

Nasal cholinergic hyperresponsiveness in atopic subjects studied out of season

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Background: Atopic individuals have previously been shown to have an autonomic imbalance consisting of heightened cholinergic responsiveness in the lung, skin, and eyes, and β -adrenergic hyporesponsiveness in the lungs, eyes, and vasculature. This array of abnormalities is often accompanied by nonspecific bronchial hyperresponsiveness, as well as α -adrenergic hyperresponsiveness in individuals with asthma.

Methods: To determine whether atopic individuals have intrinsic nasal airway hyperresponsiveness to methacholine, 21 nonatopic subjects and 37 subjects with allergic rhinitis were studied. All subjects were studied out of their allergy seasons, and all allergy-related medications were discontinued before the study began. Subjects underwent nasal challenge with methacholine (1 to 25 mg), and lavaged nasal secretions were analyzed for total protein, the plasma marker albumin, and the glandular marker lactoferrin.

Results: Atopic subjects demonstrated increased glandular responsiveness to methacholine as evidenced by an increase in the secretion of lactoferrin in response to individual doses of methacholine. Although the maximal lactoferrin secretion did not increase, glandular sensitivity to methacholine was heightened because the dose of methacholine required to induce lactoferrin secretion achievable by 60% of the study population was significantly lower in the atopic group. The volume of lavaged secretions recovered and congestion scores were also higher in the atopic group as compared with the normal control group.

Conclusions: These data strongly suggest that atopic individuals have intrinsic nasal glandular hyperresponsiveness to cholinergic stimulation. (*J ALLERGY CLIN IMMUNOL* 1993;92:278-87.)

Key words: Nasal glandular hyperresponsiveness, methacholine, lactoferrin, albumin, cholinergic stimulation

One of the hallmarks of asthma is an increased nonspecific bronchoconstrictive response to methacholine and other agonists. This bronchial hyperreactivity has been noted in patients with asthma and in nonasthmatic subjects with allergic rhinitis.^{1, 2} Heightened cholinergic responsiveness has been found in the sweat glands and pupils of patients with asthma, subjects with allergic rhinitis, and preatopic subjects (patients exhibiting positive skin tests to allergens but who are free of symptoms).^{3, 4} In addition, bronchial responses to methacholine are increased in patients with asthma,⁵ and bronchial hyperresponsiveness to both histamine and antigen can be enhanced by viral upper respiratory tract infections.⁶ Similarly,

Abbreviation used

PD₆₀ Dose of methacholine required to induce the 60 percentile response (for a given protein)

patients with asthma, subjects with rhinitis, and preatopic subjects have been demonstrated to have decreased responses to β -adrenergic stimulation as reflected by changes in pulse pressure.⁷ Moreover, the administration of a β -blocker may produce wheezing in the individual with asthma and bronchospasm in the patient with allergic rhinitis when an allergen bronchial challenge is given.^{8, 9} The pathophysiologic mechanism that mediates these abnormal nonspecific responses is not known.

Allergic rhinitis is the most common manifestation of allergic disease, and there is evidence to suggest that nasal (and/or lower) airways become increasingly responsive to nonspecific stimuli such as methacholine and histamine during the course of the allergy season or after experimental nasal

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allergen challenge.¹⁰⁻¹⁵ However, the nasal mucosal responses to methacholine in atopic subjects compared with nonatopic individuals have not been thoroughly examined. Like the lung, the nasal mucosa is capable of responding to various stimuli with increased vascular permeability, glandular secretion, and inflammation but not with smooth muscle contraction. Unlike the lung, the nasal mucosa has large venous sinusoids, which can fill, causing nasal congestion and increased nasal airway resistance. At least two reports, which demonstrate that methacholine-induced changes in nasal resistance do not differ between atopic and nonatopic subjects, exist,^{16, 17} suggesting that vascular reactivity is not abnormal in atopic individuals. In contrast, methacholine-induced secretion weight and protein concentration are elevated in atopic individuals as compared with normal subjects.^{17, 18} It is unclear whether this increased secretory response is characteristic of atopic individuals or whether it is induced by antigen stimulation or antiallergy drug exposure. Thus in one study¹⁷ atopic subjects were studied during symptom-free periods, but the study does not indicate whether the subjects were receiving medications or how long they had been free of symptoms. Limitations were the exclusive selection of male subjects for study and the fact that nasal proteins were not assessed. In the other article¹⁸ atopic individuals were not specifically studied out of their allergy seasons. In addition, the specific source of the increased proteins in the nasal secretions was not determined. In the current study we examined the symptomatic and secretory responses to nasal methacholine challenge in atopic subjects, studied out of season, as compared with normal control subjects and found a clear demonstration of nasal glandular hyperresponsiveness in atopic individuals.

In contrast to previous reports the data herein are analyzed both in terms of absolute secretion of proteins and in terms of provocation doses of methacholine required to induce a targeted increase in protein. Thus the dose-response curves can be reduced to a single statistical term. This form of analysis may provide investigators with a useful method for analyzing the effects of various provocation substances or drugs on nasal glandular responsiveness.

