Nitroprusside-Induced Vascular Relaxation in DOCA Hypertensive Rats

DAVID M. COHEN, PH.D., R. CLINTON WEBB, PH.D., AND DAVID F. BOHR, M.D.

SUMMARY Vascular responsiveness to nitroprusside and to norepinephrine was examined in two different preparations from DOCA hypertensive and normotensive control Sprague-Dawley rats. The blood-perfused renal vasculatures of DOCA hypertensive rats were significantly more sensitive than those of normotensive controls to the vasodilator action of low doses of nitroprusside. At high doses, responses in DOCA hypertensive and normotensive rats were similar. Since basal "structural" vascular resistances were greater in the hypertensive rats, it is possible that further vasodilation with nitroprusside was impeded more in DOCA-treated than in control rats. Nitroprusside produced a greater degree of vascular smooth muscle relaxation in tail artery strips from DOCA hypertensive rats than in those from normotensive controls. The current study is the first characterization of the effects of a vasodilator in mineralocorticoid hypertension.

The two preparations gave divergent results with respect to vascular sensitivity to norepinephrine. When compared with control rats, the DOCA hypertensive rats showed a greater sensitivity to norepinephrine in tail arteries but a lesser renal vascular reactivity.

It is evident that one must take a number of variables into consideration when characterizing changes in vascular responses that occur in a given model of hypertension: 1) the region of the vasculature (renal vs caudal artery); 2) the level of the arterial tree (conduit vs resistance vessels); 3) the technique employed for measurement of vascular changes (smooth muscle contraction vs vascular resistance changes); 4) the initial vasoconstrictor tone of the preparation; and 5) the agonist used (nitroprusside vs norepinephrine).

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KEY WORDS • vasodilation • vascular reactivity • norepinephrine • renal vasculature • tail artery

Vasodilator responses in hypertensive man and animal models have received relatively little attention in the literature. Investigators, utilizing a variety of techniques, find that vascular smooth muscle relaxation or vasodilation is impaired, unchanged, or enhanced during hypertension (table I).1-11

We have studied the effects of the vasodilator, sodium nitroprusside (the most potent inorganic nitrite known), in the renal vascular beds of DOCA hypertensive rats in order to determine if the high renal vascular resistance seen in this type of hypertension might be due to an impaired ability of the renal vasculature to relax. Fink and Brody9 reported no difference in renal vascular sensitivity to acetylcholine between spontaneously hypertensive rats and their normotensive controls, whereas Hollenberg and Adams12 found renal vascular beds of human essential hypertensive patients to be more responsive to acetylcholine than normotensive patients. This study, therefore, was intended to add evidence bearing on the controversial reports assessing the nature of changes in vasodilation that occur in hypertension. To determine if the effects of nitroprusside are specific to the kidney, an entirely different vascular preparation (isolated strips from tail arteries) was also used.

