HISTAMINE RECEPTORS IN THE BRONCHIAL MUSCULATURE AND VASCULATURE OF THE DOG*

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Participation of histamine H$_1$- and H$_2$-receptors in the bronchial musculature and vasculature of the dog was investigated by using the method for evaluating airway responses. A peristaltic pump and a Starling pneumatic resistance were used for a constant pressure perfusion. Dogs given 0.1–10 $\mu$g histamine by a close intraarterial injection showed increases in ventilation overflow (bronchoconstriction) and in blood flow (bronchial vasodilatation) in a dose-dependent manner. The bronchoconstriction produced by histamine was antagonized strongly by chlorpheniramine, a H$_1$-receptor antagonist, but not modified by cimetidine, a H$_2$-receptor antagonist. The bronchial vasodilatation produced by histamine was antagonized by both chlorpheniramine and cimetidine. These results suggest that histamine evokes bronchoconstriction through H$_1$-receptors and bronchial vasodilatation through H$_1$- and H$_2$-receptors.

Keywords — histamine receptors; chlorpheniramine; cimetidine; bronchial musculature; bronchial vasculature

INTRODUCTION

Airway smooth muscle of numerous species is sensitive to histamine and the bronchoconstriction is antagonized by the histamine H$_1$-receptor antagonists. On the other hand, Maengwyn-Davies$^1$ reported that histamine causes a relaxation which was antagonized partly by mepyramine in the cat isolated tracheal chain. Eyre$^2$ found that the relaxation response of the isolated sheep bronchus to histamine was antagonized by burimamide but not by mepyramine, and the relaxation of the isolated cat trachea in response to histamine was effectively abolished by both mepyramine and burimamide. In the guinea pig, Levi et al.$^3$ reported that an increase in bronchial resistance by histamine is inhibited by pro-methazine, and potentiated by burimamide. Okpako$^4$ demonstrated that the guinea pig tracheobronchial muscle contains H$_2$-receptors which modulate the effects of H$_1$-receptor activation. Yen and Kreutzer$^5$ reported that histamine at low concentrations caused a slight relaxation which was potentiated by chlorpheniramine and abolished by metiamide, and higher concentrations of histamine produced a dose-related contraction which was antagonized competitively by chlorpheniramine or potentiated by metiamide in guinea pig peripheral airway smooth muscle. In human bronchus,$^6$ both H$_1$- and H$_2$-receptors participate in allergic bronchospasm, H$_1$-receptors stimulating and H$_2$-receptors inhibiting muscle tone.

In the dog, there are only few reports on the distribution of histamine H$_1$- and H$_2$-receptors in the airway smooth muscle. Himori and Taim$^7$ investigated the role of histamine H$_1$- and H$_2$-receptors and their relative predominance in the tracheal musculature of the dog. In a previous

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report, we attempted to characterize histamine receptors responsible for airway constriction which occurs in histamine-induced asthma in dogs.

In most vascular beds of the dog, histamine H₁- and H₂-receptors are involved in vasodilatation in response to histamine. There are, however, no specific reports on the distribution of histamine receptors in the dog bronchial vasculature.

The present study was designed to characterize the role of histamine H₁- and H₂-receptors in the bronchial musculature and vasculature of the dog by using the method for evaluating airway responses.

MATERIALS AND METHODS

The experiments were carried out mostly according to the method for evaluating airway responses as described previously. Male mongrel dogs weighing between 11 and 14 kg were anesthetized with sodium pentobarbital (30 mg/kg i.v.). The animals were immobilized with decamethonium bromide (initial dose 0.4 mg/kg i.v. and supplemental doses 0.2 mg/kg i.v. every hour), and ventilated artificially through a tracheal cannula connected to an artificial respirator (Natsume, KN-50) at a constant volume and a frequency of 20 breaths/min.

