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COMMENTARY

CENTRAL VASOPRESSOR ACTIONS OF ANGIOTENSIN

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The role of the renin–angiotensin system in the pathogenesis of cardiovascular hypertensive disease has been extensively studied by many investigators; however, there has been little correlation between the concentration of angiotensin II in plasma and the blood pressure of essential hypertensive patients [1]. The possibility that the renin–angiotensin system might alter cardiovascular activity via the central nervous system was first suggested by the studies of Bickerton and Buckley in 1961 [2]. Their initial studies, utilizing the dog cross-circulation preparation in which the head of the recipient was neurally intact but vascularly isolated from the trunk, suggested that angiotensin II, in sufficient dosage, was capable of stimulating structures within the central nervous system, thereby producing an increase in peripheral blood pressure and that this effect appeared to be due to an increase in sympathetic outflow from the central nervous system. Further studies demonstrated that the centrally induced pressor effects were not due to an action of the peptide on baro- and/or chemoreceptors [3, 4] and were not due to hypoxia in the central circulation of the recipient [4]. The administration of angiotensin II into the cerebrospinal fluid (CSF) via the lateral ventricles in doses as low as 0.01 μg produced marked pressor effects accompanied by an increase in heart rate and contraction of the nictitating membrane [5, 6]. These pressor effects were markedly attenuated by the administration of an alpha-adrenergic blocker to the peripheral circulation, further implicating increased sympathetic outflow from the central nervous system as a major mechanism of action. Additional evidence for an increase in sympathetic outflow induced by an action of angiotensin on central nervous system centers has been presented by other investigators [7–13].

Possible sites of action

Preliminary experiments reported by Severs *et al.* [9] demonstrated that bilateral lesions in the midbrain of alpha-chloralose anesthetized cats abolished the centrally induced pressor effects of angiotensin II administered via the lateral ventricles. Deuben and Buckley [14] found that small electrolytic lesions placed within the periaqueductal gray, 4 mm anterior to Horsley–Clarke Zero, significantly reduced the pressor response obtained from the intraventricular administration of angiotensin II, whereas similar lesions placed 1 mm caudal did not alter the pressor response. Administration of the polypeptide into the aqueduct of Sylvius, 6 or 5 mm anterior to Horsley–Clarke Zero, produced marked pressor effects, whereas administration of identical doses of angiotensin II 4 or 3 mm anterior to Horsley–Clarke Zero produced significantly lower pressor effects [14, 15]. These data suggested that a central site of action of angiotensin II was located in the periaqueductal gray region of the mesencephalon, between 4 and 5 mm anterior to Horsley–Clarke Zero and that the subnucleus medialis of the periaqueductal gray [16, 17] is one of the sites of action of angiotensin II within the central nervous system. This area lies in close proximity to the aqueduct and the pathway has been shown to be functionally involved with the control of systemic peripheral resistance. This intrinsic pressor pathway turns abruptly lateral after synapsing in the subnucleus medialis and, therefore, lesions below this area would not be expected to disrupt these tracts. Finkielman *et al.* [18] have identified a polypeptide similar to angiotensin I in cerebrospinal fluid and found a significant correlation between the concentration of this peptide and the degree of hypertension in essential hypertensive patients. Therefore, an angiotensin sensitive site, which can easily be reached via the cerebrospinal fluid, may be of physiological importance.

Minute doses of angiotensin II perfused via a vertebral artery of cats [11, 15, 19], dogs [20–24] and rabbits [25, 26] have been shown to produce marked pressor effects. Gildenberg [20] localized the site of action of angiotensin II administered via a vertebral artery to be the area postrema. 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 [27].

Gildenberg *et al.* [22] infused angiotensin II into both vertebral arteries of anesthetized dogs, as well as via the lateral ventricles. The pressor response to perfusion of angiotensin into the vertebral arteries was abolished by destruction of the area postrema, using heat cautery. Infusion of angiotensin II via the vertebral arteries after transection of the midbrain at the level of the tentorium rather than destroying the area postrema did not alter the pressor response induced by angiotensin II administered via the vertebral arteries. Administration of small doses of angiotensin II via the cerebral lateral ventricles produced pressor responses which were unaltered by heat coagulation of the area postrema. Transection of the midbrain eliminated the pressor effect induced by intraventricular administration of the peptide, suggesting that there are at least two sites of action in the dog brain by which angiotensin can induce pressor effects. Administration of the peptide into the cerebrospinal fluid (administration via the lateral ventricles) stimulates an area of the midbrain, namely the subnucleus

medialis, whereas administration of the peptide via the bloodstream (vertebral arteries) affects the area postrema.

