Influence of 5- and 6-Hydroxydopamine on Adrenergic Transmission and Nerve Terminal Morphology in the Canine Pulmonary Vascular Bed

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SUMMARY We studied the effects of 5- and 6-hydroxydopamine on adrenergic neurotransmission, fluorescence histochemistry, and nerve terminal ultrastructure in the canine pulmonary vascular bed. Fluorescence histochemistry on stretched preparations and sections of intrapulmonary artery and vein demonstrated that these vessels are well supplied with adrenergic nerves. Electron microscopy revealed adrenergic terminals in the adventitia and outer third of the media in the artery, but only in the adventitia in the vein. Adrenergic terminals in artery and vein contained many small and a few large dense-core vesicles. At least 20% of the terminals in the artery contained many small agranular vesicles and a few large opaque vesicles; this suggests that they were of the cholinergic type. Such terminals were not found in intrapulmonary veins. Under conditions of controlled blood flow, stimulation of the sympathetic nerves to the lung and intralobar injection of norepinephrine increased pressure in the perfused lobar artery and small intrapulmonary vein in a stimulus-related manner. The rise in pressure in the lobar artery and vein in response to nerve stimulation was blocked after administration of either 5- or 6-hydroxydopamine. Neither agent modified the response of the pulmonary vascular bed to norepinephrine. In contrast, the rise in pressure in the lobar artery and vein in response to both norepinephrine and to nerve stimulation was blocked by phenoxybenzamine, an α-receptor blocking agent. The attenuated neurogenic vasconstrictor response in dogs treated with 5- or 6-hydroxydopamine was associated with a marked decrease in intensity of fluorescence of the abundant adrenergic innervation in both intrapulmonary artery and vein, and with the appearance of an osmiophilic material in dense-core vesicles of adrenergic terminals in artery and vein. We believe that these data suggest that 5- and 6-hydroxydopamine interfere with adrenergic transmission in intrapulmonary vessels by depleting norepinephrine from adrenergic terminals. Furthermore, we conclude from hemodynamic, histochemical, and ultrastructural studies that vasomotor tone in the pulmonary vascular bed can be regulated by the sympathetic nervous system.

THE PULMONARY vascular bed is innervated by the adrenergic nervous system and norepinephrine has been demonstrated in canine pulmonary arteries and veins. However, the role of the adrenergic system in regulating the pulmonary vascular bed is uncertain. Although it has been reported that stimulation of the sympathetic nerves increases pulmonary vascular resistance in the dog, other investigators reported no increase in resistance to flow but found instead that nerve stimulation decreased the distensibility of the canine pulmonary vascular bed. The purpose of the present investigation was to provide additional evidence that the pulmonary vascular bed is innervated by the sympathetic nervous system by use of pharmacological, fluorescence histochemical, and ultrastructural techniques. To do this we investigated the effects of 5- and 6-hydroxydopamine on sympathetic transmission, nerve terminal fluorescence, and nerve terminal ultrastructure.

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Received April 9, 1975; accepted for publication March 26, 1976.

Methods

IN VIVO STUDIES

Forty-two mongrel dogs unselected as to sex and weighing 13-24 kg were anesthetized with pentobarbital sodium (30 mg/kg, iv), and strapped to a fluoroscopic table. A specially designed 20 Fr. double-lumen balloon catheter was positioned under fluoroscopic guidance in the arterial branch to the left lower lung lobe through the external jugular vein. A Teflon catheter with its tip positioned about 2 cm distal to the balloon catheter was used to monitor pressure in the perfused lobar artery. Catheters with side holes were passed into the main pulmonary artery and the aorta and into a small intrapulmonary vein and the left atrium transseptally. Precautions were taken to ensure that pressure measurements were made without wedging in the intrapulmonary veins that were 2-3 mm in diameter. Briefly, a 0.9-mm Teflon catheter with side holes near the tip was passed through a 3-mm Teflon catheter that previously had been wedged into a small intrapulmonary vein. The 0.9-mm catheter was then withdrawn 1-3 cm from the wedge position until pressure dropped abruptly. The 0.9-mm catheter then was fixed in place with a Cope adaptor after the 3-mm Teflon catheter had been withdrawn to the left atrium. These methods have been described in detail and validated previously. All intravascular pressures were measured with Statham P23D transducers zeroed at the level of the middle of the right atrium, and mean pressures were recorded on an oscilloscopic recorder (Elec-
tronics for Medicine, model DR-12). After all catheters had been positioned and the animals heparinized (500 U/kg, iv), the balloon on the perfusion catheter was distended with 2-4 ml of sodium diatrizoate, 50% (Hyopaque, Winthrop) until pressure in the lobar artery and small vein decreased to a value near left atrial pressure. The vascularly isolated left lower lobe then was perfused with a Sarns roller pump (model 3500) with blood withdrawn from the right atrium. The pumping rate was adjusted so that mean pressure in the perfused lobar artery approximated mean pressure in the main pulmonary artery and thereafter was not changed during the experiment. The pumping rate averaged 310 ml/min in these experiments. The trachea was intubated with a cuffed endotracheal tube and the dogs were ventilated with room air with a Harvard respirator.

