Renin Release Regulation During Acute Renin Inhibition in Normal Volunteers

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Blockade of the renin-angiotensin system by an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II (Ang II) antagonist is accompanied by a reactive rise in renin release. This rise is generally attributed to interruption of the short feedback loop between Ang II and renin release. Similarly, after the administration of a renin inhibitor, the plasma concentrations of active and total renin are increased and plasma renin activity is suppressed. The aim of the present study was to investigate if a fall in the plasma Ang II level is the unique determinant of the rise in the active renin (AR) level that follows renin inhibition. Six normal male volunteers participated in three successive 240-minute experiments at weekly intervals according to a single-blind randomized Latin square design. For experiment 1, Ang II was infused at 2 ng/kg/min from 0 to 60 minutes and at 4 ng/kg/min from 60 to 120 minutes. For experiment 2, 0.3 mg/kg of the new potent renin inhibitor Ro 42-5892 was injected at 30 minutes followed by infusion at 0.1 mg/kg/hr from 30 to 240 minutes. For experiment 3, Ang II and Ro 42-5892 were administered simultaneously at the same doses as described above. The mean±SEM Ang II concentration increased from 10.2±1.6 to 33.7±11.2 pg/ml after infusion of exogenous peptide. It decreased from 9.5±0.9 to 1.4±0.3 pg/ml after the injection of Ro 42-5892 and increased from 15.6±2.9 to 37.1±11.8 pg/ml after the simultaneous infusion of both compounds. At 120 minutes, Ang II infusion decreased the AR level from 30±5 to 12±4 pg/ml and Ro 42-5892 increased it from 28±4 to 209±40 pg/ml. After the combined infusion of Ang II and Ro 48-5892, the AR level rose by only 42% (from 22±4 to 38±5 pg/ml) and was still threefold higher than during the infusion of Ang II only. It is concluded that the exogenous infusion of an excess of Ang II minimizes but does not completely suppress the renin stimulation secondary to the administration of renin inhibitor. Although the fall in the plasma Ang II level appears to be a major stimulus of renin release, our results suggest that Ro 42-5892 may also have a direct intrarenal effect, possibly at the level of the juxtaglomerular cells, where renin and Ang II have been codetected and are locally produced. (Hypertension 1991;18:257-265)

The direct feedback effect of angiotensin II (Ang II) on renin release has been described in humans by de Champlain et al and in dogs by Vander and Geelhoed. Later, in rats Bing observed a rise in plasma renin activity (PRA) after the administration of Ang II antagonist or angiotensin converting enzyme (ACE) inhibitor and suggested that this rise was due to interruption of the short feedback loop linking Ang II to renin. These animal results have been largely confirmed in hypertensive patients, and the increase in renin release after the administration of saralasin or captopril has been used as a dynamic test to investigate the reactivity of renin release in various forms of hypertension. The development of direct immunoradiometric plasma renin assays, using different pairs of monoclonal anti-human renin antibodies, has allowed the demonstration of a rise in renin release after the administration of renin inhibitor to monkeys or human beings; the plasma concentrations of active and total renin are increased and PRA is suppressed. The interruption of Ang II's tonic renin release inhibition can be mediated by either a fall in the plasma Ang II level or the suppression of local Ang II production in the juxtaglomerular apparatus (JGA), where Ang II and renin have been codetected by immunohistochemistry. The present clinical study was designed to investigate whether the rise in the plasma active renin level following the administration of renin inhibitor is due entirely to the fall in the plasma Ang II level or whether other factors are involved. To this end, we investigated in normal volunteers the influence of an
infusion of exogenous Ang II on the rise in active renin induced by the intravenous administration of the renin inhibitor Ro 42-5892, the antihypertensive and biochemical effects of which were recently described by Van Den Meiracker et al. Our data show that Ang II infusion increased the circulating level of Ang II above its initial value and greatly reduced the magnitude of the rise in active renin but could not completely inhibit it.

**Methods**

**Subjects**

After giving written informed consent, six normal ambulatory male volunteers on a normal sodium diet came on three occasions to the Clinical Investigation Unit at Broussais Hospital at 8 AM. The volunteers remained seated in a comfortable armchair for 30 minutes. Intravenous catheters were placed in each arm; the right arm was used for infusions of Ro 42-5892 and Ang II (Hypertensin, CIBA-GEIGY, Basel, Switzerland) and the left arm for blood sampling. Blood pressure and heart rate were recorded every 5 minutes with a Sentrom automatic blood pressure recorder (Screening Devices Inc., Costa Mesa, Calif.).

