Chronic Inhibition of Bradykinin B₂-Receptors Enhances the Slow Vasopressor Response to Angiotensin II

Paolo Madeddu, Paolo Pinna Parpaglia, Maria Piera Demontis, Maria Vittoria Varoni, Maria Caterina Fattaccio, Nicola Glorioso

Abstract The contribution of endogenous kinins in the regulation of blood pressure of angiotensin-treated rats was evaluated using the new bradykinin B₂-receptor antagonist Hoe 140 (d-Arg³[Hyp³,Thi³,D-Tic⁵,Oic⁷]-bradykinin). Chronic infusion of Hoe 140 at 75 nmol/d (a dose able to inhibit the vasodepressor effect of an intra-aortic bolus injection of 0.85 nmol/kg bradykinin) did not alter systolic blood pressure (tail-cuff plethysmography). Chronic infusion of angiotensin II (Ang II) induced a dose-related increase in systolic blood pressure and plasma Ang II levels. The vasopressor effect of 40 or 100 nmol/d Ang II was enhanced in rats given chronic infusion of Hoe 140 (by 12 and 14 mm Hg, respectively), whereas the increase in plasma Ang II levels remained unaltered. Furthermore, a low nonpressor dose of Ang II (20 nmol/d) was then able to increase blood pressure during chronic blockade of bradykinin receptors by Hoe 140 (from 126±3 to 137±3 mm Hg, P<.05). Combined infusion of 20 nmol Ang II and Hoe 140 did not alter the urinary excretion of sodium and water despite the fact that blood pressure was increased. Potentiation of the pressure effect of Ang II by Hoe 140 was confirmed by direct measurement of mean blood pressure (125±2 versus 108±2 mm Hg at 20 nmol, 123±2 versus 110±2 mm Hg at 40 nmol, and 139±2 versus 125±3 mm Hg at 100 nmol Ang II, P<.05). These findings indicate that blockade of bradykinin B₂-receptors enhances the slow pressor effect induced by moderate to severe increases in circulating Ang II levels. Therefore, endogenous kinins may play a role in preventing the chronic pressure effect of an excess of Ang II. (Hypertension. 1994;23:646-652.)

Key Words • bradykinin • kallikrein • angiotensins • blood pressure • mineralocorticoids

Kinins are endogenous vasodilators that act as local hormones by activating the release of endothelium-derived relaxing factors and prostaglandins. In addition, they could participate in the regulation of blood pressure and renal excretion of sodium and water by affecting tubular function and regional hemodynamics either directly or by interacting with other endocrine and paracrine systems.

Defective generation of kinins in the presence of enhanced activity of vasoconstrictor systems and/or sodium retention may contribute to the pathogenesis of arterial hypertension. Indeed, chronic inhibition of B₂-receptors, which mediate most cardiovascular and renal effects of bradykinin in normal conditions, increases blood pressure in deoxycorticosterone-treated rats on normal sodium intake and accelerates the development of hypertension in uninephrectomized deoxycorticosterone-treated rats on high sodium.

Some evidence also exists for an interaction between the renin-angiotensin and kallikrein-kinin systems. In the kidney, kallikrein is located at the level of luminal and basolateral membranes of the connecting tubules, in close proximity to the afferent arteriole, a major site of renin production. When injected intravenously or into the renal artery, bradykinin stimulates renin release, whereas an opposite effect reportedly occurs after administration of aprotinin, a nonspecific inhibitor of renal kallikrein. In the vasculature, the intrinsic kallikrein-kinin system and angiotensin II (Ang II) may influence each other, acting as paracrine hormones. For instance, some of the cardiovascular effects of angiotensin-converting enzyme inhibitors could be mediated by blockade of Ang II formation and concomitant enhancement of kinins generated at the vascular level. Preliminary observations have suggested that Ang II stimulates nitric oxide production in vascular endothelial cells by enhancing the synthesis and release of bradykinin. Although these data need to be confirmed, it is tempting to speculate that in vivo stimulation of kinin generation by Ang II could restore the balance between these functionally opposite hormones.

Recently, we found that the vasopressor response to intra-aortic boluses of Ang II is not altered by the new bradykinin B₂-receptor antagonist, d-Arg³[Hyp³,Thi³,D-Tic⁵,Oic⁷]-bradykinin (Hoe 140). These results do not favor a major role of endogenous kinins in modulating the cardiovascular effects induced by acute increases in the levels of circulating Ang II. However, Ang II also raises blood pressure gradually when given at low doses, and various mechanisms could contribute to this slow pressor effect. As yet, possible participation of kinins has not been explored.

