Interactions between ANG II, sympathetic nervous system, and baroreceptor reflexes in regulation of blood pressure

IAN A. REID
Department of Physiology, University of California, San Francisco, California 94143-0444

Reid, Ian A. Interactions between ANG II, sympathetic nervous system, and baroreceptor reflexes in regulation of blood pressure. Am. J. Physiol. 262 (Endocrinol. Metab. 25): E763-E778, 1992.—The renin-angiotensin system plays an important role in the regulation of arterial blood pressure and in the development of some forms of clinical and experimental hypertension. It is an important blood pressure control system in its own right but also interacts extensively with other blood pressure control systems, including the sympathetic nervous system and the baroreceptor reflexes. Angiotensin (ANG) II exerts several actions on the sympathetic nervous system. These include a central action to increase sympathetic outflow, stimulatory effects on sympathetic ganglia and the adrenal medulla, and actions at sympathetic nerve endings that serve to facilitate sympathetic neurotransmission. ANG II also interacts with baroreceptor reflexes. For example, it acts centrally to modulate the baroreflex control of heart rate, and this accounts for its ability to increase blood pressure without causing a reflex bradycardia. The physiological significance of these actions of ANG II is not fully understood. Most evidence indicates that the actions of ANG to enhance sympathetic activity do not contribute significantly to the pressor response to exogenous ANG II. On the other hand, there is considerable evidence that the actions of endogenous ANG II on the sympathetic nervous system enhance the cardiovascular responses elicited by activation of the sympathetic nervous system.

angiotensin II; renin-angiotensin system; brain; sympathetic ganglia; adrenal medulla; sympathetic transmission; baroreflex; heart rate; catecholamines; angiotensin-converting enzyme inhibitors

THE RENIN-ANGIOTENSIN SYSTEM has become established as an endocrine system that plays important roles in the physiological regulation of cardiovascular, renal, endocrine, and other functions. It also contributes to the development and maintenance of various forms of hypertension and other disorders, and drugs that inhibit the renin-angiotensin system are being used increasingly in the treatment of hypertension and congestive heart failure. The renin-angiotensin system is often thought of as a self-contained endocrine system that acts independently of the other systems that regulate blood pressure. It is now clear, however, that there are extensive interactions between the renin-angiotensin system and other blood pressure control systems. In particular, there are interactions with the sympathetic nervous system and the baroreceptor reflexes, and they are the subject of this review.

The interactions between the renin-angiotensin system, the autonomic nervous system, and the baroreceptor reflexes are summarized in Table 1 and Fig. 1. A major interaction involves actions of angiotensin II on the sympathetic nervous system. These include an action on the brain to enhance sympathetic outflow, stimulatory effects on sympathetic ganglia and the adrenal medulla, and actions at sympathetic nerve endings that serve to facilitate sympathetic neurotransmission. Second, angiotensin II interacts with the baroreceptor reflexes. There may be several such interactions, but the emphasis in this review is on the action of angiotensin on the baroreflex control of heart rate. A third interaction is the neural control of renin secretion by the kidneys. Because the rate of renin release is the rate-limiting step in the formation of angiotensin II, the sympathetic nervous system is one of the factors that ultimately determine the circulating levels of angiotensin II. The neural control of renin secretion has been reviewed elsewhere (27, 66, 119) and will not be considered here.

BIOSYNTHESIS OF ANGIOTENSIN II

The pathway for the biosynthesis of angiotensin II by the renal renin-angiotensin system is well established. The renal enzyme renin is released by the juxtaglomerular apparatus into the circulation where it cleaves angiotensin I from angiotensinogen, a glycoprotein synthesized in the liver. Angiotensin I is rapidly cleaved by the ubiquitous angiotensin-converting enzyme to form angiotensin II, the physiologically active component of the renin-angiotensin system.

In addition to the renal renin-angiotensin system,
there has been considerable recent interest in the existence of tissue renin-angiotensin systems. Evidence has been presented for the existence of renin-angiotensin systems in a wide variety of tissues including vascular smooth muscle (33, 145), heart (77, 89), brain (45–47, 114), and several endocrine glands (30). Such systems could play important physiological roles, and many of the interactions discussed in this review may involve not only circulating angiotensin II but also angiotensin II formed locally in tissues. Nevertheless, despite considerable progress in identifying components of the renin-angiotensin system in tissues and, in some cases, their mRNAs, the significance of the tissue renin-angiotensin systems remains an enigma. For this reason, the focus of this review will be on circulating angiotensin II.

INHIBITORS OF THE RENIN-ANGIOTENSIN SYSTEM

The development of drugs that inhibit the formation or actions of angiotensin II (116) has greatly facilitated investigation of the functions of the renin-angiotensin system. These drugs include renin inhibitors, which block the formation of angiotensin I, and angiotensin-converting enzyme inhibitors, which block the conversion of angiotensin I to angiotensin II. Two commonly used angiotensin-converting enzyme inhibitors are captopril and enalapril. The action of angiotensin II can be blocked by specific receptor antagonists, including angiotensin analogues such as saralasin. These are all very effective drugs, but they do have limitations. For example, angiotensin-converting enzyme inhibitors not only block the conversion of angiotensin I to angiotensin II but also inhibit the degradation of vasodilative kinins. A problem with saralasin and related receptor antagonists is that they exhibit some agonist activity. These limitations should be considered when interpreting the effects of the drugs. The recently developed nonpeptide angiotensin II receptor antagonists (121, 136) do not have these limitations and are being used for the investigation of interactions between angiotensin II and the sympathetic nervous system. These drugs, typified by Losartan (DuP 753), are selective antagonists of the AT1-receptor subtype (12).

ACTIONS OF ANGIOTENSIN II ON THE SYMPATHETIC NERVOUS SYSTEM

Sympathetic Outflow

There have been a number of studies of the effects of angiotensin II on sympathetic activity, but they have produced extremely variable results. This variability presumably reflects many differences in experimental design, including the use and type of anesthetics, dose of angiotensin (physiological to pharmacological), route of administration (intravenous, intracarotid, intravertebral, intracerebroventricular), method of administration (bolus or infusion), nerve being recorded from (splanchnic, splenic, renal, cardiac, cervical), state of baroreceptors (intact or denervated), and species of animal being tested (cat, rabbit, dog).