Methods

Animal Preparation

All studies were performed on male Sprague-Dawley rats (325-375 g). Half of the animals received subcutaneous implantations of DOCA (Sigma Chemical Company, 200 mg/kg) impregnated in
<table>
<thead>
<tr>
<th>Reference</th>
<th>Preparation</th>
<th>Agonist</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shibata and Cheng¹</td>
<td>thoracic aortic strips (SHR)</td>
<td>isoproterenol, acetylcholine, Mg⁴⁺, Mn⁴⁺</td>
<td>decreased % relaxation</td>
</tr>
<tr>
<td></td>
<td>thornacic aortic strips (renal hypertensive rate)</td>
<td>isoproterenol</td>
<td>decreased % relaxation</td>
</tr>
<tr>
<td>Cohen and Berkowitz²</td>
<td>thoracic aortic strips (SHR and renal hypertensive rats)</td>
<td>cAMP, cGMP, isoproterenol, nitroglycerin, adenosine</td>
<td>decreased % relaxation</td>
</tr>
<tr>
<td>Antonaccio, et al.³</td>
<td>aortic strip (SHR)</td>
<td>nitroglycerin</td>
<td>decreased % relaxation</td>
</tr>
<tr>
<td>Triner, et al.⁴</td>
<td>thoracic aortic strips (SHR)</td>
<td>isoproterenol</td>
<td>decreased % relaxation</td>
</tr>
<tr>
<td>Hutchins, et al.⁵</td>
<td>cremaster microvessels (SHR)</td>
<td>isoproterenol</td>
<td>decreased max. % diameter increase</td>
</tr>
<tr>
<td>Bell, et al.⁶</td>
<td>blood-perfused hindlimb (aortic coarctation rats)</td>
<td>nitroprusside</td>
<td>impaired maximal vasodilation</td>
</tr>
<tr>
<td>Godfraind and Dieu⁷</td>
<td>thoracic aortic ring (SHR)</td>
<td>isoproterenol</td>
<td>decreased relaxation</td>
</tr>
<tr>
<td>Shibata and Cheng¹</td>
<td>thoracic aortic strip (SHR)</td>
<td>nitroglycerin, papaverine</td>
<td>no difference in % relaxation</td>
</tr>
<tr>
<td></td>
<td>abdominal aortic strip (SHR)</td>
<td>isoproterenol, acetylcholine, Mg⁴⁺, Mn⁴⁺, nitroglycerin, papaverine</td>
<td>no difference in % relaxation</td>
</tr>
<tr>
<td></td>
<td>abdominal aortic strip (renal hypertensive rate)</td>
<td>isoproterenol</td>
<td>no difference in % relaxation</td>
</tr>
<tr>
<td>Deragon, et al.⁸</td>
<td>Krebs-perfused hindlimb (SHR)</td>
<td>nitroprusside</td>
<td>no difference in sensitivity</td>
</tr>
<tr>
<td>Fink and Brody⁹</td>
<td>blood perfused renal vasculature (Dahl-S rats)</td>
<td>acetylcholine</td>
<td>no difference in max. vasodilation</td>
</tr>
<tr>
<td>Castro-Tavares¹⁰</td>
<td>saphenous vein strip (perinephretic hypertensive dog)</td>
<td>nitroprusside, isoproterenol</td>
<td>no difference in sensitivity or % relaxation</td>
</tr>
<tr>
<td></td>
<td>mesenteric artery (perinephretic hypertensive dog)</td>
<td>nitroprusside, isoproterenol</td>
<td>incr. sensitivity or incr. % relaxation</td>
</tr>
<tr>
<td>Folkow, et al.¹¹</td>
<td>forearm resistance vessels (human essential hypertension)</td>
<td>vasodilator metabolites</td>
<td>no difference in ability to relax</td>
</tr>
<tr>
<td>Specter, et al.¹¹</td>
<td>thoracic aortic strip (SHR)</td>
<td>isoproterenol</td>
<td>increased % relaxation</td>
</tr>
<tr>
<td>Deragon, et al.⁸</td>
<td>Krebs-perfused hindlimb (SHR)</td>
<td>isoproterenol</td>
<td>increased sensitivity</td>
</tr>
<tr>
<td>Hutchins, et al.⁵</td>
<td>cremaster microvessels (SHR)</td>
<td>isoproterenol</td>
<td>decreased threshold dose</td>
</tr>
<tr>
<td>Hollenberg, et al.¹⁵</td>
<td>intact renal vascular bed (human essential hypertension)</td>
<td>acetylcholine</td>
<td>increased sensitivity</td>
</tr>
<tr>
<td>Cohen, et al.</td>
<td>blood-perfused renal vasculature (DOCA hypertensive rat)</td>
<td>nitroprusside</td>
<td>increased sensitivity</td>
</tr>
<tr>
<td>Cohen, et al.</td>
<td>tail artery strip (DOCA hypertensive rat)</td>
<td>nitroprusside</td>
<td>increased % relaxation</td>
</tr>
</tbody>
</table>
VASCULAR RELAXATION IN DOCA HYPERTENSION / Cohen et al.

Silastic (Dow Corning Corporation) strips, one part DOCA to two parts Silastic by weight.\(^\text{1, 14}^\) Control rats received implantations of Silastic strips without DOCA. The implantations were made in the left flank while the rats were under ether anesthesia. All rats were maintained on standard laboratory chow (Purina) and received 1% NaCl and 0.2% KCl in their drinking water.\(^\text{15}^\) Systolic blood pressures were determined by means of indirect tail cuff measurements before and at weekly intervals following implantation. Experiments were performed on rats 4–6 weeks after implantation.

