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Effect of inhaled H1 and H2 receptor antagonists in normal and asthmatic subjects

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ABSTRACT The effects on airflow resistance of an inhaled H1 receptor antagonist, clemastine, and an H2 receptor antagonist, cimetidine, have been investigated in normal and asthmatic subjects. No significant changes in specific conductance (sGaw) were seen in six normal subjects. In eight asthmatic subjects a significant increase in forced expiratory volume in one second (FEV_1) occurred at 60 min ($<0{\cdot}02$), 90 min ($<0{\cdot}02$), and 120 min ($<0{\cdot}05$) after the inhalation of clemastine, whereas inhaled cimetidine had no effect on airflow resistance. Clemastine and cimetidine were tested on histamine-induced bronchoconstriction in eight normal and eight asthmatic subjects. Clemastine significantly reduced the fall in sGaw in normal subjects and the fall in FEV_1 in asthmatic subjects, whereas cimetidine had no protective effect. Clemastine and ipratropium bromide were tested on methacholine-induced bronchoconstriction in eight normal subjects. Ipratropium bromide, but not clemastine, significantly reduced the fall in sGaw after methacholine. These results suggest that in normal and asthmatic subjects histamine-induced bronchoconstriction is mediated predominantly via H1 rather than H2 receptors in the airways.

Histamine is released when sensitised human lung tissue interacts with specific antigen in vitro.[1] Evidence for histamine acting as a chemical mediator in asthma is based on reports of raised histamine levels after oral aspirin challenge,[2] exercise challenge,[3] allergen challenge,[4] and spontaneously occurring asthma.[5] In experimental animals, histamine has been shown to constrict airway smooth muscle by a direct local effect,[6] and also by a reflex vagal pathway.[7] In normal and asthmatic subjects, however, histamine acts mainly by direct stimulation of bronchial smooth muscle.[8–11] In other tissues of the body, two types of histamine receptor have been identified.[12 13] Smooth muscle contraction is mediated by H1 receptors, while H2 receptor responses involve gastric acid secretion and cardiac stimulation. Vasodilation is mediated by both H1 and H2 receptors.[14] Recent in vitro studies[15] have indicated that H1 and H2 receptors are present in human bronchial smooth muscle.

The purpose of this study was to investigate whether H1 or H2 receptor responses or both are present on the airways of normal and asthmatic subjects.

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Methods

Seventeen patients, aged 16–45 years, with extrinsic asthma and reversible airflow obstruction were studied. All had positive skin tests to inhalant allergens. Sodium cromoglycate and bronchodilators were discontinued for 12 hours before each test was carried out. Patients on oral or aerosol corticosteroids were excluded from the study. All patients were non-smokers. Their baseline data are represented in the table. Eight normal subjects, aged 22–36 years, with no history of chronic respiratory disease were also studied, three of whom smoked 10–15 cigarettes per day. The nature and the purpose of the study were explained to both patients and normal subjects. The investigations were approved by the Ethical Committee of this hospital and all patients and normal subjects gave informed consent.

Airways resistance (Raw) and thoracic gas volume were measured simultaneously in a constant volume body plethysmograph (Fenyves and Gut). The results were expressed as specific

Table 1 *Baseline data of asthmatic subjects*

Subject	*Sex*	*Age* (yr)	*Mean baseline* FEV_1	*Precentage predicted* FEV_1
	F	17	3·24	106·2
12	M	21	4·20	109·0
3	F	31	3·00	98·3
4	M	25	3·82	81·2
5	M	18	4·16	101·4
6	F	26	2·63	87·6
7	F	19	2·23	81·7
8	M	24	4·66	112·2
9	F	36	1·71	63·3
10	M	17	2·60	72·2
11	F	28	4·13	121·4
12	M	45	4·26	118·3
13	M	24	5·36	120·4
14	M	30	4·01	109·8
15	M	34	2·33	65·6
16	F	34	2·75	94·8
17	F	16	2·57	85·6

conductance (sGaw) which is the reciprocal of airways resistance per litre of thoracic gas volume. The mean of six values recorded was taken as sGaw. All plethysmographic measurements were carried out by one observer, but analysis of the records of pressure and flow was carried out by another person who was unaware of the nature or order of agents administered. Forced expiratory volume in one second (FEV_1) was measured in triplicate using a dry wedge spirometer (Vitalograph), the best recording being used for analysis. Where necessary volumes were corrected to body temperature, pressure saturated with water vapour (BTPS). Predicted normal values for FEV_1 were taken from Cotes.[16]

All solutions were inhaled through a Wright nebuliser (using compressed air at a flow rate of 8 l/min). The subject placed the nebuliser just outside the open mouth and took tidal breaths of the aerosol. The different aerosols were always inhaled by each subject on separate days. Subjects were unaware of the sequence of the aerosols which were randomly assigned.

