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Chronic Angiotensin II Infusion Causes Differential Responses in Regional Sympathetic Nerve Activity in Rats

Misa Yoshimoto, Kenju Miki, Gregory D. Fink, Andrew King, John W. Osborn

Abstract—Angiotensin II (AngII)–induced hypertension in experimental animals has been proposed to be attributed in part to activation of the sympathetic nervous system. This sympathetic activation appears to be accentuated in animals consuming a high-salt diet (AngII-salt hypertension). However, accurate quantification of sympathetic activity is difficult, and controversy remains. It is particularly important to ask which are the critical vascular beds targeted by increased sympathetic nerve activity (SNA) in AngII-salt hypertension. To address this issue, mean arterial pressure and renal SNA or lumbar SNA were continuously recorded during a 5-day control period, 11 days of AngII (150 ng/kg per minute, SC), and a 5-day recovery period in conscious rats on a high-salt (2% NaCl) diet. Although mean arterial pressure reached a new steady-state level of 30 to 35 mm Hg above control levels by the end of the AngII period, renal SNA decreased by 40% during the first 7 days of AngII and then returned toward control levels by day 10 of AngII. In contrast, lumbar SNA remained at control levels throughout the AngII period. In another experiment we measured hindlimb norepinephrine spillover in conscious rats on normal (0.4%) or high- (2.0%) salt diets before and during 14 days of AngII administration. AngII had no significant affect on hindlimb norepinephrine spillover in either group. We conclude that chronic AngII modulates renal and lumbar SNAs differentially in rats consuming a high-salt diet and that AngII-salt hypertension in the rat is not caused by increased SNA to the renal or hindlimb vascular beds. (*Hypertension*. 2010;55:644-651.)

Key Words: hypertension ■ renal nerve activity ■ lumbar nerve activity ■ norepinephrine spillover ■ sympathetic

Hypertension caused by chronic infusion of angiotensin II (AngII) in experimental animals is likely mediated, at least in part, by activation of the sympathetic nervous system. Sympathoexcitation by circulating AngII in experimental animals was first demonstrated over 3 decades ago[1]; however, the degree to which the sympathetic nervous system contributes to AngII-induced hypertension, relative to nonneural mechanisms, remains an area of active investigation with conflicting results. Chemical sympathectomy has been reported both to have no effect[2] and to totally block[3] hypertension during chronic AngII infusion in rats. Plasma norepinephrine (NE) concentration has been reported to be unchanged by chronic AngII infusion in 1 study[4] and increased in another.[5] Other methods of assessing sympathetic control of arterial pressure consistently indicate increased net neurogenic pressor activity during chronic AngII infusion. Ganglion blockade, adrenergic receptor blockade, and centrally acting sympatholytic drugs all cause a much larger fall in arterial pressure in AngII-infused animals than in normotensive controls.[6–10]

One explanation for the apparently conflicting results obtained in studies attempting to relate AngII and sympathetic nerve activity (SNA) is that the magnitude of the sympathoexcitatory actions of AngII seems to be strongly affected by the prevailing sodium chloride (salt) intake. For example, in 1 study, chronic infusion of AngII in rats did not increase plasma NE in rats on normal salt intake but did so in rats on high-salt intake.[5] We have also reported that AngII administration increases overall sympathetic activity in rats on a high-salt diet but not in rats on a normal-salt diet. This was established using 2 methods to assess "whole body" sympathetic activity, that is, whole body NE spillover[11] and ganglionic blockade.[12]

In contrast to whole body indicators of sympathetic outflow, indirect measures of organ-specific sympathetic activity in conscious animals have not generally supported the hypothesis that chronic AngII is sympathoexcitatory. Kline et al[6] found no change in NE turnover in the heart, kidney, gastrointestinal tract, or skeletal muscle of the rat in response to AngII. Two indirect measures of renal sympathetic activity, renal NE spillover[4] and the split bladder technique,[13] suggest that AngII infusion actually decreases SNA to the kidney in conscious dogs. However, all of these studies were conducted in animals on a normal salt intake.

Assessing sympathetic activity by direct measurement of sympathetic nerve discharge is difficult because of the challenge of maintaining neural recordings for long periods of time in conscious animals. Although SNA recordings generally can be maintained for a few days after electrode implantation, stress from surgery may affect basal nerve activity and responses to interventions. Moreover, comparison of SNA between animals is not possible, because the absolute level of multiunit nerve activity is determined by the quality of electrode contact with the nerve and the degree of tissue reaction at the implantation site. Furthermore, a universally accepted method for quantifying SNA has not been established.[14,15] With this caveat in mind, there is one report that splanchnic SNA is elevated in conscious rats after 14 days of AngII administration compared with vehicle-treated animals.[16] Interpretive limitations of between-animal comparisons of SNA can be circumvented by measuring SNA before, during, and after chronic AngII administration in the same animal; however, this is technically very difficult. One group has successfully made such measurements using continuous radiotelemetric recording of renal SNA in rabbits.[17,18] The results led to the same conclusion as earlier findings using indirect methods[4,13] that chronic AngII treatment decreases sympathetic activity to the renal vascular bed. It is important to note that all of the studies discussed above were conducted in animals on a normal-salt diet. Therefore, the sympathoexcitatory actions of AngII may not have been fully expressed.

