Pulmonary Vasodilator Responses to Catecholamines and Sympathetic Nerve Stimulation in the Cat

Evidence That Vascular \( \beta-2 \) Adrenoreceptors Are Innervated

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SUMMARY We investigated the effects of catecholamines and sympathetic nerve stimulation in the feline pulmonary vascular bed under conditions of controlled pulmonary blood flow. Norepinephrine and nerve stimulation caused dose- and stimulus frequency-dependent increases in pulmonary vascular resistance. However, when pulmonary vascular tone was enhanced and \( \alpha \) receptors blocked, norepinephrine and nerve stimulation caused dose- and frequency-dependent decreases in pulmonary vascular resistance. The decreases in pulmonary vascular resistance were blocked with propranolol and were of greater magnitude than were constrictor responses observed under basal conditions. Vasodilator responses to nerve stimulation were not modified by atropine. Epinephrine and isoproterenol had marked vasodilator activity in the pulmonary vascular bed when pulmonary vascular tone was elevated. When \( \alpha \) receptors were blocked, isoproterenol and epinephrine had similar vasodilator activity, and when \( \beta \) receptors were blocked, epinephrine and norepinephrine had marked vasoconstrictor activity. Selective \( \beta-1 \) receptor antagonists had little effect on vasodilator responses to isoproterenol, whereas responses to this substance were blocked by propranolol. These results suggest the presence of \( \alpha \)- and \( \beta-2 \) adrenoreceptors in the feline pulmonary vascular bed and that both types of adrenergic receptors are innervated by the sympathetic nervous system. Circ Res 48: 407-415, 1981

THE presence of adrenergic nerves in the pulmonary vascular bed has been documented and adrenergic nerve stimulation increases pulmonary vascular resistance (Verity and Bevan, 1968; Fillenz, 1970; Daly et al., 1970; Kadowitz and Hyman, 1973; Kadowitz et al., 1976). The increases in pulmonary vascular resistance in response to adrenergic nerve stimulation are blocked by \( \alpha \) receptor and neuronal blocking agents, suggesting that the response to nerve stimulation is the result of \( \alpha \) receptor activation by neuronally released norepinephrine (Kadowitz et al., 1973, 1975, 1976). Isoproterenol has been shown to decrease pulmonary vascular resistance, suggesting that \( \beta \) receptors are present in the pulmonary vascular bed (Silvone et al., 1968; Hyman, 1969; Porcelli and Bergofsky, 1973). Although \( \beta \) adrenergically mediated vasodilation can be elicited by administration of isoproterenol or epinephrine and norepinephrine when pulmonary vascular tone is elevated by hypoxia and acidemia, the actions of neuronally released norepinephrine on \( \beta \) receptors in the pulmonary circulation are uncertain (Silvone et al., 1968; Hyman, 1969; Porcelli and Bergofsky, 1973). It has been reported that sympathetic nerve stimulation elicits vasodilation in the skeletal muscle, liver, spleen, adipose tissue, and in isolated facial vein of the rabbit (Viveros et al., 1968; Greenway et al., 1968; Greenway and Lawson, 1969; Ngai et al., 1966; Pegram et al., 1976). However, the concepts that \( \beta \) adrenergic receptors in blood vessels are innervated and that neuronally released norepinephrine can elicit vasodilation by stimulating \( \beta-2 \) receptors have been challenged recently (Russell and Moran, 1980). The present study was undertaken to investigate the actions of catecholamines and the nature of adrenergic receptors in the feline pulmonary vascular bed. The results of these studies indicate that \( \alpha \) - and \( \beta-2 \) receptors are present in the feline pulmonary vascular bed and that neuronally released norepinephrine can act on both types of receptors, but that vasodilator responses are dependent on the existing level of tone in the pulmonary vascular bed.

