Role of Histamine in Hypoxic Pulmonary Hypertension in the Rat

II. DEPLETION OF HISTAMINE, SEROTONIN, AND CATECHOLAMINES

By Anton Hauge, M.D., and Kenneth L. Melmon, M.D.

ABSTRACT

The present investigation was undertaken to see if any of the naturally occurring vasoactive substances was likely to act as a mediator for the pulmonary vasoconstrictor response to acute alveolar hypoxia. Rats were treated with agents that deplete local stores of vasoactive amines or inhibit their synthesis. Lungs from these animals were isolated, ventilated, and perfused with homologous blood at constant volume inflow. Their pressor responses to 2- to 3-minute periods of ventilation hypoxia (2% O₂) were observed.

The histamine-releasing agent 48/80 or the histidine decarboxylase inhibitor NSD 1055, or both, depleted 73% of the histamine in the lung but had no consistent effect on the pressor responses to hypoxia. When 48/80 (0.2 to 1 mg) was given in vitro, histamine in the lung was reduced to 10% of normal, or less, and the pressor response to alveolar hypoxia was completely abolished.

Reserpine, guanethidine, or alpha-methyl-tyrosine reduced catecholamine stores in heart tissue (as an index of general tissue changes) by a maximum of 90% and reserpine decreased serotonin in the lung by 93% without inhibiting the hypoxic pressor responses. The findings strengthen the concept that histamine mediates the pressor response to acute alveolar hypoxia in the rat.

ADDITIONAL KEY WORDS reserpine guanethidine alpha-methyl-tyrosine blood platelets 48/80 NSD 1055 rat lungs

Histamine long has been known as a potent constrictor of pulmonary vessels (1). An investigation of the role of vasoactive substances as mediators of the pulmonary vasoconstrictor response to acute hypoxia suggested that endogenous histamine was important for this response (2). The approach was mainly to use a series of pharmacologic agents that blocked the action of a variety of naturally occurring pressor substances. In the present work we have tried to approach this problem by another route. The vasoactive amines in the lung were reduced by agents that depleted their stores and inhibited their synthesis, and the effect of these procedures on the pressor response to alveolar hypoxia was observed. The importance of blood platelets and serotonin in platelets was also evaluated.

The results support the concept that endogenous histamine plays an important role in the hypoxic pulmonary pressor response in the rat.

Materials and Methods

Preparation.—Isolated rat lungs were perfused with heparinized homologous blood at 37 to 38°C under conditions of constant-volume, pulsatile inflow, and ventilated with a positive-pressure pump. The pulmonary arterial pressure (PpA), the ventilation overflow volume and the oxygen tension in the effluent blood were recorded continuously. The left atrial pressure was kept at 2 to 4 cm of water in each experiment.
A detailed description of the perfusion and ventilation arrangements and the recording devices used and of the normal pattern of responsiveness of the preparation to acute alveolar hypoxia was given in the preceding article (2).

"Hypoxic tests" were performed by reducing the oxygen content in the ventilation gas from 21 to 2% (maintaining 4% CO₂), the remainder being nitrogen. In most of the experiments the interval between the start of two successive hypoxic periods was 8 to 10 minutes. The peak increment in inflow pressure (ΔPp) due to hypoxic ventilation has been given as the hypoxic pressor response. The length of each hypoxic period (2 or 3 minutes) was constant throughout each individual experiment.

Drug administration.—Alpha-methyl-tyrosine (suspension) was administered orally; other in vivo administrations were by intraperitoneal injection. Drugs given in vitro were dissolved in saline in volumes of 0.2 to 0.5 ml per dose and either injected into the arterial tubing or added to the blood reservoir; the recirculating blood volume, including blood in the reservoir was 35 ml. The drugs used in these experiments are listed in Table 1.

Platelet-poor plasma was prepared by centrifuging whole blood at 5000 × g for 20 minutes and removing the supernatant plasma; the latter contained less than 20,000 platelets/mm³, counted by the method of Brecher and Cronkite (3).

