Br. J. Pharmac. (1985), **84**, 309–316

The response of cat airways to histamine *in vivo* and *in vitro*

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1 The effects of histamine have been examined in anaesthetized cats and on cat isolated lung parenchyma strip.

2 Histamine infused intravenously for 2 min produced a small and inconsistent effect on central airways and a small but consistent constriction of peripheral airways.

3 Histamine bronchoconstriction of the central airways was unmasked by non-selective and β_2-adrenoceptor blockade but not by β_1-adrenoceptor blockade. This bronchoconstriction was antagonized by atropine but not by cimetidine or prazosin.

4 Bronchoconstriction of the peripheral airways was not affected in a dose-related manner by β-adrenoceptor blockade. The bronchoconstriction was antagonized by mepyramine but not by atropine or prazosin.

5 β-Adrenoceptor antagonists produced a bell-shaped dose-response curve on histamine contractions in cat isolated lung parenchyma strip. Strips of lung parenchyma obtained from reserpine-treated cats produced a larger contraction to histamine which was not potentiated by propranolol.

6 It is concluded that in the central airways, histamine bronchoconstriction produced by an action on irritant receptors is masked by an action on β_2-adrenoceptors of catecholamines released locally and from the adrenal glands. In the peripheral airways, histamine bronchoconstriction is mediated by H_1-receptors and β_2-adrenoceptor blockade may either potentiate or antagonize the histamine response depending on the concentration.

Introduction

Dale & Laidlaw (1910) first reported the contractile effect of histamine on an airways preparation and the bronchoconstrictor effect of histamine has been confirmed in many species (Eyre & Chand, 1982). However, histamine does not produce contraction of cat isolated central airways and may produce relaxation (Maengwyn-Davies, 1968; Eyre, 1973; Persson & Ekman, 1976; Chand & Eyre, 1977). Moreover, Colebatch and his co-workers (Colebatch *et al.*, 1966; Colebatch & Engel, 1974) observed that in the cat airways *in vivo*, histamine produced a small transient and inconsistent response and they concluded that the bronchoconstrictor effect of histamine was counteracted by adrenaline released from the adrenal glands. Similar conclusions were reached by Ploy-Song-Sang *et al.* (1978) following studies in non-asthmatic human subjects.

Cat airways contain a variety of receptors which may be associated with the actions of histamine. The central airways contain β_1-adrenoceptors (Lulich *et al.*, 1976; O'Donnell & Wanstall, 1983), H_1-receptors (Maengwyn-Davies, 1968; Eyre, 1973); H_2-receptors (Eyre, 1973; Chand, 1980) and α-adrenoceptors (Fleisch *et al.*, 1970). The peripheral airways contain β_2-adrenoceptors and H_1-receptors (Lulich *et al.*, 1976). In addition, the central airways have irritant receptors which can be stimulated by histamine (Nadel & Widdicombe, 1963) and which initiate a vagal reflex resulting in bronchoconstriction of the central airways (Gold, 1977; Nadel, 1977).

In the present study a number of selective antagonists have been used to study the actions of histamine in cat lung *in vivo* and *in vitro*.

Methods

In vivo

Thirty six cats of either sex (2.5–3.5 kg) have been

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used, anaesthetized with α-chloralose (60–70 mg kg^{-1}, i.p.) and sodium pentobarbitone (6 mg kg^{-1}, i.p.). The trachea was cannulated and blood pressure recorded from the left carotid artery be means of a Millar Mikro-tip transducer (PC-350). The right external jugular vein was catheterised for drug administration and the right and left femoral veins were also catheterised for the infusion of drugs. Drugs were infused at a rate of 0.159 ml min^{-1} using a Harvard infusion pump. Airways resistance (R_{aw}) and dynamic lung compliance (C_{dyn}) were measured by the subtractor method of Mead & Whittenberger (1953) modified by Green & Widdicombe (1966) as described by Maclagan & Ney (1979). Airflow and tidal volume were measured through a Fleisch flow transducer (size 00) connected to a Gould-Godart pneumotachograph. Transpulmonary pressure was recorded by means of a Mercury (M10) micromanometer which measured the pressure difference between the tracheal cannula and a trocar (13 g) inserted through the chest wall into the pleural cavity. The cats were allowed to respire spontaneously.