The present study was designed to evaluate the possibility that endogenous kinins are able to counteract the slow pressor response to chronic Ang II infusion. Therefore, we studied the effect of chronic blockade of bradykinin B₂-receptors by Hoe 140 on blood pressure...
in rats given either pressor or low nonpressor doses of Ang II.

Methods

Female Wistar rats (Morini) weighing between 210 and 230 g were housed at a constant room temperature (24±1°C) and humidity (60±3%) with a 12-hour light/dark cycle. They had free access to rat chow (sodium, 0.12 mmol/g, Morini) and tap water for the duration of the experiment. Chow was ground and blended before use. The female rat was chosen as a model to study the cardiovascular effects of endogenous kinins according to the finding that the renal kallikrein-kinin system is more activated in female compared with male rats. In addition, growth rate of female rats is relatively slow at this weight, and this allowed continuous infusion of constant doses of Ang II and Hoe 140 throughout the duration of the study without replacing the osmotic pumps used for drug delivery.

The experimental protocol was approved by the local animal care and use committee. 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). All surgical procedures were performed with rats under ether anesthesia using disappearance of the corneal reflex to adjust the depth of anesthesia.

Blood Pressure Measurement

Unanesthetized rats were warmed for 10 to 15 minutes at 35°C in a thermostatically controlled heating cabinet. Systolic blood pressure (SBP) then was measured by the tail-cuff plethysmography method (Recorder 8002, Ugo Basile, Biological Research Apparatus) with the rat gently wrapped in a cotton hand towel. Each pressure value was obtained by averaging eight to ten individual readings. Mean blood pressure (MBP) was measured directly in unanesthetized rats with a Statham transducer (Gould).

Experiment 1: Effects of Hoe 140 on Blood Pressure in Rats Under Normal Conditions

Body weight and SBP were measured in the morning on two different occasions before starting the experimental period and then weekly.

Rats were randomly allocated to two groups (n=10 each). Group 1 received a continuous infusion of physiological saline at the rate of 60 µL/d, and group 2 received Hoe 140 (Hoechst AG) at the rate of 75 nmol/d. Infusions were delivered intraperitoneally for 4 weeks. Blood samples were collected and centrifuged at 2000g for 10 minutes to separate plasma.

Experiment 2: Effects of Hoe 140 on Blood Pressure in Rats During Chronic Infusion of Angiotensin II

After completion of basal blood pressure measurements, rats received a continuous infusion of Ang II at doses of 20, 40, or 100 nmol/d for 4 weeks combined with Hoe 140 at the rate of 75 nmol/d or physiological saline. Each of these six groups consisted of 10 rats. In preliminary experiments, we found that Ang II delivered either alone or combined with Hoe 140 was not degraded during the infusion period. Indeed, the increase in MBP induced in normotensive rats by bolus intra-arterial injections of the solutions recovered from osmotic pumps after 4 weeks was similar to that of a corresponding dose of freshly dissolved Ang II. Twenty-four-hour urine collections were obtained from rats given 20 nmol/d Ang II on two occasions before the start of Ang II infusion, over the first 5 days of the experimental period, and then once a week. Collections were obtained from individual metabolic cages, which allowed for a high degree of accuracy in the measurement of food and water intake by the inclusion of spill catches. Body weight was measured at the end of each urine collection.

At the end of the experiment, MBP was measured, and blood was collected according to the procedures indicated in experiment 1.

Analytical Procedures

Urinary volume (UV) was determined gravimetrically. Urinary sodium (U Na+V) was determined by flame photometry. Urinary creatinine was measured by an automatic analyzer (Hitachi 704). Kallikrein activity in urine was measured by an end-point amidolytic method24 using the synthetic substrate H-Leu-Arg-p-nitroanilide (S2266, Kabi Diagnostica) in the presence of soybean trypsin inhibitor (Sigma Chemical Co) and expressed in nanokatals (1 nkat represents the enzyme activity able to cleave 1 nmol p-nitroaniline per second from substrate). Plasma Ang II was measured by radioimmunoassay after extraction with Sep-Pak C18 columns (Water Associated, Inc).

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 was then used to test for differences among groups and over time. Differences within or between groups were determined using paired or unpaired Student's t tests, respectively, with the Bonferroni multiple-comparison adjustment. Mathematical and statistical analyses were performed with a STATVIEW II package (Brain Power) on an Apple Macintosh IIcx computer.

