Vasopressin-Central Nervous System Interactions in the Development of DOCA Hypertension

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SUMMARY DOCA-salt hypertension does not develop in rats with hereditary lack of vasopressin (DI rats) nor in rats with lesion of the anteroventral region of the third ventricle (AV3V), an area controlling vasopressin (VP) release. We examined, therefore, the effect of VP treatment on the development of DOCA salt hypertension in AV3V-lesioned (AV3V-L) normal Sprague-Dawley rats and in Brattleboro rats homozygous for diabetes insipidus (DI rats). We also examined changes in vascular reactivity in isolated, perfused kidneys in the experimental groups. Whereas sham-lesioned (SL) rats showed hypertension at 5 weeks, AV3V-L rats showed no change in arterial pressure (AP) after DOCA. AV3V-L rats given VP exhibited only an intermediate rise in AP in spite of the fact that plasma VP levels were comparable in DOCA-treated SL rats and AV3V-L rats. SL and AV3V-L rats given VP showed enhanced renal vascular activity whereas no vascular changes occurred in AV3V-L rats. At 5 weeks post DOCA, intact DI rats given VP were hypertensive and exhibited enhanced renal vascular reactivity. AV3V lesion in DI rats completely prevented VP-induced DOCA/salt hypertension and enhanced vascular responsiveness. These data suggest that VP plays a primary role in DOCA-salt hypertension through an induction of enhanced vascular reactivity and through central mechanisms requiring the integrity of the AV3V region. (Hypertension 4 (suppl II): II-131-II-137, 1982)

KEY WORDS • vasopressin • DOCA hypertension • central nervous system • Brattleboro rats • diabetes insipidus

DOCA/salt hypertension fails to develop in rats after ablation of the periventricular tissues surrounding the anteroventral region of the third cerebral ventricle (AV3V). Mechanisms underlying the failure to develop hypertension after AV3V lesion have not been determined.

It has also been demonstrated that DOCA/salt hypertension fails to develop in rats with hereditary lack of vasopressin (DI rat). When given vasopressin (VP), however, these rats do develop DOCA/salt hypertension with a course and magnitude similar to that seen in rats with normal hypophyseal function.

The purpose of the present studies was to examine the relationship between VP and AV3V region in DOCA/salt hypertension to determine whether alterations in VP mechanisms, possibly mediated through the AV3V region, were involved in the "protective" effect of the lesion. We examined, therefore, the development of DOCA/salt hypertension in AV3V-lesioned rats, in AV3V-lesioned rats given VP, and in AV3V-lesioned DI rats given VP. Since in earlier studies in both normal rats<sup>4</sup> and vasopressin-replaced DI rats<sup>4</sup> we found development of DOCA/salt hypertension to be associated with an increase in vascular reactivity, changes in renal vascular reactivity were also examined in the present studies.

Methods

AV3V Lesion

Lesion of the AV3V region was made in male Sprague-Dawley rats (150-200 g) by passing an anodal current (Grass DC lesion maker) of 2 mA, for 15-20 seconds through a stereotaxically placed lesioning electrode (24-gauge nichrome wire, insulated except at the tips). The coordinates for placement of the electrode (with skull levelled between bregma and lambda) were: 0.3 mm posterior to bregma, on the midline, and 7.5 mm below the dura. Sham-lesioned rats received the same treatment with the exception that the electrode was lowered 5.0 mm from the dura and no current was passed. The same lesion procedure was used for male DI rats (150-200 g, Blue Spruce...
Farms); however, these rats were given VP replacement beginning 2 weeks prior to the lesion and continuing for the duration of the experiment. We had found in preliminary studies that DI rats failed to survive AV3V lesion without VP.

At the end of the experimental protocol, the head of each lesioned rat was perfused with normal saline followed by buffered 10% formalin. The brain was removed and stored in formalin. Correct placement of the lesion, as described in previous studies, was verified in each rat by histological examination of 40 μm sections of the brain cut from the appropriate area and stained with cresyl violet. Approximately 10% of rats lesioned had incorrectly placed lesions. Data from these rats were not included in this study.