The present experiments were conducted with 2 objectives in mind. The first was to use direct continuous recording of SNA in conscious rats to establish whether chronic administration of AngII increases sympathetic outflow in rats consuming a high-salt diet. The second objective was to determine whether the response of directly recorded SNA to AngII was uniformly expressed in different vascular beds. Arterial pressure and renal or lumbar SNA were continuously recorded during a 5-day control period, 11 days of AngII, and a 5-day recovery period in rats on a 2% NaCl diet. In another experiment, we measured hindlimb NE spillover in response to chronic AngII infusion in conscious rats on normal (0.4%) and high- (2.0%) salt diets.

Methods

Animals and Diets

Male Sprague-Dawley rats (Charles River, Wilmington, MA) ranging in weight from 250 to 350 g were used in all of the studies. On arrival, rats were placed on either a 0.4% (normal) or 2.0% (high) NaCl diet (Research Diets, Inc) for ≥1 week before instrumentation and remained on these diets for the duration of the protocol. All of the studies were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the University of Minnesota and the Michigan State University Institutional Animal Care and Use Committees.

Renal SNA and Lumbar SNA Responses to AngII or Vehicle Administration in Rats on a High-Salt Diet

Surgical Instrumentation

Rats were anesthetized (pentobarbital; 65 mg/kg IP) and prepared for placement of a recording electrode on either the renal or lumbar nerve. The construction of the bipolar stainless-steel electrode, as well as the method for implantation for long-term recording in conscious rats, has been described.[19–21] Briefly, the left renal nerve was approached retroperitoneally, whereas the left lumbar nerve was approached via a ventral midline laparotomy. The quality of the signal was monitored during surgery using a differential amplifier (MEG-1200, Nihon Kohden) output to an oscilloscope (model VC 6020, Hitachi) and speaker (model AM8, Grass Instruments). Once the best signal was obtained, as subjectively determined by the oscilloscope trace and auditory signal, the electrode was secured into place using a 2-component silicone rubber (604, Wacher-Chemie). The electrode cable was then tunneled to the scapular region. Then, a telemeter for continuous recording of arterial pressure and heart rate (HR; model TA11PA-C40, DSI International, Inc) was implanted as described previously.[22] Incisions were closed and the rats were allowed to recover on a heated pad. At that time, the leads of the electrode were attached to an 8-conductor pole electric swivel (ES8, Biotex). On recovery from anesthesia, the rats were transferred to our chronic monitoring laboratory and housed individually in custom-made Plexiglas cages inside a Faraday cage to minimize electric noise. The cages were constructed from 10-inch diameter Plexiglas cylinders 17 inches high. The floor of the cage was a stainless-steel grid, which was connected to the common ground. The electric swivel was mounted above the cage, and the telemetry receiver was placed behind it to continuously monitor arterial pressure and HR.

Data Acquisition and Analysis

SNA signals renal SNA (RSNA) or lumbar SNA (LSNA) were amplified by a differential amplifier (MK-2, Bioteck; gain×10 000 and bandwidth 150 to 2000 Hz). Part of this output was fed through a voltage integrator (AD-600G, Nihon Kohden) with a time constant of 0.1 seconds. Arterial pressure signals from the telemetry receiver were converted into an analog signal using a calibrated pressure output adapter (model R11-CPA, DSI International, Inc). The analog outputs for arterial pressure and differential amplifier as well as the voltage integrator, were sampled at 1000 Hz using a 14-bit A/D converter (NI-6221, National Instruments). The sampled data were either saved directly into a computer for offline analysis of the raw waveform or saved after parameter extraction for 24-hour continuous recordings. A custom computer interface for performing these tasks was written in LabView (National Instruments).

Parameters extracted from the sampled analog signal included the area under the integrated SNA curves, the background noise for the SNA recording, HR, and mean arterial pressure (MAP). The area under the integrated SNA curves was calculated every 1 second using LabView (National Instruments). The background noise level of the SNA signal was set to be the lowest value from a 1-section segment of the integrated SNA curve. The validity of this assumption was established by comparing this parameter during free running and after IV infusion of phenylephrine (10 μg) in the same rat. There were no differences in the values obtained during these 2 conditions, indicating that the lowest value from a 1-second segment of the integrated SNA was a good estimate of the background noise (unpublished observation). HR was estimated from the arterial pressure waveform. Ten-second averages for these values were stored on a hard disk through the duration of the study.

