Endothelin antagonist reduces hemodynamic responses to vasopressin in DOCA-salt hypertension

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Yu, Ming, Venkat Gopalakrishnan, Thomas W. Wilson, and J. Robert McNeill. Endothelin antagonist reduces hemodynamic responses to vasopressin in DOCA-salt hypertension. Am J Physiol Heart Circ Physiol 281: H2511–H2517, 2001.—The contribution of endothelin to the changes in blood pressure, cardiac output, and total peripheral resistance evoked by arginine vasopressin and angiotensin II was investigated in deoxycorticosterone acetate (DOCA)-salt hypertensive rats by infusing the peptides intravenously before and after pretreatment with the endothelin receptor antagonist bosentan. Blood pressure was recorded with radiotelemetry devices and cardiac output was recorded with ultrasonic transit time flow probes in conscious unrestrained animals. The dose-related decreases in cardiac output induced by vasopressin and angiotensin II were unaffected by bosentan. In contrast, the dose-related increases in total peripheral resistance evoked by vasopressin were blunted in both DOCA-salt hypertensive and sham normotensive rats, but this effect of bosentan was greater in the DOCA-salt hypertensive group. In contrast with vasopressin, bosentan failed to change hemodynamic responses to angiotensin II. The exaggerated vascular responsiveness (total peripheral resistance) of the DOCA-salt hypertensive group to vasopressin was largely abolished by bosentan. These results suggest that endothelin contributes to the hemodynamic effects of vasopressin but not angiotensin II in the DOCA-salt model of hypertension.

angiotensin II; bosentan; blood pressure; cardiac output; total peripheral resistance; deoxycorticosterone acetate

MANY PHYSICAL AND CHEMICAL STIMULI have been reported to enhance the synthesis and release of endothelin-1 (ET-1) from endothelial cells (16). Among them, arginine vasopressin (AVP) and angiotensin II (ANG II) have been shown to induce preproET-1 mRNA expression from cultured rat endothelial cells (9) and to release ET-1 from bovine endothelial cells (7). In addition, AVP has been reported to evoke ET-1 release from the perfused rat mesenteric vascular bed (23).

In vessels isolated from the deoxycorticosterone acetate (DOCA)-salt hypertensive rat, preproET-1 mRNA expression was increased (5, 12) and ET-1 peptide levels were elevated (14). Importantly, Intengan et al. (10) reported that chronic treatment with an AVP receptor (V₁) antagonist lowered blood pressure (BP) and attenuated the increase in preproET-1 gene expression observed in mesenteric arteries of DOCA-salt hypertensive rats. Intengan et al. also demonstrated that the enhanced ET-1 gene expression observed in rats treated with the DOCA-salt regimen was absent in the Brattleboro rat (11), a rat homozygous for diabetes insipidus with no detectable levels of AVP in plasma (20). Thus there is a strong association between V₁ receptor activation by AVP and ET-1 gene expression, and this association is correlated with the development of DOCA-salt hypertension. However, the possibility that the ET system contributes directly to the hemodynamic actions of AVP in the DOCA-salt model of hypertension has not been studied. The purpose of this study was to examine this issue by recording hemodynamic responses to AVP in the conscious unrestrained DOCA-salt hypertensive rat both when the ET system was functional and when it was blocked with the nonpeptide mixed ETₐ/ETₐ receptor antagonist bosentan. To quantify the contribution of ET to the effects of AVP at the level of the resistance function of the circulation, we determined the changes in total peripheral resistance (TPR) by recording BP with radiotelemetry devices and cardiac output (CO) with ultrasonic flow-probes. For comparison, the responses to ANG II were also evaluated.

MATERIALS AND METHODS

Animal care and instrumentation. Male Sprague-Dawley rats were bred and raised in our animal quarters under standardized conditions. The breeders were purchased from Charles River (St. Constant, Quebec, Canada). At 8–10 wk of age, the right kidney was removed through a dorsal flank incision under ether anesthetization. One week later, these rats were divided randomly into two groups: DOCA-salt-treated and sham control groups. In the DOCA-salt-treated group, a Silastic strip impregnated with 100 mg/kg body wt of DOCA (Aldrich Chemical; Milwaukee, WI) was implanted subcutaneously in the midscapular region. From this point on, these rats were given a 0.9% NaCl and 0.2% KCl solution for drinking ad libitum over a 3-wk period. Under this regimen, this group of rats developed hypertension. In the sham group, a DOCA-free Silastic strip was implanted subcutane-
ously and tap water was provided as a drinking solution for the next 3 wk.

