Role of the Area Postrema in the Modulation of the Baroreflex Control of Heart Rate by Angiotensin II

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During angiotensin II (Ang II)--induced elevation of arterial pressure, there is an attenuation of the baroreflex control of heart rate (HR), but the site of this action of Ang II on the baroreflex is not known. To investigate the role of the area postrema, the effects of Ang II on arterial pressure and HR and on the baroreflex control of HR were compared in intact and area postrema--lesioned conscious rabbits. In intact rabbits, infusion of Ang II (2.5–100 ng/kg/min) produced dose-related increases in mean arterial pressure (MAP); the largest dose increased MAP by 32±3 mm Hg, HR decreased only at the highest dose of Ang II (21±6 beats/min). In lesioned rabbits, the increase in MAP was reduced (23±2 mm Hg, p<0.05) while the decrease in HR was enhanced (50±8 beats/min, p<0.01). The pressor and HR responses to infusion of phenylephrine (PE) (2–20 μg/kg/min) were not different between the two groups. In intact rabbits, the slope of the relation between HR and MAP during Ang II infusion was less than that during PE infusion; in lesioned rabbits, the slopes were not significantly different. Responses to bolus injections of Ang II and PE in intact and lesioned rabbits were similar to those obtained in the infusion study. In another series of experiments, cardiac baroreflex responses with or without background infusion of Ang II were obtained by increasing blood pressure with graded infusions of PE (2–20 μg/kg/min). In intact rabbits, infusion of Ang II at 10 ng/kg/min shifted the baroreflex to a higher pressure level (resetting) without changing its slope (sensitivity). Background infusion of PE caused comparable increases in blood pressure, but the subsequent baroreflex response was identical to the response without background PE. In lesioned rabbits, background infusion of Ang II did not change the slope, nor did it reset the baroreflex. The effects of Ang II on baroreflex responses during nitroprusside infusions (2–20 μg/kg/min) in intact and lesioned rabbits were the same as those observed during the PE infusions. These findings indicate that the attenuation of the baroreflex control of HR by Ang II results from resetting of the cardiac baroreflex and suggest that this effect is mediated via the area postrema. (Circulation Research 1990;67:1462–1473)

One of the unique characteristics of angiotensin II (Ang II) is its ability to increase arterial blood pressure without causing a reflex bradycardia.1–3 The mechanism underlying this response is not clear; some investigators4,5 have observed that Ang II resets the cardiac baroreflex in such a way that heart rate (HR) is maintained at a higher level for any given level of arterial pressure; others3,6,7 have reported that baroreflex sensitivity is reduced. Whichever is the case, the attenuation apparently results, at least in part, from inhibition of the increase in vagal tone that normally occurs in response to an increase in arterial pressure.8,9

It is well established that circulating Ang II can act centrally to produce a variety of effects, including increases in arterial pressure, HR, and sympathetic nerve activity and a decrease in parasympathetic nerve activity.1,10 For these and other reasons, it has been suggested that the modulation of the baroreflex control of HR by Ang II is also mediated via the central nervous system.3,8,9 Moreover, because many of the central cardiovascular effects of Ang II appear to be mediated via the area postrema, a circumventricular organ located in the medulla oblongata, a role for this structure has also been proposed.2,4,11 However, there is no direct evidence indicating that the area postrema is the site of this action of Ang II.

The aim of the present investigation was to test the hypothesis that the action of Ang II on the baroreflex...
control of HR is mediated via the area postrema. This was accomplished by comparing pressor and HR responses to Ang II and the effect of Ang II on the HR responses to baroreceptor loading or unloading in intact animals and in animals in which the area postrema had been lesioned. The effects of area postrema ablation on basal cardiovascular variables, the renin-angiotensin system, and plasma electrolytes were also determined. All experiments were performed in conscious, chronically prepared rabbits.

**Materials and Methods**

The experiments were carried out in male New Zealand White rabbits weighing 2.6–4.1 kg. Standard laboratory rabbit chow (Purina Rabbit Chow, St. Louis) and tap water were available ad libitum.

