Nervous Kidney
Interaction Between Renal Sympathetic Nerves and the Renin-Angiotensin System in the Control of Renal Function

Gerald F. DiBona

Abstract—Increases in renal sympathetic nerve activity regulate the functions of the nephron, the vasculature, and the renin-containing juxtaglomerular granular cells. Because increased activity of the renin-angiotensin system can also influence nephron and vascular function, it is important to understand the interactions between the renal sympathetic nerves and the renin-angiotensin system in the control of renal function. These interactions can be intrarenal, for example, the direct (by specific innervation) and indirect (by angiotensin II) contributions of increased renal sympathetic nerve activity to the regulation of renal function. The effects of increased renal sympathetic nerve activity on renal function are attenuated when the activity of the renin-angiotensin system is suppressed or antagonized with ACE inhibitors or angiotensin II–type AT1-receptor antagonists. The effects of intrarenal administration of angiotensin II are attenuated after renal denervation. These interactions can also be extrarenal, for example, in the central nervous system, wherein renal sympathetic nerve activity and its arterial baroreflex control are modulated by changes in activity of the renin-angiotensin system. In addition to the circumventricular organs, whose permeable blood-brain barrier permits interactions with circulating angiotensin II, there are interactions at sites behind the blood-brain barrier that depend on the influence of local angiotensin II. The responses to central administration of angiotensin II–type AT1-receptor antagonists into the ventricular system or microinjected into the rostral ventrolateral medulla are modulated by changes in activity of the renin-angiotensin system produced by physiological changes in dietary sodium intake. Similar modulation is observed in pathophysiological models wherein activity of both the renin-angiotensin and sympathetic nervous systems is increased (eg, congestive heart failure). Thus, both renal and extrarenal sites of interaction between the renin-angiotensin system and renal sympathetic nerve activity are involved in influencing the neural control of renal function. (Hypertension. 2000;36:1083-1088.)

Key Words: renin-angiotensin system ■ renal nerves ■ rats

The renal sympathetic nerves innervate the tubules, the vessels, and the juxtaglomerular granular cells of the kidney.1,2 In this way, changes in renal sympathetic nerve activity (RSNA) directly influence the functions of these innervated renal effector units. Increases in RSNA decrease urinary sodium and water excretion by increasing renal tubular water and sodium reabsorption throughout the nephron, decrease renal blood flow and glomerular filtration rate by constricting the renal vasculature, and increase activity of the renin-angiotensin system (angiotensin [Ang]II) by stimulating renin release from juxtaglomerular granular cells. Ang II, through direct actions on Ang II–type AT1 receptors located on tubular and vascular segments, can also increase renal tubular sodium, chloride, and water reabsorption and constrict the renal vasculature.3

It is important to understand the interactions between the renal sympathetic nerves and the renin-angiotensin system in the control of renal function. These interactions can be intrarenal, for example, the direct (by specific innervation) and indirect (by angiotensin II) contributions of increased renal sympathetic nerve activity to the regulation of renal function. These interactions can also be extrarenal, for example, in the central nervous system, where RSNA and its arterial baroreflex control are modulated by changes in activity of the renin-angiotensin system.

Intrarenal Interactions
An important starting point was the observation that intrarenal generation of Ang II facilitated renal venous outflow of norepinephrine during renal sympathetic nerve stimulation, an effect that was blocked by an Ang II receptor antagonist.4 This suggested a presynaptic action of Ang II on renal sympathetic nerve terminals to enhance norepinephrine release.

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From Departments of Internal Medicine and Physiology, University of Iowa College of Medicine, and Veterans Administration Medical Center, Iowa City, Iowa.
Correspondence to Gerald F. DiBona, MD, Department of Internal Medicine, University of Iowa College of Medicine, 200 Hawkins Dr, Iowa City, IA 52242. E-mail gerald-dibona@uiowa.edu
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Subsequently, administration of the ACE inhibitor (ACEI) captopril or an Ang II receptor antagonist attenuated the antinatriuretic response to either low-frequency electrical or reflex renal sympathetic nerve stimulation in anesthetized rats consuming a normal dietary sodium intake. When renin-angiotensin system activity was stimulated by low dietary sodium intake, captopril completely eliminated the antinatriuretic response. When renin-angiotensin system activity was suppressed by high dietary sodium intake, the antinatriuretic responses were absent but could be restored to (but not greater than) normal by Ang II given in nonpressor doses that did not affect baseline renal hemodynamic and excretory function. These results suggested that a certain degree of renin-angiotensin system activity was necessary to optimize release of norepinephrine from renal sympathetic nerve terminals (presynaptic action). Another possible sequence was release of norepinephrine from renal sympathetic nerve terminals; the subsequently formed Ang II could have either a presynaptic action or a postsynaptic action on Ang II receptors located on tubules.

