Pressor Responsiveness to Vasopressin in the Rat with DOC-Salt Hypertension

JOAN T. CROFTON, B.S., LEONARD SHARE, PH.D.
BIN C. WANG, PH.D., AND ROBERT E. SHADE, PH.D.

SUMMARY To further characterize the role of vasopressin in DOC-salt hypertension, four groups of unilaterally nephrectomized rats were studied: control rats given no further treatment, rats treated with DOC and given 1% saline to drink, or rats treated with only DOC, or 1% saline. Only rats treated with DOC or DOC-salt became hypertensive. Control rats and rats treated with only DOC or 1% saline had similar pressor responses to exogenous vasopressin and angiotensin II. Within the DOC-salt group, two populations of rats were identified: one with normal pressor responsiveness to vasopressin, and one with markedly enhanced pressor responsiveness to vasopressin. Incidence of enhanced responsiveness increased with duration of treatment. Urinary excretion of vasopressin was elevated in the 1% saline and DOC-salt groups after 1 week of treatment, and in the DOC group after 4 weeks. However, the plasma vasopressin concentration was elevated only in the rats treated with both DOC and saline. It is suggested that vasopressin is essential for the expansion of blood volume in the early stages of DOC-salt hypertension, and functions as a direct pressor agent only in the later stages. (Hypertension 2: 424-431, 1980)

KEY WORDS • vasopressin • DOC-salt hypertension • pressor responsiveness

It has been proposed that vasopressin plays an important role as a direct pressor agent in unilaterally nephrectomized rats made hypertensive by treatment with deoxycorticosterone (DOC) and substitution of 1% saline for drinking water (DOC-salt hypertension) 1-4, since plasma levels of vasopressin are elevated and the intravenous injection of an antagonist of the pressor action of vasopressin 5 or a vasopressin antiserum 6 resulted in an acute reduction in arterial blood pressure (BP) in all animals tested. This reduction was slight in some animals, whereas BP fell to normal in others. However, increases in plasma levels of vasopressin in otherwise normal individuals of the magnitude seen in rats with DOC-salt hypertension are inadequate to increase BP. 7,8 Thus, if vasopressin does play a direct pressor role in DOC-salt hypertension, an increased pressor responsiveness to vasopressin must be postulated. To test this hypothesis, the pressor responses to graded i.v. injections of vasopressin were determined in rats with DOC-salt hypertension, as well as in unilaterally nephrectomized rats that were only given 1% saline to drink, or were only treated with DOC. The urinary excretion of vasopressin and plasma concentrations of vasopressin were also determined.

Methods

Five-week-old male Long Evans rats (Blue Spruce Farms) were housed individually in stainless steel metabolism cages and kept in the laboratory. The laboratory was lighted continuously, temperature was held between 23° and 24°C, and they were given Purina Rat Chow (100 μEq NaCl/g) and water ad libitum. The rats were unilaterally nephrectomized, randomly divided into four groups, and allowed to recover for 1 week. Group I (n = 19) served as untreated controls, and were given weekly subcutaneous (s.c.) injections of vehicle for DOC (0.9% NaCl, 1.2 ml/kg body weight) and deionized water to drink. Group II received weekly injections of vehicle, and 1% NaCl was substituted for the drinking water (n = 14). Group II received weekly injections of vehicle, and 1% NaCl was substituted for the drinking water (n = 14). Group III consisted of rats receiving weekly injections of DOC (Percorten Pivalate, 30 mg/kg body weight, s.c.), and 1% NaCl to drink. Group IV were given weekly injections of DOC (30 mg/kg, s.c.) and deionized water to drink. Because of the large number of animals needed, the experiment was repeated at three separate times. To ensure that there were no differences among groups due to time effects in the three separate experiments, values obtained for urinary excretion of vasopressin and systolic blood pressure.
PRESSURE (SBP) prior to any treatment were tested by multiple t tests for within and between group differences. Since no statistically significant differences were found for either variable tested, data from the three experiments were pooled.

