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Inflammatory cells seem not to be involved in idiopathic rhinitis*

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SUMMARY

Mucosal inflammatory cellular infiltrates are correlated with nasal complaints in symptomatic allergic rhinitis. Some authors suggest inflammation of a neurogenic or immunogenic nature as an underlying disorder for idiopathic rhinitis (IR). We looked at the possible involvement of inflammatory cells in the pathogenesis of IR. Nasal biopsies were taken from sixty-five IR patients with significant nasal complaints and from twenty healthy controls with no nasal complaints. Inflammatory cells were quantified using monoclonal antibodies directed against lymphocytes, antigen-presenting cells, eosinophils, macrophages, monocytes, mast cells and other IgE-positive cells. No significant differences were found, for any cell, between IR patients and controls. We conclude that inflammatory cells do not seem to play an important role in this meticulously characterised group of IR patients.

Key words: rhinitis vasomotor, eosinophils, mast cells, T-Lymphocytes, macrophages, nasal mucosa

INTRODUCTION

Idiopathic rhinitis (IR) is a diagnosis by exclusion. This disorder probably represents a heterogeneous group of pathophysiological conditions. This implies that the study group needs to be meticulously characterised. In a group of non-atopic patients with nasal complaints, we excluded all patients with systemic, allergic, medical and anatomical disorders that could explain complaints of rhinorrhea, sneezing and/or nasal obstruction. This group with unexplained nasal complaints was then homogenised on the basis of a daily record chart on which patients had to reach a minimum symptom score. The minimum was set using as a basis the definition of rhinitis put forward by Mygind and Weeke (1985). In affected patients, periods of nasal discharge, sneezing and congestion had to persist for an average of at least 1-hour per day on at least five days during a period of fourteen days.

The proposed pathophysiological mechanisms for IR include a chronic inflammatory disorder of antigenic (local allergy) or neurogenic nature (Shatkin et al., 1994; Philip and Togias, 1995; Carney and Jones, 1996). A pivotal characteristic in the pathophysiological concept of inflammation is an influx of inflammatory cells in the affected tissue. In symptomatic allergic rhinitis, an increase of inflammatory cells has been observed in the nasal mucosa (Fokkens et al., 1990; Bentley et al., 1992; Braunstahl et al., 2001). We showed that cellular infiltrates (eosinophils, mast cells and IgE positive cells) were not significantly different in a group of IR patients compared to healthy controls (Blom et al., 1995). To ascertain the significance of inflammation, we also need to know whether regulatory cells (lymphocytes and antigen presenting cells) are involved in IR.

In this study, we examined nasal biopsies from 65 symptomatic IR patients and 20 healthy controls without nasal complaints. The cell densities of CD1, CD3, CD4, CD8, CD14, CD25, CD68, chymase, tryptase, IgE and BMK13 were studied in both layers of the nasal mucosa.

MATERIALS AND METHODS

Subjects

Patients were studied in the outpatient ENT departments of the Leyenburg Hospital in The Hague and the Erasmus Medical Centre Rotterdam University Hospital in Rotterdam, The Netherlands.

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Table 1. Selection criteria for idiopathic rhinitis.

Inclusion criteria

- Age between 16 and 64 years.
- Negative skin prick test: house dust mite, tree pollen mix, grass pollen mix, mugwort, alternaria, aspergillus, cladosporium, penicillum, dog, cat, parakeet, rabbit, hamster, horse, guinea pig. (ALK-Diephuis, Holland)
- Negative Phadiatop (Pharmacia, Uppsala, Sweden)
- Symptoms for more than 1 year.
- Periods of nasal discharge, sneezing and congestion for an average of at least 1 h per day on at least 5 days during a period of 14 days.

Exclusion criteria

- The use of systemic or inhaled corticosteroids within the previous month.
- Use of inhaled sodium cromoglycate or nedocromil sodium within the previous month.
- Use of astemizole within the previous month.
- Inability of the patient to stop taking medication affecting nasal function.
- A serious and/or unstable disease.
- Nasal surgery within the previous 6 weeks.
- Nasal polyps or a history of nasal polyps.
- Significant anatomical abnormalities affecting nasal function.
- Nasal or paranasal sinus infection (abnormal sinus X-ray).
- Pregnancy or lactation.
- Abnormal findings at physical examination.
- Abnormal laboratory results for:
  blood: Na, K, Ca, total protein, albumin, urea, creatinine, bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gammaglutamyl transpeptidase, haemoglobin, red blood cell count, plasma cell volume, mean corpuscular volume, platelets, total white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils.
  urine: blood, protein, glucose.

