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What Sets the Long-Term Level of Renal Sympathetic Nerve Activity

A Role for Angiotensin II and Baroreflexes?

Carolyn J. Barrett, Rohit Ramchandra, Sarah-Jane Guild, Aneela Lala, David M. Budgett, Simon C. Malpas

Abstract—Increasing evidence suggests elevated sympathetic outflow may be important in the genesis of hypertension. It is thought that peripheral angiotensin II, in addition to its pressor actions, may act centrally to increase sympathetic nerve activity (SNA). Without direct long-term recordings of SNA, testing the involvement of neural mechanisms in angiotensin II–induced increases in arterial pressure is difficult. Using a novel telemetry-based implantable amplifier, we made continuous recordings of renal SNA (RSNA) before, during, and after 1 week of angiotensin II–based hypertension in rabbits living in their home cages. Angiotensin II infusion (50 ng · kg⁻¹ · min⁻¹) caused a sustained increase in arterial pressure (18±3 mm Hg). There was a sustained decrease in RSNA from 18±2 normalized units (n.u.) before angiotensin II to 8±2 n.u. on day 2 and 9±2 n.u. on day 7 of the angiotensin II infusion (P<0.01) before recovering to 17±2 n.u. after ceasing angiotensin II. Analysis of the baroreflex response showed that although angiotensin II–induced hypertension led to resetting of the relationship between mean arterial pressure (MAP) and heart rate, there was no evidence of resetting of the MAP-RSNA relationship. We propose that the lack of resetting of the MAP-RSNA curve, with the resting point lying near the lower plateau, suggests the sustained decrease in RSNA during angiotensin II is baroreflex mediated. These results suggest that baroreflex control of RSNA and thus renal function is likely to play a significant role in the control of arterial pressure not only in the short term but also in the long term. (Circ Res. 2003;92:1330-1336.)

Key Words: rabbits ■ telemetry ■ angiotensin II ■ baroreflex ■ sympathetic nerve activity
is substantial evidence that angiotensin II contributes to regulation of arterial pressure via actions on several brain sites. Angiotensin II receptor–binding sites are found in discrete areas of the forebrain and brain stem that are involved in the control of RSNA.\textsuperscript{20–22} Studies using ganglionic blockade as an index of sympathetic nerve activity have shown that the blood pressure decrease in response to ganglionic blockade is greater during angiotensin II–induced hypertension than before, suggesting sympathetic activity is elevated during angiotensin II–induced hypertension.\textsuperscript{17} In contrast, measurements of plasma catecholamine levels suggest sympathetic activity is decreased during angiotensin II hypertension.\textsuperscript{23}

The aim of our study was to determine the factors that determine the long-term level of sympathetic activity. We hypothesized that angiotensin II, in addition to its direct vasoconstrictive action, increases blood pressure chronically via activation of the sympathetic nervous system. Using a novel telemetry-based implantable amplifier, we have been able to make continuous recordings of RSNA for up to 50 days in rabbits. We report the changes in mean RSNA during 1 week of angiotensin II–based hypertension.

**Materials and Methods**

**Animal Preparation**

Experiments were conducted in 7 New Zealand White rabbits with initial weights of 2.4 to 3.5 kg and were approved by the University of Auckland Animal Ethics Committee. The rabbits were housed individually in cages (height, 40 cm; width, 35 cm; and depth, 55 cm) with a telemetry blood pressure receiver (model RLA2000, Data Sciences International) positioned on the ceiling inside each cage. The rabbits were fed daily (100 g standard rabbit pellets, supplemented with hay, carrot, and apple) at 9:00 AM, and water was available ad libitum. The room was kept at a constant temperature (18°C) and dark-light cycle (lights on from 6:00 AM to 6:00 PM).

Anesthesia was induced using intravenous administration of propofol (Diprivan, 10 mg/kg) followed by intubation and then maintenance with halothane. Arterial pressure was recorded throughout the study using a radiotelemetry transmitter (model PA-D70, Data Sciences). This was implanted via an abdominal incision, and the area around the iliac bifurcation was exposed. The cannula of the transmitter was inserted into a branch of the left iliac artery and advanced so that the tip of the catheter lay in the abdominal aorta, 3 cm above the iliac bifurcation but well below the renal artery. The cannula was tied into position, the body of the transmitter was placed in the abdominal cavity, and the incision was closed. During the same surgery, a telemetry-based implantable nerve amplifier (model 2003/01, Telemetry Research, Uniservices Limited) was also inserted via a flank incision with the electrodes coiled around the left renal nerve, and the electrode and nerve were coated in a silicone elastomer (Kwik-sil, World Precision Instruments). To avoid movement artifacts affecting the RSNA signal, the implantable amplifier was placed as close to the nerve site as possible. After each surgery, the rabbits were treated prophylactically with an antibiotic (enrofloxacin, Baytril, Bayer; 5 mg/kg SC daily for 5 days) and analgesic (ketoprofen, Ketofen, Rhone Merieux; 2 mg/kg SC daily for 3 days). As soon as the rabbits regained consciousness, they were returned to their home cages. A heating pad was placed in the cage for 24 hours after the surgery.

