What Sets the Long-Term Level of Renal Sympathetic Nerve Activity : A Role for Angiotensin II and Baroreflexes?

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

A Role for Angiotensin II and Baroreflexes?

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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

Several previous studies indicate that the sympathetic nervous system plays a critical role in the development of hypertension. In young or borderline hypertensive subjects, it is clear that plasma catecholamines are elevated[1–3] and muscle sympathetic activity is increased.[4,5] Importantly, it seems that rather than generalized overactivity of the sympathetic nervous system occurring, it is specifically increased renal sympathetic nerve activity (RSNA), resulting in diminished renal function, that is important. In young borderline hypertensive patients, noradrenaline spillover from the kidney is particularly elevated.[6,7] Animal models have identified that the onset of hypertension may be delayed or the magnitude of the arterial pressure elevation may be reduced by chronic renal denervation.[8–12] Other studies have used long-term infusions of norepinephrine directly into the renal artery to mimic increased RSNA and observed the retention of sodium and water and sustained increases in arterial pressure.[13–15] These results have been interpreted to suggest that an integral relationship exists between functional sympathetic outflow to the kidneys and the development of hypertension.

Although much progress has been made in recent years on the central nervous system pathways involved in regulating sympathetic activity and its changes during different stimuli and pharmacological treatments, it has also been recognized that a serious shortfall exists in translating this knowledge into understanding its relevance for the long-term control of blood pressure. One difficulty in resolving this mechanism is because of the inability to make direct long-term recordings of sympathetic activity. All previous approaches either infer changes in sympathetic activity from changes in the control of heart rate, ganglionic blockade, measurement of plasma catecholamine levels, or sodium excretion.[16–19] Each of these approaches has major limitations; in particular, they do not allow sympathetic activity to be measured to specific organs. Furthermore, such indirect methods of assessment give little information of changes in sympathetic activity over time, because they do not generally allow continuous recording.

Direct long-term recordings of RSNA could potentially resolve several long-standing debates over how hormonal systems interact with sympathetic activity. One such example is in the role of angiotensin II in chronically regulating RSNA levels. Acutely, angiotensin II increases arterial pressure primarily through actions on the vasculature. However, there

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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.[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.[17] In contrast, measurements of plasma catecholamine levels suggest sympathetic activity does not change,[16] whereas renal norepinephrine spillover levels suggest sympathetic activity is decreased during angiotensin II hypertension.[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 via 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 $\cdot$ kg^{-1} $\cdot$ min^{-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 $\cdot$ mL^{-1}) was slowly infused to reduce arterial pressure down to $\approx$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 $\cdot$ mL^{-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 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$\pm$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$\pm$3 mm Hg above control levels ($P<0.01$) after 45 minutes and thereafter remained steady throughout the entire infusion period (Figures 1 and 2). Removing the osmotic pump and thus stopping the angiotensin II infusion led to a rapid return of arterial pressure to preangiotensin II levels again within the hour. The angiotensin II infusion did cause a small decrease in heart rate (from 236$\pm$9 bpm before the angiotensin infusion to 219$\pm$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

