Central Action of Increased Osmolality to Support Blood Pressure in Deoxycorticosterone Acetate–Salt Rats

Theresa L. O’Donoughy, Yue Qi, Virginia L. Brooks

Abstract—To test the hypothesis that increased osmolality contributes to hypertension in deoxycorticosterone acetate (DOCA)-salt–hypertensive rats by acting in the brain, DOCA-salt and Sham-salt rats were instrumented with bilateral, nonoccluding intracarotid and femoral catheters. Two weeks prior, rats were uninephrectomized and received subcutaneous implants with or without DOCA (65 mg) and began drinking salt water (1% NaCl and 0.2% KCl). DOCA-salt rats (n=28) exhibited elevated blood pressure (159±4 mm Hg; P<0.05) and heart rate (392±10 bpm; P<0.05) compared with Sham-salt animals (n=5; blood pressure: 107±5 mm Hg; heart rate: 355±10 bpm). Bilateral intracarotid infusion of hypotonic fluid (osmolality: ≈40 mOsm/L), which lowers osmolality of blood to the brain by ≈2%, rapidly decreased blood pressure in DOCA-salt rats (−22±4 mm Hg after 15 minutes; P<0.05; n=7) but not Sham-salt rats (2±2 mm Hg; n=5). Hypotonic fluid infused intravenously did not lower blood pressure (0±2 mm Hg) in DOCA-salt rats (n=7). In DOCA-salt rats pretreated with a V1 vasopressin antagonist (Manning compound, 5 μg, IV), intracarotid hypotonic infusion still decreased blood pressure (−10±3 mm Hg; P<0.05; n=9), but the response was smaller (P<0.05). Finally, in DOCA-salt rats (n=4) pretreated with the V1 antagonist and the ganglionic blocker hexamethonium, decreasing osmolality of blood to the brain did not reduce blood pressure. These data indicate that, in DOCA-salt rats, hypertonicity acts in the brain to support blood pressure, in part by stimulating vasopressin secretion and in part by stimulating another rapidly reversible mechanism, likely the sympathetic nervous system. (Hypertension. 2006;48:658-663.)

Key Words: hypertension, sodium-dependent ■ central nervous system ■ hypertension, mineralocorticoid ■ sodium ■ sympathetic nervous system ■ vasopressin

Increasing evidence supports a role for body fluid osmolality (OSM) in the regulation of blood pressure (BP) and sympathetic nerve activity (for reviews see References1–2). Acute increases in OSM rapidly elevate BP and sympathetic nerve activity to specific beds,3–5 and more chronic increases in plasma OSM, such as during water deprivation, seem to sustain this rapid sympathoexcitation.6 Moreover, recent studies suggest that increased OSM contributes to sympathoexcitation in at least one model of salt-sensitive hypertension, the deoxycorticosterone-treated rat consuming excess salt (DOCA-salt) rat. More specifically, DOCA-salt rats exhibit hypertension and elevated OSM and/or NaCl levels,7–10 and normalization of OSM results in profound decreases in BP and lumbar sympathetic nerve activity.8 However, the site at which OSM is sensed to trigger sustained sympathoexcitation in DOCA-salt rats has not been identified.

Osmoreceptors are present in numerous organs, including the liver, kidney, and brain, but significant indirect evidence implicates the brain in this action. First, forebrain circumventricular organs contain osmoreceptors that are exquisitely sensitive to minute changes in OSM.11 Second, forebrain osmoreceptors mediate the pressor and sympathoexcitatory effects of OSM during water deprivation.12 Therefore, we hypothesized that during DOCA-salt hypertension, increased OSM acts in the brain to increase sympathetic nerve activity and BP. To test this hypothesis, we determined whether acute reduction of the OSM of blood perfusing the brain, by infusion of hypotonic fluid via nonoccluding carotid artery catheters, decreases BP more in DOCA-salt rats than in Sham-salt rats.