The protocol, approved by the Ethical Committee of Broussais Hospital, is described in Figure 1. Experiments were performed according to a randomized Latin square design. No less than 1 week and no more than 3 weeks were allowed between each experiment. Experiment I involved an infusion of Ang II (2 ng/kg/min from 0 to 60 minutes and 4 ng/kg/min from 60 to 120 minutes). Experiment 2 consisted of a bolus injection of 0.3 mg/kg Ro 42-5892 at 30 minutes followed by an infusion of 0.1 mg/kg/hr from 30 to 240 minutes. Experiment 3 combined the infusion of Ang II from 0 to 120 minutes, as in experiment 1, and the administration of Ro 42-5892 as a bolus injection followed by an infusion from 30 to 240 minutes, as in experiment 2.

**Laboratory Methods**

Blood was sampled using heparinized tubes for the measurements of PRA and active and total renin, aldosterone, and Ro 42-5892 concentrations in plasma. PRA was determined on 250-μl plasma samples at pH 7.4, obtained by adding a 3 M (pH 7.2) Tris HCl buffer containing 200 mM ethylenediaminetetraacetic acid (EDTA) (1:10) and 2.8 mM phenylmethylsulfonyl fluoride to the plasma samples. The samples were incubated at 37°C, and the concentration of angiotensin I (Ang I) was measured by radioimmunoassay. Concentrations of active and total renin were measured by two different radioimmunometric assays using the two monoclonal antibodies 3E8 and 4G1, commercially available in the Diagnostics Pasteur Kit. The radioactive 4G1 antibody specifically recognizes active renin. For total renin, 3E8 was the immobilized antibody, and the labeled antibody was 3-16-16 (CIBA-GEIGY), which recognizes total renin. Circulating levels of Ro 42-5892 were determined by the radioinhibitor binding assay of Cumin et al.,using [3H]Ro 42-5892 as a tracer. Aldosterone levels were determined in methylene chloride–extracted plasma using a commercially available kit (SB-ALDO-H, Cis, Bio Int., Gif sur Yvette, France).

For the measurement of plasma angiotensins, blood was collected in chilled EDTA vacutainers that contained 62.5 mM EDTA, 100 μM Ro 42-5892, and
100 μM MK 422. The tubes were centrifuged at 4°C, and 2.2-ml plasma aliquots were immediately extracted on phenylsilysilica columns (Bondelut PH, Analytichem) according to Nussberger et al. The dried extracts containing angiotensins were diluted in 220 μl of 0.1 M (pH 7.5) Tris HCl buffer containing 2 g/l bovine serum albumin and kept frozen at -80°C. Recoveries were 98.5±3.5%. For the Ang I radioimmunoassay, we used a polyclonal antibody that cross-reacts 100% with des-Asp Ang I. For the Ang II radioimmunoassay, we used a monoclonal antibody (gift of D. Simon and B. Pau, Sanofi, Montpellier, France) that cross-reacts 190% with des-Asp Ang II, 100% with [Val5]Ang II (Hypertension, CIBA-GEIGY), and 1% with Ang I. In both standard curves, 0.5 pg/tube can be detected, and the 50% displacement of the tracer is 5 and 10 pg/tube for Ang I and Ang II, respectively. In the absence of high-performance liquid chromatographic separation, these two immunoassays measure “immunoreactive” plasma angiotensins and not “true” plasma angiotensins. In this kind of acute experiments, where no ACE inhibitor is administered, the measurement of immunoreactive angiotensins is sufficient to monitor the expected fall in concentrations of both angiotensins secondary to renin inhibition and the rise in plasma Ang II secondary to the infusion of exogenous peptide.

Statistical Methods

The changes induced by administration of Ang II, Ro 42-5892, or both were analyzed using graphical and statistical methods.

The graphical method involved display of changes in blood pressure (BP) and pulse rate recorded every 5 minutes during 240 minutes after smoking of the data by a moving average. In this display, each data point (except the first and last points) represents an average of three measures: the actual measure, the preceding measure, and the following measure.

