Adrenergic Neurotransmission in Tail Arteries from Two-Kidney, One Clip, Renal Hypertensive Rats

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SUMMARY The goal of this study was to determine if increased vascular smooth muscle sensitivity to norepinephrine in two-kidney, one clip (2K1C) hypertensive rats is the result of a decrease in adrenergic nerve function. Vascular sensitivity to norepinephrine was measured in isolated tail artery strips from 2K1C hypertensive and normotensive rats and in various arterial strip preparations from normotensive rats that exhibit varying degrees of adrenergic innervation. In each case, the characteristic of the vascular smooth muscle response in the vessel with the least amount of adrenergic innervation simulated the response of the vascular smooth muscle from the 2K1C hypertensive rats. Release or displacement of endogenous norepinephrine by electrical stimulation, tyramine, potassium-free solution, and potassium excess, and measurement of tissue content of norepinephrine suggest that the blood vessels of 2K1C hypertensive animals are depleted of catecholamine stores. Based on these observations it is concluded that the increased sensitivity of vascular smooth muscle to norepinephrine in 2K1C hypertensive rats is the result of a diminished adrenergic innervation. This increased sensitivity of the vasculature may be a response of the smooth muscle cells to a decrease in innervation or the consequence of vascular wall hypertrophy leading to an increased number of smooth muscle cells that are remote from their adrenergic supply. (Hypertension 5:298-306, 1983)

KEY WORDS • aorta • mesenteric artery • acute and chronic adrenergic denervation • norepinephrine • cocaine • vascular sensitivity

THE junction between the adrenergic nerve ending and the smooth muscle cells of the blood vessel wall makes sympathetic control of vascular function possible. Experimental evidence developed over the past two decades may be interpreted as indicating that functional changes in this nerve-muscle relationship contribute to the increase in total peripheral resistance of experimental renal hypertension. Specifically, both catecholamine content and catecholamine histochemistry have been found to be significantly decreased in vascular beds of animals with both renal clip hypertension and renal hypertension induced by figure-eight parenchymal ligation technique. Ultrastructural studies indicate a decrease in the number of dense core vesicles in adrenergic nerve endings of arteries from renal hypertensive rats and dogs. Interpretation of the significance of this catecholamine depletion in terms of vascular function has been speculative. Most authors postulate that increased norepinephrine turnover and depleted nerve-ending catecholamine stores provide evidence of an increased sympathetic influence on the vasculature. This increased sympathetic influence could be due to either an augmented sympathetic nerve activity or increased transmitter release at a normal level of sympathetic activity. Facilitation of norepinephrine release from adrenergic nerve endings by angiotensin II, liberated following renal artery clipping, also has been suggested as a possible means whereby normal levels of sympathetic activity could enhance vasoconstriction. The possibility that catecholamine depletion might imply reduced adrenergic nerve function has received little consideration.

The goal of this study was to determine if increased vascular smooth muscle sensitivity to norepinephrine in two-kidney, one clip (2K1C) hypertensive rats is the result of a decrease in adrenergic nerve function. Since somewhat similar changes in vascular sensitivity to catecholamines occur following chronic adrenergic denervation, vascular responsiveness of normotensive arteries following destruction of adrenergic nerves was determined. Additionally, vascular responsive-
ness of a densely innervated blood vessel (tail artery)\[^{14,15}\] was compared to that of the aorta which is virtually devoid of an adrenergic supply.\[^{16,17}\] Vascular sensitivity to norepinephrine of the mesenteric artery was determined since this vessel is intermediate in its density of innervation.\[^{17}\] 

**Methods**

**Animal Preparation**

All studies were performed on male, Sprague-Dawley rats (n = 40; 400–475 g body weight at the time of experimentation). Twelve of the rats were anesthetized with ether, and the left kidney was exposed through a flank incision. A silver clip (0.22 mm slit) was placed on the left renal artery. Normotensive rats did not undergo sham treatment. All rats were maintained on standard laboratory chow (Purina) and tap water ad libitum. Systolic blood pressures were determined in the conscious state by means of indirect tail cuff measurements. Experiments were performed at 4 months after surgery.

