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Hyperresponsiveness of congestive nasal reflexes in allergic rhinitis*

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SUMMARY

Background: *Nasal secretory hyperresponsiveness is well documented in allergic rhinitis, and is mediated in part by neural mechanisms. In contrast, reflex-mediated congestion is poorly documented in both normal and allergic subjects.*

Objective: *To characterize congestive responses to unilateral nasal bradykinin challenge in normal and allergic subjects, and to investigate whether congestive hyperresponsiveness is present in allergic rhinitis.*

Methods: *Normal subjects (n=13), and subjects with out-of-season seasonal allergic rhinitis (SAR) (n=16) underwent a unilateral nasal challenge protocol using filter paper disks, using Hartman's solution and bradykinin as challenge substances. Congestive responses were measured using acoustic rhinometry.*

Results: *Normal subjects demonstrated a transient ipsilateral congestive response, and a circumscribed contralateral congestive response away from the major flow limiting section. Subjects with SAR demonstrated a more persistent ipsilateral congestive response, and a more pronounced, generalized contralateral congestive response affecting all areas of the contralateral nasal cavity. Significant differences were present between normal and SAR subjects.*

Conclusion: *Congestive reflexes are present in normal and allergic subjects. Congestive hyperresponsiveness is present in allergic rhinitis.*

Key words: allergic rhinitis, nasal congestion, congestive reflex. acoustic rhinometry, bradykinin

INTRODUCTION

Allergic rhinitis is a symptomatic disorder of the nose induced after allergen exposure by IgE mediated inflammation [1]. This leads to the generation of histamine, bradykinin, and other mediators, which have direct effects on nasal glands and vasculature [2,3]. In addition, stimulation of sensory nerves has been shown to lead to activation of centrally-mediated secretory reflexes, which augment the secretory response [4].

Patients with symptomatic allergic rhinitis characteristically demonstrate exaggerated symptomatic responses to a variety of non-allergenic irritants. This tendency, termed "nasal hyperresponsiveness", is mediated, in part, by neural reflexes [2]. Hyperresponsiveness of secretory reflexes is well documented in allergic rhinitis [5-7].

Nasal mucosal blood flow, and hence, nasal patency, is regulated by the nervous system [8,9], and is subject to reflexes stimulated by changes in posture [10], extremity temperature [11], and axillary pressure [12]. There is little data in the literature regarding the existence of naso-nasal reflexes which alter nasal patency. However, if such reflexes are present, they may also be subject to hyperresponsiveness in allergic rhinitis.

Acoustic rhinometry is a technique for measuring nasal patency, which depends on the reflection of a sound impulse by the changing diameter of the nasal airway [13]. This technique allows measurement of nasal cross-sectional areas (csa) and volumes. The assumptions on which acoustic rhinometry are based are to some extent flawed, however, they have proven to be acceptable in practice [14].

In most nasal cavities, two or three narrowings in nasal cross-sectional area are present. The first (most anterior) of these (csa1) usually corresponds to the cross-sectional area at the internal nasal valve, near the junction of the nasal septum and the upper lateral nasal cartilages. The second (csa2) usually corresponds to the cross-sectional area in the region of the anterior portion of the inferior turbinate. A third narrowing (csa3) is usually also encountered, corresponding to the anterior portion of

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the middle turbinate [15]. The minimal cross-sectional area (Amin) is usually found at either csa1 or csa2 [16].

The purpose of the present study was to characterize and compare reflex changes in nasal patency in response to nasal challenge in normal and allergic subjects. We hypothesized that limited unilateral nasal challenge with bradykinin would lead to decreased patency in the vicinity of application of bradykinin due to direct effects of bradykinin on vasculature, as well as to decreased patency in parts of the nose distant to the site of application, mediated by reflex mechanisms. We further hypothesized that the degree of congestion would be increased in allergic rhinitis.