**Surgical Procedures**

Surgical procedures were performed under sodium pentobarbital anesthesia (20 mg/kg i.v.) after sedation with acepromazine maleate (2 mg/kg s.c.) and with the use of aseptic technique. All procedures were approved of by the University of California, San Francisco, Committee on Animal Research.

*Area postrema lesion.* Eleven rabbits were intubated with a tracheal tube (2.5–3.0 mm i.d.) and placed prone on a sandbag; the head was flexed downward. A midline incision in the dorsal neck muscle was made to expose the cisterna magna. The atlanto-occipital membrane was cut and removed to expose the fourth ventricle at the level of the obex. Under visual guidance with an operating microscope, the area postrema was identified and thermocoagulated by using a microcauter. A sham lesion was made in five rabbits by exposing the area postrema in the same manner, but no heat was applied to the lesioning unit. After surgery, rabbits were injected with 0.3 ml trimethoprim-sulfadiazine (DI-TRIM, Syntex, West Des Moines) subcutaneously for 3 days. The rabbits were allowed to recover for 10–20 days before surgery for catheter implantation. Most lesioned rabbits experienced transient anorexia, but their appetite returned to normal, and they were in good health by the time of catheter implantation.

*Catheters.* Under sodium pentobarbital anesthesia, a silicone catheter (0.76 mm i.d. x 1.65 mm o.d.) connected to polyethylene tubing (0.76 mm i.d. x 1.22 mm o.d.) was inserted into the abdominal aorta via the femoral artery for blood pressure and HR measurement. Two Tygon catheters (0.76 mm i.d.) were advanced into the inferior vena cava from the external jugular vein for intravenous injections. The catheters were then exteriorized dorsally between the scapulae and protected by a nylon mesh jacket (Medical Arts, Los Angeles). Catheters were flushed at least every other day with sterile isotonic saline and filled with heparin (1,000 units/ml). Catheters were also inserted in six additional rabbits that had not undergone area postrema surgery. After catheter implantation, the rabbits were treated with 0.3 ml s.c. trimethoprim-sulfadiazine for 2 days. The rabbits were allowed at least 3 days for recovery before experiments were begun. During this period, the rabbits were brought to the laboratory daily and became accustomed to the laboratory environment.

**Experimental Protocols**

On the day of the experiment, the rabbits were brought to the laboratory and placed in a cage. A stabilization period of 30–60 minutes was allowed before the start of the experiment. Arterial blood pressure was measured continuously via the arterial cannula using Statham (Gould, Cleveland) or Cobe (Cobe Laboratories, Inc., Lakewood, Colo.) pressure transducers. HR was determined by a cardiometer triggered by the arterial pressure pulse. Arterial pressure and HR were recorded on a polygraph (Grass Instruments, Quincy, Mass.). Except for the bolus injection study, cardiovascular data were also digitized at 100 Hz and collected and analyzed using a PDP 11/23 PLUS computer system (Digital Equipment Corp., Maynard, Mass.). With the use of this system, mean arterial pressure (MAP) and HR could be averaged over appropriate intervals, and their standard deviations could be obtained. The experiments were performed in random order, and at least 2 days elapsed between experiments. Experiments were carried out over a 1–2-week period in each rabbit. Because the data obtained in sham-lesioned rabbits and in those that received no area postrema surgery were not significantly different, the two groups were combined into a single control group. Phenylephrine (PE) (Winthrop Pharmaceuticals, New York), nitroprusside (NP) (Elkins-Sinn, Cherry Hill, N.J.), and Ang II (Peninsula Laboratories, Belmont, Calif.) were dissolved in 0.9% saline. Specific protocols are discussed below.