Methods

Animals
Male Sprague–Dawley rats weighing between 275 and 375 g (Sasco, Wilmington, MA) were housed in pairs in Plexiglas cages in the animal care unit with ad libitum access to a 0.4% NaCl diet (Harlan Teklad) and deionized water for at least a week before any surgeries were performed. The facility was maintained at a constant temperature of 22±2°C with a 12:12-hour light–dark cycle. All of the procedures were conducted in accordance with the NIH Guide for the Health and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of the Oregon Health and Science University.

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From the Department of Physiology and Pharmacology, Oregon Health & Science University, Portland.
Correspondence to Virginia L. Brooks, Department of Physiology and Pharmacology, L-334, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97239. E-mail brooksv@ohsu.edu

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Surgery

Animals were anesthetized with 2% isoflurane in oxygen. A 1.5-cm incision was made in the skin above the right kidney. After blunt dissection through the muscle layer, the kidney was exteriorized, tied off, and removed. The muscle layer was sutured, and a thin silicone pellet (~3 cm diameter) with (DOCA) or without (Sham) 65 mg of DOCA was placed dorsally under the skin. The skin was then sutured closed, and rats were given ~2 weeks to recover. During recovery, and for the duration of the experiment, all of the animals drank water containing 1% NaCl and 0.2% KCl.

Three to 6 days before experimentation, animals were instrumented with femoral arterial and venous catheters for measurement of arterial pressure and for infusions, respectively, and bilateral intracarotid (IC) catheters as described previously.12 Briefly, after rats were anesthetized with 2% isoflurane in oxygen, the femoral catheters were implanted. Bilateral nonocclusive IC catheters were then positioned into the common carotid with the tip pointed toward the brain and secured in place with Vet Bond (3M, Animal Care Products). The external carotid and occipital arteries were ligated to ensure that infused fluids were directed to the brain. Distal ends of the catheters were tunneled subcutaneously to exit at the nape of the neck, and all of the incisions were sutured closed. When not in use, catheters were filled with heparinized isotonic saline (500 U/mL, IC catheters; 200 U/mL, femoral catheters). To maintain patency, IC catheters were flushed daily, and femoral catheters were flushed every 2 days.

Data Acquisition

During experiments, BP and heart rate (HR) were continually recorded via the femoral arterial catheter using a Statham (Spectramed) or Transpac IV (disposable) pressure transducer, a Grass bridge amplifier (7P1), and a Grass polygraph (7D). The pulsatile signal was also fed to a Grass tachograph amplifier (7P4) for determination of HR.

Experimental Protocols

On the experimental day, vascular catheters were connected to recording equipment between 9:00 and 10:00 AM, while the rats rested, unrestrained in their home cages. Animals were allowed at least a 1-hour habituation before the start of the protocol. During this time, a baseline blood sample (350 µL) was drawn for measurement of basal hematocrit and plasma protein, Na, Cl, and OSM. Blood was replaced with an equal volume of isotonic saline. At least 30 minutes after the blood draw, when the animal was resting quietly, one of the following protocols was performed.

Protocol 1

This protocol tested the hypothesis that during DOCA-salt hypertension, increased OSM acts in the brain to support BP. To test this hypothesis, it was determined in DOCA-salt rats whether IC infusion of hypotonic fluid decreases BP. The composition of the hypotonic fluid was (in mmol/L): KCl: 4; CaCl₂: 2.2; MgCl₂: 0.9; Na₂HPO₄: 1.3; and NaHCO₃: 20; the measured OSM was ~40 mOsm/kg H₂O. The pH of the fluid was adjusted to 7.4 before each use. Control measurements of BP and HR were recorded for 15 minutes, while the measured OSM was hypotonic fluid then commenced at 0.1 mL/min per artery; this rate was achieved, the IC hypotonic infusion was administered as in protocol 1.

Protocol 3

To determine whether changes in BP and HR are secondary to changes in plasma vasopressin concentration, DOCA-salts rats were pretreated with the V₁ vasopressin antagonist (Manning Compound, 5 µg IV) 15 to 30 minutes before IC infusion of the hypotonic fluid as in protocol 1.