MATERIALS AND METHODS

Materials

Bradykinin was obtained from Bachem (Basel, Switzerland) and dissolved in Hartman's solution (compound sodium lactate) (Baxter, Norfolk, UK) with an additional 1 g/l of sodium bicarbonate, to a concentration of 10 mg/ml. This solution had a pH of 6.2 and an osmolarity of 302 mOsm/l. This was stored at -20°C until immediately prior to use. Further dilutions were made with Hartman's solution. Hartman's solution had a pH 6-6.2 and osmolarity 278 mOsm/l. Allergens for skin prick testing were obtained from HAL Allergenen Laboratorium BV (Haarlem, The Netherlands). Acoustic rhinometry was performed using an SRE2100 RhinoMetrics acoustic rhinometer, with RhinoScan software module (version 2.6, 2002), (Rhinometrics A/S, Lynge, Denmark).

Subjects

Sixteen subjects (13 female, mean age 30.5 years) with seasonal allergic rhinitis (SAR), and 13 normal control subjects (11 female, mean age 33.6 years) were recruited by volunteer advertisement. Subjects with SAR had strictly seasonal symptoms, and positive skin prick tests to at least one seasonal allergen (mixed grasses, timothy grass, mixed spring trees, or birch). All were studied outside the pollen season, at a time when they were completely asymptomatic. Normal subjects had no nasal symptoms and negative skin prick tests to a battery of common aero-allergens tested. Subjects were excluded if they had a nasal septal perforation; had suffered from a respiratory infection within the previous month; used oral or nasal corticosteroids within the previous month; used astemizole in the previous 3 months; or used short-acting antihistamines or nasal decongestants within the previous 2 days. All subjects gave written informed consent, and the study was approved by the Hospital Research Ethics Committee.

Nasal challenge protocol

All subjects underwent a unilateral nasal bradykinin challenge protocol, consisting of three successive unilateral (left-sided) nasal challenges, at 10 minute intervals, with Hartman's solution, followed by bradykinin 50 µg, followed by bradykinin 100 µg. Acoustic rhinometry was performed on both sides of the nose at baseline (prior to any nasal challenge), and then 7 minutes after each of the three challenges. Nasal challenges were performed by placing a 6 mm filter paper disk, soaked in 10 ml of the appropriate challenge solution, onto the left side of the anterior nasal septum, beyond the mucocutaneous junction, using a crocodile ear forceps. The challenge disk was removed after 60 seconds [17].

Acoustic rhinometry

Subjects remained seated throughout the experiment. Initially, anterior rhinoscopy was performed, and any dried secretions or crusts removed. Subjects were permitted to blow their noses before measurements. During measurements, subjects were asked to breathe through their mouths while an appropriate sized nose-adaptor mounted on the end of the standard probe was gently held up to the nostril on the side being tested, taking care to avoid causing deformity of the nostril through the application of excessive pressure. Once an adequate seal was obtained, the patient was asked to stop breathing, while keeping their mouth open so that the palate was raised against the posterior pharyngeal wall, and a recording was made. A minimum of three recordings was made for each side of the nose.

The resultant curves were analyzed using the RhinoScan software module. Curves were deleted if there was evidence of obvious air-leak (resulting in shifting of the curve), or excessive interference (deviation $>$ 5%, as displayed on the accuracy bar). The mean of the remaining curves for each nasal cavity was then calculated. From this mean curve, the following measure-

Table 1. Mean values ± SEM for ipsilateral csa1, csa2, csa3, Amin, vol2, vol3, vol4 in normal subjects at baseline, after challenge with Hartman's solution, bradykinin 50 µg, and bradykinin 100 µg. P-values are for comparison of values after corresponding nasal challenge to values at baseline.

