The Anteroventral Third Ventricle Region

Participation in the Regulation of Blood Pressure
in Conscious Dogs

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SUMMARY The anteroventral third ventricle (AV3V) region plays an important role in fluid and electrolyte balance and cardiovascular control in the rat; however, experiments in other species have raised questions about the universality of findings in the rat. The effects of discrete lesions placed within the AV3V area on hydromineral balance, the pressor response to angiotensin II given intravenously, and the initiation of a renin-dependent model of hypertension were examined in the dog. A transpharyngeal approach to the optic chiasm enabled us to destroy only the anterior aspects of the AV3V region (aAV3V group) or to include the entire nucleus medianus (NM) as well (aAV3V + NM group). Lesions of the aAV3V caused polydipsia and transient hypernatremia and hyperosmolality. In contrast, adipsia and a sustained increase in plasma sodium levels and osmolality were observed in dogs with lesions of the aAV3V plus the entire NM. Neither lesion altered baseline arterial pressure, heart rate, plasma levels of catecholamines and vasopressin, or total plasma protein levels. Only in aAV3V + NM lesioned dogs was there a tendency for plasma angiotensin II immunoreactivity to be elevated above control values at 2 and 4 days after operation. Neither lesion attenuated the pressor response to intravenous angiotensin II or the initiation of renal hypertension induced by aortic coarctation. As observed in other species, structures within the AV3V region participate in hydromineral balance in the dog; however, in the dog portions of the NM dorsal to the AV3V region are essential for the mediation of drinking behavior. Because initiation of a renin-dependent hypertension was not altered by either aAV3V or aAV3V + NM lesions, these structures, although involved in the regulation of fluid balance, do not appear to mediate the central pressor actions of blood-borne angiotensin II in the dog. (Hypertension 7 [Suppl I]: I-80–I-87, 1985)

KEY WORDS • angiotensin II • fluid and electrolyte control • forebrain lesions • nucleus medianus • sodium chloride • renal hypertension • thirst • vasopressin

THE endocrine hypothalamus and its associated afferent and efferent pathways are increasingly recognized as being critically involved in integrating the hemodynamic, humoral, and hormonal events that accompany the production of high blood pressure. The studies of Buggy et al.1 and Brody and Johnson2 established that structures contained within the tissue surrounding the anteroventral portion of the rat’s third ventricle (AV3V) participate in the expression of drinking behavior and the production and reversal of various forms of hypertension. Other studies in rats have validated these original experiments and uncovered additional evidence about the mechanisms involved in these effects.1-6 Given the availability of detailed anatomical maps of the rat brain, and of strains with genetic disorders of neuroendocrine function, it is not surprising that much of the knowledge about the AV3V region has been obtained in this species. It is not clear how much of the data obtained in rats is directly applicable to other species, including humans. Although studies in species other than the rat are few,7-10 questions have been raised by their findings. In sheep and rabbits an AV3V lesion produces a deficit in drinking and hypernatremia7 9 but does not prevent the development of either adrenocorticotropic hormone (ACTH)-induced hypertension8 or one-kidney, one clip hypertension.9 Further, the centrally mediated pressor effects of intravenous angiotensin II...
(ANG II) are not attenuated in rabbits\textsuperscript{11,12} and dogs\textsuperscript{10} with AV3V lesions.

The discovery by Ferrario et al.\textsuperscript{11} and Scroop and Lowe\textsuperscript{12} that in dogs ANG II exerts its centrally mediated cardiovascular effects by acting at the area postrema\textsuperscript{11,12} suggested the participation of sites other than the AV3V region in this species. In accord with this idea we showed recently that an acute lesion of the AV3V region does not alter the pressor response to ANG II infused into a carotid artery, even though it does blunt the increase in arterial pressure produced by the injection of the peptide into the third cerebral ventricle.\textsuperscript{10} As this observation indicated that the AV3V region does not mediate the neurogenic actions of blood-borne ANG II, a more detailed study of the long-term effects of AV3V lesions in the dog was required. Accordingly, we investigated the effects of discrete electrolytic lesions within the AV3V region on hydromineral balance, arterial pressure, and the acute phase of renal hypertension produced by constriction of the abdominal aorta above the renal arteries.