Methods

For studies on the actions of catecholamines and sympathetic nerve stimulation on the feline pulmonary vascular bed, 156 adult cats of either sex weighing 2.2-3.8 kg were anesthetized with pento-
barbital sodium, 35 mg/kg iv, and were strapped in the supine position to a Phillips fluoroscopic table. Supplemental doses of pentobarbital were given as needed to maintain a uniform level of anesthesia. The trachea was intubated with auffed pediatric endotrachial tube, and in all experiments except those in which the sympathetic nerves were stimulated the animals spontaneously breathed room air or room air enriched with 100% O2. In experiments in which the sympathetic nerves were stimulated, the animals were ventilated with a Harvard model 613 respirator at a rate of 12-18 breaths/min and a volume of 50-70 ml/breath. Systemic arterial pressure was measured from a catheter in the femoral artery, and systemic injections of drugs were made through a catheter in the femoral vein.

For perfusion of the left lower lobe, a specially designed 6F triple lumen balloon perfusion catheter was passed under fluoroscopic guidance from an external jugular vein into the arterial branch to that lobe. After the animals had been heparinized, 1000 units/kg, iv, and the lobar artery was isolated by distention of the balloon cuff on the catheter, the lobe was perfused by way of the catheter lumen immediately beyond the balloon cuff. The lobe was perfused with blood withdrawn from the femoral artery or vein, and no systematic difference in response to the catecholamines was observed when the lobe was perfused with femoral arterial or venous blood. The lobe was perfused by means of a Harvard model 1210 peristaltic pump, and the perfusion rate was adjusted so that lobar arterial perfusion pressure approximated mean pressure in the main pulmonary artery and was therefore not changed during an experiment. Flow rates to the lobe averaged 46 ± 0.4 ml/min. These procedures have been described recently (Hyman and Kadowitz, 1979). Left atrial pressure was measured by means of a specially designed 5 or 6F double lumen catheter placed transectally into the lobar vein draining the left lower lobe. The catheter tip was positioned in the vein so that the pressure port at the distal lumen was approximately 1 cm into the lobar vein and the second catheter port was at the veno-atrial junction. When necessary, blood could be withdrawn or infused through this second catheter lumen to maintain left atrial pressure constant during an experiment. In these experiments, left atrial pressure was maintained constant and, in various experiments, ranged between 2.5 and 4.5 mm Hg. All vascular pressures were measured with Statham P23Db transducers zeroed at right atrial level, and mean pressures obtained by electronic averaging were recorded on an Electronics for Medicine recorder model DR-12. In these experiments, responses to the catecholamines and sympathetic nerve stimulation were investigated when lobar vascular resistance was at resting levels and when lobar resistance was elevated by infusions of the prostaglandin endoperoxide analog (15S)hydroxyl-11a,9a(epoxymethano) prosta-SZ,15E dienoic acid or 15-methyl PGF2α (Upjohn). The endoperoxide analog or 15-methyl PGF2α was dissolved in 100% ethanol at a concentration of 5 mg/ml and working solutions were prepared frequently. These substances were infused into the lobar artery with a variable speed Harvard infusion pump model 945 at rates which increased lobar arterial pressure by approximately 100% and were 30-120 ng/min for the endoperoxide analog and 130-360 ng/min for 15-methyl PGF2α. The increases in lobar arterial pressure during infusion of the endoperoxide analog or 15-methyl PGF2α were well maintained, and lobar arterial pressure returned to control value 5-10 minutes after infusions were terminated.

The adrenergic blocking agents used in these studies were phentolamine, Regitine, metoprolol, Lopressor (CIBA-GEIGY), phenoxybenzamine (Dibenzyline, Smith, Kline and French), propranolol (Ayerst, Sigma), sotalol (Mead Johnson), and practolol (Ayerst). Atropine (Sigma) was used to block muscarinic receptors, and cocaine (Mallinckrodt) was employed to block uptake of norepinephrine and tyramine. All blocking agents with the exception of phenoxybenzamine were dissolved in 0.9% NaCl solution and were injected slowly over a 2- to 5-minute period into the femoral vein. Phenoxybenzamine was dissolved in a vehicle of ethanol, 10%; propylene glycol, 40%; and 0.9% NaCl 50% at a concentration of 10 mg/ml and was injected into the peripheral vein over a 5-minute period. Under basal conditions, the α blocking agents produced only small 1-2 mm Hg decreases in lobar arterial pressure, whereas propranolol increased lobar arterial pressure by 1-4 mm Hg. Practolol, sotalol, and metoprolol had small, inconsistent effects on lobar arterial pressure.