Urine was collected once a week for the measurement of the 24-hour excretion of vasopressin (U$_{OHV}$) and urine osmolality, beginning when the rats were 6 weeks old (week 1). The methods for collecting urine and extracting vasopressin are described in detail elsewhere. Each time vasopressin was extracted from urine, two urine samples to which a known amount of vasopressin had been added and two samples with no vasopressin added were also extracted, and recovery of vasopressin from urine was determined. The average recovery of vasopressin from urine (n = 16) was 84% ± 3% (se). No correction was made for incomplete recovery. Vasopressin was determined by radioimmunoassay. Urine osmolality was measured by freezing point depression with a Precision Osmette A osmometer.

The SBP was measured under light ether anesthesia by tail plethysmography on a Narco 6B physiograph immediately following each urine collection. Body weight was measured three times per week, and the volume of fluid ingested was measured daily.

Treatment with DOC, DOC-plus-1% NaCl, or 1% NaCl, was begun following the SBP measurements at week 1 and was continued for either 3 to 5, or 6 to 8 weeks. Data are presented only for the first 5 weeks of the experiment because large numbers of rats were sacrificed after that time.

At the end of each treatment period, the rats were anesthetized with ether, and catheters were inserted into a femoral artery and vein. The rats were then placed in restraining cages and allowed to recover for 2 to 3 hours. Mean arterial blood pressure (MAP) was recorded from the femoral artery by a Statham P23Gb pressure transducer connected to a Brush 2600 recorder. After MAP had stabilized for at least 1 hour, the pressor responses to graded i.v. injections (0.25 ml) of arginine vasopressin (Bachem) and angiotensin II (Bachem) were determined in each rat. Doses ranged from threshold to 125 ng (50 mU/kg) for vasopressin and from threshold to 130 ng/kg for angiotensin II. Vehicle alone (0.25 ml of 0.9% NaCl) was injected several times throughout the experiment to determine if volume responses occurred. Although there was usually no response to the vehicle, small biphasic changes in BP occurred in some rats. Both the order in which the dose-response curves were run and the doses within each dose-response curve were randomized. Between each dose-response curve, the rats were given a 1-hour recovery period.

After completing the dose-response curves, the catheters were cut and sealed by heat. The rats were returned to their cages, given free access to food and drinking fluid, and allowed to recover for 24 to 72 hours. If fluid ingested reached levels within 80% of those obtained prior to the dose-response curves, the rats were decapitated, and trunk blood was collected into heparinized tubes packed in ice. If fluid ingestion did not return to this level, the rats were omitted from this portion of the experiment. The plasma was separated by centrifugation at 2200 rpm at 4°C. Two 200 µl aliquots of plasma were taken for the measurement of plasma osmolality, and an additional 10 µl was taken for plasma sodium measurements (IL 343 flame photometer). Dismodium EDTA (4%) was added to the remaining plasma (0.1 ml per ml of plasma), which was then stored at −40°C until vasopressin was extracted. The pituitary was also removed from each rat and prepared for the measurement of vasopressin as previously described.

Vasopressin was extracted from plasma (LaRochelle, North, and Stern, personal communication) by adsorption onto octadecylsilane contained in prepacked cartridges (Waters Associates, Sep-Pak C$_{18}$). The plasma samples were thawed, and 2 ml aliquots were adjusted to pH 2 to 3 by the addition of 0.2 ml of 1 N HCl. The cartridges were primed by passing 5 ml methanol (ACS grade), 5 ml 8 M urea, and 10 ml double distilled water through them. The plasma was poured into a plastic syringe and slowly (2 to 3 min) forced through the cartridge. The sample tube was rinsed with 2 ml of double distilled water, which was drawn into the syringe and put through the cartridge. The cartridge was then washed with 10 ml of double distilled water followed by 10 ml of 4% acetic acid. Vasopressin was eluted from the cartridge into siliconized glass tubes with 10 ml of 90% ethanol-4% glacial acetic acid. Then 5 ml of the ethanol-acid mixture were forced through the cartridge over 1 to 2 minutes. After 3 to 5 minutes, the remaining 5 ml were forced through the cartridge, followed by 10 ml of air to remove any remaining elution mixture. The priming steps were repeated, and the cartridge was ready to use again. Each cartridge was used for no more than four samples. Twenty 2 ml samples of rat plasma to which 10.5 µU of U.S.P. Posterior Pituitary Reference Standard had been added, as well as six 2 ml samples with no vasopressin added, were also extracted so that recovery of vasopressin could be determined. Average recovery of vasopressin was 76% ± 2%. Samples were not corrected for incomplete recovery.