**Data Collection**

The rabbits were allowed to recover from surgery for 1 week before data collection began. RSNA, blood pressure, heart rate, and locomotor activity were then continuously recorded in rabbits before, during, and after a 1-week period of angiotensin II infusion. Thus after 7 days of baseline data collection, a mini-osmotic pump was implanted (model 2ML1, Alzet) to continuously infuse angiotensin II (Auspep) at a rate of 50 ng·kg\textsuperscript{-1}·min\textsuperscript{-1}. This osmotic pump was inserted under the same anesthesia protocol as above with the infusion catheter inserted into the right jugular vein. After 7 days of angiotensin II infusion, the rabbit was removed from its cage, and under brief propofol anesthesia, the mini-osmotic pump was removed. Data were collected continuously for the 7 days before the angiotensin II infusion, the 7 days throughout the angiotensin II infusion, and the 7 days after removal of the mini-osmotic pump. Baroreflex responses were determined in response to infusions of phenylephrine and sodium nitroprusside on four occasions in each rabbit: before the insertion of the mini-pump, on day 2 and 7 of the infusion, and then 3 days after removing the mini-pump. This involved placing the rabbits in a small box within their home cage to allow intravenous lines to be inserted into the medial ear vein so that the vasoactive drugs could be administered. Sodium nitroprusside (1 mg·mL\textsuperscript{-1}) was slowly infused to reduce arterial pressure down to ~40 mm Hg at a rate of 0.5 to 1 mm Hg/sec; all variables were then allowed to return to baseline before phenylephrine (1 mg·mL\textsuperscript{-1}) was infused to raise arterial pressure at a rate of 0.5 to 1 mm Hg/sec to between 120 and 140 mm Hg (when sympathetic nerve activity was silent). These sequences were repeated at least three times on each occasion. In addition, on each occasion, the heart rate and sympathetic responses to nasopharyngeal stimulation were assessed by exposing the rabbit to cigarette smoke dispensed by a 50-mL syringe for 2 seconds.

Arterial pressure was recorded via telemetry, and heart rate was derived from the arterial pulse. Presence of locomotor activity was detected using an infrared detector (Optex RX-40QZ). This detector registered all animal movement, including locomotor, grooming, and head movements associated with feeding. All data were sampled at 500 Hz using an analog-to-digital data acquisition card (AT-MIO64E-3, National Instruments). All subsequent data collection and analysis were performed using a data acquisition program (Universal Acquisition and Analysis version 11; Telemetry Research, Uniservices Limited). Unless otherwise stated, data presented represent the mean of the 2-second averages of heart rate and blood pressure for each 7-day treatment period, namely baseline, angiotensin II, and recovery.

**Statistical Analysis**

All RSNA values were normalized to the maximum 2 seconds of RSNA evoked by the 50 mL of smoke, with the response to the smoke nominated as 100 normalized units (n.u.). All data were then analyzed using an ANOVA, with Bonferroni post hoc pairwise comparisons where appropriate. The tests were considered significant if $P<0.05$. Data are shown as mean±SEM.

**Results**

**Changes in Baseline Variables During Angiotensin II Infusion**

Infusion of angiotensin II for 7 days caused a significant increase in arterial pressure beginning within 1 hour of osmotic pump implantation. The mean increase reached 18±3 mm Hg above control levels ($P<0.01$) after 45 minutes and thereafter remained steady throughout the entire infusion period (Figures 1 and 2). Removing the osmotic pump and thus stopping the angiotensin II infusion led to a rapid return of arterial pressure to preangiotensin II levels again within the hour. The angiotensin II infusion did cause a small decrease in heart rate (from 236±9 bpm before the angiotensin II infusion to 219±11 bpm on day 2, $P<0.05$, data being the mean over the 24-hour period), but this was no longer significant by the seventh day of the infusion. Locomotor activity was unchanged during the angiotensin II infusion. A
RSNA was decreased in all 7 rabbits during the angiotensin II infusion. In the example shown in Figure 1, RSNA is clearly diminished during the angiotensin II, although distinct bursts were still evident. On ceasing angiotensin II, RSNA abruptly returned to preangiotensin II levels within 1 hour. Importantly, bursts of RSNA were still clearly evident, with no change in baseline noise up until day 30 to 50 in most animals. One rabbit was excluded from the 24-hour calculation of the means because of movement artifacts on the data.