In vitro

Strips of lung parenchyma were set up by the method of Lulich *et al.* (1976). Sections of lung were dissected from the lower lobe with the longitudinal axis of the strip cut parallel to the bronchus. The strips were mounted in an isolated organ bath at 37°C in Krebs solution aerated with 95% O_2 and 5% CO_2. A load of 2–2.5 g force was applied and the tissue allowed to equilibrate for 1 h. Two or four strips were run simultaneously and changes in tension were recorded using Grass FTO3 force-displacement transducers.

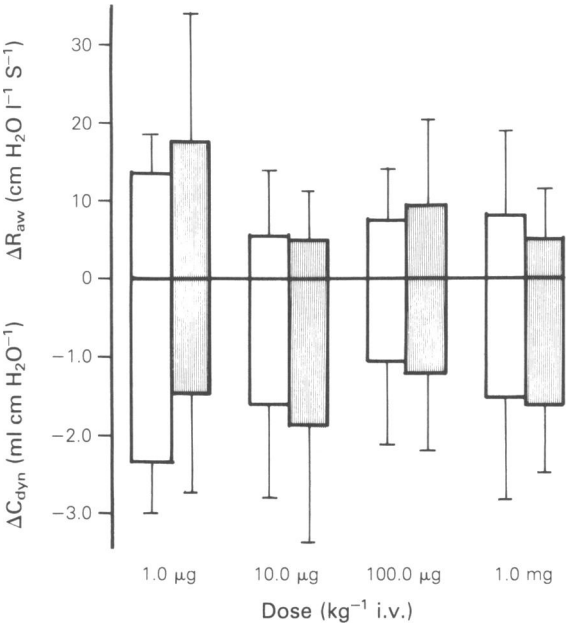

Figure 1 Effect of cimetidine (shaded columns) on histamine responses (open columns) in airways *in vivo*. ($n = 3$). Given are means with vertical lines showing s.e.mean.

Drugs and materials

The following drugs have been used: α-chloralose (Koch-Light Ltd.), sodium pentobarbitone (Sagatal, May & Baker), histamine diphosphate (Sigma), atropine sulphate (Koch-Light) and mepyramine maleate. We are grateful for gifts of the following drugs: cimetidine (Smith, Kline & French), (±)-propranolol HCl, ICI 118,551 erythro-(±)-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol, (ICI) and prazosin (Pfizer). Ro 31-1118 1-(4-(2-(4-fluorophenethyloxy)ethoxy)phenoxy)-3-isopropylamino-2-propanol hydrochloride was synthesized by Dr P.J. Machin at Roche Products Ltd. The composition of the Krebs solution was (mM): NaCl 120, KCl 2.0, $CaCl_2$ 2.5, $NaHCO_3$ 25.0, $MgSO_4$ 0.57, NaH_2PO_4 1.5 and dextrose 11.

Statistics

Mean values ± s.e.mean are given. Significance has been calculated using the paired Student's *t* test, significance has been accepted at $P < 0.05$ double tailed.

Results

In vivo

Histamine was infused for a period of 2 min at a rate of 0.16 μmol kg^{-1} min^{-1} to give a stable and measurable response. It was observed that both higher and lower concentrations produced a smaller response. The response showed an inconsistent effect on the central airways (R_{aw}); in approximately equal numbers of animals either a small bronchoconstriction was evident or a small bronchodilatation. The mean response was $+4.2 \pm 6.8$ cmH_2O l^{-1} s^{-1} (mean ± s.d., $n = 18$). The effect in the peripheral airways (C_{dyn}) was however a small, but consistent constriction; -1.8 ± 1.7 ml cmH_2O^{-1} (mean ± s.d., $n = 18$). Cimetidine, an H_2-receptor antagonist (Brimblecombe *et al.*, 1975) administered in the range 1 μg–1 mg kg^{-1} i.v. 1 min before the histamine infusion did not modify the response (Figure 1). To confirm that sufficient concentration of the antagonist was reaching the site of action cimetidine was also infused at 500 μg kg^{-1} min^{-1} and histamine infused simultaneously

