Mechanisms of Increased Venous Smooth Muscle Tone in Desoxycorticosterone Acetate-Salt Hypertension

Gregory D. Fink, Ron J. Johnson, James J. Galligan

Abstract—The purpose of the present study was to identify mechanisms that contribute to increased venous smooth muscle tone in desoxycorticosterone acetate (DOCA)-salt hypertension in rats. Male Sprague-Dawley rats were uninephrectomized, received subcutaneous implants of DOCA, and drank 1% sodium chloride/0.2% potassium chloride solutions. Sham-operated rats received only uninephrectomy and drank tap water. Three to 4 weeks later, arterial and venous catheters were implanted for measurements of arterial and central venous pressures, respectively, and a silicone balloon catheter was permanently fixed in the right atrium to produce brief circulatory arrest. Venous smooth muscle activity was estimated on the basis of repeated measurements of mean circulatory filling pressure in conscious rats resting in their home cages. DOCA-salt–treated rats were hypertensive and had elevated mean circulatory filling pressure compared with normotensive sham-operated rats. Blockade of the endothelin subtype A receptor with 1 mg/kg ABT-627 IV decreased arterial blood pressure and mean circulatory filling pressure significantly more in hypertensive rats than in normotensive rats. Ganglionic blockade with 30 mg/kg hexamethonium IV also decreased arterial blood pressure and mean circulatory filling pressure more in hypertensive than in normotensive rats. Pretreatment with ABT-627 did not affect subsequent hemodynamic responses to ganglionic blockade. We conclude that venous smooth muscle tone is increased in DOCA-salt hypertension through the independent actions of both endogenous endothelin-1 acting on subtype A receptors and sympathetically mediated venoconstrictor activity. (Hypertension. 2000;35[part 2]:464-469.)

Key Words: veins • hypertension, sodium-dependent • endothelin • nervous system, sympathetic • desoxycorticosterone

The effective driving force for venous return to the heart, mean circulatory filling pressure (MCFP), is usually increased in hypertension.1 This important physiological change is necessary to maintain normal cardiac output in the face of reduced diastolic compliance of the ventricles.2 Blood volume (BV) and compliance of the venous system are the major determinants of MCFP.3 In established hypertension, BV is either normal or reduced.2 Thus, elevated MCFP in hypertensives is caused by structural changes in the venous wall, increased venous smooth muscle contractile activity (ie, venomotor tone), or both. Reduced compliance of the extrathoracic venous system has been documented in humans4 and rats5 with established hypertension.

The mechanisms responsible for adjustments of venous capacitance function in hypertension have not been completely defined. Current evidence indicates a small but significant role for structural modifications3,6 and an important contribution of sympathetically mediated venoconstriction in humans and experimental animals.1,6,7 Older studies also implicate an unknown humoral mechanism that operates in some models of experimental hypertension.8

The endothelium-derived peptide endothelin (ET)-1 is a potent venoconstrictor in most vascular beds.9 Changes in endogenous ET-1 formation consistent with a role for the peptide in venomotor adjustments to volume stimuli have been measured in humans.10 Although ET-1 formation is typically not increased in hypertension,11 forearm venoconstriction in response to exogenous ET-1 is significantly greater in patients with essential hypertension.12 Venomotor tone induced by sympathetic nervous system activation also is potentiated by ET-1 in essential hypertensive patients but not in normotensive patients.12

We recently studied in vitro contractile responses to ET-1 in mesenteric veins from rats with desoxycorticosterone acetate (DOCA)-salt hypertension (Johnson RJ, Fink GD, Galligan JJ, submitted, 1999). This is an experimental model in which ET-1 formation in vascular tissue is increased and ET-1 is known to have a significant pathophysiological role.11 Venoconstrictor responses to ET-1 were mediated through both ET<sub>A</sub> and ET<sub>B</sub> subtypes of ET receptor. Unlike in arteries, however, where contractile responses to ET-1 are decreased,13 presumably due to receptor downregulation, contraction of veins to ET-1 was well maintained in DOCA-salt hypertensive rats. The majority of the response was mediated through ET<sub>A</sub> receptors. The present study was designed to extend those observations through an exploration of the
contribution of endogenous ET-1 to venous function in vivo in rats with DOCA-salt hypertension. Venomotor tone was assessed through the use of repeated measurements of MCFP in conscious, undisturbed animals.