EXPERIMENTAL PROCEDURES

Normal subjects

In six normal subjects, after baseline measurements of sGaw, saline (9 g/l), clemastine (1 g/l), or cimetidine (100 g/l) was inhaled through a Wright nebuliser for 5 min, sGaw then being recorded at 2, 5, 10, 20, 30, and 60 min.

In eight normal subjects measurements of sGaw were performed before and 30 min after inhaling saline (9 g/l), clemastine (1 g/l), or cimetidine (100 g/l) for 5 min. Five breaths of increasing concentrations of histamine dihydrochloride (1·5, 3·1, 6·2, 12·5, 25·0, 50·0 g/l) were then inhaled every 3 min, with sGaw recorded at 2 min after each inhalation.

In a separate series of experiments in the same eight subjects, sGaw was measured before and 30 min after inhaling saline (9 g/l), clemastine (1 g/l), or ipratropium bromide (1 g/l) for 5 min. Five breaths of increasing concentrations of methacholine dihydrochloride (3·1, 6·2, 12·5, 25·0, 50·0 g/l) were then inhaled every 3 min, with sGaw recorded at 2 min after each inhalation.

Asthmatic subjects

In eight asthmatic subjects (numbers 1–8), after baseline measurements of FEV_1, saline (9 g/l) or clemastine (0·5 g/l) was inhaled for 5 min, FEV_1 being recorded at 30, 60, 90, and 120 min.

In a further eight asthmatic subjects (numbers 3–6, 8, 9, 16, 17), after baseline measurements of FEV_1, saline (9 g/l) or cimetidine (100 g/l) was inhaled for 5 min, FEV_1 then being recorded at 10, 30, 60, 90, and 120 min.

Finally in eight asthmatic subjects (numbers 10–17), FEV_1 was measured before and 30 min after inhaling saline (9 g/l), clemastine (0·5 g/l), or cimetidine (100 g/l) for 5 min. Five breaths of increasing concentrations of histamine dihydrochloride (0·15, 0·31, 0·62, 1·25, 2·5, 5·0 g/l) were then inhaled every 3 min, with FEV_1 recorded at 2 min after each inhalation.

The statistical significance of observed changes in sGaw was determined using the Wilcoxon matched-pairs signed-rank test and Fisher, Irwin, and Yates exact probability test (experiment involving six subjects only), and of observed changes in FEV_1 by student's *t* test. Differences were considered significant if $p<0·05$.

Results

NORMAL SUBJECTS

In six subjects no significant difference was found in pretreatment sGaw, and there were no absolute changes in sGaw at 2, 5, 10, 20, 30, and 60 min after the inhalation of clemastine, cimetidine, or saline (fig 1).

In eight subjects there were no significant differences in pretreatment sGaw, or absolute changes in sGaw at 30 min after the inhalation of clemastine, cimetidine, or saline. The change in sGaw after pretreatment with clemastine was significantly smaller than the change in sGaw after pretreatment with saline after 25·0 g/l ($p<0·05$) and 50·0 g/l ($p<0·01$) of inhaled histamine or after pretreatment with cimetidine after 25·0 g/l ($p<0·05$) and 50 g/l ($p<0·01$) of inhaled