For the statistical analysis of the changes in these two parameters induced by the three treatments, we used summary measures to avoid the risk of an inaccurate conclusion due to multiple testing. Two periods were considered for definition of the area under the curve: Ang II infusion from 0 to 120 minutes, and return to baseline from 120 to 240 minutes. Statistical analysis was performed according to repeated-measures variance analysis (ANOVA) with the GLM procedure of SAS statistical software. The assumptions of ANOVA (homogeneity of variance and normality) were examined for each variable, and logarithm or square-root transformations of the data were selected where appropriate. For biochemical parameters, analysis was carried out only at 120 and 240 minutes to answer the main question of the study. When the F ratio was significant, contrasts were used to compare treatments. Two contrasts, Ro 42-5892 versus Ang II and Ro 42-5892 versus Ro 42-5892 plus Ang II, were defined a priori. The other data points are shown to reinforce the validity of the protocol through their agreement with well-known physiological phenomena and their return toward baseline levels at the end of the therapeutic maneuvers.

Data are expressed as mean±SEM. A probability value of less than 0.05 was considered significant.

Results

Blood Pressure and Heart Rate

The basal value was defined as the mean of the seven measurements performed between -30 and 0 minutes. The basal BP was 79±8 mm Hg in experiment 1, 80±8 mm Hg in experiment 2, and 75±7 mm Hg in experiment 3. Basal pulse rates were 65±11, 65±9, and 64±10 beats/min, respectively. The value at each time after 0 minutes was defined as the value at this time minus the basal value, and smoothed data are presented in Figure 2.

As shown in the upper panel of Figure 2, BP increased in response to Ang II infusion. The figure clearly shows a tachyphylaxis to Ang II at 60 minutes, followed by a further rise in BP when the higher Ang II infusion was started. Analyzed as areas under the curve, changes in BP differed significantly among the three experiments (F2,10=20.7, p<0.001); pairwise comparisons showed that curves obtained with experiments 1 and 3 both differed significantly from the curve obtained with experiment 2. From 120 to 240 minutes, BP was lowest after Ro 42-5892 alone and highest after Ang II alone, whereas intermediate values were obtained after the infusion of both compounds. The overall F ratio comparing the three curves is of borderline significance (F2,10=4.1, p=0.05), and the only significant pairwise difference was observed between experiments 2 and 1 (p=0.05).

Pulse rate changes (lower panel of Figure 2) were the inverses of BP changes. The infusion of Ang II alone and the infusion of both Ang II and Ro 42-5892 decreased pulse rate between 0 and 120 minutes; pulse rate then returned to basal values between 120 and 240 minutes. During the infusion of Ro 42-5892 alone, pulse rate changes oscillated around 0; areas under the curves before and after 120 minutes did not differ significantly.

Plasma Levels of Angiotensin I, Angiotensin II, and Aldosterone

Mean±SEM values are given in Table 1, and changes in the parameters with time are shown in Figure 3.

Plasma Ang II levels at the end of the two Ang II infusions were similar and twofold to threefold higher than their basal values. At 120 minutes, ANOVA showed a significant overall difference among the three experiments (F2,10=14.1, p<0.001). In pairwise analysis, plasma Ang II levels were similar in experiments 1 and 3, and levels in both experiments differed significantly from levels in experiment 2 (p<0.01). At 240 minutes, the plasma Ang II concentration tended to return toward its basal value. A significant difference persisted among
the three experiments ($F_{2,10}=5.0, p<0.05$). In pairwise analysis, the plasma Ang II level in experiment 2 differed significantly from that in experiment 1 ($p<0.05$), but there was no significant difference between Ang II levels in experiments 2 and 3.

At 120 minutes, the plasma Ang I level decreased by $>50\%$ in experiment 1 and returned toward the basal value when the Ang II infusion was stopped. In experiments 2 and 3, plasma Ang I levels decreased by 93% and 96%, respectively, at 120 minutes. ANOVA showed a significant difference among the three experiments ($F_{2,10}=18.7, p<0.001$). In pairwise analysis, the plasma Ang I level was lower in experiment 2 than in experiment 1 ($p<0.01$) and in experiment 3 than in experiment 2 ($p<0.05$). At 240 minutes, the plasma Ang I level started to return toward its basal value, and a significant difference persisted among the three experiments ($F_{2,10}=123.5, p<0.01$). In pairwise analysis, the Ang I level in experiment 2 remained significantly different from that in experiment 1 ($p<0.05$), whereas no difference persisted between Ang I levels in experiments 2 and 3.