**Basal Values**

The aim of this experiment was to determine the effect of the area postrema lesion on resting cardiovascular variables, plasma renin activity, plasma sodium and potassium concentrations, plasma osmolality, and hematocrit. Six intact and six area postrema-lesioned rabbits were used. After the stabilization period, resting values for MAP and HR were collected by computer for 30 minutes. At the end of this time, a 2.0-ml blood sample was drawn via the arterial catheter and replaced with an equal volume of sterile isotonic saline. The blood samples were processed and assayed as described previously.12

**Arterial Pressure and HR Responses to Ang II and PE**

**Intravenous infusions.** The purpose of this experiment was to compare the blood pressure and HR responses to intravenous infusions of Ang II and PE in intact and lesioned rabbits. Nine intact and eight area postrema-lesioned rabbits were used. After MAP and HR had stabilized, control values for MAP and HR were collected. Arterial blood pressure was then raised by intravenous infusions of graded doses of PE (2, 5, 10, and 20 µg/kg/min) or Ang II (2.5, 10,
25, and 100 ng/kg/min) using an infusion pump (model 901, Harvard Apparatus, South Natick, Mass.). Flow rates ranged from 0.0136 to 0.136 ml/min. The series of PE and Ang II infusions were given in random order, and at least 30 minutes was allowed between each series. Each step of the infusion was maintained for 3 minutes, and MAP and HR during the last 1–2 minutes were collected and averaged by computer.

*Bolus injections.* In this series of experiments, the blood pressure and HR responses to bolus injections of Ang II and PE were compared. After control measurements in six intact and six area postrema–lesioned rabbits, three bolus doses of either PE (1, 4, and 16 μg/kg) or Ang II (10, 40, and 160 ng/kg) were injected intravenously. The total volume of the injections was approximately 2.0 ml. Each bolus injection was separated by at least 10 minutes, during which time MAP and HR returned to the preinjection levels. The PE and Ang II injections were given in random order, and at least 30 minutes was allowed for stabilization between the two series of injections.

**Baroreflex Responses to PE and NP With Background Infusion of Ang II**

The purpose of this experiment was to compare the effect of Ang II on the baroreflex control of HR during baroreceptor loading with PE or baroreceptor unloading with NP in intact and lesioned rabbits. Eight intact and eight area postrema–lesioned rabbits were used. Evaluation of the baroreflex with PE and with NP was performed on a separate day. After MAP and HR had stabilized, intravenous infusions of saline (0.0136 ml/min) or Ang II (10 ng/kg/min) were begun. Ten minutes after the beginning of the infusion, during which a new steady state of arterial pressure and HR was established, and while the infusion continued, baroreceptors were loaded or unloaded with progressive intravenous infusions of PE (2, 5, 10, and 20 μg/kg/min) or NP (2, 5, 10, and 20 μg/kg/min), respectively. Each dose of PE or NP was infused for 3 minutes, and MAP and HR during the last 1–2 minutes were averaged. The order in which background saline and background Ang II were given was randomized. Baroreflex responses to PE or NP superimposed on background infusion of PE (2–4 μg/kg/min) instead of Ang II were also determined. The dose of background PE was adjusted to achieve an increase in MAP comparable with that observed with background infusion of Ang II at 10 ng/kg/min. A minimum of 30 minutes elapsed between the completion of one background infusion and the start of the next. In three lesioned rabbits, the effect of background infusion of Ang II at 25 ng/kg/min on the baroreflex response to PE infusions was also determined using the same procedure.

**Histology**

At the completion of all experiments, the rabbits were anesthetized with sodium pentobarbital (50 mg/kg). The brain was perfused via the left cardiac ventricle with saline followed by 10% formalin. The whole brain was removed and stored in 10% formalin. The medulla was sectioned serially (30 μm) in the coronal plane and stained with thionine. Microscopic examination of the sections was performed to localize and determine the extent of each lesion.13–15

**Statistical Analysis**

All results are expressed as mean±SEM. Statistical evaluation of the data was performed using one- and two-way analysis of variance for repeated measures followed by the Newman-Keuls test. Where appropriate, Student’s t test was also used. To analyze baroreflex responses, the absolute value of HR for each dose of PE or NP was plotted against the corresponding value of MAP for each rabbit, and the data were subjected to linear regression analysis. The slope of the line was taken as an index of the baroreflex sensitivity. To quantitate shifts of the response (resetting), the value of MAP at the HR before background infusion was calculated from the regression line for each rabbit and termed the “setpoint” of the baroreflex.5,16 Coefficients of variation for MAP and HR were calculated as (SD/mean)×100. A value of p<0.05 was considered to be statistically significant.