METHODS

Subjects

Fifty-eight subjects were studied; 37 atopic (22 female, 15 male) subjects with allergic rhinitis but no

other significant disorders and 21 nonatopic control (12 female, 9 male) subjects between the ages of 18 and 53. All subjects gave informed consent, and the study was approved by the National Institute of Allergy and Infectious Disease clinical research committee. All atopic subjects had a history consistent with seasonal allergic rhinitis and positive skin prick test results (wheal at least 3 mm > control) to relevant antigens (cat, oak, elm, maple, rye, Bermuda grass, ragweed). (Lyophilized, standardized cat antigen was a generous gift from Miles Inc., Hollister-Stier Div., West Haven, Conn.; lyophilized, standardized oak, elm, maple, rye, Bermuda grass, and ragweed antigens were generous gifts from ALK America Inc., Milford, Conn.). Normal subjects had no history of seasonal rhinitis and had negative skin prick test results to the following antigens: cat, oak, elm, maple, rye, Bermuda grass, ragweed, *Dermatophagoides pteronyssinus*, and *D. farinae*. Atopic subjects were studied out of their allergy season during asymptomatic periods. All subjects had refrained from using nasal corticosteroids and cromolyn for at least 4 weeks and from both orally administered and topical antihistamines and decongestants for at least 1 week before study. No concomitant medications were allowed during the study except for contraceptives.

Challenge

Nasal challenges were performed as previously described.¹⁹ Subjects were seated comfortably and a soft 8F rubber Foley catheter (Davol Inc., Cranston, R.I.) was inserted atraumatically 2.5 to 4 cm along the floor of the right naris and the catheter taped to the cheek and attached to suction. Before insertion, the tip of the catheter was removed, and two extra pairs of lateral holes were cut in the first 4 cm of tubing. The naris was then washed under suction with 16 ml of saline solution delivered via a spray bottle (generous gift of Fisons Corp., Rochester, N.Y.) to remove resident secretions. Thereafter, the right naris underwent a series of challenges (normal saline; methacholine 1, 5, 10, and 25 mg delivered), which were given approximately every 12 minutes. Each challenge solution was delivered via spray bottle (0.4 ml), and after a 10-minute resident time, the challenged naris was washed under suction with 4 ml of saline solution, and the washed secretions were measured and saved for analysis. Washed secretions were centrifuged in the cold at 40,000 g for 10 minutes to pellet mucus, then aliquotted and stored at -80° C until assayed. Subjects maintained a symptom diary during the challenge procedure, recording congestion on a scale of 0 to 3 (none, minimal, moderate, complete blockade) and flushing on a scale of 0 to 2 (none, facial only, extending beyond the face) for each challenge period.

Assays

Total protein. Total protein in the nasal washings was measured by the bicinchoninic acid protein assay

(Pierce Chemical Company, Rockford, Ill.) with bovine serum albumin as the standard. Ten microliters of lavage sample of albumin standard (Pierce Chemical Corp.) was placed in polypropylene microtiter plate wells (Dynatech Laboratories, Inc., Chantilly, Va.) in triplicate. After 30 minutes of incubation with 200 μ l bicinchoninic acid reagent at 37° C, the optical density at 570 nm was detected with the use of a microplate reader (Dynatech Lab. Inc.). The protein concentration in samples was determined from the regression analysis of the standard curve. The assay is accurate over a range of 15 to 2000 μ g/ml. Results are reported as net micrograms per milliliter protein corrected for protein measured in lavages obtained after saline challenge.

Albumin. The plasma marker, albumin, was measured by a noncompetitive ELISA modified from a previously described method.¹⁹ The assay is accurate between 1 and 100 μ g/ml. Results are reported as net micrograms per milliliter protein, corrected for protein measured in lavages obtained after saline challenge.

Lactoferrin. The glandular marker, lactoferrin, was measured by a noncompetitive ELISA as previously described.²⁰ The assay is accurate between 1 and 100 ng/ml. Results are reported as net micrograms per milliliter protein, corrected for protein measured in lavages obtained after saline challenge.

Statistics

Dose-response, symptom, and volume data are presented as means $\pm$ SEM. Maximal response data are presented as individual net results with the 60 percentile response (i.e., the maximal response achievable by 60% of the entire population studied) highlighted. The baseline level of proteins in nasal secretions and the magnitude of protein secreted in response to nasal challenge varies immensely depending on the subject, the agonist used to stimulate secretion, and the protein being measured. Thus it was not meaningful in this nasal challenge model to compare percentage increase in protein above baseline. Therefore to assess the shift between the two groups' dose-response curves, we chose to study the incremental increase in a given protein achievable by 60% of the study population in response to a given agonist. The cutoff of 60% was arbitrarily selected on the basis of preliminary analysis of the population's responses to several agonists. Indeed, a cutoff of at least 60% of the population was required to have a measurable targeted response for all proteins under all nasal challenge conditions. A PD₆₀ was computed for each protein. The PD₆₀ is defined as the dose of agonist required to induce the 60 percentile response to the agonist for any given protein. For example, methacholine was examined at a dose range of 1 to 25 mg delivered. In regard to the secretion of total protein, 60% of the subjects were able to secrete 60 μ g/ml above baseline, and this amount was the 60 percentile response. The dose of methacholine required to elicit the 60 percentile response was the PD₆₀.

