During recent years the nature of the considerable contribution of the sympathetic nervous system to renal hypertension has become somewhat more clear, due in part to the unexpected discoveries that angiotensin is not simply a direct vasoconstrictor agent but is almost ubiquitous in its actions. Among these actions are several on the sympathetic nervous system that appear to intensify its effects on the peripheral vascular system. It stimulates release of catechols from the adrenal medulla (1); at certain dose levels it facilitates ganglionic transmission (2); and it sensitizes the neurovascular effector so that the effects of sympathetic vasomotor discharge are augmented (3). This latter effect may depend in part on prevention of reuptake of released norepinephrine (4).

For a long time it was considered unlikely that angiotensin had any effect on the central nervous system since theoretically it does not cross the blood-brain barrier. Then Bickerton and Buckley (5), in 1961, cross-perfused the head of a recipient dog, isolated from its own circulation and connected to the body only by the spinal cord, with blood from a donor animal. When angiotensin was injected into the circulation of the donor animal it raised the systemic arterial pressure in the recipient’s trunk as well as in the donor animal. Because the response of the recipient could be blocked by piperoxan, a sympatholytic agent, they concluded that angiotensin had a central hypertensive effect that was mediated by the sympathetic nervous system. Unfortunately, the significance of these experiments was not fully appreciated at the time because of the very large doses of angiotensin employed, a great deal larger than might ever occur as a consequence of release of endogenous renin.

At about the same time these experiments were performed, Dickinson (6) approached the possibility of a central nervous system cause of hypertension from a different point of view. On the basis of postmortem studies of both cerebral and renal artery vessels of hypertensive man, he revived the hypothesis that increased cerebrovascular resistance causes relative ischemia of vasomotor centers and could thereby elevate basal blood pressure. While the idea was not new, dating back as it does well over a century, his approach was ingenious; he suggested that in addition to structural changes, the main cerebral vessels may be constricted during life by a renal hormonal mechanism. If the effector agent was angiotensin, the peptide should have a greater pressor effect when directly delivered into the cerebral circulation, especially that supplying the medulla, than when infused systemically. To test this hypothesis, angiotensin was infused into the circulation of the hindbrain via the vertebral arteries of dogs anesthetized with pentobarbital, but there was no difference in response to infusion of...
angiotensin into the vertebral arteries or intravenously (7). Since it had been shown earlier by Bingel and Claus (8), Dock et al. (9), Pickering and Prinzmetal (10) and Page and Helmer (11) that barbiturate anesthesia depresses response to the renin-angiotensin system, Dickinson (12) and Yu and Dickinson (13) repeated the experiments in unanesthetized rabbits. Under these circumstances, hypertension resulted when angiotensin was infused into the vertebral circulation in such low doses that they had no effect when given intravenously.

During this same period (1961-1967) Benetato et al. (14) provided additional evidence that angiotensin has an effect on vasomotor structures within the central nervous system, thus confirming the cross-circulation findings of Bickerton and Buckley (5). Scroop and Lowe observed in greyhounds (15) and Ferrario et al. in mongrel dogs (16) that the central nervous action of angiotensin was still present when morphine and chloralose were used as anesthetic agents. The onset of the pressor response was rapid (usually within 30-45 seconds) and could be produced consistently with doses as low as 0.01 ng/kg min⁻¹ (17). Since the dose response curve flattened very quickly (16), it suggested an action in the nature of a threshold effect on the central nervous system.

Lowe and Scroop (17) suggested that the rise in pressure is due to an increase in cardiac output that is dependent on withdrawal of parasympathetic activity. They measured cardiac output in greyhound dogs using a dye-dilution technique and found an increase in output during the pressor response to vertebral artery infusion to be accompanied consistently with doses as low as 0.01 ng/kg min⁻¹ (17). Since the dose response curve flattened very quickly (16), it suggested an action in the nature of a threshold effect on the central nervous system.

Ferrario et al. (16) measured cardiac output with chronically implanted flowmeters and found that the rise of blood pressure in response to vertebral infusion of angiotensin was usually due entirely to an increase in total peripheral resistance; both cardiac rate and output remained practically unchanged. This suggested that the sympathetic rather than the parasympathetic nervous system was the effector pathway, especially since the pressor response was abolished by bretylum tosylate or by cervical section of the spinal cord (19). Bilateral vagotomy or administration of atropine did not alter the response in their experiment. It is possible that the different results obtained by the two groups depend on the strain of animals used. Scroop and Lowe used greyhounds, which, bred for their enormous cardiac reserve, may respond normally to stress by increasing output rather than resistance.