Eluates were brought to dryness with a Buchler Evapo-Mix and reconstituted in 1 ml of assay buffer (0.1 M sodium phosphate buffer, 0.3% NaCl, and 0.1% bovine serum albumin, pH 7.6) on the day of the radioimmunoassay. Vasopressin was measured by a modification of our current radioimmunoassay, using disequilibrium conditions. Then 200 µl of sample in duplicate or 100 µl of standard in triplicate were pipetted into plastic test tubes. Either 225 or 325 µl of assay buffer and 25 µl of AVP antiserum (diluted 1: 15,000 in assay buffer) were added to the tubes simultaneously by a Micromedic Automatic Pipetting Station. Samples, standards, and reagents were kept on ice during this procedure. After incubation for 24 hours at 4°C, 50 µl of $^{125}$I- AVP (1000 cpm in assay buffer) were added, and the samples were incubated another 24 hours at 4°C. To each tube, 1 ml of 0.83% Norit A charcoal coated with 0.167% bovine serum
albumin was then added. The tubes were centrifuged for 20 minutes at 2200 rpm at 4°C, the supernatant was separated from the charcoal pellet, and both fractions were counted for 10 minutes by a Micromedic 588 gamma counter. Log free/bound counts were plotted against log dose of vasopressin for the standard curve. The line of best fit was estimated by computer, and the vasopressin concentration in the sample was calculated. By using the disequilibrium procedure, the sensitivity of our assay was increased approximately fourfold.

One-, two-, or three-factor analyses of variance for repeated measures were performed on the data. When appropriate, Newman Keuls a posteriori tests were performed to isolate between and within group differences. Means are given ± one standard error in figures, tables, and text; however, these standard errors were not used in calculating statistical significance. Because the plasma vasopressin data were not normally distributed, a logarithmic transformation was necessary.

Results

As expected, the rats treated with DOC and given 1% NaCl to drink became hypertensive, with a significant increase in BP (p < 0.01; fig. 1A) occurring within 1 week after the start of treatment. The SBP in rats treated with DOC alone also increased (p < 0.05 to 0.01), but to a somewhat lesser extent. Differences in SBP between these two groups were significant only in the second (p < 0.05) and fourth (p < 0.01) weeks of the experiment. The SBP remained relatively constant in the control rats and in the rats given only 1% NaCl to drink.

The U\textsubscript{ADHV} in the control rats did not change (fig. 1B), whereas the substitution of 1% saline for drinking water resulted in a doubling (p < 0.01) of U\textsubscript{ADHV} as early as the first week after the start of treatment. Treatment with DOC alone had little effect on U\textsubscript{ADHV} until the fourth week of treatment, at which time U\textsubscript{ADHV} increased twofold (p < 0.05). When treatment with DOC and 1% NaCl were combined, U\textsubscript{ADHV} was increased twofold during the first 2 weeks of treatment (p < 0.01) and almost fourfold during the third and fourth weeks of treatment (p < 0.01).