The data are presented as the cumulative number of subjects in each group who achieved the 60 percentile response at each dose of methacholine tested. For the purposes of computing mean PD₆₀s, subjects who did not achieve a PD₆₀ were assigned a PD₆₀ of 25, the highest dose of methacholine tested. The Mann Whitney U test corrected for ties was used to assess differences between the two groups. Within-group differences were assessed with a Wilcoxon signed rank test, and the chi square test for multiple groups, corrected for continuity, was used to test differences in proportions of subjects achieving a 60 percentile maximal response at various doses of methacholine. Correlations were assessed with Spearman's correlation coefficient corrected for ties. All statistics were performed with a Statview statistical program (Abacus Concepts, Inc., Berkeley, Calif.) for the Macintosh computer (Apple Computer Inc., Cupertino, Calif.).

RESULTS

Secretion weight and symptoms

Both atopic and nonatopic subjects had a dose-related secretory response to methacholine (Fig. 1, A). The volume of lavaged secretions recovered after saline challenge was equivalent for the atopic and normal control groups (3.52 ± 0.08 ml and 3.47 ± 0.06 ml, respectively). The volume of lavaged secretions recovered in the atopic group increased compared with saline challenge in response to 5 and 25 mg methacholine ($p < 0.05$ and 0.01, respectively), whereas an increase compared with baseline did not occur in the normal control group until administration of 10 and 25 mg methacholine ($p < 0.05$ and 0.01, respectively). Recovery of lavaged secretions after administration of 1 and 5 mg methacholine was greater in the atopic group as compared with the normal control group ($p < 0.05$ and 0.01, respectively). The atopic group reported significant nasal congestion (Fig. 1, B) in response to all four doses of methacholine tested ($p < 0.05$ for 1 mg methacholine, and $p < 0.005$ for 5, 10, and 25 mg methacholine). In contrast, the normal control group did not experience significant congestion in response to methacholine. Methacholine-induced flushing, however, was more pronounced in the normal control group (Fig. 1, C) because flushing in the normal group was increased above baseline in response to 10 mg methacholine, whereas 25 mg methacholine was required to induce flushing in the atopic group. However, the magnitude of flushing response did not differ between the groups at any dose of methacholine. Surprisingly, no significant correlations were found between any of these three parameters (i.e. flushing, congestion, or recovery of lavaged secretions).