Drugs used in the study were norepinephrine, L-norepinephrine, epinephrine, L-epinephrine, isoproterenol, L-isoproterenol, tyramine, and phenylephrine (all from Sigma), nitroglycerin (Parke Davis), and angiotensin II amide (CIBA-GEIGY). These substances were dissolved in 0.9% NaCl and solutions were prepared on a frequent basis and stored in a freezer. Prostaglandins (PG) E1 and F2α (Upjohn) were dissolved in 100% ethanol and stored in a freezer. On the day of use, working solutions were prepared in 0.9% NaCl. These agonists were either infused with a Harvard infusion pump model 945 or injected into the perfused lobar artery. For stimulation of the sympathetic nerves, the thorax was opened in the third interspace and a shielded Palmer electrode was placed around the left stellate ganglia. The nerve was stimulated with square wave pulses 2 msec in duration at stimulus frequencies of 3, 10, and 30 cycles/sec with a Grass model SD9 stimulator for 15- to 30-second periods.

Blood gases and pH were measured with an Instrumentation Laboratory model micro 13 blood gas analyzer. Arterial PaO2, PaCO2, and pH averaged 89 ± 2, 41 ± 3, mm Hg and 7.38 ± 0.02 in the control period and were maintained in the physiological
range. When necessary, acidosis was corrected by infusion of sodium bicarbonate solution. All hemodynamic data represent peak changes and are expressed in absolute values as mean ± SE. The data were analyzed by the methods of Snedecor and Cochran (1967) for paired and group comparison. A P value of less than 0.05 was used as the criterion for statistical significance.

Results

The effects of norepinephrine infusions and adrenergic receptor blocking agents were investigated under basal conditions and when pulmonary vascular tone had been elevated by infusion of a prostaglandin endoperoxide analog or 15-methyl PGF$_{2\alpha}$. Under resting conditions, intralobar infusions of norepinephrine at rates of 0.5, 1, 2, and 10 μg/kg per min increased lobar arterial pressure in a dose-dependent fashion while lobar venous outflow pressure was maintained constant (Fig. 1). In 11 of the animals the effects of propranolol, a β receptor blocking agent, on the pressor response to norepinephrine in the pulmonary vascular bed were investigated; these data are also presented in figure 1. After administration of propranolol, 2 mg/kg iv, the increases in lobar arterial pressure in response to norepinephrine infusions at 0.5–10 μg/kg per min were greatly enhanced ($P < 0.01$ at each infusion rate when compared to corresponding control). The dose-response curve for norepinephrine was shifted to the left and the threshold dose was decreased after administration of the β receptor blocking agent (Fig. 1). In eight of the animals, the effects of phenoxybenzamine, an α receptor blocking agent, were studied, and, in these experiments, the increases in lobar arterial pressure in response to norepinephrine infusions at 0.5 and 10 μg/kg per min were blocked completely after administration of phenoxybenzamine, 5 mg/kg, iv.

