The role of histamine receptors in asthma

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Summary

1. Eighteen non-asthmatic and 18 asthmatic subjects underwent challenge with increasing doses of histamine from a dosimeter-nebulizer system. Half the subjects in each group were atopic and half non-atopic. Bronchial response was monitored with serial measurements of specific airways conductance (sGaw) and a dose-response curve was constructed for each challenge. In addition, the nine atopic asthmatic patients underwent antigen challenges with a similar technique. In each subject the challenges were repeated, on separate days, after intravenous injections of either sodium chloride solution (150 mmol/l: saline) placebo, chlorpheniramine (an H1-receptor antagonist), cimetidine (an H2-receptor antagonist) or after both antagonists together. Baseline bronchial tone was always comparable within subjects immediately before challenge.

2. Cimetidine had no significant effect on baseline sGaw in any group, whereas chlorpheniramine raised baseline sGaw in the asthmatic subjects. Placebo did not alter the mean dose-response curves for histamine or antigen. However, there was a small, but significant, shift of the curves to the right after cimetidine and a much larger shift to the right with chlorpheniramine, whether given alone or with cimetidine. The effect of the histamine antagonists on histamine and antigen responses was very similar and there was no difference in the pattern of response among normal subjects as compared with asthmatics or among atopic as compared with non-atopic subjects.

3. In conclusion, the same pattern of histamine receptors exists in the airways of asthmatic and normal subjects. Histamine-induced bronchoconstriction is mediated predominantly via the H1-receptors, with little, if any, contribution from the H2-receptors. Histamine appears to be an important mediator in the immediate allergic response in airways since this response is blocked by an H1-receptor antagonist.

Key words: antigen, asthma, atopic, dose-response curve, histamine, H1-receptor antagonist, H2-receptor antagonist.

Introduction

Conventional antihistamines (H1-receptor antagonists) prevent histamine-induced bronchoconstriction (Curry, 1946; Herxheimer, 1949; Casterline & Evans, 1977; Woenne, Kattan, Orange & Levison, 1978; Nogrady & Bevan, 1978), but ‘antihistamines’ have been found relatively ineffective in the treatment of bronchial asthma (Karlin, 1972; Partridge & Saunders, 1979). The reason for this is not clear. However, since the definition of the H2-receptor (Black, Duncan, Durant, Ganellin & Parsons, 1972), both H1- and H2-receptors have been identified in the tracheobronchial tree of a number of animals, though there appears to be a species difference in the site and function of these receptors (Eyre, 1973; Chand & Eyre, 1977; Krell & Chakrin, 1977; Dulabh & Vickers, 1978; Holroyde & Eyre, 1978). In man evidence is conflicting on the type and role of these histamine receptors in the airways (Dunlop & Smith, 1977; Maconochie, Woodings & Richards, 1979; Nathan, Segall, Glover & Schocket, 1979; Eiser, Mills, McRae, 0143-5221/81/040363-08501.50/1 © 1981 The Biochemical Society and the Medical Research Society
Snashall & Guz, 1980; Thomson & Kerr, 1980). One of these studies (Eiser et al., 1980) has suggested that $H_1$- and $H_2$-receptors may be present in human airways and that both may mediate bronchoconstriction. In the normal subjects described the effect of the $H_1$-receptor greatly predominated over that of the $H_2$-receptor. If the pattern of receptors was different in asthmatic patients, with a relative preponderance of $H_2$-receptors, then a combination of $H_1$- and $H_2$-receptor antagonists might be a more successful form of therapy for asthma than $H_1$-receptor antagonists alone.

In the present study we have investigated the effects of $H_1$- and $H_2$-receptor antagonists on histamine inhalation challenge in normal, atopic and asthmatic subjects in order to compare the pattern of bronchial histamine receptors in these groups. We have also studied the effect of the antihistamines on the response to antigen challenge in allergic asthmatic patients in order to establish whether histamine is an important mediator in the bronchi and to establish the relative importance of the $H_1$- and $H_2$-receptors in this response. These results have been presented briefly in abstract form (Eiser, Guz, Mills & Snashall, 1978).

**Methods**

Eighteen healthy, non-asthmatic subjects and 18 patients with stable asthma were studied. Each group consisted of nine atopic (i.e. had two or more positive skin-prick tests to common allergens) and nine non-atopic subjects. One atopic non-asthmatic subject had mild perennial rhinitis and one had hay fever, but was studied out of season. No subject had a respiratory infection at the time of study nor during the preceding month. Two asthmatic and five non-asthmatic subjects were smokers, but none had smoked for at least 2 h before the study. The mean baseline specific airways conductance, $sGaw$, of the non-asthmatic subjects was 1.70 S-I kPa$^{-1}$ (SD = 0.49) and of the asthmatic patients was 1.10 S-I kPa$^{-1}$ (±0.40). All subjects gave informed consent for the procedures and the studies were approved by the Charing Cross Hospital Ethics Committee.