Experimental Protocol

All of the rats were acclimated to a 2.0% NaCl diet for 1 week before instrumentation. After a 1-week recovery period from surgery, baseline measurements of MAP, HR, and either RSNA or LSNA were taken. All of the variables were recorded continuously for 24 hours per day for the entire protocol. On the fifth day of control measurements, rats were briefly anesthetized with isoflurane, weighed, and then an osmotic minipump (ALZET model 2ML2, Durect Corp) filled with either AngII or saline vehicle was implanted. The concentration of AngII was adjusted to deliver an initial dose of 150 ng/kg per minute on the basis of body weight at the time of implantation. Rats were returned to their cage and monitored for 11 days of AngII or vehicle infusion. Then rats were again anesthe-
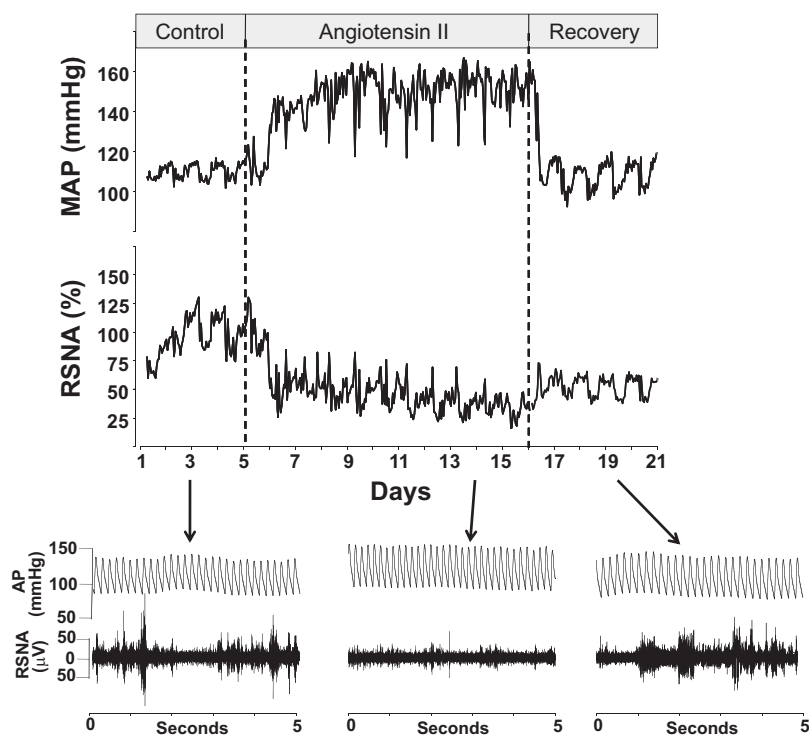
Figure 1. Representative data showing hourly values (top) for MAP and RSNA in a single rat before, during, and after AngII administration. Bottom shows 5 second traces for arterial pressure (AP) and RSNA on indicated days.

tized with isoflurane, the minipumps were removed, and the rats returned to their cage for 5 additional days of monitoring. Thus, beginning 7 days after surgery, the 21-day protocol consisted of 5 control days, 11 days of AngII or vehicle, and 5 days of recovery. To quantify the RSNA and LSNA responses to AngII or vehicle, the percentage changes in SNA were calculated by taking the mean of these values during the 5-day control period as 100%.

Hindlimb NE Spillover and Hemodynamic Responses to AngII in Rats on Normal and High-Salt Diets

Surgical Instrumentation

Because hindlimb NE spillover predominantly reflects sympathetic activity to skeletal muscle and should parallel direct measurement of lumbar SNA, we developed a technique to repeatedly assess regional NE spillover to the hindlimbs in rats receiving a chronic infusion of AngII. This required short-term infusion of ³H-NE into the jugular vein to achieve steady-state plasma concentrations, simultaneous sampling of arterial (terminal aorta) and venous (terminal vena cava) blood from the hindlimbs, and measurements of hindlimb blood flow (terminal aorta).

Under general anesthesia (2% isoflurane), silicone-tipped catheters were inserted into the terminal aorta via the left femoral artery and the terminal vena cava via the left femoral vein. Another silicone-tipped catheter was inserted into the right jugular vein and advanced 3 cm to the level of the right atrium, where it was secured in place. After a ventral midline laparotomy, the abdominal viscera were reflected and packed with saline-soaked gauze. The terminal aorta was isolated from the vena cava and surrounding tissue, and a 2-mm perivascular flow probe (2SB series, Transonic Systems, Inc) was placed on the isolated section of the aorta just proximal to the iliac bifurcation. The probe cable was passed through the abdominal wall and tunneled subcutaneously to exit the rat between the scapulae. The abdominal viscera were replaced, and the incision was closed. The free ends the catheters and the flow probe cable were tunneled subcutaneously to exit the rat between the scapulae into a stainless-steel spring attached to the rat by a loosely fitted rubber jacket (Instech Laboratories, Inc). The rats were then loosely tethered in individual plastic cages to allow continuous

access to the catheter and flow probe without handling or disturbing the animal.