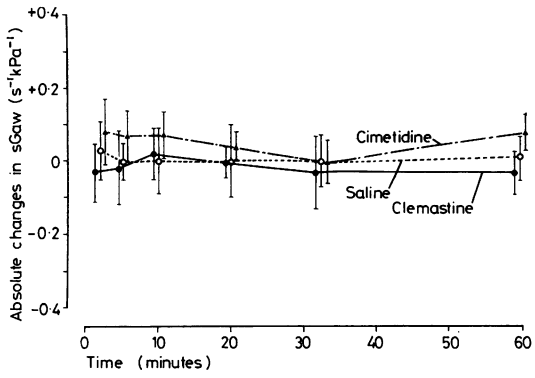

Fig 1 *Effect of inhaled clemastine, cimetidine, and saline on absolute change in sGaw (±SEM) in normal subjects (n=6). Mean baseline sGaw value ($S^{-1}kPa^{-1}$) before clemastine 1·50 ±0·26; before cimetidine 1·33±0·21; before saline 1·37±0·28.*

histamine. After pretreatment with cimetidine and saline there was no significant difference in the change in sGaw at each dose of inhaled histamine (fig 2). In the same eight normal subjects inhaled ipratropium bromide produced a significant rise in sGaw ($p<0·01$), whereas inhaled clemastine and saline had no effect. The change in sGaw after pretreatment with ipratropium bromide was significantly different from the change in sGaw after pretreatment with clemastine or saline after 12·5, 25·0 and 50·0 g/l of inhaled methacholine ($p<0·01$) (fig 3).

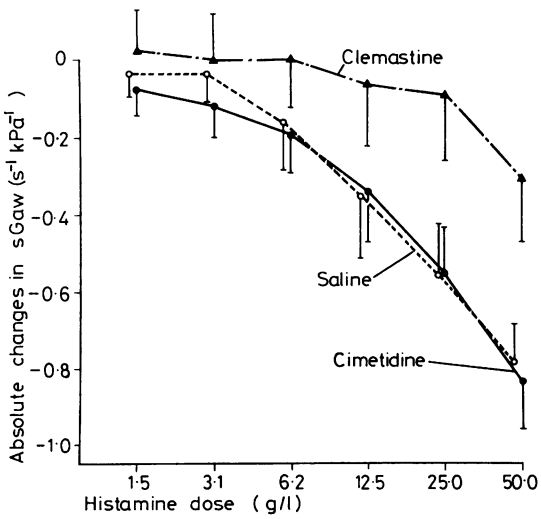

Fig 2 *Absolute change in sGaw (±SEM) plotted against cumulative log dose of inhaled histamine (g/l) in normal subjects (n=8) after pretreatment with clemastine, cimetidine, or saline. Mean sGaw value ($S^{-1}kPa^{-1}$) before and 30 min after clemastine (1·43±0·16 baseline, 1·45±0·16 after clemastine); cimetidine (1·41±0·17 baseline, 1·38±0·16 after cimetidine); saline (1·46±0·19 baseline, 1·38±0·13 after saline).*

ASTHMATIC SUBJECTS

In eight asthmatic subjects (numbers 1–8) inhaled clemastine produced significant increase in FEV_1 at 60 min ($p<0·02$), 90 min ($p<0·02$), and 120 min ($p<0·05$) after the inhalation (fig 4). The maximum mean percentage increase in FEV_1 (±1SD) after clemastine (14·3±9·7) was significantly greater than after saline (5·7±3·7) ($p<0·02$). In a separate study in eight asthmatic subjects (numbers 3–6, 8, 9, 16, 17) there was no significant difference in the absolute change in FEV_1 after pretreatment with cimetidine or saline at 10, 30, 60, 90, and 120 min after the inhalation (fig 5).

In eight asthmatic subjects (numbers 10–17) there were no significant differences in pretreatment FEV_1 or absolute changes in FEV_1 at 30 min after the inhalation of clemastine, cimetidine, or saline. After pretreatment with cimetidine there was no significant difference in the change in FEV_1 at each dose of inhaled