The effects of norepinephrine infusions on the pulmonary vascular bed were also investigated in this group of cats when pulmonary vascular tone was elevated by infusion of the endoperoxide analog. In 13 animals, lobar arterial pressure was increased from 13 ± 1 to 39 ± 2 mm Hg by infusion of the endoperoxide analog; however, increases in lobar arterial pressure in response to norepinephrine infusions, 0.5–10 μg/kg per min, were not significantly different when pulmonary vascular tone was at resting levels or when tone had been enhanced by infusion of the endoperoxide analog (Fig. 1). However, when lobar arterial pressure was increased from 13 ± 1 to 42 ± 2 mm Hg in eight cats treated with phenoxybenzamine, 5 mg/kg, iv, the pressor response to norepinephrine was reversed and infusions of norepinephrine at 0.25–10 μg/kg, iv, caused significant dose-dependent decreases in lobar arterial pressure (Fig. 1). The reductions in lobar arterial pressure in response to norepinephrine in animals treated with phenoxybenzamine were similar when lobar vascular resistance was enhanced by the endoperoxide analog or by 15-methyl PGF$_{2\alpha}$. In four of the eight animals in which phenoxybenzamine was administered and lobar vascular tone was enhanced, the effect of propranolol on the depressor responses to norepinephrine was investigated. In these four animals treated with phenoxybenzamine, 5 mg/kg, iv, and propranolol, 2 mg/kg, iv, lobar arterial pressure was increased by the endoperoxide analog, but infusion of norepinephrine, 10 μg/kg per min, had little if any effect in that lobar arterial pressure decreased from 40 ± 2 to 39 ± 3 mm Hg ($P > 0.05$). The enhanced response to norepinephrine after administration of propranolol could result from blockade of β adrenergic receptors or other actions of the drug. To examine these possibilities, the effects of propranolol on responses to phenylephrine and tyramine were investigated. Intralobar infusions of phenylephrine, an agent which acts on α receptors at 1 to 3 μg/kg per min increased lobar arterial pressure in a dose-dependent manner (Fig. 2). The increases in
Tyramine, Control

**TABLE 1**

<table>
<thead>
<tr>
<th>Lobar arterial pressure (mm Hg)</th>
<th>Control</th>
<th>Propranolol</th>
<th>Propranolol and cocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td>13 ± 1</td>
<td>18 ± 1</td>
<td></td>
</tr>
<tr>
<td>Tyramine, 50 µg</td>
<td>16 ± 1*</td>
<td>24 ± 1*</td>
<td></td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>13 ± 1</td>
<td>18 ± 1</td>
<td></td>
</tr>
<tr>
<td>Tyramine, 100 µg</td>
<td>17 ± 1*</td>
<td>25 ± 1*</td>
<td>20 ± 1</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>13 ± 1</td>
<td>18 ± 2</td>
<td></td>
</tr>
<tr>
<td>Tyramine, 200 µg</td>
<td>17 ± 1*</td>
<td>25 ± 1*</td>
<td>19 ± 0</td>
</tr>
</tbody>
</table>

*P < 0.05 when compared to corresponding control.*

The effects of epinephrine on the pulmonary vascular bed were also investigated in another group of cats using a similar experimental protocol. Under resting conditions intralobar infusion of epinephrine at 1 µg/kg per min had no significant effect on lobar arterial pressure; however, when the infusion rate increased to 2 µg/kg per min there was a small (3.4 ± 0.8 mm Hg) but statistically significant (P < 0.05) reduction in lobar arterial pressure (Fig. 3). The increases in lobar arterial pressure in response to tyramine were enhanced after administration of propranolol, 2 mg/kg, iv, but were blocked after administration of cocaine, 5 mg/kg, iv (Table 1). This dose of cocaine also enhanced the pressor response to intrapulmonary injections of norepinephrine.

In a fourth series of experiments, intralobar infusions of isoproterenol, a β agonist, at 62 and 125 ng/kg per min caused small but statistically significant reductions in lobar arterial pressure when lobar vascular resistance was at basal levels (Fig. 4). When lobar arterial pressure was increased from 14 ± 1 to 46 ± 2 mm Hg by infusion of the endoperoxide analog, intralobar infusions of epinephrine at rates of 0.125–2 µg/kg per min produced marked dose-dependent decreases in lobar arterial pressure (Fig. 3). When lobar vascular tone was enhanced in the presence of phenox ybenzamine, intralobar infusions of epinephrine at rates of 0.03–0.125 µg/kg per min produced marked dose-dependent decreases in lobar arterial pressure that were not different from responses to isoproterenol when tone was enhanced (Fig. 3).