Platelet-rich plasma was prepared by centrifuging whole blood at 300 × g for 45 minutes, removing the supernatant plasma and centrifuging this for an additional 15 minutes at 2000 × g. The upper one-third of the plasma volume was discarded and the platelets were resuspended in the remainder of the plasma. Each cubic millimeter contained 875,000 to 990,000 platelets. All surfaces in contact with blood or plasma were siliconized.

Chemical determinations.—The methods for determination of serotonin in lungs and plasma 5-hydroxyindoles (free plasma indoles) were those described by Udenfriend et al. (4). Platelet isolation, platelet serotonin, and protein determinations were as described by Weissbach and Redfield (5). Histamine (6) and catecholamines (7) in the lungs were assayed by standard methods. Lungs to be assayed for catecholamines were stored at −70°C; the lungs to be assayed for histamine and serotonin were stored at −20°C.

Results

LUNG TISSUE HISTAMINE

To reduce the lung tissue stores of histamine, rats were treated with the histidine decarboxylase inhibitor 4-bromo-3-hydroxybenzoyloxyamine (NSD 1055) and with the histamine-releasing agent 48/80 used separately or in combination. After the end of each period of treatment (see Table 2), lungs from one of the pretreated animals were perfused and tested for hypoxic responses. The blood donor for these experiments had received the same pretreatment as the lung donor. Lungs from other animals in each series were removed and frozen for tissue-histamine determination. The results of such in vivo administration of NSD 1055 and 48/80 on lung histamine content are given in Table 2. Also given is the maximum hypoxic pressor response obtained in the perfused lungs from each series.

Histamine content in lungs of normal rats was 14.6 μg/g lung tissue (n = 8, sp ± 2.1). In vivo treatment reduced the histamine levels to 23 to 35% of normal, but marked pressor

<table>
<thead>
<tr>
<th>Class and drug names</th>
<th>Dose range</th>
<th>No. expt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasocostrictor Agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenosine-5-triphosphate</td>
<td>100-300 μg</td>
<td>25</td>
</tr>
<tr>
<td>(ATP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradykinin</td>
<td>15 μg</td>
<td>25</td>
</tr>
<tr>
<td>(BRS-640)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-hydroxytryptamine</td>
<td>100-300 μg</td>
<td>5</td>
</tr>
<tr>
<td>(serotonin, 5-HT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depleting Agents</td>
<td>0.2-1 mg</td>
<td>8</td>
</tr>
<tr>
<td>48/80</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Doses of drugs administered in vivo are recorded in Tables 2, 4, and 5.
HISTAMINE AND ALVEOLAR HYPOXIA

TABLE 2

<table>
<thead>
<tr>
<th>Expt no.</th>
<th>Drug</th>
<th>Dose/day</th>
<th>No. days</th>
<th>Max. pressor response (ΔP/ΔV, mm Hg)</th>
<th>Histamine (μg/g lung)</th>
<th>Change in lung histamine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48/80:</td>
<td>1.3 mg/kg</td>
<td>4</td>
<td>11</td>
<td>4.32</td>
<td>-70.4</td>
</tr>
<tr>
<td>2</td>
<td>48/80:</td>
<td>150 mg/kg</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>NSD:</td>
<td>0.5-1.05 mg/kg</td>
<td>17</td>
<td>17</td>
<td>2.82</td>
<td>-77.3</td>
</tr>
<tr>
<td>4</td>
<td>NSD:</td>
<td>150-300 mg/kg</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>48/80:</td>
<td>0.6 mg/kg</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>48/80:</td>
<td>100 mg/kg</td>
<td>11</td>
<td>14</td>
<td>4.27</td>
<td>-70.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5 mg/kg</td>
<td>11</td>
<td>3</td>
<td>4.94</td>
<td>-66.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6 mg/kg</td>
<td>11</td>
<td>12</td>
<td>5.10</td>
<td>-65.1</td>
</tr>
</tbody>
</table>

*Normal range is an increase of 8-15 mm Hg.

response to alveolar hypoxia could still be obtained in such preparations. The large normal variation in the magnitude and number of responses that can be evoked in lungs from normal rats (2, 8, 9) does not allow a precise quantitative approach. In these experiments, in which the individual lungs could not serve as their own controls, only complete or almost complete absence of any hypoxic pressor response can be accepted as a significant effect. In about 50 previous experiments on lungs from animals which had not been pretreated with any drug, pressor responses to alveolar hypoxia had been obtained in every case.