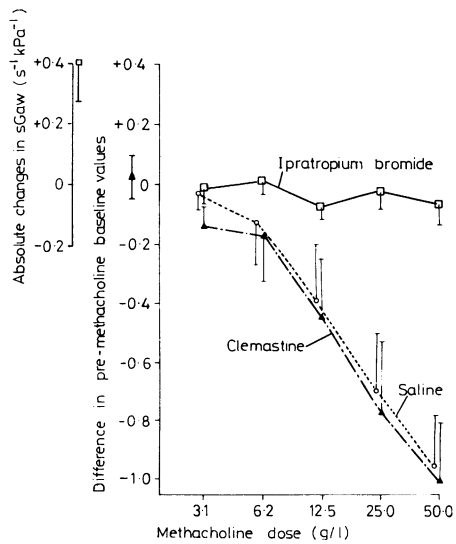

Fig 3 *Absolute change in sGaw (±SEM) plotted against cumulative log dose of inhaled methacholine (g/l) in normal subjects (n=8) after pretreatment with clemastine, ipratropium bromide, or saline. Mean sGaw value ($S^{-1}kPa^{-1}$) before and 30 min after clemastine (1·54±0·22 baseline, 1·62±0·25 after clemastine); ipratropium bromide (1·56±0·24 baseline, 1·98±0·30 after ipratropium bromide); saline (1·55±0·23 baseline, 1·58±0·21 after saline.)*

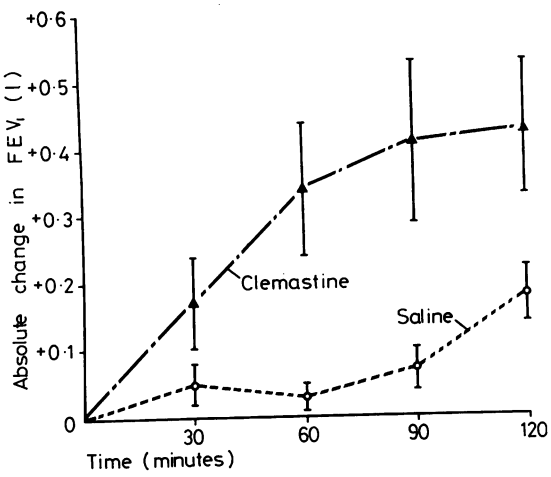

Fig 4 *Effect of inhaled clemastine and saline on absolute change in FEV_1 (±SEM) in asthmatic subjects (n=8). Mean baseline FEV_1 (l) value before clemastine 3·50±0·30; before saline 3·54±0·32.*

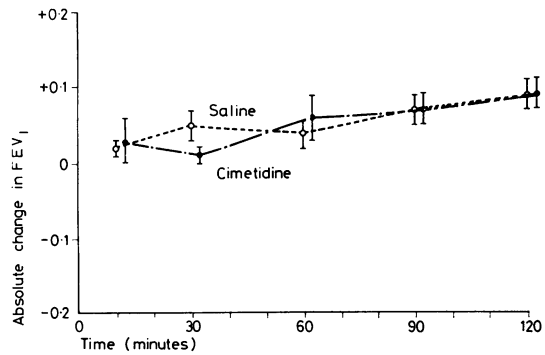

Fig 5 *Effect of inhaled cimetidine and saline on absolute change in FEV_1 (±SEM) in asthmatic subjects (n=8). Mean baseline FEV_1 (l) value before cimetidine 3·15±0·36; before saline 3·20±0·33.*

histamine when compared to that after pretreatment with saline. The change in FEV_1 after pretreatment with clemastine was significantly smaller than the change after pretreatment with saline after 0·62 g/l ($p<0·01$), 1·25 g/l ($p<0·01$), 2·5 g/l ($p<0·01$) of inhaled histamine or after pretreatment with cimetidine after 0·31 g/l ($p<0·02$), 0·62 g/l ($p<0·05$), 1·25 g/l ($<0·02$), 2·5 g/l ($p<0·01$) of inhaled histamine (fig 6). Because only three patients were able to inhale histamine at a concentration of 5·0 g/l after pretreatment with saline or cimetidine, statistical comparison with the changes in FEV_1 after pretreatment with clemastine was not possible,

