Effects of Renin Inhibition in the Conscious Primate Macaca fascicularis

Kwan Y. Hui, Delvin R. Knight, Jürg Nussberger, L. Howard Hartley, Stephen F. Vatner, and Edgar Haber

Pro-His-Pro-Phe-His-Statine-Ile-Phe-NH₂ (R-Pep-27), a potent renin inhibitory peptide, was infused into the conscious, sodium-depleted Macaca fascicularis at doses of 0, 0.1, 1, 4, 16, and 32 µg/kg/min for 10 minutes. At all doses greater than 0.1 µg/kg/min, there was a parallel decrease in mean arterial pressure (MAP), plasma renin activity, and plasma angiotensin II (Ang II) concentration. On the other hand, assays with monoclonal antibodies specific for total renin and active renin demonstrated that the peptide’s inhibition of circulating active renin stimulated the release of both. The maximal effective R-Pep-27 dose was approximately 16 µg/kg/min, which reduced MAP by an average of 15.8±1.4 mm Hg (n=14) and plasma renin activity and plasma Ang II concentration to 3% (n=9) and 15% (n=5), respectively, of the pretreatment values. At 0.1 µg/kg/min, there was no significant decrease in MAP; however, measurement of plasma renin activity showed an average decrease in activity of 42% (n=3). No significant change in the heart rate was observed at all the doses studied. For comparison, intravenous captopril (400 µg/kg bolus) was administered after the MAP of the monkeys had recovered from the peptide experiments, and it reduced MAP by 25.1±2.4 mm Hg (n=10) without significantly changing plasma renin activity. As anticipated, injection of angiotensin I (80–160 ng/kg bolus) into sodium-depleted monkeys during peptide infusion caused a transient rise in MAP of 14.8±5.4 mm Hg (n=4) above the mean pretreatment value. Similar injection under the influence of captopril had no pressor effect. Injection of purified human renin (0.01–0.02 Goldblatt units/kg/min i.v.) into sodium-replete monkeys raised the MAP by an average of 36.5 mm Hg (n=2). Simultaneous intravenous infusion of R-Pep-27 at 100 µg/kg/min for 8–12 minutes caused the elevated MAP to return to normal. This study reveals the effects of blockade of circulating renin in a conscious primate model and suggests that R-Pep-27 will find use as a clinical tool in investigations of the role of renin in essential hypertension. (Hypertension 1989; 14:480–487)

Highly specific renin inhibitory peptides help define the role of the renin-angiotensin system (RAS) in a variety of clinical and experimental hypertensive states. Although angiotensin converting enzyme inhibitors such as captopril are widely used in antihypertensive therapy to suppress the production of angiotensin II (Ang II), these compounds cannot be used in investigations of the RAS because their action is not entirely specific. Converting enzyme plays a role in the metabolism of peptides other than angiotensin I (Ang I),2–4 and in addition to inhibiting converting enzyme, captopril also stimulates prostaglandin synthesis.5,6

Using structure-activity relations of published compounds and molecular modeling to direct our work, we designed and synthesized a series of renin inhibitors containing the unusual amino acid statine, (3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid.7 We intravenously administered one of the most potent peptides, Pro-His-Pro-Phe-Statine-Ile-Phe-NH₂ (R-Pep-27; in vitro IC₅₀ of 3 nM against human plasma renin at pH 7.4), to the conscious Macaca fascicularis. R-Pep-27 proved to be both an effective hypotensive agent and a specific renin inhibitor. By direct measurement of the effects of R-Pep-27 infusion on blood pressure, heart rate (HR), and plasma renin activity (PRA) and its effects on the plasma concentrations of Ang II,
immunoreactive total renin, and immunoreactive active renin, we were able to study the physiological and biochemical consequences of blockade of the RAS in conscious nonhuman primates.

Materials and Methods
Primate Studies
R-Pep-27 was studied in the conscious adult M fascicularis with chronically indwelling arterial and venous catheters. Experiments were carried out on sodium-depleted and sodium-replete monkeys. In the sodium-replete state, the monkeys consumed usual monkey food (Monkey Chow,Ralston Purina, St. Louis, Missouri), which contains 0.56% salt. In the sodium-depleted state, the monkeys were fed only fruit. During the infusion experiments, no food was given, but water was provided ad libitum. Each monkey was given furosemide twice, at a dose of 2 mg/kg i.m. The first injection was administered 3 days before the experiment, the second on the day before the experiment.

