Adrenergic Mechanisms in the Effects of Histamine in the Pulmonary Circulation of the Cat

By H. J. H. Colebatch, M.B., F.R.A.C.P.

ABSTRACT

Histamine constricts airways and pulmonary blood vessels in isolated lungs, but it is said to dilate pulmonary blood vessels in intact animals. The present experiments test the hypothesis that histamine only constricts pulmonary blood vessels, and that dilatation depends on epinephrine released by histamine from the adrenal glands. In cats anesthetized with pentobarbital, the difference in pressure between the pulmonary artery (PA) and left atrium (LA) was related to pulmonary blood flow measured by dye dilution before, and at intervals of 0.5 to 2 minutes after PA injection of histamine. In intact or vagotomized cats histamine increased PA-LA pressure difference and pulmonary blood flow, but calculated pulmonary vascular resistance (PVR) decreased significantly at 1 minute; control values were restored in 4 minutes. In adrenalectomized cats, histamine (10 to 40 \( \mu \)g) increased PA-LA pressure and PVR, but did not change pulmonary blood flow. After beta-receptor blockade with propranolol, histamine (10 to 20 \( \mu \)g) had the same effect as in adrenalectomized cats. After adrenalectomy or propranolol, the histamine-induced increase in PVR was prolonged. When histamine had increased PVR in adrenalectomized cats, epinephrine (5 \( \mu \)g iv) reduced PA-LA pressure and PVR. Histamine infusion (5 \( \mu \)g/kg/min iv) decreased PVR in intact cats, increased PVR in adrenalectomized cats, and when epinephrine (5 \( \mu \)g/kg/min) was also infused, decreased PVR in adrenalectomized cats. The results support the proposed hypothesis. Release of histamine locally in the lungs may encourage distribution of both blood and gas flows away from damaged and toward normal respiratory tissue.

ADDITIONAL KEY WORDS

adrenalectomy propranolol pulmonary vasoconstriction pulmonary vasodilatation

In intact cats and dogs, injected histamine constricts respiratory bronchioles and alveolar ducts, airways which are perfused by the pulmonary circulation, with relatively little direct effect on the remainder of the bronchial tree (1). As a result, expansion, and therefore ventilation, of affected units are restricted. However, observations on the action of histamine in the pulmonary circulation are contradictory. It has been claimed that histamine infused or injected into the circulation of man or dog dilates pulmonary blood vessels or has no significant effect (2-5). In isolated lungs of cats, dogs, and other animals, histamine constricts pulmonary blood vessels (6, 7), and both arteries and veins are affected (8, 9).

No coherent analysis of the role of histamine in the lung is possible if it restricts ventilation of respiratory units in the lung and at the same time dilates blood vessels associated with these units. Such an action would provide a built-in mechanism to disturb gas exchange in the lungs, whereas numerous observations in man and in animals suggest an interrelation between ventilation and perfusion which tends to preserve normality of blood gases in the presence of disturbing influences. The hypothesis tested in the present experiments is that histamine constricts pulmonary blood vessels, but if released locally in the lungs, causes release of epinephrine from the adrenal glands, which dilates these vessels. In intact animals, this would be expected to increase pulmonary blood flow, with a fall in calculated pulmonary vascular resistance (PVR).

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present experiments resolves these contradictions. It postulates that histamine acts solely to constrict pulmonary blood vessels, and that dilatation in intact animals is due to epinephrine released by histamine from the adrenal glands. The results support this hypothesis and, taken in conjunction with observations of similar effects of histamine on alveolar ducts (10), indicate how release of histamine locally in the lung may provide a homeostatic mechanism tending to preserve a normal relation between the distribution of blood and gas flow within the lungs.

Methods

Eighteen cats (mean weight 3.52 kg, se ± 0.67 kg) were anesthetized with pentobarbital (30 to 32 mg/kg ip), their tracheas cannulated, and polyethylene catheters introduced into both femoral arteries, one femoral vein, and the pulmonary artery via the right external jugular vein. During artificial ventilation of the lungs with a Harvard pump, the chest was opened through the fourth left intercostal space and a polyethylene catheter placed in the left atrium. To allow removal of air from the pleural space, a small Malecot catheter was placed in the pleural space during closure of the chest. In some cats, transpulmonary pressure was measured with a Statham differential strain gauge, one side being connected to the pleural catheter and the other to the tracheal cannula. After completing the surgical preparations and before catheterizing the pulmonary artery, heparin (1000 units/kg iv) was injected.

Additional pentobarbital (15 to 30 mg/kg iv) was given to abolish response to pain before the cat was paralyzed with gallamine triethiodide (preparations of 10 mg/kg iv). Total ventilation by Harvard pump was set to achieve an arterial CO2 tension similar to that maintained during spontaneous breathing. Subsequent arterial blood samples were analyzed to show that an arterial CO2 tension similar to that maintained during spontaneous breathing. Subsequent arterial blood samples were analyzed to show that an arterial CO2 tension similar to that maintained during spontaneous breathing.

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Systolic arterial, pulmonary arterial, and left atrial pressures were measured with a Statham strain gauge, and recorded continuously. The reference level for the pulmonary arterial and left atrial pressures was the midthoracic plane. Pulmonary artery catheter in a volume of 0.1 to 0.4 ml and arterial blood samples taken from the femoral artery were analyzed by the Scholander method. No correction was made for the gas-liquid difference for Po2 of approximately 2%. All values were corrected to rectal temperature (12).

