Analysis of Pulmonary Vascular Responses in Cats to Sympathetic Nerve Stimulation Under Elevated Tone Conditions

Evidence That Neuronally Released Norepinephrine Acts on \( \alpha_1^- \), \( \alpha_2^- \), and \( \beta_2^- \)-Adrenoceptors

Albert L. Hyman, Howard L. Lippton, and Philip J. Kadowitz

The influence of an increase in vascular tone on responses to sympathetic nerve stimulation and the receptors mediating these responses were investigated in the pulmonary vascular bed of the cat. Under conditions of controlled blood flow and constant left atrial pressure, stimulation of the sympathetic nerves to the lung elicited a biphasic response characterized by an initial increase in lobar arterial pressure followed closely by a decrease. The response to nerve stimulation was reproducible with respect to time and was not altered when a delay coil was added to the perfusion circuit, indicating that the response was directly mediated. The increase in pressure was reduced by prazosin and by yohimbine, whereas the decrease in pressure was blocked by propranolol or ICI 118551. These data suggest that the pressor component of the response is mediated by \( \alpha^- \) and postjunctional \( \alpha^- \)-adrenoceptors, whereas the depressor response is mediated by \( \beta^- \)-receptors. The pressor response was enhanced by propranolol or ICI 118551, whereas the depressor response was enhanced by prazosin or yohimbine, suggesting that the response to nerve stimulation represents the net effect of the actions of neuronally released norepinephrine on \( \alpha^- \) and \( \beta^- \)-receptors. The pressor response to nerve stimulation was enhanced when tone was elevated with a prostaglandin endoperoxide analogue and when \( \beta^- \)-receptors were blocked. The effects of an increase in tone and a passive increase in pressure on responses to sympathetic nerve stimulation were different. When lobar arterial pressure was raised by obstructing lobar venous outflow, the pressor component was attenuated, and a depressor response could not be elicited. The present data suggest that neuronally released norepinephrine can act on \( \alpha^- \), \( \alpha^- \), and \( \beta^- \)-adrenoceptors and that the response to sympathetic nerve stimulation represents the summation of the effects of the adrenergic transmitter on \( \alpha^- \), postjunctional \( \alpha^- \), and \( \beta^- \)-adrenoceptors. (Circulation Research 1990;67:862–870)

The presence of adrenergic vasomotor nerves and the influence of adrenergic stimulation on the pulmonary vascular bed has been demonstrated in various species. The pulmonary vascular bed of the cat and the dog has \( \alpha^- \) and postjunctional \( \alpha^- \)-adrenoceptors mediating vasoconstriction, whereas only postjunctional \( \alpha^- \)-receptors have been identified in isolated rabbit pulmonary artery. The pulmonary vascular bed also possesses \( \beta^- \)-receptors and muscarinic receptors mediating vasodilation. Adrenergic nerve stimulation increases pulmonary vascular resistance, and when tone is elevated and \( \alpha^- \)-receptors are blocked, nerve stimulation elicits a vasodilator response. Although previous studies provide evidence in support of the hypothesis that neuronally released norepinephrine can act upon \( \beta^- \)-adrenoceptors, the vasodilator response was observed after treatment with phentolamine or phenoxybenzamine, agents that block \( \alpha^- \) and \( \alpha^- \)-adrenoceptors, and this latter effect could enhance the amount of transmitter released. The release of a larger quantity of transmitter could account for the effect of neuronally released norepinephrine on \( \beta^- \)-receptors, which are believed to be extrajunctional in location. To determine if neuronally released norepinephrine can act on \( \beta^- \)-receptors in the absence of autoreceptor (\( \alpha^- \)-presynaptic) blockade, responses to sympathetic

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nerve stimulation were investigated in the cat under conditions of elevated tone. In addition, the α-adrenoceptor subtypes mediating responses to neuronally released norepinephrine were investigated. The results of these studies under elevated tone conditions demonstrate that sympathetic stimulation elicits a biphasic response and suggest that the pressor component of the response is mediated by α<sub>1</sub>- and postjunctional α<sub>2</sub>-adrenoceptors, whereas the vasodilator component is mediated by β<sub>2</sub>-receptors. These data suggest that the response to sympathetic stimulation represents the net effect of the actions of the adrenergic transmitter on α<sub>1</sub>- , postjunctional α<sub>2</sub>- , and β<sub>2</sub>-adrenoceptors and support the concept that these three receptors are located close to adrenergic terminals in the feline pulmonary vascular bed.