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For the group of 6 rabbits, RSNA was decreased from 18\pm2 n.u. before angiotensin II to 8\pm2 n.u. during the angiotensin II, although distinct bursts were still evident. On ceasing angiotensin II, RSNA abruptly returned to preangiotensin II levels within 1 hour. Importantly, bursts of RSNA were still clearly evident, with no change in baseline noise up until day 30 to 50 in most animals. One rabbit was excluded from the 24-hour calculation of the means because of movement artifacts on the data.

In contrast, the baroreflex relationship between heart rate (HR) and MAP showed no evidence of a decrease in range or gain (Table) but rather showed a rightward resetting during the angiotensin II infusion (Figure 3). This is illustrated by the increase in the BP_{50} observed during angiotensin II infusion, with the BP_{50} increasing from 84\pm2 mm Hg before angiotensin II to 97\pm2 mm Hg on day 7 of the angiotensin II infusion, indicating a 13-mm Hg rightward shift of the curve (P<0.05, n=7). In addition, the resting points remained near the steepest point of the curve throughout, reflecting that heart rate did not alter with the angiotensin II infusion.

**Discussion**

Our results provide direct evidence that angiotensin II-induced hypertension results in a sustained decrease in RSNA. Furthermore, analysis of the baroreflex response showed that although angiotensin II-induced hypertension led to resetting of the MAP-HR relationship, there was no evidence of resetting of the MAP-RSNA relationship. We propose the lack of resetting of the MAP-RSNA curve, with the shift in the resting point to be lying near the lower plateau, suggesting the sustained decrease in RSNA during angiotensin II could be baroreflex mediated. These results have an important implication for the long-term control of RSNA, namely that arterial baroreflexes are a significant chronic mediator of the level of RSNA.
Our suggestion that the arterial baroreflex is an important modulator of RSNA in the long term contrasts the prevailing dogma that arterial baroreflexes are only important in the short-term control of arterial pressure. Three general lines of evidence are cited when suggesting that baroreflex control is unimportant in long-term control: arterial baroreflexes have been shown to rapidly reset with sustained increases in arterial pressure, baroreceptor denervation while increasing the short term variability does not alter the mean arterial pressure, and the overall gain of the baroreflex is thought to be insufficient to explain the long-term consistency of arterial pressure. However, recent experiments have begun to challenge this dogma and suggest that baroreflex resetting does not necessarily occur in conscious freely moving animals. In an elegant experiment by Thrasher, aortic and carotid baroreceptors in one sinus were denervated chronically, whereas the baroreceptors in the other carotid sinus were left functional. The innervated receptors were then chronically unloaded by placement of a ligature on the common carotid proximal to the sinus. Arterial pressure consequently increased an average of 22 mm Hg above control and remained elevated for the 7 days of carotid ligation. Removal of the ligature to restore normal flow through the carotid resulted in normalization of arterial pressure. Although sympathetic activity was not directly recorded, a significant increase in heart rate and plasma renin activity, accompanied by an initial decrease in sodium excretion that returned to control levels during the period of baroreceptor unloading and associated increased renal perfusion pressure, suggested RSNA was indeed increased. Additional supporting evidence is found in the studies of Lohmeier et al, who reported responses to 5 days of angiotensin II infusion in dogs using a split-bladder preparation combined with denervation of one kidney. During angiotensin II infusion, sodium excretion from the innervated kidney significantly increased compared with the denervated kidney, indicating a decrease in RSNA. It was proposed that this decrease in RSNA was being mediated by baroreflexes, because after cardiopulmonary and sinoaortic denervation, the sodium excretion from the innervated kidney actually decreased compared with the excretion from the denervated kidney during angiotensin II infusion. Additional experiments by the same group have confirmed that the elevated sodium excretion from the innervated kidney in response to the angiotensin II infusion is maintained for at least 10 days.