Interaction with central adrenergic receptors

The central administration of alpha-receptor agonists, clonidine [28, 29] and norepinephrine [5], antagonized the centrally induced pressor effects of angiotensin II. The alpha-adrenergic blocking agents, phentolamine, tolazoline and phenoxybenzamine, perfused intraventricularly for a period of 30 min differentially affected the pressor responses to centrally administered angiotensin II [30]. Vollmer and Buckley [30] reported that phentolamine markedly potentiated the pressor effects of angiotensin II, whereas tolazoline did not effect this response and phenoxybenzamine markedly attenuated the centrally induced pressor effect. The authors could not propose a direct relationship between the central alpha-adrenergic blockade and enhancement of the angiotensin II pressor responses. However, the dose of phentolamine was well within the range reported to block the hypotension induced by clonidine [31] and alpha-methyldopa [32, 33] and it was assumed to be related to the ability of phentolamine to block central alpha-adrenergic receptors. These authors also found that phentolamine markedly attenuated the reflexogenic bradycardia induced by the intravenous administration of norepinephrine. In contrast to phentolamine, neither tolazoline nor phenoxybenzamine altered reflex bradycardia induced by norepinephrine.

Intraventricular perfusion of either the *d*- or *l*-isomer of propranolol failed to alter the central hypertensive responses induced by angiotensin II. These data [30] suggest that the centrally mediated pressor activity of angiotensin II in the cerebrospinal fluid may be closely associated with central alpha-adrenergic receptor mechanisms involved in the regulation of blood pressure, whereas beta-adrenergic mechanisms do not appear to be involved in this activity.

Hemodynamic effects

Ferrario *et al.* [34] measured cardiac output with chronically implanted flowmeters and found that the increased blood pressure induced by infusion of angiotensin II via a vertebral artery was usually due entirely to an increase in total peripheral resistance with cardiac rate and output remaining practically unchanged. This suggested that the sympathetic rather than the parasympathetic nervous system was the effector pathway. Jandhyala *et al.* [35] investigated the hemodynamic effects of angiotensin II administered via intraventricular administration in chloralose anesthetized cats. They found that the pressor effects were not accompanied by any significant alterations in heart rate or cardiac output, but the result of an elevation of total peripheral resistance. Therefore, whether angiotensin II is administered centrally via intravertebral artery infusion to mongrel dogs [34] or via the cerebrospinal fluid in cats [35] the pressor effects were due to the increased peripheral vascular resistance. Administration of the peptide via the lateral ventricles did not produce a general increase in peripheral resistance, but rather a specific increase in resistance of selective beds [35]. For example, there was a significant increase in vascular resistance in mesenteric and renal vasculature, but only a slight increase in the resistance in skeletal muscle vasculature. Intraventricular infusion of the polypeptide produced a significant increase in left ventricular isometric pressure; however, the index of contractility was unchanged, indicating no alteration in ventricular contractility and that the alteration in ventricular pressure and dp/dt were mainly due to an increase in afterload or total peripheral resistance.

Physiological significance

Finkielman *et al.* [18] have found a pressor substance in the cerebrospinal fluid of normotensive and hypertensive patients. They reported the substance to be a polypeptide similar to angiotensin I; however, they did not exclude the possibility that this pressor polypeptide could be a precursor of angiotensin II different from angiotensin I in plasma. These investigators have found a significant correlation between the concentration of this polypeptide and the blood pressure of essential hypertensive patients and raised the question of the role of the central nervous system in the pathogenesis of essential hypertension. Other investigators have reported the presence of renin and angiotensin, mainly angiotensin I, in the central nervous system of rats and dogs [36–38]. Fuxe *et al.* [39] identified angiotensin II containing nerve terminals in the central nervous system of the rat using immunohistochemical procedures. Scattered terminals were found in the periventricular mesencephalic gray, especially in the anterior part. Single terminals were found in various parts of the hypothalamus, the preoptic area, subcortical limbic structures, limbic cortex, thalamus, ventral midbrain, reticular formation, vagus area of the medulla oblongata and the periventricular area of the pons and medulla oblongata. The location of the angiotensin II in the nerve terminals correlated with the presence of brain iso-renin in synaptosomes [40]. Schelling *et al.* [41] using tritiated angiotensin II concluded that intact angiotensin does not cross the blood-CSF barrier and that the increase in radioactive uptake by the brain was due to nonimmunoreactive degradation products of angiotensin II. This is contradictory to Volicer and Loew [42] who found intact ^{14}C-labeled angiotensin II in brain tissue shortly after intravenous adminstration of the compound.

The present data suggest that angiotensin I and II can be biosynthesized within the central nervous system [36–38, 43] and that both renin [38] and renin substrate [44] have been identified within the central nervous system. Printz and Lewicki [44] have reported that the concentration of renin substrate in the brain is sufficient to permit significant amounts of angiotensin to be generated. Although the exact role of the brain iso-renin–angiotensin system is still unclear, it would appear that angiotensin II and possibly angiotensin I, produced within the central nervous system, affects structures in the midbrain and perhaps other areas of the central nervous system, and that these actions may be significant from both a physiological and pathological standpoint. In addition, there is the strong possibility that the central vasopressor activity of angiotensin may be related to its

ability to release antidiuretic hormone [45] and/or its dipsogenic activity [46].

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