**Results**

**Basal Values**

Table 1 shows basal values determined in the present study. The basal values of MAP and HR were not different between the intact and area postrema–lesioned rabbits, nor were their coefficients of variation. Plasma renin activity, plasma sodium and potassium

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**Table 1. Basal Values in Intact and Area Postrema–Lesioned Rabbits**

<table>
<thead>
<tr>
<th>Group</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>CV (%)</th>
<th>PRA (ng/ml/2 hr)</th>
<th>PNa (meq/l)</th>
<th>PK (meq/l)</th>
<th>POsm (mosm/kg)</th>
<th>Ht (%)</th>
</tr>
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<tbody>
<tr>
<td>Intact (n=6)</td>
<td>78±3</td>
<td>210±9</td>
<td>6.5±0.6</td>
<td>4.7±0.5</td>
<td>5.9±0.7</td>
<td>139±1</td>
<td>4.1±0.1</td>
<td>284±3</td>
</tr>
<tr>
<td>Lesioned (n=6)</td>
<td>77±2</td>
<td>207±8</td>
<td>5.9±0.3</td>
<td>4.6±0.5</td>
<td>5.5±1.8</td>
<td>139±1</td>
<td>4.2±0.1</td>
<td>284±2</td>
</tr>
</tbody>
</table>

Values are mean±SEM. MAP, mean arterial pressure; HR, heart rate; CV, coefficient of variation; PRA, plasma renin activity; PNa, plasma sodium concentration; PK, plasma potassium concentration; POsm, plasma osmolality; Ht, hematocrit. There were no significant differences between the two groups.
concentrations, plasma osmolality, and hematocrit were also not different between the two groups.

Responses to Ang II and PE

Intravenous infusions. The effects of intravenous infusions of Ang II on MAP and HR in intact and lesioned rabbits are shown in Figure 1. In the intact rabbits, graded doses of Ang II produced dose-related increases in MAP. These increases were not accompanied by significant changes in HR except with the highest dose of Ang II, which decreased HR by 21±6 beats/min. In the area postrema–lesioned rabbits, pressor responses to Ang II were less than those in the intact rabbits (p<0.05), and there was a shift to the right in the dose–response curve. On the other hand, the effect of Ang II on HR was enhanced in the lesioned rabbits (p<0.01), and there was a shift to the left in the dose–response curve. The decrease in HR with the highest dose of Ang II was 50±8 beats/min.

The effects of infusions of PE are summarized in Figure 2. In the intact rabbits, increasing doses of PE produced dose-related increases in MAP, which were accompanied by reciprocal decreases in HR. The responses in the lesioned rabbits were similar, and there were no significant differences between the two groups (p>0.1).

The data in Figures 1 and 2 are reploted in Figure 3 to show the relation between HR and MAP. For clarity, grouped data are shown in the figures, but linear regression analysis was performed on individual rabbits. The slope of the line for Ang II infusion in the intact rabbits averaged -0.81±0.24 beats/min/mm Hg, and this was significantly less than the slope for PE (-2.21±0.18 beats/min/mm Hg, p<0.01). In the lesioned rabbits, the slopes for Ang II and PE were -2.25±0.32 and -3.02±0.34 beats/min/mm Hg, respectively. The slope for Ang II was significantly greater than that in the intact rabbits (p<0.01) and was not significantly different from the slope for PE (p=0.09). The slope for PE in the lesioned rabbits tended to be steeper than the slope for the intact rabbits, but this difference was not statistically significant (p=0.06).

Bolus injections. The effects of bolus injections of Ang II and PE in intact and lesioned rabbits are shown in Figures 4–6. Responses to Ang II in representative intact and lesioned rabbits are shown in Figure 4, and grouped data are shown in Figures 5 and 6. The results with bolus injections of Ang II were essentially the same as those obtained in the infusion study; that is, blunted MAP (p<0.05) and potentiated HR (p<0.01) responses to Ang II injections were observed in the lesioned rabbits (Figure 5). The difference between the HR response to Ang II in the intact and lesioned rabbits was more prominent in the bolus injection study. The pressor responses to PE injections in the lesioned rabbits tended to be attenuated compared with those in intact rabbits (p=0.06) (Figure 6). The HR response to PE was not different in the two groups.