Central administration. The effects of central administration of angiotensin II on sympathetic nerve activity have been investigated in cats, rabbits, and dogs. Severs and Buckley (132) reported that intracerebroventricular administration of angiotensin II in chloralose-anesthetized cats "generally depressed" superior cervical nerve activity. In contrast, intravertebral administration of angiotensin II in paralyzed cats caused an increase in cervical nerve activity (67). Fukiyama (44) investigated the effect of intravertebral angiotensin II on splanchnic, renal, and cardiac nerve activity in dogs anesthetized with morphine and chloralose. He observed an increase in splanchnic nerve activity, a transient increase in renal nerve activity followed by a decrease, and no change in cardiac nerve activity. Tobey et al. (137) compared the effects of bolus injections of angiotensin II into a carotid artery or lateral cerebral ventricle of baroreceptor-denervated cats. Intracarotid angiotensin II elicited increases

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Numbers refer to sites of action shown in Fig. 1.
in splenic and renal nerve activity, whereas intracerebroventricular angiotensin II increased splenic activity without significantly changing renal nerve activity. Recently, Matsumura et al. (87) reported that intraventricular infusion of angiotensin II in conscious rabbits caused a decrease in renal nerve activity.

**Intravenous administration.** The effects of acute intravenous administration of angiotensin II have been studied in dogs, rabbits, and humans. Schmitt and Schmitt (127) reported that intravenous injection of angiotensin II in chloralose-anesthetized dogs increased splanchic and cardiac nerve activity. In rabbits, angiotensin II has consistently been found to cause a reduction in sympathetic nerve activity, which is apparently a reflex response to the increase in arterial blood pressure. Aars and Akre (1) reported that intravenous infusion of a large dose of angiotensin II (0.5–3 μg·kg⁻¹·min⁻¹) in chloralose-anesthetized rabbits reduced both cervical and renal nerve activity. Guo and Abboud (53) compared the effects of intravenous angiotensin II (0.4 μg·kg⁻¹·min⁻¹) and phenylephrine on lumbar sympathetic nerve activity in chloralose-anesthetized rabbits. Both substances decreased lumbar nerve activity, but angiotensin II was less effective than phenylephrine. They proposed that angiotensin II acts centrally to modulate the reflex control of lumbar sympathetic nerve activity. In contrast, Bishop and colleagues (8, 87) found that intravenous infusion of angiotensin II and phenylephrine in conscious rabbits produced the same reduction in renal sympathetic nerve activity. They therefore concluded that angiotensin II does not produce any significant effect on the reflex control of renal sympathetic nerve activity. Intravenous infusion of angiotensin II in humans reduced muscle sympathetic nerve activity, but the reduction was less than that produced by infusion of phenylephrine (86). When the pressor effect of angiotensin II was counteracted by simultaneous infusion of nitroprusside, a small increase in sympathetic activity was observed.

The wide differences in experimental design and the corresponding variability of the results make it difficult to draw definite conclusions concerning the effect of angiotensin II on sympathetic nerve activity. It appears that angiotensin II can increase sympathetic outflow when it is administered centrally, but the doses required are large, and the significance of this effect is not clear. When angiotensin II is administered intravenously, there is generally a reflex reduction in sympathetic nerve activity. This reduction may be partially offset by the central action to enhance sympathetic activity, although no evidence for this has been seen when angiotensin II is administered in physiological doses in conscious animals (8, 87). Thus, based on the currently available evidence, it does not seem that stimulation of sympathetic outflow is likely to contribute significantly to the cardiovascular actions of circulating angiotensin II. This question is discussed in more detail below. Additional research is needed to further characterize the effects of physiological doses of angiotensin II on sympathetic nerve activity in conscious animals. Ideally, recordings should be made from more than one sympathetic nerve, and studies should be performed both in intact and baroreceptor-denervated animals.

The central site(s) at which circulating angiotensin II acts to alter sympathetic activity has not been specifically investigated. However, it appears that the area postrema, a circumventricular organ located in the medulla oblongata, plays a major role (37, 38, 88, 115). Like the other circumventricular organs, the area postrema has fenestrated capillaries and is therefore accessible to circulating angiotensin II. It contains a high density of angiotensin II receptors and has direct efferent connections with medullary centers involved in cardiovascular control. Electrophysiological studies have shown that intravenous administration of angiotensin II alters the activity of area postrema neurons (101). Destruction of the area postrema reduces the pressor response to acute or chronic intravenous infusion of angiotensin II (41, 85, 99) or to infusion of the peptide into a vertebral artery (64).

**Adrenal Medulla**

The ability of angiotensin II to stimulate the release of catecholamines from the adrenal medulla was first demonstrated indirectly on the basis of changes in blood pressure and/or contractions of the denervated nictitating membrane of the cat (36, 120). Subsequent studies by several investigators showed directly that administration of angiotensin II resulted in increases in plasma epinephrine and norepinephrine concentrations. For example, Peach et al. (104, 105) investigated the effect of intravenous infusion of angiotensin II in doses of 25, 50, and 100 μg·kg⁻¹·min⁻¹ in pentobarbital sodium-anesthetized dogs and found that the two higher doses increased plasma epinephrine and norepinephrine concentrations.
Adrenalectomy abolished the epinephrine response to angiotensin II but only reduced the norepinephrine response, indicating an extra-adrenal contribution to this response. The pressor response to angiotensin II was also not reduced after adrenalectomy (29, 105). Cline (20) observed that intravenous injection of angiotensin II in a dose of 3 μg/kg in pentobarbital-anesthetized dogs increased plasma epinephrine and norepinephrine levels. Stimulation of adrenal medullary secretion has also been demonstrated in conscious animals. For example, Rowe and Nasjletti (124) reported that infusion of angiotensin II in a dose of 500 ng·kg⁻¹·min⁻¹ increased plasma epinephrine concentration in conscious rabbits. It should be pointed out, however, that two lower doses, 5 and 50 ng·kg⁻¹·min⁻¹, did not increase plasma epinephrine concentration and that none of the three doses increased plasma norepinephrine concentration.