Methods

Animals
Experiments were performed in male Sprague-Dawley rats (Charles River Laboratories) that weighed 175 to 225 grams at the beginning of the study. All protocols were approved by the Michigan State University Committee on Animal Use and Care. Until the time of catheterization, rats were housed 2 or 3 per cage in a temperature- and humidity-controlled room under a 12-hour light/dark cycle. Free access was allowed to standard laboratory rat chow (8640 Rodent Diet; Harlan/Teklad). Housing was in strict accordance with National Institutes of Health and Michigan State University care guidelines.

DOCA-Salt Hypertension
Hypertension was produced through the use of standard, published methods. Sham-operated rats (SHAM) underwent uninephrectomy but drank tap water. Rats that received DOCA implants were provided with drinking water that contained 1% NaCl and 0.2% KCl throughout the remainder of the protocol.

Catheterization
Approximately 3 weeks after DOCA implantation or sham surgery, catheters were permanently placed in each rat for the measurement of arterial and central venous pressures (AP and CVP, respectively), for drug administration and blood sampling, and to produce brief circulatory arrest. Anesthesia was produced with sodium pentobarbital (30 to 50 mg/kg IP), and atropine (0.2 mg/kg IP) was administered to decrease bronchial secretions. Catheters with silicone rubber tips were inserted into the abdominal aorta and thoracic vena cava through the internal iliac artery and vein, respectively. A silicone rubber-tipped balloon catheter (fabricated in the laboratory from 0.047-inch OD silicone tubing) was advanced into the right atrium via the right jugular vein. It was secured at a location where rapid inflation with 0.15 to 0.25 mL saline caused a smooth decline in AP (to ~25 mm Hg within 2 to 3 seconds) and a simultaneous increase in CVP (to 6 to 8 mm Hg). The ends of all 3 catheters were tunneled subcutaneously to the head, where they exited the rat inside a stainless steel spring secured to the skull with jeweler’s screws and dental acrylic. Injections of enrofloxacin (5 mg/kg IM) and butorphanol (2 mg/kg SC) were administered for bacterial prophylaxis and postoperative pain relief, respectively. Rats were allowed to recover consciousness on a heated pad while under constant observation. They were then placed in stainless steel metabolism cages under loose tethering that allowed continuous access to all catheters without handling or otherwise disturbing the rat. Enrofloxacin (5 mg/kg IV) was administered daily to all rats for a 3-day period after surgery. Vascular catheters were filled with heparin solutions when not in use and flushed daily. Balloon catheters were partially inflated for 3 to 5 seconds daily to prevent adhesions to the atrial wall.

Hemodynamic Measurements
AP was determined by connecting the arterial catheter to a low-volume displacement pressure transducer (TXD-300; Micro-Med) linked to a digital pressure monitor (BPA-200 Blood Pressure Analyzer; Micro-Med) that provided measurements of systolic, mean, and diastolic pressures and heart rate (HR) every 0.5 second (sampling rate 1000 Hz). Except during the measurement of MCFP, all values were averaged on a minute-by-minute basis and saved with the use of a computerized data acquisition system (DMSI-200/4 System Integrator; Micro-Med). Connection of the venous catheter to a separate pressure transducer and digital monitor allowed similar continuous recordings of CVP. The transducer used to measure CVP was zeroed at midlevel of rats in a typical crouched posture and was calibrated daily against a column of water.

Estimation of MCFP was made according to established methods for the rat. Briefly, the right atrial balloon was rapidly inflated with 0.15 to 0.25 mL saline for no longer than 5 seconds. This caused an immediate decline in AP and a simultaneous rise in CVP, both of which plateaued after 3 to 5 seconds of balloon inflation. Pressure averaging rate was increased to once per second during balloon inflation. This method does not allow full equalization of pressure throughout the circulation due to “trapping” of blood on the low compliance arterial side. To correct for this, MCFP was computed from arterial plateau pressure (APP) and venous plateau pressure (VPP) with the following formula:

\[
\text{MCFP} = \text{VPP} + (\text{APP} - \text{VPP})/60
\]

This method, in which a ratio of venous to arterial compliance of 60 is assumed, has been shown previously to produce values of MCFP nearly identical to those obtained through complete equalization of AP and VPP by pumping blood from the arterial to the venous side of the circulation. In any case, the correction for blood trapping is always very small, averaging ~0.4 mm Hg.