Figure 1. Graph showing pressor and heart rate responses to intravenous infusions of angiotensin II (ANG II) in intact (○; n=9) and area postrema–lesioned (●; n=9) rabbits. Abscissa shows dose of ANG II (ng/kg/min, logarithmic scale). The increase in blood pressure was significantly attenuated (p<0.05) while the decrease in heart rate was significantly potentiated (p<0.01) in the lesioned rabbits.

Figure 2. Graph showing pressor and heart rate responses to intravenous infusion of phenylephrine (PE) in intact (○; n=9) and area postrema–lesioned (●; n=8) rabbits. Abscissa shows dose of PE (μg/kg/min, logarithmic scale). The pressor and heart rate responses were not different between the two groups.
Baroreflex Responses to PE and NP With Background Infusion of Ang II

Phenylephrine infusions. The effects of background infusion of saline, Ang II, or PE on the baroreflex responses to PE in intact rabbits are shown in Figure 7 and Table 2. Basal values of MAP and HR in each group were as follows: saline infusion, 77±3 mm Hg and 217±8 beats/min; Ang II infusion, 80±3 mm Hg and 214±11 beats/min; PE infusion, 76±3 mm Hg and 213±8 beats/min. Intravenous infusion of Ang II at 10 ng/kg/min significantly increased MAP by 14±2 mm Hg (p<0.01) but did not change HR (2±2 beats/min). The regression line for the baroreflex with background Ang II was shifted to the right of the line with background saline infusion. This shift of the response (resetting) was highly significant (p<0.01), but the slope of the line was not different from that with background saline infusion. Intravenous infusion of PE (3.5±0.4 μg/kg/min) caused a comparable increase in MAP (14±4 mm Hg, p<0.01) accompanied by a decrease in HR (38±6 beats/min, p<0.01). The subsequent baroreflex response was identical to the response with background saline; that is, resetting of the response was not observed with background infusion of PE.

The baroreflex responses to PE infusions during background infusion of saline, Ang II, or PE in area postrema–lesioned rabbits are summarized in Figure 8 and Table 2. Basal values of MAP and HR in each group were as follows: saline infusion, 77±3 mm Hg and 210±8 beats/min; Ang II infusion, 80±2 mm Hg and 217±12 beats/min; PE infusion, 80±3 mm Hg...
and 227±9 beats/min. Infusion of Ang II at 10 ng/kg/min increased MAP by 8±2 mm Hg, an increase that was significantly less than that in the intact rabbits (p<0.05). Despite this, HR decreased significantly (13±5 beats/min, p<0.05). Background infusion of Ang II did not change the slope or setpoint of the baroreflex compared with background saline. Background infusion of PE (2.6±0.3 μg/kg/min) in the lesioned rabbits increased MAP by 8±2 mm Hg (p<0.05) and decreased HR by 27±6 beats/min (p<0.05). The infusion of PE had no effect on the baroreflex.

Because the increase in blood pressure during infusion of Ang II at 10 ng/kg/min in the lesioned rabbits was less than the increase in intact rabbits, the effect of background infusion of Ang II at 25 ng/kg/min was also examined in three lesioned rabbits. This dose of Ang II increased MAP by 15±1 mm Hg, an increase comparable with the increase in the intact rabbits during infusion at 10 ng/kg/min. The increase in blood pressure was accompanied by a decrease in HR of 26±11 beats/min. The slope and setpoint of the baroreflex during Ang II infusion in the lesioned rabbits (−2.49±0.27 beats/min/mm Hg and 79±8 mm Hg) were similar to those during saline infusion (−2.71±0.26 beats/min/mm Hg and 78±2 mm Hg).
Histology