Experimental Protocol

In this experiment, rats were acclimatized to a 2.0% NaCl (n=6) or 0.4% NaCl (n=4) diet and, 10 days after surgery, control measurements were made for 2 days and during 14 days of AngII, as described above. Hindlimb NE spillover and hemodynamic variables were measured on control day 2 and AngII infusion days 6, 10, and 14. Hindlimb flow was recorded for ≈60 minutes each day by connecting the flow probe to a dual channel flowmeter (T206, Transonic Systems, Inc) linked to a computerized data acquisition program (PowerLab). MAP was measured simultaneously by connecting the arterial catheter to a pressure transducer, which was linked to the computerized data acquisition program. Hindlimb resistance (HLR) was calculated from hindlimb blood flow (HLF) and MAP as follows: HLR=MAP/HLF.

Hindlimb vascular bed NE spillover was measured by applying the radioisotope dilution principle as described previously in our study of whole body NE spillover.[11] This requires short-term infusion of ³H-NE to achieve steady-state plasma concentrations, simultaneous sampling of arterial and venous blood from the hindlimbs, and hindlimb blood flow measurements. Levo-[ring-2,5,6-³H] NE (specific activity: 40 to 80 Ci/mmol; concentration: 1 mCi/mL; Perkin-Elmer) was infused into the jugular vein as described previously.[11] At the end of the 90-minute ³H-NE infusion period, a 1-mL arterial blood sample and 1-mL venous blood sample were obtained simultaneously from the aortic catheter and vena cava catheter. Hematocrit was measured in duplicate from the arterial blood sample, and NE and ³H-NE concentrations were determined as described previously.[11] Calculation of hindlimb NE spillover was made using the established methods for radioisotope dilution estimation of regional NE spillover, published by Eisenhofer.[23]

Statistical Analysis

Data were analyzed by 2-way ANOVA for repeated measures followed by the Holm-Sidak method for all post hoc comparisons (SigmaStat version 3.5, SigmaPlot). The responses of all of the variables to AngII were compared within groups by comparison to

the final day of the control period. A $P<0.05$ was considered to be statistically significant.

Results

RSNA and LSNA Responses to AngII or Vehicle Administration in Rats on a High-Salt Diet

Figure 1 illustrates the responses of MAP and RSNA to AngII administration in a single rat consuming a high-salt diet. Values represent 1-hour averages beginning 7 days after implantation of the electrode and telemeter. AngII increased MAP ≈40 mm Hg by the end of the infusion period, and MAP returned promptly to control levels during the recovery period. In this rat, RSNA decreased by ≈50% from control levels during the entire period of AngII administration, with a slight rebound during the recovery period. Five-second traces for both variables for days 3, 14 (AngII day 9), and 19 (recovery day 3) are also shown.

The mean responses of MAP, RSNA, and HR of rats on a high-salt diet to either AngII or vehicle are shown in Figure 2. AngII resulted in a steady-state increase in MAP of ≈35 mm Hg during the first 5 days of administration. During this same period, RSNA decreased by ≈40% from control levels. Although MAP remained stable for the duration of the AngII infusion period, RSNA tended to return to control levels such that it was not significantly lower compared with the control period or the vehicle group. HR decreased over the course of the protocol, but there was no difference between the AngII and vehicle groups at any time.

The responses of MAP and LSNA to AngII administration in a single rat consuming a high-salt diet are shown in Figure 3, and the group data for responses to AngII or vehicle are shown in Figure 4. Although the MAP and HR responses were similar to those observed in the RNSA protocol, LSNAs remained at control levels during the entire period of AngII administration.

Hindlimb NE Spillover and Hemodynamic Responses to AngII Administration in Rats on Normal and High-Salt Diets

