Histamine Receptor Antagonism Does Not Inhibit Hypoxic Pulmonary Vasoconstriction in Dogs


Histamine has been suggested to be a mediator of hypoxic pulmonary vasoconstriction.1–3 However, histamine has been reported to have both pulmonary vasoconstrictor (H1-receptor) and vasodilator (H2-receptor) actions in isolated, perfused guinea-pig lungs.4,5 These observations raise certain reservations regarding histamine as a mediator of the hypoxic pulmonary pressor response. First, histamine apparently has dual actions in the pulmonary circulation, and second, previous investigators have employed only H2-receptor antagonists in their studies of hypoxia.4,5 Therefore, this study was conducted to characterize histamine receptors in the canine lung, and then to use appropriate histamine antagonist analogs in studies of hypoxic pulmonary vasoconstriction in the intact dog.

**Materials and Methods**

Characterization of canine pulmonary histamine receptors was achieved by using both specific antagonists and agonists of H1- and H2-receptors. In aerobated (sodium pentobarbital or Innovar), spontaneously breathing dogs, histamine phosphate infusions (10 μg/kg/min for 5 min) were administered to animals before and after either H1-receptor blockade with chlorpheniramine (1 mg/kg, n = 6), H2-receptor blockade with metiamide (5 mg/kg/min for 35 min, n = 6), or combined H1- and H2-receptor blockade (n = 8). Intravenous infusions of the histamine agonists were administered to another group of 6 dogs. H1-receptor stimulation was achieved by infusing 2-methylhistamine dibydrochloide (35 μg/kg/min for 5 min). The pulmonary vascular responses to these specific agonists were compared to responses obtained with histamine (combined H1- and H2-receptor stimulation).

The possible involvement of H1- and H2-receptors in hypoxic pulmonary vasoconstriction was then investigated using the histamine antagonists. Pulmonary vascular resistance was determined before and after specific histamine (H1- and H2-receptor) blockade. Combined H1- and H2-receptor blockade was achieved by infusing both metiamide and metiamide dibhydrochloide (35 μg/kg/min for 5 min). The pulmonary vascular responses to histamine were recorded before and after specific histamine blockade.

**RESULTS**

Pulmonary vascular resistance (PVR) responses to histamine before and after histamine receptor antagonism are shown in Table 1. Slight pulmonary vasoconstriction was observed during histamine infusion alone. However, after blockade of H2-receptors, histamine-induced marked vasoconstriction. After blockade of H1-receptors, the vasoconstriction seen with histamine was reversed into a vasodilation. Infusion of specific histamine receptor agonists yielded similar results. Combined H1- and H2-receptor stimulation with histamine increased PVR by + 0.48 ± 0.34 units. H1-receptor stimulation with 2-methylhistamine increased PVR by + 2.72 ± 0.50 units, whereas H2-receptor stimulation with 4-methylhistamine decreased PVR by − 0.74 ± 0.17 units.

**Table 1—Change in PVR with Histamine before and after Specific Histamine Receptor Antagonism**

<table>
<thead>
<tr>
<th>Control</th>
<th>Histamine Antagonism</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1-blockade (n = 6)</td>
<td>0.94 ± 0.28</td>
</tr>
<tr>
<td>H2-blockade (n = 6)</td>
<td>0.81 ± 0.19</td>
</tr>
<tr>
<td>H1 + H2-blockade (n = 8)</td>
<td>0.93 ± 0.17</td>
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</table>

5 min histamine infusion (*Different from comparable control value at P < 0.05. All values are mean ± SE.

Exposure to hypoxia elicited consistent increases in PVR of 95%, 97%, and 116% in the H1-, H2-, and H1 + H2-receptor blocked groups, respectively, prior to administration of the antagonist (Table 2). H1-receptor blockade did not alter the PVR response to hypoxia (+ 100%), whereas H2-receptor blockade with metiamide potentiated the increase in PVR (+ 145%). Combined H1- + H2-receptor blockade also did not alter the increase in PVR with hypoxia (+ 98%). Arterial oxygen tension (33 to 36 mm Hg), carbon dioxide tension, and pH during hypoxia were similar, before and after drug treatment, for each group of dogs.