After 3 wk, the animals were anesthetized with Somnotol (60 mg/kg pentobarbital sodium) intraperitoneally. The trachea was intubated and connected to a rodent ventilator (Harvard Apparatus; South Natick, MA). A thoracotomy was performed under aseptic conditions. A 2.5 SB series ultrasonic flow probe (Transonic Systems) was implanted on the ascending aorta of each rat for the recording of CO. A catheter connected to a radiotelemetry capsule (TA11PA-C40, Data Sciences; Minneapolis, MN) was inserted into the left femoral artery and pushed so that its tip reached the abdominal aorta above the iliac bifurcation for monitoring BP. The capsule containing the transducer and radiotransmitter was positioned in the left flank region subcutaneously. The left femoral vein was cannulated with MRE040 tubing (Braintree Scientific; Braintree, MA) for drug infusion. The cannula was tunneled subcutaneously and emerged at the neck. The end of the cannula was plugged.

Ten days later, with the rat in the conscious and unrestrained state, the plug on the venous cannula was removed. A catheter attached to a needle and syringe was connected to the venous cannula. BP and CO were recorded in these conscious unrestrained rats during the intravenous infusions of AVP and ANG II. Pressure data were collected with a computer-driven data acquisition system (Data Sciences). The pressure waveform was sampled every 30 s with a 5-s sample duration. CO was recorded by feeding the signal from the flowmeter (T206 Transonic Systems) to a pen recorder (Grass Instruments; Quincy, MA). TPR was calculated as the quotient of BP and CO.

**Responses to AVP.** After a 2-h control period, AVP was infused intravenously at rates of 1, 3, 10, or 30 ng·kg⁻¹·min⁻¹ for 15 min in DOCA-salt-treated and sham rats. Each rat was infused twice with one of these four doses of AVP, once in the presence and once in the absence of bosentan, on separate days in a randomized crossover design to control for any time- or sequence-related variation. Bosentan (30 mg/kg) was injected intravenously, and the response to AVP was studied 100 min after the injection of bosentan. This dose and protocol was adopted on the basis of previous work and on pilot experiments. In pilot experiments, this dose was found to effectively antagonize exogenous ET-1 (0.03–0.3 nmol/kg). The 100-min period after bosentan treatment was chosen because, in other experiments, the response to bosentan had been pretreated with bosentan. This effect of bosentan was particularly dramatic in the DOCA-salt-treated group, because, in other experiments, the response to bosentan had reached a plateau at this time and it was well before recovery from the effects of bosentan (27).

**Responses to ANG II.** The protocol for administration of ANG II was similar to that for AVP. After a 2-h control period, ANG II was infused intravenously at rates of 3, 9, 30, and 90 ng·kg⁻¹·min⁻¹ for 10 min in DOCA-salt-treated and sham rats. Each rat was infused twice with one of these four doses of ANG II, once in the presence and once in the absence of bosentan, on separate days in a randomized crossover design to control for any time- or sequence-related variation. Bosentan (30 mg/kg) was injected intravenously, and the response to ANG II was studied 100 min after the injection of bosentan. This dose and protocol was adopted on the basis of previous work and on pilot experiments. In pilot experiments, this dose was found to effectively antagonize exogenous ET-1 (0.03–0.3 nmol/kg). The 100-min period after bosentan treatment was chosen because, in other experiments, the response to bosentan had reached a plateau at this time and it was well before recovery from the effects of bosentan (27).

**Materials.** AVP and ANG II were purchased from Bachem California (Torrance, CA) and dissolved in 0.9% saline. Bosentan, kindly provided by Dr. M. Clozel (Actelion; Allschwil, Switzerland), was dissolved in sterile water.

**Data analysis.** All values are expressed as means ± SE. Graphs of the residuals were plotted to detect heterogeneity of variances. If needed, homogeneity of variance was achieved by log transformation of the data. Control values and the relationships among dose, treatment (bosentan and vehicle), and group (DOCA and sham) were compared by ANOVA. If ANOVA indicated significance, simultaneous multiple comparisons were based on the Games-Howell multiple-comparisons procedure.