The stimulatory effect of angiotensin II on adrenal medullary secretion appears to result from a direct action of the peptide on the adrenal medulla. The adrenal medulla contains a high density of high-affinity angiotensin receptors (61, 146), and angiotensin II increases catecholamine release when administered into the blood supply to the adrenal gland in vivo (36) or into the isolated perfused adrenal gland (122). Angiotensin II also stimulates secretion of epinephrine and norepinephrine by cultured adrenal medullary cells (14). Autoradiographic studies indicate that the majority of angiotensin II receptors in the rat adrenal medulla are of the AT₂ subtype (19). Despite this, the angiotensin II-induced increase in epinephrine secretion is blocked by the specific AT₁-receptor antagonist Losartan (148).

The mechanism by which angiotensin stimulates adrenal medullary secretion is not fully understood. In cultured adrenal medullary cells, the stimulation is dependent on extracellular calcium and is partially blocked by nifedipine, and it has been proposed that the catecholamine response to angiotensin is mediated by calcium entry via membrane calcium channels (14). It has also been shown that angiotensin II increases inositol phosphate accumulation (14) and activates protein kinase C (139) in cultured adrenal medullary cells. These changes may also contribute to the catecholamine response.

The renin-angiotensin system has been implicated in the increased secretion of adrenal medullary catecholamines which occurs in response to a variety of stimuli. For example, it has been reported that the increased secretion of catecholamines by the adrenal medulla in response to isoproterenol administration (40), insulin-induced hypoglycemia (13), and hemorrhage (39) can be blocked by an angiotensin II antagonist or by nephrectomy. Because these stimuli all increase renin secretion, and since the adrenal medullary response to hemorrhage requires an intact motor innervation to the gland, it was proposed that the release of catecholamines is mediated by an increase in circulating angiotensin II acting indirectly through central stimulation of sympathetic outflow. Experiments utilizing intracerebroventricular administration of angiotensin II or an angiotensin II antagonist provided support for this proposal (23).

MacLean and Ungar (82) proposed an alternative mechanism. They observed that the adrenal medullary response to reflex activation of the sympathetic nervous system by a reduction in carotid sinus pressure was reduced by captopril and was restored by infusion of angiotensin II. Because the adrenal medullary response was not accompanied by an increase in plasma renin activity, they proposed that the response was not mediated by the renin-angiotensin system but instead required the presence of a permissive level of angiotensin II. They also proposed a direct adrenal action of angiotensin II, since the adrenal medullary response to splanchic nerve stimulation was also reduced by captopril (82).

Recent experiments by Vollmer et al. (140) provide additional evidence for facilitation by angiotensin II of neurally mediated catecholamine release. They observed that the increase in epinephrine secretion in response to electrical stimulation of the nerve supply to the adrenal medulla in pithed rats was enhanced in animals maintained on a low-sodium diet. This enhancement was decreased by blockade of the renin-angiotensin system with saralasin or captopril. The adrenal medullary response to splanchic nerve stimulation in anesthetized dogs is also reduced by captopril or saralasin and potentiated by angiotensin II (42).

It is important to note that the facilitatory effect of angiotensin II in all of the above studies was observed in anesthetized animals that had often undergone a considerable amount of surgery. Moreover, not all studies have revealed a stimulatory effect of angiotensin II on adrenal medullary secretion. This is particularly true in humans. For example, Mendelsohn et al. (90) reported that infusion of angiotensin II at 1, 5, and 10 ng·kg⁻¹·min⁻¹ in normal subjects failed to alter plasma epinephrine or norepinephrine concentrations. Similarly, Nicholls et al. (96) observed no change in plasma catecholamines when angiotensin II was infused in normal subjects in doses ranging from 0.5 to 4.0 ng·kg⁻¹·min⁻¹. These investigators also reported that inhibition of angiotensin II formation by captopril failed to alter plasma catecholamine levels in patients with severe hypertension or congestive heart failure. Beretta-Piccoli et al. (7) reported that infusion of angiotensin II in normal subjects and in patients with essential hypertension in doses that increased diastolic pressure by as much as 25 mmHg did not alter plasma catecholamine levels.

The difference between the results obtained in the human and animal studies can probably be attributed to differences in experimental design. For example, the doses of angiotensin II infused in the animal studies have generally been higher (to 500 ng·kg⁻¹·min⁻¹) than in the human studies (to 10 ng·kg⁻¹·min⁻¹). In addition, most animal studies utilized anesthetized preparations, whereas the human studies were performed in the conscious state. It is possible that, in the conscious state, the stimulatory effect of angiotensin II on adrenal medullary secretion is opposed by activation of the baroreceptor reflexes by the pressor effect of angiotensin. This effect may be absent or reduced in the anesthetized state, since it is known that most anesthetics interfere with the baroreceptor reflexes (70).

In summary, administration of exogenous angiotensin II in experimental animals can stimulate the release of catecholamines by the adrenal medulla. Most evidence indicates that large supraphysiological doses of angio-
Sympathetic Ganglia

The ability of angiotensin II to stimulate the release of catecholamines from the adrenal medulla led Lewis and Reit (75, 76, 120) to determine whether it also acts on sympathetic ganglia. They showed that close intra-arterial injection of angiotensin II to the superior cervical ganglion in cats produced contraction of the ipsilateral nictitating membrane. It was subsequently shown that angiotensin II stimulates the caudal cervical ganglion in dogs (35) and the stellate ganglion in cats (3). The action of angiotensin II on the superior cervical ganglion is apparently due to a direct action on the ganglion cells, because it occurs after chronic denervation of the ganglion (75). The effect of angiotensin II resembles that of muscarine (11).

Specific angiotensin binding sites have been demonstrated in the superior cervical and stellate ganglia of rats (17, 106). Interestingly, the density of the binding sites in spontaneously hypertensive rats is higher than in normotensive controls and is reduced by preganglionic denervation (106). In pithed rats, the ganglion-stimulating action of angiotensin II appears to be mediated by way of AT₁ receptors (148).

The levels of angiotensin II required to stimulate sympathetic ganglia have not been defined, and the physiological significance of this action of the peptide is not known.