Results in Tables 1–3 expressed as mean ± SE.
contrast, when lobar vascular tone was enhanced by the endoperoxide analog, the decreases in lobar arterial pressure in response to isoproterenol infusions at 25–125 ng/kg per min were decreased significantly but not blocked after metoprolol, 2 mg/kg, iv, or practolol, 4 mg/kg, iv, and when tone was enhanced in those treated with propranolol, 2 mg/kg, iv. Under control conditions, isoproterenol produced small but significant reductions in lobar arterial pressure. When tone was enhanced responses to isoproterenol were greatly increased. Under enhanced tone conditions, metoprolol or practolol produced significant reductions in responses to isoproterenol. After propranolol, responses to isoproterenol were abolished when tone was enhanced. n indicates number of animals.

In the last series of experiments, the effects of neuronally released norepinephrine and adrenergic blocking agents were investigated in the feline pulmonary vascular bed. Under resting conditions, stimulation of the sympathetic nerves at 3, 10, and 30 cycles/sec caused significant frequency-related increases in lobar arterial pressure while lobar venous outflow pressure was held constant (Fig. 5). In 13 of the cats, the effects of phenoxybenzamine on responses to nerve stimulation and bolus injections of norepinephrine were investigated, and these data are shown in Figure 5. Under resting conditions, responses to the 1-μg dose of norepinephrine and nerve stimulation at 3 and 10 cycles/sec were completely blocked after phenoxybenzamine, 5 mg/kg, iv, whereas responses to nerve stimulation at 30 cycles/sec and norepinephrine at 3 μg were reversed (Fig. 5). In additional experiments under resting conditions, responses to norepinephrine were enhanced after administration of β receptor blocking agents, whereas the β blocking agents had no significant effect on the response to sympathetic nerve stimulation (Fig. 5). In these experiments both propranolol, 2 mg/kg, iv (n = 1), and sotalol, 4 mg/kg, iv (n = 4), an agent which may have less membrane
TABLE 2 Influence of Phentolamine and Atropine on Responses to Sympathetic Nerve Stimulation When Lobar Vascular Resistance was Elevated by an Endoperoxide Analog

<table>
<thead>
<tr>
<th>Lobar arterial pressure (mm Hg)</th>
<th>Control</th>
<th>3 cycles/sec</th>
<th>Control</th>
<th>10 cycles/sec</th>
<th>Control</th>
<th>30 cycles/sec</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phentolamine</td>
<td>Phentolamine</td>
<td>Atropine</td>
<td>Phentolamine</td>
<td>Atropine</td>
<td>Phentolamine</td>
</tr>
<tr>
<td>Control</td>
<td>42 ± 1</td>
<td>38 ± 1*</td>
<td>43 ± 1</td>
<td>33 ± 1*</td>
<td>43 ± 1</td>
<td>32 ± 1*</td>
</tr>
<tr>
<td>3 cycles/sec</td>
<td>43 ± 1</td>
<td>38 ± 1*</td>
<td>43 ± 1</td>
<td>33 ± 1*</td>
<td>43 ± 1</td>
<td>32 ± 1*</td>
</tr>
<tr>
<td>10 cycles/sec</td>
<td>43 ± 1</td>
<td>38 ± 1*</td>
<td>43 ± 1</td>
<td>33 ± 1*</td>
<td>43 ± 1</td>
<td>32 ± 1*</td>
</tr>
<tr>
<td>30 cycles/sec</td>
<td>43 ± 1</td>
<td>38 ± 1*</td>
<td>43 ± 1</td>
<td>33 ± 1*</td>
<td>43 ± 1</td>
<td>32 ± 1*</td>
</tr>
</tbody>
</table>

* P < 0.05 when compared to corresponding control.