Water intake (fig. 2A), corrected for body weight, decreased with time in the control rats (p < 0.01) while remaining constant in the rats treated with DOC. Initially, water intake in the control rats was greater than in the DOC-treated rats (p < 0.01); however, from the third to fifth weeks of the experiment, water intake in the DOC-treated rats exceeded that in the control animals (p < 0.01). Control measurements of water intake were not obtained in the rats treated with DOC-plus-1% NaCl or with 1% NaCl alone. After the first week of treatment, however, the intake of 1% NaCl in the rats treated with DOC was 30% to 40% greater than in the rats that did not receive DOC (fig. 2A, B).

Urine osmolality (fig. 2C) in the control group decreased transiently during the second week of the experiment (p < 0.05). There was a sustained reduction in urine osmolality in the rats treated with 1% NaCl, DOC, and DOC-plus-1% NaCl (p < 0.01), being greatest in the DOC-salt rats.

Mean body weight (table 1) increased in all four groups of rats during the course of the experiment (p < 0.01). There were no statistically significant differences in body weight among the control rats and rats treated with 1% NaCl alone or DOC-salt. The average body weight in the rats treated with DOC, however, was lower than that in the other three groups in the pretreatment period, and this difference persisted through the first 4 weeks of the experiment (p < 0.01).

Plasma concentrations of vasopressin and sodium, plasma osmolality, and pituitary vasopressin content were determined either 3 to 5 weeks or 6 to 8 weeks after the initiation of treatment. The plasma vasopressin concentration (fig. 3A) was higher (p < 0.05) after 3 to 5 weeks of treatment than after 6
TABLE 1.  Effect of Treatment with 1% NaCl, DOC, and DOC Plus 1% NaCl on Body Weight*

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>1% NaCl</th>
<th>DOC + 1% NaCl</th>
<th>DOC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Control</td>
<td>211 ± 8</td>
<td>253 ± 6†</td>
<td>288 ± 6†</td>
<td>320 ± 6†</td>
</tr>
<tr>
<td>1% NaCl</td>
<td>206 ± 11</td>
<td>245 ± 10†</td>
<td>289 ± 9†</td>
<td>324 ± 9†</td>
</tr>
<tr>
<td>DOC + 1% NaCl</td>
<td>203 ± 9</td>
<td>241 ± 8†</td>
<td>276 ± 8†</td>
<td>298 ± 8†</td>
</tr>
<tr>
<td>DOC</td>
<td>156 ± 3†</td>
<td>194 ± 4†</td>
<td>246 ± 5†</td>
<td>291 ± 7†</td>
</tr>
</tbody>
</table>

*All rats were unilaterally nephrectomized prior to week 1. Treatment with DOC, 1% NaCl, or DOC + 1% NaCl was begun after measurements at week 1. Means ± SE.

†p < 0.01 when compared to the first week of observation.
‡p < 0.01 when compared to the control group.

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FIGURE 2. Fluid intake (A), NaCl intake (B), and urine osmolality (Uosm, C) in unilaterally nephrectomized untreated (H2O) rats and rats treated with DOC, 1% NaCl, and DOC + 1% NaCl. Asterisks above the bars designate significant differences from week 1. Asterisks within the bars signify significant differences from the H2O group. Asterisks between the bars designate differences between these 2 groups. Treatment was begun immediately following measurements at week 1.

Pressor responsiveness to vasopressin and angiotensin II was studied in the conscious restrained rat. Because there was no statistically significant effect of the duration of treatment on the pressor responses to vasopressin in the control and 1% NaCl groups, the data for the 3-5 and 6-8 week periods were pooled within these two groups to simplify presentation. Prior to testing with vasopressin and angiotensin II, MAP was elevated substantially in the DOC-plus-1% NaCl group and to a large extent in the DOC group when compared to both the control and 1% NaCl groups (table 2). The pressor responses to graded i.v. injections of vasopressin in the control group were similar to those in the 1% NaCl group and the DOC-plus-1% NaCl group treated for 3-5 weeks (fig. 4). However, pressor responsiveness to vasopressin was substantially increased (p < 0.05) in the rats treated 6 to 8 weeks with DOC-plus-1% NaCl (fig. 4).