	Baseline	Control	p-value 50 µg	Bradykinin	p-value 100 µg	Bradykinin	p-value
csa1	0.65 ± 0.04 cm^2	0.68 ± 0.03 cm^2	0.20	0.66 ± 0.03 cm^2	0.90	0.70 ± 0.03 cm^2	0.07
csa2	0.58 ± 0.05 cm^2	0.56 ± 0.03 cm^2	0.58	0.54 ± 0.05 cm^2	0.24	0.59 ± 0.05 cm^2	0.75
csa3	1.26 ± 0.12 cm^2	1.19 ± 0.14 cm^2	0.21	1.01 ± 0.13 cm^2	0.03	1.13 ± 0.16 cm^2	0.12
Amin	0.53 ± 0.03 cm^2	0.56 ± 0.02 cm^2	0.20	0.50 ± 0.04 cm^2	0.26	0.56 ± 0.04 cm^2	0.24
vol2	1.72 ± 0.13 cm^2	1.74 ± 0.12 cm^3	0.23	1.57 ± 0.10 cm^3	0.01	1.67 ± 0.13 cm^3	0.58
vol3	3.57 ± 0.27 cm^2	3.71 ± 0.29 cm^3	0.67	3.55 ± 0.27 cm^3	0.09	3.57 ± 0.29 cm^3	0.12
vol4	4.24 ± 0.19 cm^2	4.42 ± 0.16 cm^3	0.81	4.27 ± 0.26 cm^3	0.86	4.38 ± 0.24 cm^3	0.79

ments were taken: csa1, csa2, and csa3 (corresponding to the first, second, and third minimum cross-sectional areas), vol2 (the volume from the nostril to the level of csa2), vol3 (the volume from the nostril to the level of csa3), and vol4 (the volume from the nostril to 4cm inside the nasal cavity). Amin (minimal cross-sectional area) was the minimum of csa1, csa2, and csa3. In the case of any csa being less than 0.2 cm^2, measurements of distal areas and volumes were discarded.

Statistical analysis

Statistical analysis was performed using WinStat for Microsoft Excel (version 2001.1). In order to test whether data were distributed normally, a chi-squared test for discrete variables was used. Non-normal data were analyzed using non-parametric tests. Nasal cross-sectional area and volumes obtained by acoustic rhinometry after control and bradykinin challenge were compared to the values obtained at baseline using a Wilcoxon ranked-pairs test. Differences in the changes in nasal patency in response to nasal challenge between normal subjects and subjects with SAR were analyzed by firstly calculating the changes in each area and volume measurement from the baseline measurement, and then by comparing the differences in these changes between the two groups using a Mann-Whitney U-test. For convenience, data is displayed graphically as the mean percentage change from baseline values ± SEM.

RESULTS

Congestive responses: Normal subjects

The mean values of nasal cross-sectional areas and volumes at baseline in normal subjects are shown in Tables 1 and 2. Challenge with Hartman's solution in normal subjects did not lead to any significant changes in ipsilateral nasal patency. After challenge with bradykinin 50 µg, significant decreases compared to baseline were seen for csa3 (p=0.03) and vol2 (p=0.01). Other areas and volumes showed smaller, non-significant reductions. This decrease in ipsilateral nasal patency occurring after challenge with bradykinin 50 µg did not persist after challenge with bradykinin 100 µg (Figure 1 and Table 1).

On the contralateral side, a circumscribed decrease in nasal patency in the region of csa3 (p=0.04) and vol3 (p=0.03) was seen after challenge with Hartman's solution. This response persisted after challenge with both bradykinin 50 µg and bradykinin 100 µg. Significant decreases in nasal patency were not seen in any other contralateral area or volume (Figure 2 and Table 2).

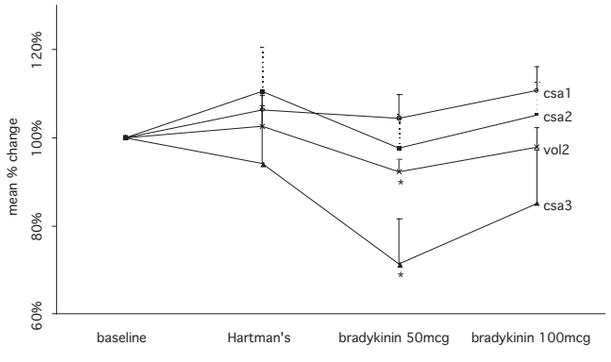

Figure 1. Challenge with bradykinin 50 mg in normal subjects leads to transient ipsilateral congestion at sites distant to the site of application (csa2, csa3), suggesting a reflex mechanism, and at vol2, suggesting congestion due to direct effects. Data expressed as mean percentages of baseline values ± SEM. * = $p<0.05$ for comparison to baseline values and values after control challenge.

