Hypothalamic Vasomotor Pathways Mediating the Development of Hypertension in the Rat

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SUMMARY The integrity of the anteroventral third ventricle (AV3V) region is necessary for the development of several models of hypertension in the rat. Humoral stimuli (angiotensin II (AII), hypertonic saline, or carbachol) act in the region to promote an increase in blood pressure due partially to an increase in sympathetic vasomotor activity and partially to the release of vasopressin from the posterior pituitary. Electrical stimulation in the region also elicits vasomotor activity (mesenteric and renal vasoconstriction accompanied by hindlimb vasodilation). These studies were designed to: 1) to identify vasoconstrictor pathways projecting from the AV3V region; and 2) to determine if these pathways are involved in the development of experimental hypertension. The results indicate that at least two separate vasoconstrictor pathways project from the AV3V region. The first projects via a periventricular route through the anterior hypothalamus to the ventromedial hypothalamic region. It is involved in the vasoconstrictor responses to centrally and peripherally administered AII and to centrally administered hypertonic saline and carbachol. The second pathway projects from the AV3V region and joins the medial forebrain bundle, converging with the first pathway along the midline in the ventromedial hypothalamus. This second pathway conveys both the vasoconstrictor and vasodilator responses elicited by electrical stimulation in the medial preoptic region. Selective destruction of the periventricular pathway attenuates renin-dependent renal hypertension but does not prevent the development of non-renin-dependent hypertension. The physiological stimuli that activate the second pathway are unknown. Since this lateral vasoconstrictor pathway is the only other known vasoconstrictor system projecting from the AV3V region, we speculate that it may be involved in the neurogenic component of several models of nonrenin-dependent hypertension that are prevented by electrolytic destruction of the AV3V region. (Hypertension 4 (supp III): 111-68—111-71, 1982)

KEY WORDS • AV3V region • hypertension • blood pressure regulation • angiotensin II • hypertonic saline • carbachol • central nervous system • hypothalamus

This laboratory1 has demonstrated that an electrolytic lesion in the periventricular-preoptic region of the hypothalamus prevents the development of several different types of hypertension in the rat. The spread of electrical current from an electrode placed in the anterior tip of the third ventricle damages tissue along the ventricle walls ventral to the anterior commissure. Specific anatomical structures destroyed by such a lesion include the ventricular ependyma, the periventricular nucleus in the region, portions of the medial preoptic nucleus, the organum vasculosum lamina terminalis (OVLT), and the nucleus medianus. Generally, the lesion does not extend into the optic chiasm or suprachiasmatic nuclei. Since the area affected by the lesion is anatomically heterogeneous, it is referred to as the “AV3V” (anteroventral third ventricle)2 region. Models of hypertension shown to be prevented by AV3V lesion include both renin-dependent and non-renin-dependent renal hypertension, steroid/salt hypertension, neurogenic models and Dahl strain, salt-sensitive genetic hypertension. Since the etiologies of these various forms of hypertension are distinct, it is necessary to understand how one brain lesion could prevent each of them. Increased sympathetic vasoconstriction is characteristic of most models of experimental hypertension.

It has been well established that chemical or electrical stimulation of the AV3V region elicits sympathetic vasomotor activity. The region is involved in the pressor responses to both blood-borne and cerebrospinal fluid (CSF)-borne AII.3 The AV3V lesion also blocks the pressor responses produced by cerebroventricular administration of hypertonic saline and carbachol.4 Electrical stimulation in the AV3V region produced increases in mesenteric and renal vascular resistance that are dependent upon the sympathetic nervous system.5 The AV3V region appears to contain neural elements capable of activating sympathetic outflow to the vasculature. We postulate that the AV3V lesion may...
The goal of the present studies is to define the mechanisms by which the AV3V lesion protects against the development of several different models of experimental hypertension. To achieve this aim, projections from the AV3V region that are involved in the vasomotor activity associated with chemical and electrical activation of the area were mapped.

The results indicate that at least two separate vasomotor systems project from the AV3V region. Elimination of the vasoconstrictor pathways activated by chemical stimulation left the pathways responsive to electrical stimulation intact and attenuated renin-dependent but not renin-independent renal hypertension. Since the AV3V lesion prevents both forms of renal hypertension, it is apparent that distinct pressor mechanisms dependent upon integrity of the AV3V region are involved in the development of these two categories of renal hypertension.