### Methods

Eleven adult male mongrel dogs (body weight range, 8–14 kg) were used in these experiments. Throughout the study the dogs were housed in individual pens, fed a solid diet (Lab Canine Chow, Ralston Purina Company, St. Louis, MO), and given water ad libitum. Water intake, body weight, and rectal temperature were determined daily.

#### Surgical Procedures

Dogs were anesthetized with morphine (2 mg/kg i.m.) and sodium pentobarbital (30 mg/kg i.v.), and catheters (Tygon, Norton Plastics and Synthetics Division, U.S. Stoneware Inc., Akron, OH) were inserted into an iliac artery and vein under aseptic conditions. Three to four weeks later, they were anesthetized with halothane (Ayerst Laboratories, Inc., New York, NY) and the periventricular tissue of the third ventricle was lesioned. As previous experience\textsuperscript{10} showed that it was difficult to lesion the AV3V region reproducibly with the technique described by Thrasher et al.,\textsuperscript{11} we used a new approach. Briefly, the AV3V region was reached through the roof of the mouth instead of through the ventral surface of the brain. The OC then was incised. With the aid of a surgical microscope the dura was incised. After splitting the mucosa and muscle layers of the soft palate, a small hole was drilled in the caudal portion of the presphenoid bone. The edges of the bone were sealed with bone wax (Ethicon Inc., Sommerville, NJ), and the dura was incised. With the aid of a surgical microscope the dura was incised. The hole was expanded to visualize the confluence of the optic nerves with the rostral border of the optic chiasm (OC) and the anterior communicating artery. A monopolar electrode (RNEX 300, 0.2 mm outside diameter; tip 0.5 mm; Rhodes Medical Instruments, Inc., Woodland Hill, CA) was inserted through the ventral surface of the exposed brain 1 mm anterior to the OC at an angle of 25 degrees in 7 of the 11 dogs. Between five and seven anodal electrolytic lesions (4 mA DC for 20 seconds) were placed 1.0 mm apart in the vertical plane, between either 3 and 7 mm or 3 and 9 mm from the ventral surface of the brain. The OC then was covered with Gelfoam (Upjohn Co., Kalamazoo, MI), and the hole in the bone was sealed with epoxy (EPOXE E glue, Locute Co., Cleveland, OH). A non-absorbing 6-0 suture (Ethicon Inc., Sommerville, NJ) was used to obtain a tight closure of the soft palate. In four sham-operated dogs the OC was exposed but the electrode was not lowered into the brain. While convalescing, the dogs were fed a liquid diet (Compleat B, Doyle Pharmaceutical Co., Minneapolis, MN) and given antibiotics (Polycillin N, Bristol Laboratories, Syracuse, NY; 250 mg/kg i.v., t.i.d. for 5 days) and dexamethasone sodium phosphate (Hexadrol, Organon Inc., Orange, NJ; 4 mg for 3 days). Both sham-operated and lesioned dogs received an i.v. infusion of 0.9% sodium chloride at a slow rate (2.5 ml/kg/hr) for 5 days after operation.

#### Experimental Protocol

During the first 2 weeks following implantation of arterial and venous catheters dogs were brought to the laboratory for daily training. After this period, arterial pressure and heart rate were recorded for about 90 minutes every other day as described previously.\textsuperscript{11} Measurements were resumed 48 hours after brain surgery and continued for 1 week.

The effect of the electrolytic lesions on the acute development of renal hypertension produced by constriction of the abdominal aorta above the renal arteries was studied 1 week after operation. On the day of the experiment, the dogs were anesthetized with halothane and mechanically ventilated. The mean arterial pressures (MAP) in the brachial and femoral arteries were monitored continuously using matched strain-gauge manometers. The abdominal aorta just below the diaphragm was exposed, and a vascular clamp was inserted around the vessel a few centimeters above the right renal artery. One hour later, the aorta was clamped to produce a brachial-femoral arterial pressure gradient of about 50 to 60 mm Hg. This degree of constriction was maintained for 4 hours. Two hours after aortic coarctation (AoC), captopril was infused intravenously at a rate of 50 μg/kg/minute for 60 minutes; a bolus injection of the drug (1 mg/kg) was also given just before starting the infusion. This treatment combination has been shown by us\textsuperscript{10} to produce a blockade of the angiotensin-converting enzyme (ACE) that was sustained for the duration of the experiment. At the end of 1 hour, the infusion of captopril was stopped and a competitive inhibitor of the vasoconstrictor action of arginine vasopressin [d(CH2)5Tyr (Me) AVP] was injected at a dose (20 μg/kg i.v.) causing sustained blockade of the pressor effects of AVP.\textsuperscript{10} At the completion of the study the brain was removed for histological analysis.
Biochemical Techniques

