Blood Pressure and Small Arteries in DOCA-Salt–Treated Genetically AVP-Deficient Rats
Role of Endothelin
Hope D. Intengan, Jeong Bae Park, Ernesto L. Schiffrin

Abstract—Hypertension is associated with structural and mechanical abnormalities of resistance arteries. We have recently reported that vasopressin may be involved in the blood pressure elevation and remodeling of resistance arteries in deoxycorticosterone acetate (DOCA)-salt hypertension, perhaps by modulating vascular endothelin-1 expression. We tested this hypothesis further by examining DOCA-salt hypertension in homozygous vasopressin-deficient Brattleboro (BB) rats in comparison with Long-Evans (LE; control) rats. Mesenteric resistance arteries (lumen \( <300 \mu m \)) were studied on pressurized myographs. After 5 weeks, systolic blood pressure was greater in LE DOCA-salt–treated rats (189±5 mm Hg) compared with uninephrectomized (UNx) LE control rats (117±4 mm Hg; \( P<0.01 \)). The increase in blood pressure induced by DOCA-salt treatment was attenuated in vasopressin-deficient rats, such that BB DOCA-salt–treated rats exhibited only a slight elevation of blood pressure (134±6 mm Hg) compared with BB-UNx rats (111±4 mm Hg; \( P<0.05 \)). Resistance arteries in LE DOCA-salt–treated rats had a smaller lumen diameter and a larger media width, media cross-sectional area, and media-lumen ratio compared with LE-UNx rats. Isobaric stiffness was unaltered in resistance arteries from LE DOCA-salt–treated rats, despite stiffening of the arterial wall components as indicated by a significant increase in the slope of the media stress–incremental elastic modulus relationship. DOCA-salt treatment in the absence of endogenous vasopressin, ie, in homozygous di/di BB rats, failed to alter vascular structure or wall component stiffness and resulted in a lesser degree of blood pressure elevation. Reverse transcription–polymerase chain reaction analysis revealed that DOCA-salt treatment enhanced endothelin gene expression in LE rats but failed to do so in BB rats. These data indicate that vasopressin plays a critical role in modulating vascular structure and mechanics, as well as blood pressure, in DOCA-salt–induced hypertension. Moreover, these effects of vasopressin are in part mediated by enhancement of endothelin expression. (Hypertension. 1999;34[part 2]:907-913.)

Key Words: deoxycorticosterone salt ■ vasopressin ■ vascular resistance ■ hypertrophy ■ endothelin ■ elastic modulus ■ rats, inbred BB

Hypertension is associated with altered structure and mechanical properties of resistance arteries. In deoxycorticosterone acetate (DOCA)-salt hypertension, resistance arteries present with morphological changes within 2 weeks of elevation of blood pressure. These include narrowing of the lumen and external diameters, consistent with remodeling, and growth of the vascular wall that is manifested as increases in media width and media cross-sectional area.1

We previously suggested a link between vasopressin, endothelin (ET), and small-artery remodeling in this model of hypertension.2 \( V_1 \)-vasopressin receptor antagonism with the use of OPC-21268 attenuated DOCA-salt–induced increases in media-lumen ratio and expression of the preproET-1 gene, suggesting that \( V_1 \)-vasopressin receptor–mediated activation of the ET system occurs in DOCA-salt hypertension, resulting in vascular growth. These findings were consistent with abnormal vasopressin levels and function in this model. For example, active pressure responses to vasopressin are enhanced in mesenteric resistance arteries from DOCA-salt rats.1 \( V_1 \)-vasopressin receptors are also decreased in the mesenteric vasculature along with a rise in plasma vasopressin levels, suggesting potentiation of postreceptor signaling.3

We further tested the hypothesis that (1) vasopressin plays a critical role in producing abnormalities of resistance arteries in DOCA-salt hypertension and (2) vasopressin mediates such effects by activating the ET system. Homozygous vasopressin-deficient Brattleboro (BB) rats were treated with DOCA-salt (BB-DOCA-salt) and compared with uninephrectomized Brattleboro rats (BB-UNx). The parent strain of Brattleboro rats, the Long-Evans (LE) rat, was also treated with DOCA-salt and served as a control. Development of high blood pressure and abnormal vascular structure were investigated. Vascular remodeling must be described in the context of the intrinsic mechanical properties (stiffness) of
the vessel wall,\textsuperscript{4} so the mechanics of resistance arteries in this study were also determined. Finally, aortic preproET-1 mRNA levels were analyzed by reverse transcription–polymerase chain reaction (RT-PCR) analysis.