Catheterization was performed as described. In brief, while the monkeys were under general anesthesia, polyethylene catheters were inserted into the internal iliac artery (for blood pressure measurement) and vein (for drug administration). The catheters were then tunneled to the interscapular area and exteriorized. They were kept patent by flushing with saline three times a week. The evening before the experiment, the monkeys were anesthetized with ketamine (Ketalar, Bristol Laboratories, Syr-

cul) and water was provided ad libitum. Each monkey was given furosemide twice, at a dose of 2 mg/kg i.m. The first injection was administered 3 days before the experiment, the second on the day before the experiment.

Two studies were performed: one to examine the in vivo specificity of activity of R-Pep-27. In the hemodynamic study, R-Pep-27, diluted in 5% dextrose in water (D5W), was delivered through a constant infusion pump (Harvard Apparatus, South Natick, Massachusetts) over 10-minute periods in doses of 0.1, 1, 4, 16, and 32 μg/kg/min. A control infusion of D5W at 0.5 ml/min before the peptide infusion was considered the zero peptide dose. After 9 minutes of infusion, arterial blood was withdrawn for determination of PRA and the concentrations of Ang II, immunoreactive total renin, and immunoreactive active renin. In cases where the arterial cannula had become occluded, blood was withdrawn from the venous cannula.

Because of the large volumes of blood necessary for the measurements and the need to flush the cannulae before collection, the infusion experiments had to be performed separately to avoid excessive depletion of the monkeys' blood volume. For the PRA assays, 2 ml blood was collected at each dose studied and placed immediately into a Terumo Venject tube (Terumo Medical, Elkton, Maryland) containing ethylenediaminetetraacetic acid (EDTA) chilled to 0° C. For plasma Ang II measurements, 5 ml blood was collected at each peptide dose and added to a tube containing EDTA (4 mM final concentration), o-phenanthroline (1.25 mM final concentration), neomycin (0.1 mg/ml final concentration), and ethanol (0.1% final concentration) chilled to 0° C. For the measurements of immunoreactive total renin and immunoreactive active renin, 1.5 ml blood was heparinized at 0° C. The blood samples were centrifuged at 4° C to separate the plasma, which was then frozen to -70° C and stored at -20° C until assay. After the R-Pep-27 studies had been completed, captopril was administered intravenously at a bolus dose of 400 μg/kg.

Renin activity was determined by a radioimmunoassay for Ang I based on the method of Haber et al. Each plasma sample (700 μl) was divided into two portions for incubation for 1 hour at 37° C and 0° C. The renin enzymatic reaction was quenched at pH 8.5 by the addition of saturated Tris solution (approximately 2 μl/100 μl plasma). PRA was measured as the rate of Ang I generation detected at pH 8.5 by a radioimmunoassay with immobilized rabbit anti-Ang I antibodies. The inhibitory potency of R-Pep-27 against monkey plasma renin (in vitro IC50 of 5.8 nM) was ascertained as described for human plasma renin. Plasma Ang II concentrations were measured by a high-performance liquid chromatography (HPLC) method that detects exclusively Ang II octapeptide. Immunoreactive total renin and immunoreactive active renin were measured according to the methods of Nussberger et al.

The study of the in vivo specificity of activity of R-Pep-27 was designed to investigate the effect of R-Pep-27 on converting enzyme in the sodium-depleted state (experiment A) and human renin infused into sodium-replete monkeys (experiment B). Experiment A measured the pressor response to Ang I (80–160 ng/kg in D5W) and Ang II (20–80 ng/kg in D5W) before the infusion of R-Pep-27 (at 16 μg/kg/min) and that of Ang II during infusion of R-Pep-27. After the monkeys' blood pressure had recovered from the sequential Ang I and R-Pep-27 studies, captopril (400 μg/kg in D5W) was administered intravenously followed by injections of Ang II and Ang I. In experiment B, purified human kidney renin was administered into the iliac vein while R-Pep-27 was administered into a femoral vein (through a catheter that had been inserted under ketamine anesthesia before the experiment). The blood pressure response to human renin (infused
at 0.01–0.02 Goldblatt units (GU)/kg/min) was measured before and during infusions of R-Pep-27 at doses of up to 100 µg/kg/min.

