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# THE EFFECTS OF $H_1$- AND $H_2$-RECEPTOR AGONISTS AND ANTAGONISTS ON TOTAL LUNG RESISTANCE, DYNAMIC LUNG COMPLIANCE AND IRRITANT RECEPTOR DISCHARGE IN THE ANAESTHETIZED DOG

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**1** The effects of histamine and 4 methylhistamine (i.v.) alone, and in the presence of chlorpheniramine or cimetidine, on total lung resistance ($R_L$), dynamic lung compliance ($C_{dyn}$) and irritant receptor activity have been studied in dogs anaesthetized with chloralose.

**2** Histamine produced dose-related increases in $R_L$ and irritant receptor activity with associated falls in $C_{dyn}$ which were blocked by chlorpheniramine but unaffected by cimetidine.

**3** 4 Methylhistamine produced small insignificant changes in $R_L$ and $C_{dyn}$ and small significant increases in irritant receptor activity which were reduced with chlorpheniramine but unaffected by cimetidine.

**4** The results suggest that histamine increases irritant receptor activity, either directly or indirectly, via $H_1$-receptors.

## Introduction

It has been shown repeatedly, in several species, that histamine given by aerosol or intravenously can excite the rapidly adapting receptors in the lung known as lung irritant receptors (see reviews by Fillenz & Widdicombe (1972) and Paintal (1973)).

Since histamine is now known to act on two types of receptors termed $H_1$- (Ash & Schild, 1966) and $H_2$-receptors (Black, Duncan, Durant, Ganellin & Parsons, 1972), it is of interest to know whether irritant receptor activation by histamine can be classified as $H_1$ or $H_2$.

This paper deals with the effects of histamine, 4 methylhistamine ($H_2$-receptor agonist; Black *et al.*, 1972), chlorpheniramine ($H_1$-receptor antagonist) and cimetidine ($H_2$-receptor antagonist; Brimblecombe, Duncan, Durant, Ganellin, Parsons & Black, 1975) on lung irritant receptor activity, total lung resistance ($R_L$) and dynamic lung compliance ($C_{dyn}$) in dogs anaesthetized with chloralose.

## Methods

Beagle dogs (9 to 12 kg) of either sex were initially sedated with thiopentone sodium (5 to 10 mg/kg i.v.) and then anaesthetized with chloralose (80 mg/kg i.v.). The animals were maintained at a level of surgical anaesthesia by giving supplementary doses of chloralose 10 to 15 mg/kg every 15 min via a cannula inserted in the right saphenous vein.

The trachea was cannulated just below the cricoid cartilage with a plastic cannula (1 cm internal diameter and 3 cm long with a resistance of 0.04 kPa $l^{-1}$ s) and the animals were ventilated with air at constant pressure (0.98 kPa) using a Bird Mark VII ventilator. The lungs were inflated to 1.96 kPa transpulmonary pressure ($P_{TP}$) after severe drug-induced falls in lung compliance and also periodically to reverse the gradual decrease in lung volume, which occurs during positive pressure ventilation. A thoracotomy was routinely performed.

A catheter was inserted in the muscularis branch of the right femoral artery for recording blood pressure with a Statham P23 Db pressure transducer. Heart rate was derived from the blood pressure signal using a Devices ratemeter. Catheters were placed in the left saphenous vein and the muscularis branch of the left femoral artery for the injection of drugs and the removal of arterial blood for blood-gas analysis respectively.

The body temperature of the dogs was maintained at 38.6°C with a thermostatically controlled heating blanket in conjunction with a rectal thermocouple.

The partial pressures of $O_2$ ($Po_2$) and $CO_2$ ($Pco_2$) in the blood and the blood pH were monitored regularly with a Radiometer ABL 1 acid-base analyser.

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**Figure 1** An irritant receptor discharging to histamine 10 μg/kg intravenously in the anaesthetized dog.