This was clarified by determining the effects of Ang II on rat proximal tubular chloride and water reabsorption before and after renal denervation. After renal denervation, the effect of Ang II to increase proximal tubular chloride and water reabsorption was decreased by \( \sim 75\% \). This suggests that only a very small portion of the Ang II effect, \( \sim 25\% \), can be ascribed to a direct action on Ang II receptors located on proximal tubules; the majority of the effect is dependent on intact renal innervation. This indicates that an important action of Ang II in the kidney is to facilitate the release of norepinephrine from renal sympathetic nerve terminals through a presynaptic site of action. Further studies showed that the Ang II presynaptic effect was tonic in that in kidneys with intact innervation, the Ang II AT1-receptor antagonist losartan decreased proximal tubular chloride and water reabsorption. The \( \alpha \)-adrenoceptor antagonist prazosin decreased proximal tubular chloride and water reabsorption to a similar extent as losartan, and the effects of losartan and prazosin were additive.

These presynaptic effects of Ang II are also found in the renal vasculature. Losartan dose-dependently decreased the renal vasoconstrictor response to renal sympathetic nerve stimulation but not to injection of norepinephrine.

These observations suggest that Ang II has an important presynaptic action on renal sympathetic nerve terminals on both renal tubular epithelial cells and vessels to facilitate the release of norepinephrine. This Ang II facilitation of norepinephrine release is manifested as a greater effect on renal tubular sodium reabsorption, urinary sodium excretion, and blood flow when Ang II is present in normal (but not increased) amounts and a lesser effect when Ang II is decreased or absent.

A physiological role for this facilitatory effect of Ang II on renal neuroeffector junctions has been more difficult to observe in conscious animals. Urinary sodium excretion was similar in the denervated and contralateral innervated kidney of conscious dogs subjected to modest dietary sodium restriction during control, ACEI and ACEI plus Ang II infusion periods. Although no interaction was seen between renal sympathetic nerve activity (ie, the innervated kidney) and Ang II, the similar urinary sodium excretion from innervated and denervated kidneys during the control period may suggest that basal RSNA was not increased by the degree of sodium restriction used to levels comparable to those seen during low-frequency renal sympathetic nerve stimulation, in which such an interaction has been observed. Similarly, when nonhypotensive hemorrhage was used to produce reflex increases in RSNA in conscious dogs, the associated antinatriuretic response was unaffected by renal arterial administration of either an ACEI (captopril) or losartan. As renal denervation blocked the antinatriuretic response to this maneuver, it may be taken that RSNA is increased in this setting. Whereas increases in RSNA that produce antinatriuresis will also increase renin secretion rate, it appears that in conscious conditions, this increase is not sufficient to markedly influence the magnitude of the antinatriuretic response.

Studies in this context involving reflex activation of RSNA in human subjects have not been explored. However, it is known that the antinatriuretic response to norepinephrine infusion is attenuated by treatment with an ACEI (enalapril). This suggests that the norepinephrine infusion, which slightly increased arterial pressure and decreased renal blood flow, was stimulating renin release and the derived Ang II was contributing to the antinatriuretic response. As the increase in arterial pressure would have reflexly decreased RSNA, the Ang II, rather than acting presynaptically to facilitate norepinephrine release from renal sympathetic nerve terminals, was more likely having an effect on tubular renal Ang II receptors to increase renal tubular sodium reabsorption.

Central Actions

There is substantial evidence that Ang II, in addition to its peripheral actions, contributes to the regulation of arterial pressure and intravascular volume through actions on several brain sites. The distribution of type 1 (AT1) and type 2 (AT2) Ang II receptors in the brain of several species, including humans, has been examined with the use of both nonpeptide AT1- and AT2-receptor antagonists in autoradiographic binding studies and in situ hybridization histochemistry for expression of AT1- and AT2-receptor mRNA. Ang II receptor binding sites are found within discrete areas of the forebrain and the brain stem, which are importantly involved in regulation of RSNA. This can occur through direct projections to sympathetic preganglionic neurons in the intermediolateral column (IML) of the spinal cord or by participation in major reflexes that modulate RSNA, for example, arising from peripheral arterial and cardiac baroreceptors, chemoreceptors, and somatic receptors.