Patients were admitted to the study if they had a history of nasal complaints such as nasal obstruction, sneezing, and rhinorrhea for a period of over 1 year which could not be attributed to allergic rhinitis, nasal or paranasal sinus infection, anatomical disorders affecting nasal function, pregnancy or lactation, systemic disorders and/or the use of medication affecting nasal function (Table 1). Patients with nasal polyps were excluded, since they may belong to a different pathophysiological group and their polyps may contribute to a higher symptom score for nasal blockage and/or rhinorrhea.

In affected patients, periods of nasal discharge, sneezing and congestion scored using a daily record chart (DRC, Table 2) had to persist for an average of at least 1h per day on at least 5 days during a period of 14 days. Sixty-five patients participated under conditions of informed consent (male/female: 32/33); the mean age was 34 years (range: 17-62). The ethnic origin of the patients was: 56 Caucasian, 6 Asian, 2 Negroid and 1 Oriental. The control group consisted of twenty healthy volunteers (male/female: 11/9); mean age 36 years (range: 18-62), 16 Caucasian, 3 Oriental, and 1 Asian, without nasal complaints or nasal abnormalities on ENT examination, a negative skin prick test for the common inhalation allergens and a negative Phadiatop (Pharmacia, Uppsala, Sweden). Patients and healthy controls were biopsied once. Procedures were approved by the local Medical Ethics committees.

Nasal biopsies

At the time of the biopsy, all patients had nasal complaints, as confirmed by their daily record charts. Controls did not suffer from nasal complaints. After randomisation of the biopsy side, a biopsy of nasal mucosa was taken from the lower edge of the inferior turbinate, about 2 cm posterior to the front edge, using a Gerritsma forceps with a cup diameter of 2.5 mm (Fokkens et al., 1988). Local anaesthesia was obtained by placing a cotton-wool carrier with 50 mg of cocaine and one drop of adrenaline (1:1000) under the inferior turbinate without touching the biopsy site. The specimens were embedded in Tissue-Tek II O.C.T. compound and frozen immediately.

Staining procedures

Monoclonal antibodies (mAb) directed against CD1, CD3, CD4, CD8, CD14, CD25, CD68, chymase, tryptase, IgE, and BMK13 (Table 3) were used together with the super-sensitive immuno-

Table 2. Specimen of the daily record card for defining nasal symptoms in patients with idiopathic rhinitis.

Possible scores on the daily record chart	
Nasal blockage: (not being able to breathe freely through the nose) Clear nasal discharge: (runny nose)	0 = absent 1 = between 0-1 h per half day 2 = between 1-2 h per half day 3 = more than 2 h per half day
Sneezing Coughing	0 = absent 1 = less than 5 periods per half day 2 = between 5-10 periods per half day 3 = more than 10 periods per half day
Mucus production: (yellow, green or brown)	0 = absent 1 = present

Table 3. Monoclonal antibodies used to study mucosal biopsies in patients with idiopathic rhinitis and controls.

Antibody	*Specificity*	*Titer*	*Source*
CD1	OKT6	1:100	Dept. Immunology, Erasmus University, Rotterdam, The Netherlands (NL)
CD3	leu4	1:25	BDH, Dorset, UK
CD4	leu3	1:50	
CD8	leu2	1:100	
CD25	IL2-r	1:150	
B7	Chymase	1:100	Chemicon, Temecula, Calif, USA
G3	Tryptase	1:250	
BMK13	MBP	1:200	Sanbio, Uden, NL
CD14	mon/1	1:20	Central laboratory of the Netherlands Red Cross Blood Transfusion
anti-IgE	IgE	1:250	service (CLB), Amsterdam, NL
CD68	KI-M6	1:50	Behring, Marburg, Germany

alkaline phosphatase (ss-AP) method. Six-μm-thick sections of nasal mucosa were cut on a cryostat (Jung Frigocut 2800E/20/40), transferred to poly-L-lysine-coated microscope slides, dried, and fixed in acetone for 10 minutes at room temperature. They were then rinsed in phosphate-buffered saline (PBS, pH 7.2), placed in a half-automatic stainer (Sequenza, Shandon), incubated with 2% bovine serum albumin in PBS for 10 minutes and incubated with normal goat serum (CLB, Amsterdam, The Netherlands) for 10 minutes. The slides were then incubated with the mAb for 30 minutes at room temperature.

The sections were then rinsed again in PBS for 5 minutes and incubated for 30 minutes with a biotinylated goat anti-mouse (1:50) immunoglobulin antiserum, rinsed successively in PBS, incubated with strept Avidin AP (1:50) (Biogenics, Klinipath, Duiven, the Netherlands) for 30 minutes at room temperature, rinsed in PBS and TRIS buffer (pH 8.0), and incubated for 30 minutes with a new fuchsin substrate (Chroma, Kongen, Germany). Finally, the sections were rinsed with distilled water, counterstained with Gills hematoxylin and mounted in glycerin-gelatin. Control staining was performed by substitution with PBS and incubation with an irrelevant mAb of the same subclass.