Results

Body weight gain was similar among groups (data not shown).

Neither Hoe 140 nor saline infusion altered arterial blood pressure of rats that did not receive Ang II (Fig 1D and Table 1). The antagonist inhibited the vasopressor effect of an intra-aortic bolus of bradykinin completely (0±1 versus 22±3 mm Hg in controls, P < .01).

Chronic Ang II infusion induced a dose-related increase in SBP. The vasopressor effect of 100 and 40 nmol/d Ang II was enhanced by the combined administration of Hoe 140 (Fig 1A and 1B). In addition, a low nonpressor dose of Ang II (20 nmol/d) became able to increase SBP during chronic blockade of bradykinin B₂ receptors (Fig 1C).
As shown in Fig 2, potentiation of the response to Ang II was particularly evident at the fourth week of the experimental period. The effect of Hoe 140 was confirmed by direct measurement of MBP (Table 1).

As shown in Table 2, ANOVA did not detect any difference between groups given 20 nmol Ang II alone or combined with Hoe 140 as far as the daily intake of water and food was concerned. No change from baseline was detected over time within each group, although a mild nonsignificant decrease in food intake occurred in both groups on day 1, which followed implantation of osmotic pumps into the abdominal cavity. No difference between groups was observed regarding the cumulative intake of food during the first 5 days of treatment (34.5±0.3 versus 36.1±0.8 g/100 g body wt in controls, NS), whereas the cumulative intake of water was greater in rats given Ang II plus Hoe 140 (80.2±4.1 versus 69.3±3.0 mL/100 g body wt in controls, P<.05).

As shown in Fig 3, UV and UNaV were similar in rats given 20 nmol Ang II plus Hoe 140 compared with controls, despite the fact that blood pressure was increased in the Hoe 140-treated group only. No significant difference was observed between groups regarding the cumulative excretion of water (32.1±2.6 versus 26.8±2.1 mL/100 g body wt in controls, NS) and sodium (3.29±0.14 versus 3.49±0.88 mmol/100 g body wt in controls, NS) during the first 5 days of treatment. ANOVA did not detect any change in UV and UNaV over time in either group.

Urinary kallikrein levels did not change from basal values (Ang II group, from 58±4 to 56±4 nkat/24 h; Ang II-Hoe 140 group, from 64±3 to 62±4 nkat/24 h; NS).

As shown in Fig 4, the increase in plasma Ang II levels was proportional to the dose of Ang II infused.

### Discussion

The finding that chronic administration of 75 nmol/d Hoe 140 (a dose that abolishes the vasodepressor effect of exogenous bradykinin) does not alter blood pressure is consistent with previous studies in which inhibition of endogenous kinins was achieved by the antagonist in rats on normal sodium intake.9 In addition, infusion of the same dose for 4 weeks does not affect blood pressure in rats allowed to drink 0.15 mol/L NaCl ad libitum.10 However, a recent report from Majima et al25 showed a significant increase in systolic blood pressure

### Table 1. Effect of Kinin Receptor Blockade on Blood Pressure of Angiotensin-Treated Rats

<table>
<thead>
<tr>
<th>Angiotensin II, nmol</th>
<th>0</th>
<th>20</th>
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<tbody>
<tr>
<td></td>
<td>Bas</td>
<td>Exp</td>
<td>Bas</td>
<td>Exp</td>
</tr>
<tr>
<td>SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>128±4</td>
<td>123±3</td>
<td>126±3</td>
<td>121±3</td>
</tr>
<tr>
<td>Hoe 140</td>
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<td>123±3</td>
<td>126±3</td>
<td>137±3†</td>
</tr>
<tr>
<td></td>
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<td>160±4†</td>
</tr>
<tr>
<td>MBP</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>106±2</td>
<td>108±2</td>
<td>110±2</td>
<td>125±3</td>
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<tr>
<td>Hoe 140</td>
<td>106±2</td>
<td>125±2*</td>
<td>123±2*</td>
<td>139±2*</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure (tail-cuff plethysmography); MBP, mean blood pressure (direct intra-arterial measurement); Bas, before the experimental period; and Exp, at the 4th week of the experimental period. Rats were given chronic infusion of angiotensin II in combination with Hoe 140 or vehicle. Values represent mean±SEM and are expressed in mm Hg (n=10, each group). *P<.05 vs vehicle group; †P<.05 vs baseline.
after salt loading in Brown Norway Katholiek rats, which have very low levels of kininogen. They observed a similar hypertensive effect also in normal rats, provided that a very high dose of Hoe 140 (5 mg/kg per day, corresponding to approximately 5000 nmol/kg per day) is superimposed to salt load for 1 week. Taken together, these results do not favor a major role of kinins in the regulation of basal blood pressure in rats on normal sodium intake, although contribution during alterations in sodium balance remains controversial.