Figure 2. Mean responses from 6 rabbits to a continuous infusion of angiotensin II for 7 days. Data are presented from the mean value for each 20-minute period of record. The error bars represent the SEM for each day of recording. The angiotensin II infusion began at time 0 and ceased after 7 days, as indicated by the vertical dotted lines.
The baroreceptor reflex is an important mechanism for regulating arterial pressure. It involves the detection of changes in blood pressure by baroreceptors and the subsequent modulation of sympathetic nerve activity (RSNA) to restore arterial pressure to a normal range. The reflex pathway is capable of suppressing sympathetic activity under conditions of chronic hypertension. The baroreflex pathway is capable of suppressing sympathetic activity observed after 5 days of angiotensin infusion suggests that the ventrolateral medulla (CVLM) plays an important role in the regulation of arterial pressure. Together with our present results, these experiments suggest that arterial baroreflex control of RSNA, and thus renal function, plays an important role in the regulation of arterial pressure over periods of days to weeks.

In support of the contention that the baroreflex may account for the sympathoinhibition during the angiotensin II hypertension are our findings that the MAP-RSNA relationship over time. Numerous studies, including the present one, show resetting of the MAP-HR relationship. However, our results suggest that baroreflex control of RSNA does not reset for at least 7 days after a maintained increase in arterial pressure. The difference in resetting of the HR and RSNA components of the baroreflex may be a consequence of either the vagal component to the control of heart rate or alternatively a consequence of the differential nature of the central control of sympathetic activity. The myelinated and nonmyelinated baroreceptor afferents show differences in their distribution of projections within the NTS, and reports of differences in baroreflex control of sympathetic activity to specific vascular beds are widespread. It is perhaps not surprising then that just because one branch of the efferent baroreflex pathway may reset, this does not necessarily mean all reflex pathways will be reset, with evidence that reflex resetting of RSNA may occur at a slower rate than resetting of the heart rate.

Previously, one of the major limitations in determining the role of RSNA in the long-term control of arterial pressure has been because of the technical difficulties in obtaining long-term nerve recordings. As a consequence of the lack of direct nerve recordings, alternate methods of assessing sympathetic nerve activity have been used; this has led to conflicting opinions in the literature with regard to the effect of chronic changes in angiotensin II on sympathetic activity. For example, measurement of plasma catecholamine levels suggest sympathetic activity does not change in response to angiotensin II infusions, yet ganglionic blockade indicates sympathetic activity increases with angiotensin. The present study found a consistent decrease in RSNA in every rabbit during angiotensin II. We have great confidence in the validity of this result, because the RSNA was recorded directly using a telemetry system, which allowed for the first time continuous nerve recordings in the same rabbit over the entire experimental period.

We observed a profound decrease in the range of the MAP-RSNA relationship throughout the entire period of angiotensin II infusion. This finding is similar to that described by Sanderford and Bishop after only 5 minutes of intravenous infusions of angiotensin II in conscious rabbits. They described a dose-dependent attenuation of the maximum RSNA achievable at low arterial pressures. This effect of angiotensin on the MAP-RSNA relationship seemed to be attributable to a central action of angiotensin as opposed to a direct pressure effect, because when the pressor effects of angiotensin were prevented using sodium nitroprusside, angiotensin II still caused a similar decrease in the range of the MAP-RSNA curve. It has been proposed that the attenuation of the baroreflex control of RSNA in long-term hypertension is additionally illustrated under conditions of increased salt intake, with increasing dietary salt intake resulting in hypertension in sinoaortic denervated but not baroreceptor-intact rats.

An important distinction needs to be presented with regard to resetting of baroreflexes; previous studies have in general concentrated on the arterial pressure to heart rate baroreflex relationship because of the inability to record the MAP-RSNA relationship over time. Numerous studies, including the present one, show resetting of the MAP-HR relationship. However, our results suggest that baroreflex control of RSNA does not reset for at least 7 days after a maintained increase in arterial pressure. The difference in resetting of the HR and RSNA components of the baroreflex may be a consequence of either the vagal component to the control of heart rate or alternatively a consequence of the differential nature of the central control of sympathetic activity. The myelinated and nonmyelinated baroreceptor afferents show differences in their distribution of projections within the NTS, and reports of differences in baroreflex control of sympathetic activity to specific vascular beds are widespread. It is perhaps not surprising then that just because one branch of the efferent baroreflex pathway may reset, this does not necessarily mean all reflex pathways will be reset, with evidence that reflex resetting of RSNA may occur at a slower rate than resetting of the heart rate.

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including the CVLM. The model of long-term recording of action in the brain, solitary tract and the rostral and caudal regions of the postrema, makes these organs prime targets for circulating angiotensin II.

