Nasal response of rhinitic and non-rhinitic subjects to histamine and methacholine: a comparative study

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ABSTRACT   The nasal responses to provocation with histamine and methacholine were compared in 20 subjects with and 20 without rhinitis. Two variables were measured: nasal airways resistance and the development of rhinorrhoea. Histamine had a greater effect than methacholine in increasing nasal airways resistance while the converse was true for rhinorrhoea. Rhinitic subjects had a significantly greater response to histamine induced changes in nasal airways resistance ($p < 0.05$), rhinorrhoea ($p < 0.05$) and methacholine induced rhinorrhoea ($p < 0.01$) than those without rhinitis. No significant differences were found between the two groups in methacholine induced changes in nasal airways resistance. The findings show that, like the lower airways of patients with asthma, the nasal mucosa of rhinitic subjects shows a greater responsiveness to non-specific agonists than that of non-rhinitic subjects.

It is well recognised that the lower airways of subjects with asthma show a greater responsiveness to various non-specific stimuli, including the pharmacological agents histamine and methacholine, than those of subjects without asthma.[1-4] The enormous number of reports on various aspects of bronchial reactivity provides a striking contrast to the limited attention devoted to the study of the upper respiratory tract. The results of studies of the upper respiratory tract have generally shown poor agreement and it remains unclear whether the nasal mucosa of patients with rhinitis is more responsive to pharmacological agonists than that of non-rhinitic subjects.[5-12]

The nasal response to provocation can be measured in several ways.[13] A nasal challenge may cause pruritus and sneezing from stimulation of nerve endings, nasal obstruction from vascular dilatation and oedema, and rhinorrhoea from stimulation of mucosal glands.[13 14] The purpose of this study was, firstly, to re-examine whether an increased level of non-specific responsiveness of the nasal mucosa is a feature of rhinitis and, secondly, to determine whether any differences exist in the pattern of response to provocation with histamine and metha-

choline by measuring change in both nasal airways resistance and rhinorrhoea in the same subjects.

Methods

SUBJECTS

We studied 20 patients with perennial allergic rhinitis who had symptoms and who were selected at random from those attending outpatient clinics. The 13 female and seven male subjects were aged 17–40 (mean 26) years. They had suffered from perennial rhinitis[7] for from one to 25 years (mean nine years), experiencing symptoms for one to 16 hours a day (mean seven hours). All patients had a positive skinprick test response and a positive response to a nasal provocation test with either *Dermatophagoides pteronyssinus* (18 subjects) or cat fur extract (two subjects). Seventeen patients were having no current medication for their rhinitis, one patient had regularly been using the H_1 antihistamine chlorpheniramine maleate (slow release) 10 mg at night, and two were using intranasal beclomethasone dipropionate. These patients discontinued all treatment three days before the study.

We also studied a control group of 20 healthy volunteers (11 female, age range 19–35, mean 26 years) with no history of rhinitis or other nasal disease, asthma, or eczema, and with negative skinprick test responses to four common allergens (*Dermatophagoides pteronyssinus,* house dust, grass pollen, and *Aspergillus fumigatus*). Control subjects were

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matched with the rhinitic subjects for age and sex so far as possible. None of the 40 subjects had evidence of either nasal polyposis or deformity on anterior rhinoscopy. Solutions were made of methacholine bromide (Sigma Chemical Co Ltd, Poole, Dorset) in distilled water[7] at concentrations of 15, 30, 60, 120, and 240 mg/ml and histamine acid phosphate (BDH Chemicals Ltd, Dagenham, Essex) in isotonic saline (0·9% w/v) at concentrations of 1, 2·5, 5, 10, and 25 mg/ml. Fresh solutions of both agonists were prepared at two week intervals. Buffered phenol saline (0·5% w/v saline, 0·275% w/v sodium bicarbonate, 0·4% w/v phenol), pH 7·0, was used as the control solution.