MAP, hindlimb blood flow, and hindlimb NE spillover were measured on the second day of the control period and on the sixth, 10th, and 14th days of AngII administration in rats on a normal or high-salt diet (Figure 5). Before AngII administration, there were no differences between groups for MAP, hindlimb blood flow, hindlimb vascular resistance or hindlimb NE spillover. On the sixth day of AngII, MAP was significantly increased in rats on a high-salt diet but not in rats on a normal salt diet in contrast to hindlimb flow, which remained at control levels in both groups. Hindlimb vascular resistance was increased on day 6 of AngII in the high-salt group but did not change in rats on a normal salt diet. By the 10th and 14th days of AngII, MAP remained elevated in high-salt rats, but hindlimb blood flow and vascular resistance were not different between groups. Finally, although hindlimb NE spillover tended to decrease on day 6 of AngII and appeared to steadily increase above control levels on days 10 and 14 of AngII, it was not statistically different between groups during the control period or on days 6, 10, and 14 of AngII administration.
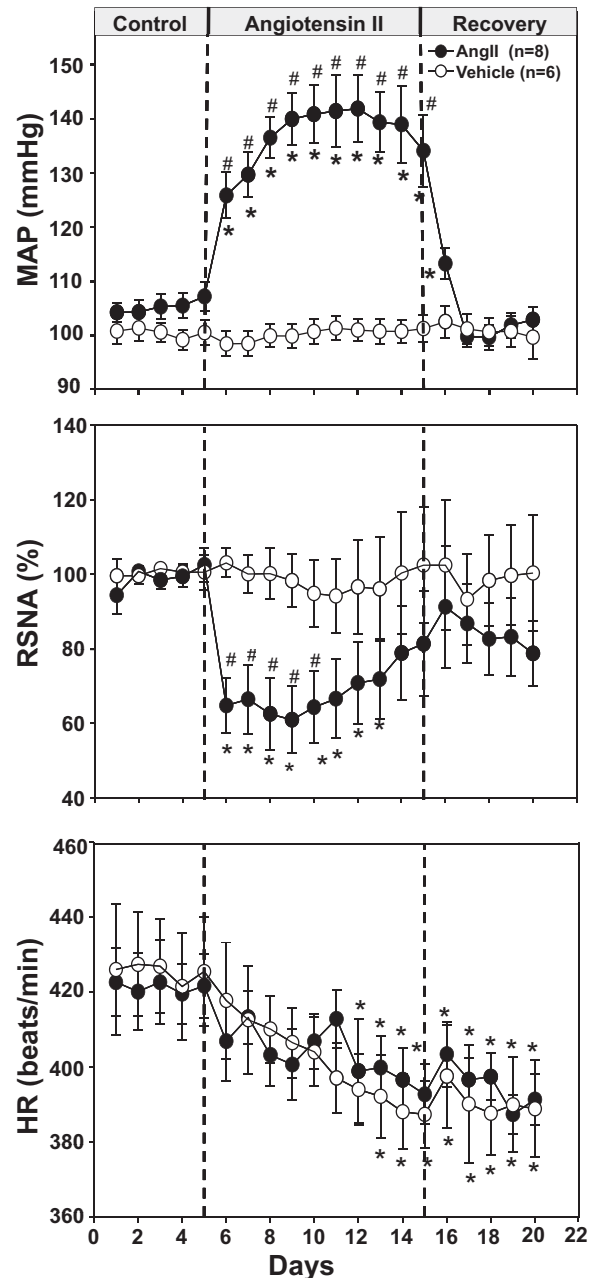

Figure 2. Group data shows the responses of MAP, RSNA, and HR to AngII or vehicle administration in rats consuming a high-salt diet. *$P<0.05$ vs control period (within group). #$P<0.05$ between groups.

Discussion

The hypothesis that AngII-induced hypertension is at least partly neurogenically mediated has been tested by numerous investigators over the last 40 years, and the topic has been reviewed extensively.[1,24,25] However, the contribution of dietary salt to the chronic sympathoexcitatory actions of circulating AngII has not consistently been considered and may partially explain the disparate results between some reports in which sympathetic activity is increased by AngII[6–10,12,26] and others where it is not.[2,13,17] In other words, the contribution of the sympathetic nervous system to "AngII-induced hypertension" may not be the same as
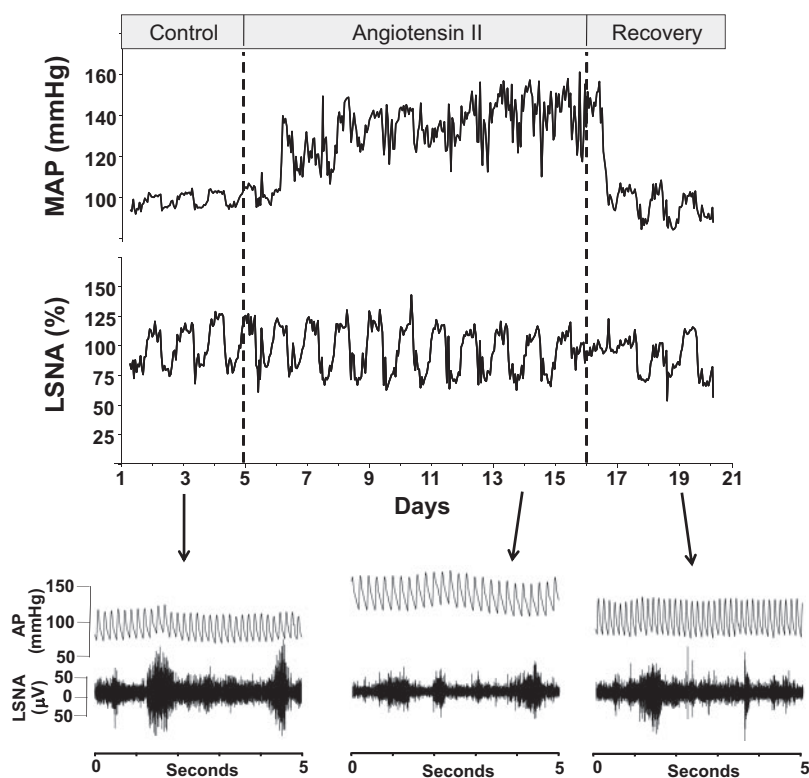
Figure 3. Representative data showing hourly values (top) for MAP and LSNA in a single rat before, during, and after AngII administration. Bottom shows 5 second traces for arterial pressure (AP) and LSNA on indicated days.