TABLE 3 Effects of Phentolamine and Propranolol on Responses to Pressor and Depressor Substances in the Feline Pulmonary Vascular Bed

<table>
<thead>
<tr>
<th>Lobar arterial pressure (mm Hg) under conditions</th>
<th>Control</th>
<th>Phentolamine (2.5 mg/kg, iv)</th>
<th>Propranolol and enhanced tone (2 mg/kg, iv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10 ± 1</td>
<td>10 ± 1</td>
<td>30 ± 2</td>
</tr>
<tr>
<td>Angiotensin II, 1 µg</td>
<td>15 ± 1*</td>
<td>15 ± 2*</td>
<td>21 ± 1*</td>
</tr>
<tr>
<td>Control</td>
<td>10 ± 2</td>
<td>11 ± 1</td>
<td>20 ± 2*</td>
</tr>
<tr>
<td>PGF_{2α}, 0.03 µg</td>
<td>20 ± 2*</td>
<td>20 ± 2*</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>28 ± 2</td>
<td>30 ± 2</td>
<td></td>
</tr>
<tr>
<td>PGE_{1}, 0.03 µg</td>
<td>19 ± 2*</td>
<td>21 ± 1*</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>28 ± 2</td>
<td>32 ± 2</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin, 3 µg</td>
<td>19 ± 2*</td>
<td>23 ± 1*</td>
<td></td>
</tr>
</tbody>
</table>

* P < 0.05 when compared to corresponding control.

Discussion

Results of the present study show that stimulation of the sympathetic nerves to the lung and norepinephrine administration increase lobar arterial pressure in the cat. Inasmuch as lobar blood flow and lobar venous outflow pressure were maintained constant, the increases in lobar arterial pressure indicate that nerve stimulation and norepinephrine increase pulmonary lobar vascular resist-
The increases in lobar arterial pressure in response to norepinephrine and nerve stimulation were dose- and frequency-dependent and these responses were blocked after administration of $\alpha$ receptor blocking agents. These data indicate that the feline pulmonary vascular bed is functionally innervated by the sympathetic nervous system and that under basal conditions both exogenously administered and neuronally released norepinephrine cause vasoconstriction by stimulating $\alpha$ receptors. These results are similar to those of previous studies on the canine pulmonary vascular bed (Daly et al., 1970; Kadowitz and Hyman, 1973; Kadowitz et al., 1973, 1975, 1976). However, the present experiments extend the work of previous studies by showing that, when pulmonary vascular tone was elevated in animals treated with $\alpha$ receptor blocking agents, adrenergic nerve stimulation caused frequency-dependent decreases in lobar arterial pressure that were not blocked by atropine. The atropine-resistant neurogenically induced vasodilator responses were well maintained during the period of stimulation, and these responses were of greater magnitude than were the increases in lobar arterial pressure observed under basal conditions. Norepinephrine also caused dose-dependent decreases in lobar arterial pressure after a $\alpha$ receptor blockade when pulmonary vascular tone was elevated. The vasodilator responses to norepinephrine and nerve stimulation were blocked by propranolol, a $\beta$ receptor blocking agent. These data indicate that the adrenergic transmitter acts on both $\alpha$ and $\beta$-adrenergic receptors and when pulmonary vascular tone is elevated and $\alpha$ receptors are masked, norepinephrine causes vasodilation in the pulmonary vascular bed. The present data for the pulmonary vascular bed are in agreement with previous studies in skeletal muscle, liver, spleen, and adipose tissue and in isolated facial vein of the rabbit and support the hypothesis that norepinephrine liberated from sympathetic nerves can act on $\beta$-2 receptors in blood vessels (Ngai et al., 1966; Viveros et al., 1968; Greenway et al., 1968; Greenway and Lawson, 1969; Lundvall and Jarhult, 1974, 1976; Pegram et al., 1976). However, other investigators have not been able to elicit vasodilator responses to adrenergic stimulation in a variety of organ systems (Glick et al., 1967; Rosell and Belfrage, 1975; Dawes and Falkner, 1975; Russell and Moran, 1980).