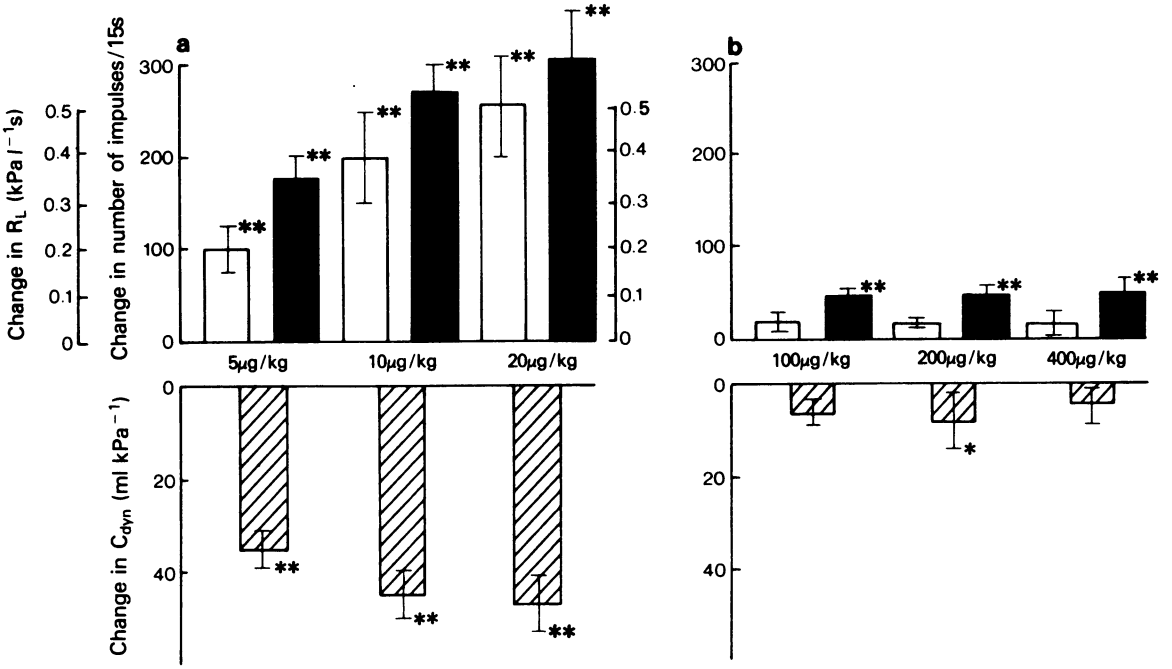


**Figure 2** The effects of histamine (a) and 4 methylhistamine (b) given intravenously on $R_L$ (open columns), irritant receptor activity (closed columns) and $C_{dyn}$ (hatched columns) in the anaesthetized dog. (Values are mean of $n = 12$ for histamine and 11 for 4 methylhistamine; vertical lines show s.e. mean). Test for significance against zero effect, $^{**}P < 0.01$; $^{*}P < 0.05$.

By adjusting the ventilation of the animal at the beginning of the experiment, or during the control periods, it was possible to maintain $Po_2 > 13.3$ kPa, $Pco_2$ between 3.32 kPa and 5.32 kPa and the pH between 7.36 and 7.46.

Air flow rate was measured with a Fleisch pneumotachograph (Type 0; 9.8 Pa = 43.16 ml/s) and a Furness Controls micromanometer (100-0-100 Pa) and tidal volume obtained by electrical integration of the flow signal with a Devices integrator. $P_{TP}$ was measured by a Furness Controls micromanometer (1-0-1 kPa) one side of which was connected to the tracheal cannula and the other side of which was left open to the atmosphere. All recordings were displayed on a Devices M19 recorder. Total lung resistance ($R_L$) and dynamic lung compliance ($C_{dyn}$) were measured by a manual graphic method using the displayed signs of flow, volume and $P_{TP}$ (Amdur & Mead, 1958). The respiratory computer described by Carney, Pugh & Sheard (1972) was also used for the calculations of $R_L$ and $C_{dyn}$, its displayed output being calibrated and checked for accuracy by comparison with simultaneous manual determinations of $R_L$ and $C_{dyn}$. The computer was accurate to $\pm 0.02$ kPa $l^{-1}$ s for $R_L$ and $\pm 6.2$ ml $kPa^{-1}$ for $C_{dyn}$.