"AngII-salt–induced hypertension." Another issue is that the sympathoexcitatory actions of AngII may not be uniformly expressed to all of the organs, and, therefore, measurements of whole body SNA may not be consistent with "region-specific" SNA.

We reported recently that AngII-induced hypertension increases whole body sympathetic activity in rats consuming a high-salt (2.0% NaCl) diet but not rats on a normal salt (0.4% NaCl) diet. This was established by 2 indirect measures of sympathetic activity, the depressor response to ganglion blockade[12] and whole body NE spillover.[26] We have also reported that the arterial pressure response to AngII is salt sensitive in this model.[27] Taken together, these observations led us to the hypothesis that circulating AngII and dietary salt act synergistically to cause neurogenic hypertension.[28]

The present study was designed to test this hypothesis by direct continuous measurement of SNA in conscious rats over an ≈4-week period. Direct 24-hour-per-day recording of arterial pressure and either RSNA or LSNA was begun 1 week after instrumentation and continued during a 5-day control period, 11 days of AngII, and a 5-day recovery period in rats consuming a high-salt diet. To our knowledge, this is the first reported study in the rat in which long-term continuous recording of SNA has been successfully used to characterize the role of the sympathetic nervous system in the pathogenesis of any model of hypertension. It is also the first report, in any species, to use direct long-term recording methods to measure the response of 2 sympathetic nerves, in this case, renal and lumbar, in any model of hypertension.

Contrary to our hypothesis, renal SNA decreased by ≈40% during the first 7 days of AngII-salt hypertension and then returned to control levels by the end of the 11-day AngII period. This response contrasted with LSNA, which remained at control levels during the entire protocol. Failure of LSNA to change during AngII administration in rats on a high-salt diet was consistent with the observation that hindlimb NE spillover also did not change in rats on either normal or high-salt diets. We conclude that AngII-salt hypertension in the rat is not mediated by increased sympathetic activity to the renal or hindlimb vascular beds.

The response of RSNA measured in this study is nearly identical to that reported in the elegant studies of Barrett et al.[17] Intravenous infusion of AngII for 7 days in conscious rabbits resulted in an ≈60% fall in RSNA, as determined by continuous direct measurement by radiotelemetry. Similar to the present study, RSNA tended to return to control levels by the end of the AngII period despite a sustained increase in arterial pressure. A subsequent study from the same group showed that the fall in RSNA during AngII administration does not occur in sinoaortic denervated rabbits,[18] suggesting that this response is mediated by the arterial baroreceptor reflex. It is important to note, however, that the steady-state response of arterial pressure to AngII in that study was not affected by sinoaortic denervation, suggesting that baroreceptor reflex control of RSNA does not determine the steady-state response of arterial pressure to AngII administration. This is consistent with the seminal studies by Cowley et al[29] in which sinoaortic denervation did not affect the steady-state hypertensive response to AngII in conscious dogs.