Each measurement of MCFP was taken at least 10 minutes after the previous measurement to allow time for the circulation to restabilize. The rats exhibited no visible adverse reactions to balloon inflation and deflation.

Volume Measurements
Plasma volume (PV) was estimated with the use of the 10-minute distribution volume of Evan’s Blue dye. Hematocrit (Hct) was measured in duplicate from an arterial blood sample. Blood volume (BV) was computed with the following formula:

\[
\text{BV} = \text{PV}/[1 - \text{Hct}(0.8)/100]
\]

The value of 0.8 corrects for differences in arterial and whole body hematocrit.

Experimental Protocols
Experimentation began 2 days after surgery for catheter and balloon implantation. Catheters were flushed and attached to pressure transducers. Rats were then allowed to sit undisturbed for 10 to 20 minutes, with all hemodynamic measures being averaged and recorded in 1-minute time bins. The initial protocol in all rats was a time control. The first control measurement (C1) of MCFP was obtained, followed 10 minutes later by a second control measurement (C2). Then, drug vehicle (saline or a mixture of 70% water, 10% ethanol, and 20% propylene glycol) was injected intravenously. Measurements of MCFP were repeated every 15 minutes for 1 hour (labeled A1, A2, A3, and A4). Values reported for mean arterial pressure (MAP), HR and CVP are the averages of the values obtained during the final 3 minutes before balloon inflation.

In most rats, the effects of selective ET\(_{A}\) receptor antagonism and ganglion blockade were investigated with the use of the same protocol in experiments conducted on subsequent consecutive days. Initially, instead of drug vehicle injections, rats received either the ETA receptor antagonist ABT-627 (1 mg/kg IV) or the ganglion blocker hexamethonium (30 mg/kg IV). Only 1 protocol was run per day, and the order was randomized. Finally, the ability of ET\(_{A}\) receptor antagonism to modify hemodynamic responses to ganglion blockade was examined through pretreatment of the rats with ABT-627 (1 mg/kg IV) 1 hour before the administration of hexamethonium (30 mg/kg IV).

In 5 SHAM rats, immediately after completion of the procedures just described, a 1% NaCl/0.2% KCl solution was substituted for the drinking water; they continued to consume normal rat chow. After 3 to 4 days, hemodynamic responses to ABT-627 (1 mg/kg IV) were recorded with the same protocol as previously indicated. Rats were then subjected to 3 to 4 days of sodium depletion. Distilled water was the sole drinking solution; the only food available was a modified diet containing negligible quantities of sodium (sodium deficient test diet, TD 170950; Harlan/Teklad), and furosemide (5 mg/kg IV) was administered daily. A final determination of hemodynamic responses to ABT-627 was then made.
Volume measurements were made at least 24 hours after the completion of the initial hemodynamic protocols.

Statistical Analyses

Comparisons between SHAM and DOCA rats were made with the use of a mixed-design ANOVA, in which significant overall between-group differences were found, and comparisons at individual times were achieved through the testing of simple main effects. Changes in variables within groups over time were evaluated according to the method of contrasts, in which values at each time point after drug injection were compared with the average of the 2 control values. Comparisons between rats on high-salt versus low-salt intakes were performed with a 2-factor ANOVA, with both factors being repeated measures. Comparisons of maximum changes in response to drug treatment were performed with the use of t tests for paired or independent samples where appropriate. For all tests, the significance level was set at $P<0.05$.