Control measurements of vascular pressures, pulmonary blood flow, and arterial gas tensions were obtained. In one series of experiments, histamine (10 to 40 µg, as the phosphate salt in 0.9% saline) was infused into the pulmonary artery catheter in a volume of 0.1 to 0.4 ml and flushed with 1.5 ml of saline. In another series of experiments, histamine in 0.9% saline was infused at a constant rate of 1 ml/min iv (each milliliter containing histamine equivalent to 5 µg/kg) for 3 to 5 minutes. Measurements of pulmonary blood flow were obtained at intervals of 0.5 to 2 minutes, for 6 minutes or longer after injecting histamine and at similar intervals for 3 to 5 minutes after starting infusion of histamine. The measurements were repeated 3 to 4 minutes after stopping the infusion of histamine. In different animals these procedures were repeated after bilateral adrenalectomy or after injecting propranolol (0.3 mg/kg iv). As an indication of an antibradycardic action, heart rate was measured before and after injecting propranolol. In five cats, propranolol decreased heart rate 20% (mean; range 10 to 27%). After histamine infusion,
adrenalectomized cats were tested with a combined infusion of histamine and epinephrine. In two adrenalectomized cats the effect of an increase in pulmonary blood flow on pulmonary vascular resistance was tested. Pulmonary blood flow was increased by injecting 4.5 to 9 ml/kg of 10% dextran (approximate molecular weight 40,000) in 0.9% saline iv, or intra-arterially both after injection of histamine and during infusion of histamine. Dextran was injected on the first occasion, and subsequently blood withdrawn to restore blood volume was injected. Epinephrine and propranolol were standard commercial preparations.

For the most part in these studies, the physical factors influencing calculated pulmonary vascular resistance, which reflects the cross-sectional area of the vascular bed rather than the state of tone of pulmonary blood vessels (13, 14), do not interfere with interpretation of resistance changes in terms of pulmonary vasoconstriction or vasodilatation.

At the conclusion of the experiment, the cats were killed with pentobarbital (120 to 180 mg iv). After occluding the trachea, the chest was opened and the lungs excised. The larger bronchi and the cut surface of the lungs were examined for excess liquid or foam in the airways. Whenever possible, statistical analysis was made on paired measurements using Student's t-test; when the differences were not normally distributed, the ranking test of Wilcoxon was used (15).

Results

After completion of the preparation in 16 cats, the mean arterial Pco₂ was 28.8 mm Hg (±4.2 mm Hg), arterial Po₂, 102 mm Hg (±8.6 mm Hg), and the arterial pH 7.405 (±0.047). Measurements obtained later in the experiment showed that arterial Pco₂ remained within 4 mm Hg of the control value. Arterial Po₂ decreased after injection or infusion of histamine, but except in one case remained above 80 mm Hg.

Histamine (2.2 to 12.5 µg/kg) injected into the pulmonary artery increased the pressure difference between the pulmonary artery and the left atrium (PA – LA pressure) which reached a peak after 20 to 30 seconds and returned to the control value after 4 minutes (Fig. 1, Table 1). Pulmonary blood flow increased greatly during the first minute after injection and then declined; pulmonary vascular resistance decreased slightly 1 minute after injection, but otherwise did not change significantly. A small, but statistically significant, increase in left atrial pressure was found at 0.5, 1, 2 and 4 minutes after injecting histamine. Systemic arterial pressure decreased significantly. The decrease in pulmonary vascular resistance at 1 minute was not related to the increase in left atrial pressure; vascular resistance decreased 16% whether left atrial pressure increased 0 to 0.5 mm Hg (six injections) or 1 to 3 mm Hg (nine injections). The decrease in vascular resistance at 1 minute was not related to the dose of histamine; resistance decreased a mean of 14% in two cats given 12.5 µg/kg histamine, which was similar to the decrease for all injections. Histamine produced the same changes whether the vagus nerves were intact (seven
TABLE 1

Effect of Injected Histamine on Pulmonary Circulation in Cats

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>No. of injections</th>
<th>Dose histamine (µg/kg)</th>
<th>PA — LA pressure (mm Hg)</th>
<th>Pulm. blood flow (ml/min)</th>
<th>Pulm. vase. resistance (mm Hg/100 ml/min)</th>
<th>Systemic arterial pressure (mm Hg)</th>
<th>LA pressure (mm Hg)</th>
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<tr>
<td>3.56 ± 0.22</td>
<td>15</td>
<td>5.3 ± 0.8</td>
<td>12.3 ± 0.52</td>
<td>175 ± 9†</td>
<td>103 = 7</td>
<td></td>
<td>148 ± 11†</td>
</tr>
<tr>
<td>3.29 ± 0.38</td>
<td>6</td>
<td>7.1 ± 1.7</td>
<td>14.4 ± 1.86</td>
<td>174 ± 18†</td>
<td>103 = 7</td>
<td></td>
<td>163 ± 12†</td>
</tr>
<tr>
<td>3.91 ± 0.22</td>
<td></td>
<td>3.4 ± 0.5</td>
<td>13.6 ± 1.15</td>
<td>174 ± 19†</td>
<td>103 = 7</td>
<td></td>
<td>152 ± 10†</td>
</tr>
<tr>
<td>Intact, propranolol</td>
<td>3.91 ± 0.22</td>
<td>7</td>
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<td>13.6 ± 1.15</td>
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<tr>
<td>Adrenalectomy</td>
<td>3.29 ± 0.38</td>
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Values are means ± SE. PA = pulmonary arterial; LA = left atrial; C = control. Statistical significance of difference from control value: *P < 0.05; †P < 0.01. Statistical significance of difference from values at same time interval before adrenalectomy or propranolol: ‡P < 0.05. (In adrenalectomy group, three values only were obtained for each measurement at 6 min after injection of histamine.) Number in parentheses is number of cats.