Serum Na⁺ and K⁺ levels were determined by flame photometry. Plasma osmolality was measured by freezing point depression. The ANG II immunoreactivity (irANG II) was determined from samples of blood collected in a prechilled (0°C) syringe containing 200 μL of a solution of 15% ammonium EDTA and 9.25 mM o-phenanthroline. After centrifugation at 4°C, the plasma was stored at −20°C until assayed.

Levels of irANG II were determined by radioimmunoassay that used an antibody with less than 1% cross-reactivity with ANG I. The concentration of AVP in plasma was measured as described by Crofton et al. Plasma concentrations of norepinephrine (NE) and epinephrine (EPI) were measured with a radioenzymatic assay.

Histological Analysis

Brains were stored in a solution of 10% formalin and 30% sucrose for at least 1 month before the diencephalon was serially sectioned at 50 μm. Alternate sections were stained with either luxol fast blue, neutral red, or with cresyl violet and examined microscopically to determine the extent of damage to anatomical structures.

Analysis of Data

All data are expressed as means ± SEM. Analysis of variance was employed to assess differences between groups followed by the Newman-Keuls’s test for individual comparisons. Differences of single variables within a group before and after lesion were evaluated with Student’s t test for paired observations. Differences were considered to be significant for p < 0.05.

Results

For clarity, the data obtained in these experiments are grouped on the basis of postlesion examination of the structures destroyed by the electrolytic lesion. Detailed histological analysis of coronal brain sections extending from the rostrum of the corpus callosum through the level of the mammillary bodies showed the following. In four animals (Figure 1 A, B), the lesion destroyed the organum vasculosum of the lamina terminals (OVLT), the periventricular tissue located at the level of the medial preoptic nucleus (POM), and the ventral nucleus medianus (NM). Minor damage to the ventral anterior commissure (AC) was seen in some brains. Because the lesion in these four dogs was restricted to the anterior portion of the AV3V region as originally defined by Brody and Johnson, these animals were grouped as the anterior AV3V (aAV3V) subgroup.

In the other three dogs (see Figure 1 C, D) the OVLT, the periventricular tissue of the lamina terminalis, the dorsal, anterior, and ventral NM, and portions of the AC were damaged. As these lesions extended dorsal to the AC to include the entire NM as well as the aAV3V region, these animals were classified as the aAV3V + NM subgroup.

Effects of Forebrain Lesions on Hydromineral Balance and Blood Pressure in Conscious Dogs

Prelesion values for water intake, MAP, heart rate (HR), and body weight were nearly the same in sham-operated and lesioned dogs. Twenty-four hours after operation, water intake increased markedly in the aAV3V dogs but decreased in the dogs with an aAV3V + NM lesion (Figure 2). There were no significant changes in either MAP or body weight (Figure 2).

Figure 3 shows that 2 days after operation hypertenntia and hyperosmolarity developed in both groups of lesioned dogs. By the sixth day, however, these changes were present only in the group of dogs with a lesion in the aAV3V + NM region. Both the concentration of K⁺ in the plasma (Figure 3) and the levels of NE, EPI, and AVP (Table I) were not statistically different when compared with either corresponding prelesion values or the sham-operated group. On the other hand, in the dogs in which the lesion produced a deficit in water intake (aAV3V + NM) and sustained increases in plasma Na⁺ concentration and osmolality, there was a tendency for plasma irANG II levels to be elevated on the second and fourth days postlesion (Table I).

These increases did not attain statistical significance (p > 0.05) because of the small size of the sample (n = 3 dogs).