Affinity Purification of Human Kidney Renin

Human kidney renin was purified on an affinity chromatography adsorbent composed of agarose (Affi-gel-15, Bio-Rad, Richmond, California) and the ligand Pro-His-Pro-Phe-His-Statine-Ile-His-Lys, according to the procedure of McIntyre et al. Renin was eluted from the affinity column with 110 ml of 3 M ammonium thiocyanate. Fractions of 26.5 ml each were collected and immediately dialyzed for 16 hours in 0.01 M sodium citrate and 0.9% NaCl buffer, pH 7.4. Four fractions were found to contain renin in a renin activity assay conducted at pH 7.4 (with anephric sheep plasma used as substrate). This solution of purified renin in buffer was infused directly into the primate.

Results

In sodium-replete normotensive monkeys, infusion of R-Pep-27 at 16 µg/kg/min over a period of 10 minutes did not significantly alter MAP (Figure 1). However, PRA decreased from an average of 2.7±0.8 to approximately 0 ng Ang I/ml/hr (n=4) (Figure 2). To study the renin dependency of blood pressure regulation, the primates were placed on a low sodium diet and given an intramuscular injection of furosemide before the experiment. As with the sodium-replete monkeys, the peptide was infused intravenously over 10-minute periods. The hypotensive response in sodium-depleted monkeys occurred from 2-5 minutes after commencement of the infusion. At a dose of 16 µg/kg/min, there was a pronounced decrease in MAP by, on average, 15.8±1.4 mm Hg (n=14) (Figure 1). At this dose, the PRA decreased from an average of 18.1±4.3 to almost 0 ng Ang I/ml/hr (n=9) (Figure 2).

The hypotensive effects of R-Pep-27 and captopril were compared after each monkey's MAP had returned to normal. An intravenous bolus injection of captopril at 400 µg/kg induced a decrease in MAP in both sodium-replete and sodium-depleted monkeys (Figure 1). In the sodium-replete monkeys, the drop in MAP was 14.5±4.7 mm Hg on average (n=4). In the sodium-depleted monkeys, an even more pronounced decrease in MAP was obtained (on average, a decrease of 25.1±2.4 mm Hg, n=10) (Figure 1). In contrast with R-Pep-27, captopril caused an elevation in the PRA of sodium-replete monkeys (increase from 4.1±1.7 to 8.1±4.7 ng Ang I/ml/hr, n=4) even though it reduced MAP. Furthermore, captopril's influence on the PRA of sodium-depleted monkeys was inconsistent. Figure 2 shows that PRA values both increased and decreased after the administration of captopril to sodium-depleted monkeys, although the average PRA values before and after captopril administration were similar (48.9±18.5 vs. 46.5±31 ng Ang I/ml/hr, n=5).

Figure 3B summarizes the dose-response relation that holds for the MAP-lowering effect of R-Pep-27. An average decrease of 8.8±1.7 mm Hg (n=10) could be obtained with a dose as low as 1 µg/kg/min. At 4 µg/kg/min, there was an average decrease in MAP of 12.5±1.4 mm Hg (n=12). An infusion of 16 µg/kg/min lowered MAP by, on average, 15.8±1.4 mm Hg (n=14). The hypotensive effect (on average, a decrease of 18.2±4.2 mm Hg, n=6) at the higher dose (32 µg/kg/min) did not significantly differ from that at 16 µg/kg/min. The subsequent intravenous bolus injection of captopril at 400 µg/kg resulted in a maximal reduction in MAP of 25.1±2.4 mm Hg, on average (n=12). For both R-Pep-27 and captopril, there was no significant effect on HR at any of the doses studied (Figure 3A). As anticipated, PRA and plasma Ang II concentration decreased in relation to dose in
sodium-depleted primates. The average PRA value in the sodium-depleted primates before R-Pep-27 infusion was 18.03±4.3 ng Ang I/ml/hr (n=9) (see Figure 2). At a dose of 0.1 μg/kg/min, there was an average inhibition of PRA of 42% (n=3) (Figure 3B). The percentage of residual PRA decreased as the dose increased. At doses of 1, 4, and 16 μg/kg/min, the average residual PRA fell to 25, 13, and 3%, respectively, of the value before infusion. At a dose of 32 μg/kg/min, there was no measurable PRA. The maximal effective dose was approximately 16 μg/kg/min. Figure 4 summarizes the measurements of plasma Ang II concentration. The measurements followed the trend of the changes in MAP and residual PRA. At doses of 1, 4, and 16 μg/kg/min, the average plasma Ang II concentrations were 50, 40, and 15%, respectively, of the values before peptide infusion. The inhibition of PRA by R-Pep-27—a measurement of the generation of Ang I—was to be expected. To examine more thoroughly the effects of R-Pep-27 on other components of the RAS, we quantified the actual concentration of both total and active renin. By using a monoclonal antibody specific for a region common to active renin and inactive renin (or total renin) and a monoclonal antibody specific solely for active renin, we were able to directly measure the plasma concentration of immunoreactive renin during each infusion. Figure 5 summarizes the effect of acute renin inhibition by R-Pep-27 on the release of renin into the circulation. With the exception of the lowest dose (0.1 μg/kg/min), there was a dose-related increase in the plasma concentrations of both active renin and total renin. At doses of 1, 4, and 16 μg/kg/min, the average increases in the concentration of total renin were 127, 180, and 309%, respectively. Simultaneous measurement of the active renin concentration in the same plasma sample revealed a more pronounced change. At doses of 1, 4, and 16 μg/kg/min, active renin concentrations respectively increased by an average of 164, 253, and 515% of the value before peptide infusion.