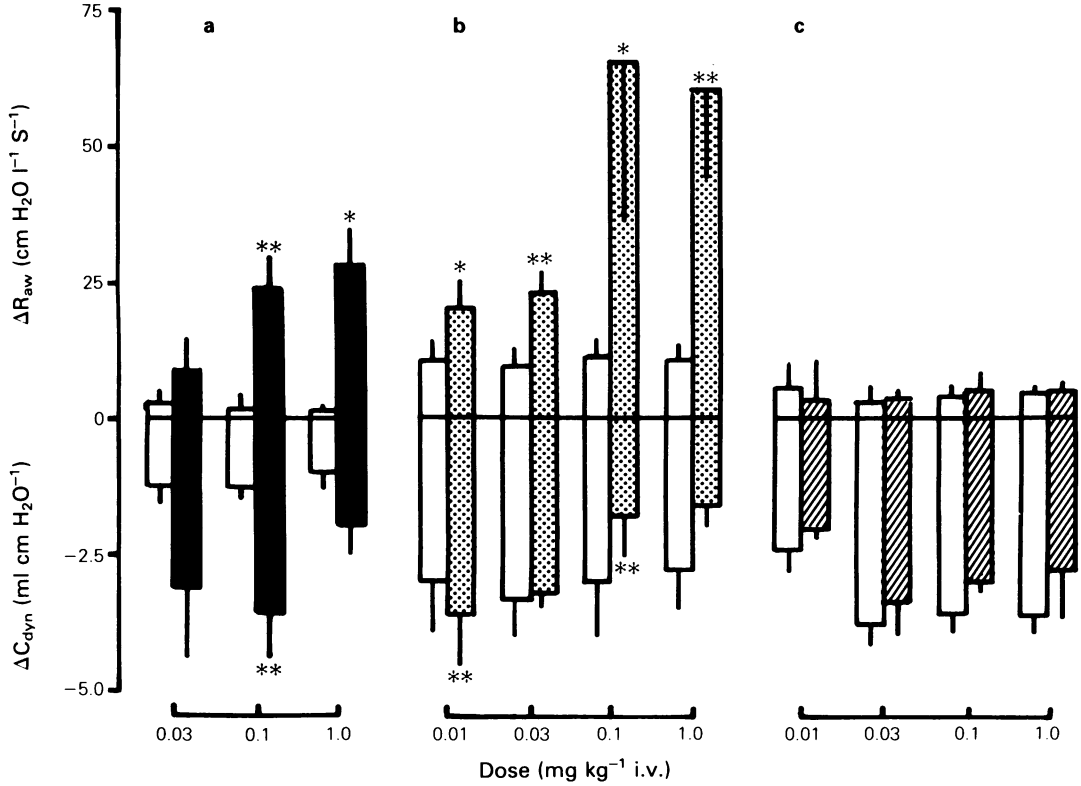

Figure 2 The effect of β-adrenoceptor antagonists on histamine responses in cat airways *in vivo*: Control, open columns; propranolol, solid columns; ICI 118,551, stippled columns; Ro 31-1118, hatched columns. ($n = 3$). Significant difference from control histamine responses: $*P < 0.05$; $**P < 0.01$. Given are means; vertical lines show s.e. mean.

3 min after the start of the cimetidine infusion; again there was no change in the histamine response (results not shown).

β-Adrenoceptor antagonists

The effects of (±)-propranolol are shown in Figure 2a. In the presence of propranolol, histamine produced bronchoconstriction of the central airways; this effect of propranolol was dose-related. The histamine-induced constriction of the peripheral airways was also potentiated although not as consistently and not in a dose-related manner. Propranolol had no direct effect on the airways (Blaber, 1982).

Pretreatment with the β_2-selective adrenoceptor antagonist, ICI 118,551 (Bilski *et al.*, 1983) which also had no direct effects on the airways, also potentiated the bronchoconstrictor effect of histamine in the central airways in a dose-related manner (Figure 2b). In the peripheral airways, ICI 118,551 10 μg kg^{-1} i.v. potentiated the histamine-induced bronchoconstriction whereas 100 μg kg^{-1} i.v. significantly antagonized it. Doses of 30 μg and 1.0 mg kg^{-1} i.v. of ICI 118,551 did not significantly change the histamine response in the peripheral airways.

Ro 31-1118 has been shown to be a specific β_1-adrenoceptor antagonist *in vivo* in the cat (Blaber *et al.*, 1983). Figure 2c illustrates that the compound did not change significantly the response to histamine in either the central or peripheral airways, also no direct effects of Ro 31-1118 were observed.