**Methods**

**Animals**

This study was done according to recommendations of the Animal Care Committee of the Clinical Research Institute of Montreal and the Canadian Council of Animal Care. Male LE and homozygous BB rats (\textit{di/di}) (Harlan Sprague Dawley, Inc, Indianapolis, Ind) were exposed to a 12-hour light/dark cycle and housed at 22°C/60% humidity. DOCA-salt hypertension was induced by the method of Ormsbee and Ryan.\textsuperscript{5} Rats were anesthetized (sodium pentobarbital, 40 mg/kg) and unilaterally nephrectomized. Silicone rubber impregnated with DOCA (200 mg) was implanted subcutaneously, and rats were offered 0.5% saline/0.2% KCl to drink. Control rats were also uninephrectomized but received a silicone rubber implant without DOCA and were offered tap water to drink. DOCA-salt treatment continued for 5 weeks. Systolic blood pressure was measured weekly by the tail-cuff method.\textsuperscript{6}

**Preparation of Resistance Arteries**

When the experiment was completed, the rats were decapitated. The mesenteric vasculature was dissected,\textsuperscript{6} and a third-order branch (>2 mm long) was placed on 2 microcannulas in a pressure myograph and adjusted so that the vessel walls were parallel without being stretched.\textsuperscript{7} Vessels were equilibrated (1 hour, 37°C) under myograph and adjusted so that the vessel walls were parallel without 2 mm long) was placed on 2 microcannulas in a pressure (those vessels were parallel without being stretched.\textsuperscript{7} Vessels were equilibrated (1 hour, 37°C) under constant intraluminal pressure (45 mm Hg) with physiological salt solution\textsuperscript{8} that was bubbled with 95% air/5% CO\textsubscript{2} to achieve a pH of 7.4 to 7.45. Vessels were used if they constricted >50% in response to norepinephrine (125 mmol/L and 10\textsuperscript{5} mol/L, respectively) and to norepinephrine alone. Endothelial integrity was confirmed if acetylcholine (10\textsuperscript{5} mol/L) relaxed the precontracted vessels by >75%.

**Experimental Protocol**

Vessels were deactivated by perfusion with Ca\textsuperscript{2+}-free physiological salt solution containing 10 mmol/L EGTA for 30 minutes. Lumen and media dimensions (vascular structure) were measured with intraluminal pressure maintained at 45 mm Hg. Intraluminal pressure was raised to 140 mm Hg 3 times, and the cannula was adjusted until the artery was unbuckled. To assess mechanics, pressure was increased stepwise to 140 mm Hg,\textsuperscript{6} and in the absence of intravascular flow, medial and luminal dimensions were measured at 5 points along the vessel and averaged for further calculations. The initial diameter was measured at 3 mm Hg unless the vessel collapsed. In these cases, pressure–lumen diameter data (10 to 140 mm Hg) were fit to a third-order polynomial equation, and luminal diameter was estimated.

**Calculation of Morphology and Mechanics**

For definitions, see Reference 8.

\[
\text{Media cross-sectional area} = (\pi/4) \cdot (D_i^2 - D_e^2), \quad \text{where } D_i \text{ and } D_e \text{ are external and luminal diameters, respectively.}
\]

\[
\text{Circumferential strain } \varepsilon = (D_i - D_e)/D_e, \quad \text{where } D_i \text{ is the observed luminal diameter for a given intraluminal pressure and } D_e \text{ is the original diameter at } 3 \text{ mm Hg.}
\]

\[
\text{Circumferential stress } \sigma = (PD)/2M, \quad \text{where } P \text{ is intraluminal pressure (dyn/cm}^2) \text{ and } D \text{ and } M \text{ are luminal diameter and medial thickness, respectively.}
\]

\[
\text{Elastic modulus } = \sigma = \sigma_\varepsilon e^\beta, \quad \text{where } \sigma_\varepsilon \text{ is stress at } D_e \text{ and } \beta \text{ is a constant related to the rate of increase of the stress-strain curve. The tangential elastic modulus (ET) was calculated at several values of stress from the derivative of the exponential curve: } ET = \dot{\sigma}_\varepsilon = \dot{\sigma}_\varepsilon e^\beta.
\]

The percent difference between luminal diameters of hypertensive and normotensive vessels that is not attributable to growth was calculated as the remodeling index.