The hypotheses that vascular $\beta$ ($\beta$-2) receptors are innervated and that neuronally released norepinephrine elicits vasodilation have been challenged recently (Russell and Moran, 1980). These investigators were unable to confirm the classic studies of Viveros et al. (1968) that nerve stimulation caused atropine-insensitive vasodilation in skeletal muscle. In the studies of Viveros et al. (1968) responses to adrenergic stimulation were reversed after intraarterial administration of dibozane, a substance which is poorly soluble at neutral pH, whereas responses to nerve stimulation were not reversed by phentolamine. However, when dibozane was administered iv at a dose of 10 mg/kg, vasodilator responses to nerve stimulation were blocked by atropine (Russell and Moran, 1980). Moreover, results of the present study show that neuronally released norepinephrine can cause vasodilation and indicate that $\beta$-2 receptors in the pulmonary vascular bed are innervated. In the present study, responses to nerve stimulation were reversed by phenoxybenzamine or phentolamine in doses that did not significantly alter responses to PGF$_2\alpha$, angiotenin II, PGE$_\nu$, or nitroglycerin in the pulmonary vascular bed. In addition, vasodilator responses to nerve stimulation were not modified by doses of atropine that reduced responses to acetylcholine in the feline pulmonary vascular bed (Hyman et al., unpublished observations). These data suggest that reversal of the response to nerve stimulation was not dependent on the type of $\alpha$ blocker employed and did not involve a cholinergic mechanism. The reasons for the difference in results in the present study and in the studies of Russell and Moran (1980) are uncertain but may suggest differences in nerve terminal-adrenergic receptor relationships in the skeletal muscle and the pulmonary vascular beds. The hypothesis that the feline pulmonary vascular bed is well supplied with $\beta$ receptors is suggested by the observation that isoproterenol, a potent $\beta$ agonist, had marked vasodilator activity when pulmonary vascular tone was elevated. Moreover, the observation that vasodilator responses to isoproterenol were only partially decreased by metoprolol or practolol but were almost completely blocked by propranolol suggests that the vascular $\beta$ receptors in the lung are of the $\beta$-2 type, as suggested by Lands et al. (1967). Although metoprolol or practolol had only a small effect on the pulmonary vasodilator response to isoproterenol, these agents almost completely blocked the increases in heart rate in response to isoproterenol, confirming the cardioselective nature of these antagonists (Lertora et al., 1975; Frishman, 1979).

It has been reported that vasoconstriction tone in the feline pulmonary vascular bed is minimal under resting conditions and that vasodilator responses to prostaglandins and nitroglycerin are dependent on the existing level of tone in the bed (Hyman and Kadowitz, 1979). Vasodilation in response to $\beta$ receptor activation is caused by relaxation of basal tone, and variations in response to $\beta$ agonists may result from variations in the level of existing tone (Greenway and Lawson, 1969). The present studies with isoproterenol are consistent with the results of studies in the hepatic bed and support the concept that responses to $\beta$ agonists are dependent on the existing level of vasoconstrictor tone (Greenway and Lawson, 1969; Bevan, 1979).

Epinephrine stimulates both $\alpha$ and $\beta$ receptors, and its potency on $\beta$ receptors is between that of norepinephrine and isoproterenol (Russell and
Moran, 1980). Reports in the literature on the pulmonary vascular effects of epinephrine vary with the study (Hauge et al., 1967; Porcelli and Bergofsky, 1973). Results of the present study show in the cat with an intact chest that epinephrine infusions produced modest decreases in pulmonary vascular resistance. Moreover, these decreases were greatly enhanced when pulmonary vascular tone was elevated. In addition, when tone was elevated and α receptors were blocked, epinephrine had potent vasodilator activity. Moreover, vasodilator responses to epinephrine after α blockade were nearly equal to vasodilator responses to isoproterenol when vasoconstrictor tone was elevated. These results indicate that epinephrine has good β receptor stimulating activity in the feline pulmonary vascular bed but suggests that this activity is dependent on the existing level of tone in the bed. These data support our hypothesis that the feline pulmonary vascular bed is well supplied with β receptors. The present data are in agreement with results of a recent study in skeletal muscle in regard to the relative potency of isoproterenol, epinephrine, and norepinephrine in stimulating vascular β receptors (Russell and Moran, 1980). Although epinephrine had no apparent vasoconstrictor activity when infused at rates of 1 or 2 μg/kg per minute these concentrations caused significant vasoconstriction when β receptors were blocked with propranolol. In addition, vasoconstrictor responses to norepinephrine were increased greatly after β adrenergic blockade. These data suggest that in the feline pulmonary vascular bed epinephrine and norepinephrine act on both α and β receptors and that the resulting response is the algebraic summation of these two opposing actions. Therefore, when β receptors are blocked, both catecholamines have potent α-stimulating activity.

