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 laboratory 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) 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. The AV3V lesion also blocks the pressor responses produced by cerebroventricular administration of hypertonic saline and carbachol. Electrical stimulation in the AV3V region produced increases in mesenteric and renal vascular resistance that are dependent upon the sympathetic nervous system. The AV3V region appears to contain neural elements capable of activating sympathetic outflow to the vasculature. We postulate that the AV3V lesion may...
prevent experimental hypertension by interrupting at a
central level the neurogenic mechanisms necessary for
maintaining chronically elevated blood pressure.

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, projec-
tions from the AV3V region that are involved in the
vasomotor activity associated with chemical and elec-
trical activation of the area were mapped.

The results indicate that at least two separate vaso-
motor systems project from the AV3V region. Elimi-
nation of the vasoconstrictor pathways activated by
chemical stimulation left the pathways responsive to
electrical stimulation intact and attenuated renin-de-
pendent 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.5-8 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 over-
lapping electrolytic lesions or knife cuts blocked these
pressor responses. By analyzing the extent of each
lesion or knife cut, tissue critical to the pressor re-
sponses was determined by eliminating from consider-
ation all tissue that could be destroyed without elimi-
nating 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 con-
scious unrestrained animals.

In studies that required electrical stimulation of the
AV3V region, bipolar stimulating electrodes were im-
planted 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 arti-
cries, and a carotid catheter was inserted for blood pres-
sure 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 hypothal-
amic regions could be determined. Stereotaxic coordi-
nates 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 dam-
aged by the lesions were mapped.

All animals that failed to respond to centrally admin-
istered All had bilateral lesions in structures along the
lamina terminalis or the periventricular tissue in the
anterior hypothalamus. Destruction of the paraventric-
ular nuclei without attendant damage to the anterior
hypothalamus had no effect on the central All pressor
response. However, lesions in the anterior hypothala-
mus 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 de-
stroyed tissue only at the lamina terminalis (organum
vasculosum of lamina terminalis (OVLT) and/or ven-
tral 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 ad-
ministered All originated in the AV3V region at the
OVLT. The pathway appears to ascend along the lam-
ina terminalis to the anterior commissure and then de-
send almost vertically through the anterior hypothala-
mus before projecting caudally to the ventromedial
hypothalamic region. A previous experiment had dem-
onstrated that this pressor response was eliminated by
electrolytic lesion in the ventromedial hypothalamus.9

This hypothesis was tested by making knife cuts in
the anterior hypothalamus that would bilaterally tran-
sect 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 cen-
trally administered hypertonic saline and carbachol as
well as to All. An experiment was designed to deter-
mine if these responses were mediated by vasocon-
strictor pathways that were separate from the All press-
or 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 hypo-
thalamus. The animals were tested for pressure respon-
siveness 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 pres-
sor 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-
oconstrictor pathways involved in the pressor responses to carbachol and hypertonic saline mapped in the same periventricular route as the AHK pressor pathway.

**Electrical Stimulation: Mapping Analysis**

It has been demonstrated in our laboratory that electrical stimulation in the AV3V region causes an integrated pattern of peripheral vascular resistance changes. The typical hemodynamic response pattern is renal and mesenteric vasoconstriction accompanied by hindlimb vasodilation. 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.

**AV3V Vasomotor Pathways and Experimental Hypertension**

The AV3V lesion prevents the development of aortic ligation, one-kidney Grollman hypertension and deoxycorticosterone (DOCA)/salt hypertension. 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 resistance. Since destruction of the AV3V region by electrolytic lesions prevented several models of hypertension, we hypothesized that the vasoconstrictor responses elicited by chemical or electrical stimulation were systems that participated in the pathogenesis of hypertension.

In these studies we have identified two anatomically and functionally distinct vasoconstrictor systems that originate in the AV3V region. Since these projections take different routes through the anterior hypothalamus, it proved possible to selectively eliminate one without affecting the other. Using this approach, we demonstrated that elimination of the periventricular pressor pathway, that carries vasoconstrictor responses...
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.

References
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