Sympathetic Nerve Terminal

Presynaptic actions. One of the most investigated mechanisms by which angiotensin II enhances sympathetic nervous activity is facilitation of sympathetic neurotransmission at the adrenergic nerve terminal. Such facilitation has been observed in many different tissues including vascular smooth muscle, heart, kidney, and vas deferens from species including the dog, rat, rabbit, monkey, and human (9, 16, 24, 63, 78, 84, 102, 138, 152–156). There is general agreement that the facilitation of neurotransmission by angiotensin II results from an increase in the amount of norepinephrine in the synaptic cleft. This may result from increased release or decreased reuptake of norepinephrine, or both (102).

There is some evidence that angiotensin II can directly stimulate the nerve terminal to release norepinephrine, although the concentration of angiotensin II required for this is high (109). Other investigators have concluded that angiotensin II does not itself cause release of norepinephrine but instead enhances the release of norepinephrine evoked by nerve stimulation (102, 152). In other words, angiotensin II is only effective when there is active nerve firing. This conclusion is based on observations that angiotensin II potentiates responses in a variety of tissues during sympathetic nerve stimulation (102). This is an important point and may help to explain why angiotensin II usually fails to increase circulating norepinephrine levels when administered in intact animals and humans (see Role of Sympathetic Nervous System in Blood Pressure Response to Angiotensin II).

The action of angiotensin II to enhance norepinephrine release can be brought about by physiological concentrations of angiotensin II and is most pronounced at low physiological frequencies of sympathetic nerve stimulation (102). The facilitation can be brought about by endogenous as well as exogenous angiotensin II (83, 154, 156). It appears to be due to an action on prejunctional angiotensin II receptors (157), but beyond this the mechanisms involved are not well understood. Starke (133) concluded that the prejunctional action of angiotensin II involves an increase in the amount of transmitter released per nerve impulse. In a recent study of sympathetic transmission in the guinea pig vas deferens, Zogas and Cunnane (157) obtained evidence that angiotensin increases the probability of transmitter release. Studies by Wong et al. (147, 148) indicate that the prejunctional angiotensin II receptors are of the AT₁ subtype.

Another mechanism by which angiotensin II facilitates adrenergic transmission is by inhibiting the reuptake of norepinephrine by the nerve terminal. Several investigators have reported that angiotensin II decreases the uptake of norepinephrine in a variety of tissues from different animal species (68, 69, 100, 102, 103). It has also been reported that angiotensin II can inhibit norepinephrine reuptake in concentrations that approximate circulating physiological levels (108).

Finally, angiotensin II has been reported to increase the synthesis of norepinephrine (123). This apparently results from induction of the synthesis of tyrosine hydroxylase. This action of angiotensin II is slower than its other actions at adrenergic nerve endings.

Postsynaptic actions. There have been many reports that angiotensin II enhances vasoconstrictor responses to norepinephrine. Enhanced vasoconstrictor responses have been observed in perfused blood vessels, and enhanced pressor responses to intravenous norepinephrine have been described in various animal models as well as in normotensive and hypertensive humans (84, 110, 112, 134, 143, 155). Angiotensin II enhances pressor responses to norepinephrine when it is infused in pressor or suppressor doses and is effective during both acute and chronic administration of the peptide. It generally enhances both the diastolic and systolic blood pressure responses to norepinephrine (143), although in one study only the systolic pressure response was enhanced (134). There is evidence that endogenous angiotensin II can produce the same effect as exogenous angiotensin. For example, blockade of the renin-angiotensin system with an angiotensin-converting enzyme inhibitor has been reported to reduce the pressor response to norepinephrine in both animals and humans (22, 59, 126). The responses could be restored by administration of a suppressor dose of angiotensin II.

The mechanism by which angiotensin II enhances vasoconstrictor responses is not known, but increases in intracellular calcium concentration and protein kinase C activity in vascular smooth muscle cells apparently are involved (72, 110). It should also be pointed out that, in the intact animal, angiotensin II may enhance pressor responses by mechanisms other than its action on vascular smooth muscle. For example, angiotensin II also mod-
ulates the baroreflex control of heart rate. This action is discussed later in this review.

In summary, it is clear that angiotensin II can exert several actions at the adrenergic nerve terminal, any of which could facilitate responses to sympathetic stimulation. The relative importance of these pre- and postsynaptic actions remains to be determined.

PHYSIOLOGICAL SIGNIFICANCE OF EFFECTS OF ANGIOΤENSIN ON SYMPATHETIC NERVOUS SYSTEM

It is clear from the preceding section that angiotensin II can exert multiple actions on the sympathetic nervous system. What is the physiological significance of these actions? This question will be addressed from two standpoints. First, does the sympathetic nervous system contribute to the blood pressure response to angiotensin II (i.e., does angiotensin II require the sympathetic nervous system? Second, do the actions of angiotensin to enhance sympathetic activity contribute to the cardiovascular responses to activation of the sympathetic nervous system (i.e., does the sympathetic nervous system require angiotensin II)?

Role of Sympathetic Nervous System in Blood Pressure Response to Angiotensin II

It is clear that an intact sympathetic nervous system is not required for angiotensin II to increase arterial blood pressure, since angiotensin II retains most or all of its pressor activity after pharmacological blockade or destruction of the sympathetic nervous system. Indeed, ganglion-blocked or pithed rat preparations were used previously for the routine bioassay of angiotensin II. Instead, most evidence indicates that the pressor response to angiotensin II is primarily due to the direct vasoconstrictor action of the peptide. Nevertheless, it is possible that, under some conditions, there may also be a sympathetic component to the pressor response. This possibility has been investigated using a number of approaches, including measurement of sympathetic nerve activity, circulating catecholamine levels, or catecholamine turnover during angiotensin II-induced elevation of blood pressure. The effects of autonomic blocking drugs on the pressor response to angiotensin II have also been investigated.

The effects of systemically administered angiotensin II on sympathetic nerve activity are discussed above. In general, administration of physiological doses of angiotensin II in conscious animals results in a decrease in sympathetic nerve activity, which is apparently a reflex response to the pressor action of the peptide. These observations do not support the hypothesis that an increase in sympathetic activity contributes to the pressor response to angiotensin II. On the contrary, they suggest that, rather than contributing to the pressor response, the sympathetic nervous system actually buffers it. Consistent with this are reports that the pressor activity of angiotensin II is enhanced after sinoaortic baroreceptor denervation (25, 43).