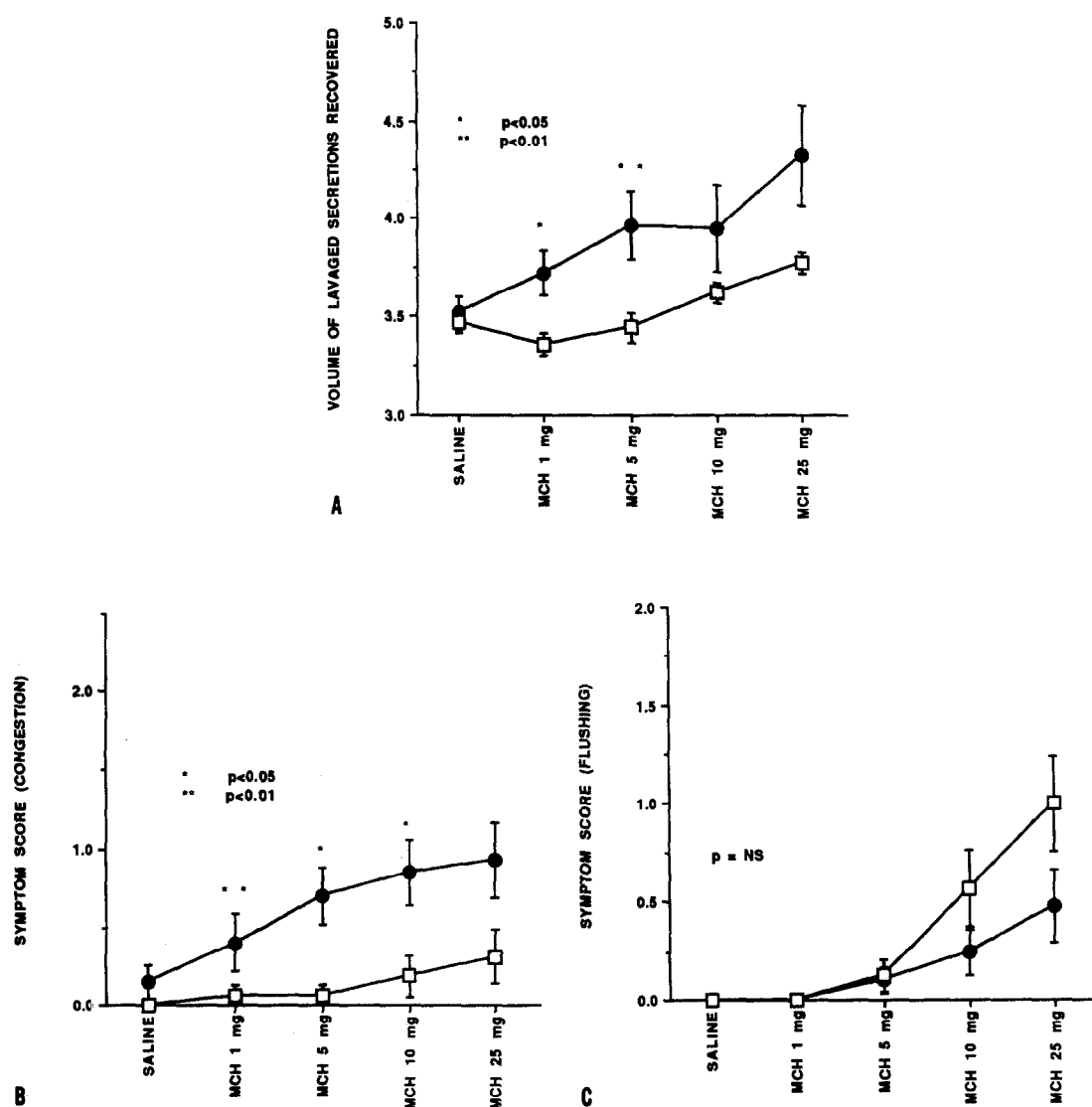


FIG. 1. Secretion volume and symptom scores elicited by methacholine challenge. **A**, Volume of lavaged secretions recovered after nasal challenge with saline or various doses of methacholine; **B**, nasal congestion scores of subjects challenged with saline or various doses of methacholine; **C**, flushing scores of subjects challenged with saline or various doses of methacholine. All data are presented as means $\pm$ SEM for atopic subjects (closed circles) and nonatopic subjects (open squares). Asterisks denote between-group differences.

Total protein secretion

Total protein secreted in response to saline challenge was similar in atopic and nonatopic subjects (117.9 ± 42.2 $\mu\text{g/ml}$ and 107.1 ± 255.4 $\mu\text{g/ml}$, respectively, $p = \text{NS}$). Both atopic and nonatopic subjects secreted protein in response to nasal methacholine challenge (Fig. 2, *A*). There was a trend for the atopic group to secrete more total protein than the nonatopic group in response to lower doses of methacholine (area under the curve = 2665 vs 1083, respectively, $p = 0.14$). There was also a trend for a higher maximal

secretion of total protein across the methacholine dose-response curve in the atopic subjects as compared with the nonatopic subjects (231 vs 108 $\mu\text{g/ml}$, respectively, $p = 0.08$; data not shown). Sixty percent of the population studied showed an increase in the total protein in their nasal washings by at least 60 $\mu\text{g/ml}$ above baseline (Fig. 2, *B*). The mean dose of methacholine required to achieve a 60 percentile increase in total protein above the saline control did not differ between the groups (data not shown). However, a higher proportion of the atopic group achieved a