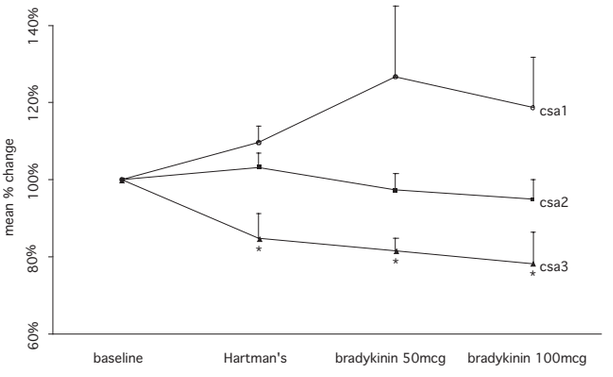

Figure 2. Nasal challenge in normal subjects leads to a circumscribed contralateral congestive response at csa3, away from the major flow-limiting section. Data expressed as mean percentages of baseline values ± SEM. * = $p<0.05$ for comparison to baseline values.

Table 2. Mean values ± SEM for contralateral csa1, csa2, csa3, Amin, vol2, vol3, vol4 in normal subjects at baseline, after challenge with Hartman's solution, bradykinin 50 µg, and bradykinin 100 µg. P-values are for comparison of values after corresponding nasal challenge to values at baseline.

	Baseline	Control	p-value	Bradykinin 50 µg	p-value	Bradykinin 100 µg	p-value
csa1	0.65 ± 0.06 cm^2	0.69 ± 0.55 cm^2	0.05	0.72 ± 0.03 cm^2	0.03	0.69 ± 0.03 cm^2	0.33
csa2	0.61 ± 0.05 cm^2	0.63 ± 0.05 cm^2	0.30	0.60 ± 0.05 cm^2	0.39	0.59 ± 0.04 cm^2	0.18
csa3	1.45 ± 0.16 cm^2	1.27 ± 0.14 cm^2	0.04	1.17 ± 0.13 cm^2	<0.01	1.04 ± 0.11 cm^2	0.02
Amin	0.53 ± 0.05 cm^2	0.56 ± 0.05 cm^2	0.13	0.57 ± 0.04 cm^2	0.44	0.54 ± 0.04 cm^2	0.94
vol2	1.86 ± 0.13 cm^3	1.79 ± 0.13 cm^3	0.86	1.85 ± 0.12 cm^3	0.24	1.78 ± 0.12 cm^3	0.72
vol3	4.26 ± 0.42 cm^3	3.89 ± 0.40 cm^3	0.04	3.60 ± 0.36 cm^3	0.01	3.40 ± 0.37 cm^3	0.02
vol4	4.40 ± 0.26 cm^3	4.26 ± 0.29 cm^3	0.81	4.17 ± 0.27 cm^3	0.06	4.02 ± 0.31 cm^3	0.13

Congestive responses: SAR

The mean values of nasal cross-sectional areas and volumes at baseline in subjects with SAR are shown in Tables 3 and 4. There were no significant differences in the baseline values between normal subjects and subjects with SAR. Challenge with Hartman's solution in subjects with SAR did not lead to any significant changes in any of the ipsilateral areas or volumes. After challenge with bradykinin 50 µg, significant decreases were seen for ipsilateral csa2 and Amin ($p=0.01$), and near-significant decreases for csa3, vol2, and vol4 ($p<0.1$) (Figure 3 and Table 3). Unlike normal subjects, this congestive response persisted after bradykinin 100 µg, with significant decreases seen for csa2, csa3, Amin, and vol4. The decreases in ipsilateral patency compared to baseline after bradykinin 100 mg were significantly greater in SAR subjects than in normal subjects, for example, csa2 fell by 0.09 ± 0.03 cm^2 in SAR subjects, compared with an increase of 0.01 ± 0.03 cm^2 for csa2 ($p=0.05$), while Amin fell by 0.07 ± 0.03 cm^2 in SAR subjects, compared to an increase of 0.03 ± 0.02 cm^2 in normal subjects ($p<0.01$) (compare Figure 1 with 3 and Table 1 with 3).