Results

A total of 19 rats (9 SHAM and 10 DOCA) were included in the study. At the time of catheterization, body weight was $412\pm12$ g in SHAM rats and $336\pm8$ g in DOCA rats. All rats were tested 2 days after catheterization in a time control protocol; additional experiments were conducted in rats not experiencing catheter or balloon failure. Balloon rupture occurred in several rats early in the study (especially in the DOCA group). Prestretching of the balloons for 24 to 48 hours before implantation virtually eliminated this problem. Time control data (not shown) from both SHAM and DOCA rats demonstrated that all hemodynamic variables were stable during the course of the 80-minute protocol with the exception of CVP, which tended to decline gradually. This was significant only in the SHAM group. In DOCA rats, HR rose, but this achieved statistical significance only at the final time point. Compared with SHAM rats, DOCA animals had significantly higher MAP ($156\pm3$ versus $113\pm2$ mm Hg) and MCFP ($8.0\pm0.4$ versus $6.7\pm0.4$ mm Hg), whereas HR ($370\pm10$ versus $379\pm13$ bpm) and CVP ($-0.9\pm0.3$ versus $-1.2\pm0.2$ mm Hg) were similar. To evaluate the stability of these same measures during a period of days, control period values (C1 and C2) were averaged in 11 rats in which data could be collected during 3 consecutive days (days 2 to 4 after catheterization surgery). The results were as follows. In SHAM rats, MAP ($114\pm2$ to $100\pm1$ mm Hg) and HR ($382\pm15$ to $347\pm14$ bpm) declined significantly during the 3 days, whereas CVP and MCFP were stable. In DOCA rats, MAP, HR, and CVP were stable, but MCFP rose gradually and significantly between days 2 and 4 after catheterization (7.6$\pm0.4$ to 8.8$\pm0.5$ mm Hg).

Hemodynamic responses to the administration of the ET$_1$ receptor antagonist ABT-627 are shown in Figure 1. Peak changes were defined as those occurring 15 minutes (A1) after drug injection, because in all except 1 rat, the largest change in hemodynamic variables occurred at this time. MAP decreased significantly in SHAM and DOCA rats after ABT-627 injection, but the peak fall was significantly larger in the DOCA group ($-28\pm3$ mm Hg). Significant decreases in HR occurred in both groups, but the peak response in DOCA rats was significantly larger ($-55\pm14$ versus $-20\pm8$ bpm). Modest decreases in CVP were observed in both groups of rats, but these reached statistical significance only in SHAM animals. MCFP fell in all rats in response to hexamethionium, but the decrement was significantly larger in the DOCA group ($5.5\pm0.4$ to 5.5$\pm0.2$ mm Hg) compared with the SHAM group (6.8$\pm0.2$ to 5.0$\pm0.2$ mm Hg).

Figure 3 illustrates the hemodynamic changes in response to hexamethionium in DOCA rats 1 hour after the administration of ABT-627 (1 mg/kg IV) compared with the responses of the same rats a few days earlier to hexamethionium alone. The values of all hemodynamic variables were the same in pretreated and nonpretreated rats before the injection of hexamethionium. On the day when the combined drug effects were tested, we did not measure hemodynamics before

![Figure 1. Response of hemodynamic variables to selective endothelin subtype A receptor blockade with intravenous ABT-627 administered immediately after C2 time point. MABP indicates mean arterial blood pressure; C1 and C2, control period measurements separated by 10 minutes; A1 to A4, treatment period measurements separated by 15 minutes; n, number of rats per group; and b/m, beats per minute. *Significant difference ($P<0.05$) between SHAM and DOCA rats at a specific measurement time. +Significant difference ($P<0.05$) between an A1- to A4-time point value and average of C1 and C2 time point values.](image)
the administration of ABT-627 so we cannot absolutely confirm that this group of rats showed an acute fall in MAP and MCFP during the 1 hour after drug dosing, as illustrated in Figure 1. Because the combined drug protocol was always run 4 to 5 days after catheterization surgery and because MAP and MCFP tended to rise from days 2 to 4 after surgery, we presume that both variables were higher before ABT-627 treatment. No hemodynamic response to hexamethonium was significantly altered by 1-hour pretreatment with ABT-627. Similar results were obtained in SHAM rats that were administered hexamethonium 1 hour after ABT-627 treatment (data not shown).

Hemodynamic changes produced by ABT-627 (1 mg/kg IV) were studied in SHAM rats (n = 5) maintained on high- and low-salt intakes for 3 to 4 days. During the control period, MAP was slightly but significantly higher when rats were on a high-salt intake (111 ± 2 mm Hg) but no other variable, including MCFP (7.3 ± 0.2 mm Hg for high salt versus 7.0 ± 0.5 mm Hg for low salt), differed between the 2 conditions. The injection of ABT-627 caused a small, delayed decline in MAP in rats during high-salt intake (111 ± 2 to 98 ± 4 mm Hg) but not during salt restriction. Tachycardia occurred to a similar degree under both levels of salt intake. Neither CVP nor MCFP was affected by ABT-627 under high- or low-salt intake conditions.