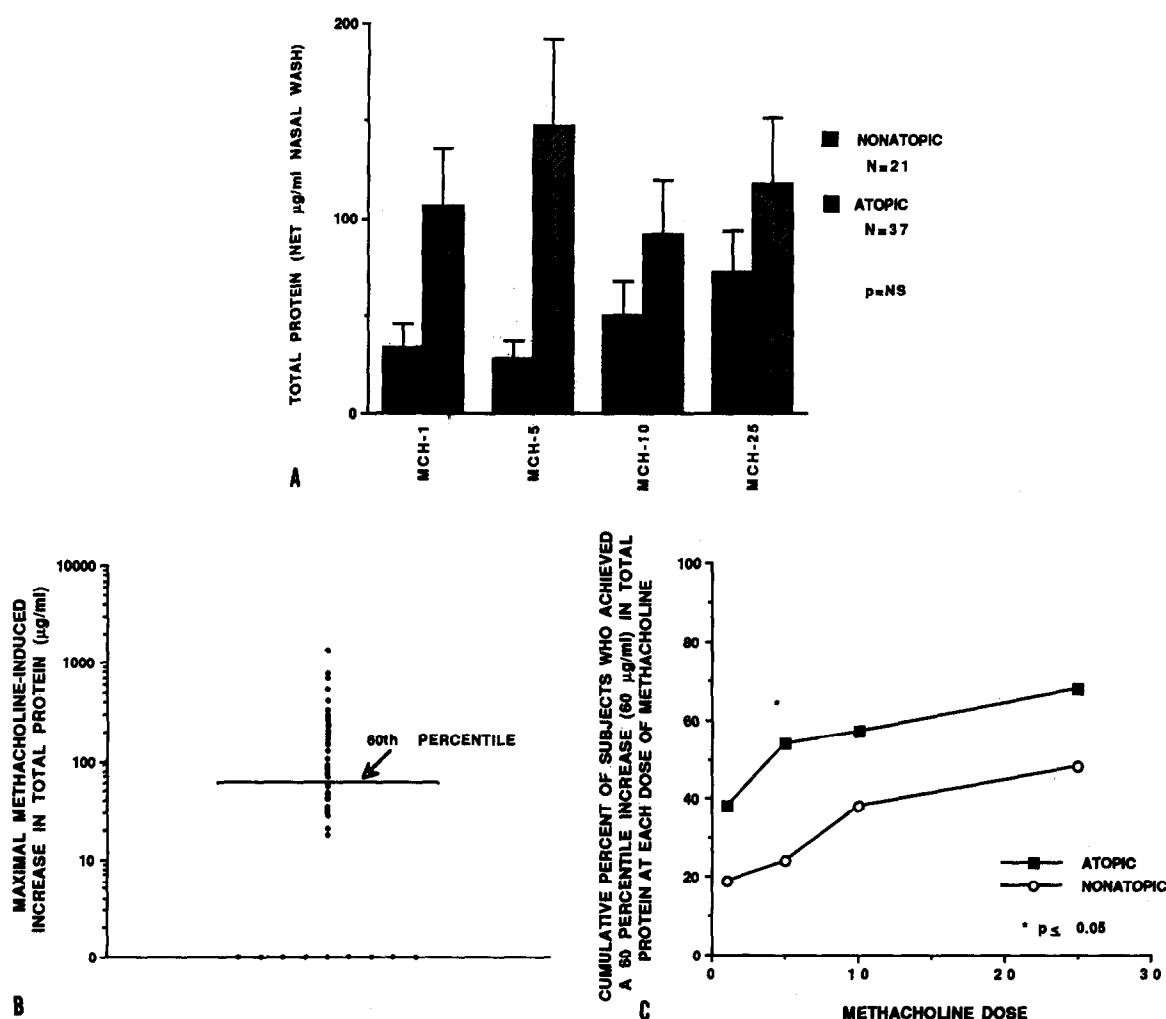


FIG. 2. Total protein secretion in response to nasal methacholine challenge. **A,** Net total protein secretion in response to various doses of nasal methacholine. Means $\pm$ SEM are shown. **B,** Shown are net maximal increases in total protein in nasal washings obtained in response to the dose-response study shown in **A** for each individual subject. The horizontal line represents the net maximal response achieved by 60% of the population studied (60 percentile response). **C,** Sixty percent of the subjects studied were able to achieve a maximal increase in total protein of at least 60 μ g/ml in response to methacholine. Shown are the cumulative percentages of subjects in each group who were able to achieve this 60 percentile response at each dose of methacholine tested. Asterisks denote between-group differences.

60 percentile increase in total protein in response to 5 mg of methacholine than did the control subjects (Fig. 2, C).

Glandular secretion

Lactoferrin secreted in response to saline challenge was similar in atopic and nonatopic subjects (12.87 ± 3.3 μ g/ml and 7.3 ± 1.6 μ g/ml, respectively, *p* = NS). Both atopic and nonatopic subjects secreted the glandular protein, lactoferrin, in a dose-related fashion in response to methacholine challenge (Fig. 3, A). The magnitude of lactoferrin secretion in response to 1 and 5 mg

methacholine was significantly higher for atopic subjects as compared with nonatopic subjects (*p* < 0.05). The maximal increase in lactoferrin did not differ between the atopic and normal control groups (data not shown). Sixty percent of the population studied showed an increase in lactoferrin of at least 4 μ g/ml above baseline in their nasal washings (Fig. 3, B). The dose of methacholine required to achieve a 60 percentile increase in lactoferrin above the saline control was significantly lower in the atopic group as compared with the nonatopic group (10.54 vs 16.62 mg methacholine, respectively, *p* < 0.05;