In contrast to normal subjects, challenge with Hartman's solution led to significant decreases in nasal patency throughout the contralateral nasal cavity in subjects with SAR, with significant reductions seen for all areas and volumes with the exception of contralateral csa1. This contralateral congestive response persisted after challenge with both bradykinin 50 µg, and bradykinin 100 µg (Figure 4 and Table 4). There were significant differences between normal subjects and subjects with SAR for the decreases in contralateral nasal patency. For example, in SAR subjects csa2 fell by 0.06 ± 0.02 cm^2 in response to challenge with Hartman's solution, whereas in controls csa2 increased 0.01 ± 0.02 cm^2 ($p=0.03$). In SAR subjects, Amin fell by 0.05 ± 0.02 cm^2 in response to challenge with Hartman's solution, compared to an increase of 0.02 ± 0.02 cm^2 in normals ($p=0.02$).

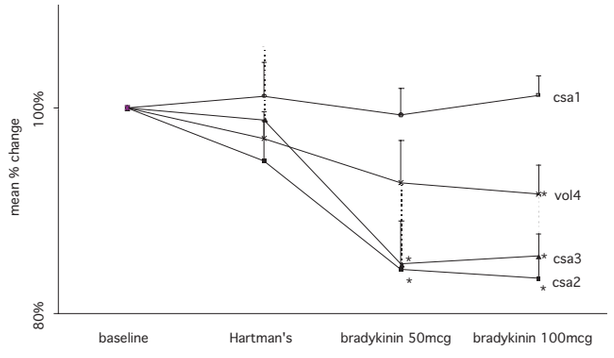

Figure 3. Challenge with bradykinin 50 mg in subjects with SAR leads to an ipsilateral congestive response, which persists after bradykinin 100 mg, unlike the case for normal subjects. Data expressed as mean percentages of baseline values ± SEM. * = $p<0.05$ for comparison to baseline values.

DISCUSSION

The purpose of this study was to characterise direct and reflex reductions in nasal patency in response to nasal challenge in normal subjects and subjects with SAR. Our results demonstrate reductions in nasal patency at sites distant to that of application of nasal challenge, suggesting reflex mechanisms. Hyperresponsiveness of these reflex responses is present in SAR.

In the present study, we wished to investigate whether nasal congestion in response to nasal challenge with Hartman's solution, a non-specific irritant, or bradykinin, a vaso-active peptide, may occur through local naso-nasal reflexes. Thus, it was important that our study design allowed us to distinguish local, direct effects of the nasal challenge substance from the remote, reflex, effects. With this in mind, we performed nasal challenge unilaterally, using small filter paper disks, to minimize the area of nasal mucosa directly affected by the challenge substance [4]. We then measured changes in nasal patency using acoustic rhinometry. This allowed us to measure changes in nasal patency both in the vicinity of the site of application of nasal challenge (ipsilateral csa1 / vol2), and at distant sites (ipsilateral csa2 / csa3, and all contralateral areas and volumes), which are unlikely to be subject to the direct effects of bradykinin, and so are likely to reflect reflex mechanisms.

Hartman's solution and bradykinin were used as challenge substances. Hartman's solution (compound sodium lactate) was used as a non-specific nasal irritant. The mechanisms regarding

Table 3. Mean values ± SEM for ipsilateral csa1, csa2, csa3, Amin, vol2, vol3, vol4 in subjects with SAR at baseline, after challenge with Hartman's solution, bradykinin 50 µg, and bradykinin 100 µg. P-values are for comparison of values after corresponding nasal challenge to values at baseline.

