Role of Nitric Oxide and Angiotensin II in the Regulation of Sympathetic Nerve Activity in Spontaneously Hypertensive Rats

Hiroo Kumagai, David B. Averill, Mahesh C. Khosla, and Carlos M. Ferrario

This study evaluated the actions of nitric oxide on the blood pressure and renal sympathetic nerve activity responses produced by angiotensin II (Ang II) blockade in conscious spontaneously hypertensive rats. Two days after implantation of electrodes, we measured mean arterial pressure, heart rate, and renal sympathetic nerve activity. Baroreceptor reflex function was assessed with a logistic function curve; the maximum slope of the curve estimated the baroreceptor reflex gain. Data were obtained in rats given acute intravenous administration of either vehicle, the Ang II type 1 receptor antagonist losartan, the type 2 antagonist CGP 42112A, or the converting enzyme inhibitor lisinopril. In comparison with vehicle (−1.1±0.2 %/mm Hg), both losartan (−1.8±0.3 %/mm Hg) and lisinopril (−2.4±0.2 %/mm Hg) significantly increased the maximum gain of the baroreceptor reflex control of nerve activity (p<0.05). In contrast, the type 2 receptor antagonist did not alter baroreceptor reflex function. Similar studies were performed in rats that received an intravenous injection of NO- monomethyl L-arginine (10 mg/kg). The nitric oxide synthase inhibitor increased baseline blood pressure and decreased renal sympathetic nerve activity. Subsequent administration of losartan or lisinopril returned blood pressure to initial hypertensive level, whereas sympathetic nerve activity was increased to a level above the initial control value. The maximum gain of the baroreceptor reflex control of renal nerve activity was increased after the nitric oxide inhibition. The present study demonstrates that blunted baroreceptor reflex function in conscious spontaneously hypertensive rats is mediated by an Ang II type 1 receptor. Moreover, nitric oxide may play a dual role in the antihypertensive effect of Ang II blockade. First, nitric oxide contributes to the antihypertensive effects of losartan and lisinopril. Second, the enhancement of the baroreceptor reflex after inhibition of the actions of Ang II may be related to the fall in arterial pressure. (Hypertension 1993;21:476–484)

KEY WORDS • angiotensin II • baroreceptors • angiotensin converting enzyme inhibitors • hypertension, primary • sympathetic nervous system • nitric oxide

The importance of an interaction between endogenous angiotensin II (Ang II) and the sympathetic nervous system is well documented. Ang II modulates the activity of the sympathetic nervous system by facilitating adrenergic nerve transmission and inhibiting the arterial baroreceptor reflex.1,2 One action of Ang II blockade is improvement of the baroreceptor reflex.3 In conscious rabbits with Ang II–dependent hypertension, the Ang II receptor antagonist [Sar1, Ala8]Ang II not only reversed the high blood pressure but increased the maximum gain of the baroreceptor reflex control of renal sympathetic nerve activity (RSNA).3 These data support the hypothesis that the antihypertensive effects of angiotensin converting enzyme (ACE) inhibitors are in part due to a centrally mediated decrease in sympathetic outflow.

Because there are no in vivo studies on the Ang II receptor subtype that is functionally involved in the baroreceptor reflex, we compared the effects of angiotensin type 1 (AT1) and type 2 (AT2) receptor antagonists on the baroreceptor reflex control of RSNA and heart rate (HR) in conscious spontaneously hypertensive rats (SHRs). We contrasted the effects of these two Ang II receptor antagonists with results obtained in rats treated with the ACE inhibitor lisinopril to assess the role of the renin-angiotensin system in the actions of lisinopril. Recent data have demonstrated that the antihypertensive effects of both an AT1 receptor antagonist and an ACE inhibitor are in part mediated by release of endothelium-derived nitric oxide (NO).4,5 Moreover, Lewis et al.6–7 found that endothelium-derived relaxing factors are involved in the regulation of baroreceptor reflexes. Therefore, we evaluated the effects of an AT1 antagonist or ACE inhibitor on hemodynamics and RSNA in the absence or presence of NO. In these experiments, we pursued the possibility that NO participated in the baroreceptor reflex control of arterial pressure in conscious SHRs.
Surgical Procedures

