Role of Catecholamines and Vasopressin in Cardiovascular Responses to Bilateral Dorsolateral Transection of the Medulla Oblongata in the Rat

ZOFIA ZUKOWSKA-GROJEC, M.D., MOHAMED A. BAYORH, PH.D., ROBERT L. ZERBE, M.D., MIKLOS PALKOVITS, M.D., AND IRWIN J. KOPIN, M.D.

SUMMARY The role of sympathetic and other pressor systems in the development of fulminant hypertension induced by baroreceptor deafferentation is still unclear. We studied the effects of acute hypertension produced by bilateral dorsomedullary knife cuts lateral to the nucleus tractus solitarii (DMK-cut) on plasma norepinephrine (NE), epinephrine (E), and vasopressin (VP) in conscious, tail-artery-cannulated rats. In saline-pretreated (SAL) rats, DMK-cut caused a significant (p < 0.001) rise in mean blood pressure (MAP, +68 ± 3 mm Hg), heart rate (HR, + 97 ± 19 bpm), NE (+ 2.5 ± 0.3 ng/ml), E (+ 2.7 ± 0.4 ng/ml), and VP (+115 ± 34 pg/ml) compared to sham-operated rats. Neither sympathetic blockade with chlorisondamine (CHLO, 10 mg/kg, s.c.) nor elimination of the pressor effects of VP by use of Brattleboro rats or the VP pressor antagonist resulted in a maximal MAP response significantly different from that in the SAL + DMK-cut group. However, CHLO-pretreatment of Brattleboro rats completely abolished the increase in MAP and HR. It is suggested that the bilateral DMK-cut causes acute hypertension, probably due to the abolition of baroreceptor reflexes by central interruption of neural connections of the nucleus tractus solitarii. It appears that both the increased sympathetic and vasopressin normally contribute to this hypertension; however, either one is sufficient to sustain the elevated blood pressure.

(Hypertension 5: 908-915, 1983)

KEY WORDS • norepinephrine • epinephrine • heart rate • neurogenic hypertension

OVER the past several years, peripheral or central interruption of baroreceptor reflex pathways has been shown to produce acute hypertension in several different species.1-4 In rats, Doba and Reis1 have shown that bilateral electrolytic lesions of the nucleus tractus solitarii (NTS) rapidly produce fulminating arterial hypertension. Intense vasoconstriction in specific systemic vascular beds causes a marked increase in total peripheral resistance; this reduces cardiac output and eventually leads to pulmonary edema.2 Similar cardiovascular responses have been produced in rats by dorsolateral medullary knife-cut (DMK-cut) lateral to the NTS.3

A number of mechanisms appear to contribute to this acute and extreme elevation of blood pressure. It has been suggested that hypertension due to NTS lesions is a result of a marked augmentation of sympathetic neural discharge,1-2,4,5 since ganglionic and alpha-adrenergic blockade reverses the pressor response.1 Plasma renin activity (PRA) and epinephrine (E) levels were found to be elevated in the later phase of NTS lesion-induced hypertension, but neither nephrectomy3 nor adrenalectomy1,9 prevented the development of high blood pressure unless preceded by chemical sympathectomy with 6-hydroxy-dopamine.1 It has been established that the baroreceptor reflex is also a potent nonosmotic stimulus for the release of vasopressin.10 Moreover, elevated plasma levels of this peptide have been found in several forms of hypertension.11-15 Thus, development of neurogenic hypertension may also be dependent on increased vasopressin secretion.

The purpose of our present study was to clarify the mechanisms involved in the development of an acute hypertension produced by intracranial transection of baroreceptor fibers. The contributions of peripheral sympathetic activation, adrenomedullary secretion, and vasopressin release to the hemodynamic responses evoked by DMK-cut have been evaluated by direct measurements of the plasma levels of catecholamines and vasopressin in intact rats with and without blockade of sympathetic ganglionic transmission or treatment with a vasopressin pressor antagonist prior to DMK-cut and in vasopressin-deficient rats pretreated with a ganglionic blocking agent.
Methods

Eighty-one female Osborne-Mendel rats (NIH) weighing 225–250 g and 12 female Brattleboro (homozygous for diabetes insipidus) rats weighing 200–250 g (Blue Spruce Farms, Ahlmburst, New York) were housed six per cage in our research animal facility with controlled temperature, humidity, and 12-hour lighting cycle. They were maintained on regular Purina rat chow and tap water ad libitum for about 1 week before the experiments.