After these initial injections of histamine in five cats, both adrenal glands were excised and the same dose of histamine as had been injected before adrenalectomy was repeated. Adrenalectomy did not change the control values for PA — LA pressure, slightly decreased left atrial pressure, decreased pulmonary blood flow, increased pulmonary vascular resistance and decreased systemic arterial pressure (Table 1). After adrenalectomy, histamine injected into the pulmonary artery increased PA — LA pressure to a peak at 1 minute, and in three cats the pressure remained increased for at least 10 minutes.
Effect of injecting histamine (arrow) into the pulmonary artery of a cat (weight 3.6 kg) with intact adrenal glands (•) and after bilateral adrenalectomy (○). After adrenalectomy, the increased pressure difference between the pulmonary artery and the left atrium produced by histamine was more prolonged. Pulmonary blood flow did not increase, and pulmonary vascular resistance increased. Histamine decreased systemic arterial pressure to a similar extent before and after adrenalectomy. Abbreviations as in Figure 1.

At each measurement after injecting histamine, mean left atrial pressure did not differ significantly from the control value and in individual animals changed by only 0.5 mm Hg. Pulmonary blood flow did not change significantly. Pulmonary vascular resistance increased, and as this increase occurred in the presence of an increased distending pressure, it was not a passive change but indicated pulmonary vasoconstriction. Histamine decreased systemic arterial pressure.

Compared with the same animals with intact adrenal glands, significant differences were found in the effects of histamine after adrenalectomy. The increase in PA—LA pressure was more prolonged, pulmonary blood flow failed to increase, and pulmonary vascular resistance increased to a much greater extent; systemic arterial pressure decreased more at 0.5 minutes.

After control injections of histamine, five cats were given propranolol (0.3 mg/kg iv over 2 to 4 minutes). One other cat died after administration of propranolol. Propranolol did not change PA—LA pressure, increased left atrial pressure, decreased pulmonary blood flow, increased pulmonary vascular resistance and decreased systemic arterial pressure. After propranolol, histamine increased PA—LA pressure, and in four cats the increase persisted for at least 20 minutes (Fig. 3). Left atrial pressure and pulmonary blood flow did not change significantly, and pulmonary vascular resistance increased, reflecting pulmonary vasoconstriction; systemic arterial pressure decreased transiently. The increase in pulmonary vascular resistance was not related to the decrease in arterial Po2. In one cat, when vascular resistance had increased 130% at 0.5 minute, arterial Po2 was 91 mm Hg and at 3.5 minutes, when vascular resistance was
Effect of injecting histamine (arrow) into the pulmonary artery of a cat (weight 4.34 kg) before (•) and after (○) propranolol (0.3 mg/kg iv). After propranolol the increased pressure difference between the pulmonary artery and the left atrium was more prolonged, pulmonary blood flow increased only slightly, and pulmonary vascular resistance increased. After propranolol and 3 minutes after injecting histamine, arterial $P_o_2$ was 80 mm Hg. Histamine decreased systemic arterial pressure to a similar extent, whether given before or after propranolol.

In a cat given propranolol, the effects of histamine infused with epinephrine (5 μg/kg/min iv of each) were compared with those of infusing histamine alone. The combined infusion did not increase PA—LA pressure or pulmonary vascular resistance (30% and 15%, respectively) as much as histamine infusion alone (67% and 64%, respectively).

In five adrenalectomized cats in which PA—LA pressure and pulmonary vascular resistance had been increased by injection or infusion of histamine (see below), epinephrine (1 to 3 μg/kg, seven experiments) was injected into the pulmonary artery or intravenously. PA—LA pressure decreased 5 to 8 seconds after injection to a minimum after 20 to 30 seconds; pulmonary blood flow increased; pulmonary vascular resistance decreased; systemic arterial pressure increased; but left atrial pressure did not change significantly (Fig. 4, Table 2). The changes were still present 1 minute after injection of epinephrine, but after 3 minutes the values had returned close to the level before injecting epinephrine. This decrease in distending pressure and vascular pressure difference in the presence of an increase in blood flow...
HISTAMINE-EPINEPHRINE ANTAGONISM

Effect of injecting epinephrine (at each arrow) in an adrenalectomized cat after pulmonary vascular resistance had been increased by histamine. Epinephrine decreased the vascular pressure gradient and pulmonary vascular resistance, slightly increased pulmonary blood flow and increased systemic arterial pressure. The effects of epinephrine were greatest at 30 seconds and largely reversed at 1 minute. A second injection of epinephrine had an effect similar to the first. Abbreviations as in Figure 1.

shows that epinephrine dilates pulmonary blood vessels constricted by histamine.

The results show that while histamine itself constricted pulmonary blood vessels, constriction was prevented or reversed when the adrenal glands were intact, presumably owing to release of epinephrine. To test the interaction between histamine and epinephrine more precisely, similar studies were made during infusion of histamine.

