The pattern of renal functional parameters observed during hemorrhagic hypotension and infusion of vehicle (Figure 2, left panel) is consistent with results of our previous study. Relative maintenance of RCBF at values of approximately 84% of control was observed at MAP levels between 100 and 70 mm Hg, together with maintenance of GFR at values of approximately 78% of control for the same range of MAP. Renal cortical resistance declined slightly and FF was maintained at constant levels. As depicted in Table 2, urinary kallikrein excretion increased almost fourfold at a MAP of 90 mm Hg compared with the control period and was significantly elevated at MAP levels of 100 to 70 mm Hg. The PRA continuously increased throughout the period of hemorrhagic hypotension. Heart rate
Table 1. Systemic and Renal Functional Parameters Before, During, and After Infusion of Aprotinin or Vehicle

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Infusion of vehicle (n = 7)</th>
<th>Infusion of aprotinin (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stabilization period</td>
<td>20 min</td>
</tr>
<tr>
<td></td>
<td>MAP (mm Hg)</td>
<td>126.7±2.8</td>
</tr>
<tr>
<td></td>
<td>KGA (μg BK/min)</td>
<td>8.1 ± 1.3</td>
</tr>
<tr>
<td></td>
<td>UN,V (μEq/min)</td>
<td>13.5 ± 2.8</td>
</tr>
<tr>
<td></td>
<td>V (ml/min)</td>
<td>0.3 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>PRA (ng/ml/hr)</td>
<td>2.01 ± 0.51</td>
</tr>
<tr>
<td>Infusion of aprotinin (n = 7)</td>
<td></td>
<td>127.2 ± 6.5</td>
</tr>
<tr>
<td></td>
<td>MAP (mm Hg)</td>
<td>9.25 ± 1.47</td>
</tr>
<tr>
<td></td>
<td>KGA (μg BK/min)</td>
<td>16.6 ± 3.9</td>
</tr>
<tr>
<td></td>
<td>UN,V (μEq/min)</td>
<td>0.31 ± 0.03</td>
</tr>
<tr>
<td></td>
<td>V (ml/min)</td>
<td>5.8 ± 0.5 *</td>
</tr>
</tbody>
</table>

*Statistical significance (aprotinin versus vehicle), Bonferroni test
†Statistical significance (aprotinin versus vehicle), analysis of variance
All values are means ± SEM
MAP = mean arterial pressure, KGA = kinin-generating activity, UN,V = sodium excretion rate, V = urine flow, PRA = plasma renin activity, BK = bradykinin

Figure 1. Pattern of renal hemodynamic parameters during infusion of aprotinin in pigs without hemorrhagic hypotension (n = 7). Values for renal cortical blood flow (RCBF), glomerular filtration rate (GFR, §), filtration fraction (FF; §), and renal resistance are shown as mean ± SEM. Significant differences are indicated by * (Bonferroni test) and by § (analysis of variance). STAB = stabilization period. During vehicle infusion RCBF remained constant at 3.3 ± 0.5 ml/min/g and GFR at 0.7 ± 0.08 ml/min/g.

Figure 2. Pattern of renal hemodynamic parameters during infusion of either vehicle (left panel, n = 7) or aprotinin (right panel, n = 7) in pigs subjected to hemorrhagic hypotension. Values are shown as mean ± SEM and the stars indicate significant differences (Bonferroni test). The pattern of all parameters during infusion of aprotinin is significantly different compared with infusion of vehicle (analysis of variance). CO = control period.
increased from a mean value of 131.6 to 185.2 beats/min, and the blood loss at the end of the experiments was 28.38 ± 2.09 ml/kg (mean ± SEM, approximately 39% blood loss).

**Infusion of Aprotinin During Hemorrhagic Hypotension**

Infusion of aprotinin instead of vehicle significantly altered the pattern of renal functional parameters during hemorrhagic hypotension (Figure 2, right panel; Table 2). Control RCBF was only slightly lower than in the vehicle-treated animals but was already significantly reduced at 100 mm Hg and was not maintained at a constant level but declined concomitantly with the decline of MAP. The GFR, however, did remain constant at a MAP of 100 to 80 mm Hg, but at a level as low as 66% of control. The pattern of RCBF and GFR resulted in an increase in FF and in renal cortical resistance. No increase in urinary kallikrein excretion rate as seen in vehicle-treated animals (Table 2) could be observed. Values for urinary sodium excretion and urine flow decreased; PRA and heart rate did not differ significantly from those of vehicle-treated animals. The blood loss at the end of the experiments was 24.09 ± 2.31 ml/kg (approximately 34%).