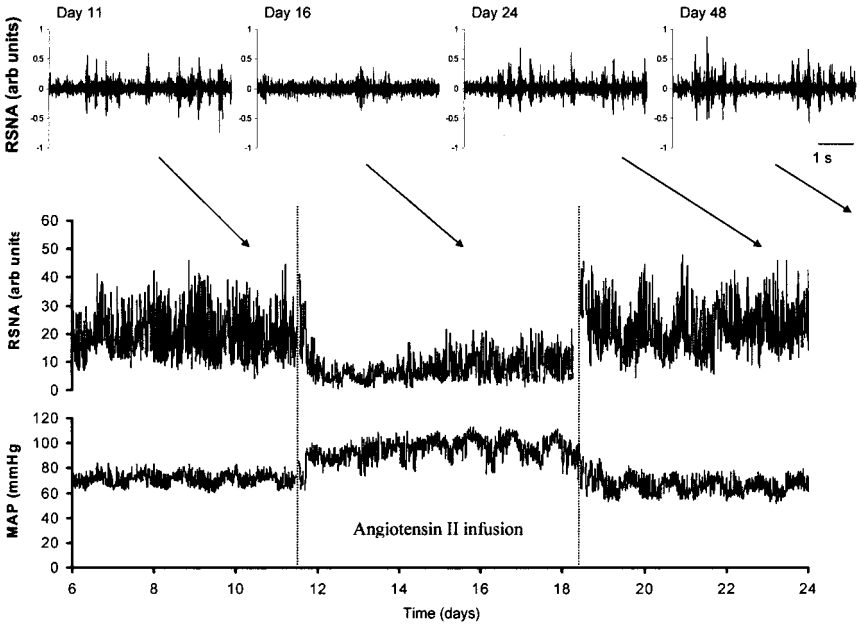

Figure 1. Original recording from one rabbit showing arterial pressure and RSNA responses to 7 days of continuous angiotensin II (50 ng · kg^{-1} · min^{-1}). The top panels display 5 seconds of the neurogram recorded on 4 different days. Baseline levels of noise were stable throughout the experimental period. In the bottom panels, the integrated renal sympathetic nerve activity and mean arterial pressure recorded over 18 days are displayed. The vertical dotted lines indicate the beginning and end of the angiotensin II infusion period. RSNA is displayed as arbitrary units.

circadian variation was most evident in heart rate and to a lesser extent in other variables (Figure 2). This variation was associated with feeding at 9:00 AM each day and was unaffected by angiotensin II.

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. For the group of 6 rabbits, RSNA was decreased from 18±2 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, all values representing the mean for the 24-hour period. Although the mean RSNA levels reduced considerably during angiotensin II, the response to the nasopharyngeal stimulus (smoke) remained consistent within each rabbit, with the maximum nerve activity reached not varying on the 4 different days it was assessed (the mean RSNA response to the smoke stimuli was 79±15 arbitrary units [au] before angiotensin, 79±22 on day 2 and 78±25 on day 7 of the angiotensin II infusion, and 78±22 au during the recovery).

Changes in Arterial Baroreflexes During Angiotensin II Infusion

On examining the baroreflex relationship between the mean arterial pressure (MAP) and RSNA (Figure 3), there was an obvious decrease in the range of the reflex during the angiotensin II infusion (from 38±6 n.u. before angiotensin II to 23±5 n.u. on day 2, Table, $P<0.05$, n=7). This reduction in range was also evident at day 7 of angiotensin II. Significantly, before the angiotensin II infusion, the resting point of the baroreflex curve lay near the steepest point of the MAP-RSNA curve; however, during the angiotensin II infusion, the resting point lay close to the lower plateau. Thus, producing an increase in arterial pressure from this point using the rapid phenylephrine infusion did not result in any additional decrease in nerve activity. The MAP at half the reflex range (BP_{50}) was not altered during the angiotensin II infusion; in other words, the overall curve was not shifted to the left or right. The gain of the curve was also unaffected despite the decrease in range. On ceasing angiotensin II, all baroreflex parameters had returned to control values when measured 2 days after stopping angiotensin II.

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±2 mm Hg before angiotensin II to 97±2 mm Hg on day 2 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.