\[
\text{Remodeling index} = 100 \cdot [(D_i)_{\text{normotensive}}/D_i] - (D_i)_{\text{hypertensive}}, \quad \text{where } (D_i)_{\text{normotensive}} \text{ and } (D_i)_{\text{hypertensive}} \text{ are luminal diameters of normotensive and hypertensive vessels, respectively, and } (D_i)_{\text{normotensive}} = (D_i)_{\text{normotensive}}^2 - (4 \cdot \text{CSA}_n/\pi)^{1/3}, \quad \text{where } (D_i)_{\text{normotensive}} \text{ is the external diameter of hypertensive vessels and } \text{CSA}_n \text{ is the cross-sectional area of normotensive vessels.}\textsuperscript{9}
\]

\[
\text{Growth index} = (\text{CSA}_h - \text{CSA}_n)/\text{CSA}_n, \quad \text{where } \text{CSA}_h \text{ and } \text{CSA}_n \text{ are cross-sectional areas of normotensive and hypertensive vessels, respectively.}\textsuperscript{10}
\]

**Relative RT-PCR Analysis of PreproET-1 mRNA**

Expression of the ET gene in aortas from LE-UNx, LE-DOCA-salt, BB-UNx, and BB-DOCA-salt rats was studied by RT-PCR. Total RNA was extracted from frozen aortas as previously described.\textsuperscript{2} Reverse transcription was done in a 30-μL volume containing 1 μg RNA, 1.5 μL of 10 mmol/L dNTP, 6 μL of BRL 5X buffer, 0.6 μL of oligo-(dT)\textsubscript{12-18} primer (0.5 μg/μL), 1.5 μL of 200 U/μL M-MLV reverse transcriptase (GIBCO-BRL), 0.9 μL of rNasin (RNase inhibitor; 40 U/μL), and 3 μL of dithiothreitol (0.1 μL) for 1 hour at 37°C. The reaction was stopped by heating at 95°C for 5 minutes. Five microliters of the resulting cDNA mixture was amplified using specific primers. For amplification of ET gene cDNA, sense 5’-TTT TTG CCC TCC TCT TCT TC-3’ and antisense 3’-CTG AGT TAT GGC CTA TAA-5’ primers were used. PCR was conducted with an initial denaturing interval (95°C, 5 minutes) and then 30 sequence cycles for preproET-1; 94°C (45 seconds), 47.5°C (30 seconds), and 72°C (1 minute); for GAPDH: 94°C (45 seconds), 55°C (30 seconds), and 72°C (1.5 minutes). Amplification products were electrophoresed on 1.5% agarose gels containing ethidium bromide (0.5 μg/mL). Bands corresponding to RT-PCR products were visualized by UV light and digitized using Alphalmager software. Band intensity was quantified using ImageQuant (version 3.3, Molecular Dynamics) software.

**Data Analysis**

Data are presented as mean±SEM. Nonrepeated measurements were compared using 1-way ANOVA and the Newman-Keuls test. Repeated measurements were compared using ANOVA for repeated measures. Interaction means were analyzed for "simple main effects" using the Newman-Keuls test. \(P<0.05\) was considered significant.

**Results**

**Blood Pressure, Tibia Lengths, and Body and Heart Weights**

Five weeks of DOCA-salt treatment increased systolic blood pressure (Figure 1) in both LE (189±5 mm Hg; \(P<0.05\)) and BB (134±6 mm Hg; \(P<0.05\)) rats compared with strain-matched UNx controls (117±4 and 111±4 mm Hg, respectively). However, the DOCA-salt–induced rise in blood pressure was significantly attenuated in BB-DOCA-salt versus LE-DOCA-salt rats (\(P<0.05\)).

Body weights of LE-UNx, LE-DOCA-salt, and BB-UNx rats were similar. The body weight of BB-DOCA-salt rats was significantly less than that of all of these, at 241±9.4 g (\(P<0.05\)). Tibia lengths were similar except in BB-DOCA-salt rats, in which tibia length was shorter than that in both groups of LE rats. There was no difference in tibia length.
between BB-UNx and BB-DOCA-salt rats. Wet and dry weights of LE-DOCA-salt rat hearts, normalized by tibia length, were greater than those of LE-UNx rats, whereas there was no difference between BB-UNx and BB-DOCA-salt rats (Table).