Experiments were done in 15-week-old male SHRs purchased from Taconic Farms (Germantown, N.Y.) and in accordance with guiding principles of the American Physiological Society. Devices were implanted surgically using aseptic conditions in rats in which inhalation anesthesia was first induced with 2% halothane (Halocarbon Lab, S.C.) in a mixture of 65% air–35% oxygen. Anesthesia was maintained at a halothane concentration of 1%. Polyethylene catheters (PE-50, Clay Adams, Parsippany, N.J.) were placed into a femoral artery and a femoral and jugular vein. The free ends of these catheters were exteriorized at the back of the neck.

Implantation of Renal Nerve Electrode

The left renal artery and vein were exposed by blunt dissection of the retroperitoneal space via a flank incision. A fascicle of the renal nerve plexus was then isolated. Teflon-coated stainless-steel wires (0.001 in. diameter, A-M Systems Inc., Wash.) were looped around the renal nerve fascicle. Both nerves and electrodes were imbedded in silicone gel (Silgel 604A and 604B, Wacker Chemie, Munich, FRG) as described elsewhere. The free ends of the wires were also exteriorized at the back of the neck. After completion of the surgical procedure, rats were hydrated by a subcutaneous injection of 10 mL 5% dextrose in lactated Ringer’s solution. Penicillin G (30,000 units) was administered intramuscularly.

Recording and Quantification of Renal Sympathetic Nerve Activity

Recordings of arterial pressure, HR, and RSNA were obtained from conscious animals. Rats were habituated to the experimental conditions, the arterial pressure was varied by an intravenous infusion (Combit Infusion Pump, model 975, Harvard Apparatus, South Natick, Mass.) of either a pressor or a depressor agent. Phenylephrine was infused to raise MAP by 50 mm Hg. The drug (dissolved in 0.9% NaCl) was given at doses between 0.48 and 29 μg/kg per minute through flow rates that ranged from 0.013 to 0.760 mL/min for 2 minutes. Blood pressure was then allowed to return to baseline level over the next 15 minutes. We then infused nitroglycerin (1,200 μg/kg, dissolved in 0.9% NaCl) at a flow rate of 0.068 mL/sec to decrease MAP by 40 mm Hg over a period of 15 seconds. Alternate infusions of phenylephrine and nitroglycerin resulted in a wide range of blood pressure, HR, and RSNA. Values of integrated RSNA and HR were obtained at each 5 mm Hg change in MAP. The validity of this method to examine the baroreceptor reflex in conscious rats is described elsewhere.

The logistic function used for data analysis conformed to the mathematical expression described elsewhere. The formula is RSNA or HR = \( P_1 \left\{ 1 + \exp \left[ P_2 (MAP - P_3) \right] \right\} + P_4 \), where \( P_1 \) is the range of the response of RSNA or HR, \( P_2 \) is the slope coefficient, \( P_3 \) is the MAP at the midpoint of the range of RSNA or HR, and \( P_4 \) is the minimum value of RSNA or HR. We used two methods for analysis of the baroreceptor reflex control of RSNA. One method used the maximum value of RSNA as 100%, and the other used the initial baseline value of RSNA as 100%. In both analyses, data were fit to a logistic function with a nonlinear regression program (NLIN PROC, SAS). The maximum gain of the arterial baroreceptor reflex was defined as the maximum slope (\( -P_2 \times P_3 / 4 \)) of the logistic function curve.