**Results**

Control values for BP, CO, and TPR are shown in Table 1. BP was significantly higher in DOCA-salt hypertensive rats than in sham control rats. This elevation was due to the increased TPR, because the values for CO were not significantly different. Bosentan lowered BP and TPR in the DOCA-salt hypertensive group but did not change CO. In contrast with the DOCA-salt-treated group, bosentan did not change BP or TPR in the sham group.

**Responses to AVP.** The hemodynamic responses to AVP in DOCA-salt hypertensive and sham rats in the presence or absence of bosentan are shown in Fig. 1. AVP induced dose-related increases in TPR and BP and decreases in CO. Bosentan significantly blunted the increase in TPR observed in both DOCA-salt hypertensive and sham control rats (Fig. 1A); except for the highest dose of 30 ng·kg⁻¹·min⁻¹ AVP, the increases in TPR were significantly less when the animals had been pretreated with bosentan. This effect of bosentan was particularly dramatic in the DOCA-salt-treated group: an increase of 0.6 mmHg·ml⁻¹·kg⁻¹·min⁻¹ in TPR was evoked by a dose of −2.7 ng·kg⁻¹·min⁻¹ when ET receptors were blocked (bosentan treated), a more than threefold difference. In the sham group, a 0.6 mmHg·ml⁻¹·kg⁻¹·min⁻¹ increase in TPR was evoked by 5.5 ng·kg⁻¹·min⁻¹ in vehicle-treated animals and 10.2 ng·kg⁻¹·min⁻¹ in bosentan-treated animals, a less than twofold increase. In contrast with TPR, bosentan failed to change CO responses to AVP in either DOCA-salt hypertensive or sham rats (Fig. 1B). Similar to TPR, BP responses to AVP were blunted by bosentan (Fig. 1C).

**Responses to ANG II.** Changes in BP, CO, and TPR to intravenous infusion of ANG II in DOCA-salt hypertensive and sham rats are shown in Fig. 2. ANG II induced dose-related increases in BP and decreases in CO. However, the increases in BP were significantly less when the animals had been pretreated with bosentan. This effect of bosentan was particularly dramatic in the DOCA-salt-treated group: a 0.6 mmHg·ml⁻¹·kg⁻¹·min⁻¹ increase in BP was evoked by 2.87 ng·kg⁻¹·min⁻¹ when ET receptors were blocked (bosentan treated), a more than threefold difference. In the sham group, a 0.6 mmHg·ml⁻¹·kg⁻¹·min⁻¹ increase in BP was evoked by 5.5 ng·kg⁻¹·min⁻¹ in vehicle-treated animals and 10.2 ng·kg⁻¹·min⁻¹ in bosentan-treated animals, a less than twofold increase. In contrast with BP, bosentan failed to change CO responses to ANG II in either DOCA-salt hypertensive or sham rats (Fig. 2B). Similar to BP, CO responses to ANG II were blunted by bosentan (Fig. 2C).

**Table 1. Control values in AVP and ANG II studies**

<table>
<thead>
<tr>
<th></th>
<th>DOCA-Salt-Treated Rats</th>
<th>Sham Rats</th>
<th>DOCA-Salt-Treated Rats</th>
<th>Sham Rats</th>
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<tr>
<td><strong>AVP study</strong></td>
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<tr>
<td>n</td>
<td>32</td>
<td>33</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>BP</td>
<td>149 ± 3†</td>
<td>126 ± 3†</td>
<td>104 ± 2</td>
<td>101 ± 2</td>
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<tr>
<td>CO</td>
<td>186 ± 5</td>
<td>201 ± 6</td>
<td>191 ± 7</td>
<td>200 ± 7</td>
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<tr>
<td>TPR</td>
<td>0.83 ± 0.04†</td>
<td>0.64 ± 0.03†</td>
<td>0.57 ± 0.02</td>
<td>0.52 ± 0.02</td>
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<td><strong>ANG II study</strong></td>
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<tr>
<td>n</td>
<td>25</td>
<td>26</td>
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<tr>
<td>BP</td>
<td>155 ± 2†</td>
<td>134 ± 3†</td>
<td>103 ± 1</td>
<td>98 ± 2</td>
</tr>
<tr>
<td>CO</td>
<td>190 ± 5</td>
<td>205 ± 8</td>
<td>192 ± 5</td>
<td>203 ± 8</td>
</tr>
<tr>
<td>TPR</td>
<td>0.84 ± 0.03†</td>
<td>0.68 ± 0.04†</td>
<td>0.56 ± 0.02</td>
<td>0.51 ± 0.02</td>
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Values are means ± SE; n = no. of rats. Values are shown for blood pressure (BP, in mmHg); cardiac output (CO, in ml·min⁻¹·kg⁻¹), and total peripheral resistance (TPR, in mmHg·ml⁻¹·min⁻¹·kg⁻¹) in deoxycorticosterone acetate (DOCA)-salt hypertensive and sham control rats before and after bosentan treatment. *P < 0.05 compared with bosentan treatment; †P < 0.05 compared with sham rats.
tensive and sham rats in the presence or absence of bosentan are shown in Fig. 2. ANG II induced dose-related increases in BP and TPR and decreases in CO. In contrast with AVP, bosentan failed to change TPR and BP responses to ANG II.