All lesioned rats were placed on Valenstein's solution (0.25 g sodium saccharin plus 3.0 g glucose/100 ml distilled water) for 2 days prior to the lesion and for 3 days postlesion. The rats were then weaned to tap water by successive dilution of the sugar solution with 3000 X g for 30 minutes

removal by centrifugation (3000 X

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Rats were allowed 1 month to recover from the lesion before beginning DOCA/salt treatment. By that time, the lesioned rats were healthy, active, and had a normal water intake (30-40 ml/rat/day). Deoxycorticosterone acetate (DOCA, Sigma, 100 mg/kg) was given to unilaterally nephrectomized AV3V-lesioned (AV3V-L) rats and sham-lesioned (sham-L) rats in a single Silastic implant. Sham-L control rats received a Silastic implant without DOCA. Sprague-Dawley rats received 0.9% NaCl plus 0.2% KCl as drinking water; DI rats received 0.3% NaCl plus 0.07% KCl. Rats given VP received daily subcutaneous injections of VP tannate (Pitressin, Parke Davis, 100 m units/100 g rat), a mixture of lysine and arginine vasopressin. In AV3V-L Sprague-Dawley rats, VP treatment began on the day of DOCA implantation.

Systolic arterial pressure was monitored 1-2 times per week in conscious, restrained rats prewarmed at 37°C for 5-10 minutes using an indirect tail cuff method (automatic cuff-inflator, pulse detector, IITC, Inc.). The rats were conditioned to the restraining devices and cuff inflations prior to determination of baseline parameters. Separate groups of AV3V-L and sham-L Sprague-Dawley rats treated with DOCA/salt were prepared and used for plasma arginine VP determinations, which were done 6-8 weeks post DOCA. These rats were rapidly decapitated and the trunk blood collected for measurement of plasma arginine VP.

Plasma proteins were precipitated by acetone and removed by centrifugation (3000 X g for 30 minutes

Renal perfusion experiments were performed 6-8 weeks after DOCA/salt treatment under sodium pentobarbital (Nembutal-Abbott Labs) anesthesia (50 mg/kg, i.p.). The right kidney was surgically isolated and perfused using previously described techniques, which were modified for the current study. Kidneys were perfused at constant flow with a modified Krebs-Henseleit solution containing Ficoll (Pharmacia AB, 35g/liter). The pH of the perfusate was 7.4; it was maintained at a temperature of 37°C and aerated with a mixture of 95% O₂ and 5% CO₂.

Perfusion pressure, measured from the side arm of the perfusion cannula (transducer = Century EP-01) was recorded on a Beckman Type RM dynograph recorder. Perfusion flow was periodically measured from a renal venous catheter. An equilibration period of 60 minutes was allowed before the experimental protocol was started.

Vascular reactivity to norepinephrine (NE) (Levophed bitartrate, Breon Lab, Inc.), VP (Pitressin, Parke Davis), and angiotensin II (AlI) (Hypertensin, Ciba-Geigy) was assessed. The experimental protocol in this study has been previously described. Cumulative dose response curves to the vasoconstrictors were obtained. All drugs were injected intrarterially in bolus amounts from subthreshold to maximum doses.

All values presented in the text and in tables and figures are group means ± standard errors (SE). Data from the Sprague-Dawley groups and DI groups were analyzed separately. One-way analysis of variance was
used to evaluate weekly measurements of arterial pressure, plasma VP levels, and hemodynamic characteristics of the rat at perfusion. Dose-response curves obtained from renal perfusion experiments were compared on the bases of slope, determined by linear regression; ED₅₀, determined by probit analysis, and maximum response. Differences in these parameters among the various groups was determined through one-way analysis of variance. In all cases of multiple comparisons when a significant \( p < 0.05 \) F-ratio was obtained, the Newman-Keuls test was used to determine which of the comparisons was significantly different.

### Results

#### Sprague-Dawley Rats

Sham-L rats showed a significant \( p < 0.01 \) rise in arterial pressure 2 weeks after DOCA/salt treatment; arterial pressure averaged 195 mm Hg at 5 weeks post DOCA (fig. 1). AV3V-L rats showed no rise in arterial pressure after DOCA/salt. In contrast, AV3V-L rats given vasopressin showed a significant \( p < 0.01 \) rise in arterial pressure, which averaged 155 mm Hg at 5 weeks post DOCA.