**Arterial Strip Preparation**

All rats were terminated by a blow to the head, and aortas, mesenteric arteries, and/or tail arteries excised. The arteries were stored in physiological salt solution (PSS) and cut helically into strips (1.0 × 10 mm) under a dissecting microscope. The helical strips were mounted vertically on either a glass or plastic holder in a tissue bath containing PSS. The upper ends of the strips were connected to force transducers (Grass FT.03), and the resting force placed on each strip was adjusted so that the strip produced maximum active force in response to a standard dose of norepinephrine (10⁻⁷ g/ml). The bathing medium was maintained at 37°C and aerated with a mixture of 95% O₂ and 5% CO₂. The pH of the solution was 7.4 and the composition (mM/liter) was as follows: NaCl (130), KCl (4.7), KH₂PO₄ (1.18), MgSO₄·7H₂O (1.17), CaCl₂·2H₂O (1.6), NaHCO₃ (14.9), dextrose (5.5), and CaNa₂EDTA (0.03). Potassium-free solution was of the same composition except that KC1 was omitted and the resting force on each strip was 20% greater. Potassium-free solution was of the same composition except that KC1 was omitted and NaCl was replaced with an equimolar substitution of NaCl with KCl. Before the start of experiments, the strips were allowed to equilibrate for 90–120 minutes in PSS.

Arterial strips were electrically stimulated by the use of two platinum wire electrodes placed parallel to the preparations. Electrical impulses consisted of square waves (9 V, 2.0 msec) provided by a direct current power supply and switching transistor triggered by a stimulator (Grass, Model S4E).

**Acute and Chronic Denervation Procedures**

In some experiments, helical strips of tail artery from hypertensive and normotensive rats were acutely denervated with 6-hydroxydopamine according to the method of Aprigliano and Hermsmeyer.\[^{18}\] Following a 90-minute equilibration period, the strips were placed in a bicarbonate-free PSS containing 300 μg/ml 6-hydroxydopamine for 10 minutes. The pH of this unbuffered PSS was adjusted to 4.0 by the addition of 20 μM glutathione. The O₂-CO₂ mixture to the muscle bath was turned off during the denervation procedure. Following denervation, the strips were allowed to recover in normal PSS for 3 hours.

Chronic denervation of the tail artery was performed in six normotensive rats. Each rat was anesthetized with ether, and a 10 mm portion of the artery was exposed at the origin of the tail. The surface of the vessel was mechanically scraped with serrated forceps and the artery was painted with tyrosine (5 mm of its length with 10% phenol in ethanol). Two to 3 weeks after surgery, the rats were terminated by a blow to the head, and the tail artery distal (1–2 cm) to the treatment area was excised and cut into helical strips as described above.

**Norepinephrine Measurements**

The tissue content of norepinephrine in tail arteries and the plasma levels of the catecholamine were determined radioenzymatically using a commercially available kit (Cat-a-Kit, Upjohn Diagnostics) as described by Vanhoutte et al.\[^{19}\]

**Statistical Methods**

The results of these experiments were analyzed by several statistical procedures. The responses of each arterial strip were normalized to its maximal response to exogenous norepinephrine to allow interpretation of the results in terms of vascular reactivity and sensitivity. Dose-response and frequency-response curves were calculated as geometrical means. Paired and unpaired t tests and curve fitting analyses (logit-log transformation) were performed. A p value less than 0.05 was considered to be statistically significant.

**Drugs**

Drugs used were: norepinephrine bitartrate (Breon Laboratories, Inc.), 6-hydroxydopamine hydrobromide (Sigma Chemical Company, St. Louis, Missouri), glutathione (Sigma Chemical Company), tyramine (Sigma Chemical Company), and cocaine (supplied by University of Michigan Hospital Pharmacy, Ann Arbor, Michigan).

**Results**

At the time of experimentation (4 months after surgery), the systolic blood pressure of rats used in this study were: 2K1C hypertensive = 198 ± 3 mm Hg (n = 12) and normotensive = 121 ± 2 mm Hg (n = 22; p < 0.05). Chronic denervation of the tail artery did not alter the systolic blood pressure of normotensive rats (118 ± 3 mm Hg; n = 6).