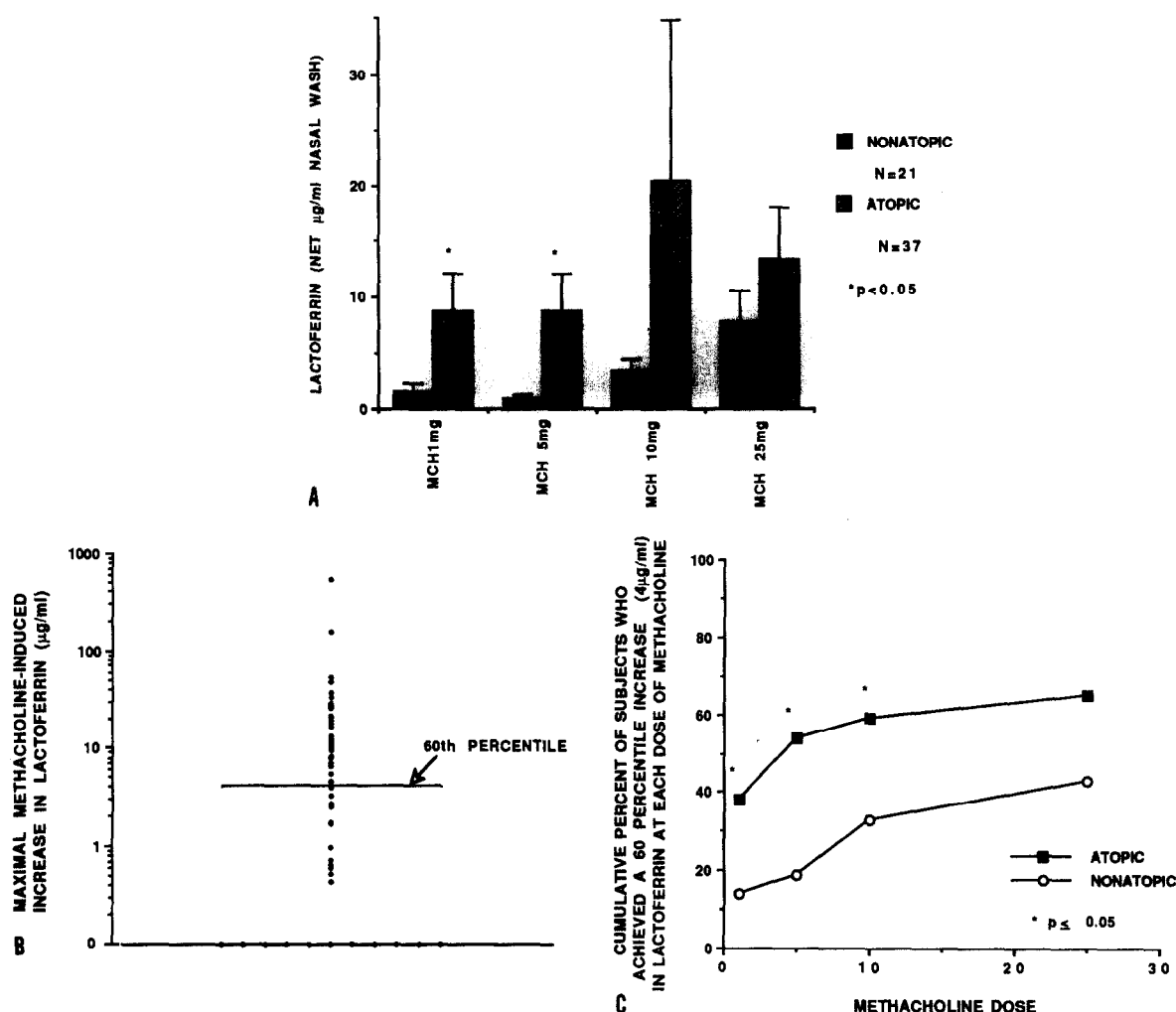


FIG. 3. Lactoferrin secretion in response to nasal methacholine challenge. **A**, Net lactoferrin secretion in response to various doses of nasal methacholine. Means $\pm$ SEM are shown. **B**, Shown are net maximal increases in lactoferrin in nasal washings obtained in response to the dose-response study shown in **A** for each individual subject. The horizontal line represents the net maximal response achieved by 60% of the population studied (60 percentile response). **C**, Sixty percent of the subjects studied were able to achieve a maximal increase in lactoferrin of at least 4 μ g/ml in response to methacholine. Shown are the cumulative percentages of subjects in each group who were able to achieve this 60 percentile response at each dose of methacholine tested. Asterisks denote between-group differences.

data not shown). Likewise, a significantly higher proportion of the atopic population had achieved a 60 percentile increase in lactoferrin in response to 1, 5, and 10 mg methacholine as compared with the normal subjects ($p < 0.05$, Fig. 3, C). Thus atopic subjects studied out of season, have increased glandular secretion of lactoferrin in response to methacholine.

Albumin secretion

Albumin secreted in response to saline challenge was similar in atopic and nonatopic subjects ($42.8 \pm 14.8 \mu$ g/ml and $23 \pm 10 \mu$ g/ml, respec-

tively, $p = \text{NS}$). Both atopic and nonatopic subjects had increased albumin secretion in response to methacholine (Fig. 4, A), and there were no differences between the two groups in either the magnitude of response to individual doses of methacholine or in the maximal albumin secretion across the entire methacholine dose-response curve ($64.7 \pm 19.6 \mu$ g/ml and $39.8 \pm 16 \mu$ g/ml for atopic and control groups, respectively). Sixty percent of the population studied showed an increase in albumin of at least 3 μ g/ml above baseline in their nasal washings (Fig. 4, B). The dose of methacholine required to achieve a 60 percentile