Forebrain Lesions and the Pressor Response to Angiotensin II

The infusion of ANG II has been shown to produce a reduced pressor response in AV3V lesioned rats. In the anesthetized dog, Marson et al. showed that the infusion of ANG II into a carotid artery produced the same increase in pressure before and after an acute AV3V lesion. To obtain more detailed information, we assessed the role of chronic aAV3V lesions in altering the magnitude of the rises in MAP produced by the administration of [H]²⁻¹²⁵I Ang II in the resting conscious dog twice before and again on the fourth and sixth days postlesion. As shown in Figure 4, systemic injections of ANG II (2 and 5 μg) caused similar increases in MAP in sham-operated, aAV3V, and aAV3V + NM lesioned dogs.

Aortic Coarctation Hypertension

Figure 5 illustrates the effect of acute AoC on MAP and HR. In sham-operated dogs, constriction of the abdominal aorta above the renal arteries caused a 35 ± 3 mm Hg fall in femoral artery pressure and a 26 ± 3 mm Hg increase in brachial artery pressure (see Figure 5). The hypertension was sustained during the first 2 hours of observation, and it was accompanied by a peak increase in plasma irANG II levels of 47 ± 13% (p < 0.05). On the other hand, plasma concentrations of AVP did not change (79 ± 34 pg/ml before versus 35 ± 11 pg/ml 2 hours after AoC) and HR remained at baseline levels. Two hours after AoC, an i.v. infusion of captopril in sham-lesioned dogs caused MAP to fall to the baseline values while HR did not change. Plasma irANG II levels fell from 111 ± 37 pg/ml to 16 ±
**Figure 1** The locations of discrete lesions placed within the AV3V are illustrated schematically and with photomicrographs of cresyl violet-stained brain sections. A Diagram of a sagittal section of the dog brain indicating the placement of the lesion in four dogs (dotted area) This lesion is restricted to the anterior portion of the AV3V region (aAV3V group) and included the organum vasculosum of the lamina terminalis (OVLT), the preoptic periventricular tissue (POM), and the ventral portion of the nucleus medianus (NM). B Coronal section of an aAV3V lesion The lesion was ventral to the anterior commissure (AC) and included the OVLT, the ventral NM, and the periventricular tissue of the preoptic region (arrows). C A diagram illustrating the placement of the lesion in three dogs (cross-hatched area) This lesion involved the aAV3V region and extended dorsal and rostral to the AC to ablate the entire NM. D This coronal section demonstrates that the OVLT and the entire NM were ablated by this lesion (arrows). Bar = 2 mm CC = corpus callosum; LV = lateral ventricle. MI = massa intermedia. P = pituitary. III = third ventricle. OC = optic chiasm.

**Table 1** Neurohormonal Effects of Forebrain Lesions in Conscious Dogs

<table>
<thead>
<tr>
<th>Group</th>
<th>rAng II (pg/ml)</th>
<th>AVP (pg/ml)</th>
<th>NE (pg/ml)</th>
<th>EPI (pg/ml)</th>
<th>TP (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham AV3V</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>20 ± 13</td>
<td>2.6 ± 1.0</td>
<td>384 ± 97</td>
<td>182 ± 81</td>
<td>6.4 ± 0.2</td>
</tr>
<tr>
<td>2nd day</td>
<td>18 ± 14</td>
<td>0.3 ± 0.3</td>
<td>250 ± 42</td>
<td>125 ± 43</td>
<td>6.9 ± 0.3</td>
</tr>
<tr>
<td>4th day</td>
<td>15 ± 14</td>
<td>1.4 ± 1.0</td>
<td>335 ± 49</td>
<td>80 ± 20</td>
<td>—</td>
</tr>
<tr>
<td>6th day</td>
<td>12 ± 12</td>
<td>4.3 ± 2.8</td>
<td>312 ± 23</td>
<td>103 ± 24</td>
<td>6.7 ± 0.1</td>
</tr>
<tr>
<td>aAV3V</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>8 ± 4</td>
<td>1.4 ± 0.9</td>
<td>445 ± 94</td>
<td>213 ± 30</td>
<td>6.0 ± 0.2</td>
</tr>
<tr>
<td>2nd day</td>
<td>10 ± 2</td>
<td>ND</td>
<td>561 ± 109</td>
<td>156 ± 66</td>
<td>—</td>
</tr>
<tr>
<td>4th day</td>
<td>13 ± 6</td>
<td>0.5 ± 0.5</td>
<td>474 ± 142</td>
<td>94 ± 38</td>
<td>6.3 ± 0.2</td>
</tr>
<tr>
<td>6th day</td>
<td>19 ± 6</td>
<td>ND</td>
<td>511 ± 99</td>
<td>134 ± 42</td>
<td>6.4 ± 0.2</td>
</tr>
<tr>
<td>aAV3V + NM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1 ± 1</td>
<td>2.6 ± 1.6</td>
<td>426 ± 116</td>
<td>200 ± 110</td>
<td>6.9 ± 0.2</td>
</tr>
<tr>
<td>2nd day</td>
<td>27 ± 15</td>
<td>1.9 ± 1.2</td>
<td>682 ± 125</td>
<td>65 ± 20</td>
<td>—</td>
</tr>
<tr>
<td>4th day</td>
<td>85 ± 64</td>
<td>2.7 ± 1.4</td>
<td>632 ± 114</td>
<td>165 ± 81</td>
<td>7.3 ± 0.6</td>
</tr>
<tr>
<td>6th day</td>
<td>14 ± 8</td>
<td>20 ± 17</td>
<td>990 ± 294</td>
<td>469 ± 134</td>
<td>6.5 ± 0.6</td>
</tr>
</tbody>
</table>