The control solution and each concentration of agonist were nebulised in a volume of 100 μl, at an air flow rate of 7 l min^{-1}, from a cuvette using a modified air spray (Humbrol, Hull). The administration of each solution took about three seconds. To reduce exposure of the lower airways to the agonist solutions, subjects were instructed to hold their breath in inspiration while the solutions were being nebulised and to exhale through the mouth immediately after delivery.

The response to nasal provocation was measured in terms of nasal airways resistance and nasal secretions. Nasal airways resistance was measured in each nostril separately, by a technique of passive anterior rhinomanometry, with the nasal airways resistance tester (PK Morgan Ltd, Chatham, Kent) originally described by Britton and coworkers.[15] Each measurement of nasal airways resistance was taken as the mean of five consecutive readings recorded within 30 seconds. Nasal secretions were collected by asking subjects to incline their head slightly forward over a graduated test tube equipped with a glass funnel held below the challenged nostril.

PROTOCOL
Nasal provocation tests with histamine and methacholine were performed one week apart, in a random order, on each subject. The study had an open design. Nasal airways resistance was measured in each nostril before provocation. Buffered phenol saline was nebulised into the nostril with the lower initial level of nasal airways resistance and the resistance was measured again two and five minutes later. Increasing concentrations of the agonist were then administered to the same nostril and measurements of nasal airways resistance made two and five minutes after each administration. Nasal secretions were collected from the time of administration of each dose of agonist and continued between measurements of nasal airways resistance. The total volume of nasal secretions collected during each provocation test was recorded.

ANALYSIS OF RESULTS
The sample size (n) required to detect a significant difference in change in nasal airways resistance of 0·75 kPa l^{-1} s between the agonist and the control solution with a power of 80% was 20 subjects in each group. These calculations were based on a one tail test, at a significance level of 5%, with the difference in nasal airways resistance normally distributed with a variance equal to 1·85.

Change in nasal airways resistance was evaluated in the challenge nostril only The maximum change in resistance recorded at two or five minutes after each dose of agonist was used in the analyses. Analysis of nasal airways resistance at each dose, plots of group means against standard deviation (SD) and variance, and probability plots showed that the SD varied directly with the mean, that the variances were heterogenous, and that the data were heavily skewed to the right, indicating non-normality of distribution. More formal assessments using Kolmogorov-Smirnov and Cochran's tests confirmed these findings and suggested that logarithmic transformation of the data would be appropriate, as concluded by Britton et al.[15]

Comparisons of nasal airways resistance values before provocation, and change in resistance after the control solution in the two groups of subjects were made on log transformed values with paired and unpaired Student's *t* tests as appropriate. Changes in resistance after administration of each agonist were related and compared with those produced by the instillation of the control solution, a two factor analysis of variance (ANOVA) being used for repeated measures. Multiple comparisons were made with the Newman-Keuls test. The analyses were performed by means of the statistical package for the social sciences (SPSS)[16] on the computer at the University College of North Wales, Bangor. The number of subjects in each group producing nasal secretions in response to provocation with each agonist were compared with the help of 2 × 2 contingency tables and Fisher's exact test.

Results

The nasal provocation tests with histamine and methacholine in the doses used in this study were well tolerated, although the two highest doses of methacholine (22·5 and 46·5 mg) produced transient facial flushing in almost all subjects, as noted previously.[7]