Recently, an interesting possibility emerged from studies in which the first-generation antagonist D-Arg°,[Hyp3,8,3-Thi5',8,3-D-Phe7]-bradykinin was administered for a short period of time in rats given nonpressor doses of Ang II or methoxamine and pressor doses of vasopressin and methoxamine. In each case, the antagonist alone did not alter blood pressure, whereas it caused a hypertensive effect when combined with vasoconstrictor substances. Thus, endogenous kinins may attenuate the blood pressure increase induced by acute elevation in the plasma levels of vasoconstrictor hormones. Unfortunately, B2-receptor antagonists of the first generation were characterized by low selectivity, residual agonistic activity, and an ability to stimulate prostaglandin and renin release. Thus, the effects caused by this class of compounds might be unrelated to their kinin-blocking ability. Indeed, studies using the newly synthesized antagonist Hoe 140 failed to demonstrate potentiation of the pressor response to short-term administration of Ang II, phenylephrine, and endothelin-1, a finding that does not favor participation of kinins in acute conditions.

Besides being able to increase blood pressure rapidly by direct vasoconstriction, Ang II also increases it gradually when infused at doses below the threshold of the direct pressor effect. Various mechanisms may contribute to this effect, including interaction of Ang II with endocrine and paracrine systems, activation of the sympathetic nervous system, and enhanced receptor sensitivity.

As far as we know, possible participation of endogenous kinins has not been explored yet. Chronic blockade of bradykinin B2-receptors not only enhanced the slow pressor response to Ang II but increased blood pressure of rats infused with a low nonpressor dose of Ang II. This finding favors the hypothesis that endogenous kinins can attenuate the pressor effect caused by chronic elevation in plasma Ang II levels. However, a limitation of our study is represented by the fact that neither regional blood flow nor cardiac output was measured.

### Table 2. Water and Food Intake in Angiotensin-Treated Rats

<table>
<thead>
<tr>
<th>Time, d</th>
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<th>Food</th>
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<tr>
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<td>Hoe 140</td>
</tr>
<tr>
<td>3</td>
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<td>15.3±1.0</td>
</tr>
<tr>
<td>4</td>
<td>14.5±1.0</td>
<td>16.9±1.4</td>
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<tr>
<td>5</td>
<td>11.7±0.8</td>
<td>13.2±0.8</td>
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<tr>
<td>6</td>
<td>16.9±1.4</td>
<td>15.3±1.0</td>
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<td>7</td>
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<td>8</td>
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<tr>
<td>9</td>
<td>15.5±1.1</td>
<td>16.5±1.9</td>
</tr>
<tr>
<td>10</td>
<td>16.5±1.4</td>
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<td>11</td>
<td>17.0±1.0</td>
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<td>17.0±1.0</td>
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<tr>
<td>28</td>
<td>17.0±1.0</td>
<td>14.3±2.7</td>
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Rats were given chronic infusion of angiotensin II (20 nmol/d) during the experimental period (starting at day 0) in combination with Hoe 140 or vehicle.

Values represent mean±SEM. Water Intake is expressed in mL/100 g body wt and food intake in g/100 g body wt.
Drugs that interfere with the sympathetic nervous system activity reportedly alter the gradual rise in blood pressure induced by Ang II. However, Hoe 140 does not increase the release of catecholamines, histamine, or prostaglandins. Plasma renin activity levels also are unaffected during chronic infusion of Hoe 140. In addition, the antagonist proved to be specific because it did not alter the action of unrelated vasodilators. Therefore, the effect of Hoe 140 does not appear to be related to properties other than its kinin-blocking ability.