	Baseline	Control	p-value	Bradykinin 50 µg	p-value	Bradykinin 100 µg	p-value
csa1	0.71 ± 0.04 cm^2	0.72 ± 0.04 cm^2	0.85	0.71 ± 0.04 cm^2	0.51	0.72 ± 0.04 cm^2	0.72
csa2	0.54 ± 0.04 cm^2	0.52 ± 0.05 cm^2	0.21	0.45 ± 0.05 cm^2	0.01	0.45 ± 0.04 cm^2	<0.01
csa3	1.34 ± 0.15 cm^2	1.28 ± 0.15 cm^2	0.60	1.14 ± 0.14 cm^2	0.07	1.10 ± 0.17 cm^2	0.03
Amin	0.49 ± 0.03 cm^2	0.46 ± 0.03 cm^2	0.19	0.42 ± 0.03 cm^2	0.02	0.42 ± 0.03 cm^2	0.01
vol2	1.84 ± 0.06 cm^3	1.79 ± 0.08 cm^3	0.24	1.75 ± 0.07 cm^3	0.07	1.76 ± 0.07 cm^3	0.12
vol3	3.95 ± 0.28 cm^3	3.70 ± 0.33 cm^3	0.57	3.80 ± 0.36 cm^3	0.24	3.68 ± 0.34 cm^3	0.17
vol4	3.91 ± 0.20 cm^3	3.77 ± 0.18 cm^3	0.42	4.60 ± 0.21 cm^3	0.07	3.57 ± 0.20 cm^3	0.02

Table 4. Mean values ± SEM for contralateral csa1, csa2, csa3, Amin, vol2, vol3, vol4 in subjects with SAR at baseline, after challenge with Hartman's solution, bradykinin 50 mg, and bradykinin 100 mg. P-values are for comparison of values after corresponding nasal challenge to values at baseline.

	Baseline	Control	p-value	Bradykinin 50 µg	p-value	Bradykinin 100 µg	p-value
csa1	0.76 ± 0.03 cm^2	0.78 ± 0.05 cm^2	0.08	0.79 ± 0.05 cm^2	0.18	0.80 ± 0.05 cm^2	0.26
csa2	0.56 ± 0.04 cm^2	0.50 ± 0.05 cm^2	0.01	0.50 ± 0.04 cm^2	0.02	0.49 ± 0.05 cm^2	0.06
csa3	1.21 ± 0.13 cm^2	1.06 ± 0.10 cm^2	0.02	1.06 ± 0.12 cm^2	0.03	1.03 ± 0.11 cm^2	0.08
Amin	0.52 ± 0.03 cm^2	0.47 ± 0.04 cm^2	0.07	0.47 ± 0.03 cm^2	0.06	0.46 ± 0.04 cm^2	0.03
vol2	2.06 ± 0.08 cm^3	1.97 ± 0.09 cm^3	0.04	1.97 ± 0.07 cm^3	0.06	1.94 ± 0.08 cm^3	0.01
vol3	4.17 ± 0.20 cm^3	3.71 ± 0.17 cm^3	<0.01	3.61 ± 0.19 cm^3	<0.01	3.82 ± 0.28 cm^3	0.04
vol4	4.13 ± 0.20 cm^3	3.83 ± 0.18 cm^3	0.06	3.82 ± 0.20 cm^3	0.04	3.80 ± 0.19 cm^3	0.05

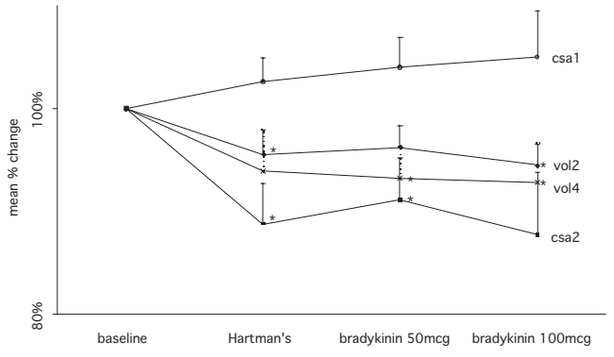

Figure 4. Nasal challenge in subjects with SAR leads to a contralateral congestive response. This response is generalized throughout the contralateral nasal cavity, with the exception of csa1. Data expressed as mean percentages of baseline values ± SEM. * = p<0.05 for comparison to baseline values.

irritant-related nasal congestion are poorly defined, however, they would appear not to involve either mast cell degranulation or parasympathetic reflexes [18]. Candidate mechanisms thus include axon reflexes or sympathetic reflexes. Of note, Hartman's solution has a pH of 6-6.2, thus the induced responses may reflect those to an acidic solution. Recent studies have described the presence of a family of acid sensing ion gated channels, the ASICs and vanilloid channels [19]. In the lower airways, these have been implicated in cough [20]. On the other hand, bradykinin is known to have strong direct effects on blood vessels, leading to vasodilatation and plasma extravasation [3]. Bradykinin is also capable of activating sensory nerves and has been shown to give rise to reflex secretory responses in allergic subjects [5].