**Table 2—PVR Responses to Hypoxia before and after Specific Histamine Receptor Antagonism**

<table>
<thead>
<tr>
<th>Control</th>
<th>Histamine Antagonism</th>
</tr>
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<tbody>
<tr>
<td>Hypoxia</td>
<td>Normal</td>
</tr>
<tr>
<td>H1-blockade (n = 8)</td>
<td>4.4 ± 0.4</td>
</tr>
<tr>
<td>H2-blockade (n = 6)</td>
<td>3.8 ± 4.3</td>
</tr>
<tr>
<td>H1 + H2-blockade (n = 8)</td>
<td>3.8 ± 0.4</td>
</tr>
</tbody>
</table>

Hypoxia value was that obtained at 5 min of hypoxia. All values are mean ± SE.
DISCUSSION

The existence of both H1 (vasoconstrictor) and H2 (vasodilator) receptor antagonists was demonstrated in the canine pulmonary circulation with the use of both histamine receptor antagonists and agonists. Therefore, either exogenous or endogenous histamine is potentially capable of eliciting pulmonary vasoconstriction or vasodilation. The failure of H2-receptor blockade to prevent hypoxic pulmonary vasoconstriction, and the potentiating of the response after H1-receptor blockade, indicate that histamine is not the mediator. However, histamine did appear to be released during hypoxia, but it acted to oppose the hypoxia-induced vasoconstriction.

This possible vasodilator action of histamine during hypoxia was tested by infusing histamine during hypoxia. Indeed, histamine reduced the degree of vasoconstriction induced by hypoxia, as has been shown previously in species other than the dog. Thus, histamine acted as a pulmonary vasoconstrictor under normoxic (normotensive) conditions, and as a vasodilator under hypoxic (hypertensive) conditions. Histamine appears to be a modulator, rather than a mediator, of hypoxic pulmonary vasoconstriction in the dog.

REFERENCES

Catecholamine Mechanisms in the Canine and Feline Lung

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Fluorescence histochemical methods were used to study freeze-dried, sectioned lungs and air-dried, stretched preparations of pulmonary blood vessels of dogs. A rich perivascular plexus of nerves that showed a yellow-green fluorescence and had many fine branches was seen around the lobar pulmonary arteries of dogs. Individual varicosities were visible at high magnification. The walls of arteries as small as 70 microns (intra-luminal diameter) contained fluorescent nerves, but none was found in the walls of smaller arterial branches. A rich perivascular plexus of fluorescent nerves also surrounded the lobar pulmonary veins of dogs. The nerve bundles were more uniform in size than those that innervated the lobar arteries, and they formed a network of uniform mesh. There was a rich plexus around the origin of branches of the lobar vein, and some nerve bundles extended onto these branches. Individual varicosities could be seen at high magnification. Fine fluorescent nerve fibers were seen around the vasa vasorum. Fluorescent nerves in the distal part of the lobar pulmonary vein were more sparse than in the proximal part. Fluorescent nerves in the medium-sized pulmonary veins were more sparse than in the lobar veins. The innervation of the medium-sized veins was variable. No nerves were seen in the walls of the small pulmonary veins. The distribution of fluorescent nerve terminals in the pulmonary arteries of dogs indicates that autonomic control of these vessels is of greater functional significance than has generally been believed.

Fluorescence histochemical and electron microscopic methods were also used to study SIF (small intensely fluorescent) cells in the lungs of 5 cats. Some of the peri-bronchial ganglia of cats contained small clusters of SIF cells. It is generally accepted that the SIF cells seen with the fluorescence microscope are identical with the granule-containing cells seen with the electron microscope.

Of the many large peri-bronchial ganglia of kittens examined with the electron microscope, there had associated granule-containing cells. Two of the ganglia each contained a cluster of 20 or more granule-containing cells. Each of these clusters consisted of a compact group of cells and other cells that were surrounded by many capillaries of the continuous type. Numerous granules or dense-core vesicles of the type known to contain biogenic amines were dispersed throughout the cytoplasm of the cells. Most of these vesicles were 900 to 1850A in diameter and contained highly electron-dense cores that almost filled the vesicles. A few of the vesicles contained a particulate core of moderate electron density that almost filled the vesicles. A few other vesicles were 1500 to 2500A in diameter and contained highly electron-dense cores that occupied only a small part of each vesicle.

The granule-containing cells had large processes that were simply finger-like extensions of the cytoplasm and smaller processes that contained a few dense-core vesicles and numerous microtubules and resembled the axons of nerve cells. Many of the large processes were near capillaries. There were cholinergic terminals near the granule-containing cells, often ensheathed by the...