The effects of other antagonists

Atropine (1 mg kg^{-1} i.v.) had little or no effect on the histamine response. However in cats pretreated with propranolol (100 μg kg^{-1} i.v.) atropine completely abolished the potentiation of histamine-induced bronchoconstriction in the central airways but did not affect the histamine responses in the peripheral airways (Table 1). Prazosin (1 mg kg^{-1}, i.v.) did not affect the airways response to histamine either in untreated cats or those pretreated with propranolol (Table 1). In a cat in which both propranolol (100 μg kg^{-1}, i.v.) and

Table 1 Antagonism of histamine responses in the anaesthetized cat

	n	ΔR_{aw}	ΔC_{dyn}
Histamine control	6	+3.9 ± 1.5	−2.1 ± 0.1
Histamine following treatment with:			
Propranolol (100 μg kg^{-1})	8	+16.1 ± 3.1**	−2.2 ± 0.8[a]
+ Atropine (1 mg kg^{-1})	4	+1.3 ± 0.5[a]	−3.0 ± 0.05[a,b]
+ Prazosin (1 mg kg^{-1})	6	+12.0 ± 2.8[b]	−1.4 ± 0.5[b]
+ Propranolol + atropine			
+ Mepyramine (100 μg kg^{-1})	1	0	0

**$P < 0.01$ compared to histamine control.
[a]Not significantly different from histamine control.
[b]Not significantly different from propranolol treatment.

Table 2 Histamine responses in cat isolated lung parenchyma strip

	Histamine (μM) *0.1*		*1.0*		*10.0*	
Untreated	27.8 ± 3.9	(18)	106.2 ± 11.2	(18)	211.8 ± 18.4	(18)
Reserpinised	78.5 ± 18.2*	(11)	194.4 ± 24.1**	(11)	272.8 ± 25.8	(11)
Reserpinised + propranolol 0.1 μM	1.6 ± 8.7[a]	(8)	46.9 ± 14.8[b]	(8)	105.0 ± 20.5[b]	(8)
Reserpinised + propranolol 1.0 μM	9.4 ± 6.2[a]	(8)	31.6 ± 13.4[b]	(8)	109.8 ± 15.1[b]	(8)
Reserpinised + propranolol 10 μM	23.5 ± 6.0[a]	(8)	28.3 ± 7.8[b]	(8)	100.1 ± 10.3[b]	(8)

Number of preparations given in parentheses. Data from untreated preparations are the same as in Figure 3. Results given represent increase in tension following the addition of histamine.
*$P < 0.01$; **$P < 0.001$ compared to untreated preparation.
[a]$P < 0.01$; [b]$P < 0.001$ compared to reserpinised preparations.

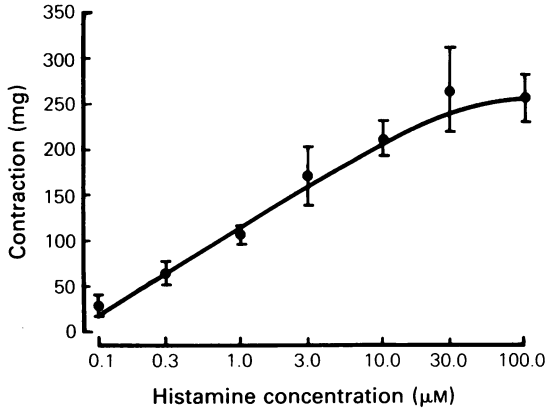

Figure 3 Histamine dose-response curve in cat isolated lung parenchyma strip. (n = 18). Given are mean values with vertical lines showing s.e.mean.

atropine (1 mg kg^{-1}, i.v.) had been administered, mepyramine (100 μg kg^{-1}, i.v.) completely abolished the histamine response in both the central and peripheral airways (Table 1). In untreated animals, mepyramine (100 μg kg^{-1}, i.v.) markedly reduced but did not abolish the histamine response in either the central or peripheral airways.

In vitro

Histamine produced a dose-related contraction of the cat isolated parenchyma strip (Figure 3). The effects of propranolol on the responses to three concentrations of histamine are shown in Figure 4a. The dose-response curve to propranolol was bell-shaped; the concentration which produced the greatest potentiation of histamine was 1.0 μM.

The effects of ICI 118,551 are shown in Figure 4b. This compound was more potent and a wider range of