Figure 9 shows a photomicrograph of the caudal medulla in representative sham-operated and area postrema–lesioned rabbits. Total or near total ablation of the area postrema was achieved in 10 of 11 rabbits. In these rabbits, varying amounts of damage to surrounding tissue, including the gracile nucleus, commissural nucleus, and medial solitary nucleus, was observed. However, with the exception of one rabbit, lesions were mainly restricted to the area postrema, and neither the location nor the extent of damage to surrounding tissues correlated with the magnitude of the hemodynamic changes caused by the lesion. In one rabbit, in which there was significant damage to the medial solitary nucleus and dorsal motor nucleus of the vagus, lability of blood pressure, tachycardia, and impairment of the baroreflex response to PE were observed. Data obtained from this rabbit were omitted from the analysis. Another rabbit, in which a large part of the area postrema remained, was also excluded from the analysis. Accordingly, nine of 11 lesioned rabbits were included in the analysis.

Discussion

In the present study, we investigated the effect of area postrema ablation on the pressor and HR responses to Ang II and on the reflex HR responses to increases or decreases in arterial pressure produced by infusions of PE or NP. Our major findings were as follows: 1) Ablation of the area postrema resulted in attenuation of the pressor and potentiation of the HR responses to intravenous infusions and bolus injections of Ang II. 2) In intact rabbits, background infusion of Ang II displaced the cardiac baroreflex response to a higher pressure level (reset-

<table>
<thead>
<tr>
<th>Group</th>
<th>Background infusion</th>
<th>Slope (beats/min/mm Hg)</th>
<th>Setpoint (mm Hg)</th>
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<tr>
<td>Intact (n=8)</td>
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<td>-0.95±0.02</td>
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<td></td>
<td>Ang II</td>
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<td>79±7</td>
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<tr>
<td></td>
<td>PE</td>
<td>-3.17±0.39</td>
<td>77±4</td>
<td>-0.93±0.02</td>
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Values are mean±SEM. Setpoint, value of mean arterial pressure at the heart rate before background infusion calculated from the regression line for each rabbit; SAL, during saline infusion; Ang II, during angiotensin II infusion; PE, during phenylephrine infusion; r, correlation coefficient. The slopes of the baroreflex were not different during background infusion of any agent. The setpoint was significantly increased during angiotensin II infusion in intact rabbits, and this increase was almost completely abolished in the area postrema–lesioned rabbits.

*p<0.01 compared with saline infusion.

*p<0.05 compared with phenylephrine infusion.

<p>| Table 3. Baroreflex Response to Nitroprusside Infusions During Saline, Angiotensin II, or Phenylephrine Infusion in Intact and Area Postrema–Lesioned Rabbits |
|-----------------|-----------------|--------------|-----|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>Background infusion</th>
<th>Slope (beats/min/mm Hg)</th>
<th>Setpoint (mm Hg)</th>
<th>r</th>
</tr>
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<tr>
<td>Intact (n=8)</td>
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<td>Ang II</td>
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<tr>
<td></td>
<td>PE</td>
<td>-3.38±0.28</td>
<td>79±3</td>
<td>-0.97±0.01</td>
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</tbody>
</table>

Values are mean±SEM. Setpoint, value of mean arterial pressure at the heart rate before background infusion calculated from the regression line for each rabbit; SAL, during saline infusion; Ang II, during angiotensin II infusion; PE, during phenylephrine infusion; r, correlation coefficient. The slopes of the baroreflex were not different during background infusion of any agent. The setpoint was significantly increased during angiotensin II infusion in intact rabbits, and this increase was almost completely abolished in the lesioned rabbits.

*p<0.01 compared with saline infusion.

*p<0.05 compared with phenylephrine infusion.
MEAN ARTERIAL PRESSURE (mmHg)

MEAN ARTERIAL PRESSURE (mmHg)

FIGURE 7. Graph showing reflex changes in heart rate during increases in mean arterial pressure with phenylephrine in intact rabbits (n=8). Responses were determined during infusion of saline, angiotensin II, or phenylephrine. Top panel: Responses with background saline (○) or angiotensin II (×). Bottom panel: Responses with background saline (○) or phenylephrine (×). Values are mean ± SEM. Background angiotensin II shifted the regression line to a higher pressure level; background phenylephrine had no effect on the baroreflex.