In Situ Renal Vascular Perfusion

Studies were performed on six normotensive control and nine DOCA hypertensive rats anesthetized with sodium pentobarbital (50 mg/kg; i.p.). Supplemental anesthesia was administered through a catheterized jugular vein.

The procedure used to study the effects of vasoactive agents on renal vascular resistance was modified from Fink and Brody.\(^\text{16}^\) The left renal pedicle was exposed through a midline abdominal incision. This kidney was prepared for perfusion by placing a loose ligature around the aorta just above the left renal artery and a bulldog clamp on the aorta just below the artery. Renal nerves were left intact. Blood from the left carotid artery was diverted through a short (30 cm, 0.8 ml) extracorporeal circuit which passed through a pre-calibrated constant flow peristaltic pump (Harvard apparatus, Model 1202). The tip of the catheter from the outflow side of the pump was positioned in the aorta just distal to the bulldog clamp and tied in place. The clamp was removed, perfusion begun, and the ligature above the renal artery was tied off. In this manner, the left kidney received a continuous blood supply during the switch to the perfusion system.\(^\text{17}^\) Renal perfusion pressure was monitored through a T-tube placed between the pump and kidney. Flow through the pump, and hence the renal vasculature, was gradually increased until renal perfusion pressure was within 5% of systemic arterial pressure (monitored by means of contralateral carotid catheterization). The preparation was stable throughout the experimental period (2–3 hours).

Intraarterial (i.a.) injections of norepinephrine (Levophed bitartrate, Winthrop Laboratories) and nitroprusside (Nipride, Roche) were made through a short segment of rubber tubing placed just proximal to the inflow side of the pump to permit thorough mixing with blood.\(^\text{18}^\) The drugs were injected rapidly (1–2 sec) in 0.1 ml saline and 5–10 minutes elapsed between injections. The schedule of injections was randomized with respect to agonist and dose. The response to drug injection was recorded as the maximal change in perfusion pressure (expressed as absolute change or as a percentage of control perfusion pressure) which occurred prior to any change in systemic arterial blood pressure.\(^\text{18}^\) Control injections of saline (0.1 ml) were given in each study to insure that the responses to drug injection were not mechanical artifacts.

In Vitro Tail Artery Strips

Helical strips (0.8 X 10 mm) were cut from tail arteries (0.7–0.8 mm, O.D.) isolated from 10 DOCA-treated and 10 control rats. The strips were mounted vertically on a glass holder in a tissue bath containing 50 ml of physiological salt solution (PSS). The upper end of each strip was connected to a force transducer (Grass FT.03) and the resting tension of each strip was adjusted so that it produced maximum active tension in response to a standard dose of norepinephrine (10\(^{-7}\) g/ml). Before the start of experiments, the strips were allowed to equilibrate for 90 min in PSS. The bathing medium was maintained at 37° C and aerated with a mixture of 95% O\(_2\) and 5% CO\(_2\). The pH of the PSS was 7.4 and the composition (mmole/liter) was as follows: 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; CaNa\(_2\) EDTA, 0.03.

Vascular responsiveness to norepinephrine or nitroprusside was examined. The drugs were added to the muscle bath in a cumulative manner. When the effects of nitroprusside were examined, the strips were first contracted with 10\(^{-7}\) g/ml norepinephrine. Changes in tension in response to norepinephrine were normalized to their maximal responses; in the case of nitroprusside, changes in tension were expressed as a percent of the contractile response to 10\(^{-7}\) g/ml norepinephrine.

Statistical Analysis

The results of these experiments were analysed by a variety of statistical procedures. Dose response curves were calculated as geometrical means. Paired and unpaired r tests and curve fitting analyses (logit transformation) were performed. A p value less than 0.05 was considered to be statistically significant.

Results

In Situ Renal Vascular Perfusion

Mean arterial blood pressures of the DOCA hypertensive rats were significantly higher than those of the normotensive control rats; renal blood flows in the hypertensive and normotensive rats were not significantly different. Since initial renal perfusion pressures matched arterial blood pressures in all rats, initial vascular resistances in the kidneys from DOCA-treated rats were significantly higher than those from control rats. When relaxed with supermaximal doses of papaverine, the renal vascular beds of hypertensive rats, likewise, had higher “structural” resistances than those of the control rats (see table 2).