**Passive Force and Contractile Responses to Norepinephrine**

Before the start of the experiments, the arterial strips were stretched to successively greater levels of passive force. At each 100 mg increment of passive force applied to the strips, contractile responses to 10⁻⁷ g/ml norepinephrine were determined. The optimum pas-
sive force for generation of active contractile responses was defined as the passive force that gave no further increase in active force generation for two successive 100 mg increments. In tail arteries from 2K1C hypertensive and normotensive rats, contractile responses to norepinephrine increased to a maximum as the passive force applied to the strips increased to approximately 500 mg. The optimum passive force for maximum response to norepinephrine was similar for strips from 2K1C hypertensive rats (634 ± 42 mg; n = 12) and those from normotensive rats (608 ± 37 mg; n = 22). The optimum passive force for aortic strips was 1425 ± 138 mg (n = 6) and that for mesenteric arteries was 542 ± 24 mg (n = 6). The chronic denervation procedure did not alter this passive force-active force relationship (optimum passive force in chronically denervated tail arteries = 637 ± 35 mg, n = 6).

**Dose Response to Norepinephrine**

Cumulative addition of norepinephrine (10⁻¹² to 10⁻⁵ g/ml) to the muscle bath produced contractile responses in all arterial strips (fig. 1). Experimental observations for tail arteries from normotensive rats, which did not undergo the surgical denervation procedure, were averaged and analyzed together (i.e., the tail arteries labeled as “normotensive” in the left panel of figure 1 are the same as those labeled as “tail artery” and “innervated” in the middle and right panels of figure 1, respectively; this averaging process was used in subsequent analyses in figures 2 and 5).

The dose-response curve for norepinephrine was shifted to the left in tail artery segments from 2K1C hypertensive rats with respect to that obtained in tail arteries from normotensive rats (left panel, fig. 1). The dose of norepinephrine which caused a half-maximal response (ED₅₀) was significantly less in tail arteries from hypertensive rats (2.2 × 10⁻⁹ g/ml) as compared to that in tail arteries from normotensive rats (10.8 × 10⁻⁹ g/ml; p < 0.05). The maximal contractile force developed was significantly less for arterial strips from hypertensive rats (1792 ± 112 mg) as compared to that developed by tail arteries from normotensive rats (2183 ± 117 mg; p < 0.05).

Comparison of sensitivity to norepinephrine in three different arteries from normotensive rats (middle panel, fig. 1) indicated that aortic strips were most sensitive to the catecholamine (ED₅₀ = 0.4 × 10⁻⁹ g/ml); whereas tail arteries were the least sensitive (ED₅₀ = 10.8 × 10⁻⁹ g/ml); mesenteric arteries were intermediate in sensitivity to norepinephrine (ED₅₀ = 4.5 × 10⁻⁹ g/ml). Maximal contractile force developed in response to norepinephrine was: aorta = 967 ± 62 mg; mesenteric artery = 672 ± 42 mg; tail artery = 2183 ± 117 mg).

There was a significant shift to the left in the dose-response relationship for norepinephrine following chronic denervation of the tail artery in normotensive rats (right panel, fig. 1). The ED₅₀ value for norepinephrine was significantly lower in chronically denervated arterial strips (2.7 × 10⁻⁹ g/ml) than in innervat-

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**Figure 1.** Dose-response to norepinephrine. Helical strips of aortas and mesenteric and tail arteries from 2K1C renal hypertensive or normotensive rats were made to contract in response to the cumulative addition of norepinephrine to the muscle bath. **Left panel:** Tail arteries from hypertensive rats were more sensitive to the catecholamine than those from normotensive rats. **Middle panel:** Tail arteries were less sensitive to norepinephrine than mesenteric arteries or aortas. **Right panel:** Denervation of the tail artery resulted in an increased sensitivity to norepinephrine. Asterisks indicate statistical differences between arteries from hypertensive rats and those from normotensive rats (left panel), differences between tail arteries and aortas or mesenteric arteries (middle panel), and differences between innervated and chronically denervated tail arteries (right panel, p < 0.05). Values are the means ± standard error of the mean (SEM). The values in parentheses are the number of rats.
ed control arterial strips (10.8 \times 10^{-9} \text{ g/ml}; p < 0.05). Maximal contractile responses to norepinephrine were less in denervated tail arteries (1337 \pm 202 mg) than in innervated tail arteries (2183 \pm 117 mg; p < 0.05). Maximal contractile responses to norepinephrine were: tail arteries = 1681 \pm 128 mg (n = 8); mesenteric arteries = 260 \pm 35 mg (n = 6); aortas = 16 \pm 16 mg (n = 6).