The resetting of the baroreflex response with background infusion of Ang II in intact rabbits was almost completely abolished by ablation of the area postrema. These findings suggest that the impairment of reflex bradycardia during Ang II–induced elevation in blood pressure results from resetting of the baroreflex by Ang II and that this action is mediated by the area postrema.

There have been reports that ablation of the area postrema causes transient hypophagia and persistent polyuria and natriuresis. If these changes occurred in the present study, there may have been increases in endogenous Ang II and/or change in fluid and electrolyte balance, which in turn could have changed baroreflex function and complicated the interpretation of our results. Furthermore, although it has not been a consistent finding, there have been reports that resting blood pressure and HR are changed by ablation of the area postrema in rats and in dogs. This change in blood pressure per se could also reset the baroreflex. For the same reasons, we measured basal blood pressure, HR, and variables that would reflect changes in the renin-angiotensin system and fluid and electrolyte balance. We found no differences in these variables between the intact and area postrema–lesioned rabbits. These results suggest that the changes in cardiovascular responses to Ang II observed in the area postrema–lesioned rabbits were not due to indirect effects caused by changes in basal blood pressure, the renin-angiotensin system, or fluid and electrolyte balance.
but were the direct result of destruction of the area postrema.

We also determined the lability of blood pressure and HR by measuring their coefficients of variation and found that these values were not different between intact and lesioned rabbits. It is known that destruction of the nucleus tractus solitarius, which is adjacent to the area postrema, increases lability of blood pressure with or without an overall increase in blood pressure and decreases baroreflex sensitivity to PE infusion.\textsuperscript{23,24} The area postrema-lesioned rabbits included in the present study did not display any of these effects. This provides functional evidence that the area postrema lesion did not cause any significant damage to the region of the nucleus tractus solitarius that modulates cardiovascular regulation. In addition, histological analysis showed that lesions were mainly restricted to the area postrema and that this region was the only area that was consistently destroyed in the rabbits included in the present analysis.

The present observation that the pressor response to intravenous Ang II is attenuated by area postrema ablation is in good agreement with the results of a previous investigation in dogs\textsuperscript{22} and indicates that, in addition to its peripheral pressor action, Ang II exerts a central pressor effect that appears to be mediated by the area postrema. We also found that, despite the attenuated pressor response, the decrease in HR produced by intravenous Ang II was potentiated in the area postrema-lesioned rabbits. Accordingly, the regression line for the relation

\[ \text{MEAN ARTERIAL PRESSURE (mmHg)} \]
between HR and MAP during Ang II infusion closely approached the line for PE infusions.

On the other hand, in similar studies in rats, Fink and associates observed that ablation of the area postrema did not affect the pressor or HR response to short-term Ang II infusions. It has been proposed that the area postrema in rats is not involved in the centrally mediated pressor effect of Ang II, but the difference between the present results and those of Fink et al may not be due to a species difference, because accumulating evidence indicates that even in rats the area postrema does play an important role in cardiovascular regulation. Furthermore, Mangiapanet al observed that the slope of the relation between HR and MAP during Ang II infusion in rats was significantly increased after ablation of the area postrema, as was observed in the present study.

We assessed pressor and HR responses by two methods, namely, intravenous infusions and bolus injections. The results obtained with both methods were essentially the same, although the decrease in HR in response to bolus injections of Ang II in the lesioned rabbits tended to be potentiated more than the response to infusions. Konner et al reported that the reflex decrease in HR at the beginning of an acute rise in blood pressure is primarily mediated by increased vagal efferent activity, while cardiac sympathetic nerves also participate in the response at the steady state. In addition, there have been reports that the impairment of bradycardia during the pressor response to Ang II is mainly mediated by inhibition of the increase in cardiac vagal efferent activity. Taken together with these reports, our results might be interpreted as indicating that Ang II produces vagal inhibition by an action on the area postrema. However, further studies are needed to clarify the contribution of vagal and/or sympathetic nerves to the central action of Ang II on HR mediated by the area postrema.