**Methods**

The methods used in these studies are described more completely elsewhere. Briefly, vasoconstrictor pathways associated with the pressor responses to All (intracerebroventricular, (i.c.v.) or intravenous, (i.v.)), hypertonic saline (i.c.v.), and carbachol (i.c.v.) were mapped by determining which of a series of overlapping electrolytic lesions or knife cuts blocked these pressor responses. By analyzing the extent of each lesion or knife cut, tissue critical to the pressor responses was determined by eliminating from consideration all tissue that could be destroyed without eliminating the pressor response. Each animal received either a lesion or a knife cut. One to 2 weeks later the animals were instrumented with lateral ventricular cannulas and carotid catheters. Pressor response to intraventricular chemical stimuli were recorded in conscious unrestrained animals.

In studies that required electrical stimulation of the AV3V region, bipolar stimulating electrodes were implanted 2 to 4 days before the experiment. On the day of the experiment each animal was anesthetized with urethane, instrumented with pulsed-Doppler flow probes on the renal, mesenteric, and lower aortic arteries, and a carotid catheter was inserted for blood pressure recording. Changes in arterial pressure and in blood flow were measured in each vascular bed during electrical stimulation of the AV3V region and vascular resistance changes were calculated.

**Results**

**Chemical Stimulation: Mapping Analysis**

Electrolytic lesions were placed in a large number of animals so that tissue critical to the central All pressor response in the medial preoptic and anterior hypothalamic regions could be determined. Stereotaxic coordinates for electrode placement were chosen to produce a spectrum of overlapping lesions in order to study the entire midline region. The area tested includes the AV3V region. Pressor responses to All (i.c.v.) were determined in each animal, and the brain areas damaged by the lesions were mapped.

All animals that failed to respond to centrally administered All had bilateral lesions in structures along the lamina terminalis or the periventricular tissue in the anterior hypothalamus. Destruction of the paraventricular nuclei without attendant damage to the anterior hypothalamus had no effect on the central All pressor response. However, lesions in the anterior hypothalamus that did not overlap with the typical AV3V lesion blocked the pressor responses. In addition, it was found that small lesions in the AV3V region that destroyed tissue only at the lamina terminalis (organum vasculosum of lamina terminalis (OVLT) and/or ventral nucleus medianus) blocked the central All pressor response. Also, dorsal lesions involving midline tissue surrounding the anterior commissure eliminated the response.

Interpretation of these data led us to propose that a vasoconstrictor pathway responsive to centrally administered All originated in the AV3V region at the OVLT. The pathway appears to ascend along the lamina terminalis to the anterior commissure and then descend almost vertically through the anterior hypothalamus before projecting caudally to the ventromedial hypothalamic region. A previous experiment had demonstrated that this pressor response was eliminated by electrolytic lesion in the ventromedial hypothalamus. This hypothesis was tested by making knife cuts in the anterior hypothalamus that would bilaterally transect the route of the proposed pathway without causing extensive damage to nuclei in the region. (See figure 1 for position of anterior hypothalamic knife cut, AHKC.) These knife cuts also blocked the pressor response to centrally administered All. These results suggested that the All pressor response was mediated by a fiber tract that coursed through the periventricular hypothalamus.

The AV3V lesion produces pressor deficits to centrally administered hypertonic saline and carbachol as well as to All. An experiment was designed to determine if these responses were mediated by vasoconstrictor pathways that were separate from the All pressor pathway. Animals were prepared with anterior hypothalamic knife cuts (AHKCs) designed to transect the previously described All pressor pathway at some locus between the OVLT and the ventral anterior hypothalamus. The animals were tested for pressure responsiveness to central doses of All, hypertonic saline, and carbachol. Without exception, animals that exhibited a pressor response to central All (indicating that the pathway was not transected bilaterally) also had pressor responses when administered either carbachol or hypertonic saline. Conversely, each animal that did not respond to All did not respond to carbachol or to hypertonic saline. These results indicated that the vas-
Figure 1. Positions of knife cuts used to determine projections of vasomotor pathways from the AV3V region. The coronal section depicted is at the level of 6570 µ (König JFR, Klippel RA: The Rat Brain: A Stereotaxic Atlas of the Forebrain and Lower Parts of the Brain Stem. Huntington, New York: Krieger Publishing Company, 1963). The black horizontal bar depicts the position of the anterior hypothalamic knife cut (AHKC). The path followed by the knife is depicted by a unilateral vertical stippled line. This knife cut eliminates the pressor responses produced by intraventricular administration of All, hypertonic saline, and carbachol. In addition, the AHKC attenuates renin-dependent hypertension in the rat. The diagonally striped rectangular area represents the region of the lateral hypothalamus critical for the vasomotor responses produced by the electrical stimulation in the AV3V region. There is no attenuation of these responses as the blades are lowered bilaterally through the stippled tracks above these regions. This medial forebrain knife cut (MFKC) transects part of the medial forebrain bundle. These lateral knife cuts did not attenuate the pressor responses to centrally administered All, hypertonic saline, or carbachol. Regional hemodynamic alterations were monitored by the pulsed-Doppler flow probe technique. The results indicated that elimination of the pathway which mediates the pressor responses to chemical stimulation of the AV3V region had no effect on the resistance changes that occur during electrical stimulation of the region. It was obvious that another vasoconstrictor system was in the region. Subsequently, we found that bilateral vertical knife cuts in the lateral hypothalamus that transected part of the medial forebrain bundle eliminated all hemodynamic responses to electrical stimulation in the AV3V region. (See figure 1 for position of medial forebrain knife cut, MFKC.) Furthermore, these lateral knife cuts did not attenuate the pressor responses to centrally administered All, hypertonic saline, and carbachol.