Protocol 4

To investigate the contribution of the sympathetic nervous system, a final group of DOCA-salt rats was pretreated with the V₁ vasopressin antagonist before infusion of the ganglionic blocker hexamethonium (30 mg/kg). Once stable baseline hemodynamic parameters were achieved, the IC hypotonic infusion was administered as in protocol 1.

Blood Analyses

Plasma electrolytes were either measured from whole blood samples using a Nova CRT electrolyte analyzer (Nova Biomedical Corporation) or from plasma with a Beckman Lablyte System (model 810, Beckman Instruments). Plasma OSM was determined from triplicate 20-µL plasma samples using a micro-osmometer (Model 3300, Advanced Instruments). Duplicate hematocrit tubes were filled with approximately 30 µL of arterial blood and spun. Hematocrit was determined with an Adams microhematocrit reader. Tubes were then broken, and the plasma was used for determination of plasma protein with either a SUR-Ne (Atago Instrumentation) or a Hitachi (National Instruments) handheld protein refractometer.

Statistical Analysis

All of the data are presented as mean±SE. Statistical analyses were performed using GB Stat v 7.0 software (Dynamic Microsystems). Baseline blood values were compared using Student’s t tests. Changes in BP and HR secondary to administration of the V₁ vasopressin antagonist or hexamethonium were determined using paired t tests. Two-way ANOVA for repeated measures on all 5 of the groups was used to determine changes in BP, HR, and blood chemistries following infusion of hypotonic fluid. In cases in which significant interactions were evident, a Bonferroni post hoc test was performed to determine specific differences. Significance was indicated by P<0.05.

Results

Baseline Values

As summarized in Table 1, DOCA-salt rats exhibited hypertension and basal tachycardia relative to Sham-salt rats, but plasma Cl and protein concentrations and hematocrit were not different between groups. OSM and Na levels tended to be elevated in the DOCA-salt animals, but these differences did not achieve statistical significance.

### Table 1. Baseline Blood Parameters

<table>
<thead>
<tr>
<th>Blood Parameter</th>
<th>DOCA-Salt (n=28)</th>
<th>Sham-Salt (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP, mm Hg</td>
<td>159±4*</td>
<td>107±5</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>392±10*</td>
<td>355±10</td>
</tr>
<tr>
<td>OSM, mOsm/L</td>
<td>306±2</td>
<td>299±4</td>
</tr>
<tr>
<td>Na, mEq/L</td>
<td>145.7±0.8</td>
<td>142.9±1.4</td>
</tr>
<tr>
<td>Cl, mEq/L</td>
<td>110.6±1.0</td>
<td>112.1±1.3</td>
</tr>
<tr>
<td>Protein, g/dL</td>
<td>5.7±0.1</td>
<td>5.6±0.2</td>
</tr>
<tr>
<td>Hct, %</td>
<td>39.1±0.6</td>
<td>35.4±1.9</td>
</tr>
</tbody>
</table>

Values are means±SE. BP indicates mean arterial blood pressure; Hct, hematocrit.

*P<0.05 vs Sham-salt group.
Effects of Decreasing Central Osmolality in DOCA- and Sham-Salt Rats

BP was unaltered by IC hypotonic infusion in the Sham-salt animals (Figure 1). In contrast, BP rapidly decreased when the hypotonic fluid was infused IC in DOCA-salt rats and rebounded to control levels immediately on cessation of the hypotonic fluid infusion (Figure 1). HR did not change significantly in either DOCA-salt or Sham-salt animals (Figure 1).

As summarized in Table 2, the IC hypotonic infusion decreased plasma protein and Cl concentrations, OSM, and hematocrit (ANOVA, time and interaction: \( P<0.05 \)), indicating significant systemic recirculation of the infused fluid; plasma Na levels also tended to fall, but this did not reach statistical significance (ANOVA, time: \( P=0.08 \)). Nevertheless, no differences in these changes were observed between DOCA-salt rats receiving the IC hypotonic infusion and the other groups. Therefore, because of the recirculation, to establish a central site of action, a second group of DOCA-salt rats was infused with the hypotonic fluid IV. Despite similar decreases in plasma OSM, neither HR nor BP changed with IV hypotonic infusion (Figure 1).