Experimental Protocols

Protocol 1. In conscious SHRs, MAP, HR, and RSNA were continuously recorded before and after intravenous administration of either vehicle (0.9% NaCl, \( n = 6 \)), losartan (\( n = 6 \); E.I. Du Pont de Nemours & Co., Wilmington, Del.), or CGP 42112A (\( n = 5 \); CIBA-GEIGY, Summit, N.J.). The dose of losartan (10 mg/kg dissolved in 0.9% NaCl, bolus injection) used in these experiments was effective in abolishing the pressor response to an intravenous infusion of 0.1 μg/kg Ang II in conscious SHRs. The dose of CGP 42112A (100 μg/kg per minute in 0.9% NaCl for 60 minutes) was based on our observation that larger doses of this antagonist evoked pressor responses in conscious SHRs (see “Results”). In one group of eight rats, baroreceptor reflex function was assessed 30 minutes after injection of vehicle and again 30 minutes after injection of losartan. In another group of five rats, baroreceptor reflex function was evaluated 30 minutes after initiation of an infusion of CGP 42112A.

Protocol 2. In one group of SHRs (\( n = 6 \)), MAP, HR, and RSNA were recorded before and after intravenous injection of lisinopril (20 mg/kg in 0.9% NaCl; Merck Sharp & Dohme Research Laboratories, Rahway, N.J.). The dose of lisinopril used in these experiments was adjusted to decrease MAP by a magnitude comparable to that obtained by injection of 10 mg/kg of losartan in conscious SHRs (protocol 1). This dose of lisinopril was effective in blocking the conversion of Hip-His-Leu to His-Leu (C.M. Ferrario and K. Kohara, unpublished observations, 1991). In a second group of SHRs (\( n = 6 \)),...
the baroreceptor reflex control of RSNA and HR was determined 30 minutes after vehicle injection and again 30 minutes after injection of lisinopril.

Protocol 3. To determine the effect of endogenous NO on MAP, HR, RSNA, and baroreceptor reflex function, we gave an intravenous injection of 10 mg/kg (dissolved in 0.9% NaCl) of the NO synthase inhibitor N^G-monomethyl L-arginine (L-NMMA) to conscious SHRs. Gardiner et al^16 showed that this dose of L-NMMA inhibits NO production in rats. In a group of five SHRs, the effects of L-NMMA on MAP, HR, and RSNA were recorded continuously for 120 minutes. In another group of six rats, baroreceptor reflex control of RSNA and HR was determined 30 minutes after vehicle injection and again 30 minutes after the injection of L-NMMA.

Protocol 4. To elucidate the participation of NO in the hypotensive effect of losartan or lisinopril and in the modulation of sympathetic nerve activity, we determined the effect of either losartan or lisinopril on MAP, HR, RSNA, and baroreceptor reflex in rats pretreated with L-NMMA. In one group, SHRs were given either losartan (n=4) or lisinopril (n=4) 20 minutes after injection of L-NMMA. MAP, HR, and RSNA were then continuously recorded for 90 minutes. In another group of 12 SHRs, either losartan or lisinopril was injected 20 minutes after the injection of L-NMMA. Thirty minutes later, baroreceptor reflex function was assessed in SHRs treated with the combination of L-NMMA and losartan (n=6) or L-NMMA and lisinopril (n=6). In all 12 SHRs, baroreceptor reflex function was examined 30 minutes after vehicle injection and before administration of L-NMMA.

Statistical Analysis

Data are mean±SEM. To compare the effects of vehicle, losartan, CGP 42112A, and lisinopril (protocols 1 and 2) and the effects of vehicle, L-NMMA, L-NMMA plus losartan, and L-NMMA plus lisinopril (protocols 3 and 4), we performed one-way analysis of variance and Duncan's multiple-range test. The unpaired Student's t test was used for comparisons of the proportion of the increase in RSNA relative to the decrease in MAP produced by losartan or lisinopril with and without L-NMMA treatment. A value of p<0.05 was required to establish statistical significance.

Results

Effects of Angiotensin II Blockade on Hemodynamics and Baroreceptor Reflexes

Figure 1 shows that both losartan and lisinopril produced comparable reductions in the MAP of conscious SHRs and no significant changes in HR. Thirty minutes after injection of either losartan or lisinopril, MAP averaged 110±2 and 112±2 mm Hg, respectively. In vehicle-treated rats, MAP remained stable at an average level of 145±3 mm Hg. CGP 42112A did not significantly alter MAP (148±2 mm Hg) in SHRs. Both losartan and lisinopril significantly increased RSNA above baseline values by an average of 21±3% and 36±3%, respectively. The pronounced effect of lisinopril on RSNA was statistically significant (p<0.05) when compared with the change elicited by losartan.
than the maximum gain (−1.1±0.2 %/mm Hg, p<0.05) obtained in vehicle-treated SHRs (Table 1).