Figure 6 shows the pressor effects of Ang I and Ang II before the infusion of R-Pep-27. In sodium-depleted monkeys, intravenous bolus injections of Ang I at doses of 80–160 ng/kg and of Ang II at doses of 20–80 ng/kg caused transient rises in MAP of 16.3±1.5 (n=4) and 17.3±2 (n=4) mm Hg, respectively, above the mean control value (89±5.3 mm Hg, n=4). An infusion of R-Pep-27 at 16 μg/kg/min resulted in a sustained fall in MAP of 16.5±3.8 mm Hg (n=4). At the point of maximum fall in MAP, the simultaneous injection of Ang I (80

Figure 3. Line graphs showing heart rate (Panel A), change in mean arterial pressure (ΔMAP) (Panel B), and percent (%) residual plasma renin activity (PRA) of sodium-depleted primates after 10 minutes intravenous infusion of R-Pep-27 at various doses (0–32 μg/kg/min) or approximately 20 minutes after intravenous bolus injection of captopril at 400 μg/kg. Solid signs represent effects of R-Pep-27, open signs represent effects of captopril. Values are mean±SEM.

Figure 4. Line graph showing plasma angiotensin II (Ang II) concentration of sodium-depleted primates after 10 minutes intravenous infusion of various doses of R-Pep-27 (0, 1, 4, and 16 μg/kg/min). Values are mean±SEM.
ng/kg bolus) and infusion of R-Pep-27 caused a rise in MAP of 14.8±5.4 mm Hg (n=4) above the mean control value. Captopril (400 μg/kg i.v., injected after the monkeys' blood pressure had recovered after termination of the R-Pep-27 infusion) resulted in a fall in MAP of 24.6±4 mm Hg (n=5). A subsequent intravenous bolus injection of Ang I at either 80 or 160 μg/kg did not cause a significant rise in MAP (which was maintained at 23.2±4.5 mm Hg [n=5] less than the control MAP). However, an intravenous injection of Ang II at 40 or 80 μg/kg increased the MAP by 28.4±2.4 mm Hg (n=5) over the mean control value.

The inhibitory activity of R-Pep-27 against human renin in vivo was studied by measurement of the change in the primate's MAP during infusion of purified human renin and the peptide. Figure 7 shows the results from a study in two sodium-replete, conscious monkeys. (The large quantity of purified human kidney renin required for these experiments limited the number of monkeys that could be studied to two.) Intravenous infusion of purified human renin at 0.01–0.02 GU/kg/min for 6–12 minutes caused an average rise in MAP of 36.5 mm Hg. This increase in MAP was rapidly and totally suppressed by simultaneous intravenous infusion of R-Pep-27 at a dose of 100 μg/kg/min for 8–12 minutes. Control studies (Figure 7B) show that the elevated MAP dropped spontaneously to half the maximal value 6–10 minutes after cessation of renin infusion. Thus, the suppression of elevated MAP caused by renin infusion (Figure 7A) must have been because of the renin-inhibitory effect of R-Pep-27.