Changes in plasma norepinephrine levels generally provide a reliable index of changes in sympathetic activity (52). Studies of the effect of angiotensin II on plasma norepinephrine levels, however, have produced conflicting results. Plasma norepinephrine increased in some studies (20, 104, 105) but remained unchanged (7, 50, 51, 90, 96, 124, 131) (Fig. 2) or even decreased (26, 57) in others. These differences can probably be attributed to differences in experimental design, including the use of anesthetics and the dose of angiotensin II. In general, increases in plasma norepinephrine have only been observed when large supraphysiological doses of angiotensin have been administered in anesthetized animals; physiological doses in conscious animals or humans have almost invariably been without effect.

The lack of an increase in plasma norepinephrine does not necessarily rule out a change in sympathetic activity. It is possible, for example, that during infusion of angiotensin II, increases in sympathetic activity in some regions are offset by decreases in others, so that overall sympathetic activity as reflected by the circulating norepinephrine level does not change. As discussed above, however, electrophysiological recordings have not shown this to be the case. Moreover, Kline et al. (71) recently reported that norepinephrine turnover in the kidney, heart, intestine, and skeletal muscle, as well as epinephrine turnover in the adrenal, were not changed during chronic infusion of angiotensin II in rats. Again, these
results fail to provide evidence that an increase in sympathetic activity contributes to the pressor response to physiological doses of angiotensin II.

If the sympathetic nervous system contributes to the pressor response to angiotensin II, it would be expected that the response would be reduced by blockade of the autonomic nervous system. To test this, Fujii and Vatner (43) investigated the effect of ganglionic blockade on the pressor and vasoconstrictor actions of angiotensin II in conscious dogs. They observed that ganglionic blockade enhanced the pressor response to angiotensin II, but only after denervation of the arterial baroreceptors. The vasoconstrictor response to angiotensin II, however, was reduced by ~50% after ganglionic blockade in both intact and baroreceptor denervated dogs. They concluded, therefore, that “in the conscious dog without baroreflex buffering, nearly one-half of the pressor and vasoconstrictor actions of angiotensin are not direct, but are mediated by the autonomic nervous system” (43).

The observations of Fujii and Vatner (43) constitute some of the most compelling evidence that the autonomic nervous system contributes to the vasoconstrictor action of angiotensin II. It should be pointed out, however, that these investigators only studied very transient cardiovascular responses to bolus injections of angiotensin, and it is possible that the situation with infusion of the peptide may be different. For example, although Fujii and Vatner observed that bolus injections of angiotensin II elicited a reflex bradycardia, others have reported that pressor responses to angiotensin infusions are generally not accompanied by a reduction in heart rate. The effects of angiotensin II on the baroreflex control of heart rate are discussed below.

It has been reported that the pressor response to angiotensin II is reduced after depletion of norepinephrine stores, but this has not been a consistent finding (28). Chemical sympathectomy with 6-hydroxydopamine does not reduce the blood pressure response to chronic infusion of angiotensin II (98). Other investigators have studied the effect of adrenergic-blocking drugs on the pressor response to angiotensin II. It has been reported that alpha-adrenergic blockade reduces the pressor response to high doses of angiotensin II in rabbits (125) and dogs (21). However, negative results have also been obtained (20). Recently we investigated the effect of the alpha-adrenoceptor antagonist prazosin, the alpha-2-adrenoceptor antagonist yohimbine, and the beta-adrenoceptor antagonist propranolol on the pressor response to graded doses of angiotensin II in conscious rabbits (I. A. Reid and A. Biasson, unpublished observations). None of these drugs altered the pressor response. These experiments thus failed to reveal an important role for alpha- or beta-adrenoceptors in the pressor response to angiotensin II.

In summary, although positive results have been obtained by some investigators, several different approaches have failed to provide evidence that the sympathetic nervous system contributes significantly to the pressor response to exogenous angiotensin II.

Role of Angiotensin II in Cardiovascular Responses to Sympathetic Stimulation

There have been many studies of the effect of inhibition of the renin-angiotensin system on the cardiovascular responses to sympathetic activation. These studies have been performed both in animal models and in humans. A variety of drugs have been used to inhibit the renin-angiotensin system, including angiotensin receptor antagonists and renin inhibitors, but the majority of studies have utilized angiotensin converting enzyme inhibitors, the most common one being captopril. These drugs have frequently been observed to impair the cardiovascular responses to sympathetic stimulation.

A commonly used preparation has been the pithed rat. Antonaccio and Kerwin (4) investigated the effect of inhibition of the renin-angiotensin system on cardiovascular responses to sympathetic nerve stimulation in pithed spontaneously hypertensive rats. Acute administration of captopril reduced the pressor but not the heart rate response to sympathetic stimulation. The pressor response to norepinephrine was unaffected. Teprotide (another angiotensin-converting enzyme inhibitor), saralasin, or nephrectomy did not reduce the pressor response to sympathetic stimulation. Based on these results, it was proposed that captopril reduced the pressor response to sympathetic stimulation by inhibiting angiotensin II formation in vascular tissue at a site not accessible to teprotide or saralasin. Furthermore, it was suggested that the reduction in angiotensin II levels in turn decreased the release of norepinephrine from sympathetic nerve terminals. In a similar study, Wong et al. (149) observed that the pressor response to sympathetic stimulation in pithed rats was reduced by captopril but not by a monoclonal antibody to angiotensin II. Again, a role for vaeolarly generated angiotensin II was proposed.

Other investigators have also observed that captopril impairs the cardiovascular responses to sympathetic stimulation in pithed rats and have shown that the response can be restored by infusion of angiotensin II (22, 55, 65). However, saralasin and nephrectomy were also found to be effective, and the results were therefore interpreted in terms of blockade of the circulating renin-angiotensin system. In addition, responses to norepinephrine were also reduced, suggesting that inhibitors of the renin-angiotensin system may interfere with both pre- and postsynaptic actions of angiotensin II.