Twenty-four hours before the experiment, all rats were anesthetized with halothane (2% in oxygen) and polyethylene cannulas (PE-50) filled with heparinized saline were inserted into the tail arteries, as previously described. On the day of the experiment, the arterial catheters were connected to a blood pressures transducer (Type 4-327-C, Beckman Dynograph 511A), and blood pressures and heart rates were recorded continuously while animals were conscious and unrestrained in their home cages (screened to minimize external stimuli). After recording resting blood pressure and heart rate for 20 minutes, a basal blood sample (0.8 ml) was obtained from each rat. Immediately after the blood was withdrawn, at this time and subsequently, an equal volume of blood from a pool of blood from anesthetized (2% halothane in oxygen) donor rats was administered. Rats were divided into five groups. The first (n = 30) and second (n = 25) groups of rats were pretreated with chlorisondamine (CHLO, 10 mg/kg, s.c), a long-acting ganglion blocker, which has been demonstrated to block ganglionic transmission for at least 4 hours, or 0.2 ml saline alone, respectively. Sixty minutes after administration of CHLO or vehicle, blood pressures and heart rates were recorded for 5 minutes and blood samples (0.8 ml) again obtained for assay of catecholamines and vasopressin. Each of these two groups of rats were subsequently subdivided into DMK-cut and sham-operated groups.

The third (n = 8) and fourth (n = 7) groups of rats were pretreated with an antagonist of pressor responses of vasopressin: 1-(β-mercaptop-β-cyclopentamethyl- enepropionic acid), 2-(O-methyl) tyrosine arg vasopressin (10 μg/kg in 0.2 ml 0.9% NaCl, i.a.), or an equal volume of 0.9% NaCl, respectively, 5 minutes prior to the DMK-cut. The fifth group of animals were Brattleboro rats (n = 11), of which five were treated with chlorisondamine (10 mg/kg, s.c.) 60 minutes prior to the DMK-cut. In Groups 3, 4 and 5, all rats received DMK-cuts, and blood samples (0.4 ml) for catecholamines were obtained before, 5, and 15 minutes after operation (with an exception of CHLO-pretreated Brattleboro rats, which did not have any blood withdrawn).

After anesthesia was induced a second time with halothane (2% in oxygen), the rats were placed in a stereotaxic apparatus. The obex region of the medulla oblongata was exposed and fibers just lateral to the NTS (fig. 1) were transected bilaterally using a glass microknife under an operating microscope. The DMK-cut penetrated 1.2 to 1.5 mm deep into the medulla, transecting afferent and efferent fibers from/to the nucleus of the solitary tract and dorsal vagal nucleus and other fibers of the IXth and Xth cranial nerves in the solitary tract, at the level of the obex (fig. 1). DMK-cut performed by a 0.08 mm wide glass knife is very fine, it does not lesion the NTS or other neighboring cell groups. Sham operation, performed on half of the rats in the first and second groups, consisted of a more rostral, coronal cut without transection of the NTS fibers. The whole procedure lasted 6 to 7 minutes.

Immediately after the DMK-cut or sham operation, the wound was closed and the anesthesia ended by returning the rats to room air. During the following 15 to 25 minutes, blood pressures and heart rates were monitored continuously except during blood sampling and replacement at 5 and 15 minutes after operation. After 15 minutes (Groups 1–2) or 25 minutes (Groups 3–5), the rats were killed by decapitation and the brains removed from the skull for microscopic examination of the transection site. The pituitary glands of DMK-cut and sham operated, saline- and CHLO-pretreated rats were taken out and kept frozen at −60°C until assayed for vasopressin.
Assay of Plasma Norepinephrine (NE) and Epinephrine (E) in Plasma

Plasma levels of E and NE were assayed by a radioenzymatic thin-layer chromatographic procedure, as previously described. In brief, aliquots (200 μl) of protein-free plasma were incubated with catechol-O-methyltransferase and tritiated S-adenosyl-methionine. After incubation, the reaction was stopped by the addition of borate buffer (pH 8) containing metanephrine, normetanephrine, and 3-methoxytyramine. The amines were extracted into toluene-isoamyl alcohol (3:2) and then into 0.1 M acetic acid. The radioactive products were separated by thin-layer chromatography, the appropriate areas identified under ultraviolet light, and the areas separately scraped into counting vials. After periodate oxidation of the O-methylated compounds to vanillin, phosphor-containing toluene was added and the tritium content determined by liquid scintillation spectrometry.