Upon examining the data from the individual rats treated with DOC-plus-1% NaCl, it was apparent that there were two populations of animals: one with a pressor responsiveness similar to that in the control rats, and one with a greatly enhanced pressor responsiveness. For quantitative purposes, increased pressor responsiveness to vasopressin was defined as pressor responses to 62.5 and 31.3 ng/kg of vasopressin that were at least two standard deviations greater than the average responses to these doses in the control group. Six rats treated with DOC-plus-1% NaCl were classified as having an enhanced pressor response to...
Results

We would like to emphasize that no rats with increased pressor responsiveness were found in the groups treated with only 1% NaCl or DOC. In figure 5, we have compared the pressor responses to vasopressin in the DOC-plus-1% NaCl rats with increased pressor responsiveness to the responses in the remainder of DOC-plus-1% NaCl rats and in the control rats. The dose-response curves in the latter two groups are virtually identical, whereas the dose-response curve for the rats with increased pressor responsiveness is shifted substantially to the left. The dose of vasopressin required to produce an increase in MAP of 30 mm Hg was 14 ng/kg in the rats with increased responsiveness and 40 ng/kg in the control rats and the DOC-salt rats lacking enhanced responsiveness.

Since duration of study was without statistically significant effect on the pressor responsiveness to angiotensin II, the data within each treatment group were pooled (fig. 6). There was, however, a tendency for increased pressor responsiveness to angiotensin II in the rats treated with DOC-plus-salt for 6 to 8 weeks. No statistically significant differences were found between groups with respect to pressor responsiveness to angiotensin II, and only two of the 15 rats treated with DOC and 1% NaCl could be classified as having an enhanced pressor responsiveness to angiotensin II. Both of these rats were in the 6-8 week treatment group, and both also had an increased pressor responsiveness to vasopressin. A third rat with enhanced responsiveness to vasopressin failed to show an increased pressor responsiveness to angiotensin II. Only three of the six rats with increased pressor responsiveness to vasopressin were also tested with angiotensin II. It should be noted that in the control rats the pressor potency of angiotensin II (fig. 6) is almost identical to that of vasopressin (fig. 4).

Discussion

Evidence accumulated in the past several years indicates quite clearly that vasopressin plays a major role in the development and maintenance of DOC-salt hypertension in the rat. This model of hypertension cannot be produced in the rat with either hereditary1 or surgically induced2 hypothalamic diabetes insipidus. In rats with established DOC-salt hypertension, administration of either a vasopressin antiserum1 or a competitive antagonist of the pressor activity of vasopressin1 resulted in a substantial acute reduction in BP. Finally, there is evidence that the release of vasopressin from the neurohypophysis is elevated in DOC-salt hypertension, in that the urinary excretion of vasopressin1 and plasma levels of vasopressin1 are

Table 2.

<table>
<thead>
<tr>
<th>Group</th>
<th>DOC + 1% NaCl</th>
<th>DOC</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>125 ± 3</td>
<td>184 = 5†</td>
</tr>
<tr>
<td>118 = 2</td>
<td>125 ± 3</td>
<td>184 = 5†</td>
</tr>
</tbody>
</table>

*Measurements were made prior to injection of vasopressin and angiotensin II. Means ± se.
†p < 0.05 when compared to the control rats.
‡p < 0.01 when compared to the control rats.
Responsiveness to Vasopressin in DOC-Salt Hypertension

Elevated. In the present experiments, we have confirmed these last two observations.

There appear to be several factors responsible for the increased secretion of vasopressin in the rat with DOC-salt hypertension. During the first 2 weeks of the treatment period, the relative increase in the urinary excretion of vasopressin in the rats treated with DOC-plus-1% NaCl was almost identical to that seen in the rats that were only treated with substitution of saline for drinking water. This suggests that, initially, the primary stimulus for the increased release of vasopressin was a consequence of the increased salt intake, i.e., an increased plasma osmolality. Our failure to find a statistically significant increase in plasma osmolality in these two groups of rats, or, indeed, an increased plasma vasopressin concentration in the latter group, probably is due to small changes in these variables combined with our inability to make sequential measurement of these variables in the same rat. The further increase in the urinary vasopressin excretion that occurred in the third and fourth weeks of treatment with DOC-salt may have been due, at least partially, to the effect of DOC itself since there was an increase in vasopressin excretion in the fourth week of treatment with DOC alone. A reduction in blood volume in any of the rats treated with DOC-salt that were in the "malignant" phase of the hypertension would also have contributed to an increased release of vasopressin.