Inhibition of ACE activity with lisinopril caused a significant shift of the baroreceptor reflex curve to lower blood pressures (Figures 3 and 4 and the P3 values in Tables 1 and 2). The greater activation of RSNA was associated with a significant increase in the maximum gain (−2.4±0.2 %/mm Hg, p<0.05 compared with vehi-

**TABLE 1. Parameters and Maximum Gain of Baroreceptor Reflex Control of Renal Sympathetic Nerve Activity in Conscious Spontaneously Hypertensive Rats**

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>CGP 42112A</th>
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<td>P2</td>
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<td>109±4*</td>
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<td><strong>Normalization to baseline RSNA</strong></td>
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<td>0.09±0.01*</td>
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<td>107±4*</td>
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<tr>
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<td>−6.0±0.5*</td>
<td>−7.4±0.5*</td>
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</table>

RSNA, renal sympathetic nerve activity; P1, range of RSNA; P2, slope coefficient; P3, mean arterial pressure at midrange; P4, minimum RSNA; Gmax, maximum gain.

*p<0.05 vs. vehicle.
†p<0.05 vs. lisinopril.
FIGURE 3. Top panel: Graph illustrates average logistic function curves expressing the relation between mean arterial pressure (MAP) and renal sympathetic nerve activity (RSNA) in spontaneously hypertensive rats (SHRs). Solid circles show baseline values. Bottom panel: Graph demonstrates gain for the baroreceptor reflex obtained from the first derivative of the logistic function. Losartan and lisinopril improved baroreceptor reflex function of SHRs, because these agents shifted the function curves to lower prevailing blood pressures and significantly increased maximum gain.

FIGURE 4. Top panel: Graph illustrates average logistic function curves expressing the relation between mean arterial pressure (MAP) and heart rate (HR). Solid circles show baseline values. Bottom panel: Graph demonstrates gain for baroreceptor reflex function obtained from the first derivative of the logistic function.

Discussion
The present study demonstrates that blockade of AT₁ receptors increased the maximum gain of the arterial baroreceptor reflex control of RSNA and HR in con-
TABLE 2. Parameters and Maximum Gain of Baroreceptor Reflex Control of Heart Rate in Conscious Spontaneously Hypertensive Rats

<table>
<thead>
<tr>
<th></th>
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<th>Losartan</th>
<th>Lisinopril</th>
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<tr>
<td>$P_1$</td>
<td>162±15</td>
<td>202±17</td>
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<tr>
<td>$P_2$</td>
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<td>0.04±0.01</td>
<td>0.06±0.01*</td>
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<td>$P_3$</td>
<td>144±6</td>
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<td>113±7*</td>
<td>115±3*</td>
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<td>$P_4$</td>
<td>309±13</td>
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<td>294±12</td>
</tr>
<tr>
<td>$G_{max}$</td>
<td>-1.9±0.3</td>
<td>-2.0±0.4</td>
<td>-2.6±0.3*</td>
<td>-3.1±0.2*</td>
</tr>
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$p$, range of heart rate; $P_2$, slope coefficient; $P_3$, mean arterial pressure at midrange; $P_4$, minimum heart rate; $G_{max}$, maximum gain.

*<0.05 vs. vehicle.