The left stellate ganglion was exposed through a thoracotomy and the nerve was carefully isolated and placed on a Harvard shielded electrode. The ganglion was excited with rectangular pulses, 2 msec in duration and of supramaximal voltage (9-16 V) with a Grass model S48 stimulator and SIU5 isolation unit. The nerve was stimulated at frequencies of 3, 10, and 30 Hz for periods of 30-45 seconds. Norepinephrine (l-norepinephrine hydrochloride, Sigma, dose in terms of base) was injected into the lobar arterial perfusion circuit in volumes of 0.03 ml and 0.1 ml of a solution containing 100 /ug/ml. 5-Hydroxydopamine hydrochloride and 6-hydroxydopamine hydrobromide (Regis) were infused into the perfusion circuit at a rate of 500 /ug/min (0.2 ml/min) and phenoxybenzamine (Smith, Kline, and French) and norepinephrine were infused at a rate of 200 /ug/min (0.1 ml/min) with a Harvard infusion pump.

**FLUORESCENCE HISTOCHEMISTRY**

Fluorescence histochemical studies were carried out on 11 dogs. In five dogs, 6-hydroxydopamine was infused into the lobar artery at a rate of 500 /ug/min for 40-60 minutes. In three dogs receiving 6-hydroxydopamine, the left lower lobe was removed rapidly and portions of the lobe, as well as of intrapulmonary artery and vein, were rapidly frozen in propane cooled to the temperature of liquid nitrogen. Identical samples were removed from two other control dogs after administration of saline instead of 6-hydroxydopamine. The tissues were freeze-dried and treated for 1 hour with formaldehyde vapor at 80°C generated from paraformaldehyde powder equilibrated to 55% relative humidity. Treated samples were embedded in paraffin, sectioned (5-10 /um) mounted in Entellan (EM Laboratories), and viewed with a Leitz Orthoplan fluorescence microscope equipped with epi illumination, a mercury lamp, and 510K barrier filter. In two dogs receiving 6-hydroxydopamine (500 /ug/min) and in two others receiving 5-hydroxydopamine (500 /ug/min) for 40-60 minutes the left lower lobe was removed and intrapulmonary arteries and veins 1-5 mm in diameter were dissected from the lung and stretched out on microscope slides. Intrapulmonary vessels also were removed from two control dogs. The stretched vessels were dried under vacuum for 24 hours and treated for 1 hour with formaldehyde vapor at 80°C. The vacuum-dried, stretched preparations were viewed with the fluorescence microscope.

**ELECTRON MICROSCOPY**

Seven dogs were used for electron microscopic evaluation of intrapulmonary vessels. In three dogs, 5-hydroxydopamine was infused into the lobar artery at a rate of 500 /ug/min for 30-40 minutes and in two others 6-hydroxydopamine (500 /ug/min) was infused for 40 minutes. Two other dogs were treated with saline (0.2 ml/min) and served as controls. After administration of 5-hydroxydopamine, 6-hydroxydopamine, or saline, the left lower lobe was perfused in situ with cold 3% glutaraldehyde in 0.1 m phosphate buffer, pH 7.2, at a rate of 100-150 ml/min for 8-10 minutes. The lobe then was removed and blocks of intrapulmonary artery and vein were removed and placed in cold 3% glutaraldehyde, postfixed in osmium tetroxide, dehydrated in alcohol, passed through propylene oxide, and embedded in Maraglass (Acme Chem. Co.). Thin sections were obtained with an LKB ultramicrotome, stained with lead citrate and uranyl acetate, and studied with an RCA 3G electron microscope.