Plasma arginine vasopressin (AVP) levels were approximately threefold \( p < 0.05 \) greater in sham-L chronic DOCA hypertensive rats than in normotensive sham-L control rats (table 1). AV3V-L rats treated with DOCA/salt showed a small, but insignificant rise in plasma AVP. DOCA/salt-treated AV3V-L rats given VP showed plasma levels that were 3.5 times greater than sham-L control rats and not significantly different from sham-L DOCA/salt-treated rats.

Figure 2 shows the mean arterial pressure and renal vascular resistance in AV3V-L and sham-L rats at the time of perfusion. The renal vascular resistance is the resistance at maximal vasodilation of the vascular bed with papaverine HCl. Renal vascular beds of AV3V-L rats treated with DOCA/salt showed a resistance that was not different from that seen in control sham-L rats. In contrast, DOCA-treated sham-L rats and AV3V-L rats given VP that showed a rise in arterial pressure also demonstrated a significant increase in renal vascular resistance. However, the magnitude of the change in resistance was not as great in the AV3V-L rats treated with VP as it was in the sham-L rats.

#### Table 1. Plasma Arginine Vasopressin (VP) Levels

<table>
<thead>
<tr>
<th>Rat group</th>
<th>VP (units/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham-lesioned controls (n = 6)</td>
<td>1.9 ± 0.25</td>
</tr>
<tr>
<td>Sham-lesioned + DOCA/salt (n = 6)</td>
<td>5.2 ± 0.7*</td>
</tr>
<tr>
<td>AV3V-lesion + DOCA/salt (n = 7)</td>
<td>3.0 ± 0.8</td>
</tr>
<tr>
<td>AV3V-lesion + DOCA/salt + VP (n = 6)</td>
<td>7.2 ± 1.3*</td>
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</tbody>
</table>

\* \( p < 0.05 \) indicates significant difference from sham-lesioned controls and AV3V lesions + DOCA/salt rats.

### Figure 1. Systolic arterial pressure (mm Hg) in sham-lesioned DOCA/salt-treated rats (●), in AV3V-lesioned DOCA/salt-treated rats (○), and in AV3V-lesioned DOCA/salt-treated rats given vasopressin (☆). Responses are expressed as group means ± se. Systolic arterial pressure was monitored by an indirect tail cuff method.

### Figure 2. Mean arterial pressure (mm Hg, direct measurement) and renal vascular resistance (mm Hg/ml ⋅ g⁻¹ ⋅ min⁻¹, at maximal vasodilation with papaverine HCl) in anesthetized rats at the time of perfusion. Asterisks indicate significant differences in arterial pressure and resistance determined by one-way analysis of variance among the group responses and the Kewman-Keuls test. Responses are expressed as means ± se. Numbers in the bars represent the number of rats per group, \( n = 6 \) for the control sham group.
Changes in renal vascular reactivity were found to parallel the rise in arterial pressure. At 8 weeks post DOCA/salt, renal vascular beds from hypertensive DOCA/salt-treated sham-L rats showed an enhanced reactivity to vasopressin (fig. 3). The curves were characterized by a leftward shift, a decreased ED50, an increased slope, and a greater maximal response (fig. 3, table 2). AV3V-L rats treated with VP that showed a rise in arterial pressure after DOCA/salt treatment also showed enhanced reactivity to VP, although the change was not as great as that seen in the hypertensive sham-L rats. AV3V-L rats that failed to develop DOCA/salt hypertension showed no change in renal vascular reactivity to VP.

DI Rats

Lesion of the AV3V region in DI rats was found to completely prevent the development of DOCA/salt hypertension induced by VP in these rats (fig. 4). At 5 weeks post DOCA/salt, intact DI rats replaced with VP showed a rise in systolic arterial pressure, which averaged 185 mm Hg. In contrast, the arterial pressure of AV3V-L rats treated with DOCA/salt and VP was 120 mm Hg, not significantly different from before DOCA/salt treatment. Intake of 0.3% NaCl + 0.07% KCl in AV3V-L DI rats that failed to develop hypertension after DOCA/salt treatment (65.0 ± 6.4 ml/day) did not differ significantly from the intake in DI rats replaced with VP that did become hypertensive after DOCA/salt (73.0 ± 6.0 ml). The average intake of DI rats treated with DOCA/salt alone was 387.1 ± 15.8 ml/day.