An infusion of histamine (5 μg/kg/min iv) increased pulmonary blood flow significantly, and decreased pulmonary vascular resistance and systemic arterial pressure, but did not change PA – LA pressure significantly (Table 3, Fig. 5). Left atrial pressure increased significantly 4 minutes after starting the infusion. After adrenalectomy the same infusion of histamine increased PA – LA pressure (Fig. 6) and pulmonary vascular resistance, did not change pulmonary blood flow, and decreased systemic arterial pressure. Left atrial pressure did not change significantly. The increased PA – LA pressure (Fig. 6) and pulmonary vascular resistance reached a maximum 2 minutes after the start of the infusion, persisted while the infusion was maintained and even after the infusion was stopped (Fig. 8). The prolonged increase in PA – LA pressure and vascular resistance after stopping infusion of histamine was significantly different from the rapid return to control values when the adrenal glands were intact.

When epinephrine and histamine were infused together (5 μg/kg/min iv), PA – LA pressure and vascular resistance (increased by the preceding histamine infusion) promptly decreased (Figs. 7 and 8); they tended to return to the control level before adrenalectomy. Pulmonary blood flow increased to an extent similar to that after histamine infusion before adrenalectomy, and systemic arterial pressure increased (but not significantly). Left atrial pressure increased slightly at 2 and 4 minutes after starting the infusion. After stopping the infusion, pulmonary blood flow decreased and vascular resistance increased again, but both PA – LA pressure and vascular resistance remained lower than before the combined infusion was given.

In two adrenalectomized cats, pulmonary blood flow was increased by injection of dextran, blood, or both, after injection (8.7 μg/kg iv) and after infusion (5 μg/kg/min iv) of histamine. After injection of histamine, when blood flow was increased 6% and 9%, pulmonary vascular resistance remained increased 17% and 30%, respectively, for 2 to 3 minutes, whereas in animals with intact adrenal glands a similar increase in pulmonary blood flow was associated with a significant decrease in vascular resistance 1 minute after injection. In one of the cats, pulmonary vascular resistance was reduced to the control level 5 minutes after injection of histamine.
TABLE 2
Effect of Injected Epinephrine on Pulmonary Circulation of Adrenalectomized Cats

<table>
<thead>
<tr>
<th>Minutes after Injection</th>
<th>Minutes 2:30</th>
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</thead>
<tbody>
<tr>
<td>PA – LA pressure (mm Hg)</td>
<td>26.1 ± 2.5</td>
</tr>
<tr>
<td>Percent of control</td>
<td>81 ± 4t</td>
</tr>
<tr>
<td>0.5</td>
<td>90 ± 6*</td>
</tr>
<tr>
<td>1.0</td>
<td>92 ± 5</td>
</tr>
<tr>
<td>3-6§</td>
<td>92 ± 5</td>
</tr>
<tr>
<td>Pulm. blood flow (ml/min)</td>
<td>412 ± 39</td>
</tr>
<tr>
<td>Percent of control</td>
<td>122 ± 8*</td>
</tr>
<tr>
<td>0.5</td>
<td>101 ± 4</td>
</tr>
<tr>
<td>1.0</td>
<td>101 ± 4</td>
</tr>
<tr>
<td>3-6§</td>
<td>101 ± 4</td>
</tr>
<tr>
<td>Pulm. vascular resistance (mm Hg/100 ml/min)</td>
<td>6.68 ± 1.15</td>
</tr>
<tr>
<td>Percent of control</td>
<td>68 ± 4t</td>
</tr>
<tr>
<td>0.5</td>
<td>76 ± 6t</td>
</tr>
<tr>
<td>1.0</td>
<td>76 ± 6t</td>
</tr>
<tr>
<td>3-6§</td>
<td>94 ± 4</td>
</tr>
<tr>
<td>Systemic arterial pressure (mm Hg)</td>
<td>109 ± 5</td>
</tr>
<tr>
<td>Percent of control</td>
<td>150 ± 15f</td>
</tr>
<tr>
<td>0.5</td>
<td>125 ± 6f</td>
</tr>
<tr>
<td>1.0</td>
<td>125 ± 6f</td>
</tr>
<tr>
<td>3-6§</td>
<td>125 ± 6f</td>
</tr>
<tr>
<td>LA pressure (mm Hg)</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>Percent of control</td>
<td>1.9 ± 0.4</td>
</tr>
<tr>
<td>0.5</td>
<td>1.9 ± 0.4</td>
</tr>
<tr>
<td>1.0</td>
<td>1.9 ± 0.4</td>
</tr>
<tr>
<td>3-6§</td>
<td>1.8 ± 0.5</td>
</tr>
</tbody>
</table>

Seven injections of epinephrine (1 to 3 μg/kg iv) in five cats after pulmonary arterial pressure and pulmonary vascular resistance had been increased by histamine. Statistical significance of difference from control value: †P < 0.01; ‡P < 0.05; §five injections only. Abbreviations as in Table 1.