The method used for bronchial challenge with histamine aerosol was exactly as previously described (Eiser et al., 1980). The aerosol was inhaled from a Hudson nebulizer triggered via a breath-actuated dosimeter and the response was monitored by serial measurements of $sGaw$ by the method of Dubois, Botelho & Comroe (1956). During each challenge $sGaw$ was measured before and 2 min after inhalation of five breaths of histamine acid phosphate. The nebulizer was washed and dried after each dose. Every 3 min another dose was delivered, double the previous concentration. The concentrations used ranged from 2 to 64 g/l for the non-asthmatic subjects. For the asthmatic patients it was necessary to perform a pilot study to determine a suitable starting concentration of histamine, usually 0.5 or 1 g/l. Further doses were then delivered until a definite response occurred. The duration of the histamine challenge was 6–18 min.

The antigen challenges were performed in a similar manner, with an antigen known to produce both skin and bronchial immediate reactions. Seven subjects were challenged with *Dermatophagoides farinae*, one with *Aspergillus fumigatus* and one with rat urine. Initially a bronchial challenge with Coca’s solution was performed on each subject, since the antigen was preserved in this solution. No subject developed significant bronchoconstriction after three doses of the Coca’s solution delivered through the dosimeter–nebulizer system. Skin tests with serial dilutions of antigen were undertaken on each subject. The highest concentration of antigen that failed to produce a weal was used as a starting concentration for subsequent antigen challenge. Every 10 min double the previous concentration of antigen was delivered until a definite response occurred. After the first challenge the subjects were observed for several hours for evidence of a late allergic reaction. Not more than two antigen challenges were performed on the same subject in any one week.

Histamine and antigen responses were performed in duplicate in all subjects and the mean curves were used to compare the effects of the antihistamines. Though the asthmatic patients were in a stable clinical state their baseline $sGaw$ varied considerably from day to day and therefore mean histamine and antigen dose–response curves were calculated from the two responses whose baselines were within 20% of each other.

On separate days histamine challenges were repeated 10 min after intravenous injections of either a placebo of saline, chlorpheniramine (20 mg; $H_1$-receptor antagonist), cimetidine (200 or 400 mg; $H_2$-receptor antagonist) or chlorpheniramine (20 mg) with cimetidine (200 mg). Where the effect of the premedication had been to change the baseline $sGaw$ to a value more than 20% from that of the baseline $sGaw$ of the mean histamine or antigen dose–response curve for that subject, the study was repeated as often as necessary on other days until the effect of the premedication
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FIG. 1. Histogram showing the mean effect (±1 so) on baseline sGaw of intravenous injections of saline, cimetidine (200 and 400 mg), chlorpheniramine (20 mg) and chlorpheniramine (20 mg) with cimetidine (200 mg) in normal subjects (B) and asthmatic patients (O). There are 18 observations in each column. N.S., Not significant.

Effect of antihistamines on histamine dose-response curves

With minor differences the same pattern of response was found in the asthmatic and non-asthmatic groups of subjects (Fig. 2a,b) and also when these groups were subdivided into atopic and non-atopic subjects (Fig. 3a,b,c,d). Placebo premedication did not significantly alter the histamine response in either group, whereas chlorpheniramine (20 mg) given either alone or with

Results

Effect of antihistamines on baseline sGaw

The mean effect of saline and the antihistamines on baseline sGaw of the non-asthmatic and the asthmatic subjects is shown on Fig. 1. Placebo produced significant bronchodilatation in the asthmatic subjects ($P < 0.05$), but no significant change in the non-asthmatic subjects. The effect of the antihistamines on the bronchial tone of the non-asthmatic subjects was not significantly different from the effect of placebo. However, among the asthmatic patients chlorpheniramine, whether alone or with cimetidine, produced significant bronchodilatation ($P < 0.01$ and $< 0.001$ respectively). The detailed data documenting the effect of the premedication on baseline sGaw in each subject have been deposited as Clinical Science Table 80/3 with the librarian.
subjects and was statistically significant when compared with the placebo premedicated curve at the last two doses of histamine in the asthmatic group and at the highest dose of histamine in the non-asthmatic group of subjects.

