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Research Article

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Role of AT_1 Receptors in the Resetting of the Baroreflex Control of Heart Rate by Angiotensin II in the Rabbit

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Abstract

Angiotensin II (Ang II) resets the baroreflex control of heart rate to a higher blood pressure. This action is apparently mediated via Ang II receptors in the area postrema, but it is not known if these are of the AT_1 or AT_2 subtype. In the present study the effects of losartan, a selective AT_1 receptor antagonist, and PD 123319, a selective AT_2 antagonist, on the cardiac baroreflex response to Ang II were investigated in conscious rabbits with chronically implanted arterial and venous catheters. Baroreflex curves were generated with intravenous infusions of phenylephrine and nitroprusside (2.6–25 μg/kg per min) and analyzed using a four-parameter logistic model to yield their upper and lower plateaus, arterial pressure at the midpoint of the heart rate range (BP_{50}), and slope coefficient. From these four parameters, the gain and range of the baroreflex were calculated. Background intravenous infusion of Ang II at 10 ng/kg per min increased mean arterial pressure by 17 mmHg but did not change heart rate. Ang II shifted the baroreflex curve to the right as indicated by an increase in BP_{50} from 70.9±2.0 to 89.3±2.7 mmHg ($P < 0.05$), but did not change baroreflex gain significantly. Ang II did not alter the upper plateau of the baroreflex, but decreased the lower plateau from 119.4±10.3 to 73.6±11.5 beats per minute (bpm) ($P < 0.05$), extending the heart rate range by 52.5 bpm. Pretreatment with losartan completely abolished the pressor and cardiac baroreflex responses to Ang II. In contrast, PD 123319 had no effect on these responses. Administration of losartan alone to block endogenous Ang II shifted the baroreflex curve to the left as indicated by a decrease in BP_{50} from 71.2±2.7 to 64.7±2.5 mmHg ($P < 0.05$). These results demonstrate that the resetting of the baroreflex control of heart rate by Ang II is mediated by AT_1 receptors, and that basal levels of endogenous Ang II exert a tonic action on the cardiac baroreflex to increase the setpoint around which the baroreflex regulates heart rate. (*J. Clin. Invest.* 1993. 1516–1520.) Key words: losartan • PD 123319 • rabbit • AT_2 receptors • baroreflex resetting

Introduction

The pressor response to systemic administration of angiotensin II (Ang II) results primarily from direct constriction of vascular smooth muscle. However, Ang II also affects blood pressure indirectly by modulating the baroreceptor reflex control of heart rate (1, 2). As a result, the pressor response to the peptide is accompanied either by no decrease in heart rate, or a bradycardia that, for a given increase in blood pressure, is much smaller than that produced by other vasoconstrictors (1, 3–8). This action of Ang II apparently serves to minimize the buffering action of the baroreceptor reflexes (9).

The modulation of the cardiac baroreflex by Ang II results primarily from a resetting of the reflex to a higher blood pressure (3, 10–12) although, depending on the species being tested and the experimental conditions, there may also be a reduction in baroreflex gain (3, 13, 14). There is evidence that the modulation is due to an action of Ang II at the area postrema, a circumventricular organ located in the medulla oblongata (15–20). The area postrema contains a high density of angiotensin receptors that are accessible to circulating Ang II and sends a projection to the nucleus of the solitary tract where the baroreceptor afferents terminate. Studies in rabbits have shown that the resetting of the cardiac baroreflex control of heart rate by Ang II is eliminated by destruction of the area postrema (21, 22).

Binding studies have shown that the majority of the angiotensin receptors in the area postrema are of the AT_1 subtype (23, 24). The aim of the present investigation was to determine if the modulation of the cardiac baroreflex by Ang II is mediated by AT_1 receptors. This was accomplished by comparing the effects of losartan (DuP 753), a selective AT_1 antagonist, and PD 123319, a selective AT_2 antagonist, on the cardiac baroreflex response to Ang II in conscious rabbits.

Methods

The experiments were performed in male New Zealand White rabbits, weighing 2.5–3.5 kg. They were fed a commercial diet (Purina rabbit chow, Ralston-Purina, St. Louis, MO) and provided with water ad lib.

Surgical procedures

All surgical procedures were performed under xylazine and ketamine anesthesia, using sterile technique. The procedures were approved by the University of California, San Francisco Committee on Animal Research.