All data were analyzed by the methods described for paired and group comparison. All values are presented as the mean ± SEM and a P value of less than 0.05 was considered significant.

**RESULTS**

**INFLUENCE OF 5- AND 6-HYDROXYDOPAMINE ON ADRENERGIC RESPONSES IN THE DOG**

The response of the pulmonary vascular bed to sympathetic nerve stimulation and norepinephrine was compared before and during infusion of 6-hydroxydopamine (500 /ug/min) into the perfused lobar artery. Nerve stimulation and norepinephrine produced a significant stimulus-related increase in pressure in the perfused lobar artery and small intrapulmonary vein, and a small but significant decrease in left atrial pressure. The maximum increase in resistance to flow across the left lower lobe was 28, 39, and 46% at stimulation rates of 3, 10, and 30 cycles, and 35 and 47% for

![Figure 1](file_url)  
**Figure 1** Influence of 6-hydroxydopamine on responses to nerve stimulation and norepinephrine in the pulmonary vascular bed. Responses were compared before and 30-40 minutes after onset of the 6-hydroxydopamine infusion. n = number of dogs tested, and statistical significance was determined by the paired t-test.
Table 1  Effects of 5- and 6-Hydroxydopamine, Phenoxybenzamine, and Saline Infusion on Vascular Pressures in the Dog

<table>
<thead>
<tr>
<th></th>
<th>Pressure (mm Hg ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lobar artery</td>
</tr>
<tr>
<td>Control</td>
<td>21.8 ± 0.8</td>
</tr>
<tr>
<td>5-OHDOP (peak)*</td>
<td>27.0 ± 0.9†</td>
</tr>
<tr>
<td>5-OHDOP†</td>
<td>24.6 ± 1.1†</td>
</tr>
<tr>
<td>Control</td>
<td>20.8 ± 1.2</td>
</tr>
<tr>
<td>Saline†</td>
<td>20.3 ± 2.0</td>
</tr>
<tr>
<td>Control</td>
<td>21.7 ± 1.5</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>18.0 ± 1.1†</td>
</tr>
<tr>
<td>Control</td>
<td>24.0 ± 2.6</td>
</tr>
<tr>
<td>6-OHDOP (peak)*</td>
<td>30.7 ± 3.0†</td>
</tr>
<tr>
<td>6-OHDOP†</td>
<td>27.3 ± 3.4</td>
</tr>
</tbody>
</table>

5- and 6-OHDOP = 5- and 6-hydroxydopamine. The number of dogs in each of the four groups was 9, 4, 6, and 6, respectively.

* Peak increase in pressure (3-9 minutes after onset of infusion).
† Significantly different from control; p < 0.05, paired comparison.
‡ 30-40 minutes after onset of infusion.

Administration of 3 and 10 µg of norepinephrine. The increase in lobar arterial and venous pressure in response to nerve stimulation was significantly less than the control 30-40 minutes after onset of the 6-hydroxydopamine infusion (Fig. 1). The increase in lobar arterial and venous pressure in response to norepinephrine was not significantly different from control 30-40 minutes after onset of the 6-hydroxydopamine infusion (Fig. 1). The 6-hydroxydopamine infusion produced a marked increase in pressure in the lobar artery and vein, the aorta, and the main pulmonary artery; however, these pressures returned toward preinfusion levels 20-40 minutes later (Table 1).

The effect of 5-hydroxydopamine on responses to nerve stimulation and norepinephrine was evaluated in a second group of dogs. The maximum increase in resistance to flow in response to norepinephrine and nerve stimulation was similar in this group of dogs and the rise in lobar arterial and small vein pressure at all stimulus frequencies studied was significantly less than control 30-40 minutes after onset of the 5-hydroxydopamine infusion (Fig. 2). The rise in lobar arterial and venous pressure in response to norepinephrine was not significantly different from control during infusion of this dopamine analogue (Fig. 2). Pressure in the lobar artery and vein, the aorta, and the main pulmonary artery were increased markedly; however, these pressures returned toward control value 30-40 minutes after the infusion of 5-hydroxydopamine was instituted (Table 1).

