NADPH Oxidase–Derived Superoxide Augments Endothelin-1–Induced Venoconstriction in Mineralocorticoid Hypertension

Lixin Li, Stephanie W. Watts, Amy K. Banes, James J. Galligan, Gregory D. Fink, Alex F. Chen

Abstract—Deoxycorticosterone acetate (DOCA)–salt hypertension is characterized by low renin/angiotensin but increased arterial superoxide levels. We have recently reported that the arterial endothelin-1 (ET-1) level is increased, resulting in NADPH oxidase activation and superoxide generation. However, the effect of ET-1 on venous superoxide production and its relation to vеноconstriction are unknown. The present study tested the hypotheses that ET-1 stimulates venous NADPH oxidase and superoxide via its ETₐ receptors, resulting in enhanced vеноconstriction in DOCA-salt hypertensive rats. Treatment with ET-1 (0.01 to 1 nmol/L), but not the selective ETₐ receptor agonist sarafotoxin s6c, of vena cava of normal rats concentration-dependently increased superoxide levels, an effect that was abolished by the selective ETₐ receptor antagonist ABT-627. Although the ET-1 level was not increased in the vena cava and plasma, both venous NADPH oxidase activity and superoxide levels were significantly higher in DOCA-salt compared with sham rats. Moreover, ET-1 treatment (10⁻⁸ mol/L, 10 minutes) of isolated vena cava further elevated superoxide levels in DOCA-salt rats only but not sham rats, an effect that was abrogated by the superoxide scavenger tempol. Similarly, ET-1–induced contractions of isolated vena cava of DOCA-salt but not sham rats were significantly inhibited by tempol. The NADPH oxidase inhibitor apocynin significantly reduced superoxide levels in vena cava of DOCA-salt rats and in ET-1–treated vena cava of normal rats. Finally, in vivo ETₐ receptor blockade by ABT-627 significantly lowered venous superoxide levels and blood pressure in DOCA-salt but not sham rats. These results suggest that superoxide contributes to ET-1–induced vеноconstriction through an elevated venous NADPH oxidase activity in mineralocorticoid hypertension. (Hypertension. 2003;42:●●●●●●●.)

Key Words: endothelin ▪ vеноconstriction ▪ oxidative stress ▪ hypertension, mineralocorticoid

Accumulating evidence indicates that increased arterial superoxide (O₂⁻) contributes to hypertension development in both animals and humans by inactivating nitric oxide (NO) and impairing arterial endothelium-dependent relaxation.⁴⁻³ An increase in venous O₂⁻ might also inactivate NO and alter venous functions (eg, impaired relaxation or augmented constriction). However, the role of venous O₂⁻ production in hypertension and its effect on vеноconstriction are unknown. Because hypertension involves multifactorial hemodynamic alterations, vеноconstriction augmented by O₂⁻ might contribute to increased blood pressure by enhancing cardiac output and shifting blood from the veins to arteries.⁴⁻⁶ Consistent with this notion, endothelin-1 (ET-1) stimulates venous constriction, resulting in significant changes in blood volume distribution, cardiac output, and blood pressure.⁵⁻⁶

The factors controlling vеноconstriction are complex and include both neural and humoral mechanisms. The increased sympathetic nerve activity results in augmented vеноconstriction, which predominates in the development of spontaneous hypertension.⁴ Various humoral factors, such as angiotensin II (Ang II) and ET-1, also induce vеноconstriction.⁷ Ang II causes impaired arterial NO-mediated relaxation by increasing O₂⁻ in Ang II–Induced hypertensive rats.⁸ We and others have recently reported that arterial O₂⁻ levels are also elevated in deoxycorticosterone acetate (DOCA)–salt hypertension,⁹⁻¹⁴ a model known for its suppressed plasma renin level.¹⁵ Studies from our laboratory and others have also shown that both ET-1 and NADPH oxidase activities are increased in arteries of DOCA-salt hypertension models,¹¹⁻¹³,¹⁶ resulting in NADPH oxidase activation and O₂⁻ formation by way of ETₐ receptors.¹³ In contrast, ETₐ receptors have been shown to mediate the protective effect against vascular and renal injuries in DOCA-salt hypertension.¹⁷ On the other hand, our most recent studies have demonstrated that venous O₂⁻ levels are also increased in DOCA-salt hypertension,¹⁸ and ET-1 and its receptors play important roles in maintaining venous tone in this model.¹⁹,²⁰ However, the effect of increased venous O₂⁻ on ET-1–induced vеноconstriction remains unknown. Based on the
aforementioned findings, the present study tested the hypotheses that ET-1 stimulates venous NADPH oxidase and O$_2^-$ via its ET$_A$ receptors, resulting in enhanced venoconstriction in DOCA-salt hypertensive rats. Our results demonstrate, for the first time, that (1) ET-1 increases O$_2^-$ levels through its ET$_A$ receptors in both ET-1–treated vena cavae of normal rats and vena cavae of DOCA-salt rats, (2) O$_2^-$ augmented ET-1–induced venoconstriction, and (3) enhanced venous NADPH oxidase activity plays a key role in increased venous O$_2^-$ levels in response to ET-1 in this model.