Vascular Structure
In LE rats, DOCA-salt stimulated the growth of resistance arteries, resulting in a growth index of 39.5±9.9%. Growth was evident as apparent narrowing of the lumen (Figure 2; \( P<0.05 \), Student’s \( t \) test) and increased media width, media cross-sectional area, and media-lumen ratio. In contrast, in BB rats, DOCA-salt treatment failed to induce changes in lumen diameter, media width, media cross-sectional area, or media-lumen ratio versus BB-UNx rats. The growth index of mesenteric resistance arteries was \(-18.6±4.7\%\), indicating a lack of vascular growth.

Vascular Mechanics
Owing to altered vascular structure, increasing intraluminal pressure increased media stress to a lesser degree in LE-DOCA-salt arteries than in LE-UNx, BB-UNx, or BB-DOCA-salt arteries, where there were no differences in arterial geometry (Figure 3). The stress-strain curve was shifted leftward in arteries from LE-DOCA-salt rats versus other groups (Figure 3). The slope of incremental elastic modulus versus stress was greater in LE-DOCA-salt versus LE-UNx arteries (Figure 4), indicating increased stiffness of the vessel wall components in LE-DOCA-salt rats. Pressure is transduced differentially to the vessel wall as stress, depending on its geometry, so the relationship between elastic modulus (stiffness) versus stress depicts geometry-independent stiffness of wall components (elastin, collagen, etc). Incremental elastic modulus at a given pressure, ie, stiffness determined by wall component stiffness and vessel geometry, was similar in all groups. DOCA-salt treatment did not shift the stress-strain relationship nor increase vessel wall component stiffness in BB rats (Figures 3 and 4).

PreproET-1 Gene Expression in Aortas
Figure 5 shows results of RT-PCR analysis of total RNA extracted from the aortas of LE and BB rats, treated or not with DOCA-salt. Whereas preproET-1 mRNA was significantly increased in LE-DOCA-salt versus LE-UNx, there was no significant difference between aortas from BB-UNx and BB-DOCA-salt rats.

Discussion
These data implicate vasopressin in blood pressure elevation, resistance-artery growth, and vascular stiffening by DOCA-salt treatment, in part by stimulating ET gene expression. We have first shown that in LE rats, DOCA-salt elicits the characteristic elevated blood pressure, activation of the ET system, and vascular growth, including increased media width, media cross-sectional area, and media-lumen ratio and a growth index of 39.5±9.9%. While isobaric stiffness is normal in resistance arteries from LE-DOCA-salt rats, stiffening of arterial wall components occurred, so that the slope of the media stress–incremental elastic modulus relationship increased to 6.33±0.79 from 3.64±0.40 in LE-UNx vessels. DOCA-salt treatment in the absence of endogenous vasopressin, ie, in homozygous \( dd/\) BB rats, failed to alter vascular structure, ET expression, or wall component stiffness and resulted in a lesser degree of blood pressure elevation. Thus, vasopressin is required for DOCA-salt treatment to exert its full blood pressure and vascular effects, and it acts in part by enhancing ET production.
Several pharmacological studies have implicated vasopressin in DOCA-salt–related blood pressure elevation, with the use of V₁- and V₂-vasopressin receptor antagonists. Likewise in this model, development of hypertension is prevented by lesions in the paraventricular nucleus, a region where DOCA and salt elicit increased vasopressin mRNA. Berecek et al have shown that in homozygous di/di BB rats DOCA-salt treatment had no effect on blood pressure. Here, we found that in the absence of endogenous vasopressin, DOCA-salt treatment did increase blood pressure slightly, by 23 mm Hg, but this pressor effect was attenuated, resulting in a rise in blood pressure of 55 mm Hg less than in LE-DOCA-salt rats. This attenuation was considerably more dramatic than in our previous report, wherein chronic V₁-vasopressin receptor antagonism decreased the rise in blood pressure by only 13 mm Hg. Whether vasopressin influences blood pressure by acting at V₁- or V₂-vasopressin receptors remains unclear. Burrell et al reported a similar blood pressure–lowering effect of a selective V₁-vasopressin receptor antagonist, in which oral administration of OPC-21268 decreased blood pressure in DOCA-salt rats by 27 mm Hg. Okada et al have also reported that both V₁- and V₂-vasopressin receptor subtypes are involved in the development of hypertension, whereas only V₁-receptors play a role in maintaining the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LE UNx</th>
<th>DOCA-Salt</th>
<th>BB UNx</th>
<th>DOCA-Salt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>362±3.4</td>
<td>377±6.7</td>
<td>338±14</td>
<td>241±9.4†</td>
</tr>
<tr>
<td>Tibia length, mm</td>
<td>41.0±0.2</td>
<td>41.5±0.2</td>
<td>40.9±0.2</td>
<td>40.4±0.2‡</td>
</tr>
<tr>
<td>Wet heart weight, g</td>
<td>1.06±0.025</td>
<td>1.47±0.076*</td>
<td>1.02±0.050‡</td>
<td>0.92±0.037‡</td>
</tr>
<tr>
<td>Wet heart weight/tibial length, g/mm</td>
<td>0.026±0.0007</td>
<td>0.035±0.0019*</td>
<td>0.025±0.0011‡</td>
<td>0.023±0.0009‡</td>
</tr>
<tr>
<td>Wet heart weight/100 g body weight</td>
<td>0.293±0.006</td>
<td>0.389±0.017*</td>
<td>0.302±0.006‡</td>
<td>0.383±0.016‡</td>
</tr>
<tr>
<td>Dry heart weight, g</td>
<td>0.252±0.005</td>
<td>0.329±0.022</td>
<td>0.236±0.007‡</td>
<td>0.226±0.009‡</td>
</tr>
<tr>
<td>Dry heart weight/tibial length, g/mm</td>
<td>0.006±0.0001</td>
<td>0.008±0.0005*</td>
<td>0.006±0.0002‡</td>
<td>0.006±0.0002‡</td>
</tr>
<tr>
<td>Dry heart weight, g/100 g body weight</td>
<td>0.070±0.002</td>
<td>0.087±0.005</td>
<td>0.070±0.002‡</td>
<td>0.095±0.006‡</td>
</tr>
<tr>
<td>Plasma immunoreactive-ET, fmol/mL</td>
<td>4.90±0.51</td>
<td>4.12±0.44</td>
<td>6.39±0.45‡</td>
<td>6.09±0.28‡</td>
</tr>
</tbody>
</table>