The possibility that propranolol was enhancing pressor responses to norepinephrine and epinephrine by a mechanism other than β receptor blockade was investigated by evaluating the effects of the antagonist on responses to phenylephrine, tyramine, PGF₂α, and angiotensin II. Since phenylephrine is a selective α receptor agonist, propranolol would not be expected to enhance the response to this agent (Eckstein and Abboud, 1962). The present studies show that propranolol in doses that blocked vasodilator responses to isoproterenol and enhanced vasoconstrictor responses to norepinephrine was without significant effect on the pressor response to phenylephrine. Tyramine is an indirectly acting amine which must be taken up by the adrenergic nerves in order to displace norepinephrine (Trendelenburg et al., 1962). However, propranolol in doses that blocked β receptors in the feline pulmonary vascular bed, enhanced the pressor response to tyramine. In addition, propranolol did not modify pressor responses to PGF₂α, and angiotensin II which are nonadrenergic agonists.

These data suggest that propranolol does not enhance pressor responses to norepinephrine or epinephrine by blocking uptake of these substances into adrenergic nerves or by a nonspecific effect on vascular smooth muscle. Although propranolol did not block responses to tyramine, the effects of this indirectly acting substance are inhibited by cocaine, an agent which blocks neuronal uptake (Tainter and Chang, 1927). The doses of cocaine that blocked responses to tyramine enhanced responses to norepinephrine suggesting that neuronal uptake may be an important mechanism for terminating the actions of catecholamines in the pulmonary vascular bed. In addition, the observation that tyramine causes an indirectly mediated pressor response supports our hypothesis that the feline pulmonary vascular bed is innervated by the adrenergic nervous system. The enhanced pressor response to norepinephrine and the significant vasoconstrictor response to epinephrine after propranolol provide further support for the hypothesis that these catecholamines act on both α and β receptors in the feline pulmonary vascular bed.

Although responses to sympathetic nerve stimulation were reversed after α receptors were blocked and tone was elevated, these responses were not enhanced after administration of β blocking agents. Thus, in the same group of cats in which pressor responses to exogenously administered norepinephrine were augmented, responses to nerve stimulation were not modified. The explanation for the inability to enhance neurogenic responses is uncertain; however, it is possible that the β blocking agents may have a depressant action on the processes by which norepinephrine is liberated by stimulation of the sympathetic nerves. Neither sotalol nor propranolol enhanced the response to nerve stimulation, and since sotalol has little, if any, "membrane stabilizing activity," the depressant action is probably not nonspecific (Frishman, 1979). The inability of the β blockers to enhance responses to nerve stimulation, whereas these agents enhanced responses to tyramine and norepinephrine in the present study suggests a very specific action on the neurogenic release process for norepinephrine in the adrenergic terminal. It has been reported that activation of presynaptic β receptors enhances neuronal release of norepinephrine and that β blocking agents such as sotalol decrease the release of the adrenergic transmitter (Adler-Graschinsky and Langer, 1975; Yamaguchi et al., 1977). It is, therefore, possible that the β blocking agents may block presynaptic receptors and decrease the release of norepinephrine in response to nerve stimulation. This action would oppose the effects of blockade of vascular β-2 receptors.

In summary, results of the present study indicate that the feline pulmonary vascular bed is innervated by the sympathetic nervous system and that α- and β-2 adrenergic receptors are present. In addition,
these results suggest that neuronally released and blood-borne norepinephrine can act on β receptors, but vasodilator responses are dependent on the existing level of vasoconstrictor tone in the bed.

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References


Pulmonary vasodilator responses to catecholamines and sympathetic nerve stimulation in the cat. Evidence that vascular beta-2 adrenoreceptors are innervated.

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