Values are means ± SEM from four sham-operated, four aAV3V lesioned animals, and three with an aAV3V + NM lesion. TP = total plasma proteins, ND = nondetectable, AVP = arginine vasopressin, NE = norepinephrine, rAng II = immunoreactive angiotensin II, EPI = epinephrine, NM = nucleus medianus, aAV3V = anterior aspects of the anteroventral third ventricle.
FIGURE 2 Water intake, mean blood pressure, and body weight 1 week before and 1 week after operation (indicated by the arrow). Lesions of the aAV3 region caused a significant increase in water intake compared with the control values (p < 0.05). In contrast, lesions of the aAV3 + NM resulted in a marked decrease in water intake. There were no differences in blood pressure or body weight among the three groups at any time. Values are means ± SEM. Sh AV3V = sham AV3V.

* = p < 0.05 when experimental values are compared with the control values.

FIGURE 3 Plasma electrolyte, osmolality, and hematocrit values before operation (C) and on Days 2 and 6 after operation for the three groups of dogs studied. * = p < 0.05 when experimental values are compared with the control values.

FIGURE 4 Dose-response curves for two doses of angiotensin II (2 and 5 µg) administered intravenously both before and after sham operation, aAV3V, and aAV3V + NM lesions. Increases in arterial pressure induced by ANG II were similar in all groups of dogs before and after sham surgery or lesioning. Baseline MAP was similar before (112 ± 4 mm Hg, 113 ± 6 mm Hg, and 109 ± 4 mm Hg) and after (102 ± 6 mm Hg, 119 ± 6 mm Hg, and 104 ± 2 mm Hg) operation in sham-operated, aAV3V, and aAV3V + NM animals, respectively.
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The changes in MAP and heart rate following aortic occlusion (AoC) and subsequent administration of a converting-enzyme inhibitor (CEI) and a vasopressin antagonist (AVP-A). The AoC produced similar increases in MAP in the sham-operated, aAV3V, and aAV3V + NM lesioned dogs during the first 2 hours. Treatment with CEI in the third hour reversed the hypertension in all three groups. The AVP-A did not further reduce blood pressure significantly. No alterations in heart rate were observed.

12 pg/ml (p < 0.05) at the end of the 1-hour infusion of captopril. Plasma AVP levels averaged 35 ± 11 pg/ml just before and 88 ± 36 pg/ml 1 hour after ACE blockade. This difference was not statistically significant (p > 0.05). The additional administration of an AVP antagonist had no effect on MAP, HR, or plasma concentration of irANG II.