After chronic denervation of the tail artery, contractile responsiveness to electrical stimulation of adrenergic nerve endings was depressed compared to control innervated tail artery segments (right panel, fig. 2). Maximal contractile responses were: innervated = 1681 \pm 128 mg (n = 8); and denervated = 547 \pm 125 mg (n = 4). These observations suggest that the surgical technique produced a partial denervation of the tail artery.

**Dose Response to Tyramine**

Cumulative addition of tyramine (10^{-7} to 10^{-2} \text{ M}) to the muscle bath produced contraction in tail artery strips from 2K1C hypertensive and normotensive rats (fig. 3). Innervated arterial strips from hypertensive rats responded similarly to tyramine as those from normotensive rats. Statistical differences (unpaired t test) were evident at only two doses of tyramine (3 \times 10^{-6} \text{ M} and 10^{-5} \text{ M}). Acute denervation with 6-hydroxydopamine reduced the contractile effect of tyramine; contractile responsiveness of tail artery strips from hypertensive rats were less affected by destruction of adrenergic nerve endings than those from normotensive rats as indicated by the smaller shift to the right and depression of the maximal response to tyramine.
following treatment with 6-hydroxydopamine. Maximal contractile responses to tyramine were: 2K1C hypertensive rats, innervated = 1022 ± 132 mg (n = 6); normotensive rats, innervated = 1418 ± 231 mg (n = 6); 2K1C hypertensive rats, denervated = 549 ± 147 mg (n = 6); normotensive rats, denervated = 267 ± 85 mg (n = 6).

Cocaine, Acute Adrenergic Denervation and Contractile Responses to Norepinephrine, Electrical Field Stimulation, and Tyramine

Cocaine (10^-6 M), a neuronal uptake inhibitor, and acute denervation with 6-hydroxydopamine potentiated contractile responses to exogenous norepinephrine in tail artery strips from normotensive rats, whereas contractile responsiveness to the catecholamine was not significantly altered by these interventions in tail arteries from 2K1C hypertensive rats (left panel, fig. 4).

Treatment of tail artery strips from normotensive rats with 10^-6 M cocaine potentiated contractile responses to 2 Hz electrical stimulation of adrenergic nerve endings; contractile responses to 8 Hz stimulation were not altered by the neuronal uptake inhibitor (middle panel, fig. 4). Cocaine had no effect on contractile responses to field stimulation in tail arteries isolated from 2K1C hypertensive rats.

Contractile responses to 10^-4 M tyramine were depressed by treatment with 10^-6 M cocaine in tail arteries from both normotensive and 2K1C hypertensive rats (right panel, figure 4). The magnitude of the depression of the percent contractile response was greater (untreated values minus values obtained in the presence of cocaine) in tail arteries from normotensive rats (-26%) than in those from hypertensive rats (-13%).

Contraction in Response to Potassium-Free Solution

Exposure of arterial strips to potassium-free solution resulted in contraction (fig. 5). These contractions were slow in development, reaching a maximum at 15 to 20 minutes after exposure to the potassium-free solution. The contractions were absent in arterial strips acutely denervated with 6-hydroxydopamine and abolished by 10^-6 M phentolamine. Contractile responses of tail artery strips from 2K1C hypertensive rats were significantly less than those from normotensive rats at 15, 20, 25, and 30 minutes into the potassium-free cycle (left panel, fig. 5). Tail artery segments from normotensive rats contracted the most in response to potassium-free solution, aortic strips contracted the least, and mesenteric arteries were intermediate in responsiveness to the absence of potassium (middle panel, fig. 5). Chronic surgical denervation of tail arteries reduced the contractile effect of potassium-free solution (right panel, fig. 5). Maximal contractile responses were: 2K1C hypertensive rats = 633 ± 163 mg (n = 6); normotensive rats = 1268 ± 128 mg (n = 10); aortas = 126 ± 49 mg (n = 6); mesenteric arteries = 138 ± 38 mg (n = 6); denervated tail arteries = 480 ± 101 mg (n = 6).