Effect of antihistamines on antigen response

The mean antigen dose–response curves for the nine atopic asthmatic patients is shown in Fig. 4. Placebo premedication did not alter the mean antigen dose–response curve, whereas the response to antigen was inhibited by chlorpheniramine (20 mg), with or without cimetidine. From each patient’s original dose–response curves the percentage change in baseline sGaw after chlorpheniramine was compared with the ratio of the dose of antigen required to decrease baseline sGaw by 50% after chlorpheniramine (numerator) and after placebo premedications (denominator). There was no correlation between the effect of chlorpheniramine on baseline tone and on the subsequent antigen dose–response curve. Cimetidine, in both doses, shifted the antigen dose–response curve significantly to the right (Fig. 4). The shift, which was greater after 200 mg than after 400 mg of cimetidine, was statistically significant after all but the first dose of antigen after cimetidine (200 mg) and after the last two doses of antigen after cimetidine (400 mg).

Anticholinergic effect of chlorpheniramine in asthmatic patients

Both chlorpheniramine and atropine induced bronchodilatation in the eight asthmatic patients and so the baseline conditions before methacholine challenge were not always comparable. Fig. 5 illustrates the results obtained. When baseline sGaw values were similar chlorpheniramine did not alter the methacholine dose–response curve (Fig. 5a) or shifted it to the left (Fig. 5b). However, when the baseline sGaw was raised by chlorpheniramine (Fig. 5c,d), the subsequent methacholine dose–response curve was shifted to the right.

Side effects

A metallic taste was reported immediately after injections of cimetidine (200 mg) (four asthmatic), cimetidine (400 mg) (seven asthmatic, six non-asthmatic) and chlorpheniramine (20 mg) with cimetidine (200 mg) (seven asthmatic subjects). Within 5 min of the injection of cimetidine (400 mg) seven asthmatic and two
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FIG. 3. Mean histamine dose–response curves for (a) non-atopic non-asthmatic, (b) atopic non-asthmatic, (c) non-atopic asthmatic and (d) atopic asthmatic subjects. sGaw, as a percentage of baseline, is plotted against cumulative units of histamine on a log scale. The symbols are as in Fig. 2.

non-asthmatic subjects developed weals at the injection site and one asthmatic subject also had weals on the rest of that arm. These weals were not itchy and were not associated with erythema. All subjects reported some degree of drowsiness after chlorpheniramine (20 mg). No subject developed a late bronchial reaction after antigen challenge.

Discussion

Bronchial tone

This carefully standardized method of bronchial challenge and the reasons for the use of an analysis of variance to evaluate the results have been discussed in detail (Eiser et al., 1980). It has been suggested that the degree of pre-existing bronchomotor tone may influence the response to bronchoconstrictor stimulation (Benson & Graf, 1977). For this reason the effects of the ‘antihistamines’ were only studied when, within subjects, the baseline sGaw was similar. In this, as in previous studies, the ‘antihistamines’ had a
different effect on basal bronchomotor tone in normal and asthmatic subjects; neither H1- nor H2-receptor antagonists altered the airway tone of normal subjects (Maconochie et al., 1979; Eiser et al., 1980), whereas the H1-receptor antagonists, chlorpheniramine and clemastine, were bronchodilators in asthmatic subjects (Popa, 1977; Woenne et al., 1978; Thomson & Kerr, 1980). A possible explanation of these findings in asthmatic subjects is that there is continuous histamine release in the resting state which is responsible for the initial bronchomotor tone and that the H1-receptor antagonists relieve this tone. It is unlikely that bronchodilatation was due to concomitant anticholinergic properties of chlorpheniramine, since, in normal subjects, neither bronchial tone nor the methacholine response was altered by chlorpheniramine (Eiser et al., 1980). Because of the bronchodilatation in asthmatic patients anticholinergic effects of chlorpheniramine were more difficult to assess in this group. Nevertheless, when, within asthmatic patients, bronchial tone was similar immediately before challenge chlorpheniramine did not inhibit the methacholine response.

**Histamine response**

The present study confirms, in a quantitative way, the protective effect of H1-receptor antagonists on histamine challenge in normal and asthmatic subjects suggested by others (see the Introduction section), but the role of the H2-receptor is still unresolved. Work *in vitro* on excised human bronchi suggested that, while H1-receptors mediated bronchoconstriction, H2-receptors mediated bronchodilatation (Dunlop & Smith, 1977). However, very large doses of the H2-receptor antagonist were used and dose–response relationships were not investigated. Nevertheless, similar conclusions were drawn from more recent work on asthmatic patients by Nathan and coworkers (1979), though the effect of the H2-receptor appeared to be small. In