The rabbits were anesthetized with a mixture of 2–5 mg/kg i.m. xylazine (Lloyd Laboratories, Shenandoah, IA) and 35–50 mg/kg i.m. ketamine (Parke-Davis, Morris Plains, NJ). A catheter consisting of 5 in. medical grade Silastic (i.d., 0.03 in.; o.d., 0.065 in.) (Dow-Corning Corp., Midland, MI) connected to PE60 tubing was inserted into a femoral artery and advanced into the aorta to a point below the kidneys. Two Tygon catheters (i.d., 0.03 in.) were inserted into a jugular vein and positioned near the heart. All catheters were led subcutaneously to a point between the scapulae, where they emerged and were protected in the pockets of a nylon mesh jacket (Alice King Chatham Medical Arts, Los Angeles, CA). The rabbits were allowed at least 3 d to recover from surgery, during which time they were treated with 0.5 ml SID Di-Trim (Trimethoprim and Sulfadiazine; Syntex, West Des Moines, IA). The catheters were flushed at least every other day with

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sterile isotonic saline and filled with heparin (1,000 U/ml). During the recovery period, the rabbits were brought to the laboratory and acclimated to the experimental environment.

Experimental protocols

On the day of an experiment, rabbits were brought to the laboratory and placed in a stainless steel cage. Blood pressure and heart rate were monitored continuously using a blood pressure transducer (Cobe Laboratories, Inc., Lakewood, CO) and a polygraph (Grass Instrument, Co., Quincy, MA). In addition, cardiovascular data were digitized at 100 Hz, stored and analyzed using a PDP 11/23+ computer (Digital Equipment Corp., Maynard, MA). When blood pressure and heart rate had stabilized, a blood sample (4 ml) was collected from the femoral artery and immediately centrifuged at 4°C and stored at −20°C for later assay. This sample was used for the measurement of plasma renin activity.

Baroreflex curves (heart rate vs. mean arterial pressure) were generated by measuring the heart rate responses to increases or decreases in arterial blood pressure produced with intravenous infusions of four doses of phenylephrine (Elkins-Sinn, Inc., Cherry Hill, NJ) and four doses of nitroprusside (Elkins-Sinn, Inc.). The doses of each drug were 2.6, 6.3, 12.5, and 25.0 μg/kg per min contained in a volume of 0.02–0.21 ml 0.9% NaCl per min. Each infusion lasted for 3–5 min, and approximately 10 min elapsed between each infusion, during which time blood pressure and heart rate returned to near control values. Blood pressure and heart rate data collected during the last 1–2 min of each infusion were averaged and used to generate baroreflex curves. Following control measurements, an experiment was started according to one of the following protocols. Experiments were performed in random order, and only one experiment was performed on a rabbit in one day.

Effect of Ang II on the cardiac baroreflex (n = 8). The purpose of this experiment was to determine the effect of Ang II on the baroreflex control of heart rate. After control measurements were made, eight rabbits received a 1.3-ml i.v. bolus of saline, and 10–15 min later, a background intravenous infusion of saline or Ang II (10 ng/kg per min; Peninsula Laboratories, Inc., Belmont, CA) (vol = 0.02 ml/min) was started. Baroreflex curves were generated during the saline and Ang II infusions.

Effect of losartan on the cardiac baroreflex response to Ang II (n = 8). The purpose of this experiment was to investigate the effect of an AT_1 receptor antagonist on the cardiac baroreflex response to Ang II. The rabbits from the first protocol were used, each rabbit serving as its own control. The rabbits received an intravenous bolus of losartan (5 mg/kg; DuPont, Wilmington, DE), and 15 min later a background intravenous infusion of Ang II at 10 ng/kg per min was started. Baroreflex curves were generated during the Ang II infusion. In preliminary experiments we determined that a single 5-mg/kg i.v. dose of losartan blocks the pressor response to infusion of Ang II at 20 ng/kg per min for at least 2 h.

Effect of PD 123319 on the cardiac baroreflex response to Ang II (n = 4). The aim of this experiment was to investigate the effect of an AT_2 receptor antagonist on the action of Ang II on the cardiac baroreflex. The effect of Ang II on the baroreflex was tested in four rabbits as described in the first protocol. These four rabbits subsequently received an intravenous bolus of the AT_2 antagonist PD 123319 (25 mg/kg; Parke-Davis, Ann Arbor, MI) and then the effect of Ang II on the baroreflex was tested again.