As Zimmerman et al. (155) pointed out, there are problems with the pithed rat preparation, including a very low baseline blood pressure and high plasma renin and angiotensin II levels. Nevertheless, results consistent with those obtained in pithed rats have been obtained in other animal preparations. For example, Adigun et al. (2) investigated the effect of inhibition of the renin-angiotensin system on the cardiovascular responses to lower body negative pressure in anesthetized cats, a maneuver that reduces central blood volume and arterial pressure, which in turn activates sympathetic reflexes. They observed that an angiotensin-converting enzyme inhibitor or an angiotensin II receptor antagonist increased the hypotensive response to lower body negative pressure. Because the blocking drugs themselves did not decrease blood pressure and because plasma renin levels did not increase during lower body negative pressure, they suggested that angiotensin II augments the activity of the sympathetic nervous system even at concentrations less than those required to constrict the blood vessels directly.
The effect of inhibition of the renin-angiotensin system on the responses to lower body negative pressure has also been investigated in patients with essential hypertension. Morganti et al. (92) observed that captopril diminished the increase in forearm vascular resistance and amplified the decrease in arterial pressure that occurred during lower body negative pressure. The reduction in the response for forearm vascular resistance was not thought to result from removal of the direct vasoconstrictor action of angiotensin II, because it occurred before there was any change in plasma renin activity. Instead, the authors proposed that it resulted from removal of a facilitatory influence of angiotensin II on the neurally mediated vasoconstriction of the forearm vessels either at a pre- or postjunctional site. Based on these observations, they concluded that "even in the sodium-replete state, Ang II exerts a facilitatory action on adrenergic function that is physiologically relevant for the regulation of forearm blood flow and the maintenance of blood pressure during the application of gravitational stresses" (92).

This conclusion is consistent with the results of Webb and colleagues (130, 142). They observed that infusion of angiotensin II into a brachial artery of normal human subjects, in a dose that itself caused no reduction in forearm blood flow, augmented the reduction in blood flow in response to lower body negative pressure. Because the vasoconstrictor response to norepinephrine was not altered, they concluded that angiotensin II acted presynaptically to enhance norepinephrine release. Direct evidence for such an action was recently provided by the observation that infusion of angiotensin II into a brachial artery of hypertensive subjects increased forearm norepinephrine release in response to lower body negative pressure (135).

Recently, we investigated the effect of captopril on the cardiovascular responses to reflex activation of the sympathetic nervous system by bilateral carotid occlusion in conscious aortic depressor nerve-sectioned rabbits (60). In this model, bilateral carotid occlusion increases blood pressure by ~40 mmHg and heart rate by 20 beats/min but does not change plasma renin levels. Captopril markedly reduced both the pressor and heart rate responses to bilateral carotid occlusion in parallel with a decrease in plasma angiotensin II concentration (Fig. 3). Infusion of a subpressor dose of angiotensin II increased plasma angiotensin II concentration to precaptopril levels and restored the pressor and heart rate responses to carotid occlusion. This appeared to be a specific action of angiotensin II, since the responses to carotid occlusion were not restored by administration of phenylephrine. Captopril or angiotensin II did not appear to affect baroreflex sensitivity (as judged by changes in heart rate in response to infusions of nitroprusside or phenylephrine) and only exerted a small postsynaptic effect (as judged by changes in the pressor response to intravenous norepinephrine). By the process of elimination, therefore, we concluded that the impairment of the cardiovascular responses to bilateral carotid occlusion by captopril was due to removal of a predominantly presynaptic action of angiotensin to facilitate norepinephrine release. In other experiments in rabbits with an intact renin-angiotensin system, we observed that administration of angiotensin II did not enhance the cardiovascular responses to bilateral carotid occlusion. Taken together, the results suggest that endogenous angiotensin at basal levels exerts a permissive action that produces maximal facilitation of norepinephrine release.

The conclusion that captopril acts by removing a presynaptic action of angiotensin II was not tested in our experiments. However, a study by MacLean and Ungar (82) is relevant. They reported that the adrenal medullary response to decreased carotid sinus pressure in anesthetized dogs was inhibited by captopril and restored by administration of angiotensin II. To the extent that changes in adrenal catecholamine output reflect more generalized changes in sympathetic activity and catecholamine release, these observations are consistent with captopril removing a presynaptic action of angiotensin II to enhance norepinephrine release. Also consistent are reports that the hypotensive response to angiotensin-converting enzyme inhibition is not accompanied by the expected increase in plasma norepinephrine concentra-

![Fig. 3. Blood pressure (MABP) and heart rate (HR) responses to bilateral carotid occlusion and plasma ANG II concentration in conscious rabbits before and after captopril treatment and during ANG II replacement. bpm, beats/min. [From Isaacson and Reid (60), by permission of the American Heart Association, Inc.]](http://ajpendo.physiology.org/)[Downloaded from http://ajpendo.physiology.org/](http://ajpendo.physiology.org/)
activation. For example, Schwieler et al. have not found that inhibition of the renin-angiotensin system results in impaired responses to sympathetic vasoconstrictor responses to nerve stimulation or exogenous norepinephrine. After α-adrenoceptor blockade, angiotensin-converting enzyme inhibition did reduce evoked norepinephrine overflow, but this was not reversed by administration of angiotensin II. These results were interpreted as evidence against a role for circulating angiotensin II in the control of sympathetic transmission in canine skeletal muscle.

In summary, considerable evidence supports the proposal that endogenous angiotensin II facilitates sympathetic transmission. However, negative results have been obtained in some studies, and these have raised questions concerning the role of angiotensin II in sympathetic transmission. It is clear that further study of this important question is required.

**EFFECT OF ANGIOTENSIN II ON BAROREFLEX CONTROL OF HEART RATE**

One of the unique characteristics of angiotensin II is that its pressor effect is accompanied by either no change in heart rate or by a reduction in heart rate that, for a given increase in arterial pressure, is much smaller than that produced by other vasoconstrictors such as phenylephrine or vasopressin (15, 53, 79, 81, 91, 95, 117). Similarly, the hypotensive response to blockade of the renin-angiotensin system is usually accompanied by little or no increase in heart rate (32, 54, 58, 62, 141).