There is controversy whether circulating Ang II attenuates the sensitivity of the cardiac baroreflex. Lee and Lumbers reported that in the presence of Ang II in sheep the baroreflex sensitivity to increases in blood pressure with PE was blunted. Guo and Abboud observed the same results with PE in rabbits but noted no change in the response to decreases in blood pressure with NP. Garner et al reported that in baboons the sensitivity to both PE and nitroglycerin was reduced. On the other hand, Brooks and Reid and Matsumura et al reported that Ang II did not alter the baroreflex sensitivity to decreases or increases in blood pressure. Goldstein et al and Cowley et al also showed that Ang II did not significantly affect baroreflex sensitivity, using an isolated carotid sinus technique. The results of investigations of the effects of endogenous Ang II on the baroreflex sensitivity using angiotensin I converting enzyme inhibitors have also been inconsistent. Some investigators reported increases in sensitivity; others observed no change or even decreases. Although the reasons for these discrepancies are not known, some of them may result from differences in the dose of Ang II, methods of baroreceptor stimulation, use of anesthetics, methods of analysis, and species differences. In contrast to the inconsistency of results regarding baroreflex sensitivity, several studies of the effect of exogenous and endogenous Ang II on the baroreflex control of HR have demonstrated resetting of the reflex to a higher pressure level. The present results are in good agreement with the results of a recent study in this laboratory and show that in conscious rabbits, background infusion of Ang II shifts the baroreflex response to a higher pressure level without changing its sensitivity. A major finding in the present study is that this resetting of the baroreflex by Ang II is markedly attenuated by ablation of the area postrema, suggesting that the resetting is mediated via this circumventricular organ.

The present results indicate that the action of Ang II to reset the baroreflex control of HR to a higher pressure level is responsible for the impairment of reflex bradycardia during Ang II–induced elevation.

**Figure 9.** Photomicrograph of the dorsal medulla at the level of the obex in a representative sham (top panel) and area postrema–lesioned (bottom panel) rabbit. The lesion extended throughout the area postrema and caused minimal damage to surrounding structures.
in arterial pressure. Thus, Ang II exerts two opposing effects on HR: one to load the baroreceptors and reflexly decrease HR; the other to reset the baroreflex control of HR to a higher pressure so that HR is maintained at a higher level for the prevailing arterial pressure. With lower doses of Ang II, these two effects apparently offset each other, and there is little or no change in HR. However, when higher doses of Ang II are infused, the effect of baroreceptor loading predominates, and HR decreases. Nevertheless, even with high doses of Ang II, the decrease in heart rate is substantially less than that produced by PE. This difference in the HR response to Ang II and PE was markedly reduced after ablation of the area postrema, indicating that this structure plays an important role in the impairment of reflex bradycardia by Ang II.

The present study shows the importance of the area postrema in the blood pressure and HR responses to Ang II, but this does not necessarily mean that the area postrema is the only central site of action of Ang II on blood pressure and HR. In addition to the possibility that the lesion might have damaged surrounding structures, which is always inevitable with this kind of ablation study, we cannot determine whether the effects observed in the present study were mediated by receptors located in the area postrema or resulted from disruption of connections between the area postrema and some other receptive site. Nevertheless, it is known that the area postrema lacks a blood–brain barrier and contains Ang II receptors. Blood pressure increases during intravertebral infusion of Ang II in doses that are ineffective when given intravenously, and ablation of the area postrema abolishes this response. Recently, it was demonstrated that intravenous Ang II specifically alters neuronal activity in the area postrema. It is also known that neurons of the area postrema project to structures such as the nucleus tractus solitarius, the dorsal motor nucleus of the vagus, the ventrolateral medulla, and the lateral parabrachial nuclei, all of which have important roles in cardiovascular regulation. Therefore, it is reasonable to propose that circulating Ang II binds to Ang II receptors in the area postrema and alters neuronal activity in the area postrema and associated structures, resulting in changes in blood pressure and HR.

In conclusion, the present results demonstrate that ablation of the area postrema results in attenuated pressor and potentiated HR responses to Ang II. The results also suggest that the impairment of bradycardia during Ang II–induced elevation in arterial pressure is caused by resetting of the cardiac baroreflex and that this effect is also mediated by the area postrema. These results provide further evidence that the area postrema plays an important role in centrally mediated cardiovascular responses to Ang II.

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