Technique for Perfusioning the Bronchial Artery and Measuring Bronchovascular Activities —The chest was opened at the right fifth intercostal space. After heparinization (initial dose 500 units/kg i.v. and supplemental doses 200 units/kg i.v. every hour), the right bronchial artery originating from one of the right intercostal arteries was cannulated and perfused with the dog’s own blood delivered from the right femoral artery. A peristaltic pump (Tokyo Rikakikai, C-16) and a Starling pneumatic resistance were used for constant pressure perfusion. The perfusion pressure was adjusted initially to approximate the mean systemic blood pressure. Blood flow through the perfused area was measured with an electromagnetic flowmeter (Nihon Kohden, MF-26).

Perfused area in the lungs of the cannulated right bronchial artery was visualized with 1% pontamine sky blue dye after excising the lungs and confirming blueing area at the end of each experiment. The area was found, in most cases, to be entire bronchi and bronchioles in the right lung and the right main bronchus.

The systemic arterial blood pressure and heart rate were monitored from the cannulated left femoral artery via a pressure transducer (Nihon Kohden, MPU-0.5) and tachometer (Nihon Kohden, RT-5), respectively.

Techniques for Measuring Bronchomotor Activities —Responses of the bronchial musculature were measured by a modification of the Konze-Rössler method. Insufflated air from the artificial respirator was warmed and humidified by passing through a water bath at 32°C, and was introduced into the airway through the side arm of the tracheal cannula. The lung was inflated at a fixed volume of air under a constant pressure (10 cm H₂O) and the ventilation overflow was measured using a pneumotachograph (Nihon Kohden, MFP-IT) as an index of the change in airway resistance. Tidal volume was adjusted at the beginning of each experiment so that the overflow was exactly 2.5 ml/kg body weight, and

![Graph](image)

**FIG. 1.** Responses of the Dog Bronchial Vasculature and Airway Smooth Muscles to Histamine injected into the Bronchial Artery

Upper and lower tracings are the blood flow (B.F.) and ventilation overflow (V.O.), respectively. Histamine was injected at the dots below recordings.
was kept constant throughout the experiment.

Drugs — The drugs used were histamine dihydrochloride (Wako Pure Chemicals), chlorpheniramine maleate (Sankyo) and cimetidine (Smith, Kline & French). Solutions of cimetidine were prepared by dissolving the base in a small volume of 0.1 N HCl, neutralizing the solution with 0.1 N NaOH and making up to required volume with 0.9% NaCl solution immediately before use. All doses were expressed in terms of the base. Saline and all drug solutions were closely injected in a volume of 0.025 ml in 20 s into the perfused bronchial artery through the rubber tubing.

RESULT
Effects of Histamine on Bronchovascular and Bronchomotor Tones
The average normal perfused blood flow rate was 9.7±0.5 ml/min (n = 24). Physiological saline solution did not produce any change in the parameters measured.

Histamine was given at intervals of 15 to 20 min in random order. Typical recordings of the changes in blood flow through the bronchial vascular bed and ventilation overflow by close i.a. injection of histamine are shown in Fig. 1. The i.a. injections of 0.1 to 10 μg of histamine produced increases in blood flow, viz., bronchial vasodilatation and in ventilation overflow, viz., bronchoconstriction in a dose-dependent manner. Minimal effects on systemic blood pressure and heart rate were obtained up to 10 μg for histamine.

Effects of Chlorpheniramine and Cimetidine on Bronchial Vasodilatation and Bronchoconstriction caused by Histamine
Pretreatment drugs such as chlorpheniramine

![Graphs showing the effects of histamine and chlorpheniramine on blood flow and ventilation overflow.](image)

**Fig. 2. Effects of Histamine and of Histamine in the Presence of Chlorpheniramine on the Bronchial Vasculature (blood flow) and Musculature (ventilation overflow)**

Each point is the mean value with S.E. for five to six experiments. The changes are significant at *p < 0.05, **p < 0.01 and ***p < 0.001 against control values.
and cimetidine were injected *i.a.* into the perfused bronchial artery 5 min before injection of histamine. None of the two drugs produced any change in ventilation overflow and blood flow.

The dose-response curves of blood flow and ventilation overflow to histamine in the absence

![Graphs showing the effects of histamine and cimetidine on blood flow and ventilation overflow.](image)

**Fig. 3. Effects of Histamine and of Histamine in the Presence of Cimetidine on the Bronchial Vasculature (blood flow) and Musculature (ventilation overflow).**

Each point is the mean value with S.E. for five to seven experiments. The changes are significant at **p < 0.01** against control values.