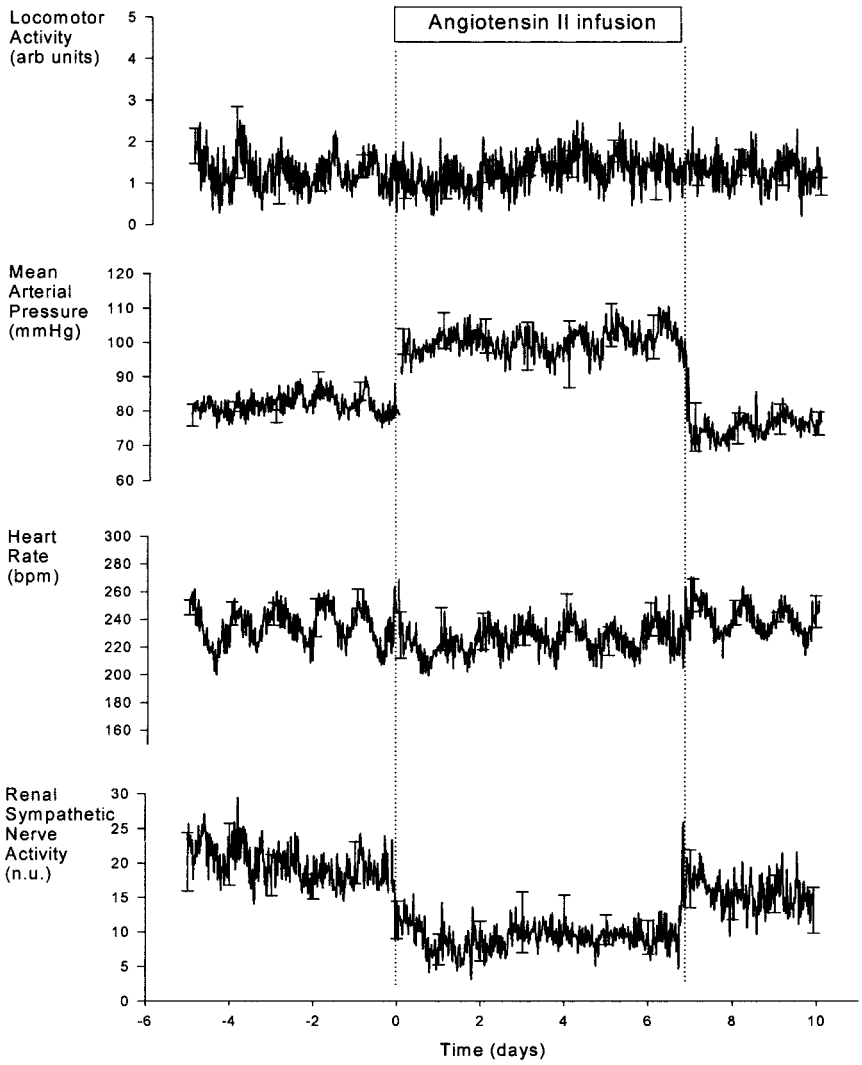

Figure 2. Mean responses from 6 rabbits to a continuous infusion of angiotensin II for 7 days. Data are presented from the mean value for each 20-minute period of record. The error bars represent the SEM for each day of recording. The angiotensin II infusion began at time 0 and ceased after 7 days, as indicated by the vertical dotted lines.

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.[24] 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,[25] baroreceptor denervation while increasing the short term variability does not alter the mean arterial pressure,[26] and the overall gain of the baroreflex is thought to be insufficient to explain the long-term consistency of arterial pressure.[24] 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,[27] 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,[19] 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.[28]