A hormonal-sympathetic reflex model for the long-term control of arterial pressure has been proposed. A critical element of the model is that chronic increases in Ang II produce sustained increases in peripheral sympathetic nerve activity. Acute increases in circulating Ang II concentration affect sympathetic nervous system activity through actions on the brain, sympathetic ganglia, and sympathetic nerve end-
ings. However, how chronic increases in Ang II influence peripheral sympathetic nerve activity is unclear. Two general pathways may be considered, one that deals with the effects of circulating Ang II on the central nervous system and a second that deals with the central nervous system effects of Ang II originating within the central nervous system.

Circulating Ang II Increases Peripheral (Renal) Sympathetic Nerve Activity

As to the site of action of circulating Ang II within the central nervous system, there are a limited number of specialized central nervous system areas wherein the normal blood-brain barrier is lacking, thus enabling ready access to circulating Ang II. These are called circumventricular organs and consist (inter alia) of subfornical organ (SFO), organum vasculosum of the lamina terminalis, median eminence, and area postrema (AP). Of these, substantial evidence supports the importance of the SFO and AP as major sites of action of circulating Ang II in the central nervous system. Both sites contain Ang II–immunoreactive nerve terminals and predominant AT1-receptor mRNA and AT1-receptor binding sites. Projections from the SFO to the paraventricular nucleus (PVN) and from there to both the medulla and the IML provide the connectivity for modulation of peripheral sympathetic nerve activity by the SFO.

The AP is an important site at which circulating Ang II modulates peripheral sympathetic nerve activity. Ablation of the AP prevents hypertension caused by chronic intravenous administration of Ang II, a hypertensive model known to be caused by increased neurogenic pressor activity. The beneficial effects of intravenous AT1-receptor antagonist on the impaired arterial baroreflex control of both heart rate and RSNA in rabbits with pacing-induced heart failure were abolished by lesions of the AP. The major established efferent connections of the AP are the nucleus tractus solitarius (NTS) and the lateral parabrachial nucleus, both of which provide substantial input to sympathetic preganglionic neurons in the IML of the spinal cord. Lesions of the lateral parabrachial nucleus also impair chronic Ang II–induced hypertension. Losartan injected into the rostral ventrolateral medulla (RVLM) attenuated the increases in mean arterial pressure (MAP), heart rate, and RSNA produced by injection of bicuculline into the PVN, suggesting that the excitatory input into the RVLM arising from PVN is mediated by Ang II AT1 receptors. It has been reported that electrical activation of the AP both excites and inhibits neurons in the RVLM, which provides input to sympathetic preganglionic neurons in the IML of the spinal cord. Anatomical studies support the existence of such connections. Thus, circulating Ang II activation of the AP may increase peripheral sympathetic nerve activity through an excitatory direct connection from the AP to the RVLM.

The blood-brain barrier would prevent access of circulating Ang II to the RVLM. However, there is indirect evidence that circulating Ang II can activate RVLM neurons. With the use of an in vivo microdialysis technique, an intravenous Ang II infusion (subpressor) was shown to increase the release of glutamate, the excitatory amino acid neurotransmitter, from the RVLM. More importantly, intravenous administration of an ACEI decreased basal arterial pressure as well as the basal rate of glutamate release. Prevention of the reduction in arterial pressure with intravenous administration of Ang II also prevented the decrease in glutamate release.

There is strong evidence to indicate that circulating Ang II can increase peripheral sympathetic nerve activity and that this can be influenced by physiological alterations in the level of activity of the endogenous renin-angiotensin system (ie, alterations in dietary sodium intake). A major central nervous system site of action whereby circulating Ang II increases peripheral sympathetic nerve activity is the AP; an additional site is the SFO. These effects are mediated by AT1 receptors. There is preliminary evidence that circulating Ang II and the level of activity of the endogenous renin-angiotensin system can influence the activity of neurons in the RVLM. These central nervous system sites have efferent pathways that result in activation of sympathetic preganglionic neurons in the IML of the spinal cord.

Ang II of Central Nervous System Origin Increases Peripheral (Renal) Sympathetic Nerve Activity

It has been considered that Ang II fulfills the criteria to be considered a peptidergic neurotransmitter within the central nervous system. Here, Ang II of central nervous system origin would act on brain sites involved in the regulation of peripheral sympathetic nerve activity. These brain sites, not being circumventricular organs, would not be affected by circulating Ang II. However, the concentration of Ang II at the synapse is not known, and microinjections may deliver pharmacological or subthreshold concentrations, thus failing to mimic the in vivo situation. However, such studies do identify functional Ang II receptors, characterize their postsynaptic effects, and, with the use of pharmacological antagonists, classify the Ang II–receptor type.