In accordance with previous studies, these observations confirm the premise that endogenous NO is linked to the antihypertensive actions of ACE inhibitors and AT$_1$ receptor antagonists. By itself, NO appears to reduce the maximum gain of the baroreceptor reflex function. Much interest has been focused on the effects of endogenous Ang II on the sympathetic nervous system and the baroreceptor reflex. Studies from our laboratory showed that Ang II stimulates sympathetic outflow and modulates the baroreceptor reflex control of peripheral sympathetic nerve activity.12 Kumagai et al17 found that captopril improved the baroreceptor reflex regulation of RSNA in conscious Ang II–dependent hypertensive rabbits. They showed that the Ang II receptor antagonist [Sar$^1$.Ala$^2$]Ang II infused into a vertebral artery increased the maximum gain of baroreceptor reflex control of RSNA and HR in conscious Ang II–dependent hypertensive rabbits. However, the increased sensitivity of the baroreceptor reflex control of RSNA was smaller than that produced by ACE inhibition, even though both agents reduced MAP by equivalent amounts. Our data also suggest that release of NO contributes in part to the antihypertensive action of either losartan or lisinopril.

![Mean Arterial Pressure](image1)

**Figure 5.** Line graphs show effect of initial intravenous injection (first arrow) of nitric oxide synthase inhibitor N$^\text{W}$-monomethyl L-arginine (LNMMA) followed 20 minutes later by injection of either losartan or lisinopril (second arrow) on average time courses of mean arterial pressure, heart rate, and integrated renal sympathetic nerve activity in conscious spontaneously hypertensive rats. Both losartan and lisinopril brought blood pressure and heart rate back to levels that prevailed before nitric oxide synthase inhibition. In contrast, losartan and lisinopril significantly enhanced renal sympathetic nerve activity. Values are mean±SEM.

![Mean Arterial Pressure](image2)

**Figure 6.** Top panel: Graph illustrates average logistic function curves expressing the relation between mean arterial pressure (MAP) and renal sympathetic nerve activity (RSNA) in conscious spontaneously hypertensive rats treated with vehicle, nitric oxide synthase inhibitor (LNMMA), LNMMA plus losartan, or LNMMA plus lisinopril. Solid circles are baseline values. Bottom panel: Graph shows gain for the baroreceptor reflex obtained from the first derivative of the logistic function. LNMMA shifted the baroreceptor reflex curve to the right and increased maximum gain of the baroreceptor reflex control of RSNA.
II–dependent hypertensive rabbits. We have recently demonstrated that the baroreceptor reflex control of RSNA and HR is blunted in conscious SHRs compared with age-matched Wistar-Kyoto rats. Moreover, in the latter study, long-term treatment with lisinopril substantially enhanced the maximum gain of the baroreceptor reflex in SHRs. In keeping with these observations, we now show that an AT₁ receptor antagonist caused a significant depressor effect and improved the baroreceptor reflex control of RSNA and HR in conscious adult SHRs. Our new studies determined that Ang II does not act through AT₂ receptors either to change the blood pressure or to modulate the baroreceptor reflex of SHRs. Therefore, our data suggest that the attenuation of the baroreceptor reflex control of RSNA and HR by endogenous Ang II is mediated by AT₁ receptors.

The present study showed that the maximum gain of the baroreceptor reflex induced by the AT₁ receptor antagonist was less than that obtained by an equipotent depressor dose of the ACE inhibitor. The enhancement exerted by the ACE inhibitor may be partly due to the aggregated effects of increased production of tissue prostaglandins, reduced metabolism of vasodilator kinins, or both. A recent study by Chen et al showed that prostaglandins potentiated the sensitivity of the carotid sinus baroreceptors, which may have contributed to the difference in the maximum gain of baroreceptor reflex between losartan and lisinopril.

Another issue that deserves attention are the factors that stimulate formation and/or release of NO and the role of this substance as a contributor to the difference in the baroreceptor reflex function between AT₁ receptor antagonist and ACE inhibitor. Vanhoutte et al demonstrated that bradykinin is involved in NO production by ACE inhibitors. Cachofeiro et al have shown that increased NO production may not be related solely to an increase in accumulated bradykinin after inhibition of ACE. They suggest that AT₁ blockade may increase tissue blood flow, thereby stimulating release of NO from the vascular endothelium. A third factor acting as a stimulus for NO formation in our experiments may be the increase in RSNA associated with the blood pressure reduction produced by losartan and lisinopril. On the basis of a recent study by Lacolley et al, we suggest that an increase in sympathetic nerve activity may act as a stimulus for NO formation. Therefore, several factors may contribute to increase NO release.