Dose Response to Potassium

Tail artery strips from 2K1C hypertensive and normotensive rats were made to contract in response to the cumulative addition of potassium to the muscle bath in the presence and absence of 10^-6 M phenolamine (fig. 6). In the absence of phenolamine, arterial strips from 2K1C hypertensive rats and normotensive rats responded similarly. Phenolamine (10^-6 M) reduced the contractile effect of elevated potassium; contractile responses to potassium in arterial strips from hypertensive rats were less affected by alpha adrenergic blockade than were those from normotensive rats. Maximal contractile responses to potassium were: for 2K1C hypertensive rats, untreated = 1023 ± 122 mg (n = 6); for normotensive rats, untreated = 1666 ± 154 mg (n = 6); for 2K1C hypertensive rats, phenolamine = 702 ± 74 mg (n = 6); and for normotensive rats, phenolamine = 848 ± 75 mg (n = 6).

Plasma Levels and Tissue Content of Norepinephrine

Plasma levels of norepinephrine were similar in hypertensive and normotensive rats, whereas the tissue content of the catecholamine was significantly less in tail artery strips isolated from hypertensive rats than in those from normotensive rats (fig. 7).
FIGURE 4. Cocaine, acute adrenergic denervation and vascular responses to norepinephrine, field stimulation, and tyramine. Helical strips of tail arteries from hypertensive and normotensive rats were made to contract in response to norepinephrine, electrical field stimulation, and tyramine. Left panel: Cocaine (10^-6) and acute denervation potentiated vascular responses to norepinephrine in arterial strips from normotensive rats but not those in arterial strips from hypertensive rats. Middle panel: Contractile responses of normotensive arterial strips to 2 Hz stimulation were potentiated in the presence of 10^-6 M cocaine; contractile responses to 2 Hz in hypertensive arterial strips and to 8 Hz in both normotensive and hypertensive strips were not altered by 10^-6 M cocaine. Right panel: Cocaine (10^-6 M) inhibited contractile responses to 10^-4 M tyramine to a greater degree in arterial strips from normotensive rats than in those from hypertensive rats. Asterisks indicate statistical differences between untreated and treated condition (p < 0.05). Values are means ± SEM for six normotensive rats and six hypertensive rats.

FIGURE 5. Contraction in response to potassium-free solution. Helical strips of aortas and mesenteric and tail arteries from 2K1C renal hypertensive or normotensive rats contracted when placed in potassium-free solution. Left panel: Tail arteries from hypertensive rats contracted less in response to potassium-free solution than those from normotensive rats. Middle panel: Aortic strips contracted less than mesenteric and tail arteries. Right panel: Chronically denervated tail arteries contracted less than control innervated tail arteries. Asterisks indicate statistical differences between arteries from hypertensive rats and those from normotensive rats (left panel), differences between tail arteries and aortas or mesenteric arteries (middle panel) and differences between innervated and chronically denervated tail arteries (right panel, p < 0.05). Values are means ± SEM. The values in parentheses are the number of rats.
FIGURE 6. Dose-response to potassium. Helical strips of tail arteries from hypertensive and normotensive rats were made to contract in response to the cumulative addition of KCl to the muscle bath. Dose-response curves were performed before and after treatment with $10^{-6}$ M phentolamine. Asterisks indicate statistical differences between untreated strips and those treated with $10^{-6}$ M phentolamine ($p < 0.05$). Daggers indicate statistical differences between hypertensive and normotensive rats ($p < 0.05$). Values are means ± sem for six normotensive rats and six hypertensive rats.

Discussion

Extensive evidence from broadly different types of experiments support the hypothesis that the sympathetic nervous system is involved in the development of renal hypertension.1-12 The current study uses two different systems to evaluate the effect that adrenergic innervation has on vascular smooth muscle responsiveness. The effect of the naturally occurring variability in adrenergic nerve density of three different blood vessels (aorta, mesenteric artery, tail artery) was studied. In the second system, the effect of chronic surgical denervation was evaluated. In both of these systems, the characteristic of the vascular smooth muscle response in the vessel with the least amount of adrenergic innervation simulated the response of the vascular smooth muscle from the 2K1C hypertensive rat.