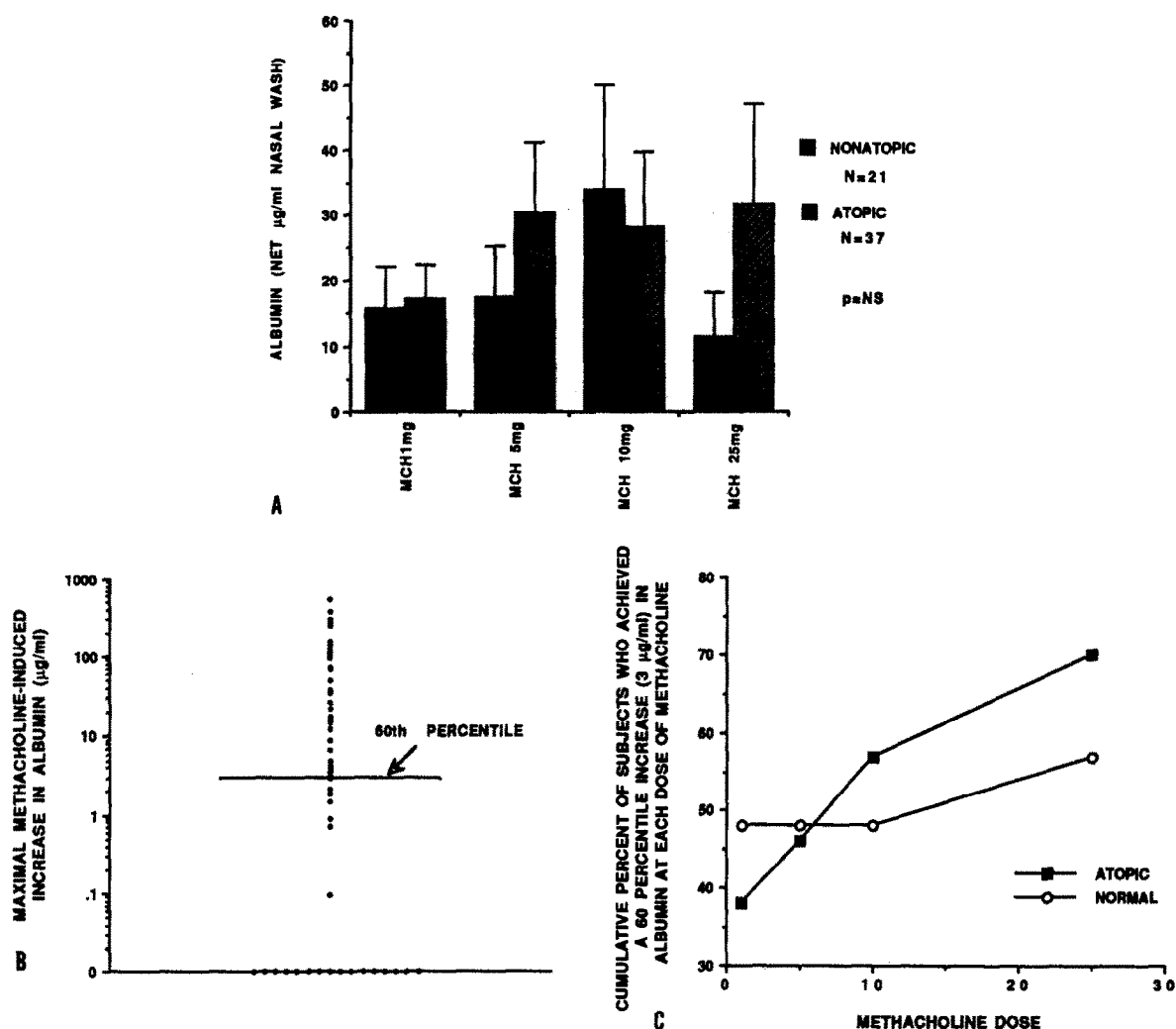


FIG. 4. Albumin secretion in response to nasal methacholine challenge. **A**, Net albumin secretion in response to various doses of nasal methacholine. Means $\pm$ SEM are shown. **B**, Shown are net maximal increases in albumin in nasal washings obtained in response to the dose-response study shown in **A** for each individual subject. The horizontal line represents the net maximal response achieved by 60% of the population studied (60 percentile response). **C**, Sixty percent of the subjects studied were able to achieve a maximal increase in albumin of at least 3 μ g/ml in response to methacholine. Shown are the cumulative percentages of subjects in each group who were able to achieve this 60 percentile response at each dose of methacholine tested.

increase in albumin above the saline control did not differ between the groups (data not shown), nor were there differences in the proportion of subjects who achieved a 60 percentile increase in albumin at any dose of methacholine tested (Fig. 4, C).

Correlations between symptoms and protein secretion

Correlations between symptoms and protein secretion are shown in Table I. There was a strong positive correlation ($r = 0.96$) between the provocative dose of methacholine required to in-

duce a 60 percentile increase in total protein and that required to induce a 60 percentile increase in albumin. In contrast, the provocative dose of methacholine required to induce a 60 percentile increase in lactoferrin was only moderately correlated with the maximal secretion of total protein ($r = 0.56$) and weakly correlated with the maximal secretion of lactoferrin and albumin ($r = 0.34$ and 0.33 , respectively), suggesting an inverse relationship between the threshold of glandular responsiveness and maximal glandular secretion in response to methacholine. Neither the volume of lavaged secretions recovered nor congestion

TABLE 1. Correlations between symptoms and protein secretion

	PD ₆₀			Maximal secretion					
	TP	LF	ALB	TP	LF	ALB	VOL	FLU	CONG
PD ₆₀									
TP	—								
LF	-0.12	—							
ALB	0.96*	-0.07	—						
MAX									
TP	0.01	0.56*	0.03	—					
LF	-0.21	0.34†	-0.09	0.19	—				
ALB	-0.05	0.33†	-0.11	0.59*	-0.16	—			
VOL	0.03	-0.06	-0.04	0.05	0.05	0.11	—		
FLU	-0.38*	-0.05	-0.37†	0.05	-0.34†	0.14	0.15	—	
CON	0.13	0.07	0.10	0.09	0.01	0.13	0.14	-0.23	—

TP, Total protein; LF, lactoferrin; ALB, albumin; VOL, cumulative net volume of lavaged secretions recovered after each methacholine challenge; FLU, net sum of the flushing cores for each methacholine challenge; CONG, net sum of the congestion scores for each methacholine challenge; MAX, maximal secretion of given protein in response to methacholine.

* $p < 0.001$.

† $p < 0.05$.

correlated with protein secretion. However, flushing scores were weakly negatively correlated with the provocative dose of methacholine required to induce a 60 percentile response to both total protein and albumin ($r = 0.38$ and 0.37 , respectively), suggesting that the degree of flushing correlates positively with the threshold degree of responsiveness of protein and albumin secretion to methacholine. In contrast, flushing was weakly negatively correlated with maximal lactoferrin secretion ($r = 0.34$), suggesting an inverse relationship between flushing and maximal glandular secretion in response to lactoferrin.