Effect of losartan on the cardiac baroreflex (n = 6). The effect of administration of losartan alone was studied to investigate whether endogenous Ang II exerts an action on the baroreflex control of heart rate in sodium replete rabbits. Six of the rabbits from the first protocol were used. Baroreflex curves were generated during background intravenous infusion of saline following losartan pretreatment (5 mg/kg i.v.).

Plasma renin activity

Plasma renin activity was measured by radioimmunoassay using a minor modification of the method of Menard and Catt (25) and an angiotensin I antibody generated in this laboratory. Plasma renin activity is expressed as nanograms of Ang I generated per milliliter plasma during a 2-h incubation at 37°C and pH 6.5 (ng/ml per 2 h).

Analysis of baroreflex curves

Steady state values of heart rate (HR) and mean arterial pressure (MAP) were analyzed using the four-parameter sigmoidal logistic function:

$$HR = \frac{A - D}{1 + \left(\frac{MAP}{C}\right)^B} + D$$

where A and D are the upper and lower plateaus of the baroreflex curve, C is the mean arterial pressure at the midpoint of the heart rate range (BP_{50}), and B is the slope coefficient (26). Curves were fitted to the data by computer using a nonlinear curve-fitting program (NFIT; Island Products, Galveston, TX) based on the Marquardt-Levenberg algorithm (26, 27). The chi-square value was used as an index of goodness of fit, and the standard deviation of each parameter was estimated. In some cases, insufficient data were available to define the upper or lower plateau of the baroreflex curve. In such cases, the upper plateau was set at the highest HR recorded for that rabbit, or 350 bpm, whichever gave the lowest chi-square value. Similarly, the lower plateau was set at the lowest HR or 100 bpm.

Baroreflex gain was calculated as the first derivative of the logistic function:

$$GAIN = \frac{d(HR)}{d(MAP)} = -\frac{\left(\frac{B(A-D)}{C}\right)\left(\frac{MAP}{C}\right)^{B-1}}{\left(1 + \left(\frac{MAP}{C}\right)^B\right)^2}$$

and the gain at the BP_{50} (i.e., when MAP = C) was calculated as:

$$GAIN_{50} = -\frac{B(A-D)}{4C}$$

The range of the baroreflex was calculated as:

$$RANGE = A - D$$

Baroreflex curves for each individual experiment were analyzed in this fashion and the resulting parameters were used for statistical analysis. In addition, HR and MAP data for each group of experiments were averaged, and the means fitted to construct a baroreflex curve for each treatment group.

Statistics

All results are expressed as mean±SE. Data were analyzed using one-way analysis of variance for repeated measures and the Neuman-Keul's multiple range test (28). Where appropriate, the paired *t* test was also used. Changes were considered to be statistically significant when $P < 0.05$.

Results

Baseline values (mean±SE) in the rabbits used in this study were as follows: MAP, 69.3±2.4 mmHg; heart rate, 205.1±9.7 beats per min (bpm); plasma renin activity, 7.3±1.2 ng/ml per 2 h. These values are within the normal range for rabbits in this laboratory (12).

Effect of Ang II on the cardiac baroreflex. Intravenous infusion of Ang II at 10 ng/kg per min increased MAP from 75.5±1.4 to 92.7±3.5 mmHg ($P < 0.001$) with no change in heart rate (206.4±6.2 to 204.4±6.4 bpm). The effect of Ang II on the cardiac baroreflex is shown in Fig. 1 and Table I. Ang II increased BP_{50} from 70.9±2.0 to 89.3±2.7 mmHg ($P < 0.05$), indicating a shift of the baroreflex curve to the right. The $gain_{50}$

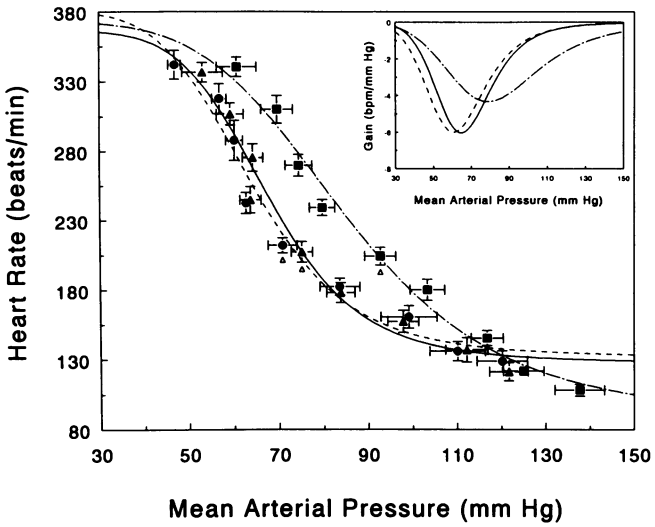

Figure 1. Baroreflex curves generated during background intravenous infusion of saline (— ▲ —), Ang II (— ■ —), and Ang II, following administration of losartan (— ● —). Values are means±SE for eight rabbits. Points indicated by open triangles are control values for MAP and HR recording during background infusion but before the start of the phenylephrine and nitroprusside infusions. (*Inset*) Baroreflex gain plotted as a function of MAP.