**Discussion**

Anesthetics stimulate renin release and can modify the responsiveness of the cardiovascular system to drugs; thus, the use of conscious primates avoids uncertainties that anesthesia can introduce. The design of renin inhibitors is based on the hypothesis that the compounds will inhibit the enzymatic activity of renin and eventually lead to a decrease in plasma Ang II concentration. An experiment that minimizes extraneous influences on
plasma renin concentration, one that also offers direct measurements of the concentrations of Ang II, total renin, and active renin, is critical to the verification of this hypothesis. This report may clarify some of the uncertainties of other studies of renin inhibition in which the animals were anesthetized and direct measurements were not made of Ang II and plasma active renin concentrations.

In sodium-depleted, normotensive conscious primates, hypotension was obtained within 5 minutes of R-Pep-27 infusion at a dose as low as 1 µg/kg/min. The maximal hypotensive effect was achieved at a dose of approximately 16 µg/kg/min, and a dose of 32 µg/kg/min for 10 minutes did not cause further change in blood pressure. R-Pep-27 thus appears to be a potent hypotensive agent. The effects of R-Pep-27 on blood pressure versus PRA decreased in MAP, PRA, and plasma Ang II concentration at all doses greater than 0.1 µg/kg/min. At 1 µg/kg/min, MAP was reduced by 8.8±1.7 mm Hg on average (n=10), with 75% (n=8) and 55% (n=5) decreases in PRA and plasma Ang II concentrations, respectively. At 16 µg/kg/min, MAP was reduced by an average of 15.8±1.4 mm Hg (n=14), while the average values for PRA and the plasma Ang II concentration were 3% (n=9) and 12% (n=5), respectively, of the preinfusion control value. The significantly higher residual plasma Ang II percentage value in comparison with the PRA value, which was virtually zero, may have been because of the in vitro conversion of Ang I to Ang II during the blood sampling procedure. Because the PRA was near zero, a further increase in dose (to 32 µg/kg/min) did not cause a significant, further decrease in MAP. Thus, we did not observe the dissociation between MAP and PRA or plasma Ang II concentration that Blaine and colleagues reported, and who in conscious, sodium-depleted dogs observed that MAP began to drop when residual PRA was close to zero or when the plasma Ang II concentration was reduced to very low levels.

Our measurements (by HPLC) of plasma Ang II concentrations revealed the biochemical consequences of blockade of the RAS. The dose-dependent lowering of circulating Ang II in sodium-depleted monkeys suggests that the hypotensive effect of R-Pep-27 was due to a decreased production of circulating Ang II, which would have resulted from blockade of the first step in the renin-angiotensin enzymatic cascade. The Ang II measurement also supports our conclusion that, in the sodium-depleted monkey, the effective dose for lowering blood pressure is approximately 1 µg/kg/min. The experiments described here were conducted on normotensive monkeys, subjects whose PRA would have been enhanced by the increased release of endogenous renin that a low sodium diet and blood-volume depletion would bring about.

An interesting observation was obtained during the 0.1 µg/kg/min infusion. Although no significant decrease in MAP could be observed after 10 minutes of infusion, PRA measurements showed an average decrease in activity of 42% (n=3). Therefore, PRA decreased significantly at the subhypotensive dose (0.1 µg/kg/min). However, at the hypotensive dose (beginning at 1 µg/kg/min), our study showed a direct, dose-associated relation between inhibition of circulating renin and lowering of MAP in conscious, sodium-depleted primates. The dose-effect relation observed in our study agrees with other reports on renin inhibition in sodium-depleted monkeys. The results of our hemodynamic study show that the RAS plays a role in supporting the blood pressure of sodium-depleted primates. Also, the insensitivity of the MAP at an R-Pep-27 dose (0.1 µg/kg/min) that partially blocks the RAS, and the maintenance of adequate blood pressure under conditions of 100% renin blockade,
suggest that mechanisms other than the RAS operate to support the blood pressure of sodium-depleted monkeys.

An examination of the kinetics of renin inhibition reveals features common to ours and several other studies,15,20-22 namely, that its effects on MAP, PRA, and plasma Ang II concentration are not linearly proportional to the dose of inhibitor. A two-phase, dose-response effect was typical. The present study shows 1) a very fast drop in MAP, PRA, and plasma Ang II concentration at the low dose (1 μg/kg/min) and 2) a slower response at doses larger than 1 μg/kg/min. It is well documented that intravenous injection of exogenous Ang II causes an immediate elevation in MAP (Figure 6). On the other hand, depletion of Ang II appears to have a delayed effect on MAP. Only prolonged depletion of circulating Ang II appears to bring the blood pressure down.