Nitroprusside produced dose-dependent decreases in renal perfusion pressure and, hence, renal vascular resistance in both hypertensive and control rats (fig. 1). The responses were rapid in onset (10–20 sec), reached maximal levels within 60 seconds, and returned to preinjection levels in 2–4 minutes. When high doses of nitroprusside also caused a fall in systemic arterial pressure, this fall occurred after the
maximum fall in renal perfusion pressure. At low and medium doses of nitroprusside, the vasculatures from DOCA hypertensive rats were clearly more responsive to the agonist than were vasculatures from control rats ($p < 0.001$). However, at high doses, the two vascular beds were equally responsive to nitroprusside.

Dose/response curves to norepinephrine were also constructed (fig. 2). At low doses, no significant differences existed between responses elicited in normotensive and hypertensive rats. However, at high doses, DOCA-treated rats responded less than did control animals. This difference was significant when the data were expressed either as percent of initial perfusion pressure ($p < 0.005$) or as an absolute increase in perfusion pressure ($p < 0.05$).

### In Vitro Tail Artery Strips

Helical strips of tail arteries from DOCA-treated and control rats were made to contract in response to cumulative additions of norepinephrine to the muscle chamber. Arterial strips from hypertensive rats were more sensitive to the catecholamine than were those from control rats (fig. 3). The concentration of norepinephrine necessary to produce a threshold response ($EC_{50}$) in DOCA-treated rats ($2.7 \times 10^{-10}$) was significantly less than that of the control rats ($1.2 \times 10^{-9}$). Similarly, the $EC_{50}$ of DOCA-treated rats ($4.7 \times 10^{-6}$) was less than that of control rats ($1.4 \times 10^{-5}$). The maximal contractile responses to norepinephrine of tail artery strips from hypertensive were less ($1631 \pm 102$ mg) than those of control rats ($1947 \pm 90$ mg).

Cumulative additions of nitroprusside produced relaxation in tail arteries which were made to contract with $10^{-7} \text{ g/ml}$ norepinephrine (fig. 4). Initial tension levels of norepinephrine contracted vessels were $1164 \pm 78$ mg (hypertensive rats) and $1469 \pm 84$ mg (control rats). When expressed as percent change from their initial contractile tension, arterial strips from

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**Table 2. Hemodynamic Variables in DOCA and Control Rats**

<table>
<thead>
<tr>
<th>Rat group</th>
<th>Renal perfusion pressure (mm Hg)</th>
<th>Renal blood flow (ml/g/min)</th>
<th>Renal vascular resistance (initial)</th>
<th>Renal perfusion pressure (papaverine)</th>
<th>Renal vascular resistance (basal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 6)</td>
<td>106 ± 4</td>
<td>5.94 ± 0.32</td>
<td>18.15 ± 0.94</td>
<td>29.0 ± 1.6</td>
<td>4.92 ± 0.31</td>
</tr>
<tr>
<td>DOCA (n = 9)</td>
<td>161 ± 4</td>
<td>6.24 ± 0.30</td>
<td>26.58 ± 1.73</td>
<td>38.1 ± 1.6</td>
<td>6.26 ± 0.48</td>
</tr>
</tbody>
</table>

* $p < 0.001$        
* NS

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**Figures**

**Figure 1. Renal vascular response to nitroprusside.** Renal vascular beds from DOCA hypertensive and normotensive rats received graded doses of nitroprusside. Nitroprusside produced decreases in renal perfusion pressure (renal vascular resistance) which were greater ($p < 0.001$) in the hypertensive vasculatures than in normotensive rats at the first three doses tested. Values are the means ± standard error of the mean. The values in parentheses are the number of rats.

**Figure 2. Renal vascular response to norepinephrine.** Renal vascular beds from DOCA hypertensive and normotensive rats were stimulated with graded doses of norepinephrine. Norepinephrine produced increases in renal perfusion pressure (renal vascular resistance) which were greater ($p < 0.005$) in the vascular beds from normotensive rats than in hypertensive vasculatures at the last two doses tested. Values are the means ± standard error of the mean. The values in parentheses are the number of rats.
hypertensive rats relaxed to a greater degree than did those from control rats. Furthermore, the concentration required to produce a 10% change in tension in hypertensive rats ($6.4 \times 10^{-4}$) was significantly less ($p < 0.01$) than that of control rats ($2.1 \times 10^{-4}$).