The observation that RSNA is transiently decreased during AngII administration is consistent with our recent report that bilateral renal denervation does not prevent this model of hypertension.[30] Indeed, the initial response of arterial pres-
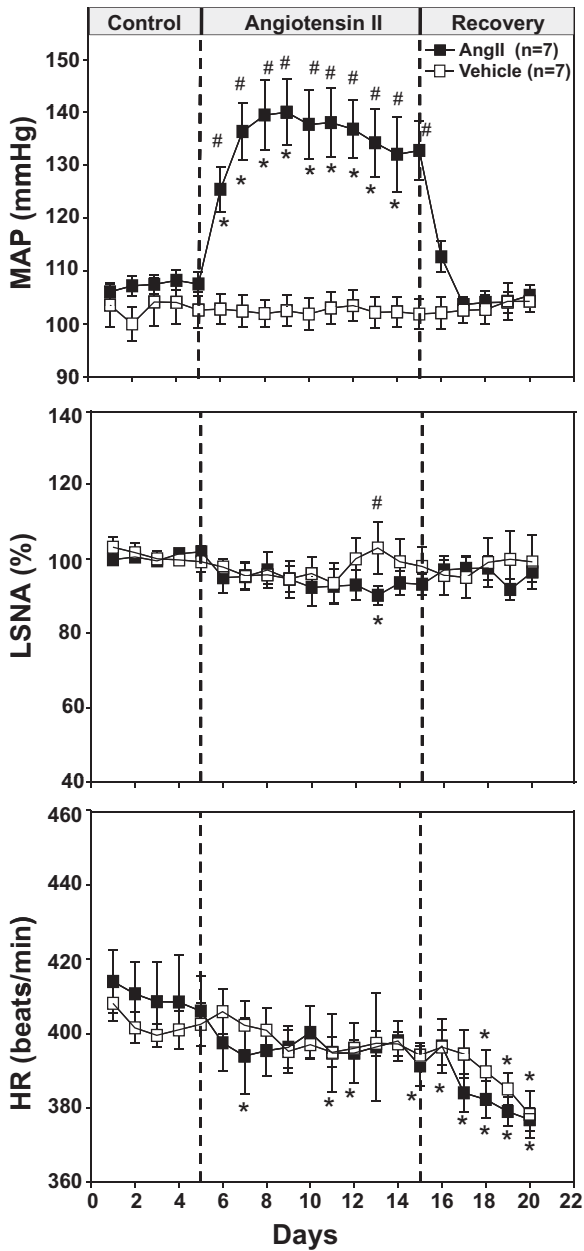
Figure 4. Group data showing the responses of MAP, LSNA, and HR to AngII or vehicle administration in rats consuming a high-salt diet. *$P<0.05$ vs control period (within group). #$P<0.05$ between groups.

Figure 5. Response of MAP (MA), hindlimb NE spillover, hindlimb flow, and hindlimb resistance to AngII in rats on a normal salt (0.4%) diet (▨) or high-salt (2.0%) diet (■). *$P<0.05$ vs control period (within group). #$P<0.05$ between groups.

sure to AngII was greater in renal denervated compared with sham control rats, suggesting that the decrease in RSNA observed in the present study may in fact act to buffer the initial hypertensive actions of AngII. The results of the present study, combined with the effects of renal denervation in this model,[30] and the studies of Barrett et al[18] strongly suggest that baroreceptor reflex control of RSNA buffers the initial pressor response to AngII. However, neither the arterial baroreceptor reflex nor RSNA determined the steady-state level of AngII-induced hypertension.

In contrast to RSNA, we observed that LSNA remained at control levels, and hindlimb NE spillover did not change during AngII administration. This finding is consistent with
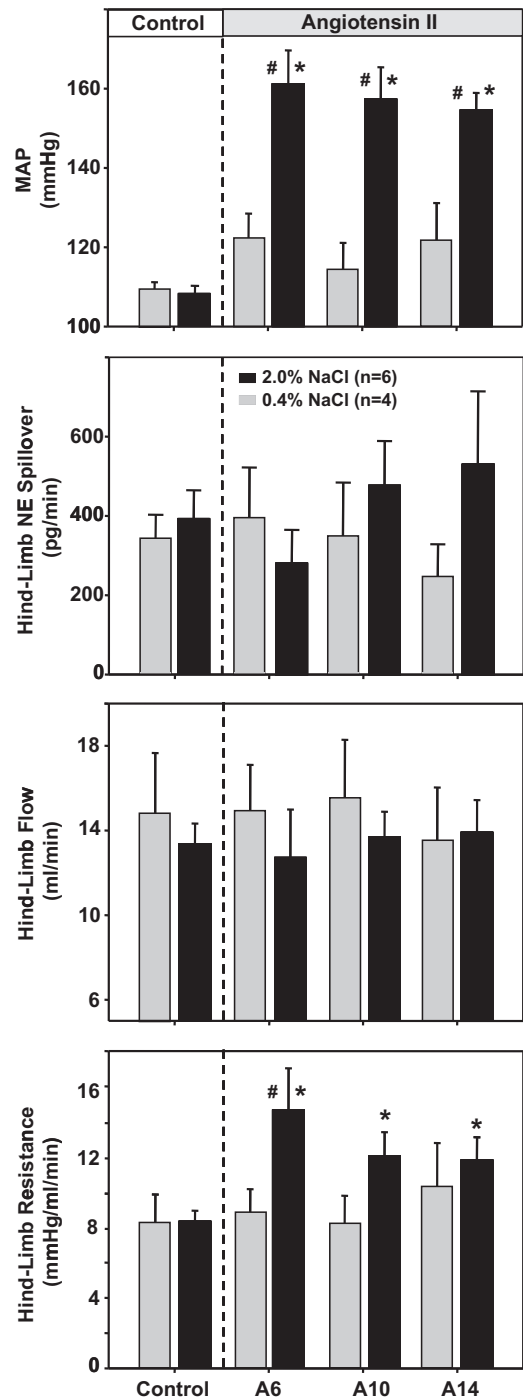
reports that acute infusion of AngII has no effect on LSNA (which largely targets the skeletal muscle vascular bed) in rats under normal conditions, but, when the buffering capacity of the baroreceptor reflex is prevented, a sympathoexcitatory response is observed.[31] Similarly, in humans, acute intravenous infusion of AngII increases muscle SNA as long as baroreflex-mediated sympathoinhibition is prevented.[32] These observations suggest that the direct effect of circulating

AngII to acutely increase SNA to skeletal muscle is effectively buffered by the arterial baroreceptor reflex.