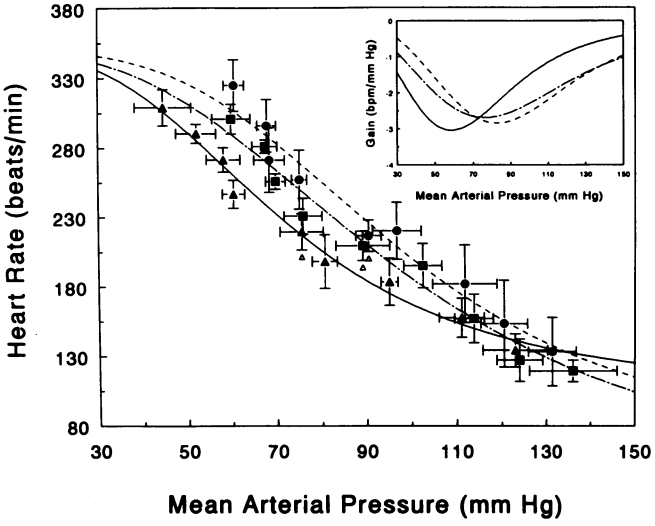

Figure 2. Baroreflex curves generated during background intravenous infusion of saline (— ▲ —), Ang II (— ■ —), and Ang II following administration of PD 123319 (— ● —). Values are means±SE for four rabbits. Points indicated by open triangles are control values for MAP and HR recording during background infusion but before the start of the phenylephrine and nitroprusside infusions. (*Inset*) Baroreflex gain plotted as a function of MAP.

of the baroreflex decreased from −6.9±1.1 to −4.3±0.4 bpm/mmHg, but this change was not statistically significant. Ang II also decreased the lower plateau of the baroreflex from 119.4±10.3 to 73.6±11.5 bpm ($P < 0.05$) without changing the upper plateau, thereby extending the heart rate range by 52.5 bpm ($P < 0.05$).

Effect of losartan on the cardiac baroreflex response to Ang II. Pretreatment with losartan completely blocked the pressor response to intravenous infusion of Ang II (69.5±3.0 to 70.8±3.2 mmHg). The effect of losartan on the resetting of the cardiac baroreflex by Ang II is shown in Fig. 1 and Table I. Losartan completely blocked the resetting of the baroreflex by Ang II. Indeed, the BP_{50} of the baroreflex during Ang II infusion following losartan treatment, 66.2±3.0 mmHg, was less than that of the control curve, 70.9±2.0 mmHg ($P < 0.05$), indicating a shift of the baroreflex curve to the left. The action of Ang II to decrease the lower plateau of the baroreflex was also completely blocked by losartan. Thus, the actions of Ang II on the cardiac baroreflex were completely blocked by an AT_1 receptor antagonist.

Effect of PD 123319 on the resetting of the cardiac baroreflex by Ang II. In this series of experiments, infusion of Ang II increased MAP from 71.8±6.4 to 89.1±6.0 mmHg, $P < 0.01$ without changing HR. The BP_{50} increased by 11.8 mmHg ($P < 0.05$) indicating a shift of the curve to the right (Fig. 2 and Table II). Baroreflex gain did not change. Pretreatment with PD 123319 did not block the pressor response to Ang II (76.1±5.7 to 90.4±2.8 mmHg) or the increase in the BP_{50} of the baroreflex. Thus, an AT_2 receptor antagonist did not block the actions of Ang II on the baroreflex control of heart rate.

Effect of losartan on the cardiac baroreflex. Injection of losartan decreased MAP from 68.5±1.7 to 65.2±2.0 mmHg ($P < 0.02$) but did not change HR. The effect of losartan alone on the baroreflex is shown in Fig. 3 and Table III. Losartan decreased the BP_{50} from 71.2±2.7 to 64.7±2.5 mmHg ($P < 0.05$), indicating a shift of the baroreflex curve to the left. In addition, losartan decreased the heart rate range by 19.4 bpm. Thus, blockade of basal levels of endogenous Ang II with losartan produced changes in the cardiac baroreflex opposite to those produced by administration of exogenous Ang II.