In a third group of dogs the increase in lobar arterial and venous pressure in response to injected norepinephrine and to nerve stimulation was decreased significantly 10-20 minutes after onset of infusion of phenoxybenzamine (200 µg/min) into the lobar artery (Fig. 3). Administration of phenoxybenzamine decreased pressure significantly in the lobar artery and vein and in the aorta (Table 1). In four other dogs we evaluated the effects of infusion of the saline vehicle for the nerve terminal blocking agents and the

![Figure 2](http://circres.ahajournals.org/)

**Figure 2** Influence of 5-hydroxydopamine on responses to nerve stimulation and norepinephrine in the pulmonary vascular bed. Responses were compared before and 30-40 minutes after onset of infusion. n = number of dogs tested, and statistical significance was determined by the paired t-test.

![Figure 3](http://circres.ahajournals.org/)

**Figure 3** Effect of phenoxybenzamine on responses to nerve stimulation and norepinephrine in the pulmonary vascular bed. Responses were compared before and 10-20 minutes after onset of infusion. n = number of dogs tested, and statistical significance was determined by the paired t-test.
passage of time. Responses to norepinephrine and nerve stimulation were not significantly different from control 20–40 minutes after onset of infusion of saline (0.1–0.2 ml/min) into the perfused lobar artery. Infusion of the saline vehicle for the dopamine analogues was without significant effect on pressures in the lobar artery and vein, the left atrium, the main pulmonary artery, and the aorta (Table 1).

INFLUENCE OF 5- AND 6-HYDROXYDOPAMINE ON NERVE TERMINAL FLUORESCENCE

Fluorescence histochemical examination of the canine pulmonary vascular bed demonstrated a dense adrenergic neuroeffector plexus in virtually all segments of the pulmonary vascular tree. Adrenergic innervation was seen in the main pulmonary artery, in pulmonary lobar arteries, and in intrapulmonary arteries down to 25 μm in diameter. Innervation of pulmonary veins was observed in all but the smallest vessels. Adrenergic innervation in the lung was not restricted to pulmonary vessels. Fluorescent nerve fibers were seen in association with bronchial smooth muscle and were observed in the thick-walled bronchial arteries. Stretched preparations of intrapulmonary artery and vein (Fig. 4, panels A and B) show that these vessels 1–5 mm in diameter are extensively innervated by the adrenergic nervous system and that after treatment with 6-hydroxydopamine (500 μg/min, 40–60 minutes) fluorescent nerve fibers no longer were seen in these vessels (Fig. 4, panels C and D). Administration of 5-hydroxydopamine (500 μg/min) into the perfused lobar artery for 40–60 minutes also removed the histochemical evidence of adrenergic innervation in stretched preparations of intrapulmonary artery and vein (Fig. 4, panels E and F). It is difficult to prepare stretched preparations of very small intrapulmonary vessels, therefore the innervation of these vessels was studied in section. Cross sections of small intrapulmonary artery and vein revealed fluorescent nerve fibers in the adventitia near the media in vessels less than 50 μm in diameter (Fig. 5, left panels). After administration of 6-hydroxydopamine, histochemical evidence of adrenergic innervation in stretched preparations of intrapulmonary artery and vein (Fig. 4, panels E and F). It is difficult to prepare stretched preparations of very small intrapulmonary vessels, therefore the innervation of these vessels was studied in section. Cross sections of small intrapulmonary artery and vein revealed fluorescent nerve fibers in the adventitia near the media in vessels less than 50 μm in diameter (Fig. 5, left panels). After administration of 6-hydroxydopamine, histochemical evidence of adrenergic innervation no longer was present in small intrapulmonary vessels (Fig. 5, right panels). In addition, the histochemical evidence of adrenergic innervation of bronchial smooth muscle and bronchial arterial smooth muscle was diminished after treatment with 6-hydroxydopamine.