As shown in Figure 3, the increases in plasma aldosterone concentration induced by Ang II infusion did not differ in experiments 1 and 3. In experiment 2, the maximum fall in the plasma aldosterone level, to 54% of its basal value, was observed at 240 minutes. At 120 minutes, ANOVA showed an overall difference among the three experiments ($F_{2,10}=47.9, p<0.001$). In pairwise analysis, plasma aldosterone levels were similar in experiments 1 and 3, and both

![Figure 2](image-url) Changes in mean arterial blood pressure and heart rate during three experiments. Values are mean of values recorded in six volunteers. Data are smoothed by moving average (see "Methods").
these levels differed significantly from that in experiment 2 \((p<0.001)\). At 240 minutes, the overall difference among the three experiments remained significant \((F_{2,10}=5.7; p<0.05)\). As for BP, the lowest plasma aldosterone concentration was observed in experiment 2 and the highest in experiment 1, with intermediate values observed in experiment 3. The plasma aldosterone level in experiment 2 differed significantly from that in experiment 1 \((p<0.01)\), and the difference between experiments 2 and 3 was of only borderline significance \((p=0.08)\).

**Plasma Renin Parameters**

Mean±SEM values of PRA and the concentrations of active renin, total renin, inactive renin, and Ro 42-5892 are shown in Table 2, and the changes of the active renin concentration with time are shown in Figure 4. In experiment 1, the infusion of Ang II progressively decreased PRA to 41% of its basal value at 120 minutes. When the Ang II infusion was stopped, PRA returned toward its basal value. In experiments 2 and 3, infusion of Ro 42-5892 completely inhibited PRA until 180 minutes. At 240 minutes, PRA was still at the lower limit of detection on six of 12 occasions.

The plasma level of active renin decreased by 60% in parallel with PRA \((-59\%)\) and the plasma level of Ang I \((-52\%)\) during experiment 1. The active renin level then returned toward its basal value, as shown in Figure 4. During experiment 2, the infusion of Ro 42-5892 induced a 10-fold increase in the plasma level of active renin, which stayed high at 180 and 240 minutes. During experiment 3 the active renin level, after an initial fall from 29 to 22 pg/ml, increased by 42% and was almost threefold higher than in experiment 1. At 120 minutes, ANOVA showed a highly significant difference among the three experiments \((F_{2,10}=28.5, p<0.001)\). In pairwise analysis, the plasma level of active renin in experiment 2 differed significantly from that in both experiments 1 \((p<0.001)\) and 3 \((p<0.001)\). At 180 and 240 minutes, when Ang II infusion was stopped, the active renin level rose to that observed in experiment 2. At 240 minutes, the overall \(F\) ratio remained significant \((F_{2,10}=37.6, p<0.001)\). The active renin level in experiment 2 was significantly higher than that in experiment 1 \((p<0.001)\) but did not differ from that in experiment 3.

Changes in the total renin concentration measured at 120 and 240 minutes paralleled those observed in active renin. The plasma concentration of inactive renin was calculated as the difference between the concentrations of total and active renin at 0, 120, and 240 minutes. At 120 minutes, the plasma inactive renin levels were higher in experiment 2 than in experiments 1 and 3, as for active renin, but the differences were not significant. At 240 minutes, the overall \(F\) ratio was significant \((F_{2,10}=5.7, p<0.05)\). As for active renin, the inactive renin level was significantly higher in experiment 2 than in experiment 1 \((p<0.05)\), but there was no difference between experiments 2 and 3.

**Plasma Levels of Ro 42-5892**

Plasma levels of Ro 42-5892 are shown in Table 2. Similar levels were obtained during experiments 2 and 3.