Discussion

These experiments show that in the dog neural structures contained within the AV3V region participate in the regulation of drinking and hydromineral balance. By correlating the alterations in water intake with the extent of the lesions, we have shown that in dogs these functions are modulated by structures located within or just dorsal to the anterior portion of the AV3V region as defined by Brody and Johnson in the rat. On the other hand, the current studies also reveal that in the dog the OVLT, the periventricular tissue at the level of the POM nucleus, and the entire NM are not required for the rises in MAP produced by either acute AoC or the intravenous injection of ANG II. Thus, these new studies in the dog demonstrate that there are important similarities, as well as differences, between the effects of lesions in the AV3V region in the two species.

A number of important findings were obtained in these experiments in conscious dogs. First, the lesions had divergent effects on water intake and plasma Na+ concentration. The second finding concerns the effects of these lesions on the plasma concentrations of irANG II and AVP. The third major observation is the dissociation between altered fluid regulation and the cardiovascular pressor effects of exogenously and endogenously raised levels of blood ANG II. With respect to water intake, lesions restricted to the aAV3V region caused polydipsia while those that also destroyed the NM produced sustained adipsia. These opposing changes in water consumption contrasted with the striking increases in plasma Na+ concentration and osmolality occurring in all dogs after ablation of the tissue. Forty-eight hours after operation, the increases in plasma Na+ concentration and osmolality were about the same in both groups of animals even though water intake was markedly reduced in one group (aAV3V + NM) and more than doubled in the other (aAV3V). Beyond the fourth day, animals within the aAV3V lesion group were able to correct the hypernatremia, apparently because of their enhanced water intake. Similarly, the presence of sustained adipsia may account for the lack of correction of the hypernatremia and hyperosmolality observed in the aAV3V + NM lesioned dogs.
We suspect that the increases in osmolality and plasma Na⁺ concentration observed in lesioned dogs during the first few days after operation reflect a disruption of mechanisms other than drinking behavior alone. Extracellular dehydration due to hypovolemia may not be a factor as the hematocrit, body weight, and plasma protein levels were comparable in both groups of lesioned and sham-operated dogs. Accordingly, it is necessary to consider that the early hyponatremia and hyperosmolality following lesions of the aAV3V region may be due to loss of a circulating hormonal factor(s) contributing to the preservation of osmotic equilibrium. As plasma levels of AVP were not increased in either aAV3V or aAV3V + NM lesioned dogs, a resetting or disruption, or both, of the central Na⁺ or osmostat mechanisms involved in the secretion of AVP must be considered. This interpretation is in agreement with data obtained in AV3V lesioned rats demonstrating an impaired release of AVP to acute stimuli. It is also possible that the early increases in plasma Na⁺ concentration in both groups of lesioned dogs are partly due to a fall in urinary Na⁺ excretion. Enhanced sympathetic nerve activity (SNA), augmented formation of ANG II and aldosterone, and/or a fall in the production and release of a putative brain natriuretic hormone may play a role. Although in the current experiments the possible contributions of these factors were not evaluated directly, measurements of the blood concentration of catecholamines and irANG II do not suggest a major involvement of the sympathetic or renin-angiotensin systems. Although in the aAV3V + NM lesioned dogs there was a tendency for the plasma levels of irANG II to be higher than those recorded in aAV3V or sham-operated dogs, the small number of measurements performed in lesioned dogs precludes any strong conclusion. It has been shown before that in rats with chronic AV3V lesions plasma renin concentration is significantly elevated above normal levels. Whether the increases in plasma irANG II in aAV3V + NM lesioned dogs suggest the interruption of a central negative feedback for the regulation of plasma renin activity and plasma irANG II remains unclear. The possibility that the hyponatremic state in aAV3V lesioned dogs may be accounted for by a disruption in the release of a factor that is important for the excretion of Na⁺ is an attractive explanation. Although we have direct evidence to support its involvement, Bealer et al. found that blood from AV3V lesioned rats had suppressed levels of natriuretic hormone activity. Thus, the studies in the dog have confirmed the hypothesis that structures within the AV3V region are involved critically in the integration of humoral and neurohormonal effector pathways controlling the osmotic equilibrium of the extracellular fluid.