At 6 weeks post DOCA, renal vascular beds from intact DI rats replaced with VP that developed hypertension with DOCA/salt showed enhanced renal vascular reactivity to VP. Curves were characterized by a parallel leftward shift, decreased ED50 (p < 0.01), and a greater maximal response (fig. 5). In a previous study, we showed that DI rats treated with DOCA/salt alone showed a marked depression in renal vascular reactivity when compared to untreated DI rats. AV3V-L DI rats treated with VP that failed to develop hypertension did not show the depressed reactivity seen in the DI rats treated with DOCA/salt alone. However, these rats failed to develop enhanced reactivity to VP that was comparable to that seen in DOCA hypertensive DI rats replaced with VP. Average ED50 for the three DI groups tested were (10-6 g VP) DI + DOCA + VP = 0.55 ± 0.23; DI + DOCA + VP + AV3V-L = 3.68 ± 0.17%; and DI + DOCA = 15.6 ± 0.17. Using data from a previous study, we found that the average ED50 for VP in untreated DI rats was 4.0 ± 0.36. Changes in reactivity to NE and AII in the DI groups followed a pattern similar to that seen in response to VP.

Discussion

The AV3V region is a critical receptor site for central actions of AII and hyperosmotic NaCl.
TABLE 2. \( ED_{50} \), Dose Response Curve Slopes, and Maximum Responses to Norepinephrine, Vasopressin, and Angiotensin II

<table>
<thead>
<tr>
<th></th>
<th>Norepinephrine ( (10^{-8} \text{ g}) )</th>
<th>Vasopressin ( (10^{-9} \text{ g}) )</th>
<th>Angiotensin II ( (10^{-9} \text{ g}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control/sham</td>
<td>24.5 ± 3.0</td>
<td>18.6 ± 1.9</td>
<td>25.6 ± 5.0</td>
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<tr>
<td>DOCA/AV3V</td>
<td>23.9 ± 3.0</td>
<td>15.7 ± 2.2</td>
<td>7.06 ± 0.83</td>
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<tr>
<td>DOCA/AV3V/VP</td>
<td>5.25 ± 0.59**</td>
<td>5.1 ± 0.52**</td>
<td>0.02 ± 0.01**</td>
</tr>
<tr>
<td>DOCA/sham</td>
<td>4.25 ± 0.46**</td>
<td>3.06 ± 0.46**</td>
<td>1.08 ± 0.33**</td>
</tr>
</tbody>
</table>

Slopes

<table>
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<tr>
<th></th>
<th>Control/sham</th>
<th>DOCA/AV/3V</th>
<th>DOCA/AV3V/VP</th>
<th>DOCA/sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control/sham</td>
<td>6.9 ± 0.64</td>
<td>1.4 ± 0.13</td>
<td>5.1 ± 0.46</td>
<td></td>
</tr>
<tr>
<td>DOCA/AV/3V</td>
<td>6.9 ± 0.19</td>
<td>1.8 ± 0.18</td>
<td>0.57 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>DOCA/AV3V/VP</td>
<td>20.6 ± 1.2**††</td>
<td>4.1 ± 0.36*</td>
<td>298 ± 41.0**††</td>
<td></td>
</tr>
<tr>
<td>DOCA/sham</td>
<td>13.0 ± 1.34**</td>
<td>8.5 ± 3.0*</td>
<td>41.7 ± 4.7**</td>
<td></td>
</tr>
</tbody>
</table>

Maximum responses

<table>
<thead>
<tr>
<th></th>
<th>Control/sham</th>
<th>DOCA/AV3V</th>
<th>DOCA/AV3V/VP</th>
<th>DOCA/sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control/sham</td>
<td>45.0 ± 1.5</td>
<td>47.9 ± 2.0</td>
<td>23.9 ± 0.92</td>
<td></td>
</tr>
<tr>
<td>DOCA/AV3V</td>
<td>44.9 ± 2.6</td>
<td>47.9 ± 3.7</td>
<td>22.3 ± 2.4</td>
<td></td>
</tr>
<tr>
<td>DOCA/AV3V/VP</td>
<td>57.9 ± 1.02**††</td>
<td>56.7 ± 3.0**††</td>
<td>28.0 ± 0.85**††</td>
<td></td>
</tr>
<tr>
<td>DOCA/sham</td>
<td>67.9 ± 1.2**</td>
<td>68.9 ± 2.7**</td>
<td>36.6 ± 1.7**</td>
<td></td>
</tr>
</tbody>
</table>