Assay of Plasma and Pituitary Vasopressin

Vasopressin was measured by a previously described radioimmunoassay. An aliquot of stored plasma (250 μl) was extracted with acetone and petroleum ether, dried in a vacuum centrifuge (Speed-Vac, Savant, Hicksville, New York), resuspended in 500 μl of assay buffer, and duplicate 200 μl aliquots assayed for vasopressin. The extraction yielded 65% recovery; no correction was made for extraction losses. Iodinated vasopressin (New England Nuclear, Boston, Massachusetts; SA, 1273 μCi/μg, 1500 cpm/tube) served as the tracer, and synthetic arginine vasopressin (Calbiochem, La Jolla, California) was used as the standard. The synthetic vasopressin, which has a biological activity of 410 U/mg, was diluted in assay buffer for the standard curve. The rabbit antivasopressin antibody provided by Dr. Jacques Durr, University of Chicago, was used in a final assay dilution of 1/2,500,000. Each tube, containing a total volume of 500 μl, was incubated for 7 days at 4°C and was separated using polyethylene glycol. There was less than 1% cross-reactivity with oxytocin. Assay sensitivity was 0.2 to 40 pg/assay tube. Therefore, the range of levels detectable (not correcting for extraction losses) was 2 to 400 pg/ml. The intraassay coefficient of variation was 3.9% at 1 pg/tube and 6.2% at 10 pg/tube.

After completion of the experiment, animals were sacrificed by decapitation. The posterior pituitary was microdissected and extracted in 100 μl 0.1 N HCl. The tissue sample was diluted 25,000-fold in assay buffer so that concentrations were approximately in the middle of the assay standard curve. Protein content was determined by the method of Lowry, and values are expressed as ng/mg protein.

Drugs

Ecolid — hydrochloride (chlorisondamine-HCl, Ciba-Geigy, Summit, New Jersey), 1-(β-mercaptopropionyloxy) arginine vasopressin (Peninsula Laboratories, Inc., San Carlos, California), and prazosin hydrochloride (Pfizer, Brooklyn, New York) were obtained from the indicated sources.

Statistical Evaluation of Data

Blood pressure, heart rate, catecholamine, and vasopressin responses in DMK-cut and sham-operated rats were compared by analysis of variance for repeated measures. Dunnett's test for multiple comparisons was applied to isolate within and between group differences where appropriate. Results were considered significant if p < 0.05. All results are mean (± SEM) values for the indicated number of animals.

Results

Cardiovascular and Sympathetic Responses to Bilateral Dorsolateral Medullary Knife-Cut in Saline-Pretreated Rats

In saline-pretreated rats, bilateral DMK-cut evoked an immediate, marked elevation of systolic and diastolic blood pressures and heart rates (fig. 2, two upper panels). The maximal increase in MAP (68 ± 3 mm Hg, fig. 3 and table 1) occurred 5 minutes after DMK-cut, declined slightly thereafter, but remained significantly elevated throughout the whole experimental period (p < 0.01, fig. 3). Heart rate increased by 97 ±
19 bpm 5 minutes after the transection \((p < 0.01, \text{fig. } 3)\) and remained at this high level for 15 minutes. Analysis of variance for repeated measures indicated that pressor and heart rate responses of saline-pretreated DMK-cut rats were significantly greater than those of saline-pretreated, sham-operated rats \((p < 0.01, \text{fig. } 3)\).

In these animals 5 minutes after bilateral DMK-cut, there was a sharp increase in the plasma levels of NE \((2.53 \pm 0.28 \text{ ng/ml, } p < 0.01, \text{fig. } 3)\) and E \((2.65 \pm 0.44 \text{ ng/ml, } p < 0.01, \text{fig. } 2)\). Plasma NE levels remained significantly elevated \((2.89 \pm 0.33 \text{ ng/ml, } p < 0.01)\), and E levels continued to rise to \(4.83 \pm 0.93 \text{ ng/ml, } p < 0.01\) at 15 minutes after DMK-cut.