NASAL AIRWAYS RESISTANCE
Measurements of nasal airways resistance before provocation on the two test days ranged from 0·04 to 0·54 (geometric mean (GM) 0·12) kPa l^{-1} s and from 0·02 to 0·49 (GM 0·09) kPa l^{-1} s in rhinitic subjects
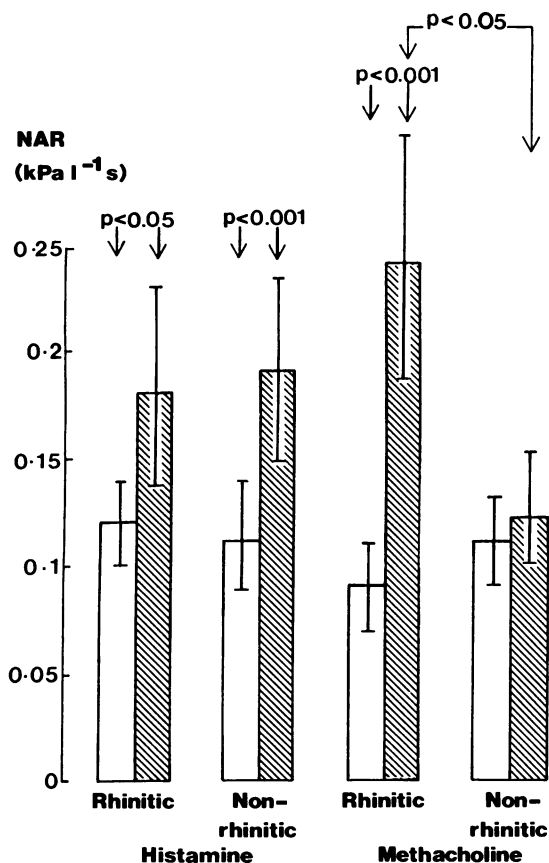
Fig 1   *Nasal airways resistance (NAR) in the challenge nostril of subjects with and without rhinitis before provocation □ and after buffered phenol saline ▨.*

two groups varied significantly ($p < 0.01$) with the dose of histamine, producing dose-response curves of different shapes for the two groups, (fig 2). In rhinitic subjects increasing doses of histamine produced significantly greater increases in nasal airways resistance, while in the non-rhinitic subjects only the highest dose of histamine used (4·35 mg) produced a significantly greater nasal airways resistance than buffered phenol saline.

Methacholine produced a greater increase in nasal airways resistance than did buffered phenol saline in both groups of subjects ($p < 0.01$), but this was less than the change produced by histamine, and not dose related (fig 2). There were no significant differences between subjects with and without rhinitis ($p < 0.10$).

NASAL SECRETIONS
Rhinorrhoea occurred in 12 subjects with and three without rhinitis in response to methacholine and in five subjects with but none without rhinitis in response to histamine, the difference between methacholine and histamine being significant for all subjects combined ($p < 0.02$). Four of the five subjects who produced secretions in response to histamine also produced secretions in response to methacholine. Rhinitic subjects had a significantly greater response to methacholine ($p < 0.01$) and histamine ($p < 0.05$)
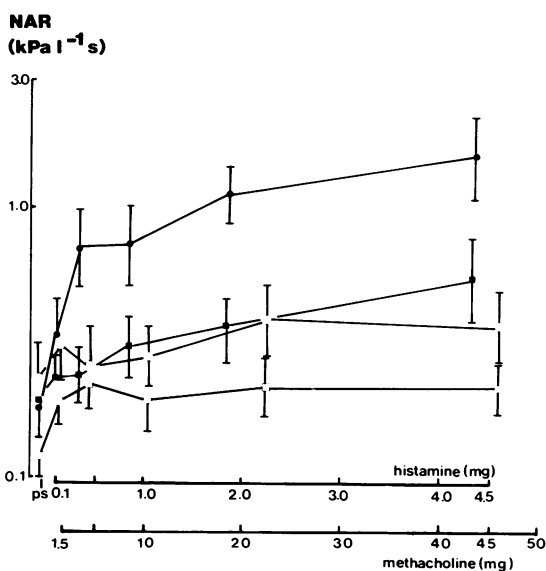
and from 0·01 to 0·92 (GM 0·11) kPa l⁻¹ s and from 0·01 to 0·48 (GM 0·11) kPa l⁻¹ s in non-rhinitic subjects. There were no significant differences between these measurements (fig 1).

The changes in nasal airways resistance after buffered phenol saline were not consistent. On the histamine test day there was a significant increase in resistance in both rhinitic and control subjects, while on the methacholine test day only those with rhinitis showed a significant increase, which was greater than that occurring in those without rhinitis (*t* test; $p < 0.05$—fig 1).