Although we did not observe an increase in LSNA in AngII-salt rats, we cannot rule out skeletal muscle vasculature as a neural target in the pathogenesis of hypertension in this model. Maintenance of a normal level of SNA to this large vascular bed, in the face of elevated arterial pressure, may represent an "inappropriate" level of sympathetic nerve discharge under such conditions. In addition, it was reported recently that the pattern, but not the mean level, of LSNA, was altered in a manner that affected vascular resistance in the spontaneously hypertensive rat.[33] Additional studies (eg, lumbar sympathectomy) are required to more directly address this issue in AngII-salt hypertension.

What is the explanation for the combined results of the present study, in which AngII did not increase SNA to 2 vascular beds, and those of previous reports from our group,[12,26] which suggest that whole body sympathetic activity is increased by AngII administration in rats on a high-salt diet? On the basis of our previous studies using indirect indicators of SNA,[12,30,34] we hypothesize that the neurogenic component of AngII-salt hypertension is caused by increased sympathetic activity to the splanchnic vascular bed. This idea is consistent with an early study that reported that intravertebral artery infusion of AngII increased splanchnic SNA but decreased RSNA in the anesthetized dog.[35] This hypothesis is also supported by a study in which splanchnic SNA was directly recorded and found to be increased in conscious rats after chronic AngII.[7] However, the level of dietary salt intake was not reported, and these recordings were conducted within hours of electrode implantation and were essentially a "snapshot" taken at the steady-state phase of AngII-induced hypertension. The hypothesis that splanchnic SNA is increased in AngII-salt hypertension remains to be confirmed by continuous, direct SNA recordings in unstressed rats.

Finally, although the underlying mechanisms remain to be established, the concept that sympathetic outflow is controlled in a differential manner to maintain homeostasis in response to acute stimuli is now well established.[36] The present study is the first demonstration, using long-term continuous recording of SNA in conscious animals, that differential control of SNA also occurs in response to a chronic hypertensive stimulus. The mechanisms responsible for this differential pattern of SNA remain to be established. One recent study showed that an acute increase in circulating AngII has disparate effects on firing rates of barosensitive sympathetic premotor neurons in the brain stem.[37] Whether such a mechanism can account for differential changes in peripheral SNA during long-term elevations of plasma AngII remains to be established.

Limitations of the Study

Although direct recording of SNA in conscious animals provides, in some ways, a more detailed insight than indirect assessment of neural control of cardiovascular function, the ideal method for quantification of multiunit nerve activity over time has not been agreed on,[14,15] and, therefore, interpretation of such data is not straightforward. In the present study, measurements of SNA were not started until 7 days after electrode placement to ensure that the stress of surgery was not a confounding factor in our interpretation. SNA was normalized to the 5-day control period and time-control groups were included in the study. On the basis of the time-control groups and the inclusion of a recovery period after 11 days of continuous AngII infusion, we are confident that SNA was stable over the duration of the protocol. In addition, we have interpreted the results of our SNA measurements in combination with indirect assessment of SNA in the AngII-salt model. For example, our observations that RSNA only transiently decreases in AngII-salt rats are consistent with our observation that renal denervation does not alter the steady-state response of arterial pressure in this model.[30] In the present study, the observation that LSNA did not change is consistent with measurements of hindlimb NE spillover and hemodynamics in AngII-salt rats. We conclude that this consistency of the results using direct and indirect measures lessens the limitations of these approaches when used individually.

Perspectives

Elevated SNA as an etiologic factor in human essential hypertension was once controversial but is now widely accepted.[38,39] However, at the present time, our collective understanding of the mechanisms linking changes in SNA to the pathogenesis and maintenance of hypertension is fairly limited. The question of how the sympathetic nervous system is linked to hypertension is much more complex than "is SNA increased?" because it is unlikely that SNA is uniformly increased to all target organs. Although some forms of hypertension may be associated with 1 "sympathetic signature," for example, increased cardiac and RSNA, other forms may be characterized by an entirely different signature. The results of the present study suggest that, although the AngII-salt model in the rat is neurogenically driven,[26,30] increased SNA to the renal and skeletal muscle vascular beds is not critical for the pathogenesis of this form of hypertension. Our previous work on this model suggests that increased SNA to the splanchnic vascular bed is central to the development of hypertension in AngII-salt rats.[12,30] We propose that a clear understanding of the sympathetic signature associated with different forms of neurogenic hypertension is critical to the development of novel antihypertensive therapies designed to manipulate regional-specific SNA.[27]

Disclosures

None.

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