INFLUENCE OF 5- AND 6-HYDROXYDOPAMINE ON NERVE TERMINAL ULTRASTRUCTURE

Electron microscopic examination of intrapulmonary arteries revealed small bundles of unmyelinated axons enclosed by Schwann cell processes in the adventitia (Fig. 6A). Schwann cell units also extended into the outer third of the media (Fig. 6B and C). Varicosities containing small (300–600 Å) and large (900–1,200 Å) granular vesicles often were observed in these vessels. Some of these varicosities were only partially enclosed by Schwann cell processes and a few of them were in close relationship to smooth muscle cells. In control dogs most varicosities contained predominantly small and a few large dense-core vesicles characteristic of the adrenergic type (Fig. 6A). How-

ever, in controls in which glutaraldehyde fixation was used, the small vesicles contained little if any dense-core material (Fig. 6A). In the intrapulmonary artery 20–40% of the varicosities contained many small agranular vesicles and a few large opaque vesicles characteristic of the cholinergic type (Fig. 6B). After treatment with 5-hydroxydopamine (500 μg/min) for 40–60 minutes the small vesicles of adrenergic varicosities were clearly recognizable because they contained expanded dense-cores that almost filled the vesicles (Fig. 6B and C). In addition, after 5-hydroxydopamine the density of cores in large vesicles was increased (Fig. 6C). 5-Hydroxydopamine did not change the appearance of cholinergic-like vesicles in the artery (Fig. 6B). In controls it often was difficult to determine whether varicosities were of the adrenergic or cholinergic type (Fig. 6A). After administration of 6-hydroxydopamine (500 μg/min, 40–60 minutes), the small vesicles of adrenergic varicosities also contained expanded dense-cores and the density of cores in large vesicles was increased (Fig. 6D).

Electron micrographs of intrapulmonary vein also revealed small bundles of unmyelinated axons enclosed by Schwann cell processes in the adventitia (Fig. 7A–D). Varicosities containing dense-core vesicles characteristic of the adrenergic type often were seen (Fig. 7A–D). However, in untreated dogs the vesicles contained little, if any, dense-core material (Fig. 7A). After treatment with 5-hydroxydopamine, the small vesicles of adrenergic varicosities seen to contain enlarged dense-cores whereas the cores of large vessels increased in density (Fig. 7B and C). After administration of 6-hydroxydopamine, the small vesicles of adrenergic varicosities were observed to contain expanded dense-cores whereas in large vessels the density of cores was enhanced (Fig. 7D). None of the varicosities in the vein appeared to be of the cholinergic type (Fig. 7A–D). In addition, varicosities of the adrenergic type were found only in the adventitia of the vein.

Discussion

Results of our study show that sympathetic stimulation increases pressure in the perfused lobar artery and small intrapulmonary vein, and that these responses are attenuated by 5- and 6-hydroxydopamine. However, the increase in lobar arterial and venous pressure in response to norepinephrine is not modified by either agent. In contrast, responses to both nerve stimulation and exogenous norepinephrine are attenuated by phenoxybenzamine, an α-receptor blocking agent. Inhibition of the response to nerve stimulation in the absence of an effect on the response to norepinephrine suggests that these dopamine analogues may interfere with the disposition of the adrenergic transmitter in pulmonary vessels. Histochemical examination of intrapulmonary artery and vein revealed that these vessels are well supplied with fluorescent nerve fibers that have the characteristic beaded appearance of adrenergic vasomotor nerves. Treatment with 5- or 6-hydroxydopamine, analogues which, like dopamine, are taken up by adrenergic nerves removed the histochemical evidence of adrenergic innervation in intrapulmonary vessels. These data indicate that the effects of 5- and 6-hydroxydopamine on nerve terminal fluorescence correlate closely with their effects on
the response of the pulmonary vascular bed to sympathetic stimulation. Results of the present investigation are consistent with the studies of Fillenz\textsuperscript{1} in which intrapulmonary arteries 30–300 µm in diameter and larger intrapulmonary veins were found to have fluorescent nerve fibers in the wall.

In addition to attenuating responses to nerve stimulation, the electron microscope revealed that 5- and 6-hydroxydopamine increased the size and density of dense-cores in small and large vesicles of adrenergic varicosities of intrapulmonary vessels. These substances, therefore, serve as
markers for identification of adrenergic terminals because, in glutaraldehyde-fixed tissues, adrenergic varicosities may contain little or no dense-core material as seen in control vessels in the present study. Results of the present investigation are in agreement with a number of studies in which 5- and 6-hydroxydopamine have been shown to increase the electron density of dense-core vesicles in a variety of adrenergically innervated tissues. The present data indicate that there is close correlation between the decreased neurogenic vasoconstrictor response and the accumulation of osmiophilic material in adrenergic terminals of intrapulmonary vessels.