The sympathoadrenomedullary responses of DMK-cut rats were significantly greater \((p < 0.001\) by ANOVA, fig. 3) than those of sham-operated rats, which showed only a transient and moderate increase in plasma E \((p < 0.05, \text{fig. } 3)\), presumably as a response to the stress of sham operation.

**Effect of Ganglionic Blockade on the Cardiovascular and Sympathetic Responses to Bilateral Dorsolateral Medullary Knife-Cut**

One hour after treatment with CHLO (fig. 4), there were decreases in blood pressure \((27 \pm 5 \text{ mm Hg, } p < 0.01)\) and heart rate \((78 \pm 17 \text{ bpm, } p < 0.01)\). At this time, bilateral DMK-cut evoked a significant increase of mean blood pressure \((61 \pm 11 \text{ mm Hg, } p < 0.01, \text{fig. } 4)\) similar to that obtained in saline-pretreated rats, but heart rate remained slowed (fig. 4, table 1).

In the CHLO + SHAM and CHLO + CUT groups of rats, CHLO significantly lowered plasma levels of NE \((282 \pm 23 \text{ pg to } 59 \pm 2 \text{ pg/ml, or from } 333 \pm 42 \text{ to } 56 \pm 4 \text{ pg/ml, respectively, } p < 0.01, \text{fig. } 4)\) and of E \((187 \pm 33 \text{ to } 109 \pm 14 \text{ pg/ml, and from } 148 \pm 33 \text{ to } 64 \pm 12 \text{ pg/ml, } p < 0.05, \text{fig. } 4)\). The elevation of plasma catecholamines induced by DMK-cut was markedly attenuated in CHLO-pretreated rats.

**Response of Plasma and Pituitary Vasopressin to Bilateral Dorsolateral Medullary Knife-Cut**

DMK-cut evoked similar marked increases in plasma vasopressin levels in both saline- and CHLO-pretreated rats \((116 \pm 34 \text{ and } 88 \pm 22 \text{ pg/ml, respectively, fig. 5 and table 2})\). Although vasopressin levels were not significantly elevated after CHLO, they were

**Table 1. Cardiovascular and Plasma Catecholamine Responses at 5 Minutes after Bilateral Dorsolateral Medullary Knife-Cut (DMK-Cut) in Rats**

<table>
<thead>
<tr>
<th></th>
<th>SAL + CUT</th>
<th>CHLO + CUT</th>
<th>Ant AV + CUT</th>
<th>Bratt + CUT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MAP (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 6)</td>
<td>+ 67.5</td>
<td>+ 60.7</td>
<td>+ 57.8</td>
<td>+ 53.0</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>(\pm 2.9)</td>
<td>(\pm 10.7)</td>
<td>(\pm 6.6)</td>
<td>(\pm 8.1)</td>
</tr>
<tr>
<td><strong>HR (bpm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 6)</td>
<td>+ 97</td>
<td>(\pm 67)</td>
<td>+ 83</td>
<td>+ 50</td>
</tr>
<tr>
<td>(n = 5)</td>
<td>(\pm 19)</td>
<td>(\pm 32)</td>
<td>(\pm 25)</td>
<td>(\pm 18)</td>
</tr>
<tr>
<td><strong>NE (ng/ml)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 6)</td>
<td>+ 2.53</td>
<td>(\pm 1.3^*)</td>
<td>+ 1.52</td>
<td>+ 1.33</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>(\pm 0.28)</td>
<td>(\pm 0.05)</td>
<td>(\pm 0.60)</td>
<td>(\pm 0.43)</td>
</tr>
<tr>
<td><strong>E (ng/ml)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 6)</td>
<td>+ 2.65</td>
<td>(\pm 0.29^*)</td>
<td>+ 2.03</td>
<td>+ 1.39</td>
</tr>
<tr>
<td>(n = 4)</td>
<td>(\pm 0.44)</td>
<td>(\pm 0.13)</td>
<td>(\pm 0.94)</td>
<td>(\pm 0.63)</td>
</tr>
</tbody>
</table>

\(^*p < 0.01\), compared to SAL + CUT group, using Dunnett’s t test for multiple comparisons.