Vascular Sensitivity to Norepinephrine

Vascular sensitivity to norepinephrine was increased in isolated tail arteries from 2K1C hypertensive rats as evidenced by the leftward shift in the dose-response relationship relative to that in tail arteries from normotensive rats (fig. 1). Other investigators have observed a similar increased sensitivity to the catecholamine in perfused vascular beds and isolated blood vessel preparations from renal hypertensive animals (see ref. 20 for review). This increased sensitivity to norepinephrine in hypertension is strikingly similar to that observed in tail arteries from normotensive rats which had been partially denervated by surgical procedure (right panel, fig. 1). Additionally, it was observed that the variability of adrenergic nerve density in aorta, mesenteric arteries and tail arteries correlated inversely with sensitivity to norepinephrine. The aorta which is virtually devoid of adrenergic innervation, based on its catecholamine content (~0.2 μg/g wet weight)7 was the most sensitive to norepinephrine (lowest ED₅₀), whereas the tail artery, which has the highest catecholamine content (8.5 μg/g wet weight; fig. 7), was the least sensitive to the catecholamine. Mesenteric arteries were intermediate in sensitivity to the catecholamine, and these arteries contain intermediate levels of norepinephrine (6.0 μg/g wet weight).15

This similarity in performance of vascular smooth muscle in 2K1C hypertension and that of poorly innervated muscle from a normotensive animal was evident also in the maximal force developed by tail artery strips from the respective groups. The maximal force developed in response to norepinephrine was less in tail artery strips from 2K1C hypertensive rats than in those from normotensive rats; and the maximal force developed by chronically denervated tail arteries was less than control innervated tail arteries. Other investigators have observed a similar decreased maximum force generating ability in arterial strips from hypertensive animals21-25 and in vascular smooth muscle which
has been chronically denervated. The reasons for this difference in force generating ability between vascular smooth muscle from hypertensive animals and that from normotensive muscles is not clear, but it does not appear to be related to the resting force placed on the arterial strips. 15, 16, 25 Berner et al.26 induced vascular hypertrophy by partial ligation of the rabbit portal-anterior mesenteric vein. At 14 days after ligation there was a massive increase in the intermediate filaments surrounding the dense bodies in which actin filaments insert. The proliferation of intermediate filaments was concomitant with a decrease in number and distribution of myosin filaments. A similar change in the contractile proteins may occur in hypertrophied vascular smooth muscle from hypertensive animals and thus account for the decreased maximal force generating ability. Bevan and Tsuru13 suggest that the diminution in force generating ability in chronically denervated arteries is due to qualitative change in the contractile machinery.

**Release and Pharmacological Displacement of Norepinephrine from Adrenergic Nerve Endings**

The release of norepinephrine in blood vessels of the intact animal is mediated by nerve impulses. The released transmitter that reaches the vascular smooth muscle produces activation of the contractile machinery after binding to receptor sites on the cellular membranes. In this study, a variety of experimental conditions (table 1) that cause the release or displacement of norepinephrine from nerve endings were used to characterize adrenergic neurotransmission in tail arteries from 2K1C hypertensive and normotensive rats and that in poorly innervated smooth muscle.

Regardless of the technique used to cause release or displacement of norepinephrine from adrenergic nerve endings, the maximal response of tail arteries from 2K1C hypertensive rats which could be attributed to endogenous norepinephrine was always less than that in tail arteries from normotensive rats (table 1). This response pattern was similar for chronically denervated tail arteries from normotensive rats and for arteries with less dense adrenergic innervation. Blockade of the neuronal uptake process did not potentiate vascular responses to exogenous norepinephrine nor electrical stimulation in tail arteries from hypertensive rats suggesting that the adrenergic nerve endings may have a deficient neuronal uptake process. Vascular responses to tyramine were less inhibited in the presence of cocaine in tail arteries from hypertensive rats than in those from normotensive rats. Since this pharmacological displacement is dependent upon the uptake of tyramine by the neuronal pump, this observation suggests that tail arteries from 2K1C hypertensive rats do not store norepinephrine as well as arteries from normotensive rats or that there are fewer storage sites in arteries from hypertensive rats. Furthermore, the tissue content of norepinephrine was less in tail arteries from 2K1C hypertensive rats than in those from normotensive rats (fig. 7). Based on these observations, it may be concluded that the adrenergic nerve endings in blood vessels of 2K1C hypertensive rats release less norepinephrine than do those in blood vessels from normotensive rats. This defect is probably the result of a reduced amount of norepinephrine available for release.