The lack of a consistent heart rate response to angiotensin II or blockade of the renin-angiotensin system has been attributed to an action of angiotensin II to alter the baroreflex control of heart rate. As pointed out by Lumbers et al. (79) and Hatton et al. (54), such an action could result from a shift in the set point of the reflex to a higher pressure (resetting) or a decrease in baroreflex sensitivity. This is illustrated in Fig. 4. In the former case (curve B), angiotensin could increase blood pressure without changing heart rate but would not prevent the heart rate response to changes in blood pressure produced by other agents. In the latter case (curve C), angiotensin could inhibit heart rate responses not only to its own pressor action but to changes in blood pressure produced by other agents.

There is some disagreement in the literature as to whether the attenuated heart rate response to angiotensin II is due to a decrease in baroreflex sensitivity, a resetting of the reflex to a higher pressure, or both. Some investigators have reported that angiotensin II decreases baroreflex sensitivity (48, 53, 74) and that blockade of the renin-angiotensin system increases it (48, 58, 74). On the other hand, others have reported that angiotensin II or blockade of the renin-angiotensin system resets the baroreflex without changing its sensitivity (10, 32, 49, 54, 87, 141). The reason for these differences is not clear but probably reflects differences in experimental design, including the dose of angiotensin II, the use of anesthetics, the method used to assess the baroreflex, and the species studied (5, 144).

In a recent study in this laboratory (118), the action of angiotensin II on the baroreflex control of heart rate was examined in conscious chronically prepared rabbits. Baroreflex curves (heart rate vs. mean arterial pressure) were generated with intravenous infusions of phenyleph-

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**Fig. 4. Possible actions of ANG II on baroreflex control of heart rate.**

*Curve A,* relationship between heart rate and mean arterial pressure during intravenous infusions of phenylephrine and nitroprusside in a conscious rabbit; *curve B,* effect of resetting baroreflex to higher pressure with no change in sensitivity; *curve C,* effect of reducing baroreflex sensitivity with no change in set point.
Angiotensin increased arterial pressure without changing heart rate and reset the baroreflex curve to a higher pressure without changing its sensitivity (Fig. 5). This resetting was not simply a result of the increase in arterial pressure produced by angiotensin (18), because an equipressor dose of phenylephrine did not cause resetting. Angiotensin also shifted the baroreflex curve with nitroprusside to a higher pressure, again without significantly changing its sensitivity.

The finding that angiotensin II can reset the baroreflex control of heart rate without changing its sensitivity is in good agreement with the results obtained in conscious dogs by Brooks and Reid (10) and in conscious rabbits by Matsumura et al. (87). It also agrees with a report by Guo and Abboud (53) that the heart rate response to nitroprusside in rabbits is unchanged in the presence of angiotensin II. However, Guo and Abboud also reported that angiotensin II attenuated the heart rate response to phenylephrine. The reason for this difference is not clear, but it should be noted that the rabbits in the study by Guo and Abboud were anesthetized, and it is known that anesthetics can have marked effects on baroreflex function (70). In addition, the dose of angiotensin II used by Guo and Abboud was very high (400 ng·kg\(^{-1}\)·min\(^{-1}\)).

Angiotensin has also been reported to decrease baroreflex sensitivity in conscious sheep (74). However, in that study, the pressor effect of angiotensin was counteracted by simultaneous infusion of a vasodilator. Angiotensin has also been reported to decrease baroreflex sensitivity in the baboon (48), but it should be pointed out that it also caused a marked resetting of the reflex. Taken together, most of the available evidence indicates that, at least with physiological doses of angiotensin II in conscious animals, the major action of angiotensin II on the baroreflex control of heart rate is to reset the reflex to a higher pressure. Under some circumstances, baroreflex sensitivity may also be reduced.

The resetting of the baroreflex control of heart rate by angiotensin II could conceivably be due to an action of the peptide on the baroreceptors, the brain, or the heart. A number of studies have provided evidence that angiotensin II does not act directly on the baroreceptors (53, 79), although it was recently reported that angiotensin II can inhibit the firing of aortic arch baroreceptors by causing local vasoconstriction of the aortic arch (94). It should be pointed out that all these studies were performed in acute experiments in anesthetized animals, in which endogenous angiotensin II levels were probably very high.
before angiotensin was administered. Studies by Potter (107, 108) have shown that angiotensin II can inhibit the action of the vagus on the dog and guinea pig heart, but the doses used were high. Angiotensin II may facilitate the chronotropic action of the cardiac sympathetic nerve (78), but this is controversial (4, 113). On the other hand, there is abundant evidence that angiotensin II can act on the brain to increase blood pressure and heart rate and decrease vagal tone to the heart (38, 109, 111, 115). For this reason, most investigators proposed that the action of angiotensin II on the baroreflex control of heart rate is mediated via the brain (5, 48, 53, 79, 87).

The hypothesis that angiotensin II exerts a central effect on the baroreflex control of heart rate was tested by Matsumura et al. (87). They compared the effects on blood pressure and heart rate of infusion of angiotensin II intravenously and into a vertebral artery of conscious rabbits. They found that vertebral artery infusion was associated with a significantly blunted baroreflex inhibition of heart rate compared with intravenous infusion and proposed a hindbrain site of action. The doses of angiotensin II infused in those studies were high (20, 40, and 80 ng·kg\(^{-1}\)·min\(^{-1}\)).

Studies in this laboratory provided further evidence for a central site of action of angiotensin II on the baroreflex control of heart rate (118). Infusion of angiotensin II into the third cerebral ventricle of conscious rabbits in a dose of 1.0 ng·kg\(^{-1}\)·min\(^{-1}\) had the same effect on the baroreflex control of heart rate as intravenous infusion at 10 ng·kg\(^{-1}\)·min\(^{-1}\); the baroreflex curve was reset to a higher pressure, but the sensitivity was not changed. Intravenous infusion of angiotensin II at 1 ng·kg\(^{-1}\)·min\(^{-1}\) had no effect on the baroreflex, confirming that the effect of intraventricular administration was central in origin.