**Discussion**

Investigation of the reciprocal changes of plasma levels of Ang II and renin is an important aspect in the analysis of renin-angiotensin system blockade. The vascular smooth muscle cells lining the afferent arteriole of the JGA are differentiated endocrine cells. Ang II increases their intracellular Ca\(^{2+}\) levels in a dose-dependent manner, stimulating the production of phosphatidylinositol triphosphate and diacylglycerol, which activates protein kinase C. This results in inhibition of renin release. The same intracellular events occur during Ang II-induced constriction of other vascular smooth muscle cells. Therefore, regulation of the renin-angiotensin system is such that decreased renin secretion accompanies Ang II-induced vasconstriction and increased renin secretion accompanies vasodilation induced by
interruption of either Ang II production by renin inhibitors or ACE inhibitors or of Ang II action by Ang II antagonists. All renin inhibitors except one induce an increase in the plasma level of active renin, and the goal of our study was to investigate whether the fall in the plasma Ang II level entirely explained this rise in the plasma renin level.

As shown in Figures 2 and 3, the biological effects of Ang II infusion in experiments 1 and 3 were reproducible for all parameters directly dependent on Ang II (i.e., BP and the plasma level of aldosterone). However, the experiment was not an exact substitution of endogenous Ang II ([Ile³]Ang II); the exogenously administered peptide was [Val³]Ang II, and the selected rates of Ang II infusion induced a threefold rise in the plasma Ang II level, which represents an excess of the active peptide compared with endogenous levels of Ang II.

Experiment 1 showed that a pharmacological dose of Ang II, which increased plasma Ang II levels by twofold to threefold and diastolic BP by 10–20 mm Hg, decreased renin release as measured by two different methods (enzymatic assay and immunoradiometric assay). No change in the level of inactive renin was observed, which confirms previous data by Millar. A fall in the plasma Ang I level resulted from the decrease in the plasma active renin level, which makes it likely that the endogenous Ang II levels, although not quantifiable, decreased in the presence of this excess of exogenous Ang II.

Experiment 2 showed that Ro 42-5892 is a powerful inhibitor of the renin-angiotensin system and a major stimulus of renin release. Ro 42-5892 suppressed the circulating levels of Ang I and Ang II, measured by sensitive radioimmunoassays capable of detecting 1 pg/ml. As expected in normotensive volunteers, no fall in BP was detected, whereas a dose-dependent BP-lowering effect of this renin inhibitor has been reported in hypertensive patients. There was a trend for BP and the plasma aldosterone level to be slightly lower at the end of experiment 2 than at the end of experiments 1 and 3. However, it is not possible to conclude that the Ro 42-5892 infusion was responsible for these decreases since the study design did not include a placebo and therefore did not permit the differentiation between a possible drug effect and a time effect.

The inhibition of renin by Ro 42-5892 was accompanied by a 10-fold increase in the plasma level of active renin, which stayed high during the whole experiment. This massive rise in the active renin level was accompanied by very modest increases in the plasma level of inactive renin (increases of 31±18 pg/ml at 120 minutes and 43±6 pg/ml at 240 minutes). The magnitude of these changes was so small that no significant differences were detected by ANOVA performed on the absolute value of plasma inactive renin levels. The existence of a rise in the inactive renin level is reinforced by the results of experiment 3. No rise (29±34 pg/ml) was observed at 120 minutes, when the stimulation of renin release was minimized by the Ang II infusion, and a delayed increase similar to the one detected in experiment 2 (67±37 pg/ml) was present at 240 minutes. Two difficulties are encountered in the analysis of these small changes: 1) inactive renin in the plasma is not exclusively of renal origin, and 2) its measurement is indirect (difference between the total and active renin levels) and influenced by the intra-assay variability of the two immunoradiometric assays. Finally, a small rise in the plasma level of inactive renin is possible, although not certain, but at least this experiment excludes the possibility of an increased conversion of inactive to active renin to explain the rise in plasma levels of active renin secondary to renin inhibition. A similar conclusion was reached after ACE inhibition.
Table 2. Values of Plasma Renin Activity (pg Ang I/ml/hr), Active Renin (pg/ml), Total Renin (pg/ml), Inactive Renin (pg/ml), and Ro 42-5892 (ng/ml)

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Values are mean±SEM. Ang I, angiotensin I.