Comparison of vascular responsiveness between DOCA-salt hypertensive and sham rats. The changes in TPR evoked by AVP in the DOCA-salt-treated and sham groups are compared in Fig. 3 and those evoked by ANG II are compared in Fig. 4. Vascular responsiveness to AVP was enhanced in the DOCA-salt-treated group compared with the sham group when ET function remained functional (Fig. 3A): a 0.6 mmHg·min⁻¹·kg⁻¹ change in TPR was evoked by ~2.7 ng·kg⁻¹·min⁻¹ AVP in the DOCA-salt-treated group and 5.5 ng·kg⁻¹·min⁻¹ in the sham group, a twofold difference. In the bosentan-treated animals, ANOVA indicated a significant difference, but this was due entirely to the highest dose of AVP (Fig. 3B). Thus except for the highest dose of AVP, the enhanced vascular responsiveness of the DOCA-salt-treated group to AVP was abolished by bosentan. Similar to AVP, vascular responses to ANG II were also enhanced in the DOCA-salt-treated group compared with the sham group (Fig. 4A). However, in contrast with AVP-evoked responses, responses evoked by ANG II were unchanged by bosentan (Fig. 4B).

DISCUSSION

The data reported in this article suggest that ET contributes acutely to the hemodynamic effects of AVP, and this effect appears to be greater in the DOCA-salt hypertensive model. Bosentan, a mixed ETA/ETB re-
ceptor antagonist, blunted the increases in TPR by more than threefold in the DOCA-salt-treated group and less than twofold in the sham group (Fig. 1). This appears to be the first study to examine the contribution of ET in the DOCA-salt model at the hemodynamic level by recording BP and CO simultaneously in the conscious unrestrained rat. A feature of these studies is that BP was recorded with radiotelemetry devices and CO was recorded with ultrasonic transit time flowmeters. The devices can be implanted well in advance of any experimental interventions, permitting longer recovery times from surgery and conditioning of the animals to the recording room. In addition, pressure and flow can be recorded for several weeks. BP tends to be lower in hypertensive animals when pressure has been recorded by radiotelemetry, an observation that has been attributed to the longer recovery periods from surgery and the reduced level of stress associated with this technique (2, 4). By recording CO and BP, we were able to calculate TPR, a true measure of the resistance function of the circulation and a better index of vascular responsiveness than BP.

The changes in CO do not appear to explain the results. Regional blood flow is regulated by the resistance function of the circulation. Except in the failing heart and under conditions of heavy exercise, total flow (i.e., CO) is regulated by the peripheral circulation, notably the resistance function (afterload) and capacitance function (venous tone) of the circulation. Capacitance function is regulated to a major extent by baroreflex control of sympathetic activity. Although ANG II blunts and AVP enhances baroreflex-mediated changes in CO in the dog, rabbit, and cat, the changes in CO to AVP and ANG II in the rat are independent of baroreflex mechanisms (17). In the final analysis, bosentan failed to alter the changes in CO evoked by AVP and ANG II, but it did alter the TPR responses to AVP, demonstrating the effects of bosentan are exerted...
ET ANTAGONIST ON AVP-EVOKED RESPONSES