**Methods**

**DOCA-Salt Hypertensive Rats and In Vivo Pharmacologic Intervention**

DOCA-salt hypertension was created in adult, male Sprague-Dawley rats as previously described. DOCA-salt rats were placed subcutaneously between the shoulder blades. Sham rats were also uninephrectomized but received no implant. DOCA-salt rats received 1.0% NaCl and 0.2% KCl in water, and sham rats received tap water. All animals were fed standard rat chow and had ad libitum access to both food and drinking solution. Hypertension develops gradually in this model, with arterial pressure rising gradually but steadily over a 4-week period. During the third week, some DOCA-salt rats received ABT-627 (Abbott Laboratories), a selective ET$_A$ receptor antagonist, 2 mg/kg body weight per day in their drinking water, for 2 weeks. Blood pressure was measured by noninvasive, tail-cuff methods in conscious but restrained rats. The vessels used were collected between weeks 4 and 6 after DOCA implantation. All animal procedures were in accordance with the institutional guidelines of Michigan State University.

**Venous O$_2^-$ Measurements**

Venous O$_2^-$ was quantified by lucigenin chemiluminescence, as previously described. Isolated vena cava segments (4 mm long) were assayed for O$_2^-$ levels, which were expressed as nanomoles per minute per milligram tissue weight. In addition, in situ detection of O$_2^-$ was performed by confocal microscopy with use of the oxidative fluorescent dye dihydroethidium (DHE, Sigma), as described previously. DHE is freely permeable to cell membranes and fluoresces red when oxidized to ethidium bromide by O$_2^-$.

To determine the direct effects of ET-1 and ET receptors on O$_2^-$ production, vein segments of normal rats were incubated in Eagle’s minimum essential medium (Fisher) at 37°C with the ET$_A$ receptor agonist sarafotoxin S6c (S6c, 10$^{-9}$ mol/L, 4 hours; Sigma) or ET-1 (10$^{-11}$ to 10$^{-9}$ mol/L, 4 hours) and preincubated with or without the selective ET$_A$ antagonist ABT-627 (3×10$^{-9}$ mol/L, 1 hour). To determine the effects of ET-1, tempol, flavoprotein, NADPH oxidase, xanthine oxidase, and nitric oxide synthase (NOS) on O$_2^-$ production, vein segments of normal, DOCA-salt, or sham rats were incubated at 37°C with or without ET-1 (10$^{-9}$ mol/L, 10 minutes) or preincubated with the superoxide dismutase mimetic tempol (10$^{-3}$ mol/L, 30 minutes; Sigma), ABT-627 (3×10$^{-9}$ mol/L, 1 hour), diphenylene iodonium (DPI, 10$^{-4}$ mol/L, 30 minutes; Sigma), apocynin (10$^{-4}$ mol/L, 1 hour; Calbiochem), allopurinol (10$^{-4}$ mol/L, 1 hour; Sigma), or N$	ext{-}$l-arginine methyl ester (l-NAMe, 10$^{-4}$ mol/L, 1 hour; Sigma), respectively. All concentrations used were based on our preliminary experiments and published studies.