Abbreviations: SAL + CUT = saline-pretreated, DMK-cut rats; CHLO + CUT = chlorisondamine-pretreated, DMK-cut rats; Ant AV + CUT = pretreated with an antagonist of vasopressin, DMK-cut rats; Bratt + CUT = DMK-cut Brattleboro rats; MAP = mean blood pressure; HR = heart rate; NE = norepinephrine; E = epinephrine.
increased to 47 ± 11 pg/ml after sham operation (p < 0.01, fig. 5). In CHLO-treated rats, the vasopressin content (table 2) in pituitary (13.4 ± 1.1 ng/mg protein) was not significantly different than in saline-pretreated control rats (15.0 ± 0.4 ng/mg protein). The lowest pituitary content of vasopressin was found in CHLO-pretreated, DMK-cut rats (11.6 ± 1.3 ng/mg protein, table 2), although not significantly different from that of saline-pretreated sham-operated rats.

**Effect of Vasopressin-Antagonist on the Cardiovascular and Sympathetic Responses to Bilateral Dorsolateral Medullary Knife-Cut**

The first injection of vasopressin antagonist (10 µg/kg, mg/kg, i.a.) in the DMK-cut, hypertensive rats induced a marked but short-lasting reduction of MAP (by 46 ± 7 mm Hg, p < 0.01, fig. 2) but not of heart rate (−14 ± 7 bpm).

Pretreatment of rats with vasopressin antagonist (10 µg/kg, i.a.) somewhat slowed the onset of the hypertension induced by DMK-cut (fig. 2) but did not prevent it (table 1). The increases of heart rate in vasopressin antagonist-pretreated rats were comparable to those of saline-pretreated rats 5 minutes after DMK-cut (83 ± 25 and 97 ± 19 bpm, respectively, table 1) but were transient and disappeared by 7–10 minutes. This pattern of heart rate response was similar to that of DMK-cut Brattleboro rats. An additional dose of vasopressin antagonist (25 µg/kg, i.a.) had no further effect on blood pressure or heart rate (fig. 2).

In rats pretreated with the vasopressin antagonist, DMK-cut induced increases in plasma NE (+1.52 ±

---

**TABLE 2. Maximal Plasma Vasopressin Responses and Pituitary Content of Vasopressin in DMK-Cut (CUT) and Sham-Operated (SO) Rats With or Without Chlorisondamine Pretreatment (CHLO)**

<table>
<thead>
<tr>
<th></th>
<th>SAL + SO</th>
<th>CHLO + SO</th>
<th>SAL + CUT</th>
<th>CHLO + CUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma vasopressin (pg/ml)</td>
<td>12.4 ± 5.3</td>
<td>46.7* ± 10.9</td>
<td>116.4† ± 33.8</td>
<td>88.1† ± 21.6</td>
</tr>
<tr>
<td>Pituitary vasopressin (ng/mg protein)</td>
<td>15.3 ± 0.4</td>
<td>13.4 ± 1.1</td>
<td>14.0 ± 1.6</td>
<td>11.6 ± 1.3</td>
</tr>
</tbody>
</table>

Rats were treated with saline (SAL) or chlorisondamine (CHLO) as described in Methods. Comparisons between the groups vs saline-pretreated, sham-operated rats (SAL + SO), by Dunnett's test for multiple comparisons; *p < 0.05, †p < 0.01.
0.60 ng/ml) and E (+2.03 ± 0.94 ng/ml) which were similar to those of saline-pretreated rats (table 1).

In rats treated with vasopressin antagonist both before and after DMK-cut, hypertension was reversed completely by prazosin (0.1 mg/kg, i.a., fig. 2) which lowered mean blood pressure from 154 ± 5 to 56 ± 6 mm Hg.

Cardiovascular and Sympathetic Responses to Bilateral Dorsolateral Medullary Knife-Cut in Brattleboro Rats

The pressor responses to DMK-cut were similar in vasopressin-deficient Brattleboro rats and in normal rats (+53 ± 8 and +68 ± 3 mm Hg, respectively, fig. 6 and table 1). In Brattleboro rats, a moderate transient tachycardia at 5 minutes (+50 ± 18 bpm, p < 0.05, fig. 6) attended the rise in blood pressure, whereas in normal rats the tachycardia was greater and persisted longer.