**Effect of Decreasing Central Osmolality in V1-Blocked DOCA-Salt Rats**

Administration of the V1 vasopressin antagonist significantly decreased BP (158±8 to 146±7 mm Hg; \( P<0.05 \)) and tended to increase HR (382±10 to 401±5 bpm; \( P=0.07 \)). Hypotonic fluid infusion into the carotid arteries of V1 vasopressin-blocked DOCA-salt animals still produced a rapid and significant decrease in BP; however, the ultimate fall in pressure was significantly smaller than in the DOCA-salt animals not receiving the V1 antagonist (Figure 2). HR did not change with the fluid infusion (Figure 2). These data reveal that both vasopressin and another rapidly reversible component contribute to central OSM-induced hypertension.

**Effect of Decreasing Central Osmolality in V1-Ganglionic–Blocked DOCA-Salt Rats**

Treatment of DOCA-salt rats with both the V1 vasopressin antagonist and the ganglionic blocker hexamethonium chloride resulted in dramatic hypotension (149±13 to 51±4 mm Hg; \( P<0.05 \)). HR also fell, although the decrease did not quite achieve significance (392±19 to 310±25 bpm; \( P=0.054 \)).

In rats in which both vasopressin and the autonomic nervous system were blocked, BP did not decrease further with hypotonic IC infusion (Figure 2). HR did not change with IC hypotonic fluid infusion, although it was lower relative to the response in the DOCA-salt intact rats (Figure 2). Osmolality did not fall with infusion of hypotonic fluid (Table 2), which is likely because of increased plasma solutes in response to the hypotension.\(^{13–15}\) Thus, these data suggest that a decrease in sympathetic activity also contributes to the

**Table 2. Change in Blood Parameters With Hypotonic Infusion**

<table>
<thead>
<tr>
<th>Blood Parameters</th>
<th>DOCA-Salt Hypo IC (n=8)</th>
<th>DOCA-Salt Hypo IV (n=7)</th>
<th>Sham-Salt Hypo IC (n=4)</th>
<th>DOCA-Salt V1 Blocked Hypo IC (n=9)</th>
<th>DOCA-Salt V1 and V1 Blocked Hypo IC (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSM, mOsm/kg H2O</td>
<td>–3±1</td>
<td>–6±2*</td>
<td>–2±3</td>
<td>–5±2*</td>
<td>2±3</td>
</tr>
<tr>
<td>Na, mEq/L</td>
<td>–1.4±0.8</td>
<td>–1.2±1.1</td>
<td>–2.1±0.9</td>
<td>–0.4±0.7</td>
<td>0.2±1.6</td>
</tr>
<tr>
<td>Cl, mEq/L</td>
<td>–0.4±0.8</td>
<td>–3.3±1.3</td>
<td>–1.8±0.9</td>
<td>–1.9±0.6</td>
<td>0.9±0.8</td>
</tr>
<tr>
<td>Hct, %</td>
<td>–1.4±0.2</td>
<td>0.7±0.9</td>
<td>–0.9±0.7</td>
<td>–1.1±0.2</td>
<td>–2.7±1.3*</td>
</tr>
<tr>
<td>Plasma protein, g/dL</td>
<td>–0.5±0.1*</td>
<td>–0.2±0.2</td>
<td>–0.3±0.3</td>
<td>–0.6±0.1*</td>
<td>–0.7±0.1*</td>
</tr>
</tbody>
</table>