**ELISA Enzyme Immunoassay for ET-1**

The ET-1 levels of vena cava tissue and rat plasma were determined as described previously. In brief, blood from vena cavae of DOCA-salt and sham rats was collected with EDTA as an anticoagulant, and plasma was obtained by centrifuging at 1000g. The cleaned and weighed veins from sham or DOCA-salt rats were frozen in liquid N$_2$, homogenized for 1 minute in 1 mol/L acetic acid (1 mL/50 mg tissue) containing 1.5×10$^{-3}$ mol/L peptatin (Sigma), and immediately boiled for 10 minutes. After being chilled, the homogenate was centrifuged at 20 000g for 30 minutes at 4°C, and the supernatant was stored at −80°C until use. The supernatant and plasma were subjected to enzyme immunoassay for ET-1 with a commercial ELISA kit (R&D Systems). Tissue ET-1 levels were expressed as picograms per gram tissue weight, and plasma ET-1 levels were expressed in moles per liter.

**NADPH Oxidase Assay**

Vena cavae of sham and DOCA-salt rats were homogenized in lysis buffer (10$^{-1}$ mol/L, K$_2$HPO$_4$, 10$^{-3}$ mol/L phenylmethylsulfonyl fluoride, and 0.2% Triton X-100). The homogenates were centrifuged at 12 000g at 4°C for 30 minutes and then subjected to protein assay (Bio-Rad). NADPH oxidase activities were measured by lucigenin chemiluminescence assay (5×10$^{-6}$ mol/L lucigenin, Sigma) in the presence of its substrate NADPH (10$^{-4}$ mol/L, Sigma) as previously described. No enzymatic activity could be detected in the absence of NADPH. Reactions were initiated by addition of 10 to 20 µL tissue homogenates containing 25 to 50 µg extracted protein. The enzyme activity was expressed as nanomoles per minute per milligram protein.

**Venoconstriction Study**

Isolated vena cava ring segments (4 mm long) were placed in physiologic salt solution consisting of (in mmol/L) NaCl, 130; KCl, 4.7; KH$_2$PO$_4$, 1.18; MgSO$_4$, 7H$_2$O, 1.17; CaCl$_2$, 2H$_2$O, 1.6; NaHCO$_3$, 14.9; dextrose, 5.5; and Na$_2$EDTA, 0.03. Vessels were cleaned of fat and connective tissue, left with an intact endothelium, mounted on stainless steel hooks, and placed on stainless steel holders in tissue baths (30 mL) for isometric-tension recordings with Grass polygraphs and transducers (Astro-Med) or PowerLab for the Macintosh (ADInstruments). Vessels were placed under 1 g optimal resting tension. Vessels from sham and DOCA-salt rats were placed in the same bath, thus controlling for experimental variations. Tissue baths were filled with warmed, aerated (95% O$_2$, 5% CO$_2$) physiologic salt solution. Vessels were challenged with a maximal contraction to norepinephrine (10$^{-5}$ mol/L). Functional integrity of the endothelial cells was evaluated by testing relaxation to acetylcholine (10$^{-5}$ mol/L) in strips contracted with the adrenergic agonist norepinephrine (10$^{-5}$ to 10$^{-6}$ mol/L). Cumulative concentration-response curves to agonists were generated. ET-1 contracts tissues slowly, so tissues were exposed to each concentration of ET-1 for a minimum of 5 minutes before a higher concentration of the agonist was added. In some experiments, the selective ET$_A$ receptor antagonist ABT-627 (3×10$^{-9}$ mol/L), the superoxide dismutase mimetic tempol (10$^{-5}$ mol/L), or vehicle was incubated with the vessels for 1 hour before addition of ET-1. Venoconstrictions are represented by percentages of maximal contraction to norepinephrine at 10$^{-5}$ mol/L.

**Data Analysis**

Data are expressed as mean±SEM. Repeated-measures ANOVA was used for comparison of multiple values obtained from the same subject, whereas factorial ANOVA was used for comparing data obtained from 2 independent samples of subjects. The Bonferroni procedure was used to control type I error. A value of P<0.05 was considered significant.