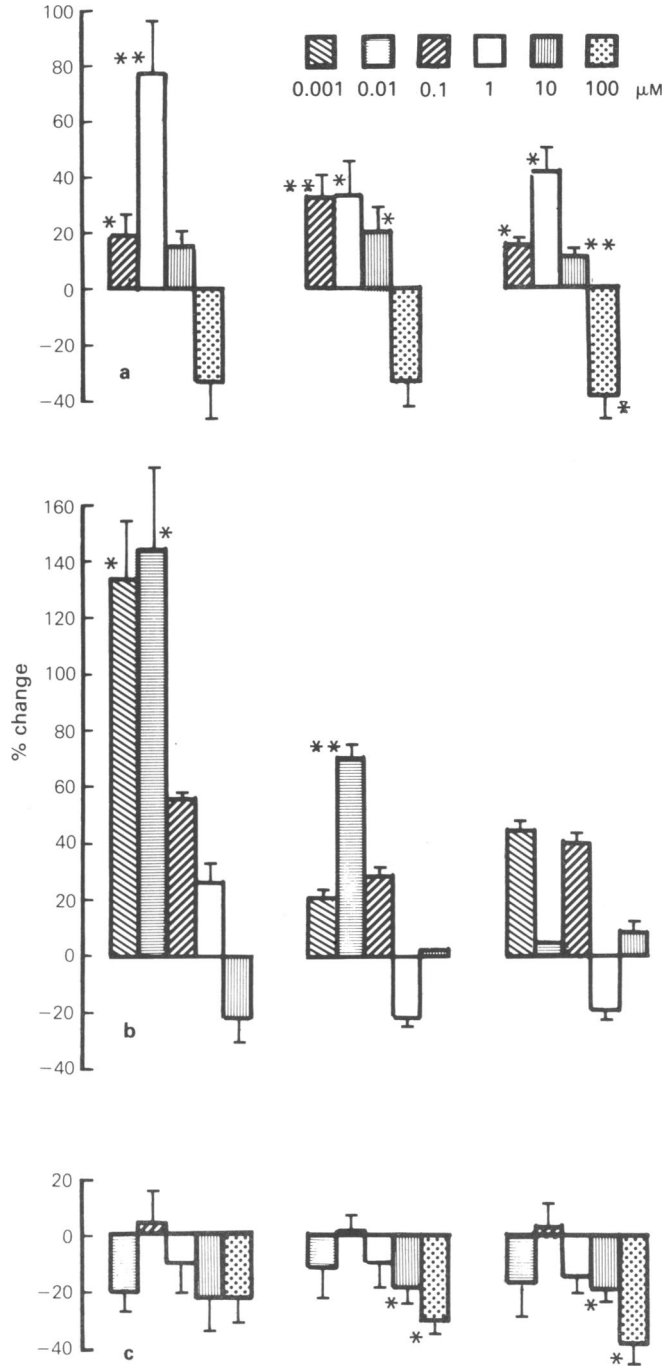

Figure 4 The effects of β-adrenoceptor antagonists on histamine contractions in cat isolated lung parenchyma strip. (a) Propranolol; (b) ICI 118,551; (c) Ro 31-1118. The histamine concentrations used were: left hand column 0.1 μM; centre column 1.0 μM; right hand column 10.0 μM. Concentrations of antagonists used are given in the key. $*P < 0.05$; $**P < 0.01$. Each point represents the mean with vertical lines showing s.e.mean from six preparations; histamine was added to the bath 15 min after the antagonist without washing.

concentrations was used. Bell-shaped dose-effect curves were seen only at the lower two histamine concentrations. None of the changes was significant at the highest concentration of histamine used.

Ro 31-1118 did not potentiate the histamine contractions at any concentration used (Figure 4c); however, concentrations greater than 1.0 μM produced antagonism at the two highest histamine concentrations.

In cat isolated lung parenchyma strips taken from cats treated 16 h previously with reserpine (0.5 $\mu g\,kg^{-1}$, i.p.), histamine produced a larger contraction than in preparations taken from untreated animals (Table 2). Propranolol (0.1–10.0 μM) did not potentiate the response to histamine in this preparation. All concentrations of propranolol produced antagonism of the histamine response although the effects were not dose-related.

Discussion

The administration of intravenous histamine produced a weak and transient effect on cat airways confirming the report of Colebatch & Engel (1974). However, the present studies have shown that in the central airways histamine produced either bronchoconstriction or bronchodilatation in approximately equal numbers of cats. Isolated trachea is relaxed by histamine (Maengwyn-Davies, 1968; Eyre, 1973; Chand & Eyre, 1977); Eyre (1973) and Maengwyn-Davies (1968) suggested that the effect of histamine was due to a combination of catecholamine release and actions at both H_1- and H_2-receptors; however, Chand & Eyre (1977) could not confirm this. In the peripheral airways, histamine produced a weak but consistent bronchoconstriction *in vivo* and contraction of the isolated lung parenchyma strip.

In the anaesthetized cat, mepyramine markedly reduced the response to histamine whereas cimetidine did not affect the response showing that both the bronchoconstriction and bronchodilatation were mediated by H_1-receptors. Atropine and prazosin also had no effect on the response to histamine and therefore there was no observable contribution to the response either by vagal reflex action or α_1-adrenoceptors.