Values are mean±SE.
*P<0.05 vs uninephrectomized (UNx) LE.
†P<0.05 vs BB-UNx.
‡P<0.05 vs DOCA-salt–treated LE.

Figure 2. Lumen diameter, media width, medial cross-sectional area, and media-lumen ratios in relaxed mesenteric arteries from Long-Evans (LE) and Brattleboro (BB) rats, treated or not with deoxycorticosterone acetate (DOCA)-salt measured at a constant intraluminal pressure of 45 mm Hg. Results are presented as mean±SEM, n=6. *P<0.05 vs LE-UNx. †P<0.05 vs LE-DOCA-salt.
hypertensive state after it has been established. Our previous finding that V1-receptor antagonism decreased blood pressure only slightly in DOCA-salt hypertensive rats, compared with the dramatic decrease in vasopressin-deficient rats, suggests that indeed, both V1- and V2-receptor subtypes may determine hypertensive status in this model. The majority of the pressor response to DOCA-salt clearly requires the presence of vasopressin but probably precedes induction of ET and subsequent vascular abnormalities.

ET does contribute to development of high blood pressure and vascular growth in DOCA-salt rats. Reduction of blood pressure in DOCA-salt rats with ET antagonists is modest, between 14 and 20 mm Hg. Moreover, antagonizing V1-vasopressin receptors abolished vascular overexpression of ET and induced a 60% and 44% correction in media-lumen ratio and media thickening, respectively, while decreasing blood pressure only slightly (13 mm Hg). Thus, the vasopressin-ET system may play a role in establishing DOCA-salt hypertension, but it appears to be only 1 of several mechanisms involved. Moreover, this argument underlines the blood pressure–independent nature of vasopressin/ET effects on vascular structure.