Table I. Analysis of Cardiac Baroreflex Curves Obtained During Background Infusion of Saline, Angiotensin II (Ang II), and Angiotensin II Following Administration of the AT_1 Receptor Antagonist Losartan

Treatment	Upper plateau	Lower plateau	Slope coefficient	BP_{50}	$Gain_{50}$	Range
	bpm	*bpm*		*mmHg*	*bpm/mmHg*	*bpm*
Saline	366.4±8.7	119.4±10.3	8.5±1.8	70.9±2.0	−6.9±1.1	246.9±15.7
Ang II	373.0±6.3	73.6±11.5*	5.2±0.5	89.3±2.7*	−4.3±0.4	299.4±10.9*
Ang II + Losartan	380.5±9.5	122.3±6.4‡	6.4±0.6	66.2±3.0‡,§	−6.2±0.6	258.2±12.6‡

Values represent the mean±SE of observations made in eight rabbits. * $P < 0.05$ compared with corresponding saline value; ‡ $P < 0.05$ compared with corresponding Ang II value; § $P < 0.05$ compared with corresponding saline value.

Table II. Analysis of Cardiac Baroreflex Curves Obtained During Background Infusion of Saline, Angiotensin II (Ang II), and Angiotensin II Following Administration of the AT_2 Receptor Antagonist PD 123319

Treatment	Upper plateau	Lower plateau	Slope coefficient	BP_{50}	$Gain_{50}$	Range
	bpm	*bpm*		*mmHg*	*bpm/mmHg*	*bpm*
Saline	335.3±14.8	113.5±8.0	4.9±1.6	74.5±2.1	−3.6±1.3	221.8±21.3
Ang II	333.8±16.3	98.5±1.8	4.5±0.4	86.3±3.1*	−3.1±0.3	235.3±14.4
Ang II + PPD 123319	361.3±11.3	120.8±29.7	4.9±0.8	81.5±2.3‡	−3.5±0.3	240.5±18.8

Values represent the mean±SE of observations made in four rabbits. * $P < 0.05$ compared with corresponding saline value; ‡ $P < 0.05$ compared with corresponding saline value.

Discussion

A unique characteristic of Ang II is that its pressor response is accompanied either by no decrease in heart rate or a bradycardia that, for a given increase in blood pressure, is smaller than that produced by other vasoconstrictors (1, 3–8). This modulation of the baroreflex control of heart rate has variously been attributed to a resetting of the cardiac baroreflex to a higher pressure (2, 10, 11, 29–31), a decrease in baroreflex gain (3, 13, 14), or a combination of both. It apparently serves to minimize the buffering action of the baroreflex and thereby increase the pressor action of the peptide (9).

In the present study, infusion of Ang II at 10 ng/kg per min increased mean arterial pressure by 17 mmHg but did not decrease heart rate. This lack of bradycardia could be accounted for by a resetting of the baroreflex to a higher pressure, as reflected by a shift in the baroreflex curve to the right with no significant reduction in baroreflex gain. This agrees well with previous results from this laboratory (12, 21). We have also found that the resetting of the cardiac baroreflex by Ang II is eliminated following destruction of the area postrema (21). This finding, together with the fact that the area postrema contains a high density of Ang II receptors that are accessible to circulating Ang II (15–20), suggests that the resetting is mediated by an action of Ang II at this circumventricular organ.

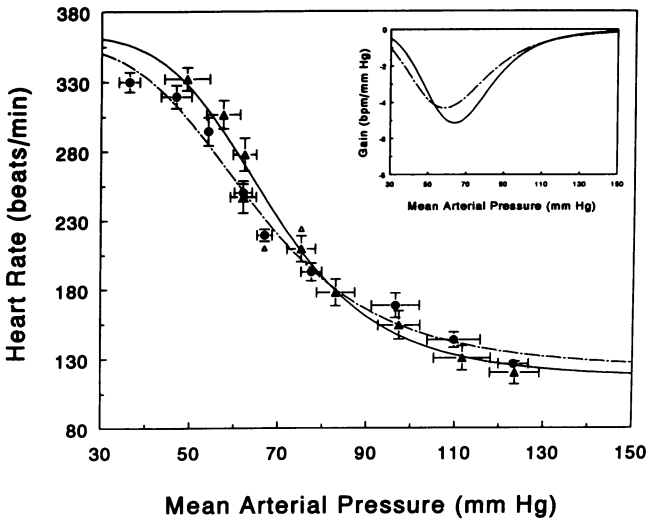

Figure 3. Baroreflex curves generated following administration of saline (— ▲ —) or losartan (— ● —). Values are means±SE for six rabbits. Points indicated by open triangles are control values for MAP and HR recording during background infusion but before the start of the phenylephrine and nitroprusside infusions. (*Inset*) Baroreflex gain plotted as a function of MAP.