Two mechanisms of action whereby Ang II of central nervous system origin acting on brain sites may increase peripheral sympathetic nerve activity have received attention. One postulates an inhibition of arterial baroreflex regulation of peripheral sympathetic nerve activity wherein neuronal Ang II originating from the PVN and released in the NTS inhibits neurotransmitter release at the first synapse in the arterial baroreflex pathway through presynaptic AT1 receptors. In the NTS, Ang II injection decreases, whereas the nonselective peptide Ang II receptor antagonist [Sar1, Thr3]Ang II increases, arterial baroreflex gain.

The second postulates that Ang II originating from neurons in the PVN and released in the NTS, RVLM, or IML leads to activation of sympathetic preganglionic neurons. The RVLM plays a central role in the autonomic neural control of the circulation, including arterial baroreflex regulation of peripheral sympathetic nerve activity. The RVLM contains Ang II–immunoreactive nerve terminals, predominant AT1-receptor mRNA, and AT1-receptor binding sites, which, however, are less in rat compared with rabbit or human. Microinjection of Ang II into the RVLM increases arterial pressure and/or peripheral sympathetic nerve activity and facilitates arterial baroreflex modulation of RSNA; these effects of exogenous Ang II are blocked by AT1-receptor blockers.
Experimental strategies used to differentiate these two general pathways relate to the administration of agonists and antagonists of the renin-angiotensin system. Initial studies used intravenous Ang II infusions and a variety of methods, each with unique advantages and disadvantages, to measure peripheral sympathetic nerve activity, for example, ganglionic blockade, plasma norepinephrine concentrations or turnover, and recordings of peripheral sympathetic nerve activity in both conscious and anesthetized animals (reviewed in Reference 23). The results were variable, with increases, decreases, and no change having been reported. A confounding factor was the change in arterial pressure induced by the intravenous Ang II infusion, which, by pressure-dependent resetting of the arterial baroreflex regulation of peripheral sympathetic nerve activity, could complicate the analysis of the results. When arterial baroreflex regulation of heart rate and plasma norepinephrine concentration were compared during similar increases in arterial pressure produced by intravenous Ang II or phenylephrine infusion, it was evident that there was an additional pressure-independent effect of Ang II to increase heart rate and plasma norepinephrine concentration at any level of arterial pressure.44,45

These studies with exogenous Ang II produce limited insight into the effects of endogenous Ang II on peripheral sympathetic nerve activity. With the use of physiological interventions such as alterations in dietary sodium content to manipulate endogenous Ang II or animal models characterized by increased endogenous Ang II such as normal birth,49,50 congestive heart failure,51–57 and hypertension,58,59 together with agents that interrupt the renin-angiotensin system (ACEI, Ang II AT1-receptor antagonist), important information on the effects of endogenous Ang II on peripheral sympathetic nerve activity has emerged.

A general finding is that when alterations in arterial pressure are prevented either by intracerebroventricular administration of the agent or restoration of arterial pressure with infusion of appropriate vasoactive substances, agents that interrupt the renin-angiotensin system decrease the basal level of peripheral sympathetic nerve activity and shift the arterial baroreflex regulation of peripheral sympathetic nerve activity to a lower level of arterial pressure. This is exemplified in the results from intracerebroventricular administration of losartan, a nonpeptide-selective Ang II AT1-receptor antagonist, to rats consuming low, normal, or high dietary sodium.46,53 Plasma renin activity (PRA) in rats given a low sodium diet was increased, whereas it was decreased in rats given a high sodium diet relative to rats given a normal sodium diet. While intracerebroventricular losartan did not affect basal levels of MAP in the 3 dietary groups, it decreased basal RSNA in the low and normal but not high dietary sodium groups. The arterial baroreflex relation between RSNA and MAP is shifted leftward to a lower level of MAP (arterial pressure at midpoint of curve) after intracerebroventricular losartan administration in the low and normal but not the high dietary sodium groups. Similar results and conclusions were obtained by intravenous administration of losartan with restoration of arterial pressure by intravenous methoxamine infusion.46 Thus, the effect is a lower level of RSNA for a given level of MAP. These results indicate that the level of endogenous Ang II tonically supports the level of RSNA and resets the arterial baroreflex regulation of RSNA to a higher level of arterial pressure. The effect is proportional to the degree of activation of the renin-angiotensin system, being greatest during low sodium diet (high PRA), least during high sodium diet (low PRA), and tonic during normal sodium diet (normal PRA).