**Table I. Effects of Chlorpheniramine (CP) and Cimetidine (CM) on Bronchial Vasodilatation caused by Histamine**

<table>
<thead>
<tr>
<th>Dose of histamine (μg)</th>
<th>Increase in blood flow (ml/min) caused by histamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>0.1</td>
<td>1.5 ± 0.2 (5)</td>
</tr>
<tr>
<td>0.3</td>
<td>2.3 ± 0.1 (5)</td>
</tr>
<tr>
<td>1.0</td>
<td>2.7 ± 0.3 (5)</td>
</tr>
<tr>
<td>3.0</td>
<td>3.2 ± 0.3 (5)</td>
</tr>
</tbody>
</table>

*Each value represents the mean ± S.E. of the number of experiments indicated in the parenthesis. The changes are significant at *p < 0.05 and **p < 0.01 against control values.*
or presence of chlorpheniramine, a histamine H₁-receptor antagonist, is shown in Fig. 2. Chlorpheniramine in a dose of 1 mg produced a shift of the dose-flow response curves for histamine without significantly affecting their slopes. On the other hand, the bronchoconstriction induced by histamine was also inhibited significantly by chlorpheniramine (1 mg i.a.).

Cimetidine, a histamine H₂-receptor antagonist, in doses of 1–3 mg produced a dose-dependent inhibition of the histamine-induced vasodilatation. However, the histamine-induced bronchoconstriction was not inhibited by cimetidine in doses of 1–3 mg (Fig. 3).

The combination of the H₁- and H₂-receptor antagonists (chlorpheniramine 1 mg plus cimetidine 3 mg) produced greater inhibition of the bronchial vasodilator responses to histamine than did chlorpheniramine given alone. The amount of inhibition produced by the combination of both antagonists was roughly the sum of the amounts of inhibition caused by the individual antagonists (Table I). On the other hand, in the bronchial musculature, the combinations of both antagonists (chlorpheniramine 1 mg plus cimetidine 3 mg) had similar inhibitory effects as was seen by the administration of chlorpheniramine alone.

DISCUSSION

The preparation utilized in the present study can determine the actions of drugs on the bronchi and bronchioles. In this preparation histamine injected intrarterially into the bronchial vascular bed produced bronchoconstriction and vasodilatation.

The present experiments have demonstrated that the bronchoconstriction caused by histamine was antagonized by chlorpheniramine but not by cimetidine, the highly specific histamine H₂-receptor antagonist. Thus, in the dog bronchi, histamine receptors are exclusively of the H₁-receptors which mediate constrictions.

On the other hand, in some species, histamine constricts the airway smooth muscle through histamine H₁-receptors and dilates it through H₂-receptors.⁴-⁶

In the present study, however, the bronchoconstriction caused by histamine was not potentiated by cimetidine in the dog bronchi. Himori and Taira⁷ reported that histamine receptors are exclusively of the H₁-type which mediate constrictions in the dog trachea.

Therefore, there seems to be species differences on participation of histamine H₂-receptors in the airway smooth muscle.

In the bronchial vascular bed, both chlorpheniramine and cimetidine displaced the histamine dose-flow response curves to the right. The displacement of the curves was greater by chlorpheniramine than by cimetidine. Thus, this effect of chlorpheniramine and cimetidine provides evidence of bronchial vasodilatation associated with H₁- and H₂-receptors.

The amount of inhibition of the histamine-induced bronchial vasodilatation produced by the combination of chlorpheniramine and cimetidine was roughly equal to the sum of the amount of inhibition caused by each antagonist. Thus these results also provide a clear evidence that both H₁- and H₂-receptors contribute to bronchial vasodilatation by histamine.

The nature of the modification of histamine responses by histamine receptor antagonists in the bronchial vascular bed of the dog was very similar to the modification previously reported in the tracheal vascular bed.⁷ Furthermore, these findings are in agreement with the results on the other vascular beds of dog.⁹

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REFERENCES