Data are mean±SE. Hypo IC indicates hypotonic intracarotid infusion; Hypo IV, hypotonic intravenous infusion; Hex, hexamethonium chloride; Hct, hematocrit.
*\( P<0.05 \) compared to baseline.
Several factors contribute to hypertension development in DOCA-salt–treated animals, including volume expansion and vasopressin release and in part by activation of the sympathetic nervous system. The goal of this study was to examine the central actions of brain osmolality in DOCA-salt rats. Specifically, we found that a decrease in osmolality of blood perfusing the brain, by IC infusion of hypotonic fluid, produced a prompt decrease in BP of \( \approx 25 \) mm Hg. A similar IV infusion was without effect, indicating the central site of action. Interestingly, whereas we and others have observed small but significant increases in plasma osmolality or Na levels in the DOCA-salt animals compared with Sham-salt controls, in the current study, osmolality and Na were insignificantly increased by \( 2\% \). Earlier studies have also failed to detect significant increases in plasma Na concentration (eg, see References 22–24). Yet, despite the small magnitude, our data clearly suggest that these extremely small, at times undetectable, elevations in osmolality are sufficient to produce hypertension. Previous work provides an explanation for this potency. First, the pressor and sympathoexcitatory effects of intracerebroventricular or IV hypertonic saline administration are increased in rats with elevated mineralocorticoid levels. Moreover, we found that the ability of chronic increases in osmolality to support lumbar sympathetic nerve activity and hypertension were appreciably greater in DOCA-salt rats compared with rats made similarly hypertensive by consumption of hypertonic 1.7% saline in the absence of DOCA. Thus, it seems that high mineralocorticoid levels amplify the sympathoexcitatory actions of chronic increases in osmolality, such that even undetectable OSM increases become powerfully pressor.

The exact brain site(s) at which OSM is detected and the mechanism by which this signal is amplified by DOCA is unknown. In addition, the present experiments do not reveal whether it is OSM, Na, or an interaction that is sensed. Nevertheless, it is noteworthy that the carotid arteries do not perfuse the hindbrain, implicating forebrain osmoreceptors, such as the organum vasculosum of the lamina terminalis (OVLT) and the subfornical organ, in the hypertensive action of salt. Indeed, previous work indicates that very increases in vasopressin and sympathetic activity. Until recently, the etiology of the sympathoexcitation had been largely unknown; however, our recent studies indicate that increased plasma NaCl levels drive lumbar sympathetic nerve activity and the hypertension. Nevertheless, the question of the site at which these changes in OSM are sensed remained unanswered.

Previous work implicates central osmoreceptors. First, increased osmolality acting centrally is pressor in part by increasing arginine vasopressin release and in part by activation of the sympathetic nervous system. Second, Pennington and McKinley reported that, in aldosterone-treated sheep, reduction of brain osmolality by intracerebroventricular infusion of mannitol slowly decreases BP. Third, in DOCA-salt–treated rats consuming excess salt, c-fos expression is induced in multiple osmosensitive circumventricular organs; brain regions lacking a blood–brain barrier. Moreover, we demonstrated recently that in water-deprived rats, lowering osmolality of blood perfusing the brain, by bilateral IC infusion of hypotonic fluid, decreases BP and lumbar sympathetic nerve activity, suggesting that increased OSM acts centrally to support arterial pressure in these normotensive animals.

The present results indicate that activation of brain osmoreceptors also underlies a significant component of the hypertension in DOCA-salt rats. Specifically, we found that a decrease in osmolality of blood perfusing the brain, by IC infusion of hypotonic fluid, produces a prompt decrease in BP of \( \approx 25 \) mm Hg. A similar IV infusion was without effect, indicating the central site of action. Interestingly, whereas we and others have observed small but significant increases in plasma osmolality or Na levels in the DOCA-salt animals compared with Sham-salt controls, in the current study, osmolality and Na were insignificantly increased by \( 2\% \). Earlier studies have also failed to detect significant increases in plasma Na concentration (eg, see References 22–24). Yet, despite the small magnitude, our data clearly suggest that these extremely small, at times undetectable, elevations in osmolality are sufficient to produce hypertension. Previous work provides an explanation for this potency. First, the pressor and sympathoexcitatory effects of intracerebroventricular or IV hypertonic saline administration are increased in rats with elevated mineralocorticoid levels. Moreover, we found that the ability of chronic increases in osmolality to support lumbar sympathetic nerve activity and hypertension were appreciably greater in DOCA-salt rats compared with rats made similarly hypertensive by consumption of hypertonic 1.7% saline in the absence of DOCA. Thus, it seems that high mineralocorticoid levels amplify the sympathoexcitatory actions of chronic increases in osmolality, such that even undetectable OSM increases become powerfully pressor.