**Results**

**Effect of ET-1 on O$_2^-$ Levels and Venoconstriction in Vena Cavae of Normal Rats**

After 4 hours of incubation, ET-1 concentration-dependently increased O$_2^-$ levels and venoconstriction in vena cavae of normal rats. Pretreatment with ABT-627 (3×10$^{-9}$ mol/L), a selective ET$_A$ receptor antagonist, completely reversed the
Figure 1. A, Effect of ET-1/ET receptors on O$_2^-$ levels in vena cavas of normal rats. Vessel segments were incubated at 37°C for 4 h with or without ET-1 at increasing concentrations. Some vessels were incubated with ABT-627 (3 × 10$^{-8}$ mol/L) for 1 h before ET-1 (10$^{-9}$ mol/L) treatment or with S6c (10$^{-8}$ mol/L) for 4 h. Vessels were subjected to O$_2^-$ measurement by lucigenin-enhanced chemiluminescence assay. n = 5 or 6 rats, *P < 0.01 vs control, #P < 0.01 vs 10$^{-9}$ mol/L ET-1–treated group. B, Effect of ET-1 on venoconstriction in vena cavas of normal rats. Vessels were incubated with ABT-627 (3 × 10$^{-8}$ mol/L) or vehicle solution (control) for 1 h, and venoconstriction was then determined by isometric-tension recordings. ET-1–induced contraction responses were expressed as percent contraction induced by norepinephrine (NE; 10$^{-5}$ mol/L) or vehicle solution (control) for 1 h. Percent contraction vs log ET-1 (mol/L) for NE: 10$^{-5}$ mol/L. n = 8 rats, *P < 0.05 vs control by repeated-measures ANOVA.

Effect of ET-1 on O$_2^-$ production. However, the selective ET$_A$ receptor agonist S6c had no effect on O$_2^-$ production (Figure 1A). ET-1 also induced venoconstriction that was concentration dependent, which was significantly inhibited by ABT-627, as shown by the rightward shift of the dose-response curve (Figure 1B).

In Vivo Blockade of ET$_A$ Receptors on Blood Pressure and Increased Venous O$_2^-$ Levels in DOCA-Salt Rats

There was a significant increase in average systolic blood pressure (170 ± 3 vs 115 ± 2 mm Hg; n = 24, *P < 0.01) and venous O$_2^-$ levels (Figure 2) in DOCA-salt rats compared with sham-operated controls. In vivo blockade of ET$_A$ receptors for 2 weeks with ABT-627 (in drinking water) significantly lowered blood pressure in DOCA-salt rats (175 ± 3 vs 149 ± 6 mm Hg; n = 5, P < 0.05), with a concomitant decrease in venous O$_2^-$ levels in the same group of DOCA-salt rats (Figure 2).

Venous ET-1, NADPH Oxidase, and O$_2^-$ Levels in DOCA-Salt Rats

There was no significant difference in ET-1 levels in vena cavas between sham and DOCA-salt rats (0.88 ± 0.28 vs 0.80 ± 0.18 pg/g tissue). Similarly, the plasma ET-1 levels were not significantly different between sham and DOCA-salt rats (5.02 ± 0.26 vs 5.74 ± 1.18 × 10$^{-13}$ mol/L, n = 5–8, P > 0.05).

Although venous ET-1 levels were not different between sham and DOCA-salt rats, the endogenous NADPH oxidase activity of vena cavas was significantly increased in DOCA-salt rats compared with that of sham rats, which was reduced by the NADPH oxidase inhibitor apocynin (10$^{-4}$ mol/L; Figure 3A). As a result, short-term treatment of vena cavas with ET-1 (10$^{-9}$ mol/L, 10 minutes) further increased O$_2^-$ levels in DOCA-salt rats but not in sham rats in vitro, an effect that was abolished by both ABT-627 and the superoxide dismutase mimetic tempol (Figure 3B).

Role of O$_2^-$ on ET-1–Induced Venoconstriction in DOCA-Salt Rats

Consistent with the aforementioned biochemical data, tempol (10$^{-3}$ mol/L) significantly reduced ET-1–induced venoconstriction in vena cavas of DOCA-salt rats (Figure 4A). In contrast, such an inhibitory effect was not observed in sham rats (Figure 4B). There was no difference in the logarithm of the median effective concentration (logEC$_{50}$; 8.25 ± 0.03 vs 8.29 ± 0.06, P > 0.05) or maximum response (553.2 ± 68.5 vs 482.4 ± 58.5, P > 0.05) induced by ET-1 between sham and DOCA-salt rats in either the absence or presence of tempol (−8.19 ± 0.01 vs −8.30 ± 0.00 in logEC$_{50}$; 503.1 ± 57.7 vs 367.3 ± 21.2 in maximum response).