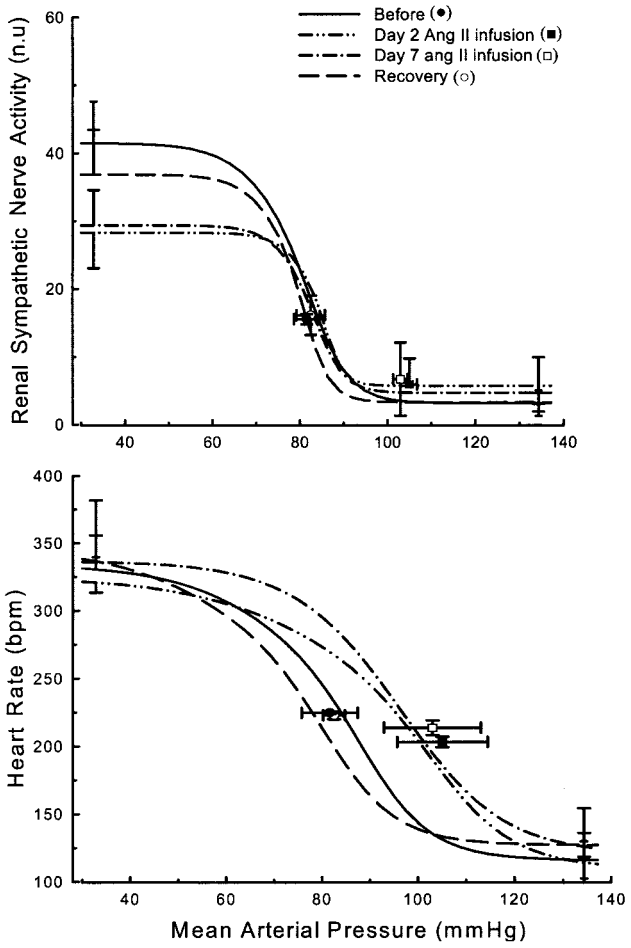

Figure 3. Mean baroreflex curves (n=7) relating the MAP-RSNA relationship (top) and the relationship between MAP and heart rate (bottom). Solid line indicates the control response before commencing the angiotensin II infusion. Dashed line with two dots is after 2 days of angiotensin II, and dashed line with one dot is after 7 days of angiotensin II. Dashed line shows data obtained after ceasing angiotensin II. Symbols represent the resting point of the curve with the respective SEMs. ●, Resting point on the day before; ■, day 2; □, day 7; and ○, 3 days after completion of the angiotensin II infusion.

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 did not reset, with the arterial pressure at half the reflex range (BP_{50}) not altering during the 7 days of angiotensin infusion. In addition, previously, intravenous administration of angiotensin II has been found to cause sustained activation of central neurons involved in the baroreflex,[29] with activation of neurons in the nucleus tractus solitarius (NTS) and caudal ventrolateral medulla (CVLM). That such an expression was observed after 5 days of angiotensin infusion suggests that the baroreflex pathway is capable of suppressing sympathetic nerve activity under conditions of chronic hypertension. The importance of baroreflex control of RSNA in long-term regulation of arterial pressure 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.[30,31]

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,[32] and reports of differences in baroreflex control of sympathetic activity to specific vascular beds are widespread.[33,34] 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.[35]

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,[16] yet ganglionic blockade indicates sympathetic activity increases with angiotensin.[17] 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[36,37] 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.[37] It has been proposed that the attenua-

Baroreflex Parameter Values Obtained Before and After 2 and 7 Days of Angiotensin

Variable	Before	Day 2	Day 7	Recovery
Mean arterial pressure, mm Hg	84±3	105±4†	103±5†	80±3
Renal sympathetic nerve activity, n.u.	16±3	6±2†	7±2†	16±3
Heart rate, bpm	225±6	203±9	214±10	222±2
Renal sympathetic nerve activity parameters				
Lower plateau, n.u.	3±2	6±3	5±5	3±1
Range, n.u.	38±6	23±5*	24±5*	34±6
Lower plateau curvature, n.u./mm Hg	−0.15±0.01	−0.25±0.06	−0.23±0.05	−0.20±0.03
BP_{50}, mm Hg	80±4	85±5	83±7	80±3
Upper plateau curvature, n.u./mm Hg	−0.21±0.03	−0.43±0.09*	−0.30±0.07	−0.31±0.07
Average gain, n.u./mm Hg	−1.53±0.30	−1.41±0.30	−1.63±0.55	−1.82±0.55
Heart rate parameters				
Lower plateau, bpm	116±14	110±17	120±28	127±9
Range, bpm	219±9	216±7	216±14	221±19
Lower plateau curvature, bpm/mm Hg	−0.08±0.01	−0.06±0.01	−0.09±0.03	−0.07±0.01
BP_{50}, mm Hg	84±2	97±2*	96±6*	76±4
Upper plateau curvature, bpm/mm Hg	−0.13±0.01	−0.10±0.02	−0.10±0.02	−0.12±0.03
Average gain, bpm/mm Hg	−4.87±0.47	−3.86±0.70	−3.67±0.42	−4.16±0.62

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.

tion of the maximum RSNA during infusions of angiotensin II involves the area postrema, because in area postrema lesioned rabbits, angiotensin II has no effect on the MAP-RSNA relationship.[36] The lack of a blood-brain barrier in the region of the circumventricular organs, such as the area 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,[20–22] 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 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,[38–40] and angiotensin II can also cause sympathoinhibition when administered to specific regions of the brain, including the CVLM.[41] 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.[35] 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.[42] This result is quite different from that reported in a different strain of rabbits.[43] 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

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.