To examine the problem more closely, Fukiyama, Ferrario, and McCubbin (unpublished) measured electric activity in cardiac, renal, and splanchnic nerves during infusion of angiotensin into the vertebral circulation. During the rise in blood pressure there was an increase, or no change, in the pattern of preganglionic splanchnic vasomotor discharge. In the majority of the experiments, cardiac nerve activity did not change, but there were occasions when grouped discharges increased during the initial portion of the pressor response. The pattern of activity in renal nerves was in contrast with that in splanchnic and cardiac nerves in that typical, presumably reflex, decrease in activity occurred during the rise in arterial pressure. The changes in electrical activity recorded in these experiments are compatible with the hemodynamic findings of the same group, indicating an increase in total vascular resistance as a result of increased central sympathetic vasomotor discharge. The less frequent increase in cardiac sympathetic activity is also compatible with only occasional increases in heart rate and output that occur in mongrel dogs during intravertebral infusion of angiotensin (18). Rosendorff et al. (20) and Yu and Dickinson (21) using rabbits, Severs et al. (22) using
cats and Ueda et al. (23) in experiments on man have also concluded that the central effects of angiotensin are mediated primarily by increased sympathetic discharge. More recent data from Joy (24) indicate that what he termed the “residual pressor response” following bilateral vagotomy to infusion of angiotensin into the vertebral arteries of the anesthetized greyhound, is quite substantial, accounting for 50-70% of the pressor response obtained with the vagi intact. It was totally abolished by bethanidine.

This central action of angiotensin can be sustained. Fukiyama et al. (25) demonstrated that continuous infusion of small amounts of angiotensin into a vertebral artery of unanesthetized dogs produced a rise in blood pressure that persisted for the 7-day duration of the infusions. Doses were small enough so that they had no, or much less, effect when given intravenously for the same period of time. Sweet et al. (26) have recently confirmed these findings. It is important to consider that the calculated blood concentrations of angiotensin in the above experiments fall within a range that occur in anesthetized dogs after hemorrhage (27). It is thus possible that the central effects of the peptide may contribute in part to the cardiovascular response to angiotensin produced endogenously.

Dickinson’s suggestion (7, 12) that the pressor effect of vertebral artery infusion of angiotensin is due to selective constriction of the basilar artery with resultant brainstem ischemia has been made improbable by recent evidence that suggests that the response depends on an angiotensin-sensitive neural structure in the portion of the brainstem supplied by the vertebral arteries. The hypothalamus and midbrain were excluded from consideration as a site of activity when Gildenberg (19) showed that section of the dog’s brainstem at the level of the mesencephalon failed to alter the response to angiotensin administered into vertebral arteries. The distribution of the circulation of the vertebral arteries was then altered by successively lower ligation of the basilar artery exposed through the roof of the dog’s mouth. When a silver clip was applied at the lowermost part of the basilar artery, just below the cervicocranial anastomosis, the pressor response disappeared. Thus it was concluded that the area responsible for the central effects of angiotensin lay in the lower medulla (19). Very similar findings were reported at approximately the same time by Joy and Lowe (28) and Joy (24), who used greyhound dogs.

If the central effects of angiotensin are not due to reduction of blood flow to the brainstem, the peptide must reach the area where it is active by entering brain tissue where the blood-brain barrier is absent. The area postrema lies in the caudal medulla and is composed of paired mounds of loose vascular tissue that bulge into the lumen of the fourth ventricle (Fig. 1). It is stainable by intravascular injections of trypan blue (29, 30), which indicates a gap in the blood-brain barrier, and it lies within the area of distribution of the vertebral arteries. Microinjections of angiotensin directly into the area postrema were reported by Ueda in 1968 (31).
to cause systemic pressor responses; similar injections into adjacent areas did not. Joy (24) and Joy and Lowe (32) further studied the area postrema as the possible site of action. It was possible to show that bilateral ablation of the area postrema entirely abolished the pressor response to infusion of angiotensin into the vertebral arteries. Gildenberg et al. (33) also showed that selective cooling of the area postrema reversibly abolished the pressor response. Joy's recent work (24) indicates that it is necessary to ablate the area postrema bilaterally for the response to disappear; a unilateral lesion was not sufficient. Scroop et al. (34) have recently shown that the pressor response to intravenous infusion of angiotensin is reduced after ablation of the area postrema, again indicating a central component in the cardiovascular response to angiotensin. Destruction of the area postrema did not modify response to intravenous infusion of norepinephrine.