FIGURE 5
Effect of an intravenous infusion of histamine on mean pulmonary arterial pressure ($P_{PA}$), mean systemic arterial pressure ($P_{SA}$) and mean left atrial pressure ($P_{LA}$) in a cat with intact adrenal glands. Time markers = 5 seconds. The speed was increased during recording of the dye dilution curve. Histamine slightly increased $P_{PA}$, decreased $P_{SA}$ and did not change $P_{LA}$, only when pulmonary blood flow had increased to 270% of the control level (Fig. 9). During infusion of histamine when pulmonary blood flow was increased 52% and 54% (4

HISTAMINE-EPINEPHRINE ANTAGONISM

TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>Min.</th>
<th>Instant (M)</th>
<th>Adrenalec. (M)</th>
<th>Adrenalectomy + epinephrine infusion (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA – LA pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of control</td>
<td>C</td>
<td>13.0 ± 1.1</td>
<td>14.4 ± 1.2</td>
<td>20.0 ± 3.3†</td>
</tr>
<tr>
<td></td>
<td>1-2§</td>
<td>117 ± 7</td>
<td>219 ± 32*</td>
<td>84 ± 6*†</td>
</tr>
<tr>
<td></td>
<td>2-4§</td>
<td>114 ± 9</td>
<td>229 ± 34*</td>
<td>77 ± 10†</td>
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<tr>
<td></td>
<td>2-4†</td>
<td>101 ± 4</td>
<td>170 ± 20*</td>
<td>92 ± 8††</td>
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<td>Pulm. blood flow (ml/min)</td>
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</tr>
<tr>
<td>Percent of control</td>
<td>C</td>
<td>584 ± 30</td>
<td>410 ± 29</td>
<td>384 ± 45‡</td>
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<tr>
<td></td>
<td>1-2§</td>
<td>151 ± 13*</td>
<td>117 ± 11</td>
<td>138 ± 8‡</td>
</tr>
<tr>
<td></td>
<td>2-4§</td>
<td>147 ± 9</td>
<td>111 ± 11</td>
<td>147 ± 9†</td>
</tr>
<tr>
<td></td>
<td>2-4†</td>
<td>106 ± 9</td>
<td>100 ± 7</td>
<td>114 ± 6</td>
</tr>
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<td>Pulm. vasc. resistance (mm Hg/100 ml/min)</td>
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<tr>
<td>Percent of control</td>
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<td>3.61 ± 0.42</td>
<td>5.52 ± 1.03‡</td>
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<td>1-2§</td>
<td>82 ± 9</td>
<td>190 ± 26*</td>
<td>62 ± 17†</td>
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<tr>
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<td>2-4‡</td>
<td>78 ± 7*</td>
<td>212 ± 32†</td>
<td>51 ± 6††</td>
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<td>2-4†</td>
<td>100 ± 8</td>
<td>167 ± 29†</td>
<td>73 ± 7††</td>
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<td>Systemic arterial pressure (mm Hg)</td>
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<tr>
<td>Percent of control</td>
<td>C</td>
<td>137 ± 8</td>
<td>112 ± 8</td>
<td>105 ± 10†</td>
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<td>103 ± 2</td>
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<tr>
<td>LA pressure (mm Hg)</td>
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<tr>
<td>Percent of control</td>
<td>C</td>
<td>1.9 ± 0.2</td>
<td>1.1 ± 0.5</td>
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</tr>
<tr>
<td></td>
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<td>1.2 ± 0.6</td>
<td>1.7 ± 0.5†</td>
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Values are means ± se. Mean cat weight, 3.41 ± 0.90 kg. †After starting infusion of histamine, 5 μg/kg/min iv, or combined infusion of histamine and epinephrine, each 5 μg/kg/min iv. ‡After stopping infusion. Statistical significance of difference from control value: *P < 0.05; †P < 0.01. Statistical significance of difference from values or change found in intact group: †P < 0.05. Abbreviations as in Table 1. Number in parentheses is number of cats.

FIGURE 6

Intravenous infusion of histamine to the same cat as Figure 5 after bilateral adrenalectomy. PA increased progressively, RPA decreased, RLA showed little change. Time markers = 5 seconds.

to 6 minutes after starting the infusion), pulmonary vascular resistance was still increased by 47% and 44%, but with intact adrenal glands a similar increase in pulmonary blood
flow was associated with a significant decrease in vascular resistance. In one of the cats, pulmonary vascular resistance was reduced to the control level 65 minutes after starting the infusion of histamine when pulmonary blood flow had increased to 239% of the control value (Fig. 10).

After adrenalectomy or administration of propranolol, histamine constricts airways more severely than before these procedures (10). Therefore a test was made to determine if increased airway pressure contributed to an increased pulmonary arterial pressure. In three adrenalectomized cats in which pulmonary arterial pressure had been increased by histamine, ventilation of their lungs was stopped for several seconds (Fig. 11). During this brief apnea there was no change either in mean pulmonary arterial or in mean left atrial pressure.

At postmortem examination, the pleural cavity contained an average of 15 ml of blood. In two cats only, was there evidence of edema of the lungs; one cat from the propranolol group had received injections of histamine (100 μg and 200 μg) shortly before death; in the other, edema was confined to the left lower lobe. In half the cats, the posterior surface of the lower lobes showed evidence of collapse. Otherwise the lungs appeared normally expanded, and collapsed normally when the tracheal clamp was removed.

Discussion

In adrenalectomized cats, the constriction of pulmonary blood vessels by histamine, the dilatation of constricted vessels by epinephrine, and the conversion of constriction to dilatation when histamine is infused with epinephrine are similar to the changes observed in perfused lungs of other animals isolated from the body (16, 17).

In the presence of intact adrenal glands, the changes are more complex. The pulmonary vascular pressure difference increases substantially 30 seconds after injecting histamine, but calculated vascular resistance does not change owing to an equivalent increase in pulmonary blood flow. The increase in pulmonary blood flow does not explain the increase in pulmonary arterial pressure, as in other studies in nine cats, when the total pulmonary blood flow was abruptly shifted to one lung (by clamping the hilum of one lung). Pulmonary arterial pressure increased only 21% (mean; se±4%).