* \( p < 0.05 \), significantly different from control/sham and DOCA/AV3V.
** \( p < 0.01 \), significantly different from control/sham and DOCA/AV3V.
†† \( p < 0.01 \), significantly different from DOCA/sham.

Renal Vascular Resistance

\( \text{mmHg} / \text{ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1} \)

**FIGURE 5.** Dose-response curves in isolated perfused kidneys from untreated DI rats (△), intact DI rats treated with DOCA/salt alone (●), intact DI rats treated with DOCA/salt and replaced with vasopressin (○), and AV3V-lesioned DI rats treated with DOCA/salt and replaced with vasopressin (x). Ordinate and abscissa are as in figure 3. Responses are expressed as means ± SE. \( n = \) number of rats in each group.
Moreover, ablation of this region in rats prevents the development of many forms of experimental hypertension including that induced by DOCA/salt. Recent evidence has also suggested that the AV3V region has direct control over the release of vasopressin. Johnson et al.10 found that AV3V-lesioned rats studied 24 hours after the lesion did not show increased plasma VP levels in spite of the fact that these animals were adipsic or severely hypodipsic. Furthermore, in chronic AV3V-lesioned rats, pressor responses to central AII and hyperosmotic stimulants, thought to be due in large part to VP release, were markedly attenuated as was VP release, monitored in the same animals by changes in urine conductivity.11 These data suggested that, following ablation of the AV3V region, rats cannot increase VP secretion in response to selective humoral pressor stimuli. In addition to these studies, neuroanatomical connections between the AV3V region and the VP synthetic nuclei (paraventricular, PVN, and supraoptic, SON) have been identified.12-14 Plasma levels of VP are elevated in early and chronic15-18 stages of DOCA/salt hypertension. Moreover, DI rats failed to develop hypertension when treated with DOCA/salt,19 but did so when replaced with VP.1 This constellation of experimental findings linking VP to the development of DOCA/salt hypertension and the AV3V region to the control of VP release and the development of DOCA/salt hypertension led us to postulate that the protective effect of the AV3V lesion was due to failure to lesioned rats to increase VP levels in response to DOCA/salt.

Similar to previous studies,1 we confirmed that AV3V lesion in normal rats prevented the development of DOCA/salt hypertension. Moreover, the usual increase in vascular reactivity that accompanied the development of the DOCA/salt hypertension also did not occur in AV3V-L rats. In contrast, AV3V-L rats given VP did show a significant increase in arterial pressure after DOCA; however, the increase was attenuated. Vascular reactivity was also increased in these rats, but again, the magnitude of the response was attenuated. These studies demonstrated that VP treatment could partially restore DOCA/salt hypertension in AV3V-L Sprague-Dawley rats in parallel with an increase in peripheral vascular reactivity.

Although the amount of VP given to AV3V-L rats was sufficient to raise the plasma level to an amount comparable to that seen in sham-lesioned rats, VP treatment alone did not fully restore DOCA/salt hypertension. This finding suggested that the protective effect of the AV3V lesion in DOCA/salt hypertension was not simply due to prevention of increased VP secretion. Rather, the data suggest that the lesion might have disrupted pathways or receptors sites required for a potential central mechanism of action of VP. This hypothesis was supported by our findings in DI rats that after AV3V lesion VP could no longer induce DOCA/salt hypertension. It is not readily apparent why there was a partial increase in arterial pressure in DOCA/salt-treated AV3V-L Sprague-Dawley rats given VP, but no increase in DOCA/salt-treated AV3V-L DI rats. It does not appear that AV3V-L DI rats failed to develop hypertension because of an inadequate intake of saline. There was no difference in saline intake between the intact DI rats given VP that did develop hypertension and the lesioned DI rats given VP that failed to develop hypertension after DOCA/salt treatment. We did not assess volume or electrolyte status of our lesioned rats. If changes in body fluid volumes or sodium balance are required for the development of DOCA/salt hypertension, the protective effect of the AV3V lesion may be due to a failure of lesioned animals to develop the necessary changes in fluid or electrolyte balance. Clearly, studies assessing changes in fluid and electrolyte balance and body fluid volumes are required.