Histamine produced a dose related increase in nasal airways resistance in subjects both with and without rhinitis (analysis of variance; $p < 0.001$). The response of rhinitic subjects was significantly greater than that of non-rhinitic subjects ($p < 0.05$—fig 2). The difference in nasal airways resistance between the

Fig 2   *Effect of administration of buffered phenol saline (P/S) and increasing doses (mg) of histamine (closed symbols) and methacholine (open symbols) on the nasal airways resistance (NAR) of rhinitic (●, ○) and non-rhinitic (■, □) subjects. The geometric means and standard errors are shown on a logarithmic scale.*
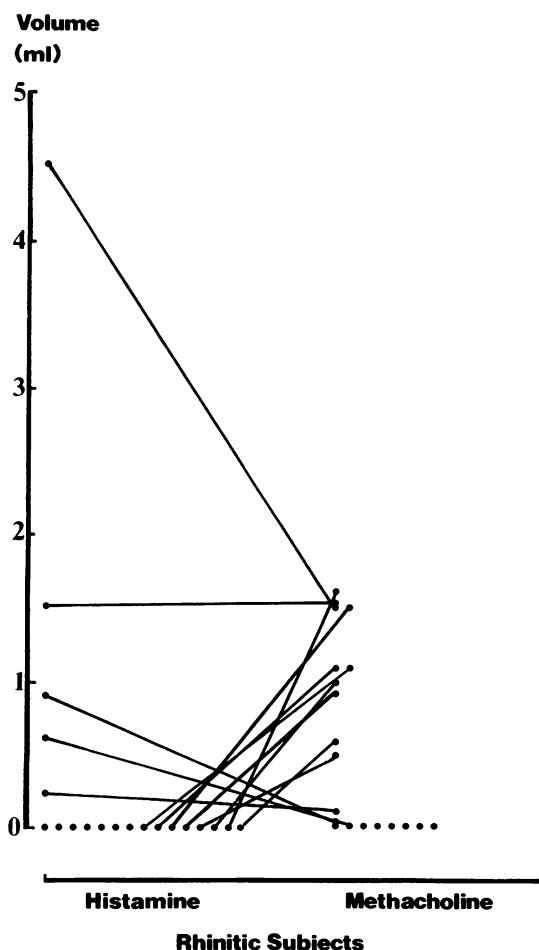
Volume (ml)

Histamine   Methacholine

Rhinitic Subjects

Fig 3 *Amount of nasal secretions produced by subjects with rhinitis in response to provocation with histamine and methacholine. The solid lines join each subject's response to histamine and methacholine.*

than non-rhinitic subjects. The difference in the proportions of rhinitic subjects who produced secretions in response to methacholine and in response to histamine was of borderline significance (p = 0·054) and there was no significant difference between the responses of non-rhinitic subjects to the two agonists (p > 0·20) (fig 3). We could not compare the volumes of secretions produced by the two groups of subjects, since only three non-rhinitic subjects produced secretions.

Discussion

This is the first report in which the nasal responses to histamine and methacholine of subjects with and without rhinitis have been compared by measuring change in nasal airways resistance and rhinorrhoea. In this study the nasal response to provocation was greater in those with than those without rhinitis.

There are important differences in the pattern of response to these agonists that may partially explain the confusing and contradictory results of previous studies. We found that histamine had a greater effect in inducing nasal obstruction than rhinorrhoea and that the opposite was true for methacholine. The increased nasal reactivity of rhinitic subjects to histamine could be detected by measuring changes in nasal airways resistance and rhinorrhoea. Differences between the responses of subjects with and without rhinitis to methacholine, however, could be detected only by recording the amount of secretions produced.