The passive effect of an increase in pulmonary blood flow and pulmonary arterial pressure is a decrease in pulmonary vascular resistance (13), so a combination of vasoco-
Effect of three separate periods of histamine infusion (5 μg/kg/min iv). Onset at first arrow, with intact adrenal glands (•); after bilateral adrenalectomy (o), and combined with infusion of epinephrine (5 μg/kg/min) (a). With intact adrenal glands, histamine increased PA—LA pressure and pulmonary blood flow without increasing pulmonary vascular resistance. After adrenalectomy, histamine greatly increased PA—LA pressure and pulmonary vascular resistance without increasing pulmonary blood flow. When combined with epinephrine, histamine decreased PA—LA pressure and pulmonary vascular resistance and increased pulmonary blood flow. Except when combined with epinephrine, histamine decreased systemic arterial pressure. After stopping the infusion in the intact animal, the variables returned to the control values. After adrenalectomy, the changes tended to persist when histamine alone was infused and to return to the preinfusion values when histamine was combined with epinephrine.

Retention and passive distension of pulmonary blood vessels would account for the findings 30 seconds after injection of histamine. Although calculated pulmonary vascular resistance decreased 1 minute after injecting histamine, it is not suggested that this decrease itself reflects a true dilatation of pulmonary blood vessels because it is consistent with the passive effect of an increase in pulmonary blood flow alone. However, when histamine was given to adrenalectomized cats, an equivalent increase in pulmonary blood flow did not abolish the increase in vascular resistance. In addition, whereas the maximum increase in pulmonary arterial pressure, and therefore distending pressure, produced by histamine was similar before and after adrenalectomy, pulmonary blood flow was higher and pulmonary arterial pressure decreased more rapidly when the adrenal glands were intact. These findings imply that the adrenal glands provide an agent opposing constriction of pulmonary blood vessels and responsible for the early reversal of an initial vasoconstriction by histamine. Other results in this study show that epinephrine has the properties of
Effect of two injections of histamine into a cat (weight 4.60 kg) after bilateral adrenalectomy. After the first injection (solid line), the measurements were made without further intervention. Histamine increased PA—LA pressure and pulmonary vascular resistance with little change in pulmonary blood flow or in left atrial (LA) pressure. Pulmonary vascular resistance was reduced to the control level by epinephrine (5 mg/hr at 20 minutes). A second injection of histamine (broken line) 30 minutes after the first produced a smaller increase in PA—LA pressure and pulmonary blood flow and decreased vascular resistance to the control level when blood flow was increased 170%. After removing the added volume, vascular resistance decreased. Such an agent and, when infused with histamine, reproduces the changes in the pulmonary circulation observed with histamine alone when the adrenal glands are intact.

This pattern of vascular constriction followed by dilatation after injection of histamine closely resembles the constriction and dilatation of alveolar ducts shown by decrease in pulmonary compliance (maximum at 15 seconds) and followed by substantial recovery after 1 to 2 minutes (1). Histamine (2 μg/kg into the pulmonary artery) released an epinephrine-like agent, equivalent to approximately similar amounts of epinephrine (by weight), which was responsible for reversal of alveolar duct constriction (10). In adrenalectomized cats, histamine caused a greater decrease in pulmonary compliance from which there was little spontaneous recovery.

Others have shown that in the cat histamine releases epinephrine by a direct action on the adrenal medulla (18, 19). Staszewska-Barczak and Vane (19) (in 14 of 26 experiments) found that 1 to 5 μg of histamine released 0.5 to 1.5 μg of epinephrine without release of norepinephrine. During infusion of histamine, in amounts comparable to those used in the present experiments, the same authors found release of epinephrine amounting to about 10%
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Figure 10

Effect of increasing pulmonary blood flow with injection of blood and dextran intra-arterially during continuous infusion of histamine (5 μg/kg/min iv). Histamine increased PA—LA pressure and pulmonary vascular resistance (broken line) without increasing pulmonary blood flow. Pulmonary vascular resistance decreased as pulmonary blood flow increased and was reduced to the control level when blood flow was increased 130%. Epinephrine (10 μg iv at third arrow) reduced PA—LA pressure and vascular resistance.

(by weight) of the infused histamine. Similarly, histamine released epinephrine in dogs, but in adrenalectomized animals even large doses of histamine resulted in no detectable release of epinephrine. Based on studies of splanchnic nerve stimulation (20, 21) Ginn and Vane (22) suggest that the cat's adrenal glands can secrete up to 5 μg epinephrine/kg body weight/min. In the present studies in adrenalectomized cats, a smaller quantity of infused epinephrine may well have sufficed to replace that released from the intact adrenal glands by histamine.