**Materials and Methods**

Seventy-three adult cats of either sex weighing 2.1–4.3 kg were sedated with ketamine hydrochloride (10–15 mg/kg i.m.) and were anesthetized with pentobarbital sodium (30 mg/kg i.v.). The cats were strapped in the supine position to a fluoroscopic table (Philips Electronics, Eindhoven, The Netherlands), and supplemental doses of anesthetic were administered as needed to maintain a uniform level of anesthesia. The trachea was intubated with auffed pediatric endotracheal tube, and the cats were ventilated with a respirator (model 613, Harvard Apparatus, South Natick, Mass.) at a tidal volume of 40–75 ml and a rate of 16–24 cycles/min. Systemic arterial pressure was measured from a catheter introduced from a femoral artery into the aorta, and intravenous injections were made into the inferior vena cava through a catheter introduced from a femoral vein.

For perfusion of the left lower lung lobe, a specially designed 6F triple-lumen balloon perfusion catheter was passed under fluoroscopic guidance from the left external jugular vein into the artery to the left lower lobe. After the cats were anticoagulated with heparin sodium (1,000 units/kg i.v.), the lobar artery was isolated by distension of the balloon cuff on the perfusion catheter. The lung lobe was then perfused by way of the catheter lumen distal to the cuff with blood withdrawn from a femoral artery with a peristaltic perfusion pump (model 1210, Harvard Apparatus). To determine if circulating catecholamines play a role in the response to nerve stimulation, a delay coil was imposed in the perfusion circuit. The delay time was 30–40 seconds under control conditions and 100–120 seconds when the delay coil was used. The perfusion rate was adjusted so that lobar arterial perfusion pressure approximated mean pressure in the main pulmonary artery and thereafter was not changed during an experiment. The pumping rate averaged 44 ml/min, and left atrial pressure was measured with a 5F double-lumen catheter passed transeptally into the vein draining the lobe. The catheter tip was positioned so that the left atrial pressure port on the tip of the distal lumen was 1–2 cm into the lobar vein and the second catheter port was near the venaatrial junction. When necessary, blood could be withdrawn or infused through this second catheter lumen to maintain constant left atrial pressure. Left atrial pressure was maintained at constant values between 2 and 5 mm Hg, and during an intervention, pressure was not permitted to change. All vascular pressures were measured with Statham P23Db or 1D transducers (Oxnard, Calif.) zeroed at right atrial level. Mean pressures obtained by electronic averaging were recorded on an Electronics for Medicine DR12 (White Plains, N.Y.) or Grass model 7 (Quincy, Mass.) recorder.

For stimulation of the sympathetic nerves, the chest was opened in the third intercostal space, a shielded Palmer electrode (Harvard Apparatus) was placed around the left stellate ganglia, and proximal nerve fibers were ligated. The nerve plexus was stimulated with square-wave pulses 2 msec in duration at stimulus frequencies of 3, 10, and 30 Hz with a Grass model SD9 stimulator for 20–30-second periods at 10–14 V. The stimulations were randomized, and sufficient time (usually 5–10 minutes) was permitted between stimulations for vascular pressures to return to baseline value. Blood gases and pH were measured with a microanalyzer (model 13 or 713, Instrumentation Laboratory, Lexington, Mass.). The α<sub>1</sub>- and α<sub>2</sub>-adrenoceptor blocking agents used in these studies were prazosin (Pfizer Laboratories, New York) and yohimbine (Sigma Chemical Co., St. Louis).<sup>9,10,17,18</sup> DL-Propranolol (Ayerst Laboratories, New York) and ICI 118551 (Imperial Chemical Industries, Cheshire, England) were used as nonselective β- and selective β<sub>2</sub>-adrenoceptor antagonists.<sup>19</sup> The doses of prazosin, yohimbine, ICI 118551, and propranolol used in the present study have been shown to be selective and efficacious in the feline pulmonary vascular bed.<sup>9,10,20</sup> Yohimbine and propranolol were dissolved in 0.9% saline, whereas prazosin and ICI 118551 were dissolved in warm distilled water using a sonicator. Norepinephrine (Sigma) was dissolved in 0.9% saline, and all solutions were prepared daily. The antagonists were administered intravenously, and norepinephrine was injected in small volumes into the lobar arterial perfusion circuit. Lobar arterial pressure was raised from baseline value to a high steady level by intralobar infusion of the prostaglandin endoperoxide analogue (15)hydroxy 11α,9α-epoxymethano prostaglandin F<sub>2</sub> and 13E dienoic acid (U46619, The Upjohn Company, Kalamazoo, Mich.) at 40–250 ng/min. In three cats, lobar arterial pressure was raised with serotonin creatinine sulfate (Sigma) (1–10 μg/min), and in three other cats, lobar arterial pressure rose to a high steady level spontaneously. In seven cats in which the effects of a passive increase in lobar arterial pressure were investigated, lobar arterial pressure was elevated by obstructing lobar venous outflow by distending a balloon cuff on the catheter positioned in the lobar vein. In these experiments, pressure upstream
from the balloon was measured through the catheter port distal to the balloon cuff. All hemodynamic values represent peak changes and are represented in absolute units as millimeters of mercury (mean ± SEM). Changes in lobar arterial pressure were analyzed by the methods of Snedecor and Cochran for paired or group comparison or by a one-way analysis of variance and Tukey's test.