The importance of measuring more than one variable in response to nasal provocation for the evaluation of nasal reactivity has been emphasised by others.[13][17] This may, however, present problems. We encountered difficulties in combining measurement of nasal airways resistance with the volume of nasal secretions. The method of rhinomanometry used in this study[15] has a tendency to clear secretions and this may have reduced the amount of secretions collected from the nose. The interpretation of the effect of agonist provocation on nasal airways resistance should ideally be related to changes in resistance produced by the administration of a control solution.[13] We used buffered phenol saline and found, like other workers, that this caused significant changes in nasal airways resistance,[18] though these were not found consistently. As phenol is a potential nasal irritant, a solution such as isotonic saline would have been a better control. It might have been better to determine the nasal response to repeated administrations of the control solution alone on a separate test day for comparison with the responses to the two agonists. Histamine and cholinergic agonists have been used to assess the reactivity of the lower respiratory tract for almost 40 years. The lower airways of subjects with asthma have a greater response to these agonists than healthy subjects with no history of pulmonary or allergic disease.[1-4] Rhinitic subjects who have no history of asthma have an increased bronchial reactivity to these agents, although less than that of asthmatic subjects.[19][20] Several studies have failed to show similar differences in the cutaneous response of atopic and non-atopic subjects to histamine and methacholine.[5][20-22] Little attention has been devoted to the study of the reactivity of the upper respiratory tract to non-specific stimuli. Many individuals with rhinitis report a heightened nasal response to irritants such as cigarette smoke and strong perfumes. There is, however, conflicting evidence on whether clear differences between the nasal reactivity of rhinitic and

non-rhinitic subjects can be detected. Girard and co-workers found that rhinitic subjects had a greater response to both histamine and bradykinin than control subject's[6]—a finding that has been confirmed by some workers[7 11 12] but not others.[5 8 9] Histamine is thought to exert an effect on the nasal mucosa in two ways[14]—by a direct effect on receptors, leading to vasodilation and oedema, and indirectly via the trigeminal and vidian neural reflex arc, resulting principally in glandular stimulation with the production of secretion. Cholinergic stimulation of the nasal mucosa is thought to cause glandular secretion mainly.[14] Although the vasculature is innervated by the parasympathetic nervous system, histologically these nerve fibres are in much greater abundance around nasal glands.[23] Our results are in keeping with this as histamine had a greater effect on nasal obstruction than on hypersecretion and the opposite was true for methacholine. Borum has previously reported similar findings after nasal provocation with methacholine.[7] The poor secretory response of our subjects to histamine may in part be explained by the short time intervals between serial administrations of this agonist. Secher and coworkers found that repeated administrations of histamine had a tachyphylactic effect on secretions but not on nasal airways resistance[24]; this effect has not been observed with methacholine.[7] Differences in the pattern of response to provocation with these agonists might account in part for some of the differing results of previous studies. McLean *et al* failed to demonstrate nasal hyperreactivity to methacholine, but only nasal airways resistance was measured.[5] The characteristics of the rhinitic subjects under study is also important, in particular whether they are allergic and whether they have perennial or seasonal symptoms. In the latter case the timing of the study in relation to the pollen season is of particular relevance. McLean *et al*[5] and Svensson *et al*[9] failed to show differences in the reactivity of subjects with seasonal rhinitis tested out of the pollen season, a time when nasal reactivity in these individuals may be normal.[25] Investigators who have found nasal hyperreactivity in rhinitic subjects have, like ourselves, included patients with perennial symptoms[6 7 10-12]

In this study the increase in nasal airways resistance in response to histamine was three to four times greater in subjects with than subjects without rhinitis. Borum and coworkers report differences of a similar order of magnitude between small numbers (5) of subjects with and without rhinitis.[11] Several theories have been advanced to explain increased bronchial reactivity in asthmatic patients, including abnormalities of the epithelium, autonomic nervous regulation, and bronchial smooth muscle.[26 27] Apart from the vasculature the nose is devoid of smooth muscle in

contrast to the airways. Otherwise similar explanations have been given for the increased response of the nasal mucosa seen in rhinitic subjects—increased epithelial permeability, increased sensitivity of sensory nerves, altered transmission of afferent impulses in the central nervous system, and an increased number or sensitivity of glandular or vascular receptors.[4 11 14] Clearly in patients with allergic disease affecting both the upper and the lower airways the whole respiratory tract shows an increased responsiveness to non-specific stimuli.

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