In an attempt to further reduce lung histamine content, 48/80 was administered in vitro. In eight experiments on lungs from untreated rats, 48/80 (5.7 to 28.5 μg/ml) was injected directly into the pulmonary artery tubing when the responses to standardized hypoxic tests were still increasing or after the first two plateau responses (8); this allowed us to compare responses obtained before and after the drug administration in the same lungs.

In four of these experiments the lungs were frozen immediately after the second or third hypoxic test following administration of 48/80 for later histamine determination. The results are given in Table 3. In all the experiments of this type the pressor response to alveolar hypoxia was abolished 5 to 15 minutes after the histamine-releasing agent had been given. The responses to injected bradykinin (10 to 15 μg) or ATP (200 μg) were not changed. Histamine in the lung was reduced to the very low levels of 0.47 to 1.40 μg/g lung (3 to 10% of normal values).

Figure 1 demonstrates the immediate effects of 48/80 on pulmonary vascular resistance and pulmonary compliance and the effect of the drug on the hypoxic pressor responses. The rise in pulmonary vascular resistance and the fall in pulmonary compliance that followed within seconds after the injection of 48/80 rapidly decreased upon repeated administration; in other experiments, it was prevented by previous addition to the perfusate of the antihistamine compound chlorpheniramine maleate (2.5 mg). Such results suggest that the immediate effects of 48/80 were caused by histamine release and not by a direct effect of the releasing agent itself.

LUNG TISSUE CATECHOLAMINES

To evaluate the role of endogenous catecholamines as the transmitter substance (9) we administered, in vivo, three agents that deplete their stores or inhibit their synthesis (reserpine, guanethidine and alpha-methyl-tyrosine).
TABLE 3
Effects of Addition of **48/80** to the Perfusate on the Pressor Response to Acute Alveolar Hypoxia and Lung Histamine Content

<table>
<thead>
<tr>
<th>Expt no.</th>
<th>Hypoxia time (min)</th>
<th><strong>48/80</strong> dose (mg)</th>
<th>Blood flow (ml/min)</th>
<th>Responses to alv. hypoxia ((\Delta P_{pa}))(mm Hg)*</th>
<th>Change in response (%)</th>
<th>Histamine ((\mu g/g) lung)</th>
<th>Change in lung histamine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>1</td>
<td>28</td>
<td>11 11 2 0 0</td>
<td>-81.8</td>
<td>1.40</td>
<td>-90.4</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>0.8</td>
<td>20</td>
<td>19 16 1 0 0</td>
<td>-94.6</td>
<td>1.40</td>
<td>-90.4</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>0.5</td>
<td>20</td>
<td>10 10 1 0 0</td>
<td>-90.0</td>
<td>0.94</td>
<td>-93.6</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>0.4</td>
<td>22</td>
<td>15 15 3 0</td>
<td>-80.0</td>
<td>1.33</td>
<td>-90.9</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>0.4</td>
<td>15</td>
<td>12 13 0 0 0</td>
<td>-100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>0.3</td>
<td>15</td>
<td>17 17 0 0 0</td>
<td>-100</td>
<td>0.47</td>
<td>-96.8</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>0.3</td>
<td>20</td>
<td>24 24 0 0 0</td>
<td>-100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>0.2</td>
<td>16</td>
<td>14 15 1 0</td>
<td>-93.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The last two responses before **48/80** and the two (or three) first after **48/80** are listed.