**Discussion**

Hemorrhagic hypotension was accompanied by an increased urinary kallikrein excretion rate within the pressure range of 100 to 70 mm Hg (Table 2), as reported previously.19 This increase corresponded to a pressure range of 100 to 70 mm Hg (Table 2), as seen in vehicle-treated animals (Table 2) could be observed. Values for urinary sodium excretion and urine flow decreased; PRA and heart rate did not differ significantly from those of vehicle-treated animals. The blood loss at the end of the experiments was 24.09 ± 2.31 ml/kg (approximately 34%).

**Table 2**

<table>
<thead>
<tr>
<th>Mean arterial pressure (mm Hg)</th>
<th>Kinin-generating activity*‡</th>
<th>Sodium excretion rate†</th>
<th>Urine flow¶</th>
<th>Plasma renin activity (ng/ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion of vehicle (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>125 ± 5.0</td>
<td>10.89 ± 3.88</td>
<td>14.06 ± 4.40</td>
<td>0.32 ± 0.03</td>
<td>1.87 ± 0.65</td>
</tr>
<tr>
<td>100 ± 2.5</td>
<td>18.51 ± 4.52</td>
<td>4.92 ± 2.44</td>
<td>0.34 ± 0.02</td>
<td>6.80 ± 0.69</td>
</tr>
<tr>
<td>90.2 ± 2.3</td>
<td>39.39 ± 11.51</td>
<td>8.33 ± 1.25</td>
<td>0.33 ± 0.05</td>
<td>7.65 ± 1.32</td>
</tr>
<tr>
<td>80.5 ± 2.7</td>
<td>20.51 ± 5.59</td>
<td>3.73 ± 0.75</td>
<td>0.20 ± 0.03</td>
<td>8.46 ± 2.06</td>
</tr>
<tr>
<td>70.1 ± 1.9</td>
<td>19.10 ± 2.60</td>
<td>1.05 ± 0.28</td>
<td>0.12 ± 0.02</td>
<td>10.84 ± 1.99</td>
</tr>
<tr>
<td>60.6 ± 2.9</td>
<td>1.07 ± 0.36</td>
<td>0.28 ± 0.12</td>
<td>0.02 ± 0.007</td>
<td>12.22 ± 1.00</td>
</tr>
<tr>
<td>Infusion of aprotinin (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>130 ± 7.5</td>
<td>7.35 ± 2.45</td>
<td>9.90 ± 3.02</td>
<td>0.29 ± 0.06</td>
<td>2.90 ± 0.98</td>
</tr>
<tr>
<td>100 ± 3.2</td>
<td>7.80 ± 4.40†</td>
<td>10.46 ± 2.36†</td>
<td>0.24 ± 0.04†</td>
<td>9.55 ± 1.77</td>
</tr>
<tr>
<td>90.1 ± 2.7</td>
<td>5.27 ± 1.49†</td>
<td>2.95 ± 0.30†</td>
<td>0.20 ± 0.06†</td>
<td>9.50 ± 1.70</td>
</tr>
<tr>
<td>80.7 ± 2.8</td>
<td>5.13 ± 1.35†</td>
<td>3.57 ± 0.26</td>
<td>0.11 ± 0.03†</td>
<td>9.50 ± 2.00</td>
</tr>
<tr>
<td>70.3 ± 1.6</td>
<td>2.97 ± 0.95†</td>
<td>3.70 ± 1.00†</td>
<td>0.11 ± 0.02</td>
<td>9.07 ± 1.65</td>
</tr>
<tr>
<td>60.5 ± 2.4</td>
<td>1.60 ± 0.40†</td>
<td>1.49 ± 0.39†</td>
<td>0.08 ± 0.02†</td>
<td>15.97 ± 2.60</td>
</tr>
</tbody>
</table>

*There was also a significant increase of kinn-generating activity over time in vehicle-infused hemorrhaged animals (not shown) 19
†Statistical significance (aprotinin versus vehicle), Bonferroni test
‡Statistical significance (aprotinin versus vehicle), analysis of variance
All values are means ± SEM

BK = bradykinin
Aprotinin is a polyvalent inhibitor of serine proteases and not a specific inhibitor of kininogenases. As it may have other unspecific effects not mediated by inhibition of kinin generation, it’s use to inhibit urinary kallikrein in vivo may be criticized. However, aprotinin has been used successfully as a kallikrein inhibitor in vitro and in vivo. On the other hand, we could still measure kinin-generating activity in urine samples during infusion of aprotinin (Tables 1, 2). This finding needs further explanation. It has been shown that injected aprotinin is bound to the brush border of the proximal tubules of the kidney and only minimal amounts are filtered and excreted into the urine. Furthermore, the levels of urinary kallikrein activity in samples excreted by rats given aprotinin daily subcutaneously decreased very slowly; a reduction of 24% on the first and 60% on the fourth day of treatment was reported. It is therefore likely that the urinary concentration of injected aprotinin is not high enough to inhibit urinary kallikrein excreted into the urine at the distal tubule level. This supposition is consistent with our finding that exogenous kallikrein added to urine samples of aprotinin-treated pigs was completely recovered and indicates the absence of free aprotinin. Additionally, in our control experiments without hemorrhagic hypotension, the excretion rate of kininogenase activity was reduced by approximately 27%; stopping the infusion of aprotinin into the aorta was followed by a sharp increase (Table 1). This finding indicates inhibition of urinary kallikrein activity during but not after infusion of aprotinin. Total kallikrein (inactive plus active) excretion might actually increase during infusion of aprotinin in normal as well as in hemorrhaged animals. The increase in kallikrein activity at 140 minutes (Table 1) might therefore represent the true rate of kallikrein excretion during aprotinin infusion, which can be measured accurately once the aprotinin infusion has been stopped.