Effect of NADPH Oxidase, NOS, and Xanthine Oxidase on Venous O$_2^-$ Levels

Both DPI (10$^{-4}$ mol/L), a flavoprotein inhibitor, and apocynin (10$^{-4}$ mol/L), an NADPH oxidase inhibitor, abolished increases in O$_2^-$ levels in ET-1–treated (10$^{-9}$ mol/L) vena cavas of normal rats (Figure 5A) and the vena cavas of DOCA-salt rats (Figure 5B).

In contrast, the xanthine oxidase inhibitor allopurinol (10$^{-6}$ mol/L) and the NOS inhibitor l-NAME (10$^{-4}$ mol/L) had no
such effects on vena cavae of either ET-1–treated normal rats (data not shown) or of DOCA-salt rats (Figure 5B).

In Situ Detection of Venous $O_2^-$

Compared with untreated vessels of normal rats (Figure 6A), incubation with the $O_2^-$-sensitive dye DHE resulted in a marked increase in ethidium bromide fluorescence (ie, red color) throughout the vessel wall of ET-1–treated vena cava of normal rats (Figure 6B) or vena cavae of DOCA-salt rats (Figure 6C). The $O_2^-$ fluorescence intensity was markedly reduced by DPI in vena cavae of DOCA-salt rats (Figure 6D) compared with the untreated vena cava (Figure 6C).

Discussion

The results of the present study demonstrate, for the first time, that (1) ET-1 increases venous $O_2^-$ levels via its ET$_A$ receptor, resulting in augmented ET-1–induced vеноconstriction in vena cavae of DOCA-salt but not sham rats and (2) enhanced venous NADPH oxidase activity is a major source of venous $O_2^-$ production in this model.

It has been reported that increased arterial $O_2^-$ contributes to vеноconstriction by inactivating NO in both animals and humans with cardiovascular diseases, including hypertension.1–3,21–23 Arterial $O_2^-$ levels are markedly increased in DOCA-salt hypertension, a model with low plasma renin but high arterial ET-1 levels.9–14 However, it was not clear whether ET-1 also elevates venous $O_2^-$ levels in this model. Furthermore, the effect of $O_2^-$ on vеноconstriction in DOCA-salt hypertension has not been reported. In the present study, our findings showed that (1) ET-1 concentration-dependently stimulated $O_2^-$ production in vitro in vena cavae of normal rats; (2) NADPH oxidase and $O_2^-$ levels were elevated in vena cavae of DOCA-salt rats compared with the sham rats; and (3) tempol, a superoxide dismutase mimetic, significantly inhibited ET-1–induced vеноconstriction in DOCA-salt but not in sham rats. Together, these data suggest that ET-1 increases venous $O_2^-$, which promotes ET-1–induced vеноconstriction in DOCA-salt hypertension.

The increased venous $O_2^-$ levels in DOCA-salt rats might augment ET-1–induced vеноconstriction by removing the venodilator effects of NO, because tempol shifted the ET-1–induced vеноconstriction curve rightward. In addition, $O_2^-$ might act as a direct vеноconstrictor, consistent with previous demonstrations of its vasoconstrictor properties.21,22 In contrast, baseline $O_2^-$ levels in sham rats were apparently too low to be scavenged by tempol, which did not shift the ET-1–induced vеноconstriction curve rightward in vessels from sham rats. The rationale of using ET-1 at a concentration of $10^{-9}$ mol/L to stimulate $O_2^-$ was based on our experimental observations that venous $O_2^-$ levels produced by $10^{-9}$ mol/L ET-1 in normal rats have already exceeded those found in DOCA-salt rats. The time period required for exogenous ET-1 treatment to induce venoconstriction was between 5 and 10 minutes in the organ chamber, as we determined in the
significant effect on venous O$_2$ levels. Hence, it might not be possible for exogenous ET-1 treatment to produce enough extra O$_2^-$ in vena cavas of sham rats in such a short period. Indeed, we found that in vena cavas of DOCA-salt but not of sham rats, exogenous ET-1 treatment for 10 minutes produced extra O$_2^-$, which was suppressed by both ABT-627 and tempol. The latter result is correlated with our finding in the present study that NADPH oxidase activity was significantly higher in vena cavas of DOCA-salt rats compared with those of sham rats. It might further explain why tempol did not significantly affect the ET-1–induced vasoconstriction in vena cavas of sham rats and why O$_2^-$ potentiated the ET-1–induced vasoconstriction in DOCA-salt rats. In contrast to the finding from our previous study, which was that arterial ET-1 levels are significantly increased in DOCA-salt rats, venous and plasma ET-1 levels were not different between DOCA-salt and sham rats. Although there was no apparent increase in venous ET-1 content, our findings of significantly elevated venous NADPH oxidase activity in DOCA-salt rats might account for the increased O$_2^-$ levels observed in vena cavas in response to the same amount of circulatory ET-1 stimulation.