![Figure 1](image)

**FIGURE 1**
Effects of **48/80** on the hypoxic pressor response. Isolated perfused lung. \(P_{pa}\) = pulmonary artery pressure; \(P_{vo2}\) = venous blood effluent blood oxygen tension; **VOF** = ventilation overflow volume; **48/80** (300 \(\mu g\)) and bradykinin (BRK, 15 \(\mu g\)) were injected into the pulmonary arterial tubing at arrows. Test number and time after start of perfusion are given for each period of hypoxia.

These agents have different types of action (10, 11).

Lungs from such pretreated animals were perfused and tested for hypoxic pressor responses. Hearts from animals pretreated with depleting agents were frozen (\(-70^\circ C\)) and cardiac tissue catecholamine concentration was determined; this was used as an index of general changes in tissue catecholamines, including lung, because of the small quantities of catecholamines in lungs. The catecholamine content of the normal rat heart was 15.1 \(\mu g/g\) (\(n = 8, s_{x} = 14.2\)).

In spite of a maximum reduction by 90% of catecholamines in heart tissue (supposedly paralleled by a reduction of lung catecholamines) no diminishing effect on the hypoxic pressor responses could be detected (Table 4). In fact, lungs from reserpine-treated animals were among those responding most vigorously to acute alveolar hypoxia.

**LUNG TISSUE 5-HYDROXYTRYPTAMINE (5-HT, SEROTONIN)**

We found the normal lung serotonin content in rats to be 62.7 \(\mu g/g\) of lung (\(n = 12, s_{x} = 7.6\)). In an effort to evaluate the role of lung serotonin in the pressor response to acute alveolar hypoxia, rats were treated with

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reserpine in three separate series. The lungs from one of the animals of each series were then tested for hypoxic responses. Lungs from the other animals in each series were frozen for later determination of serotonin. The perfusate was blood from normal, untreated rats.

The maximum reduction of lung tissue serotonin content by reserpine was 93% of normal (Table 5). Such reduction had no apparent effect on the pressor responses to alveolar hypoxia nor on the pressor responses to injections of ATP (250 µg) or bradykinin (15 µg).

PLATELETS AND PLATELET SEROTONIN

It has been shown that only few and weak hypoxic pressor responses could be elicited in perfused rat lungs when platelet-poor plasma was used as the perfusate (8). If, however, all the formed elements of the blood were added to the plasma perfusate during the first hour of perfusion, good responses to ventilation hypoxia appeared. The formed elements of blood thus seemed to be important for this response. Special interest may relate to the blood platelets because of their content of the vasoactive agents serotonin and ATP.

To evaluate the role of blood platelets, we carried out two experiments starting with platelet-poor perfusate (13,500 to 20,000/mm³). Care was taken to wash out whole blood remaining in the vascular bed of the lungs. Thus the first 10 to 15 ml of effluent perfusate was drained out of the perfusion circuit. Hypoxic tests for 3 minutes with intervals of 8 minutes were used. After 45 minutes of perfusion, the largest pressor responses elicited in these preparations were 1.5 to 2 mm Hg. The perfusate was then exchanged for platelet-rich plasma (875,000 and 990,000/mm³), and the hypoxic tests continued. A definite increase in pressor responses was seen following such exchange. During the next 30 minutes, maximum responses of 5 and 8 mm Hg were obtained.

To evaluate the possible role of platelet serotonin in the hypoxic pressor response, three additional perfusion experiments were done with platelet-rich plasma. Whole blood remaining in the pulmonary vascular bed was washed out with platelet-poor plasma pre-

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TABLE 4

Effects of Pretreatment with Reserpine, Guanethidine and α-Methyl-Tyrosine on the Pressor Response to Acute Alveolar Hypoxia and Heart Catecholamines