Results

Influence of Nerve Stimulation

The response to sympathetic nerve stimulation under elevated tone conditions is illustrated in Figure 1. When lobar arterial pressure was increased to a high steady level by intralobar infusion of U46619, stimulation of the sympathetic nerves to the lung at 30 Hz for a 20-second period elicited a biphasic response characterized by an initial increase in lobar arterial pressure that was closely followed by a secondary decrease in pressure. The response to nerve stimulation was reproducible, and similar responses were elicited each time the nerves were stimulated.

Table 1. Changes in Lobar Arterial Pressure in Cats in Response to Sympathetic Nerve Stimulation During Three Trials of Nerve Stimulation When Tone Was Raised With U46619

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Biphasic response</th>
<th>Change in lobar arterial pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10 Hz</td>
</tr>
<tr>
<td>1</td>
<td>Initial</td>
<td>4.8±0.3*</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>-3.2±0.2</td>
</tr>
<tr>
<td>2</td>
<td>Initial</td>
<td>4.4±0.2*</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>-3.4±0.2</td>
</tr>
<tr>
<td>3</td>
<td>Initial</td>
<td>4.6±0.2*</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>-3.4±0.2</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. n=5 cats. Responses were not significantly different from each other at either 10 Hz or at 30 Hz. *Significantly different from secondary response.

Table 2. Comparison of Time to Peak Increase and Peak Decrease in Lobar Arterial Pressure at 30 Hz With Normal and Long Circuit Delays Under Elevated Tone Conditions

<table>
<thead>
<tr>
<th>Time to peak (sec)</th>
<th>Increase in pressure</th>
<th>Decrease in pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal circuit delay (n=6)</td>
<td>9±1</td>
<td>39±2</td>
</tr>
<tr>
<td>Long circuit delay (n=5)</td>
<td>9±1</td>
<td>37±5</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Tone was increased by infusion of U46619. Time to peak represents time (latency) from onset of stimulation at 30 Hz to peak change in lobar arterial pressure.

(Figure 1 and Table 1). To determine if circulating factors had a role in the mediation of the vasodilator component of the response to sympathetic nerve stimulation, a delay coil was added to the perfusion circuit. In five experiments in which the 100–120-second delay coil was employed, the time of appearance and the shape of the vasodilator component of the response were not different from that observed in the nine series of experiments using the standard perfusion circuit with a 30–40-second delay. The time to the peak increase and to the peak decrease in lobar arterial pressure in response to sympathetic nerve stimulation at 30 Hz is shown in Table 2. Both pressor and depressor components of the response were related to stimulus frequency at 3, 10, and 30 Hz, and after administration of propranolol (2 mg/kg i.v.) or ICI 118551 (1 mg/kg i.v.), the pressor component of the response to nerve stimulation was significantly increased, whereas the depressor component was blocked (Figure 2, middle and right panels). However, in other cats, when lobar arterial pressure was raised to a similar high level by obstructing lobar venous outflow, responses to sympathetic nerve stimulation were blocked (Figure 3). Balloon inflation raised lobar venous and arterial pressures without significantly changing aortic pressure. When lobar arterial pressure was passively increased to a mean value of 38 mm Hg, both pressor and depressor...
components of responses to sympathetic nerve stimulation were reduced markedly \((p<0.05, \text{ when compared with responses observed during infusion of U46619})\). After the balloon in the lobar vein was collapsed and lobar arterial pressure was again raised to a value not significantly different from the level attained during the initial U46619 infusion, responses to sympathetic stimulation were not different from those recorded when tone was first raised with U46619 (Figure 3).