Epinephrine both constricts and dilates pulmonary blood vessels (23). In dogs, constriction or "stiffening" of pulmonary blood vessels is insufficient to overcome the effect of passive distention (24), and constriction is elicited only occasionally (25). In the collapsed or perfused lung of the cat, epinephrine usually dilates pulmonary blood vessels (26, 27). When pulmonary blood vessels are constricted by hypoxia (28), by perfusion with defibrinated blood (17), or in the present studies by histamine, epinephrine causes dilatation. The apparent vasodilator action of histamine on pulmonary blood vessels constricted with serotonin (29) may also depend on release of epinephrine. If pulmonary blood vessels are normally almost maximally dilated, the only possible change after injection of epinephrine is constriction. In comparison with the well-marked dilatation of constricted vessels by epinephrine, its constrictor action appears to be minor. This interpretation is supported by direct tension recording from...
FIGURE 11

Effect of stopping ventilation in an adrenalectomized cat in which pulmonary arterial pressure had been increased 100% by histamine. During apnea shown by absence of transpulmonary pressure swing (Pp), mean pulmonary arterial and mean left atrial pressures were unchanged, and systemic arterial pressure increased slightly. (Abbreviations as in Figure 5).

pulmonary vascular smooth muscle. In the dog and rabbit, in contrast to smooth muscle from renal or mesenteric vessels, pulmonary vascular smooth muscle did not contract in the presence of epinephrine unless very high concentrations were used, and then the response was delayed (30).

It is therefore not necessary to postulate a dual effect of histamine itself on pulmonary blood vessels, but, rather, that histamine constricts only pulmonary blood vessels. In intact animals variations in the degree of pulmonary vasoconstriction or vasodilatation may be explained by variations in the relative concentrations of histamine and epinephrine in the blood. Epinephrine release by injected histamine satisfactorily explains why we find only an initial transient constriction of pulmonary blood vessels by histamine in intact animals, and also the failure to detect constriction when histamine is infused and measurements made after several minutes (2).

After removal of the adrenal glands, histamine causes a prolonged increase in pulmonary vascular resistance. That this increase in vascular resistance does indeed represent vasoconstriction is supported by its prompt reversal by injected epinephrine. It is difficult to account for such findings on the basis of mechanical effects secondary to the accumulation of liquid in perivascular spaces, and gross evidence of edema of the lungs was found in only two cats. The possible influence of airway pressure and of hypoxia requires consideration. Bronchoconstriction by increasing alveolar pressure may be responsible for a minor increase in pulmonary arterial pressure (31). The present experiments do not suggest that increase in pulmonary arterial pressure after histamine depends on an increase in respiratory pressures. The increase in transpulmonary pressure swing after histamine was less than the increase in pulmonary arterial pressure, which did not decrease during apnea when the effects of respiratory pressure were absent.

Study of the mechanical properties of the lungs showed that histamine constricts airways more severely in adrenalectomized cats or after propranolol than before these procedures (10). In five cats, three adrenalectomized and two given propranolol, histamine (2.0 to 8.8 μg/kg, mean 5.0 μg/kg, 20 experiments) increased pulmonary (air flow) resistance 101% (mean; SD±25%; control resistance 13.2±4.5 cm H2O/liter/sec) and decreased pulmonary compliance 66% (mean; SD±10%; 21 experiments; control compliance 9.5±5.1 ml/cm H2O). At a pulmonary resistance of 40 cm H2O/liter/sec (exceeded only once) and a ventilation of 1 liter/min, expiratory alveolar pressure increased less than 1 mm Hg. It is therefore unlikely that bronchoconstriction made any appreciable contribution to the increase in pulmonary arterial pressure after histamine.

In the cat, the predominant action of histamine on airways is constriction of alveolar ducts rather than bronchoconstriction. For reasons similar to those given above, it is unlikely that alveolar duct constriction increased pulmonary arterial pressure secondary.
ly to an increase in airway pressure. Could alveolar duct constriction increase pulmonary vascular resistance directly? While such a possibility cannot be definitely excluded, some observations are inconsistent with such a view. Whereas after histamine administration in adrenalectomized cats, epinephrine decreased PA — LA pressure and vascular resistance, pulmonary compliance was little changed until the lungs were subjected to a large inflation. Presumably this means that pulmonary vascular changes are independent of the degree of alveolar duct constriction. At the present stage, a more straightforward interpretation of the data in adrenalectomized cats, that increased pulmonary vascular resistance after histamine depends on contraction of pulmonary vascular smooth muscle, appears justified. The present experiments do not show the site of blood vessel constriction but are consistent with involvement of arteries as well as veins, as has been found by others (8, 9).

In adult lungs, hypoxia causes pulmonary vasoconstriction, which is probably due to a local effect of reduced alveolar oxygen tension (32). In the present experiments, ventilation was maintained at a constant level, and with only a small variation in arterial PCO2, generalized alveolar hypoxia is excluded. Systemic hypoxemia does result from histamine injection, or infusion, but recent work does not favor hypoxemia as a cause of pulmonary vasoconstriction (33). Furthermore, even if arterial PO2 had decreased in every case to 60 mm Hg and assuming that alveolar PO2 was no higher (corresponding to an inspired oxygen concentration of approximately 13%), the increase in pulmonary vascular resistance due to hypoxia alone would probably not have been detectable (34).

Prolongation of histamine-induced vasoconstriction after propranolol similar to that in adrenalectomized cats is consistent with blockade of the beta-receptor action of epinephrine. Propranolol may impair recovery from vasoconstriction to a greater extent than adrenalectomy alone because it prevents the action of catecholamine released locally or from sympathetic nerves on beta receptors of pulmonary vascular smooth muscle. After the administration of propranolol, a smaller dose of histamine sufficed to increase pulmonary vascular resistance to an extent similar to that in adrenalectomized cats. This suggests that the adrenal glands may not be the only source of catecholamine released after injection of histamine.