Approximately 20–40% of the varicosities in intrapulmonary artery contained many small agranular and a few large opaque vesicles, suggesting that these are cholinergic terminals. These data are in agreement with the study of Fillenz in which evidence of cholinergic innervation was found in canine intrapulmonary artery but not in intrapulmonary vein. The appearance of cholinergic-like terminals was not altered after administration of either 5- or 6-hydroxydopamine. The physiological function of the cholinergic innervation of the intrapulmonary artery is uncertain, although it has been reported that acetylcholine increases pulmonary vascular resistance by constricting pulmonary veins and upstream vessels. However, the effects of exogenous and neurally released acetylcholine may differ because cholinergic nerves are found in the artery, and transmitter liberated from these nerves would affect predominantly arterial segments. However, exogenously administered acetylcholine would be expected to affect both arterial and venous segments. In addition to affecting cholinergic receptors in intrapulmonary arteries, neurogenically released acetylcholine may serve to modulate the release of adrenergic transmitter because adrenergic and cholinergic terminals are in close proximity in these vessels. In this regard, it has been reported that acetylcholine has the ability to inhibit the release of adrenergic transmitter and the increase in isometric tension in response to sympathetic stimulation in isolated segments of canine pulmonary artery.
FIGURE 6 Electron micrographs of adventitial-medial zone of canine intrapulmonary artery. In untreated dogs nerve terminals (T) contain very few dense-core vesicles, making identification difficult (panel A). This type of appearance is common in glutaraldehyde-fixed tissues. In dogs treated with 5-hydroxydopamine, the density and size of dense-core vesicles of adrenergic (A) terminals are increased (panels B and C). Panel D is from a dog treated with 6-hydroxydopamine. SM = smooth muscle cells; C = cholinergic terminal; SC = Schwann cells. Bar in lower right hand corner of each picture is 1 μm.
FIGURE 7  Electron micrographs of adventitial-medial zone of canine intrapulmonary vein. Panel A is from an untreated animal. Nerve terminals (T) have very few dense-core vesicles. Panels B and C are from dogs treated with 5-hydroxydopamine, and panel D is from a dog treated with 6-hydroxydopamine. Both 5- and 6-hydroxydopamine increased the osmiophilic appearance of vesicles in adrenergic terminals (A). SM = smooth muscle cells; bar in lower right corner of each picture is 1 μm.
In intrapulmonary vein, adrenergic varicosities were found only in the adventitia, whereas in the artery they were found in the adventitia and outer third of the media. The average distance between varicosity and smooth muscle cell was greater in vein than in artery, and no varicosities of the cholinergic type were found in intrapulmonary veins. These data are in agreement with previous studies. After treatment with both 5- and 6-hydroxydopamine, the vesicles of adrenergic varicosities in intrapulmonary veins increased in size and density in much the same way as seen in intrapulmonary artery.

In a recent study, the analysis of mean pressure gradients across the lung suggested that the increase in resistance to flow in response to sympathetic stimulation was the result of vasoconstriction in veins 2-5 mm in diameter and in upstream vessels presumed to be small arteries. These data are not in agreement with the results of Ingram et al. in that sympathetic stimulation did not increase resistance to flow but instead decreased the distensibility of the canine pulmonary vascular bed. However, in both studies, although the effects of nerve stimulation were different, they were blocked by phenoxybenzamine. This finding suggests that they were mediated by α-adrenergic receptors. The present data and the studies of Ingram et al. are in agreement in regard to the effect of exogenous norepinephrine on the pulmonary vascular bed. In both studies norepinephrine increased resistance to flow, although much lower doses were used in the present study. Furthermore, both studies were similar in that the effects of norepinephrine were blocked by phenoxybenzamine. Results of the present study show that intrapulmonary veins 2-5 mm in diameter and small arteries are well supplied with adrenergic nerves and are consistent with the results of previous studies on hemodynamics.

Results of the present study suggest that the canine pulmonary vascular bed is functionally innervated by the sympathetic nervous system and that the response to nerve stimulation may be mediated by the release of norepinephrine from adrenergic terminals in intrapulmonary vessels. In addition, results of the present study suggest that 5- and 6-hydroxydopamine, when administered over periods of less than 1 hour, decrease responses to sympathetic stimulation in the pulmonary vascular bed by depleting adrenergic transmitter in intrapulmonary vessels.

References

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doi: 10.1161/01.RES.39.2.191

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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