Figure 5. Comparison of pressor responses to vasopressin between DOC + 1% NaCl rats with an increased pressor responsiveness to vasopressin (sensitive) and DOC + 1% NaCl rats with a normal responsiveness (nonsensitive). Pressor responses to vasopressin by control (H2O) rats are repeated from figure 4 for comparison.

Figure 4. Pressor responsiveness to graded bolus i.v. injections of vasopressin in control rats (H2O) and rats receiving DOC or 1% NaCl 3 to 8 weeks after initiation of treatment and in rats receiving DOC + 1% NaCl 3 to 5 and 6 to 8 weeks after initiation of treatment.

Figure 6. Pressor responsiveness to graded bolus i.v. injections of angiotensin II in control rats (H2O) and rats receiving DOC, 1% NaCl, or DOC + 1% NaCl after 3 to 8 weeks of treatment.
In our present experiments, treatment of unilaterally nephrectomized rats with DOC alone resulted in hypertension that was of a somewhat lesser magnitude than was observed in rats treated with DOC-plus-1% NaCl. Vasopressin was clearly not a pathogenetic factor in the hypertension in the rats treated with only DOC, since the urinary excretion of vasopressin did not increase until well after BP was increased, the plasma vasopressin concentration was not significantly changed, and pressor responsiveness to exogenous vasopressin was not increased. Haack et al. attributed this form of hypertension to an increased plasma volume and extracellular fluid volume. We cannot at this time explain the increased urinary excretion of vasopressin observed after 4 weeks of treatment with DOC. In contrast to the report by Haack et al., we did not observe increases in plasma osmolality and sodium concentration in rats treated with DOC alone. However, our measurements were made after 7 weeks of treatment, whereas Haack et al. studied their rats after only 5 days and used larger doses of DOC.

If vasopressin is a major factor in the pathogenesis of DOC-salt hypertension in the rat, what is its role? The observation that administration of either a vasopressin antiserum or a competitive antagonist of vasopressin's pressor action lowers BP in rats with this form of hypertension suggests that vasopressin may function as a direct pressor agent in DOC-salt hypertension. Indeed, the data presented here, as well as by others, demonstrate that the pressor potency of vasopressin is at least as great as that of angiotensin II. On the other hand, in the otherwise normal subject, plasma vasopressin levels considerably higher than those found in the present work or by Mörhing et al. are necessary for this hormone to have an effect on BP. When vasopressin was infused in rats with hereditary hypothalamic diabetes insipidus at a rate sufficient to increase BP to levels seen in rats with "benign" DOC-salt hypertension, plasma vasopressin levels 40 times greater than those in the DOC-salt hypertensive rats were required. Similarly, to elevate arterial pressure in conscious dogs, plasma concentrations of vasopressin must be increased to levels much greater than have been reported in any form of hypertension. Padfield et al. infused vasopressin in normal human subjects to produce plasma vasopressin concentrations up to 5 times those observed in patients with malignant hypertension without affecting BP. Thus, if vasopressin is directly responsible as a pressor agent for the elevated BP in rats with DOC-salt hypertension, these animals must have an increased pressor responsiveness to this hormone. The present data indicate that this may not be the case in the early stages of DOC-salt hypertension since only one of nine rats studied after 3 to 5 weeks of treatment with DOC-salt demonstrated enhanced pressor responses to exogenous vasopressin. Even after 6 to 8 weeks of treatment with DOC-salt, only five of 11 rats had a clearly demonstrable increased pressor responsiveness to vasopressin.