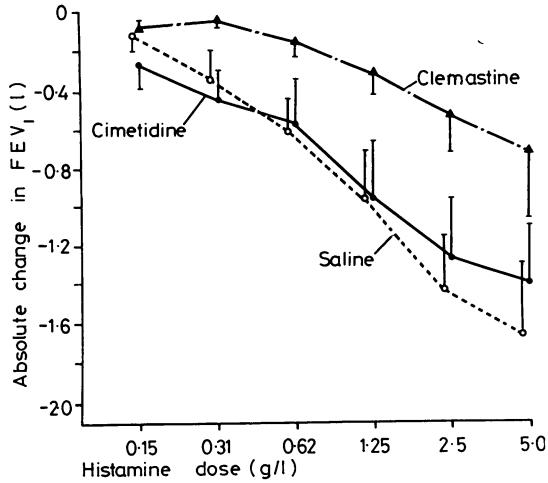

Fig 6 *Absolute change in FEV_1 (±SEM) plotted against cumulative log dose of inhaled histamine (g/l) in asthmatic subjects (n=8) after pretreatment with clemastine, cimetidine, or saline. Mean FEV_1 (l) before and 30 min after clemastine (3·46±0·38 baseline, 3·66±0·38 after clemastine); cimetidine (3·47±0·36 baseline, 3·51±0·36 after cimetidine); saline (3·59±0·40 baseline, 3·60±0·39 after saline).*

although in each case the changes in FEV_1 after clemastine were much smaller than those after saline or cimetidine. In each of the eight asthmatic patients studied, the cumulative log histamine dose-response curve was shifted to the right after pretreatment with clemastine in comparison to after pretreatment with saline or cimetidine (fig 7).

Discussion

At least two types of histamine receptor are involved in the histamine response.[12] Clemastine is an extremely potent and specific H1 receptor antagonist with no central or circulatory effects in conscious animals.[17] It possesses no significant anticholinergic or antiserotonin activity.[18 19] The concentration of clemastine inhaled by the asthmatics was half that administered to the normal subjects, since a concentration of greater than 0·5 g/l was found to produce upper airway irritation. H2 receptor responses are blocked by burimamide, metiamide, and cimetidine but not by H1 receptor antagonists clemastine and chlorpheniramine.[13] Cimetidine is a specific competitive H2 receptor antagonist with no significant interaction at catecholamine β-receptors, H1 receptors or muscarinic receptors.[20] The concentration of cimetidine used in this study

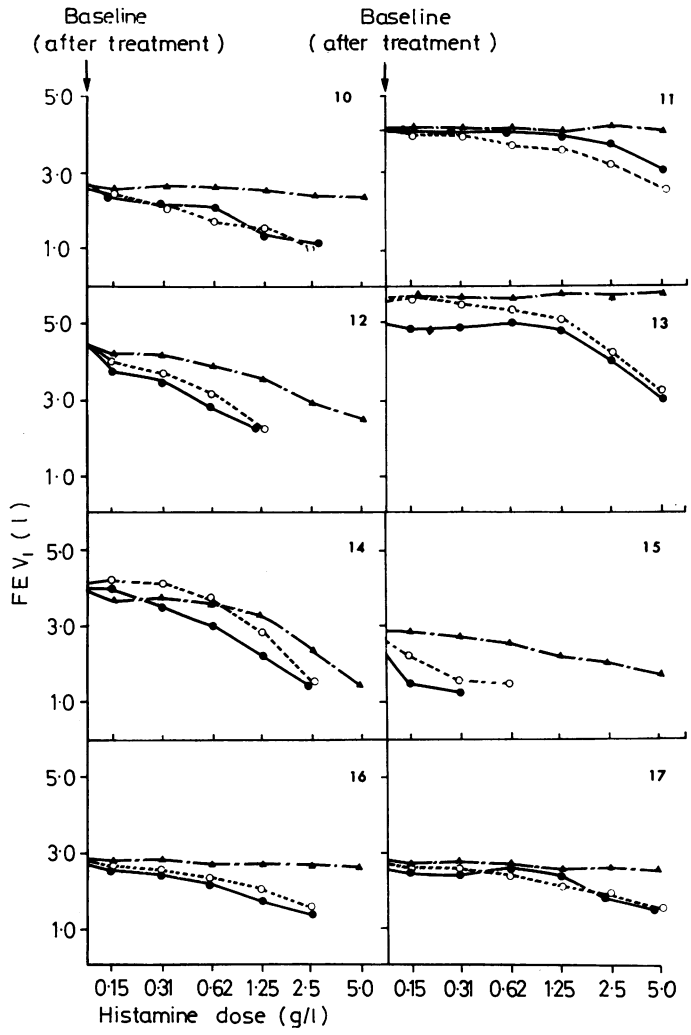

Fig 7 *Absolute values of FEV_1 plotted against cumulative log dose of inhaled histamine (g/l) for each of the eight asthmatic subjects studied. Values of FEV_1 are shown after pretreatment with clemastine (▲), cimetidine (●), or saline (○).*

has been shown to inhibit effectively H2 responses such as gastric acid secretion in humans.[21]