The area postrema consists of a loose network of neuroglia through which runs a rich plexus of arterioles and capillaries. The presence of neurons has been described in human material by Wilson (35), though they have not been found consistently in preparations from dog, rabbit, or cat (29). The histological appearance suggests a chemoreceptor zone, a likely possibility in view of the known ability of cardiac glycosides and apomorphine (see reference 36 for review) to induce vomiting by stimulation of this region. The area postrema overlies the caudal third of the nucleus vagi, and recently, connections have been shown to exist between it and the nucleus of the solitary tract (37); the latter receives fibers from the glossopharyngeal and carotid sinus nerves (38). It is possible that angiotensin may in some way modulate outflow of the autonomic nervous system. In this connection, it is interesting that renin has recently been demonstrated by Canten et al. (39) to occur in brain tissue of nephrectomized dogs, despite the fact that it does not cross the blood-brain barrier. Fischer-Ferraro et al. (40) demonstrated the presence of angiotensin as well as renin in the brain and commented on the remarkable correlation between angiotensin and norepinephrine concentrations in different portions of brain tissue. It is possible that the area postrema serves as a gate for the peptide to reach an area just lateral to the obex, where both aortic depressor and carotid sinus nerves relay (37, 38), thus modifying inhibitory activity reaching medullary vasomotor effector neurons. An interrelationship of this nature has been suggested by Barrett et al. (41), and Sweet and Brody (42) have shown that intravertebral infusion of angiotensin inhibits reflex vasodilation in the dog's hind limb that occurred in response to pressor stimuli. Kahn and Mills (43) have shown in the decerebrate cat that baroreceptor afferents act at either the medullary or the spinal level or both to produce alterations in the pattern of sympathetic discharge.

The area of distribution of the vertebral arteries seems not the only central site at which angiotensin can affect the autonomic nervous system. Severs et al. (22) showed in chloralose-anesthetized cats that intraventricular infusion of angiotensin caused a pressor response apparently evoked by an action on suprapontine structures. Nashold et al. (44), Laverty (45), and Smookler et al. (46) have provided additional evidence implicating an area within reach of fluid flowing between the cerebral ventricles. Deuben and Buckley (47) raised arterial pressure by infusing angiotensin either into the subnucleus medialis or the nucleus mesencephalicus profundus of the cat. Daniels and Buckley (48) have shown that the pressor response to intraventricular infusion of angiotensin can be prevented by the removal of calcium ions from the cerebrospinal fluid. They interpreted this finding as suggesting an interrelationship between endogenous norepinephrine, calcium ions, and central adrenergic pressor mechanisms stimulated by the peptide. Rise in arterial pressure due to intraventricular infusion of angiotensin (at doses roughly 10- to 15-fold higher than those required during infusion into vertebral arteries) cannot be adequately explained by spread of angiotensin.
to the fourth ventricle, since we were unable to evoke pressor responses by irrigation with angiotensin of the lower end of the fourth ventricle and surface of the area postrema (unpublished observations). It would not be surprising if function of the other areas of the brain devoid of a blood-brain barrier, such as the neurohypophysis, the tuber cinereum, or the pineal body of the intercolumnar tubercle, is also affected by angiotensin.

In summary, angiotensin has an effect on the central nervous system that results in an increase in arterial pressure caused by sympathetic vasomotor discharge and, to a lesser extent, withdrawal of parasympathetic discharge. Rise in pressure is due in the main to increase in peripheral resistance, though in some instances there is also increase in cardiac output. The effect is present with very small doses of angiotensin that have little or no effect when given elsewhere; it appears to involve the area postrema and possibly other areas of the brain devoid of blood-brain barrier. The finding that angiotensin and renin are present in brain tissue suggests the possibility that angiotensin may play an important, but as yet unidentified, function in the central regulation of cardiovascular control. It appears that a significant portion of the hypertensive effect of circulating angiotensin is mediated through a direct action on the brainstem.

References


Cardiovascular Effects of Angiotensin Mediated by the Central Nervous System
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Circ Res. 1972;30:257-262
doi: 10.1161/01.RES.30.3.257

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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