<table>
<thead>
<tr>
<th>Expt no.</th>
<th>Drug</th>
<th>Dose/day</th>
<th>No. days</th>
<th>Max. hypoxic pressor response* (mm Hg)</th>
<th>Total catecholamines (µg/g heart)</th>
<th>Change in catecholamines (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Reserpine</td>
<td>5 mg/kg</td>
<td>10</td>
<td>14</td>
<td>1.5</td>
<td>-90.2</td>
</tr>
<tr>
<td>2</td>
<td>Reserpine</td>
<td>5 mg/kg</td>
<td>6</td>
<td>17</td>
<td>9.6</td>
<td>-37.4</td>
</tr>
<tr>
<td>3</td>
<td>Guanethidine</td>
<td>8 mg/kg</td>
<td>4</td>
<td>14</td>
<td>6.5</td>
<td>-57.3</td>
</tr>
<tr>
<td>4</td>
<td>α-methyl-tyrosine</td>
<td>50-80 mg/kg</td>
<td>4</td>
<td>16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Hypoxic tests: 3-min ventilation with the 2% oxygen gas mixture.

TABLE 5

Effects of Pretreatment with Reserpine on the Pressor Response to Acute Alveolar Hypoxia and Lung 5-Hydroxytryptamine (5-HT)

<table>
<thead>
<tr>
<th>Expt no.</th>
<th>Dose/day</th>
<th>No. days</th>
<th>Max. hypoxic pressor response* (mm Hg)</th>
<th>Lung 5-HT (µg/g)</th>
<th>Change in lung 5-HT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 mg/kg</td>
<td>5</td>
<td>17</td>
<td>16.8</td>
<td>-73.2</td>
</tr>
<tr>
<td>2</td>
<td>5 mg/kg</td>
<td>10</td>
<td>12</td>
<td>4.4</td>
<td>-83.0</td>
</tr>
<tr>
<td>3</td>
<td>5 mg/kg</td>
<td>7</td>
<td>16</td>
<td>4.2</td>
<td>-93.3</td>
</tr>
</tbody>
</table>

*Hypoxic tests: 3-min ventilation with the 2% O₂ gas mixture.

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pared from the same blood pool as the perfusate plasma. Standard 3-minute hypoxic tests were performed at intervals of 8 to 10 minutes. Pressor responses to alveolar hypoxia appeared in all these experiments, the maximum being 7, 10, and 5 mm Hg respectively. Platelet serotonin content, given as micrograms of serotonin per milligram of platelet protein and the number of circulating platelets and plasma free indoles (as an index of serotonin release and breakdown) were determined at the outset of perfusion and after almost complete exhaustion of the responsiveness to hypoxic tests. The results are shown in Figure 2. The number of platelets decreased, but the other values were only slightly higher at the end than at the beginning of the experiments.

The concentration of indoles in plasma at the start of perfusion was greater than normal, probably due to some platelet destruction during blood handling and storage, isolation of platelets and their return to plasma. The constant concentration of serotonin in platelets indicates that there was no slow leak of serotonin from circulating platelets to plasma during the experiment. The minor increase in indole concentration of plasma could be accounted for by release of serotonin from both the lung and trapped platelets. A steady decline in the number of circulating platelets is usually seen in lung-perfusion experiments (12), a decline due partly to reversible trapping of platelets in the pulmonary vascular bed and partly to mechanical destruction. To obtain a pressor response of the order of 6 mm Hg (ΔPa) it was necessary to have perfusate concentrations of serotonin as high as 5 to 6 μg/ml. This is equivalent to indole concentrations as great as about 6 μg/ml, which is 30 times higher than the levels seen in these experiments. These data strongly suggest that serotonin from platelets or from other sources does not play a critical role in mediation of the hypoxic responses. The reason why plasma perfusate with a high number of platelets gave responses to hypoxia, whereas plasma with few or none platelets did not remains unexplained.