Light-microscopic evaluation

Stained cells were counted in two sections of each biopsy specimen. The epithelium and lamina propria were evaluated separately. The total surface area of the sections and their main parts (i.e. the epithelium and the lamina propria) were estimated using the Kontron Image Analysis System Videoplan. The number of cells/mm^2 was calculated for the epithelium and the lamina propria.

Statistical analysis

The non-parametric Mann-Whitney test was used to compare the difference in cell counts between the two groups. A p-value < 0.05 was considered to indicate a significant difference. In order to have some idea of the magnitude of a Type II error in this study, the 97.5 upper confidence limit of the mean difference between patients and controls was calculated after ln-transformation of the cell counts. The ln-transformation compensates for the positive skewness so as to justify parametric inference more properly. The antilog of this upper confidence limit divided by the antilog of this mean difference gives the maximum ratio between the larger and the smaller median that would still be accepted at the 5% level (2-sided), given the non-significantly different observed medians in patients and controls. We call this ratio (which by definition is larger than one) the smallest detectable ratio of medians between the two groups for a particular variable in this study. The more lack of power (i.e., the larger the Type II error), the higher this ratio will be. It is assumed here that the distribution of the variable considered is lognormal so that the geometric mean coincides with the median.

For instance, if the smaller of both medians for CD3 epithelium equals 512 in the control group and the calculated smallest detectable ratio of medians between the two goups is 1.57, then the patient group would be significantly different from the control group if the median is at least equal to $1.57 \times 512 = 804$.

RESULTS

Biopsy specimen

The sections of the nasal mucosa had an average surface area of 1.6 mm^2 and usually had a lining of ciliated columnar epithelium with or without goblet cells and/ or partially stratified cuboidal epithelium. The lamina propria usually consisted of a looser subepithelial cell-rich layer with most of the mucous glands and a deeper collagenous cell-poor layer. All sections were sufficiently deep to assess both layers. The sections were generally of good quality. It was not possible to evaluate two

biopsy specimens. One exclusion was made because of an artefact resulting from defrosting of the specimen and the other specimen was displaced. The mAb-ss-AP staining showed red cells against a blue counterstained background. Biopsy specimens from 2 of the 65 patients showed substantial numbers of eosinophils, mast cells and IgE-positive cells.

T-lymphocytes

These small round cells were abundantly present in the epithelium and in the lamina propria. Sometimes, clusters of T-cells (500-1000 cells) were found in the lamina propria. There was no difference between the groups in terms of the presence of these clusters.

The numbers of CD3, CD4, CD8, and CD25 positive cells/mm^2 are shown in Table 4. As can be seen, hardly any IL-2 receptor (CD25) positive cells were found in either layer of the nasal mucosa. If there were any differences between the two groups at all, they were not statistically significant. The smallest detectable ratios of medians between the groups were, respectively: CD3 epithelium (EP) 1.57, CD3 lamina propria (LP) 1.47, CD4 EP 1.78, CD4 LP 1.5, CD8 EP 1.88, CD8 LP 1.73, CD25 EP 2.63, CD25 LP 2.38.

Langerhans cells

This large dendritic cell was found mostly in the epithelium. Only a few were present in the lamina propria. The numbers of CD1-positive cells are shown in Table 4. No significant differences were found. The smallest detectable ratios of medians between the groups were, respectively: CD1 EP 1.86, CD1 LP 2.20.

Macrophages and monocytes

The CD68 positive cells were large cells with a bright staining cytoplasm. These cells were found to be equally distributed in both layers, as was CD14. The numbers of CD68 and CD14 cells are shown in Table 4. No significant differences were found. The smallest detectable ratios of medians between the groups were, respectively: CD14 EP 1.68, CD14 LP 1.55, CD68 EP 1.44, CD68 LP 1.52.

Mast cells and other IgE-positive cells

The chymase and tryptase and IgE-positive cells were found mainly in the lamina propria. The numbers are shown in Table 4. No significant differences were found. The smallest detectable ratios of medians between the groups were, respectively: anti-IgE EP 4.22, anti-IgE LP 3.17, tryptase EP 2.62, tryptase LP 1.57, chymase EP 2.47, chymase LP 1.61.

Eosinophils

The numbers of BMK13 positive cells found in the nasal mucosa of both patients and controls were negligible. The numbers are shown in Table 4. No significant differences were found. The smallest detectable ratios of medians between the groups were, respectively: BMK13 EP 1.96, BMK13 LP 2.21.