In agreement with this possibility, our data showed that short-term ET-1 treatment for 10 minutes further increased O$_2^-$ levels in vena cavas of DOCA-salt rats only but not of sham rats.

Because ET-1–induced alterations in venous tone have been shown to result in significant changes in blood volume distribution, cardiac output, and blood pressure, examination of the effect of O$_2^-$ on ET-1/ET-1 receptor–mediated vasoconstriction might provide a basic understanding of its potential contribution to blood pressure regulation in DOCA-salt hypertension. Our data showed that O$_2^-$ formation is independent of ET$_A$ receptor activation, and ET$_B$ receptors mediate both O$_2^-$ formation and vasoconstriction induced by ET-1 in the vena cava. In vivo administration of the selective ET$_A$ antagonist ABT-627 significantly decreased blood pressure in DOCA-salt rats, with a concomitant reduction in venous O$_2^-$ levels. These findings are in agreement with published data that ET-1 produces O$_2^-$ via its ET$_A$ receptors in rebound pulmonary hypertension and that the O$_2^-$ scavenger tempol reduces blood pressure in Ang II–induced hypertensive rats. More important, those studies also concur with our recent investigations demonstrating the presence of an intact and sustained ET-1–induced vasoconstriction mediated by ET$_A$ (but not ET$_B$) receptors in DOCA-salt hypertension. The latter findings argue for a shift in the balance of ET-1–induced contractions that predominate in veins versus arteries in this model, which might contribute to a rise in blood pressure by increasing cardiac output and shifting blood to the arteries. Consistent with this notion, studies in both animal and human hypertension have demonstrated that a decrease in venous capacitance due to vasoconstriction occurs preferentially in systemic veins and favors an increase in cardiac output and blood pressure. Accordingly, an increase in vasoconstriction might significantly affect cardiac output and blood pressure. Therefore, increased O$_2^-$ might contribute to the alteration in blood pressure by exaggerating the ET-1–induced vasoconstriction in DOCA-salt hypertension.

There are 3 main enzymatic sources of O$_2^-$ formation in the blood vessel wall, including NADPH oxidase, xanthine oxidase, and "..."
dase, and uncoupled NOS. In DOCA-salt hypertensive rats, aortic NADPH oxidase activity is significantly increased compared with that of normotensive controls. In the present study, we examined whether ET-1 stimulates venous O$_2^-$ production through NADPH oxidase, xanthine oxidase, or NOS. An important finding of our study is the demonstration that NADPH oxidase activity was significantly higher in vena cava of DOCA-salt rats compared with those of sham rats. Our results also showed that DPI (a flavoprotein inhibitor) and apocynin, but not l-NAME or allopurinol, inhibited the increased O$_2^-$ levels in both ET-1-stimulated vena cava of normal rats and vena cava of DOCA-salt rats, suggesting that NADPH oxidase, but not xanthine oxidase or NOS, plays a major role in the ET-1-induced venous O$_2^-$ production in DOCA-salt hypertensive rats. The selectivity of apocynin, a methoxy-substituted catechol, on NADPH oxidase has been demonstrated for the first time, that ET-1 elevates venous O$_2^-$ levels via its ET$_A$ receptors and enhanced venous NADPH oxidase, resulting in augmented ET-1–induced venoconstriction in DOCA-salt hypertensive rats. These findings might provide a novel mechanistic insight on O$_2^-$–induced venous dysfunction in hypertension.

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References


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