The hypertension evoked by DMK-cut in Brattleboro rats was accompanied by increases in plasma levels of NE (by 1.33 ± 0.43 ng/ml at 5 minutes, fig. 6) and E (by 1.39 ± 0.63 ng/ml at 5 minutes, fig. 6) which were not significantly different from the catecholamine responses of saline-pretreated DMK-cut normal rats (table 1).

Dorsolateral Medullary Knife-Cut in Ganglion-Blocked Brattleboro Rats

Chlorisondamine (10 mg/kg, s.c.) significantly lowered mean blood pressure (by 43 ± 19 mm Hg, p < 0.05) in Brattleboro rats and completely prevented DMK-cut-induced hypertension and tachycardia.

Discussion

Although it is generally believed that neurogenic hypertension, whether caused by NTS lesion or transection of its neural connections, is entirely dependent on the augmented sympathoadrenomedullary discharge due to abolition of a major inhibitory mechanism,1, 2, 4, 6, 23 there are some discrepancies in the evidence supporting this view.2, 4, 9, 23 This prompted us to measure the changes in plasma catecholamines and vasopressin in conscious rats during the pressor responses evoked by dorsolateral medullary transection of NTS neural connections. In the present study, bilateral DMK-cut in rats caused an acute marked hypertension and tachycardia, which were maintained for 15 to 25 minutes after recovery from surgery. This cardiovascular response to transection was attended by a large increase in plasma levels of both catecholamines, suggesting a massive discharge from the adrenal medulla and sympathetic nervous system. However, ganglionic blockade, which markedly reduced basal sympathetic activity prior to surgery and largely prevented the DMK-cut-induced increase in plasma catecholamines, did not significantly attenuate the blood pressure response to transection. The residual moderate increase in plasma catecholamines found in CHLO-treated rats was mostly in E levels and could be attributed to only partial blockade of adrenal medullary discharge, which is known to be relatively resistant to ganglionic blockade.24 Although insufficient to induce significant tachycardia, the residual release of adrenomedullary catecholamines in ganglion-blocked rats restored heart rates to preganglion blockade levels and could have contributed, in part, to the pressor response evoked by DMK-cut. In addition to the enhanced sympathomedullary discharge, DMK-cut may interrupt neural connections from the dorsal vagal nucleus and therefore diminish parasympathetic outflow. This mechanism could have also contributed to the cardiac acceleration, especially in ganglion-intact rats, and less in ganglion-blocked rats in which CHLO had already blocked parasympathetic activity.

The residual sympathoadrenomedullary catecholamine release cannot be entirely responsible for the hypertension observed in CHLO-pretreated DMK-cut...
rats. In both saline-pretreated and ganglion-blocked rats (Fig. 5), DMK-cut caused a marked increase of the release of vasopressin into the circulation. Plasma levels of vasopressin encountered during the acute hypertensive phase were high enough (up to 116 pg/ml) to be well above the concentration required for the pressor effect of vasopressin.25-27 There is increasing evidence that vasopressin can function as a rapid and potent pressor support system to elevate or sustain arterial pressure in response to osmotic and nonosmotic stimuli.13, 25-27 Among the latter, baroreceptors constitute the major pathway for regulation of vasopressin release.10 In baroreceptor-intact conscious dogs, vasopressin, administered at slow infusion rates yielding plasma levels of vasopressin of only 30 pg/ml, was shown to induce an increase of blood pressure.25-27 Cowley et al.25 found that the pressor effect of vasopressin was further enhanced following baroreceptor denervation, which decreased the threshold 11-fold and increased the sensitivity to vasopressin up to 100-fold. Therefore, it appears that the DMK-cut, by transecting baroreceptor fibers intracranially, produced concentrations of vasopressin significantly high enough to elevate MAP by 60–70 mm Hg.

When one pressor system is eliminated, activity of another is increased to maintain the blood pressure.25, 28, 29 Thus, if sympathetic responses are deficient, vasopressin appears to become a major pressor system, sufficient to elevate and maintain arterial pressure at hypertensive levels. However, in ganglion-blocked rats, plasma levels of vasopressin were not higher than those of hypertensive rats with intact sympathetic activity, but the increments of blood pressure in both groups were similar. Possibly CHLO (particularly in anesthetized and stressed animals), by causing a prolonged hypotension, provided a nonsomotic stimulus for vasopressin release, which depleted the pool of the peptide available for release by the pituitary10 and limited its further release. In fact, the lowest content of vasopressin in the pituitary was found in ganglion-blocked hypertensive rats, a reduction that was not statistically significant but might have been sufficient to deplete the releasable pool of the peptide, which represents only about 10%–20% of total neurohypophysial vasopressin content.10