After L-NMMA injection, the antihypertensive effect of losartan or lisinopril was attenuated compared with that obtained without L-NMMA. These results suggest that the depressor effects of these drugs are in part attributable to the action of NO. Moreover, our study demonstrated that the proportion of the increase in RSNA relative to the decrease in MAP induced by losartan or lisinopril was significantly increased in the

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**TABLE 3. Parameters and Maximum Gain of Baroreceptor Reflex Control of Renal Sympathetic Nerve Activity With Nitric Oxide Synthase Inhibitor**

<table>
<thead>
<tr>
<th>Normalization to maximum RSNA</th>
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L-NMMA, N°-monomethyl l-arginine; RSNA, renal sympathetic nerve activity; P₁, range of RSNA; P₂, slope coefficient; P₃, mean arterial pressure at midrange; P₄, minimum RSNA; Gₘₕₐₓ, maximum gain.

*p<0.05 vs. vehicle.
†p<0.05 vs. L-NMMA alone.
presence of L-NMMA. These data suggest that endogenous NO suppressed RSNA in conscious SHRs. 

It has been reported that the maximum gain of the baroreceptor reflex control of RSNA is diminished in normotensive rabbits given a prolonged infusion of phenylephrine. In contrast, we showed that L-NMMA caused a significant pressor effect that was associated with an enhanced gain of the baroreceptor reflex control of RSNA in conscious SHRs. These data suggest that endogenous NO may reduce the maximum gain of the baroreceptor reflex in SHRs. We did not identify the site at which NO modulates RSNA. Recent studies by Lewis et al. suggest that the central nervous system may be a site of action for NO. They showed that microinjection of S-nitrosocysteine into the nucleus tractus solitarius decreased MAP and HR through activation of soluble guanylate cyclase.

The experiments involving the combined effects of L-NMMA and losartan or L-NMMA and lisinopril illustrate the dichotomy that may exist regarding the baroreceptor reflex control of sympathetic nerve activity and HR. Figure 5 shows that administration of either losartan or lisinopril in the presence of L-NMMA reduced the blood pressure back to the initial hypertensive level that existed before L-NMMA injection. Under this condition, RSNA was significantly increased above initial baseline levels, whereas HR returned to the initial level observed in the absence of these agents. Thus, it appears that the mechanisms responsible for the baroreceptor reflex control of HR differ from those engaged in the regulation of RSNA. Because the signal at arterial baroreceptors was the same, other factors along the baroreceptor reflex arc may account for the differential control of RSNA and HR. An altered signal at cardiopulmonary baroreceptors may contribute to the difference. Second, L-NMMA may modify end-organ effector mechanisms responsible for the control of HR. Finally, baroreceptor reflex regulation of HR is under the control of both the parasympathetic and sympathetic nervous systems. The observation that Ang II attenuates the parasympathetic nerve activity and ACE inhibition potentiates cardiac vagal nerve activity in humans suggests that both losartan and lisinopril potentiated parasympathetic nerve activity.

In summary, we confirmed that blockade of the renin-angiotensin system produced a substantial improvement of the baroreceptor reflex function in conscious SHRs through an AT1-dependent mechanism. Inhibition of NO production counteracted the effects of both losartan and lisinopril on baroreceptor reflex function.

Acknowledgment

We gratefully acknowledge the technical advice and equipment provided by Gould Inc., Cleveland, Ohio.

References


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L-NMMA, N⁵-monomethyl L-arginine; P1, range of heart rate; P2, slope coefficient; P3, mean arterial pressure at midrange; P4, minimum heart rate; G_max, maximum gain.

*p<0.05 vs. vehicle.

fp<0.05 vs. L-NMMA alone.
Role of nitric oxide and angiotensin II in the regulation of sympathetic nerve activity in spontaneously hypertensive rats.

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