Acknowledgments

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References

1. Goldstein DS, Lake CR, Chernow B, Ziegler MG, Coleman MD, Taylor AA, Mitchell JR, Kopin IJ, Keiser HR. Age-dependence of hypertensive-normotensive differences in plasma norepinephrine. *Hypertension*. 1983; 5:100–104.
2. Goldstein DS. Plasma catecholamines and essential hypertension: an analytical review. *Hypertension*. 1983;5:86–99.
3. Goldstein DS. Plasma norepinephrine in essential hypertension: a study of the studies. *Hypertension*. 1981;3:48–52.
4. Anderson EA, Sinkey CA, Lawton WJ, Mark AL. Elevated sympathetic nerve activity in borderline hypertensive humans: evidence from direct intraneural recordings. *Hypertension*. 1989;14:177–183.
5. Floras JS, Hara K. Sympathoneural and haemodynamic characteristics of young subjects with mild essential hypertension. *J Hypertens*. 1993;11: 647–655.
6. Esler M, Jennings G, Lambert G. Noradrenaline release and the pathophysiology of primary human hypertension. *Am J Hypertens.* 1989;2: 140S–146S.
7. Esler M, Lambert G, Jennings G. Increased regional sympathetic nervous activity in human hypertension: causes and consequences. *J Hypertens*. 1990;8:S53–S57.
8. Kline RL, Kelton PM, Mercer PF. Effect of renal denervation on the development of hypertension in spontaneously hypertensive rats. *Can J Physiol Pharmacol*. 1978;56:818–822.
9. Kline RL, Denton KM, Anderson WP. Effect of renal denervation on the development of cellophane-wrap hypertension in rabbits. *Clin Exp Hypertens*. 1986;8:1327–1342.
10. Nagaoka A, Kakihana M. Effects of renal sympathectomy on sodium and water excretion in stroke-prone spontaneously hypertensive rats. *Jpn J Pharmacol*. 1982;32:591–597.
11. Vari RC, Freeman RH, Davis JO, Sweet WD. Role of renal nerves in rats with low-sodium, one-kidney hypertension. *Am J Physiol*. 1986;250: H189–H194.
12. Vari RC, Zinn S, Verburg KM, Freeman RH. Renal nerves and the pathogenesis of angiotensin-induced hypertension. *Hypertension*. 1987; 9:345–349.
13. Plato CF, Osborn JL. Chronic renal neuroadrenergic hypertension is associated with increased renal norepinephrine sensitivity and volume contraction. *Hypertension*. 1996;28:1034–1040.
14. Cowley AW, Lohmeier TE. Changes in renal vascular sensitivity and arterial pressure associated with sodium intake during long-term intrarenal norepinephrine infusion in dogs. *Hypertension*. 1979;1: 549–558.
15. Reinhart GA, Lohmeier TE, Hord CE. Hypertension induced by chronic renal adrenergic stimulation is angiotensin dependent. *Hypertension*. 1995;25:940–949.
16. Kline RL, Chow KY, Mercer PF. Does enhanced sympathetic tone contribute to angiotensin II hypertension in rats? *Eur J Pharmacol*. 1990; 184:109–118.
17. Li Q, Dale WE, Hasser EM, Blaine EH. Acute and chronic angiotensin hypertension: neural and nonneural components, time course, and dose dependency. *Am J Physiol*. 1996;271:R200–R207.
18. Lohmeier TE, Reinhart GA, Mizelle HL, Montani JP, Hester RL, Hord CE, Hildebrandt DA. Influence of the renal nerves on sodium excretion during progressive reductions in cardiac output. *Am J Physiol*. 1995;38: R678–R690.
19. Lohmeier TE, Lohmeier JR, Haque A, Hildebrandt DA. Baroreflexes prevent neurally induced sodium retention in angiotensin hypertension. *Am J Physiol*. 2000;279:R1437–R1448.
20. Allen AM, McKinley MJ, Oldfield BJ, Dampney RA, Mendelsohn FA. Angiotensin II receptor binding and the baroreflex pathway. *Clin Exp Hypertens.* 1988;10(suppl 1):63–78.
21. Allen AM, Paxinos G, McKinley MJ, Chai SY, Mendelsohn FA. Localization and characterization of angiotensin II receptor binding sites in the human basal ganglia, thalamus, midbrain pons, and cerebellum. *J Comp Neurol*. 1991;312:291–298.