It is now recognized that there are two subtypes of Ang II receptors classified as AT_1 and AT_2 (32). AT_1 receptors mediate many actions of Ang II, including vasoconstriction, but there is little information concerning the physiological role of AT_2 receptors. Both receptor subtypes are present in the brain, but their density varies from one region to another (23, 24, 33, 34). The receptors in the circumventricular organs, including the area postrema, appear to be predominantly of the AT_1 subtype although some AT_2 receptors may also be present (23, 24).

The primary aim of the present investigation was to characterize the receptors that mediate the resetting of the cardiac baroreflex by Ang II. This was accomplished by investigating the effects of losartan, a selective AT_1 receptor antagonist, and PD 123319, a selective AT_2 antagonist. Treatment with losartan completely blocked both the pressor and cardiac baroreflex responses to Ang II. On the other hand, PD 123319 did not block either the pressor effect of Ang II or the resetting of the baroreflex. These results indicate that the resetting of the cardiac baroreflex by Ang II is mediated by AT_1 receptors. As discussed above, it is likely that these receptors are located in the area postrema. However, no attempt was made to localize the receptors in the present study, and a role for AT_1 receptors located in different brain regions including other circumventricular organs cannot be excluded. It could also be argued that the ability of losartan to block the baroreflex resetting was secondary to its action to block the pressor response to Ang II. This is unlikely because we showed previously that Ang II resets the cardiac baroreflex even when changes in blood pressure are prevented by simultaneous infusion of nitroprusside (11). We have also shown that increasing blood pressure with phenylephrine instead of Ang II does not reset the baroreflex (12).

Baroreflex curves generated in the presence of Ang II following losartan treatment appeared to be slightly shifted to the left of the control curve (Fig. 1). Indeed, there was a significant reduction in the BP_{50} averaging 4.7 mmHg ($P < 0.05$) (Table I). This suggested that in addition to blocking the effect of exogenous Ang II on the baroreflex, losartan may have also blocked an action of endogenous Ang II. To test this possibility, we performed an additional experiment to test the effect of losartan alone. Losartan alone shifted the curve to the left by an average of 6.2 mmHg. Since plasma renin activity in these rabbits was in the normal range, this observation indicates that basal levels of endogenous Ang II exert a tonic action on the cardiac baroreflex, effectively increasing the set point around which the baroreflex regulates arterial pressure. It has been re-

Table III. Analysis of Cardiac Baroreflex Curves Obtained Following Administration of Saline or the AT_1 Receptor Antagonist Losartan

Treatment	Upper plateau	Lower plateau	Slope coefficient	BP_{50}	$Gain_{50}$	Range
	bpm	*bpm*		*mmHg*	*bpm/mmHg*	*bpm*
Saline	363.5±9.7	112.9±10.8	7.5±1.7	71.2±2.7	−6.3±1.1	250.6±16.6
Losartan	357.5±12.5	126.3±6.7	5.5±0.4	64.7±2.5*	−5.0±0.5	231.2±13.9*

Values represent the mean±SE of observations made in six rabbits. * $P < 0.05$ compared with corresponding saline value.

ported that blockade of the renin-angiotensin system with an angiotensin-converting enzyme inhibitor in normotensive, sodium-replete human subjects resets the baroreflex control of heart rate to a lower pressure (29, 30). In contrast, we observed that blockade of the renin-angiotensin system with the angiotensin receptor antagonist saralasin in sodium-replete dogs did not reset the baroreflex (11). This difference may reflect the partial agonist activity of saralasin, and the present results with losartan, which lacks agonist activity (35), provide support for this possibility.

In summary, these results confirm earlier studies that Ang II resets the baroreflex control of heart rate to a higher pressure and demonstrate that this action is mediated by Ang II receptors of the AT_1 subtype. In addition, the data indicate that basal levels of endogenous Ang II exert a tonic action on the cardiac baroreflex to increase the setpoint around which the baroreflex regulates heart rate.

Acknowledgments

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