DISCUSSION

Previous studies have demonstrated that atopic individuals display an array of abnormal autonomic responses, including increased sweating, and pupillary and bronchial responsiveness to cholinergic stimulation.³⁻⁵ The data presented herein also demonstrate that atopic subjects who are free of symptoms have increased nasal glandular secretory responses to methacholine compared with nonatopic subjects. The volume of lavaged secretions stimulated by methacholine challenge was increased in atopic subjects as compared with nonatopic individuals. Moreover, the net secretion of lactoferrin in response to low doses of methacholine was increased in atopic as compared with nonatopic subjects, whereas the dose of methacholine required to produce a 60 percentile maximal increase in lactoferrin was also lower in atopic subjects. In contrast, the

maximal lactoferrin secretory response to methacholine did not differ between the groups. Thus the data demonstrate a shift to the left in the methacholine dose-response curve without alteration in the maximal response. These data confirm and extend the previous observation that atopic subjects secrete more protein than do nonatopic subjects after nasal methacholine challenge.¹⁸ The data are also in agreement with the observation by Halonen²¹ that the induction of increased IgE synthesis in rabbits is associated with increased cholinergic responsiveness as reflected in heightened pupillary miotic responses to cholinergic stimulation.

Nasal challenge with methacholine has previously been demonstrated to induce nasal glandular, but not vascular, secretion.²² This response is a direct effect, mediated through muscarinic M-3 and M-1 receptors.²³ After methacholine challenge, the glandular products secretory IgA,²² lactoferrin, and lysozyme increase²⁴ in nasal washings and sometimes increase in their proportions relative to total protein. The vascular protein albumin also increases slightly after methacholine challenge²²; however, the percent of nasal wash total protein comprised of albumin is not altered by methacholine. These responses are in contrast with the observation that histamine stimulation of the nasal mucosa results in increased vascular permeability with marked elevations in the relative percent of nasal lavage protein comprised of albumin.²⁵ Moreover, it has been demonstrated immunohistochemically that albumin can extrava-

sate into nasal gland duct lumens, and thus a small amount of albumin is available to be passively transported along with nasal glandular secretions.²⁵

The mechanism by which glandular responses to methacholine are heightened in atopic subjects is not clear; however, several possibilities merit consideration. Atopic individuals may bear an increased number of or higher affinity cholinergic receptors on their nasal glands. Assuming normal acetylcholinesterase activity, an increase in the number or affinity of cholinergic receptors or nasal glands might lead to heightened responsiveness without changing maximal responses. A quantitative change is more likely than an affinity change because the latter possibility suggests structural alterations in the receptor. Alternatively, a local decrease in acetylcholinesterase activity might initially lead to heightened responsiveness, possibly followed by decreased cholinergic responsiveness because of an inability to recycle acetylcholine. The lack of myasthenia gravis-like symptoms in atopic individuals makes alterations in acetylcholinesterase activity an unlikely possibility. An additional explanation is that one or more of the neuropeptides capable of mediating nasal glandular secretion may be overly active in atopic individuals, either because of increased synthesis, increased receptor numbers or affinity, or decreased degradation. Among the neuropeptides with nasal glandular secretagogue activity are vasoactive intestinal peptide,²⁶ which is carried in parasympathetic fibers, and gastrin releasing peptide,²⁷ which is carried in sensory fibers.

In this study atopic subjects reported more congestion in response to methacholine than did the nonatopic control subjects. This observation is in contrast with results of two other studies, which failed to report a difference in methacholine-induced changes in nasal airway resistance or congestion scores between atopic and nonatopic subjects.^{16, 17} These differences could be due to the subjective nature of the self-reported symptoms in the current study as compared with more objective measurements of nasal airway caliber, which were used in the previous two studies. In the current study no differences were found in flushing responses between the two groups. Moreover, we were surprised by the lack of correlation between flushing and nasal congestion scores because both symptoms are dependent on vasodilation, albeit involving different vascular beds. Taken together, these data suggest that engorge-

ment of nasal capacitance vessels and cutaneous vasodilation may be under separate regulatory control. Blood vessels are innervated by both cholinergic and adrenergic fibers, and both are associated with vasoactive neuropeptides.²⁸ It is possible that the balance between cholinergic and adrenergic fibers differs between nasal capacitance and cutaneous vessels or that variations in the distribution of neuropeptides, such as vasoactive intestinal peptide, calcitonin gene-related peptide, neuropeptide Y, and endothelin, or of their receptors contributed to our observations. Alternatively, there may be differences between the two groups in post-receptor signal transduction events. Interestingly, flushing correlated positively with the threshold reactivity of albumin and total protein secretion. These data suggest that the mobilization of proteins, including albumin, from the nasal interstitial fluids into the glandular ducts is under the same regulatory control as cutaneous vasodilation.

In summary, atopic individuals who are free of symptoms, challenged out of their allergy season, display increased nasal glandular responsiveness to methacholine as compared with normal subjects. This increased glandular secretory response to methacholine is associated with an increase in the volume of lavaged secretions recovered after methacholine challenge and an increase in subjective nasal congestion induced by methacholine. Thus the data strongly suggest that patients with allergic rhinitis have endogenous cholinergic hyperreactivity.

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