**Effect of Prazosin and Yohimbine**

To determine which \(\alpha\)-adrenoceptor subtype is activated by norepinephrine released by electrical stimulation of the sympathetic nerves under elevated tone conditions, the effects of prazosin and of yohimbine were investigated. After administration of prazosin (0.1 mg/kg i.v.), the increases in lobar arterial pressure in response to nerve stimulation under elevated tone conditions were significantly decreased, and the depressor component of the response to nerve stimulation was significantly increased (Figure 4). In another series of cats, the administration of yohimbine (0.5 mg/kg i.v.) also significantly decreased the pressor component of the response to sympathetic nerve stimulation under elevated tone conditions and significantly increased the depressor component of the response (Figure 5).

**Effect of Propranolol or ICI 118551 Pretreatment**

Since an interaction between \(\alpha\)- and \(\beta\)-adrenoceptors has been observed in the feline pulmonary vascular bed,\(^9\) the effects of prazosin and yohimbine were investigated in six cats pretreated with propranolol (2 mg/kg i.v.) and four pretreated with ICI 118551 (1 mg/kg i.v.). In cats pretreated with \(\beta\)-adrenoceptor antagonists, prazosin (0.1 mg/kg i.v.) significantly reduced the increase in lobar arterial pressure in response to nerve stimulation at 3, 10, and 30 Hz (Figure 6). This dose of prazosin has been shown to be highly selective for \(\alpha_2\)-adrenoceptor–mediated responses in the pulmonary vascular bed of the cat.\(^9,10\) The subsequent administration of yohimbine (0.5 mg/kg i.v.) to these same cats resulted in a significantly greater \((p<0.05)\) reduction in the response to nerve stimulation than observed after treatment with prazosin alone (Figure 6). This dose of yohimbine has been shown to be highly selective for \(\alpha_2\)-adrenoceptor–mediated responses in the feline pulmonary vascular bed.\(^9,10\) In other experiments, when the order of administration of prazosin and yohimbine was reversed and yohimbine was administered first in the dose of 0.5 mg/kg i.v. in four other cats pretreated with propranolol and six pretreated with ICI 118551, the increase in lobar arterial pressure in response to nerve stimulation at 3–30 Hz was significantly reduced (Figure 7). The subsequent administration of prazosin (0.1 mg/kg i.v.) in six of these cats caused a significantly
greater \((p<0.05)\) reduction in the response to nerve stimulation than observed after administration of yohimbine alone (Figure 7). Since yohimbine can act on both prejunctural and postjunctural \(\alpha_2\)-adrenoceptors to modify the response to sympathetic nerve stimulation, experiments were carried out to determine the site of action of the \(\alpha_2\)-adrenoceptor antagonist, and these data are summarized in Figure 8. In these experiments, the effects of yohimbine on responses to sympathetic nerve stimulation and to norepinephrine were compared under elevated tone conditions in cats treated with ICI 118551 (1 mg/kg i.v.). Yohimbine (0.5 mg/kg i.v.) reduced responses to nerve stimulation at 3, 10, and 30 Hz to 53±6%, 64±5%, and 75±7% of control, respectively, and to the 1- and 3-\(\mu\)g doses of norepinephrine to 53±6% and 66±8% of control, respectively. The subsequent administration of prazosin (0.1 mg/kg i.v.) to these same cats further reduced responses to nerve stimulation to 9±3%, 12±3%, and 16±4% of control at the three stimulus frequencies. Responses to the two doses of norepinephrine were reduced to 8±3% and 11±4% of control. The percent reductions in response to nerve stimulation at 10 and 30 Hz and to the 1- and 3-\(\mu\)g doses of norepinephrine were not significantly different from each other (10 Hz nerve stimulation versus 1 \(\mu\)g norepinephrine and 30 Hz nerve stimulation versus 3 \(\mu\)g norepinephrine) after treatment with yohimbine and after treatment with yohimbine and prazosin. The responses to nerve stimulation at 10 and 30 Hz and to norepinephrine at 1 and 3 \(\mu\)g were closely matched in the control period (Figure 8, left panel).