Discussion

Hypoxia promotes vasodilation in all systemic vascular beds studied to date. Its vasoconstrictor effect in the lung is thus unlikely to be a direct effect on smooth muscle and therefore is presumed to involve some mediator. The evidence in this and the preceding article (2) stresses the role of endogenous histamine as a mediator of hypoxia-induced...
increases in pulmonary vascular resistance. (a) A spectrum of agents that prevent the peripheral vascular effects of histamine uniformly decreased or abolished the pressor response to acute alveolar hypoxia. (b) Agents that by various mechanisms augment tissue responses to histamine both potentiated and prolonged the hypoxic pressor response. (c) An agent (48/80) that depletes lung histamine stores by 90% or more can be used in vitro to abolish the hypoxic pressor response. Such agents interfered only with the pressor response to hypoxia. In other respects the lungs behaved and functioned as before drug administration; e.g., in their response to vasoactive substances other than histamine, their rate of blood deoxygenation and oxygenation during and after tests with alveolar hypoxia and with absence of significant edema formation (no gain in weight).

Several agents that do not affect histamine but alter the peripheral effects, synthesis, or release of serotonin, catecholamines, ATP, or kinins did not consistently change the pressor response to acute alveolar hypoxia.

The interpretation of depletion studies requires analogies to interpretation of depletion-function studies of other amines. Carlsson (13) has previously pointed out that profound depletion of certain brain amines would not necessarily alter organ function. In such studies critical stores could be left intact to be released under appropriate conditions resulting in a magnitude of effect equivalent to that seen before depletion. Such interpretation might be applicable to the histamine data in our work, as a 77% decrease in histamine stores did not alter the hypoxic response. Yet when stores were decreased more that 90% of control values, the hypoxic pressor responses rapidly disappeared. Clearly, most of the stored histamine is not critical for mediation of the hypoxic response. That store which is most important to the pressor response appears to be the most difficult to deplete by the agents used in this study. Data are not yet available to define whether recently synthesized histamine is responsible for the pressor response to hypoxia or whether there is a specific anatomical site that is responsible for the actual histamine released in hypoxic conditions.

That other commonly considered amines are unimportant in the pressor response to hypoxia seems indicated by findings in the preceding article (2). This is to some extent supported by the fact that reserpine, which reduced catecholamine stores to a maximum 10% of normal, produced no alteration of the pressor response to hypoxia. Likewise, combinations of stored amines do not seem critical to the response, as reserpine which depletes both catecholamines and serotonin had no remarkable effect on the lung responses to ventilation hypoxia. However, until a 100% depletion is obtained, there is no absolute proof of the unimportance of these amines in the hypoxic pressor response.

The mechanism of the potentiation of hypoxic pressor responses by exchange of platelet-poor with platelet-rich plasma is difficult to explain. Serotonin release from the platelets does not seem responsible for mediation of the hypoxic pressor response, as a specific antiserotonin agent did not block the hypoxic pressor response in the presence of whole blood perfusate (2). Nor did total indoles in the plasma rise appreciably during a period with several hypoxic pressor responses. Conclusive information against serotonin release from platelets influencing the hypoxic responses might be obtained by studying the effects of platelet-rich plasma taken from reserpine animals or from animals treated with both reserpine and an inhibitor of serotonin synthesis (para-chlorophenylalanine).

Platelets may interact with lung tissue to release or produce histamine. Microembolization has been associated with histamine release (14), and circulating platelets were decreased rapidly in the course of a perfusion. If platelets or other formed elements help mediate histamine release, they may do so either directly or possibly via effects associated with plasma reactions, such as complement activation or formation of slow-reacting substance (15).

A critical question to answer is whether
the in vitro model in this study accurately reflects in vivo responses to the same stimuli. Acute alveolar hypoxia in vivo produces increased pulmonary vascular resistance (9) and ventilation of a lobe of a lung in situ in the dog is associated with increase of the histamine content in the effluent blood from this lobe (16). Recently it has been shown in the cat that administration of 48/80 will abolish the pulmonary vasoconstriction induced by alveolar hypoxia (17, 18). What the cellular mechanism for hypoxic release of histamine is, and whether histamine degradation, which does require oxygen, is affected by the levels of hypoxia produced in these studies remain to be seen.

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References


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ANTON HUAGE and KENNETH L. MELMON

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