Experiment 3 showed that Ang II infusion before and during the intravenous administration of Ro 42-5892 has a major inhibitory effect on renin release. This effect did not persist when the Ang II infusion was ceased at 120 minutes, and active renin in the plasma increased to levels comparable to those observed in the absence of Ang II infusion. However, after the combined administration of Ang II and Ro 42-5892 the plasma active renin level was 38±5 pg/ml, higher than its basal level (29±4 pg/ml) and more than threefold higher than the level observed at the end of the Ang II infusion (12±4 pg/ml). Mersey et al28 used a similar methodology to investigate renin release during captopril administration in normal volunteers placed on a moderately low sodium diet. These authors concluded that the rise in PRA was mediated by the fall in plasma Ang II levels because an exogenous Ang II infusion (3-6 ng/kg/min) maintained PRA at 4.6 ng/ml/hr (basal level 4.8±1.2 ng/ml/hr) compared with 15.2 ng/ml/hr when the Ang II infusion was ceased. The protocol of Mersey et al28 did not permit a comparison between PRA values measured during the combined administration of Ang II and captopril and PRA values measured during the infusion of Ang II alone. Captopril was given after the Ang II infusion was started, and the reported PRA of 4.6±1.2 ng/ml/hr 45 minutes after captopril intake was already influenced by a previous 65 minutes of Ang II infusion. At 20 minutes of this Ang II infusion, just before captopril intake, PRA had already decreased to 2.9±0.8 ng/ml/hr and the study design could not provide the PRA value obtained after the next 45 minutes of infusion of Ang II alone, which very likely would have been lower. A more exact conclusion from the experiment of Mersey et al28 would be that captopril increased PRA from 2.9 to 4.6 ng/ml/hr. Therefore, in both experiments involving ACE inhibition and renin inhibition, the most obvious phenomenon is the reduction of renin release, confirmed by experimental data in rats.29 Our experiment shows that despite the Ang II infusion, some stimulation of renin release persists after the administration of Ro 42-5892, and this phenomenon of persistent renin stimulation was
possibly also present in the experiment in which captopril was used as the stimulus for renin release. This is even more impressive if one remembers that the circulating level of Ang II was increased beyond its normal physiological level by the exogenous administration of Ang II. A first explanation for this incomplete suppression of renin release by exogenous Ang II is the local effect of renin inhibition on the intrarenal formation of Ang II. Substantial amounts of angiotensin peptides are released or generated within intrarenal fluid compartments, and the high renal levels of Ang II may be a determinant of renal renin release independent of the plasma level of Ang II. At the level of the JGA cells, Ro 42-5892 may act directly on the endocrine cells of the afferent arterioles of the glomeruli, where Ang II is known to be produced, and this effect cannot be reversed by the intravenous administration of an excess of Ang II. Another explanation may be an Ang II-independent effect of renin inhibition on renin release. The first interpretation means that the dose of exogenous Ang II used in our experiments could not substitute for the locally produced endogenous Ang II. In favor of this interpretation is a previous experiment performed by Swartz et al., who investigated the mechanisms of the hypertensive effect of an ACE inhibitor, teprotide, in hypertensive patients. Teprotide decreased BP, and an infusion of exogenous Ang II was used to restore BP to its initial value. This could be achieved only by an increase in the plasma Ang II level to 50% above control values, with a rise in the plasma aldosterone level of a magnitude similar to that observed in our experiments. Instead of concluding that another system such as the kallikrein-kinin system may be involved in the hypotensive effect of teprotide, Swartz et al., could conclude that an exogenous infusion of Ang II is not equivalent to its endogenous generation. Such a conclusion is now supported by the recent demonstration of the importance of local Ang I and Ang II generation outside circulating plasma, especially within the kidney.

The persistent, although moderate, rise of the active renin level in the absence of a fall in the circulating Ang II level observed in our short-term experiment mimics what is observed during ACE inhibition, in which 24 hours after drug intake the plasma Ang II level returns to its normal value, whereas the plasma renin level stays high. This rise in the active renin level is a useful index for detecting the persistence of renin-angiotensin system inhibition, even when the plasma levels of Ang II have returned toward their basal values. This rise has already been used to interpret the results obtained with another renin inhibitor, CGP 38-560 A. Although the oral absorption of this inhibitor was minimal, it was apparently able to inhibit completely PRA but did not induce a rise in the plasma level of active renin. These results were interpreted as indicating a lack of oral efficacy of this compound. This was confirmed by the low plasma levels of inhibitor and suggested that the biological activity of renin inhibitors might be overestimated by some methods of PRA measurement.

In conclusion, the exogenous administration of Ang II massively reduces the release of active renin secondary to renin inhibition, but some renin release stimulation still persists, possibly dependent on intrarenal inhibition of Ang II generation by the renin inhibitor.

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References


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