Effects of Tone on Responses to Nerve Stimulation in \(\beta\)-Blocked Animals

The effect of an increase in tone on the pressor component of the response to nerve stimulation was investigated in the pulmonary vascular bed. When lobar arterial pressure was raised from a resting value to a high level by infusion of U46619 in cats pretreated with propranolol (2 mg/kg i.v.), the response to sympathetic nerve stimulation was enhanced (Figure 9). The effects of an elevation in tone on the response to sympathetic nerve stimulation in three cats in which tone was elevated by infusion of serotonin in and in three cats in which tone increased spontaneously were also investigated. The data from these six experiments in the \(\beta\)-blocked cats were combined and are summarized in Figure 10. Four of the cats were treated with propranolol (2 mg/kg i.v.), and two were treated with ICI 118551 (1 mg/kg i.v.). When lobar arterial pressure increased from 19±1 to 36±2 mm Hg in these cats, the pressor response to sympathetic nerve stimulation was significantly increased at 3, 10, and 30 Hz (Figure 10).
circulating catecholamines do not contribute to the response. These results indicate that the transmitter released by adrenergic nerve stimulation elicits both vasoconstriction and vasodilation in the feline pulmonary vascular bed. The pressor component of the response is in agreement with previous studies and supports the concept that sympathetic stimulation increases pulmonary vascular resistance, although the magnitude of the pressor response may be limited by the number of α-adrenoceptors in small pulmonary arteries. The observation that the depressor component is blocked by β-adrenoceptor antagonists is consistent with the hypothesis that the adrenergic transmitter can act on vascular β-receptors. The present data extend previous work in which responses to nerve stimulation were reversed when α-receptors were blocked and tone was elevated. However, in the previous study, phenoxybenzamine and phentolamine were used, and these antagonists block both α₁- and α₂-adrenoceptors. The blockade of the prejunctional α₂-autoreceptor enhances the output of transmitter, and this could, in part, account for the effects of nerve-released norepinephrine on β-receptors, which are believed to be extrajunctional in location. However, in the present study, vasodilation in response to sympathetic nerve stimulation could be demonstrated under elevated tone conditions without the use of α-adrenoceptor antagonists. In addition, the observation that the initial pressor component of the response is enhanced after β-blockade provides support for the hypothesis that neuronally released norepinephrine acts on α- and β-adrenoceptors and that the response to sympathetic nerve stimulation represents the net effect of the actions of the transmitter on both types of receptors.

The pressor component of the response to nerve stimulation was reduced, and the depressor component was enhanced after treatment with prazosin, an α₁-adrenoceptor blocking agent. The pressor component was also decreased, and the depressor component was enhanced after administration of yohimbine, an α₂-adrenoceptor antagonist. These data are consistent with the concept that the pressor component of the response is mediated by α₁- and postjunctional α₂-adrenoceptors. In addition, the experiments with prazosin and yohimbine provide support for the concept that the response to sympathetic nerve stimulation under elevated tone conditions represents the summation of the actions of the transmitter on α₁, α₂, and β-adrenoceptors in the feline pulmonary vascular bed. These data suggest that both α-adrenoceptor subtypes and β-receptors are located close to adrenergic terminals in resistance vessels of the feline lung. Moreover, when lobar arterial pressure was increased by obstructing lobar venous outflow, the pressor component of the response was attenuated, and a depressor response could not be elicited. The reduction in the pressor component of the response may be a consequence of passive distension of upstream vessels, whereas the absence of a significant depressor
response indicates that an increase in tone (an active process) is required for the demonstration of a vasodilator response.

An interaction between α- and β-adrenoceptors has been documented in peripheral and pulmonary vascular beds. Although this interaction was not apparent under elevated tone conditions in the feline pulmonary vascular bed, it can be prevented by β-adrenoceptor antagonists, and analysis of response patterns is less complicated when the vasodilator component is blocked with propranolol or ICI 118551. When β-adrenoceptors are blocked, the vasoconstrictor response to sympathetic nerve stimulation is reduced by both prazosin and yohimbine. These data provide additional support for the hypothesis that the vasoconstrictor response to neuronally released norepinephrine is mediated by both α1- and postjunctional α2-adrenoceptors. However, yohimbine can act on prejunctional and on postjunctional α2-receptors to modify the response to sympathetic nerve stimulation. Since the response to injected norepinephrine is not regulated by the prejunctional α2-autoreceptor, the effects of the antagonist on responses to nerve stimulation and exogenous norepinephrine were compared. The results of these experiments indicate that responses to nerve-released and exogenous norepinephrine are reduced to the same extent at elevated vascular tone and suggest that the effects of yohimbine are for the most part postjunctional in nature. The observation that prazosin and yohimbine were equally effective in decreasing the response to sympathetic nerve stimulation supports the hypothesis that neuronally released norepinephrine can act on both α1- and postjunctional α2-adrenoceptors in the feline lung. These data are different from studies in the peripheral vascular bed in which the response to sympathetic nerve stimulation results mainly from activation of α1-receptors. The present data, suggesting that α1-, α2-, and β-receptors are located close to the adrenergic terminal, may indicate that the localization of these receptors is different in resistance vessels of the pulmonary and systemic vascular beds.