Discussion

The results of this study show that, in two different preparations from DOCA hypertensive rats, nitroprusside was more effective in producing vascular smooth muscle relaxation than in those from normotensive controls. In the renal vascular beds from hypertensive rats there was a greater responsiveness to this agonist at low and medium doses; at higher doses, renal vascular dilation was similar in the two groups of rats (fig. 1). Similar results were obtained by Hollenberg and Adams who measured renal blood flow responses to i.a. injections of acetylcholine in patients with essential hypertension. It is possible that the smooth muscle relaxant action of high doses of nitroprusside was masked by the inability of the vasculature to dilate further because of structural changes. In our studies with maximal doses of papaverine it was evident that basal structural resistance of the renal vasculature was greater in the DOCA hypertensive than in the control rats. A similar elevated basal resistance has been previously reported in kidneys of DOCA-treated rats perfused with Krebs solution. In the second vascular smooth muscle preparation, isolated tail artery strips, in which the structural factor of wall thickness does not play a role in the normalized response, there was also a greater percentage of relaxation of the muscle from hypertensive rats than of that from controls. However, in this instance the responses do not converge at higher concentrations of nitroprusside (fig. 4). Although these results suggest that altered structural resistance in the hypertensive animals may play a role in impeding renal vasodilation at high doses of nitroprusside, it is also possible that intrinsic vasoconstrictor activity may be involved. For example, enhanced release or impaired degradation of catecholamines might compete with the vasodilator action of nitroprusside to a greater extent in the renal vasculatures from hypertensive rats.

The two preparations gave divergent results with respect to vascular sensitivity to norepinephrine. There was a greater sensitivity to this constrictor agonist in tail arteries from hypertensive rats than in those from normotensive controls. However, the renal vascular beds of hypertensive rats were no more sensitive to norepinephrine than those of normotensive controls. Indeed, at higher doses, renal vasculatures from hypertensive rats were less responsive to norepinephrine. It is possible that this depressed contractile response may be due to a greater degree of active

![Figure 3](image-url)  
**Figure 3.** Tail artery response to norepinephrine. Helical strips of tail artery from DOCA hypertensive and normotensive rats were made to contract in response to the cumulative addition of norepinephrine to the muscle bath. Arterial strips from DOCA hypertensive rats were more sensitive to the catecholamine than those from normotensive rats. Values are the means ± standard error of the mean. The values in parentheses are the number of rats. The maximal contractile response to norepinephrine was less in tail artery strips from DOCA hypertensive rats than in those from normotensive rats ($p < 0.05$).

![Figure 4](image-url)  
**Figure 4.** Tail artery response to nitroprusside. Tail artery strips from DOCA hypertensive and normotensive rats were made to contract by addition of $10^{-5}$ g/ml norepinephrine to the muscle bath. After the contractile response had reached a plateau, relaxation was induced by cumulative addition of nitroprusside. Arterial strips from DOCA hypertensive rats relaxed to a greater percent of their contractile response to norepinephrine as compared with those from normotensive rats. Values are the means ± standard error of the mean. The values in parentheses are the number of rats.
vasoconstrictor tone in the vasculatures from hypertensive rats.

It has been suggested that impaired vascular relaxation may be responsible for the development of hypertension. Aortic strips from renal and spontaneously hypertensive rats do not relax to a variety of vasodilators as well as do control vessels. These findings have been supported by data from other investigators utilizing a variety of preparations. However, several studies have shown no differences in the ability of hypertensive vasculatures to relax as compared with their controls. Indeed, some hypertensive preparations are more sensitive to isoproterenol, nitroprusside and acetylcholine than are their normotensive controls.

Hinke has shown that perfused tail arteries from DOCA hypertensive rats, made to contract with either high K⁺ or norepinephrine, relaxed more slowly in response to the removal of Ca²⁺ from the perfusate than those from control rats. However, the present study is the first characterization of the effects of a vasodilator in mineralocorticoid hypertension. In these studies, conducted after 4 to 6 weeks of treatment with DOCA, we find no support for impaired vascular relaxation as an important contributing factor to the maintenance of DOCA hypertension. It is possible, however, that vascular responsiveness to endogenous vasodilators might be depressed in DOCA hypertension.