The dogs were paralysed with succinylcholine 1.5 mg/kg given intravenously every 15 min. Both cervical vagi were exposed, cut and the distal end of the left vagus was placed in a liquid paraffin filled copper trough. Fine filaments were teased from the nerve trunk with the aid of a binocular microscope (Zeiss) to give what appeared to be a single functional receptor unit wherever possible.

The nerve action potentials were amplified by a high gain RC amplifier (Tektronix 122) and together with $P_{TP}$, airflow, tidal volume and blood pressure were recorded on magnetic tape using a seven channel recorder (Ampex SP 300).

Two criteria for selection of fibres from lung irritant receptors were used. First, the receptor was stimulated by, but adapted to, an inflation of 1 kPa and a deflation of $-1$ kPa. Any fibre having an inflation adaptation index (Widdicombe, 1954) of less than 70% was discarded. Secondly, each receptor was located in the airways by touching the lung gently with the fingers and finally locating the receptor with a cotton wool bud. Irritant receptor activity was measured by electronically counting action potentials over consecutive 15 s periods throughout the experiment. Occasional manual checks on the rate of dis-

charge of the receptors were made during the experiment. An example of a recording from a single irritant receptor is shown in Figure 1.

When a suitable fibre had been selected, and there had been no significant change in the values of $R_L$, $C_{dyn}$ or irritant receptor discharge over a 1 min period, bolus doses of histamine (5 to 20 μg/kg), 4 methylhistamine (100 to 400 μg/kg) or acetylcholine (40 μg/kg) were given intravenously and washed in with 0.5 ml 0.9% w/v NaCl solution (saline). The maximal changes in $R_L$, $C_{dyn}$ and irritant receptor discharge occurring over the following 3 min were recorded and it is these values which have been used in the results section. The effects of chlorpheniramine and cimetidine on these responses were determined by giving 100 μg/kg intravenously 15 min before the agonist.

*Drugs and solutions*

The drugs used were chloralose (Koch-Light Laboratories), thiopentone sodium (Intraval, May and Baker Ltd), succinylcholine chloride (Duncan Flockhart Ltd), acetylcholine chloride (Koch-Light Laboratories), histamine acid phosphate (BDH), chlorpheniramine maleate (Allen and Hanbury), cimetidine (Smith, Kline and French), 4 methylhistamine (Smith, Kline and French). Drug solutions were freshly prepared in saline and concentrations are given in terms of bases.

## Results

The results were obtained from studying 23 receptors from 12 dogs. No more than two receptors were studied in any one dog.

The mean initial resting values of $R_L$ and $C_{dyn}$ in the dogs used were 0.28 ± 0.016 kPa $l^{-1}$ s and 217.7 ± 16.4 ml $kPa^{-1}$ respectively. The mean resting value for irritant receptor discharge rate was 18.0 ± 11.2 imp/15 s. Chlorpheniramine or cimetidine did not affect these resting values.

Histamine (5 to 20 μg/kg) produced dose-related increases in $R_L$, and irritant receptor activity with associated falls in $C_{dyn}$ (Figure 2).

The effect of 10 μg/kg histamine was tested on 9 receptors. All 9 receptors were stimulated and this stimulation was accompanied by increases in $R_L$. Of six receptors pretreated with chlorpheniramine (100 μg/kg) two did not increase their rates of discharge when subsequently treated with histamine (10 μg/kg) although in one case there was a small increase in $R_L$. The remaining four receptors did show a reduced response to histamine (10 μg/kg) and in each instance the receptor activity was associated with an increase in $R_L$. (Table 1)

Cimetidine (100 μg/kg) did not modify the effect of histamine (10 μg/kg) on three irritant receptors or on lung mechanics (Table 1). 4 Methylhistamine (100 to 400 μg/kg) produced small, generally not significant and not dose-related increases in $R_L$, falls in $C_{dyn}$ and significant increases in irritant receptor discharge (Figure 2).

The activity of eleven receptors tested with 4 methylhistamine (200 μg/kg) was increased. However, in only six cases was this increase associated with a change in $R_L$. After pretreatment with chlorpheniramine (100 μg/kg) of eight receptors challenged with 4 methylhistamine (200 μg/kg) the activity of four was still increased (with an associated $R_L$ change) but these increases were less than the control increases, and four showed no increase (Table 2).