These studies show that vasopressin is critical to modulation of vascular structure by DOCA-salt. Resistance-artery abnormalities characteristic of DOCA-salt hypertension were absent in BB rats. In DOCA-salt rats, there are 2 components of vascular remodeling: blood pressure dependent and blood pressure independent. It is arguable that the attenuated pressor response to DOCA-salt in vasopressin-deficient rats is the sole determinant of the lack of vascular growth. While vasopressin is probably involved in the blood pressure–dependent component of remodeling, we have shown that antagonism of V1-vasopressin receptors attenuated the DOCA-salt–induced changes in structure, without dramatically reducing blood pressure. We proposed that an additional influence of vasopressin on vascular structure may be pressure independent, and it may involve activation of the ET system, since blockade of V1-receptors abolished the elevated vascular preproET-1 mRNA characteristic of DOCA-salt hypertension. Thus, vasopressin is responsible for activating the ET system in DOCA-salt rats. Accordingly, we report here that without endogenous vasopressin, DOCA-salt failed to increase expression of the ET gene. This involvement of ET-1 is consistent with blood pressure–independent effects of vasopressin. A component of the alterations of vascular structure in DOCA-salt rats does not correlate with the extent of blood pressure elevation, and ET receptor antagonism regresses vascular growth, so that the remaining hypertrophy then correlates with systolic pressure. Thus, vasopressin plays a dichotomous role in vascular remodeling in DOCA-salt rats. By first mediating the development of high blood pressure, and second, by mediating vascular ET overexpression, vasopressin contributes to both the pressure-dependent and -independent components of remodeling.

We detected apparent luminal narrowing in LE rats treated with DOCA-salt. The remodeling index of 59% could be interpreted as eutrophic remodeling, with rearrangement of...
wall material around a reduced lumen and no evidence of net growth of media mass. However, changes in mechanics must be considered when defining remodeling. In this case, decreased lumen diameter is probably due to stiffening of wall components with DOCA-salt treatment. The stiffer vessel may expand less in response to pressure and thus simulate eutrophic remodeling.

A novel finding is that stiffening of wall components occurred in arteries from LE-DOCA-salt but not BB-DOCA-salt rats, suggesting that vasopressin affects the mechanics of resistance arteries as well as structure. In a previous study, wherein we induced DOCA-salt hypertension in Sprague-Dawley rats, vascular stiffening did not occur in these vessels, perhaps owing to different strains (LE versus Dawley rats, vascular stiffening did not occur in these wherein we induced DOCA-salt hypertension in Sprague-Dawley rats, suggesting that vasopressin affects the mechanics of salt rats, suggesting that vasopressin affects the mechanics of resistance arteries as well as structure. In a previous study, wherein we induced DOCA-salt hypertension in Sprague-Dawley rats, vascular stiffening did not occur in these vessels, perhaps owing to different strains (LE versus Sprague-Dawley) or to different treatment periods (5 versus 4 weeks, respectively). Importantly, isobaric stiffness, which is determined by vessel geometry and wall component stiffness, was normal in LE-DOCA-salt rats or lower in DOCA-salt–treated Sprague-Dawley rats, suggesting strict maintenance of pressure-buffering capacity of resistance arteries.

Cardiac hypertrophy also developed in DOCA-salt hypertension. Wet and dry weights of the heart normalized for body size (tibia length) were greater in LE-DOCA-salt rats versus LE-UNx rats. However, in BB-DOCA-salt rats, wet and dry cardiac weights were similar to those of BB-UNx rats. Thus, vasopressin may also be involved in the development of cardiac hypertrophy in this model of hypertension. These findings are consistent with our previous report that vasopressin receptor antagonism also attenuated cardiac hypertrophy in DOCA-salt hypertensive rats.

Plasma ET levels were greater in BB than in LE rats (the Table). In both strains, DOCA-salt treatment did not affect this parameter, as previously described. Plasma ET levels do not reliably indicate vascular ET production because circulating ET is due, in part, to spillover from abuminlual secretion of ET from the endothelium, although some may originate from the posterior pituitary. Patients with hypothalamic diabetes insipidus exhibit augmented circulating ET, suggesting that depressed plasma vasopressin may be compensated by enhanced ET secretion from the neurohypophysis. The latter may be blood pressure dependent and unaffected by vasopressin and may compensate for decreased vasopressin to maintain blood pressure in patients with hypothalamic diabetes insipidus and in vasopressin-deficient rats. In contrast, in DOCA-salt rats, exaggerated endothelial secretion of ET is absent without endogenous vasopressin.

DOCA-salt hypertension is associated with rapid development of high blood pressure, vascular growth, vascular stiffening, and cardiac hypertrophy. The failure of DOCA-salt treatment to generate these end-organ consequences as well as augmented ET gene expression in vasopressin-deficient BB rats supports the hypothesis first, that vasopressin plays a critical role in these processes, and second, that vascular-derived ET mediates vasopressin-related vascular effects and blood pressure elevation in DOCA-salt hypertension.

Acknowledgments

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References


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