The absence of any significant change in airways calibre of normal subjects after an inhaled H1 receptor antagonist suggests that this receptor is not important in the maintenance of normal airways tone. Several H1 receptor antagonists, however, have been reported to cause bronchodilation in asthmatic patients. Popa[22] found increases in the airways calibre of 10 asthmatic patients after intravenously administered chlorpheniramine (10mg) although this was complicated by drowsiness in several subjects. Nogrady *et al*,[23] reported that inhaled clemastine produced a maximum percentage increase in FEV_1 of 21% in 12 asthmatic patients, in comparison to an increase of 14% found in this study. Although the dose and method of administration of clemastine were similar, the better baseline function of the patients in the present study may account for the smaller increase in FEV_1 after clemastine. The reason for the difference in response to an inhaled H1 antagonist between normal subjects and patients with asthma is unexplained but may indicate continuous release of histamine in the asthmatic group as has recently been suggested.[24]

In experimental animals, histamine acts locally on the airway smooth muscle causing constriction[6] and can also stimulate vagal sensory receptors in the airways causing reflex bronchoconstriction.[7] In normal subjects and patients

with asthma, however, the main action of histamine is probably direct stimulation of human bronchial smooth muscle[8-11] via H1 or H2 receptors or both. The protective action of the H1 receptor antagonist clemastine on histamine-induced bronchoconstriction in asthmatic subjects confirms the findings of Nogrady and Bevan[24] and extends this observation to normal subjects. These findings, therefore, suggest that histamine was acting at the H1 receptor in both normal subjects and asthmatic patients. A similar reduction in bronchoconstrictor effect of histamine has also been reported with less potent or specific H1 receptor antagonists than clemastine.[7 25 26] H1 receptor antagonists may possess to a variable degree anticholinergic and local anaesthetic effects.[27] In the present study, clemastine had no significant anticholinergic action in normal subjects and has been shown to have no protective effect on methacholine-induced bronchoconstriction in asthmatics.[24] A local anaesthetic effect by clemastine on sensory irritant receptors is also unlikely. Firstly, anticholinergic drugs only slightly reduce the airway response to histamine in comparison to H1 receptor antagonists.[8-11] Secondly, the inhaled local anaesthetic bupivacaine has no preventive action on histamine-induced bronchoconstriction in normal subjects.[10] Changes in baseline airflow obstruction may alter bronchial reactivity.[28] This is unlikely, however, to be relevant to the present study, since although clemastine causes bronchodilation in asthmatic patients, this is only slight at 30 min after inhaled clemastine when histamine challenge was performed. Furthermore, in normal subjects clemastine displaced the histamine dose response curve when there was no change in baseline lung function. The most likely explanation for our findings is that there are H1 receptors in human airways.

The present results do not support to the hypothesis that H2 receptors are present in the airways of normal subjects and asthmatics.[29] Slight changes in small airways function, however, could have been missed by measurement of specific conductance in normal subjects and FEV_1 in asthmatic patients. Eyre[30] showed that the relaxant effect of histamine on sheep terminal bronchus was an H2 response. In atopic and non-atopic human subjects, however, inhaled histamine caused bronchoconstriction of both large and small airways.[31] It is unknown whether the dose of cimetidine inhaled in this study was sufficient to produce complete H2 receptor blockade. The inhalation technique, however, used to give cimetidine and histamine should have resulted in a similar degree of aerosol deposition within the airways, even if their sites of action were different. Differences have been found between cimetidine and other H2 receptor blockers in their ability to reduce mediator release from sensitised tissue,[32] burimamide and metiamide but not cimetidine increasing the anaphylactic reactions in sensitised guinea pigs. It is not known whether any possible difference between cimetidine and other H2 receptors blockers would be relevant to the identifications of human bronchial smooth muscle H2 receptors. Finally, in some experimental systems, H2 antagonists have no effect alone, but act synergistically when combined with H1 antagonists.[33] A similar synergistic action in bronchial smooth muscle cannot be excluded from this study.

If histamine is shown to be an important mediator of immediate type hypersensitivity in human asthma, then the predominant site of action of histamine is probably by a direct effect on bronchial smooth muscle H1 receptors.

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