Three receptors responding to 200 μg/kg 4 methylhistamine (two with an associated $R_L$ change) were

**Table 1.** Changes in $R_L$, $C_{dyn}$ and irritant receptor activity produced by histamine (10 μg/kg) in the absence and presence of chlorpheniramine (100 μg/kg) or cimetidine (100 μg/kg)

| | $R_L$ ($kPa\ l^{-1}\ s$) | $C_{dyn}$ ($ml\ kPa^{-1}$) | *Irritant receptor activity* (*imp/15 s*) | n |
|---|---|---|---|---|
| Control | +0.32** ± 0.07 | −88.0** ± 8.0 | +220.8* ± 79.6 | 6 |
| Chlorpheniramine (100 μg/kg) | +0.03*‡ ± 0.009 | −6.6‡ ± 3.3 | +37.6† ± 21.2 | 6 |
| Control | +0.26 ± 0.13 | −50.0* ± 6.0 | +130.3* ± 22.1 | 3 |
| Cimetidine (100 μg/kg) | +0.27 ± 0.12 | −33.3 ± 9.0 | +141.3 ± 43 | 3 |

Mean values ± s.e.
For test of significance against the zero effect, $^{**}P < 0.01$; $^{*}P < 0.05$.
For tests of significance of the difference between control response and those after $H_1$ or $H_2$ antagonists, $‡P < 0.01$; $†P < 0.05$.

pretreated with cimetidine (100 μg/kg). This had no effect on receptor discharge to 4 methylhistamine but all mechanical changes were abolished (Table 2).

The increase in $R_L$ and irritant receptor activity and falls in $C_{dyn}$ produced by acetylcholine (40 μg/kg) were unaffected by chlorpheniramine (100 μg/kg on six receptors) or cimetidine (100 μg/kg on three receptors) (Table 3).

## Discussion

Histamine produced dose-related increases in $R_L$ and irritant receptor activity which were associated with falls in $C_{dyn}$. The lung responses and irritant receptor excitation produced by histamine were inhibited by the $H_1$-receptor blocking agent, chlorpheniramine, but unaffected by the $H_2$-receptor blocking agent, cimetidine (Brimblecombe *et al.*, 1975). Since the histamine receptors responsible for contracting bronchial smooth muscle have been classified as $H_1$ (Ash & Schild, 1966) the effect of chlorpheniramine on increases in $R_L$ and falls in $C_{dyn}$ are consistent with published results. The inability of cimetidine to affect significantly histamine changes in $R_L$ and $C_{dyn}$ confirm that the response was mediated primarily through $H_1$-receptors.

The response to 40 μg/kg acetylcholine was used to check any possible depressant action of the antagonists used. At the dose levels employed, chlorpheniramine and cimetidine did not significantly depress the changes in $R_L$, $C_{dyn}$ or irritant receptor activity, produced by acetylcholine.

4-Methylhistamine produced small and mainly insignificant increases in $R_L$, and falls in $C_{dyn}$ which were not dose-related. It is possible that the doses

**Table 2** Changes in $R_L$, $C_{dyn}$ and irritant receptor activity produced by 4 methylhistamine (200 μg/kg) in the absence and presence of chlorpheniramine (100 μg/kg) or cimetidine (100 μg/kg)

| | $R_L$ ($kPa\ l^{-1}\ s$) | $C_{dyn}$ ($ml\ kPa^{-1}$) | *Irritant receptor activity* (*imp*/15 *s*) | n |
|---|---|---|---|---|
| Control | +0.025 ± 0.012 | −6.3* ± 2.6 | +64.8 ± 18.3 | 8 |
| Chlorpheniramine (100 μg/kg) | +0.002 ± 0.002 | −1.3 ± 1.3 | +30.4† ± 15.5 | 8 |
| Control | +0.05 ± 0.3 | −6.7 ± 3.3 | +34.7 ± 7.05 | 3 |
| Cimetidine (100 μg/kg) | 0 | 0 | 26.7 ± 6.8 | 3 |

Mean values ± s.e.
For test of significance against the zero effect, $**P < 0.01$; $*P < 0.05$.
For tests of significance of the difference between control response and those after $H_1$ or $H_2$ antagonists, $‡P < 0.01$; $†P < 0.05$.