Other investigators have observed decreased adrenergic nerve function in resistance vessels of animals with renal hypertension. Fink and Brody1 showed that vascular responses to renal nerve stimulation and pharmacological displacement of norepinephrine by tyramine in the renal vasculature of rats with renal hypertension produced by figure 8 parenchymal ligation was less than that in normotensive rats. Changes in vascular resistance in response to intra-arterial injection of norepinephrine were either unchanged or greater in the renal vascular of hypertensive rats than in those from normotensive rats. These investigators also suggested that diminished catecholamine storage in the kidneys of renal hypertensive rats reflects a decreased capacity of adrenergic nerve stimulation to produce vasoconstriction.

The current study offers no support for the hypothesis that increased sympathetic nerve activity contributes to the maintenance of renal hypertension.11, 12 The results do suggest that alterations in the adrenergic nerve ending in hypertension may serve to attenuate vascular responsiveness to sympathetic nerve stimulation. This response of the adrenergic nerve ending may partially explain the increased sensitivity found in this study to norepinephrine of the vascular smooth muscle in hypertension. It is proposed that the smooth muscle increases its sensitivity to the catecholamine in response to the reduced release of the transmitter from

<table>
<thead>
<tr>
<th>Experimental condition</th>
<th>Mechanism of action</th>
<th>Response of tail artery from 2K1C hypertensive rat</th>
<th>Maximal response of chronically denervated tail artery</th>
<th>Response of aorta, mesenteric artery, and tail artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrical stimulation</td>
<td>Exocytotic release</td>
<td>↓</td>
<td>↓</td>
<td>Aorta &lt; mesenteric &lt; tail</td>
</tr>
<tr>
<td>Tyramine</td>
<td>Pharmacological displacement</td>
<td>↓</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Potassium-free solution</td>
<td>Exocytotic release</td>
<td>↓</td>
<td>↓</td>
<td>Aorta &lt; mesenteric &lt; tail</td>
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<td>Elevated potassium</td>
<td>Exocytotic release</td>
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the nerve ending. Alternatively, the vascular wall hypertension and/or hyperplasia (or increase in vessel wall mass per unit length)²⁸ that accompanies the development of hypertension results in an effective deformation of the smooth muscle cells that become increasingly farther away from their adrenergic supply at the adventitial-medial border of the blood vessel. This latter specification is supported by the observation that the vascular cells nearest the luminal surface are more sensitive to norepinephrine whereas those nearest the external surface are less sensitive to the catecholamine.²⁹ ³⁰

The blood pressure of the animal may also play some role in limiting the extent of adrenergic innervation in the blood vessel wall.²⁹ Keatinge and Torrie²⁹ observed that prolonged elevation of pressure throughout the vascular wall by application of a non-occluding cylindrical clip made the entire wall of sheep carotid arteries free of adrenergic nerves. They suggest that the distribution of pressure within the vascular wall is determined by two components: 1) the gradient between arterial blood pressure at the inner surface and atmospheric pressure at the outer surface; and 2) the relative degree of contraction of inner and outer layers of smooth muscle. Although the importance of local gradients in pressure are not well understood these investigators demonstrated that the adrenergic nerves did not survive when localized pressure within the vascular wall approached the pressure inside the lumen of the artery (100 mm Hg).

The observations of this study demonstrate that vascular changes in 2K1C hypertension simulate those produced by adrenergic denervation. The precise mechanism by which catecholamine depletions occur in this form of hypertension is unclear. It seems doubtful that reduced adrenergic function plays an important role in the initiation of 2K1C hypertension. However, the increased sensitivity of the vasculature may play a role in the maintenance of high blood pressure when adrenergic function is diminishing.

References

Adrenergic neurotransmission in tail arteries from two-kidney, one clip, renal hypertensive rats.

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