Postrema, makes these organs prime targets for circulating angiotensin II. One complicating feature of our experiments is in differentiating between the direct and indirect effect of angiotensin II. Acutely, angiotensin II increases arterial pressure primarily through actions on the vasculature. However, dense angiotensin receptor binding is found in the nucleus of the solitary tract and the rostral and caudal regions of the ventrolateral medulla and microinjection of angiotensin II or antagonists into these regions alters sympathetic nerve activity. All of these sites are critical nuclei involved in baroreflex pathway and suggest that angiotensin II could exert its action on sympathetic nerve activity via modulation of the baroreflex pathway. Although the vasoconstrictor properties of angiotensin II may be involved in the baroreflex-mediated decrease in RSNA observed in the present study, it is also possible that angiotensin II may be acting centrally to directly modulate neural pathways. Most studies suggest that central administration of angiotensin II results in sympathoexcitation and angiotensin II can also cause sympathoinhibition when administered to specific regions of the brain, including the CVLM. The model of long-term recording of sympathetic nerve activity and arterial pressure confers a great advantage in discriminating the components because of the vascular and neural mechanisms. Clearly, additional experiments are required to explore the importance of an intact baroreflex, the contribution of central actions, and peripheral actions of angiotensin II to additionally understand the interaction between angiotensin II and sympathetic activity.

Chronic hypertension is undoubtedly complicated not only by neural-hormonal responses but also remodeling of the vessel walls and cardiac hypertrophy. In a two-kidney one-clip model of hypertension, comparing RSNA between animals, it has been shown that whereas the range of the MAP-RSNA relationship was depressed at 3 weeks, by 6 weeks the range of the response had been restored. The authors suggest that at 6 weeks structural changes are maximum whereas the hormonal changes are lessened. These results again support the suggestion that it is angiotensin acting directly that causes the attenuation of the maximum RSNA at low arterial pressures. It is perhaps reasonable to also speculate that in the presence of arterial wall remodeling, baroreflexes will be reset as a consequence of the altered pressure-strain relationship at the level of the arterial baroreceptor sensory endings themselves. In a previous series of experiments, we have found no significant increase in heart or kidney weight, suggesting an absence of hypertrophy in response to angiotensin II–induced hypertension in our rabbit model after a period of 7 weeks. This result is quite different from that reported in a different strain of rabbits. We predict that resetting of the MAP-RSNA may be observed only in the presence of remodeling of the heart and vessel walls.

In summary, using a novel technique that allows chronic monitoring of RSNA in rabbits, we have shown that angiotensin II–induced hypertension causes a sustained decrease in RSNA for at least 7 days, consistent with baroreflex-mediated sympathoinhibition. Although it has previously been suggested that angiotensin II is sympathoexcitatory, our results suggest that when administered

<table>
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<th>Variable</th>
<th>Before</th>
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<th>Day 7</th>
<th>Recovery</th>
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<td>Mean arterial pressure, mm Hg</td>
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<td>105±4†</td>
<td>103±5†</td>
<td>80±3</td>
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<td>6±2†</td>
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<td>Lower plateau, n.u.</td>
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<td>6±3</td>
<td>5±5</td>
<td>3±1</td>
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<td>Range, n.u.</td>
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<td>23±5*</td>
<td>24±5*</td>
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<td>−0.20±0.03</td>
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<td>BP50, mm Hg</td>
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<td>84±2</td>
<td>97±2*</td>
<td>96±6*</td>
<td>76±4</td>
</tr>
<tr>
<td>Upper plateau curvature, bpm/mm Hg</td>
<td>−0.13±0.01</td>
<td>−0.10±0.02</td>
<td>−0.10±0.02</td>
<td>−0.12±0.03</td>
</tr>
<tr>
<td>Average gain, bpm/mm Hg</td>
<td>−4.87±0.47</td>
<td>−3.86±0.70</td>
<td>−3.67±0.42</td>
<td>−4.16±0.62</td>
</tr>
</tbody>
</table>

Data are mean±SEM. †P<0.05; ‡P<0.01, where data are compared with before angiotensin II infusion. Note the resting variables are taken at the time of determining baroreflexes.
intravenously, it is baroreflex-mediated sympathoinhibition that predominates. Our finding that the RSNA-MAP relationship did not reset within the 7-day period of sustained hypertension supports our conclusion that the baroreflexes do continue to influence RSNA during sustained changes in arterial pressure. These results suggest that baroreflex control of RSNA and thus renal function is likely to play a significant role in the control of arterial pressure not only in the short term but also over periods of days to weeks. We thus propose that the idea that arterial baroreflexes are unimportant in the long-term control of arterial pressure requires revision.

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References