**Table 3** Changes in $R_L$, $C_{dyn}$ and irritant receptor activity produced by acetylcholine (40 μg/kg) in the absence and presence of chlorpheniramine (100 μg/kg) or cimetidine (100 μg/kg)

| | $R_L$ ($kPa\ l^{-1}\ s$) | $C_{dyn}$ ($ml\ kPa^{-1}$) | *Irritant receptor activity* (*imp*/15 *s*) | n |
|---|---|---|---|---|
| Control | +0.68* ± 0.19 | −86.0** ± 16.7 | +139.8 ± 79.5 | 6 |
| Chlorpheniramine (100 μg/kg) | +0.54** ± 0.09 | −72.0** ± 10.4 | +142.3 ± 78.0 | 6 |
| Control | +0.57* ± 0.10 | −48.0** ± 4.4 | +32.7* ± 5.8 | 3 |
| Cimetidine (100 μg/kg) | +0.99 ± 0.32 | −57.0** ± 3.3 | +39.3 ± 25.8 | 3 |

Mean values ± s.e.
For test of significance against the zero effect, $**P < 0.01$; $*P < 0.05$.
For tests of significance of the difference between control response and those after $H_1$ or $H_2$ antagonists, $‡P < 0.01$; $†P < 0.05$.

of 4 methylhistamine used in this study were on the lower portion of the dose-response curve and that if higher doses had been employed a dose-response relationship would have been established. However, 4 methylhistamine at the doses used consistently increased the rate of discharge of lung irritant receptors and this increase was significantly reduced by the $H_1$ antagonist, chlorpheniramine, but not by the $H_2$ antagonist, cimetidine. Since 4 methylhistamine does have some $H_1$-receptor stimulating properties (Black *et al.*, 1972) it is possible that the increase in irritant receptor discharge was in part mediated via $H_1$-receptors.

Mills, Sellick & Widdicombe (1969; 1970) attribute the histamine stimulation of lung irritant receptors to contraction of underlying bronchial smooth muscle. The results of this study can, in part, be explained by this proposition since histamine-induced irritant receptor excitation did not occur when lung mechanical changes were blocked. However, 4 methylhistamine in five out of eleven cases produced irritant receptor excitation without changes in $R_L$. Also following pretreatment with $H_1$-or $H_2$-receptor antagonists, there were instances where 4 methylhistamine produced increases in irritant activity without changes in lung mechanics. These results cannot be explained by the indirect activation theory of Mills *et al* (1969).

Sampson & Vidruk (1977) and Vidruk, Hahn, Nadel & Sampson (1977) have suggested that direct chemical activation of the irritant receptor without bronchial smooth muscle contraction is possible, and the results of this study with 4 methylhistamine help to support such a view. However, it should be noted that the changes in irritant receptor activity produced by 4 methylhistamine, although significant, were small, not dose-related and were attenuated by an $H_1$ antagonist. Since 4 methylhistamine does have some activity on $H_1$-receptors, it is possible that the increase in irritant receptor activity was mediated, in part, via these receptors. However, it is equally possible that the action of 4 methylhistamine on irritant receptors was unrelated to the activity on $H_1$- or $H_2$-receptors and it may have resulted from an indirect action i.e. the release of sympathomimetic amines (Goodman & Gilman, 1975).

Dixon, Jackson, Richards & Vendy (1978), by comparing the actions of histamine with those of acetylcholine on $R_L$, $C_{dyn}$ and irritant receptor discharge in the dog, concluded that histamine excites the lung irritant receptor by a combination of indirect action on the bronchial smooth muscle and direct action on the receptor. The direct action may involve stimulation or sensitization of the receptor to mechanical distortion. Using this proposed mode of action, pharmacological antagonism of histamine contraction of the airways could prevent increased irritant receptor discharge, as it did in this present study. However, this theory would not preclude direct activation without smooth muscle contraction, and hence allows an explanation for the stimulatory effects of 4 methylhistamine seen in these experiments.

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