The contribution of ET-1 to vascular responses evoked by acute elevations in the plasma concentrations of AVP reported in this article need to be interpreted in the context of the changes of ET-1 gene expression associated with chronic elevations of AVP reported by Schiffrin's group (22). They showed that preproET-1 mRNA expression was increased (5, 12) and ET-1 peptide levels were elevated (14) in vessels isolated from the DOCA-salt hypertensive rat and that chronic treatment with a V1 receptor antagonist lowered BP and attenuated this increase in preproET-1 gene expression observed in mesenteric arteries of DOCA-salt hypertensive rats (10). Moreover, the enhanced ET-1 gene expression observed in rats treated with the DOCA-salt regimen was absent in the Brattleboro rat (11). Thus there is a strong association between vasopressin activity and ET-1 gene expression, and this association is correlated with the development of DOCA-salt hypertension. These effects of AVP on ET-1 gene expression and ET-1 content suggest that endogenous levels of ET-1 are elevated by chronic exposure to the higher circulating levels of AVP reported to occur in the DOCA-salt hypertensive rat.

In contrast with AVP, ET did not appear to contribute to the hemodynamic effects of ANG II. Bosentan failed to change the hemodynamic effects of ANG II in both the DOCA-salt hypertensive group and the sham normotensive group (Fig. 2). This differs from our results in the spontaneously hypertensive rat model, where bosentan blunted responses to both ANG II (3) and AVP (1), suggesting some degree of selectivity between agonist and the model of hypertension, at least in the case of ANG II.

Fig. 3. Noncumulative dose-response curves showing the changes in TPR evoked by intravenous infusions of 1, 3, 10, or 30 ng·kg⁻¹·min⁻¹ AVP for 15 min in DOCA-salt hypertensive rats and sham normotensive control rats. Each rat was infused twice with one of these four doses of AVP, once in the presence (bosentan treated; B) and once in the absence of bosentan (vehicle treated; A), on separate days in a randomized crossover design. Statistical notations indicate values from ANOVA. Multiple comparisons are indicated by asterisks: *P < 0.05 compared with the sham group.

Fig. 4. Noncumulative dose-response curves showing the changes in TPR evoked by intravenous infusions of 3, 9, 30, and 90 ng·kg⁻¹·min⁻¹ ANG II for 10 min in DOCA-salt hypertensive rats and sham normotensive control rats. Each rat was infused twice with one of these four doses of ANG II, once in the presence (bosentan treated; B) and once in the absence of bosentan (vehicle treated; A), on separate days in a randomized crossover design. Statistical notations indicate values from ANOVA. Multiple comparisons are indicated by asterisks: *P < 0.05 compared with the sham group.

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The blunting of vascular responses to AVP but not ANG II is difficult to explain, particularly because it is generally believed that the mechanism of stimulation of secretion of ET-1 is the same for both peptides, namely increased intracellular Ca\(^{2+}\) and protein kinase C activation. However, the discovery of regulatory pathways in the secretion of ET-1 described above, particularly from the Weibel-Palade bodies, open the possibility of differential regulation of ET-1 release by different stimuli. Alternatively, or in concert, the relative differences between AVP and ANG II could be related to receptor density. V\(_1\) receptors are downregulated (13) and AT\(_1\) receptors are upregulated (22) in vascular smooth muscle isolated from DOCA-salt hypertensive rats. Assuming the total response to AVP and ANG II is the summation of its direct (ET independent) and indirect (ET dependent) components, and assuming the total response to any given dose is limited by counterregulatory vasodilator and autoregulatory mechanisms, then the higher density of ANG II receptors might evoke a relatively greater direct response that could account for total response, whereas the lower density of AVP receptors would leave room for a contribution by an indirect ET-1 component. Of course, this possibility would be strengthened by data on the differential regulation of peptide receptors by endothelial cells versus vascular smooth muscle cells, but this issue does not appear to have been studied. In any case, it is evident that there is an indirect ET-1 component that contributes to the AVP-evoked responses, although it is proportionally smaller than the direct component. Although AVP receptor density has been reported to be reduced in mesenteric arteries of DOCA-salt hypertensive rats by Larivière et al. (13), vasoconstrictor responses to AVP in the perfused mesenteric bed with intact endothelium were increased. They reported that this phenomenon was independent of an elevation in BP and resulted from an exaggerated response mediated by postreceptor mechanisms. The role of postreceptor events in the explanation of the differences between AVP and ANG II is unknown, but it could conceivably involve selective release of ET-1 from Weibel-Palade bodies. Admittedly, these explanations for the differences between AVP and ANG II, while plausible, are speculative and will remain so until the complex mechanisms governing the secretion of ET-1 by constitutive and regulatory pathways (Weibel-Palade bodies) are further elucidated.