Propranolol had no direct effect on the airways of the cat confirming the report of Blaber (1982) and in marked contrast to the effect on guinea-pig airways (Maclagen & Ney, 1979; Ney, 1983). In the presence of propranolol, the bronchoconstrictor effect of histamine in the central airways was markedly potentiated and became dose-related; a bronchodilator effect has never been observed. Colebatch & Engel (1974) similarly observed a marked potentiation and prolongation of the bronchoconstrictor effect of histamine which they attributed to antagonism of catecholamines released from the adrenals by the histamine; Staszewska-Barczak & Vane (1965) had previously shown that histamine would release catecholamines from the adrenal glands of the cat. In the peripheral airways *in vivo* histamine bronchoconstriction was potentiated significantly only by propranolol 0.1 $mg\,kg^{-1}$ i.v. and not by a higher or lower dose. Histamine was potentiated by propranolol also in the isolated lung parenchyma strip, however, high concentrations antagonized histamine, producing a bell-shaped dose-response curve similar to that produced *in vivo*. The β_2-selective adrenoceptor antagonist, ICI 118,551 also potentiated the bronchoconstrictor action of histamine *in vivo* but to a greater extent than propranolol. The effects of ICI 118,551 were not dose-related in the peripheral airways *in vivo*, the 10 $\mu g\,kg^{-1}$ i.v. dose producing potentiation and the 100 $\mu g\,kg^{-1}$ i.v. antagonism, 30 $\mu g\,kg^{-1}$ i.v. and 1.0 $mg\,kg^{-1}$ i.v. did not significantly change the response. In the *in vitro* preparation ICI 118,551 produced a bell-shaped dose-response curve when 0.1 μM and 1.0 μM histamine were used but had no significant effect when contractions were produced by 10 μM histamine. It can therefore be concluded that potentiation of the histamine response by ICI 118,551 becomes less as the histamine concentration increases (Figure 4); moreover, when this effect is combined with the bell-shaped dose-relationship of ICI 118,551 it explains the complex interaction between the β-adrenoceptor antagonist and histamine on the peripheral airways *in vivo*. Ro 31-1118 did not significantly change the response to histamine *in vivo* in either the central or peripheral airways and the only response seen *in vitro* was antagonism of histamine at the higher concentrations of the antagonist. It has been reported that the central airways of the cat contain β_1-adrenoceptors (Lulich *et al.*, 1976; O'Donnell & Wanstall, 1983) using the isolated trachea. Measurement of airways resistance records changes in the smooth muscle tone of the central airways (Widdicombe, 1963) which in the cat extends to several generations of non-respiratory and respiratory bronchioles (Tyler, 1983). The present *in vivo* results can only be explained if the trachea does not contribute significantly to airways resistance and if the intermediate airways contain significant numbers of β_2-adrenoceptors. All three β-adrenoceptor antagonists had a tendency towards a bell-shaped dose-response relationship *in vitro*. The potentiation of histamine would suggest that histamine is releasing catecholamines *in vitro* and this has previously been suggested by Maengwyn-Davies (1968) and Eyre (1973) but was not supported by Chand & Eyre (1977). The lack of potentiation of histamine by the antagonists in reserpine-treated preparations would also support a local release of catecholamines which may either be from the sym-

pathetic innervation of the smooth muscle (Richardson, 1979) or from the sympathetic supply to the blood vessels (Ainsworth *et al.*, 1982). It must also be concluded that the bronchodilator effects of histamine seen in some animals not treated with propranolol was also due to catecholamine release mediated by H_1-receptors and not due to H_2-receptors; this is in contrast to the dog (Snapper *et al.*, 1980) and the sheep (Hartman *et al.*, 1983) but it has been reported that H_2-receptors do not mediate the histamine response in man (Maconochie *et al.*, 1980). The diminished potentiation or antagonism of histamine at higher concentrations cannot be explained on the basis of partial agonism since only Ro 31-1118 is a partial agonist (Black *et al.*, 1965; Bilski *et al.*, 1983; Blaber, *et al.*, 1983). Furthermore it is probably not due to release of catecholamines since propranolol still produced antagonism in reserpine-treated preparations.

In anaesthetized cats treated with propranolol, atropine completely reversed the potentiation of histamine in central airways which was therefore due to the effect of histamine on irritant receptors initiating a vagal reflex (de Kock *et al.*, 1966; Gold, 1977; Nadel, 1977).

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(Received May 10, 1984.
Revised September 12, 1984.
Accepted October 9, 1984.)