Renal vascular reactivity to norepinephrine has been examined in hypertensive animals (table 3). The results of this study — that contractile responses to norepinephrine are depressed in DOCA hypertensive vasculatures — confirm the results of Fink and Brody, who studied renal vascular reactivity in the spontaneously hypertensive rat under similar, blood-perfused conditions. When kidneys from hypertensive rats are perfused with a blood substitute, they are generally more sensitive to norepinephrine than are those from normotensive controls. However, Coutre and Regoli report no difference between responses elicited in DOCA hypertensive and normotensive control kidneys perfused with Krebs solution. Collis and Vanhoutte report no difference in norepinephrine sensitivities between two-kidney renal, young spontaneously hypertensive rats, and their respective controls. In these rats, the kidneys were perfused under constant flow conditions with Tyrode's solution. Under similar conditions, Folkow, et al. found that renal vascular beds of spontaneously hypertensive rats exhibited exaggerated resistance responses to suprathreshold amounts of norepinephrine as well as increased maximal strength of contraction (higher maximal pressor responses to supramaximal amounts of constrictor agents under constant flow conditions), but no difference in threshold concentrations of the agonist.

It appears as though the renal vasculatures of hypertensive animals respond differently to norepinephrine depending upon the perfusing medium. There is a tendency for reactivity to be increased with hypertension if the kidney is perfused with a blood substitute whereas contractile responses are depressed when the kidneys are perfused with blood. This latter observation may reflect the lower contractility of vascular smooth muscle observed in many hypertensive animals. Since a higher intrinsic level of constrictor tone exists in blood perfused vasculatures from hypertensive animals, a further increase in contractile force to a given agonist may appear to be

<table>
<thead>
<tr>
<th>Reference</th>
<th>Preparation</th>
<th>Results (compared w/control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fink and Brody</td>
<td>in situ, blood perfused kidney (spontaneously hypertensive rat)</td>
<td>decreased reactivity</td>
</tr>
<tr>
<td>Cohen, et al.</td>
<td>in situ, blood perfused kidney (DOCA hypertensive rat)</td>
<td>decreased reactivity</td>
</tr>
<tr>
<td>Coutre and Regoli</td>
<td>Krebs perfused kidney (spontaneously hypertensive rat)</td>
<td>increased reactivity</td>
</tr>
<tr>
<td>Collis and Vanhoutte</td>
<td>Tyrodes perfused kidney (spontaneously hypertensive rat)</td>
<td>increased reactivity</td>
</tr>
<tr>
<td>Berecek, et al.</td>
<td>modified Krebs perfused kidney (spontaneously hypertensive rat)</td>
<td>increased reactivity</td>
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<td>Krebs perfused kidney (DOCA hypertensive rat)</td>
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<tr>
<td>Collis, et al.</td>
<td>Tyrodes perfused kidney (young spontaneously hypertensive rat)</td>
<td>no difference in reactivity</td>
</tr>
</tbody>
</table>
lower than in vasculatures from control animals. Absolute responses will be masked by these differences in initial tone.

In non-blood perfused preparations, Mulvany et al.10 showed that small resistance arteries (150–250 µm, I.D.) from the mesenteric vascular beds of spontaneously hypertensive rats demonstrate higher contractile strengths compared with normotensive controls. Renal vascular beds from spontaneously hypertensive rats, also perfused with a physiological salt solution, exhibit greater maximal contractile responses to norepinephrine than do those from control rats.

Our finding of increased sensitivity and lower maximal contractile response to norepinephrine in isolated arteries from hypertensive rats is in keeping with earlier observations.21.22 This is another example of a non-blood perfused preparation having a greater sensitivity to norepinephrine. Since blood perfused vasculatures have tone whereas artificially perfused or superfused preparations are atomic, it is possible that whatever is producing tone is also inhibiting the increased responsiveness to norepinephrine. On the other hand, the current study demonstrates that the increased sensitivity of vascular smooth muscle to the vasodilator effect of nitroprusside is evident in the presence or absence of this blood-borne influence in two different vascular preparations from DOCA hypertensive rats.

References

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