Recent evidence has suggested that VP may act centrally on neural target areas involved in cardiovascular regulation. Neuroanatomical studies have shown that the nuclei containing cells that synthesize VP (paraventricular, PVN, and supraoptic, SON) send vasopressinergic projections to a number of target areas that participate in cardiovascular regulation, including the nucleus tractus solitarii, dorsal vagal complex, AV3V region, and central gray.18-18 Since these VP-containing projections make axosomatic and axodendritic connections with these target areas, one function of VP as a neurotransmitter may be as a modulator of neuronal activity.18 Several studies have suggested that VP may act centrally to alter the function of the baroreceptor reflex.19-31 Intracisternal administration of VP was found to attenuate the blood-pressure-lowering effect of carotid sinus stimulation, suggesting suppression inhibition of central sympathetic vasomotor activity.19 Matsuguchi et al.18 have shown that microinjections of VP into the area of the nucleus tractus solitarius of rats produced significant dose related increases in blood pressure and heart rate. Furthermore, electrical stimulation of the PVN and SON was found to attenuate the bradycardia produced by carotid sinus stimulation while ablation of these areas increased the magnitude of bradycardia.31 Recently, we compared the cardiovascular responses to electrical stimulation of the AV3V region in DI rats and normal Long Evans (LE) rats.32 In LE rats, stimulation of the AV3V region produced a frequency dependent decrease in mean arterial pressure and heart rate, increases in renal and mesenteric vascular resistances, and a decrease in hindquarter vascular resistance. In contrast, DI rats demonstrated significantly greater decreases in pressure and heart rate and lesser changes in vascular resistances. These results suggest that the cardiovascular responses to AV3V stimulation may depend, in part, upon the integrity of VP-containing neurons.

In the present studies, we have provided evidence that the AV3V region, VP, and increased vascular reactivity are intricately involved in the development of DOCA/salt hypertension. The precise interaction of these factors is not known. Recent studies on possi-
ble participation of a natriuretic factor in DOCA/salt hypertension provide an attractive, albeit highly speculative, potential link among these factors. A circulating substance, which inhibits the activity of the sodium-potassium ATPase in cardiac and vascular smooth muscle cells, has been found in DOCA/salt hypertension and has been suggested to be a pressor agent with the capacity to alter cardiovascular reactivity. Although the chemical nature and structure of the circulating pressor agent have not been identified, a natriuretic factor has been proposed as a likely candidate. The AV3V region has been demonstrated recently to be involved in the natriuretic response to saline infusion, perhaps through regulation of the elaboration of a natriuretic factor. Bealer et al. found that rats with chronic AV3V lesions showed deficits in sodium and water excretion in response to an acute isotonic NaCl load that was associated with an absence of natriuretic hormone in the plasma. Furthermore, Pamnani et al. have also shown that chronic AV3V-lesioned rats failed to show decreased vascular sodium-potassium ATPase activity in response to acute volume expansion as observed in normal or sham-lesioned rats.

Our data suggest that the ability of the AV3V lesion to prevent DOCA/salt hypertension may be due, in part, to an interference with pathways required for the mechanism of a potential central action of VP. Based on the studies of natriuretic factor in hypertension, it is tempting to speculate that a potential central action of VP requiring the AV3V region may involve an alteration in the production or release of natriuretic factor which, in turn, regulates peripheral vascular reactivity and induces the rise in arterial pressure.

Another aspect of the mechanism may involve disruption of receptor sites in the AV3V region linked to descending vasconstrictor pathways. Since our other studies have identified vasconstrictor deficits in response to AV3V stimulation in DI rats, integrity of vasopressinergic neurons may be, in part, necessary for the increase of sympathetic vasconstrictor activity associated with DOCA/salt hypertension.

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