In the present study, a transient reduction in ipsilateral nasal patency was seen in normal subjects in response to challenge with bradykinin 50 µg. This reduction in patency was most marked in vol2. This volume corresponds to the area surrounding the site of application of challenge disks, and includes the erectile tissue of the anterior septal tumescence [21], as well as of the head of the inferior turbinate. Thus it is likely that much of the congestion in vol2 represented direct effects of bradykinin on vasculature. It was notable that no significant reduction in nasal patency was present at the cross-sectional area closest to the site of application of challenge disks (csa1), which may reflect a lack of significant erectile tissue in the region of the anterior nasal valve. A significant reduction in ipsilateral nasal patency was also seen at csa3 in response to bradykinin challenge. This cross-sectional area is distant from the site of application of bradykinin, suggesting the possibililty that congestion occurred as a result of a reflex mechanism. Alternatively, congestion at csa3 may have occurred due to rapid transport of bradykinin from the site of application to the area of the septum opposite the head of the middle turbinate by mucociliary clearance, with bradykinin then acting directly on septal erectile tissue causing mucosal swelling.

The reasons for the absence of a congestive response in normal subjects after the second (100 µg) bradykinin challenge are unclear, but may reflect a centrally-mediated, counter-regulatory decongestive reflex [22].

In normal subjects, reductions in contralateral nasal patency were seen only in the region of csa3 and vol3. The importance of this limited response is uncertain. The area of csa3, which is located in the region of the prominence of the middle turbinate, was considerably greater than that of Amin in all subjects in the present study. Thus, csa3 did not form part of the major flow-limiting section in any case. Diminution in the patency of csa3 is therefore unlikely to increase nasal resistance, however, it may increase the turbulence of nasal airflow and increase the contact between inspired air and nasal mucosa. Such a reflex may be of practical importance during exposure to commonly encountered non-specific irritants, such as cold dry air.

In subjects with SAR, reductions in ipsilateral nasal patency occurred in response to bradykinin challenge at sites away from the site of application of challenge disks, as was seen in normal subjects. However, in contrast to normal subjects, this reduced patency persisted after the second bradykinin challenge. Subjects with SAR also demonstrated widespread reductions in nasal patency throughout the contralateral nasal. This generalized response was not seen in control subjects. These data indicate that hyperresponsiveness of congestive reflexes is present in subjects with SAR.

It is notable that in both groups of subjects, csa1 did not participate in either ipsilateral or contralateral reductions in nasal patency. This is most likely explained by the lack of erectile tissue under neural control in this part of the nose.

It is also notable that in both normal and SAR subjects, contralateral responses occurred in response to challenge with Hartman's solution, whereas ipsilateral responses were seen only after challenge with bradykinin. In addition, in subjects with SAR, contralateral responses tended to be more pronounced and generalized. The reason for this may be that a greater number of the reflex arcs involved in nasal congestion are crossed than are uncrossed, so leading to more pronounced effects on the contralateral side. In support of this observation, Miyahara at al. also reported similar findings of a lower threshold for contralateral congestive responses to histamine than for ipsilateral responses [23].

Nasal congestion is a troublesome symptom in patients with allergic rhinitis. Nasal congestion after allergen exposure occurs as a result of the direct actions of various mediators, including histamine and leukotrienes [4,24]. The data from the present study provide evidence that additional reductions in nasal patency may occur due to reflex effects. The presence of hyperresponsiveness of this response in subjects with allergic rhinitis, as demonstrated in the present study, may render them prone to symptomatic nasal obstruction after exposure to non-allergenic irritants, such as cigarette smoke, noxious fumes, changes in temperature, and exercise, and this may be an important cause of persistent symptoms even outside the allergen season [25].

In conclusion, the findings of the present study provide evidence for the existence of reflexes which lead to decreased nasal patency both in normal and allergic subjects. Hyperresponsiveness of these reflexes is present in SAR, and may be an important factor in the pathogenesis of the symptoms of rhinitis in this group.

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