Although histamine increases cardiac output in man (35) and dog (29) and, in the present experiments, in the cat, the increase was not found in adrenalectomized cats or after beta-receptor blockade with propranolol. Thus increase in cardiac output is probably not a direct effect of histamine but dependent on release of epinephrine. An increase in blood dextrose observed by Weiss and his colleagues (35) during histamine infusion in man is consistent with release of epinephrine. On the other hand, histamine appears to stimulate isolated mammalian atria directly (36, 37) but in concentrations 20 to more than 100 times greater than those maintained in the present experiments (estimated to be less than 0.1 μg/ml). With doses of histamine ordinarily used in intact animals and man, the increase in cardiac output is more likely to depend on release of epinephrine.

The level of histamine in the blood was not measured in these experiments, but an estimate can be made of the additional concentration caused by infusion of histamine. Infusion of histamine at 5 μg/kg/min in adrenalectomized cats with a pulmonary blood flow of 140 ml/min/kg would allow an initial histamine concentration of 0.006 μg/ml. From plasma volume (38) and hematocrit (39), blood volume in the cat can be estimated at 78 ml/kg. With no loss from the intravascular compartment, histamine concentration would increase by 0.06 μg/ml after 1 minute. In individual cats, the maximum increase in PA — LA pressure and in pulmonary vascular resistance was reached after infusion for 2 minutes, when the maximum increase in the level of histamine in the blood would amount to 0.12 μg/ml. Since histamine is lost by uptake and diffusion into tissues, the increase
in blood level would be less than 0.12 \mu g/ml but presumably greater than 0.036 \mu g/ml. In the case of injected histamine, the concentration would be diminishing throughout the measurement period. Histamine was injected in a volume similar to that used for the dye, for measurement of pulmonary blood flow and the dye concentration had fallen to less than 0.0016 of its concentration in the injectate within 6 seconds. With no loss of histamine, the increased blood level after 6 seconds would amount to less than 0.16 \mu g/ml. These estimates suggest that in the present experiments the increase in the level of histamine in the blood might amount to about 0.1 \mu g/ml, within the range of increase in plasma histamine found after injection into dogs of the histamine liberator 48/80 (40), but much less than the increase in plasma histamine (1 \mu g/ml) found in cats after injection of 48/80 (41). In man the average normal level of histamine in blood is 0.042 \mu g/ml (42) increasing up to 0.2 \mu g/ml in various pathological states (43). However, as far as responses within the lung are concerned, the local concentration, rather than the blood level, is significant. In cats an average of 14 \mu g of histamine/g of lung tissue was released by embolism of the pulmonary arterial circulation with BaSO4 (44). Since constriction of alveolar ducts was maximum within 5 minutes after embolism, most of the histamine was probably released during this period and would allow a local concentration of several micrograms of histamine per gram of lung tissue, about 100 times the increase in the concentration of histamine in arterial blood—0.012 and 0.028 \mu g/ml found in two cats 2 to 3 minutes after embolism. The perfused sensitized lung of guinea pig or monkey, when exposed to antigen, released 9.3 \mu g and 2 to 5 \mu g of histamine/g of lung tissue, respectively, and most of this histamine was washed out in the first 4 minutes after challenge (45). These results also suggest that the concentration in the lung of released histamine would be of the order of 1 \mu g/g of tissue.

Failure to observe severe pulmonary vasoconstriction after the injection of 48/80 (34, 40) can be explained by the fact that epinephrine released as a consequence of the increased plasma level of histamine antagonizes constriction of pulmonary blood vessels. In adrenalectomized cats or in animals treated with propranolol, the expected severe pulmonary vasoconstriction after 48/80 is observed (Colebatch, unpublished observations).

The key to understanding the role of histamine in the lung is the sensitivity of pulmonary blood vessels and alveolar ducts to constriction, combined with a remarkably effective antagonism of injected or circulating histamine by epinephrine released from the adrenal glands. Only in adrenalectomized animals is it possible to reproduce by injection of histamine its action when released locally in the lung.

Histamine is known to be present in the lungs in relatively large quantities (46), but the physiological role of this stored histamine remains uncertain. In the light of present evidence, it is possible to suggest how histamine in the lung may contribute to the homeostasis of gas exchange (Fig. 12). At a site of local release (due to microembolism, tissue damage or inflammation), histamine will constrict blood vessels as well as alveolar ducts, tending to reduce the flow of blood and gas into the affected areas. In the absence of epinephrine, this constriction will persist. If histamine escapes into the systemic circula-
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In theory, it will release epinephrine from the adrenal glands. The mixture of epinephrine and histamine returning to the lungs will tend to relax smooth muscle of blood vessels and alveolar ducts, but at a site of local release a much higher concentration of histamine will allow constriction to persist. Histamine-epinephrine interaction provides a negative feedback mechanism tending to confine constriction of blood vessels and alveolar ducts to the site of local histamine release.

Such a physiological interaction between histamine and epinephrine supports the view that one role of histamine stored in the lung is to shut down the gas exchange function of damaged lung tissue in which ventilation-blood flow relations are necessarily grossly disturbed. The present analysis has the advantage of reconciling conflicting experimental evidence from many different sources and studies. This in itself provides strong support for the final interpretation. At least it may be said that antagonism of histamine by epinephrine is so effective that it has hindered recognition of its pulmonary vasoconstrictor properties and thus has concealed its physiological role in the lung.

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H. J. H. COLEBATCH

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