![Graph](image_url)
contrast, neither Maconochie et al. (1979) nor Thomson & Kerr (1980) found evidence for the presence of H₂-receptors in normal bronchi and in the present study H₂-receptors appear to mediate bronchoconstriction. Since all three studies in vivo agree that, if present, H₂-receptors were of minor importance in human bronchi, the conflicting results reported by these workers probably reflect methodological differences in inhalation technique and measurement of response. In the present study, sGaw was used as the measure of airway calibre. Unlike forced expiratory manoeuvres sGaw is sensitive to small changes in airways calibre, but is influenced predominantly by changes in the large airways. If H₂-receptors are located predominantly in small airways, the effect of H₂-receptor blockade may be underestimated by the measurement of sGaw. In the studies by Maconochie et al. (1979), Nathan et al. (1979) and Thomson & Kerr (1980) it was possible that, in addition, local concentrations of cimetidine were inadequate, since only 200 mg of cimetidine was given. In the study by Nathan et al. (1979) this was by mouth rather than by the intravenous route and in Thomson’s study it was not known whether the dose of cimetidine inhaled was sufficient to produce H₂-receptor blockade. Finally, both Maconochie et al. (1979) and Nathan et al. (1979) compared single dose–response relationships rather than dose–response curves.

In the present study the response of all subjects to histamine and of the atopic asthmatic patients to antigen was completely blocked by chlorpheniramine (20 mg), whether given alone or with cimetidine. However, over the dose range observed, there was no final slope to any of the mean dose–response curves and so it was not possible to say definitely whether the addition of cimetidine to chlorpheniramine enhanced the effect of chlorpheniramine on these responses.

Antigen response

The finding that chlorpheniramine was such an effective antagonist of the antigen response was of interest, since histamine is only one of several mediators released in the immediate allergic response. In the classical experiment in vitro on excised bronchus and lung from an asthmatic patient, the effect of the histamine released by antigen challenge was small (Schild, Hawkins, Mongar & Herxheimer, 1951). Mepyramine, another H₁-receptor antagonist, was found to be 10⁴ times more effective in protecting against histamine-induced bronchoconstriction than against antigen-induced bronchoconstriction.

Lichtenstein & Gillespie (1973) have suggested that there is a negative feedback mechanism, controlled via the H₁-receptor, whereby the presence of histamine inhibits the further release of histamine. Thus an H₂-receptor antagonist might potentiate histamine release during an immediate allergic response by disrupting this mechanism. In the present study histamine release might have produced both the metallic taste in the mouth and the weals on the arm in some subjects after cimetidine (400 mg); both H₁ and H₂-receptors have been demonstrated in the skin and have been shown to participate in the histamine response there (Greaves, Marks & Robertson, 1977). If H₂-receptors exist in human airways and mediate bronchoconstriction one might predict that cimetidine would protect against the effect of inhaled antigen. This was indeed the case. The observation that 400 mg of cimetidine gave less protection than 200 mg of cimetidine might then be explained by the effect on histamine release by the large dose of cimetidine.

**Alternative hypothesis of H₂-receptor effects**

It is possible that, in man, H₂-receptor antagonism might inhibit both histamine- and antigen-induced airways obstruction indirectly by preventing associated pulmonary vasodilatation rather than directly by preventing bronchial muscle constriction. Animal studies suggest that inhaled histamine can produce pulmonary oedema (Pietra, Szidon, Leventhal & Fishman, 1971) and that histamine induced pulmonary vasodilatation is mediated via H₂-receptors (Eyre & Wells, 1973; Eyre, 1974; Okpako, 1974; Tucker, Weir, Reeves & Grover, 1975). Both factors might increase airways resistance (Boissier, Adventier, Guidicelli & Viars, 1971). Inhibition of both histamine- and antigen-induced bronchial hypersecretion has been demonstrated in dogs with H₁- and H₂-receptor antagonists (Yamatake, Sasagawa, Yanaura & Kobayashi, 1977). If this occurs in human bronchi measurements of airways calibre could be affected without any change in bronchial muscle tone. Further detailed studies are needed to explore these possibilities.

**Conclusion**

No difference was found in the pattern of histamine receptors in normal, atopic or asthmatic subjects. Histamine-induced bronchoconstriction in man is mediated predominantly via H₁-receptors. If H₂-receptors are present in the
tracheobronchial tree they also mediate bronchoconstriction, but their effect is trivial. Administration of H₂-receptor antagonists to asthmatic patients is unlikely to influence their bronchospasm significantly. Thus, it is safe for asthmatic patients to take H₂-receptor antagonists, it is unlikely that these agents are of potential therapeutic value in asthma. The results of the antigen challenges suggest that histamine is a powerful bronchoconstrictor and a relatively important mediator of the immediate allergic response to antigen in man.

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