Blood volume averaged 61.9 ± 2.5 mL/kg in 5 SHAM rats and 69.3 ± 2.2 mL/kg in 4 DOCA rats. This difference did not achieve statistical significance (P = 0.07).

**Discussion**

There were 3 new findings in this study. First, MCFP is increased in rats after 3 to 4 weeks of DOCA-salt hypertension. Second, the administration of a selective antagonist of the ETA subtype of ET receptor causes a larger acute fall in MCFP in DOCA-salt hypertensive rats than in normotensive rats. Third, acute ganglion blockade with hexamethonium also causes a larger fall in MCFP in DOCA-salt hypertensive rats than in normotensive rats.

Two separate studies in dogs with chronic mineralocorticoid-salt hypertension revealed increased MCFP when compared with normotensive controls. Only 1 other report exists concerning MCFP in DOCA-salt hypertensive rats. Yamamoto et al performed 1-time-only measurements of MCFP in conscious rats 1, 2, 5, and 8 weeks after the initiation of DOCA-salt treatment. Although the MCFP was numerically higher in the hypertensive rats compared with normotensive controls, the differences did not reach statistical significance. However, hemodynamic measurements were made only 3 hours after general anesthesia and surgery for catheter and balloon insertion. In contrast, values for MCFP reported here were obtained 2 to 5 days after surgery. A significantly higher MCFP was found in DOCA-salt hypertensive rats compared with SHAM at 2 days after surgery, and this difference became even larger on subsequent recovery days. Thus, we speculate that the small differences in values between the study of Yamamoto et al and ours can be accounted for by the suppression of sympathetic activity and relative dehydration associated with anesthesia and surgery in their rats. Supportive of this idea is the fact that saline drinking in the DOCA-salt hypertensive rats studied here typically did not recover to presurgery amounts until at least 4 days of recovery. We conclude that MCFP is increased in DOCA-salt hypertension of 3- to 4-week duration.
Increased blood volume, constriction of venous smooth muscle, and structural changes in the wall of venules and veins are the most likely causes of increased MCFP. Evidence of structural abnormalities in veins exists for hypertensive humans\textsuperscript{2,6} and some experimental models of hypertension (eg, spontaneously hypertensive rats\textsuperscript{5}). No similar data are available for the DOCA-salt hypertensive rat. Most studies of individuals or animals with established hypertension, including DOCA-salt hypertensive rats, reveal blood volumes (indexed to body weight) to be normal or even reduced compared with normotensive controls.\textsuperscript{2,18} We were able to measure blood volume in only a sample of the rats studied here and found that the DOCA group had moderately higher blood volumes than the SHAM group under the conditions of our study (similar to data from Yamamoto et al\textsuperscript{18}). Because of the small number of rats in which we were able to measure blood volume, we can conclude only tentatively that elevated blood volume may have contributed to higher MCFP in our DOCA-salt hypertensive rats.

One goal of our study was to test the hypothesis that ET-1 produces greater venoconstriction in conscious, intact DOCA-salt hypertensive rats than in normotensive SHAM animals. Venoconstriction in response to ET-1 can result from the stimulation of either ET\textsubscript{A} or ET\textsubscript{B} receptors,\textsuperscript{19} whereas venodilation is mediated only through ET\textsubscript{B} receptors. We demonstrated previously that small veins isolated from the mesentery of DOCA-salt hypertensive rats exhibit normal (equal to that of SHAM rats) contractile responses to ET\textsubscript{A} and ET\textsubscript{B} receptor activation in vitro (Johnson RJ, Fink GD, and Galligan JJ, submitted, 1999), even in the face of chronic increases in endogenous ET-1 formation.\textsuperscript{11} Because ET\textsubscript{A} receptor stimulation causes a larger venoconstrictor response than ET\textsubscript{B} receptor activation, in the present study we investigated changes in MCFP produced by the selective ET\textsubscript{A} receptor antagonist ABT-627, the active enantiomer of the better known A-127722.\textsuperscript{20} We chose a dose of 1 mg/kg IV on the basis of evidence that this dose produces plasma concentrations of the drug that cause significant blockade of ET\textsubscript{A} receptors with minimal effects on ET\textsubscript{B}-mediated responses in rats.\textsuperscript{20} ABT-627 has already been shown to significantly decrease AP in DOCA-salt hypertensive rats.\textsuperscript{21} That result was confirmed in the present study. In addition, the drug caused significant tachycardia in both SHAM and DOCA-salt hypertensive rats; the mechanism is unknown. Most importantly, ABT-627 produced a significant decrease in MCFP in DOCA-salt hypertensive rats but not in SHAM rats. In general, the time course of the response paralleled the decline in AP. These results are consistent with the idea that DOCA-salt hypertension is associated with enhanced venoconstriction produced by endogenous ET-1 acting on ET\textsubscript{A} receptors. This could be due to greater endothelial formation of ET-1 in DOCA-salt hypertensive rats. No data exist, however, on venous endothelial cell ET formation in the DOCA-salt model, and reports on the blood levels of ET-1 in DOCA-salt hypertensive rats are conflicting.\textsuperscript{22}