As infusion of aprotinin also affected regulation of RCBF (Figures 1, 2), a relationship between regulation of renal vascular resistance and kallikrein effects is likely. This finding also suggests that the effect of aprotinin is not a result of inhibition of urinary kallikrein activity in the distal tubular fluid, but rather that the site of aprotinin action is the renal circulation or the renal interstitium where it inhibits either newly released or activated kallikrein. Such a relationship has been proposed for many years, and several studies have indicated that at least some glandular kallikrein passes into the vascular compartment. Only recently experimental evidence was presented that kallikrein from the submandibular gland of the rat is released into the circulation to generate vasodilatory kinins locally from plasma kininogen substrates. In fact, kallikrein could be localized in the rat kidney to both a plasma membrane-enriched fraction and a basolateral membrane–enriched fraction. Both plasma membrane and basolateral membrane kallikreins were found to share common antigenic determinants with urinary kallikrein and to be inhibited by aprotinin in vitro. It has been proposed that the plasma membrane kallikrein, when released from the luminal side of the distal tubules, is the enzyme that appears in the urine, while the kallikrein from the basolateral membrane appears in renal lymph and venous effluent. In view of the body of experimental evidence we suggest therefore that a portion of the kallikrein secreted by distal tubular cells in response to a stimulus enters the renal circulation. This portion appears to be inhibited by arterial infusion of aprotinin. The remaining portion of the secreted kallikrein enters the urine at the distal tubular level and is therefore less or not accessible to inhibition by aprotinin.

Constancy of renal blood flow decrease reduction in arterial pressure is a consequence of renal vasodilatation, which is effective primarily at the afferent arterioles. During reduced renal artery pressure the activity of the vasconstricting renin-angiotensin system has been shown to increase in plasma and renal lymph and is therefore not a likely mediator of afferent vasodilatation but rather contributes to adjustment of efferent arteriolar resistance. Assuming that kallikrein secreted by the kidney enters both the renal circulation and the distal tubular fluid, increased excretion of this kinin-generating enzyme in the urine during maintenance of RCBF strongly suggests increased generation of vasodilatory kinin within the kidney. The vasodilatory kallikrein-kinin system therefore is a likely candidate to directly or indirectly mediate afferent vasodilatation and maintenance of RCBF; arterial infusion of aprotinin inhibited both kallikrein action within the kidney and afferent vasodilatation. This hypothesis is strongly supported by results from micropuncture experiments, which show that infusion of BK resulted in a significant increase in afferent arteriolar blood flow and a greater fall in afferent than in efferent resistance.

The limitations of the present study should be pointed out. The model used is highly complex and involves a variety of hormonal and nerve changes. Our results therefore have to be proved in other models such as aortic constriction, isolated perfused organs, or in animals that are genetically deficient in tissue kallikrein. Furthermore, a specific inhibitor of kallikrein is not available as yet. The use of specific antikallikrein antibodies and antikinin antibodies offers an alternative, but supply is limited. Measurement and demonstration of components of the kallikrein-kinin system including the kinin receptor at sites of their proposed action (e.g., the afferent or efferent arteriole), also would be desirable, but are presently impossible owing to methodological problems.

Conclusion

The present study provides further evidence that the renal kallikrein-kinin system directly or indirectly contributes to functional vasodilatation of the afferent arterioles. Such a relationship may be important in essential hypertension, which is characterized by reduced renal blood flow, increased renal resistance, and diminished urinary kallikrein excretion.
Acknowledgments

We thank Dr. Köhler, Bayer-AG, Vienna, for the generous supply of aprotinin (Trasylol) used in this study and Professor R Gorbett for his continued support. We express our appreciation for the valuable technical assistance of Mr. R Alt, Mrs. R Balaun, Mrs. H Hitschmann, and Mrs. J Jerabek.

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Hypertension. 1985;7:32-38
doi: 10.1161/01.HYP.7.1.32

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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