While the strategy of intracerebroventricular administration obviates the problems related to changes in arterial pressure produced by intravenous administration, it does not completely localize the source and brain site of action of the Ang II. With intracerebroventricular losartan administration, it is still possible that the losartan could be diffusing through the ventricular system to those brain sites to which circulating Ang II has ready access by virtue of absence of normal blood-brain barrier function. A more direct approach in this regard is the selective and specific microinjection of losartan into candidate brain sites that are situated behind a normal blood-brain barrier.

Because circulating Ang II does not have direct access to the RVLM, endogenous Ang II excitation probably is derived from either angiotensinergic neural inputs (vide supra) or from paracrine secretion of angiotensin peptides within the brain stem. More significant, therefore, are the findings that microinjection of Ang II receptor blockers into the RVLM produce decreases in arterial pressure and/or peripheral sympathetic nerve activity. Such observations suggest that endogenous Ang II causes tonic excitation of RVLM neurons with increased peripheral sympathetic nerve activity. Many of these studies used noneselective (peptide) Ang II receptor blockers that have partial agonist properties and did not include measurements of peripheral sympathetic nerve activity. In the anesthetized rat, microinjection of losartan, a selective nonpeptide AT1-receptor blocker, into the RVLM increased resting arterial pressure and splanchnic sympathetic nerve activity and blocked the pressor and sympathoexcitatory responses to microinjection of Ang II into the RVLM.60 These results suggest that the tonic excitation of RVLM neurons is mediated by AT1 receptors, probably being stimulated by endogenous Ang II. In the anesthetized rabbit with basal RSNA elevated by the stress of surgery and anesthesia, neither resting arterial pressure nor RSNA were affected by losartan or PD123319, a selective nonpeptide AT1-receptor blocker, but were significantly decreased by the noneselective Ang II receptor blocker [Sar1, Thr3]Ang II.61 Losartan but not PD123319 blocked the pressor and sympathoexcitatory responses to microinjection of Ang II and Ang III. These results suggest that the tonic sympathoexcitation produced by endogenous angiotensin peptides in the rabbit RVLM are mediated by receptors other than AT1 or AT2 receptors, possibly being stimulated by endogenous angiotensin peptides other than Ang II or Ang III. Evidence in support of Ang1–7 as an endogenous angiotensin peptide in RVLM derives from studies in conscious62 and anesthetized63 rats showing that RVLM microinjection of A-779 (D-Ala7-angiotensin1–7), a selective blocker of Ang1–7 receptors, decreased resting arterial pressure (no measurements of peripheral sympathetic nerve activity). These responses to A-779 are similar to those observed with RVLM microinjection of [Sar1, Thr3]Ang II.
There was no effect (anesthetized) or a pressor effect (conscious) with AT$_1$- or AT$_2$-receptor blockers. Thus, studies in both rabbits and rats suggest a role for Ang-1–7.

Physiological alterations in endogenous Ang II activity (as produced by changes in dietary sodium intake) have a distinct modulatory effect on the responses to microinjection of Ang II AT$_1$-receptor antagonists (losartan, candesartan) into the RVLM. Losartan and candesartan decreased heart rate, MAP, and RSNA dose dependently; the responses were significantly greater in rats given a low sodium diet than in rats given a high sodium diet. A-779 did not affect MAP, heart rate, or RSNA in rats given either low or high sodium diet. In rats given a low sodium diet, the lowest dose of candesartan decreased the basal level of RSNA (but not MAP) and reset arterial baroreflex control of RSNA to a lower level of arterial pressure. Rats with congestive heart failure are characterized by increases in both renin-angiotensin system activity and RSNA as well as by defective arterial baroreflex regulation of RSNA (ie, lower gain). In rats with congestive heart failure, the lowest dose of candesartan decreased the basal level of RSNA (but not MAP) and improved the arterial baroreflex gain of RSNA toward normal.

These results support the view that angiotensin peptides of brain origin may have a local paracrine or autocrine action on sites that regulate the RSNA and its arterial baroreflex control. That this action is influenced by alterations in dietary sodium intake, long known to modulate activity of the circulating renin-angiotensin system, suggests a potentially important compensatory adaptation in the overall neural regulation of renal function.

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References


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