Recently, Strick et al. reported that in anesthetized dogs administration of first-generation bradykinin antagonist fails to impair natriuresis induced by an acute increase in renal perfusion pressure. Thus, in this model an intact kallikrein-kinin system may not be necessary to induce pressure diuresis and natriuresis. However, failure of the antagonist to affect pressure natriuresis may be due to its inability to inhibit bradykinin receptors located at the intraluminal side of the renal tubule, whereas Hoe 140 effectively blocks both basolateral and intraluminal receptors. Our finding that sodium and water excretion was unaltered in Hoe 140-treated rats given 20 nmol Ang II, despite an elevated blood pressure, suggests that kinin inhibition does indeed reduce renal excretory function. A limitation of the present study is that daily sodium/water balance was determined only during the first few days of the infusion of 20 nmol Ang II. Thus, we cannot say whether an alteration in renal excretory function occurred during the following weeks or when the antagonist was given in combination with higher doses of Ang II.

Prostaglandin production is increased during chronic Ang II infusion, and kinins are known to exert their vasodilating action by stimulating the release of endothelium-derived relaxing factors and prostaglandins. Therefore, decreased production of these substances during blockade of bradykinin receptors may contribute to enhance the cardiovascular effect induced by Ang II. This implies that vasodilating and natriuretic hormones...
could be part of a homeostatic response that minimizes the slow pressor response to Ang II.26,31

The presence of glandular kallikrein in rat vasculature suggests that endogenous kinins regulate vascular resistances acting as paracrine hormones. It is possible that inhibition of kinins generated within the vasculature contributes to potentiation of the pressor response to Ang II. However, an increase in circulating Ang II levels was obtained in the present study by intraperitoneal infusion of the peptide, thus allowing us to evaluate the influence of endogenous kinins on Ang II as a blood-borne hormone only. Given this experimental design, the possible interaction between kinins and Ang II generated locally in vessels cannot be quantitatively determined.

In previous studies, we demonstrated that Hoe 140 causes hypertension in rats with an excess of deoxycorticosterone,9,10 thus suggesting that endogenous kinins counteract the pressure effect of mineralocorticoids. Stimulation of mineralocorticoid secretion can be achieved by increasing plasma Ang II concentration to levels close to the physiological range.40,41 We were able to confirm these findings in preliminary experiments in which circulating levels of mineralocorticoid hormones were measured during chronic infusion of 20 nmol/d Ang II (P.M., unpublished results, 1994). Plasma aldosterone and corticosterone levels were unaltered after 1 week of infusion, whereas they were increased at 4 weeks (from 89±20 to 140±22 pg/mL and from 147±30 to 225±33 pg/mL, respectively). Therefore, potentiation of the response to Ang II could be due, at least in part, to the fact that during chronic blockade of bradykinin B2-receptors endogenous kinins are unable to counteract the pressure effect induced by stimulation of mineralocorticoid secretion. Consistently, studies presented by Katori and Majima42 showed that infusion of 28.6 μg/d (27.3 nmol/d) Ang II for 1 week increases SBP of male Brown Norway Katholiek rats, which congenitally lack the ability to generate kinins, whereas the same dose is ineffective in normal rats of the same strain (Brown Norway Kitasato rats). In addition, the blood pressure increase observed in kinin-deficient rats is markedly reduced by administration of spironolactone, a competitive antagonist of mineralocorticoids. It should be noticed that the difference in SBP between Brown Norway Katholiek rats and normal controls averaged 44 mm Hg at the first week of Ang II infusion, whereas in our study Hoe 140 enhanced the slow pressor effect of Ang II by approximately 15 mm Hg only. The antagonist, even at a dose that completely inhibits the vasodepressor effect of exogenous bradykinin, might not be able to reproduce the condition of Brown Norway Katholiek rats, which are deficient in kininogen in plasma and devoid of kinin release in the urine. This possibility appears unlikely because, due to high affinity for receptors and resistance to kininases, Hoe 140 has been shown to exert a very potent and long-lasting inhibition of endogenous kinins within the vasculature as well as at the interstitial and tubular side of the nephron.28,29 On the other hand, before concluding that the enhanced pressor response to Ang II in Brown Norway Katholiek rats is due entirely to deficient kinin formation, one should exclude that this strain differs from normal rats for the presence of increased vascular sensitivity to Ang II and/or defective clearance of the peptide from the circulation. Our finding that plasma Ang II concentration is not affected by blockade of bradykinin B2-receptors discounts the possibility that Hoe 140 potentiates the effect of Ang II by altering the clearance of the peptide.

In conclusion, our results indicate that inhibition of bradykinin B2-receptors enhances the pressor effect induced by moderate to severe increases in circulating Ang II levels. Thus, endogenous kinins could buffer the chronic pressor effect of an excess of Ang II.

Acknowledgments

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