It is possible that DOCA-salt hypertensive rats showed greater decreases in MCFP to ABT-627 than SHAM rats merely because the former were on a high-salt intake. For example, Mortensen and Fink\textsuperscript{23} reported that pressor responses to long-term infusion of ET-1 in rats are markedly potentiated by high-salt intake. Our present results do not support that explanation: normotensive SHAM rats did not exhibit a decrease in MCFP in response to ABT-627 administration after 3 to 4 days of either sodium loading or sodium depletion.

The sympathetic nervous system has a major impact on venomotor tone and, thus, systemic vascular compliance and MCFP.\textsuperscript{24–26} There is much evidence that sympathetic nervous system activity and sympathetic support of AP\textsuperscript{27} are increased in DOCA-salt hypertensive rats. Therefore, we compared the contribution of the sympathetic nervous system to control of MCFP in DOCA and SHAM rats by using acute ganglion blockade with hexamethonium. As many have reported previously,\textsuperscript{27} we found that acute ganglion blockade caused falls in AP and HR in both SHAM and DOCA-salt hypertensive rats and that the magnitude of these effects were significantly larger in DOCA-salt hypertensive rats. CVP tended to decline in both groups as well. The decline in MCFP produced by hexamethonium was significantly larger in DOCA-salt hypertensive than in SHAM rats; in fact, at all except 1 time point (30 minutes) after hexamethonium injection, MCFP no longer differed significantly in SHAM and DOCA-salt hypertensive rats (although it remained consistently higher in the DOCA group). Although a contribution by other factors cannot be ruled out, this result suggests that increased sympathetically mediated venomotor tone plays a major role in the elevated MCFP of DOCA-salt hypertensive rats. Similar conclusions have been reached concerning the increased MCFP measured in spontaneously hypertensive rats.\textsuperscript{1}

In some vascular beds, exogenous ET-1 augments sympathetic neurotransmission; one such bed is the forearm veins in humans with essential hypertension.\textsuperscript{12} Furthermore, it has been reported that ET-1 and the sympathetic nervous system exert synergistic actions on venomotor tone in conscious rats.\textsuperscript{28} Thus, we sought to determine whether there was an interaction between endogenous ET-1 and sympathetic control of MCFP in DOCA-salt hypertensive rats. We reasoned that if endogenous ET-1 potentiated sympathetic venomotor tone through the activation of ET\textsubscript{A} receptors, then the block of ET\textsubscript{A} receptors with ABT-627 would impair subsequent MCFP responses to ganglion blockade. Such an effect could not be demonstrated, however, in either SHAM or DOCA-salt hypertensive rats. We conclude that endogenous ET-1 does not significantly influence sympathetic control of venomotor tone in SHAM or DOCA-salt hypertensive rats solely through an action on ET\textsubscript{A} receptors.

In summary, we demonstrated that conscious DOCA-salt hypertensive rats have an increased MCFP relative to that of normotensive rats. Possible mechanisms include higher blood volume, augmented ET-1-induced direct venoconstriction mediated by ET\textsubscript{A} receptors, and increased sympathetic venomotor tone. Whether this is a secondary adaptation or contributes to the development of hypertension remains to be determined.

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