The concept that responses to vasoactive agents can be modified when tone is elevated in the pulmonary vascular bed was first introduced in 1959. An increase in tone has been shown to reverse pressor responses to other agents, to enhance the depressor response to isoproterenol. Our recent study has shown that, when tone is elevated and β-adrenoceptors are blocked, vasoconstrictor responses to norepinephrine are enhanced and that this effect is relatively selective since the response to angiotensin II was not altered. The results of the present study extend this previous work by demonstrating that vasoconstrictor responses to sympathetic nerve stimulation are enhanced when tone is elevated and β-receptors are blocked. Although the mechanism by which an increase in tone enhances the response to nerve stimulation is uncertain, this effect is not dependent on the intervention used to raise tone since similar effects were seen when tone was increased with U46619 or serotonin or when tone increased spontaneously. The effect of an increase in tone was similar when β-receptors were blocked with propranolol or with ICI 118551. It is unlikely that this effect is related to lobar arterial pressure alone, since a passive increase in pressure reduced the response to nerve stimulation. Although the mechanism of enhancement is uncertain, the site of action is most likely postjunctional, since responses to nerve released and exogenous norepinephrine are both increased. The increased responses to nerve stimulation and norepinephrine could result from an increase in α-receptor number or affinity or an increase in the number of α2-receptors relative to α1-receptors, since α2-mediated responses are greatly enhanced when tone is elevated. Alternatively, a change in transmembrane coupling between the α-receptor and a second messenger system could account for the effect. It is also possible that an elevation in tone increases the concentration of free intracellular calcium to the point at which the resistance vessels are on the steep portion of the calcium concentration-response curve. In this setting the vessels would now be more responsive to small increases in intracellular calcium concentration. Anatomical studies have shown that vasoconstriction alters the morphology of the smooth muscle cell membrane and that arterioles undergo complex shape changes. It is possible that changes in membrane morphology induced by vasoconstriction could play a role in the enhanced α-adrenoceptor-mediated responses observed in the present study.

With elevated tone and β-receptor blockade, the pressor component of the response to sympathetic nerve stimulation was enhanced, and the depressor component was blocked. This effect was observed with propranolol or ICI 118551. This effect on the pressor response to nerve stimulation was not observed in previous studies when β-receptors were blocked with propranolol. However, ICI 118551, the selective β-receptor antagonist, also enhanced the response to nerve stimulation under baseline tone conditions. The explanation for the different effects of propranolol and ICI 118551 on the response to nerve stimulation under baseline conditions is uncertain but may reflect an effect of propranolol that may be obscured when tone is elevated.

The concept that neuronally released norepinephrine can stimulate β-receptors in the pulmonary vascular bed is consistent with previous studies in the systemic vascular bed and in the isolated rabbit facial vein. However, the sympathetic neurogenic vasodilator response in the pulmonary circulation can be elicited in the absence of α-adrenoceptor blockade and, on a relative basis, is larger than observed in the systemic vascular bed. In contrast, other studies in the systemic vascular bed have not been able to identify β-adrenoceptor-mediated vasodilation in response to sympathetic nerve stimulation, and the
hypothesis that vascular $\beta_2$-adrenoceptors can be stimulated by neuronally released norepinephrine has been questioned.\textsuperscript{15,16,40} Previous studies have been challenged on the basis that the $\alpha$-adrenoceptor blocking agents used to unmask the vasodilator response to sympathetic nerve stimulation may have concurrently blocked prejunctional $\alpha_2$-receptors and enhanced release of norepinephrine.\textsuperscript{15} However, in the present study under elevated tone conditions, a significant vasodilator component of the response to nerve stimulation could be elicited without using $\alpha$-adrenoceptor blocking agents. This observation provides strong support for the concept that vascular $\beta_2$-adrenoceptors are innervated in the lung.

In conclusion, results of the present study support the concept that the feline pulmonary vascular bed is functionally innervated by the sympathetic nervous system and that under elevated tone conditions neuronally released norepinephrine elicits vasodilatation by stimulating $\alpha_2$- and $\alpha_2$-adrenoceptors and vasodilation by stimulating $\beta_2$-receptors.

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References


KEY WORDS: pulmonary vascular bed • elevated tone • α-adrenoceptors • β-adrenoceptors
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