Another possibility, which does not exclude the first, is that DMK-cut caused almost maximal stimulation of both pressor systems: sympathetic and vasopressin. Either system may have been sufficient to have produced the elevation in MAP of 60–70 mm Hg, which we observed, especially since baroreceptor deafferentation enhances vascular sensitivity to pressor agents.25, 27 In pithed rats, in which reflexes are not possible, sympathetic stimulation (at 3 Hz), which results in a rise in MAP of about 80 mm Hg, is associated with an increase of plasma NE of about 2.0 ng/ml similar to that observed in DMK-cut rats,31 suggesting a maximal rate of sympathetic activation after the transection procedure.

Vasopressin deficiency in Brattleboro rats or pretreatment with the vasopressin pressor antagonist in normal rats did not prevent or attenuate the DMK-cut induced hypertension nor was there a further increase in the activity of the sympathoadrenal system. However, in those rats, the onset of hypertension was delayed and cardiac response was diminished. When administered just after the rats developed hypertension following DMK-cut, the vasopressin pressor antagonist caused a marked (about 50 mm Hg), but transient, decrease in MAP. Subsequent injections of higher doses of the antagonist were completely ineffective. This, together with a delayed onset of hypertension in vasopressin-deficient or -blocked rats, suggests that this peptide may be important in the initiation, but not in the maintenance, of neurogenic hypertension. The results of the present study contrast with those obtained in DOCA-salt14, 15 or hypertonic saline-induced22 hypertension, which suggested vasopressin is essential for the maintenance of high blood pressure.

The lack of persistant tachycardia in hypertensive Brattleboro or vasopressin antagonist-pretreated rats suggests that vasopressin may contribute to cardiac acceleration after DMK-cut. This is probably not a direct effect, since tachycardia was prevented after CHLO pretreatment, and vasopressin is known to cause bradycardia via reflex vagal stimulation31, 32 as well as by a direct cardiodepressant action.32 The bradycardiac action of vasopressin probably depends on intact baroreceptor reflex, and once this is eliminated, opposing central effects might be revealed. Indeed, it has been found that intracerebroventricular injection of vasopressin in conscious rats (unpublished observation) or its microinjection into the NTS of urethane anesthetized rats33 increases blood pressure and heart rate.

Results of our present study indicate that bilateral dorsomedullary transection lateral to the NTS causes an acute, marked hypertension and tachycardia in rats. The cardiovascular pattern is similar to that observed after electrolytic NTS lesions1, 2, 4 and is most probably due to the abolition of arterial baroreceptor reflexes, for which the nucleus tracts solitarii is a primary center. Interruption of neural connections of the NTS by bilateral DMK-cut in rats removes the major inhibitory mechanism(s) of sympathoadrenomedullary activity and vasopressin release, and causes both systems to be markedly stimulated. However, if one of these pressor systems is removed, the remaining one seems sufficient to elevate and maintain the high blood pressure. Therefore, elimination of both are required to prevent or reverse this form of hypertension. Only the increased sympathoadrenomedullary and probably diminished parasympathetic activities, however, produce the tachycardia, although this response is augmented and prolonged when vasopressin is available. The role of the third pressor system, renin-angiotensin, in this form of neurogenic hypertension remains to be established. However, based on pressor mechanisms activated by hemorrhage,28 it seems likely that activation of the renin-angiotensin system requires a much longer time than the 15- to 25-minute interval of the present studies.
REFERENCES

2. Doba N, Reis DJ: Role of central and peripheral adrenergic mechanisms in neurogenic hypertension produced by brainstem lesions in rat. Circ Res 34: 293, 1974
17. Schneider JA, Moore RF, Jr: Electrophysiological investigation of Chlorisondamine dimethochloride (Ecolid TM). A new
Role of catecholamines and vasopressin in cardiovascular responses to bilateral dorsolateral transection of the medulla oblongata in the rat.

Z Zukowska-Grojec, M A Bayorh, R L Zerbe, M Palkovits and I J Kopin

_Hypertension_. 1983;5:908-915
doi: 10.1161/01.HYP.5.6.908

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/5/6/908