Certainly, the higher baseline arterial pressure and a greater occupancy of vasopressin receptors on vascular smooth muscle could have obscured an increased pressor responsiveness to vasopressin in the hypertensive rats. Furthermore, a prolonged increase in the plasma vasopressin concentration could be more effective in raising arterial pressure than the short-term increases studied by Mörhing et al., Pullan et al., Szczepanska-Sadowska, and Padfield. However, Manning et al. have reported that the long-term infusion of vasopressin in dogs with reduced renal mass at rates calculated to increase plasma vasopressin levels two- to three-fold had only a small effect on arterial pressure. Our data, then, do not support a direct pressor role for vasopressin in the development of DOC-salt hypertension.

We have no insight into the mechanisms responsible for the development of increased pressor responsiveness to vasopressin in some rats and not in others, other than that it appeared to be a function of duration of treatment with both DOC and salt. The development of enhanced responsiveness did not appear to relate to whether the rats were in the "benign" or "malignant" phase of the hypertension, determined by the criteria established by Gavras et al. There was weight loss and increased saline intake in some rats with increased responsiveness, but not in others. It is, however, tempting to speculate that, if the treatment were continued for a long enough period of time, all of the rats treated with DOC-salt would exhibit an increased responsiveness to vasopressin.

Our observation of an increased pressor responsiveness to vasopressin in many rats with DOC-salt hypertension is consistent with the report by Hinke that the isolated ventral caudal artery from rats with DOC-salt hypertension is hyperresponsive to vasopressin. Of the six rats in our present study that had an increased pressor responsiveness to vasopressin, three were also tested with angiotensin II and two had an increased responsiveness. There are, in addition, reports of enhanced pressor responsiveness to catecholamines and to angiotensin II DOC-salt hypertension. It would appear, therefore, that the increased pressor responsiveness in this model of hypertension may not be specific.

A second mechanism by which vasopressin may function in the pathogenesis of DOC-salt hypertension is that, by virtue of its antidiuretic action, vasopressin is necessary for expansion of blood volume and that this is a volume-dependent form of hypertension. This possibility is supported by a recent observation by Saito and Yajima that DOC-treated, unilaterally nephrectomized rats with hereditary hypothalamic diabetes insipidus became hypertensive when dDAVP was included in the 1% saline that was substituted for drinking water; dDAVP is a potent long-acting antidiuretic analog of vasopressin that has minimal cardiovascular effects. In addition, Manning et al. have shown that the long-term infusion of both vasopressin in nonpressor doses and hypotonic saline in dogs with reduced renal mass resulted in a sustained increase in arterial BP. However, the observations that competitive antagonists of the pressor action of
vasopressin and a vasopressin antiserum produce acute reductions in BP in the rat with DOC-salt hypertension. It indicates that vasopressin must have some action in addition to its role in increasing blood volume.

A third possible mechanism by which vasopressin may play a role in DOC-salt hypertension is by virtue of its ability to potentiate, in subpressor doses, the pressor action of catecholamines, since there is evidence for increased circulating levels of norepinephrine in this model of hypertension. Finally, one must consider the possibility that vasopressin may participate in the development and maintenance of DOC-salt hypertension by some other mechanism that has not yet been identified.

In conclusion, evidence from several laboratories indicates that vasopressin plays a major, perhaps an essential, role in the pathogenesis of DOC-salt hypertension in the rat. The mechanism of action of vasopressin is not quite so clear. In the early stages of DOC-salt hypertension, it is unlikely that vasopressin plays a direct pressor role, but rather seems to function as an antidiuretic agent in the expansion of blood volume. In the later stages of DOC-salt hypertension, many rats develop an increased pressor responsiveness to vasopressin, and in these animals, vasopressin may function as a direct pressor agent in maintaining the elevated BP. However, other mechanisms of action for vasopressin in DOC-salt hypertension must be considered.

Acknowledgments

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