22. Allen AM, MacGregor DP, McKinley MJ, Mendelsohn FA. Angiotensin II receptors in the human brain. *Regul Pept*. 1999;79:1–7.
23. Carroll RG, Lohmeier TE, Brown AJ. Chronic angiotensin II infusion decreases renal norepinephrine overflow in conscious dogs. *Hypertension*. 1984;6:675–681.
24. Cowley AW Jr. Long-term control of arterial blood pressure. *Physiol Rev*. 1992;72:231–300.
25. Krieger EM. Arterial baroreceptor resetting in hypertension. *Clin Exp Pharm Physiol*. 1989;15:3–17.
26. Cowley AW, Liard JF, Guyton AC. Role of baroreceptor reflex in daily control of arterial blood pressure and other variables in dogs. *Circ Res*. 1973;32:564–576.
27. Thrasher TN. Unloading arterial baroreceptors causes neurogenic hypertension. *Am J Physiol*. 2002;282:R1044–R1015.
28. Lohmeier TE, Lohmeier JR, Reckelhoff JF, Hildebrandt DA. Sustained influence of the renal nerves to attenuate sodium retention in angiotensin hypertension. *Am J Physiol*. 2001;281:R434–R380.
29. Lohmeier TE, Lohmeier JR, Warren S, May PJ, Cunningham JT. Sustained activation of the central baroreceptor pathway in angiotensin hypertension. *Hypertension*. 2002;39:550–556.
30. Osborn JW, Hornfeldt BJ. Arterial baroreceptor denervation impairs long-term regulation of arterial pressure during dietary salt loading. *Am J Physiol*. 1998;275:H1558–H1566.
31. Howe PR, Rogers PF, Minson JB. Influence of dietary sodium on blood pressure in baroreceptor-denervated rats. *J Hypertens*. 1985;3:457–460.
32. Dean C, Seagard JL. Mapping of carotid baroreceptor subtype projections to the nucleus tractus solitarius using c-fos immunohistochemistry. *Brain Res*. 1997;758:201–208.
33. Ninomiya I, Nisimaru N, Irisawa H. Sympathetic nerve activity to spleen, kidney, and heart in response to baroreceptor input. *Am J Physiol*. 1971; 221:1346–1351.
34. Drummond HA, Seagard JL. Acute baroreflex resetting: differential control of pressure and nerve activity. *Hypertension*. 1996;27:442–448.
35. Head GA, Burke SL. Renal and cardiac sympathetic baroreflexes in hypertensive rabbits. *Clin Exp Pharm Physiol*. 2001;28:972–975.
36. Sanderford MG, Bishop VS. Central mechanisms of acute ANG II modulation of arterial baroreflex control of renal sympathetic nerve activity. *Am J Physiol*. 2002;282:H1592–H1602.
37. Sanderford MG, Bishop VS. Angiotensin II acutely attenuates range of arterial baroreflex control of renal sympathetic nerve activity. *Am J Physiol*. 2000;279:1804–1812.
38. Hirooka Y, Potts PD, Dampney RA. Role of angiotensin II receptor subtypes in mediating the sympathoexcitatory effects of exogenous and endogenous angiotensin peptides in the rostral ventrolateral medulla of the rabbit. *Brain Res*. 1997;772:107–114.
39. Dorward PK, Rudd CD. Influence of the brain renin-angiotensin system on renal sympathetic and cardiac baroreflexes in conscious rabbits. *Am J Physiol*. 1991;260:H770–H778.
40. Saigusa T, Head GA. Renal sympathetic baroreflex effects of angiotensin II infusions into the rostral ventrolateral medulla of the rabbit. *Clin Exp Pharm Physiol*. 1993;20:351–354.
41. Saigusa T, Iriki M, Arita J. Brain angiotensin II tonically modulates sympathetic baroreflex in rabbit ventrolateral medulla. *Am J Physiol*. 1996;40:H1015–H1021.
42. Ramchandra R, Barrett CJ, Guild SJ, Malpas SC. Neural control of the renal vasculature in angiotensin II–induced hypertension. *Clin Exp Pharm Physiol*. 2002;29:867–872.
43. Malpas SC, Groom AS, Head GA. Baroreflex control of heart rate and cardiac hypertrophy in angiotensin II–induced hypertension in rabbits. *Hypertension*. 1997;29:1284–1290.