The mechanisms underlying the divergent effects of the lesion on water consumption are not known. The uniform difference between the two types of lesions was the additional destruction of the anterior and dorsal portions of the NM in the aAV3V + NM group. These data indicate that cell groups within, and/or fiber tracts passing through, the dorsal and anterior NM may be involved in the control of drinking behavior. On the other hand, our findings in the dog suggest that the OVLT, the periventricular preoptic tissue, and the ventral portion of the NM are less critical. In dogs it has been suggested that the OVLT mediates drinking in response to changes in plasma Na⁺ and osmolality, while the subfornical organ (SFO) may be responsible for ANG II-induced drinking. On the other hand, Lind et al. have shown that transection of neural connections close to the main body of the SFO in rats attenuates the dipsogenic response to subcutaneous injection of ANG II and hypertonic NaCl. Given that Miselis has shown efferent projections from the SFO to and through the dorsal and anterior NM, and Camacho and Phillips have described similar projections from the OVLT through the ventral NM, a lesion of the aAV3V + NM may produce adipsia despite the presence of increased plasma Na⁺ levels, osmolality, and irANG II levels. Therefore, our findings suggest that pathways within the NM are critical for the integration of humoral factors triggering drinking behavior.

Both groups of lesioned dogs differed strikingly from AV3V lesioned rats with respect to the central pressor effects of blood-borne ANG II. In both acute and chronic AV3V lesioned rats Brody and Johnson showed a consistent decrease in the magnitude of the pressor response to ANG II given intravenously. In contrast, this response was not blunted in dogs with either aAV3V or aAV3V + NM lesions. These data confirm our previous study performed in anesthetized acute AV3V lesioned dogs, which show that the pressor response produced by intracarotid infusion of ANG II was the same before and after ablation of the AV3V region. On the other hand, Ferrario et al. have shown that acute and chronic lesions of the area postrema produce a significant blunting of the pressor response to i.v. ANG II. The current findings provide further evidence that the site of action of blood-borne ANG II is outside the anterior AV3V region. It could be argued that bolus i.v. injections of ANG II are not a satisfactory way to evaluate the central action of the peptide, since Lind et al. observed that in rats with knife cuts of the ventral stalk of the SFO there was a statistically significant attenuation of the pressor response during infusion but not injection of ANG II intravenously. In their study, however, both the injection and the infusion techniques produced comparable downward shifts of dose-dependent responses. Thus, their data do not necessarily invalidate the use of one or the other procedure to evaluate the central actions of ANG II. Moreover, here and in previous experiments in dogs, we have used both injection and infusion procedures to investigate the role of the area postrema and the AV3V region in the production of the centrally mediated pressor response to ANG II. In all of these studies in dogs, we have obtained similar results regardless of the technique employed.

With regard to the acute phase of hypertension due to AoC, it is not possible to make a direct comparison with studies performed in the rat because the atten-
vation of AoC hypertension reported in AV3V rats was observed days, rather than hours, after constriction of the aorta. It is clear that in the dog AoC caused an elevation in blood pressure that was renin dependent because levels of plasma irANG II were elevated and both MAP and plasma irANG II returned to baseline levels during the infusion of captopril. If the acute phase of this form of hypertension involves a central action of ANG II, our results exclude the anterior AV3V and NM regions as the responsible sites. Moreover, our findings that lesions within the AV3V region that disrupt hydromineral balance do not alter the initiation of renal hypertension are in agreement with similar observations by Fink and Bryan in the rabbit. Although chronic studies in aAV3V lesioned dogs are required to assess this possibility further, it is noteworthy that Scoop et al. found that the acute rise in blood pressure produced by constriction of one renal artery in anesthetized dogs was blunted after lesion of the area postrema. A similar effect was obtained by Ferrarino in dogs with evolving one-kidney, one chip hypertension.

By applying a new surgical approach to produce chronic AV3V-like lesions in the dog, we have been able to confirm the importance of this region in the modulation of hydromineral regulatory behavior as shown by the concomitant behavioral and humoral changes resulting from ablation of the anterior portion of the AV3V region, alone or in conjunction with the anterior and dorsal aspects of the NM. We have also shown that in dogs the aAV3V or the aAV3V + NM region is not part of a neural circuit responsible for the cardiovascular effects of ANG II administered intravenously. Moreover, the immediate cardiovascular pressor response produced by a decrease in renal perfusion pressure in anesthetized dogs does not require the integrity of the anterior AV3V region.

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