Previous studies of the moderately active renin inhibitory peptide Pro-His-Pro-Phe-His-Phe-Val-Tyr-Lys23 suggested that it possessed cardiodilatory effects in primates24 and in humans.25 In the present work, R-Pep-27 appears to have no significant effect on heart rate at any of the doses studied. Our results agree with those reported in other studies of potent renin inhibitors, in which only moderate changes in HR were observed.15,22,26 Whether higher doses of R-Pep-27 have cardiodilatory effects will require further study. It would also be interesting to investigate whether cardiodilatory effects are a consequence of the specific structure of a renin inhibitory peptide, thereby suggesting an effect not specific to the RAS, or whether these effects are typical of any renin inhibitor at higher doses. A stimulation of renin release has been noted in hypertensive patients treated with captopril.27 A report by Hofbauer et al28 provides direct evidence that interruption of the RAS increases the plasma concentration of total renin. Using monoclonal antibodies specific for total renin and active renin, we have demonstrated directly that the release of both total renin and active renin is stimulated when circulating active renin is inhibited by R-Pep-27. Despite the dramatic increase in the plasma concentration of active renin during the infusion of a high dose of R-Pep-27 (16 μg/kg/min), PRA was virtually zero because the enzyme was totally inhibited by the peptide. Szelke et al29 and Webb et al30 measured surplus active renin unbound to renin inhibitors in indirect assays of renin activity. Their measurements showed a dose-related decrease in the concentration of active renin during inhibitor infusion. Our measurement of immunoreactive active renin, which included both the inhibitor-bound and free, active species, showed a dose-related increase in the concentration of the enzyme. This observation is not in conflict with those of Szelke et al29 and Webb et al30 because the free form of active renin is expected to decrease in the presence of a potent inhibitor. Our measurement of total renin concentration agrees with the measurements reported by Blaine et al31 and Webb et al,22 who showed that the total renin concentration increases as the dose of inhibitor increases. It has been suggested that the increase in total renin concentration is mainly due to an increase in renin release caused by the negative feedback mechanism activated by the depletion of circulating Ang II.28

The Ang I, R-Pep-27 coinjection study (Figure 6) provides additional evidence that R-Pep-27 is a specific renin inhibitor. Infusion of R-Pep-27 did not affect the pressor response to Ang I, whereas infusion of captopril, as expected, did. This indicates that R-Pep-27 did not impair converting enzyme activity.

By using anesthetized, vagotomized, ganglion-blocked rats in which normotensive blood pressure was maintained by continuous intravenous infusion of partially purified hog renin, Blaine et al31 demonstrated that the renin inhibitory peptide SCRIP (IC50 for human and pig kidney renins of 0.19 and 0.31 nM,32 respectively) inhibited the pressor response to exogenous renin by 50% (approximately 7.5 mm Hg) at a dose of 40 μg/kg. Recently, Kleinert et al32 studied the effect on blood pressure of a low molecular weight renin inhibitor (A-64662) administered to anesthetized anephric monkeys continuously infused (intravenously) with tissue culture renin. Gardner and Twissell13 first reported the use of conscious, small primates (marmosets) to evaluate the inhibition of infused renin by a human substrate analogue (H142). In their study, H142 at a dose of 100 μg/kg/min for approximately 40 minutes effectively suppressed the pressor response to infused human renin. In the present study, affinity-purified human renal renin was infused intravenously into sodium-replete, conscious large primates to create a hypertensive state in which to study the hypotensive effect of R-Pep-27 (Figure 7). The effective rise in MAP after the intravenous infusion of purified human renin suggests that the monkey angiotensinogen was being hydrolyzed by the exogenous human renin, an observation that agrees with other studies showing that angiotensinogens of mammalian species are substrates for human renin.31 In our sodium-replete conscious primate model, the 36.5 mm Hg elevation in MAP induced by human renin was totally suppressed by simultaneous infusion of R-Pep-27 at 100 μg/kg/min for 6–12 minutes.

We conclude that R-Pep-27 is a potent hypotensive agent that appears to be a renin-specific inhibitor. The studies of the blockade of endogenous primate renin and of the inhibition of human renin infused into the primate suggest that R-Pep-27 will find use as a clinical tool in investigations of the role of renin in essential hypertension.

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