AV3V Vasomotor Pathways and Experimental Hypertension

The AV3V lesion prevents the development of aortic ligation,11 one-kidney Goldblatt hypertension12 and deoxycorticosterone (DOCA)/salt hypertension.13 Experiments were performed to determine if animals with knife cuts that block the central pressor responses to All, hypertonic saline, and carbachol can develop these types of hypertension. We found that the knife cut (AHKC, see figure 1) that eliminates these vasoconstrictor responses prevented only the renin-dependent model of hypertension (aortic ligation model). Since one-kidney Grossman and DOCA/salt hypertension developed in animals with this type of knife cut, we concluded that the AV3V region must contain separate neural mechanisms that are involved in nonrenin-dependent renal hypertension. Studies are currently in progress on the possible role of the lateral vasoconstrictor pathway (MFKC, see figure 1) in the development of nonrenin-dependent hypertension.

Discussion

Previous work had demonstrated that the AV3V region is involved in the pressor responses produced by central administration of All, carbachol, and hypertonic saline in the rat. Electrical stimulation in the region causes increases in renal and mesenteric vascular resistance with concomitant decreases in hindlimb vasodilation.6,10 An experiment was designed to determine if the vasoconstrictor responses activated electrically in the AV3V region were mediated by the same projections as those activated by chemical stimulation.

Animals were prepared with AHKCs that eliminate the pressor responses to All, hypertonic saline, and carbachol. Regional hemodynamic alterations were monitored by the pulsed-Doppler flow probe technique. The results indicated that elimination of the pathway which mediates the pressor responses to chemical stimulation of the AV3V region had no effect on the resistance changes that occur during electrical stimulation of the region. It was obvious that another vasoconstrictor system was in the region. Subsequently, we found that bilateral vertical knife cuts in the lateral hypothalamus that transected part of the medial forebrain bundle eliminated all hemodynamic responses to electrical stimulation in the AV3V region. (See figure 1 for position of medial forebrain knife cut, MFKC.) Furthermore, these lateral knife cuts did not attenuate the pressor responses to centrally administered All, hypertonic saline, or carbachol.

Additional considerations regarding the role of the AV3V region in hypertension and vasoconstrictor pathways in the brain are discussed in more detail elsewhere.14
to All, hypertonic saline and carbachol, attenuates renin-dependent hypertension. One-kidney Grollman and DOCA/salt hypertension, both low-renin models, did not require the integrity of this pathway. Although altered sodium intake and/or handling contributes to the development of these models of hypertension, it appears that the participation of sodium is through neural mechanisms other than those associated with the pressor response to cerebroventricular administration of sodium. Currently, our attention is focused on studying the role of the lateral vasoconstrictor pathway. If this pathway proves to be involved in the pathogenesis of some nonrenin-dependent models of hypertension, it will provide new experimental approaches to study of the mechanism(s) that underlie enhanced sympathetic vasomotor activity in these models.

The results of these studies indicate that it is possible to experimentally produce selective deficits in functions inherent to the AV3V region that are involved in renal hypertension. Continuation of efforts to identify afferent and efferent neural systems that make up the functional neuroanatomy of the AV3V region should further our understanding of the abnormalities in neurogenic and humoral control systems involved in hypertension.

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