Fig. 7. Relationship between heart rate and mean arterial pressure during graded infusions of phenylephrine with (X) and without (a) background infusion of ANG II in intact (A) and area postrema-lesioned (B) rabbits. [Adapted from Matsukawa and Reid (85).]
Similarly, Dorward and Rudd (31) reported that infusion of a low dose of angiotensin II into the fourth ventricle of conscious rabbits also reset the cardiac baroreflex to a higher pressure. Again, intravenous infusion of the same dose of angiotensin had no effect on the reflex.

As discussed above, many of the central cardiovascular effects of angiotensin are mediated by the area postrema, a circumventricular organ located in the medulla oblongata. For this reason, it has been proposed that the action of angiotensin II on the baroreflex is mediated by the area postrema. To test this possibility, we investigated the effect of ablation of the area postrema on the resetting of the baroreflex control of heart rate by angiotensin II (85). In these experiments, the cardiovascular effects of angiotensin were compared in intact and area postrema-lesioned conscious rabbits (Fig. 6). In intact rabbits, infusion of angiotensin II produced dose-related increases in arterial pressure, which were not accompanied by decreases in heart rate, except at the highest dose. In the area postrema-lesioned rabbits, the pressor activity of angiotensin II was reduced while the heart rate response was enhanced. The pressor and heart rate responses to phenylephrine were not different between the two groups. In intact rabbits, the slope of the relation between heart rate and mean arterial pressure during angiotensin II infusion was less than that during phenylephrine infusion, but in the lesioned rabbits the slopes were not significantly different.

In another series of experiments, cardiac baroreflex responses to graded infusions of phenylephrine or nitroprusside were obtained with and without background infusion of angiotensin II. In intact rabbits, angiotensin II resets the baroreflex to a higher pressure without changing its slope (Fig. 7). In lesioned rabbits, angiotensin II did not change the slope, nor did it reset the baroreflex (Fig. 7). These results provide further evidence that the area postrema plays an important role in the centrally mediated cardiovascular responses to angiotensin II. They also confirm that angiotensin II resets the baroreflex control of heart rate without changing its sensitivity and demonstrate for the first time that this effect is mediated by the area postrema. Similar findings were recently reported by Cox and Bishop (26).

The resetting of the baroreflex control of heart rate by angiotensin II could result from enhanced sympathetic activity to or withdrawal of vagal tone from the heart or a combination of both. We have reported that administration of propranolol does not block the resetting in conscious rabbits, suggesting that it is not due to an increase in sympathetic tone to the heart (118). This observation is consistent with results obtained in sheep (73). On the other hand, there is abundant evidence that angiotensin II (and angiotensin III) can inhibit cardiac vagal efferent activity (79, 80, 129). This appears to be due to a central action, because it can also be produced by infusing angiotensin II into a vertebral artery (109) (Fig. 8). It seems likely that this is the mechanism by which angiotensin II resets the baroreflex control of heart rate. The central pathway by which angiotensin II resets the baroreflex is not known, but roles for α1-adrenoceptors (97) and glutamate (93) have been proposed.

In summary, current evidence indicates that the impairment of reflex bradycardia during angiotensin II-induced elevation of arterial blood pressure results from resetting of the baroreflex control of heart rate to a higher pressure with or without a reduction in baroreflex sensitivity. The resetting apparently results from an action of angiotensin II on the area postrema, which is mediated by inhibition of vagal tone to the heart.

**OVERALL INTEGRATION**

In this review, the various interactions between angiotensin II, the sympathetic nervous system, and the baroreceptor reflexes have been discussed separately. This final section is an attempt to integrate the information concerning these interactions into a working hypothesis, with the hope that it will stimulate further research. The interactions are summarized in Table 1 and Fig. 1.

**Pressor Response to Angiotensin II**

Exogenously administered angiotensin II acts directly on vascular smooth muscle, causing vasoconstriction, which in turn results in increases in total peripheral resistance and arterial blood pressure. The increase in arterial pressure activates the baroreceptor reflexes, and this tends to buffer the vasoconstrictor action of angiotensin. However, angiotensin simultaneously acts centrally to reset the baroreflex control of heart rate to a higher pressure and, as a result, there is little or no decrease in heart rate. This resetting apparently serves to enhance the pressor response of angiotensin, since, when it is prevented by lesioning the area postrema, the pressor response to angiotensin is decreased.

The actions of angiotensin II on the brain, sympathetic ganglia, adrenal medulla, and sympathetic nerve endings to enhance sympathetic activity may contribute to the pressor response to the peptide. It appears, however, that
the contribution is minor, because most evidence indicates that the pressor response to exogenous angiotensin II is not accompanied by increases in sympathetic nerve activity or circulating catecholamine levels and is not reduced by blockade of the sympathetic nervous system. The failure of exogenous angiotensin II to significantly enhance sympathetic activity is consistent with the proposal that the facilitatory effects of angiotensin II on sympathetic activity become significant only when angiotensin II levels are increased in association with an increase in sympathetic discharge.

Role of Endogenous Angiotensin II

Renin release and sympathetic discharge are both increased in hypertensive and hypovolemic states, the former resulting in part from increases in renal sympathetic nerve activity and circulating catecholamine levels. The stimulation of renin release increases the circulating angiotensin II level, which in turn acts to increase blood pressure by the mechanisms just described for exogenous angiotensin. However, there is evidence that, under these conditions, endogenous angiotensin also contributes to blood pressure regulation by its actions on the sympathetic nervous system. This evidence includes the finding that cardiovascular responses to stimulation or reflex activation of the sympathetic nervous system are frequently reduced after blockade of the renin-angiotensin system. It seems likely that this reduction results mainly from removal of an action of angiotensin II to facilitate norepinephrine release at sympathetic nerve endings, although other sites may also be involved. Most evidence indicates that this facilitatory effect can be exerted by basal (“permissive”) or elevated levels of angiotensin.

In summary, currently available evidence indicates that there are important interactions between angiotensin II, the sympathetic nervous system, and the baroreceptor reflexes in the regulation of arterial blood pressure. However, substantial questions remain, and further research is needed to fully characterize the mechanisms as well as the physiological and pathophysiological significance of these interactions.

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Address for reprint requests: Dept. of Physiology, Box 0444, Univ. of California, San Francisco, CA 94143-0444.

REFERENCES


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