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slight increases in plasma NaCl activate OVLT neurons that project to pressure-regulating regions of the hypothalamus.29,30 After forebrain osmoreception, indirect evidence suggests that the paraventricular nucleus (PVN) may then convey the signal to sympathetic preganglionic neurons. First, the PVN receives inputs from forebrain osmosensitive sites.1,31,32 Second, rats receiving subcutaneous injections of DOCA and ingesting hypertonic saline express far more c-fos in the PVN than in most other brain regions, suggesting that this brain region is activated.33 Third, lesions of the PVN reduce BP in DOCA-salt rats,34,35 and acute blockade of the PVN by microinjection of muscimol decreases BP in another model of SSSH, Dahl-salt sensitive rats.36 Similarly, during water deprivation, a physiological model of chronically increased NaCl and mineralocorticoids, PVN microinjection of muscimol, decreases BP, lumbar sympathetic nerve activity, and, to a lesser extent, renal nerve activity, and c-fos expression is induced in PVN neurons projecting to the rostral ventrolateral medulla and spinal cord.37–39 Finally, blockade of angiotensin II type 1 receptors in the PVN attenuates the pressor and sympathoexcitatory effect of IC injection of hyperosmotic solutions,40 supporting the hypothesis that recruitment of PVN is involved in this osmotic response.

Experiments were performed in this study to investigate the participation of vasopressin in the observed depressor response. As would be expected in this model,16 there is a significant vasopressin component of the hypertension as evidenced by the significant fall in pressure after administration of the antagonist. In addition, approximately half of the depressor response produced by lowering central OSM can be explained by the actions of vasopressin. Indeed, the time course of the fall in pressure following decreased central OSM in the intact DOCA-salt animal seemed to be biphasic. The later phase, starting ≈9 minutes after initiating the infusion, was eliminated by previous V1 vasopressin blockade, indicating that it was because of removal of vasopressinergic inputs. This time course is consistent with the half-life of vasopressin of a few minutes.41–43 On the other hand, based on the rapid time course, the initial immediate fall is likely because of sympathetic withdrawal. This conclusion is supported by the studies in animals in which both the vasopressin and sympathetic inputs were blocked, because decreasing forebrain OSM had no further effect on BP. The caveat to these experiments, of course, is that the starting BP in these animals is significantly lower than in the ganglionic intact animals. Nevertheless, there are other factors that could support BP in this setting, such as angiotensin II44; therefore, we conclude that increased OSM does not seem to act via these additional factors. These data, taken in combination with our previous work showing that systemic infusion of hypotonic fluid rapidly decreases sympathetic activity,8 support the hypothesis that, in DOCA-salt rats, central osmoreceptor activation drives hypertension both by increasing vasopressin release and also by increasing sympathetic activity.8

Perspectives
Our recent studies implicate a central action of hypertonicity as key in the sympathoexcitation and hypertension induced in one model of salt-sensitive hypertension, the DOCA-salt rat. A question that naturally follows is whether a similar mechanism underlies sympathoexcitation in other salt-sensitive models. We have proposed previously a unifying hypothesis that predicts that the elevation in sympathetic tone is mediated by a failure of increased salt intake to adequately suppress sympathoexcitatory actions of systemic or brain-generated angiotensin.2,45 In addition, the relatively high angiotensin levels amplify the excitatory effects of increased OSM on the sympathetic nervous system. In support of this hypothesis, it is noteworthy that most, if not all, salt-sensitive models, including DOCA-salt,46–52 are associated with inappropriately elevated levels or actions of angiotensin. Nevertheless, significant research that involves studies of other salt-sensitive models is required before this hypothesis can be established.

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Disclosures
None.

References


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