It could be argued that measurement of plasma concentrations of ET-1 might confirm the data on the biological responses noted in the present study. However, plasma concentrations are typically very low, ranging between 1 and 5 pM and rarely exceeding 25 pM, even in pathological states (8). Frelin and Guedin (8) argue that most of the tissue ET is bound and suggest that plasma ET levels are low, probably because tissue-free ET levels are low, a point not inconsistent with the presence of high tissue levels of active (that is, bound) ET. More importantly, ET has been shown to be secreted primarily into the basolateral compartment (i.e., abluminally) and not into the apical compartment (luminally) (24). Thus plasma concentrations may not be representative of locally released ET-1 at its site of action. Finally, ET-1 plasma concentrations may be low because of the efficiency of clearance receptors. Taken together, it is generally accepted that data on the plasma concentrations of ET-1 are of limited value, a point emphasized in a review by Schiffrin (21).

Vascular responsiveness to both AVP and ANG II was greater in the DOCA-salt hypertensive rats than in the sham normotensive rats when the ET system remained functional (vehicle-treated animals in Figs. 3A and 4A). Whereas the enhanced vascular responsiveness of DOCA-salt hypertensive rats to ANG II persisted after treatment with bosentan (Fig. 4B), the enhanced vascular responsiveness to AVP was largely abolished (Fig. 3B). Only the response at the highest dose of AVP was significantly higher after bosentan. Recently, we (28) reported that responsiveness of the DOCA-salt model to AVP was not enhanced. The differences between results reported earlier and those reported in this article may be related to the stage of hypertension or the protocols employed in the two studies. In the previous study (28), rats were studied 24 days after initiation of the DOCA-salt regimen, when BP had risen to 135 ± 6 mmHg. For that study, the four doses of AVP were infused in a cumulative fashion on a single day. In the present study, rats were studied 31–36 days after beginning the DOCA-salt regimen, BP had risen to 149 ± 3 mmHg. In this study, only a single dose was infused on any one day, allowing recovery from the previous dose. These findings are somewhat similar to those of Matsuguchi and Schmid (15), who showed that pressor responsiveness to AVP was not enhanced in the early stages of development of DOCA-salt hypertension, when BP had risen to 118 ± 3 mmHg, but pressor responsiveness was enhanced when BP had increased to 158 ± 7 mmHg later in the course of development of hypertension.

The mechanism of the enhanced vascular responsiveness to AVP and to ANG II is unknown, but vascular remodeling is one possibility that must be considered. Vascular remodeling may contribute to the elevated TPR observed in the DOCA-salt model of hypertension, and the AVP system appears to contribute to this remodeling. Intengan and coworkers (10, 11) reported that small mesenteric arteries from DOCA-salt hypertensive rats had smaller lumen diameters and larger media widths, media cross-sectional areas, and media-to-lumen ratios compared with control rats and that these changes were absent or largely abolished both in the Brattleboro rat and in rats treated chronically with a V\(_1\) antagonist. The lack of remodeling under these conditions was accompanied by an attenuation of the enhanced ET-1 expression normally observed in the DOCA-salt model. Thus the interaction of AVP with the ET system may well contribute to remodeling of the vasculature and the development of hypertension in the DOCA-salt model. However, remodeling does not appear to fully explain the enhanced vascular responsiveness of DOCA-salt hypertensive
rats to AVP and ANG II. Vascular remodeling should produce a nonspecific increase to vasoconstrictor stimuli. Whereas the greater increases in TPR of DOCA-salt hypertensive rats to ANG II persisted after bosentan treatment, the enhanced vascular responses of DOCA-salt hypertensive rats to AVP were largely abolished by bosentan. Remodeling is a chronic adaptation that cannot explain the acute effect of bosentan. The greater responses of DOCA-salt hypertensive rats to AVP appear related to a more robust activation of the ET system. In the case of ANG II, a mechanism other than activation of the ET system must be invoked. The enhanced vascular responsiveness to exogenous ANG II is consistent with the upregulation of ANG II receptors.

In summary, ET appears to contribute to the increases in TPR evoked by acute elevations in the circulating levels of AVP but not ANG II, suggesting the contribution is in addition to the likely remodeling reported to occur in this model of hypertension. This contribution of ET appears to explain the enhanced vascular responsiveness of DOCA-salt hypertensive rats to AVP.

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REFERENCES