DISCUSSION

Wolf suggested that IR could be the result of an "over-active" non-adrenergic, non-cholinergic system (Wolf, 1988). Stimulation of sensory neurons results in rhinorrhea, nasal blockage and sneezing (Baraniuk, 1992). Sensory neural stimulation may produce these effects either through a central neural reflex, associated with efferent parasympathetic neurotransmission, or via anti-dromic release of neuropeptides from sensory neurons (Lundblad et al., 1983). This hypothesis was corroborated by the findings of Lacroix, who reported an increased concentration of neuropeptides in a group of chronic non-allergic rhinitis patients (Lacroix et al., 1992), improvement of symptoms by local treatment of capsaicin giving a 50% reduction in CGRP-like immunoreactivity(-LI) content in nasal biopsies (Lacroix et al., 1991), and a correlation between symptom intensity and CGRP-LI concentration in nasal mucosa (Lacroix et al., 1995).

An increase of proinflammatory neuropeptides may result in a stimulation of T-cell proliferation, stimulation of mast cells, macrophages and eosinophils, and chemoattraction of eosinophils and neutrophils (Joos et al., 1995). Substance P can increase the percentage of neutrophils recovered from nasal lavage (Braunstein et al., 1994). Capsaicin, a specific activator of sensory nerve endings, induces a neurogenic inflammation,

Table 4. Median (25th and 75th percentile) of positive cells/mm^2 in epithelium and lamina propria of the nasal mucosa.

Cell type	Controls Median (25 %-75%)	Patients Median (25%-75%)	p-value
Epithelium			
CD1	48 (15-130)	54 (15-110)	0.82
CD3	512 (299-867)	630 (347-1079)	0.27
CD4	545 (341-755)	424 (223-584)	0.18
CD8	305 (173-431)	446 (163-762)	0.11
CD14	310 (130-497)	215 (179-316)	0.68
CD25	8 (0-30)	0 (0-25)	0.43
BMK13	0 (0-0)	0 (0-0)	0.60
Tryptase	0 (0-4)	0 (0-4)	0.88
Chymase	0 (0-0)	0 (0-8)	0.06
IgE	0 (0-0)	0 (0-28)	0.30
CD68	165 (89-293)	214 (136-378)	0.06
Lamina propria			
CD1	3 (1-8)	5 (1-13)	0.54
CD3	678 (486-832)	552 (300-872)	0.31
CD4	464 (181-885)	426 (259-611)	0.65
CD8	269 (160-345)	295 (147-476)	0.51
CD14	232 (143-367)	196 (161-271)	0.58
CD25	7 (2-58)	3 (0-13)	0.30
BMK13	0 (0-0)	0 (0-3)	0.18
Tryptase	65 (41-71)	69 (38-97)	0.30
Chymase	54 (47-71)	63 (46-100)	0.35
IgE	8 (2-62)	22 (4-64)	0.67
CD68	145 (74-195)	152 (101-250)	0.30

with an influx of inflammatory cells in nasal lavage after a single provocation (Philip et al., 1996).

Another theory concerning the pathogenesis of IR is that of a local, occult allergy (Shatkin et al., 1994; Carney et al., 2001; Powe et al., 2001). The diagnosis of IR is made by exclusion. An allergy test is not 100% sensitive and systemic manifestations of atopic disease, such as a positive skin prick test or RAST, may be missed because the nose is a small shock organ. In seasonal or perennial allergic rhinitis, increased numbers of inflammatory cells, such as Langerhans cells, IgE positive cells and eosinophils, can be found in the nasal mucosa as a sign of inflammation (Fokkens et al., 1990; Bentley et al., 1992; Braunstahl et al., 2001).

By strict selection and by using a complaint threshold value, we tried to achieve a homogenous group of patients. The 2 patients of the total of 65 patients with negative allergy tests who had a substantial typical cellular allergic infiltrate in the nasal mucosa were classified as possible sufferers from an occult local allergy and or non-allergic rhinitis with eosinophil syndrome (NARES) (Mikaelian, 1989). This would mean a maximum prevalence of three percent of occult allergy / NARES in this group that can be discerned by nasal biopsies. No other signs of inflammation were found in this IR patient group.

This contrasts with a recent study of Powe et al. (2001) who found significantly more nasal mucosa mast cells and eosinophils in a group of IR (and allergic rhinitis) patients compared to a group of normal individuals. They examined whole, full-length, full-thickness concha inferior specimens resected under general anaesthesia.
The difference in study outcome may be explained by a more severe pathology in the IR group of Powe et al. warranting total turbinectomy. Another explanation could be the difference in biopsy size (average surface area of 1.6 mm^2 in our study). Nasal cellular infiltrates show a focal localisation of cell populations which can be better averaged in larger biopsies.
It may also be the case that our IR patient group contains significantly fewer NARES patients (2 of the 65) compared to the patient group studied by Powe et al. (2001). The reason for this could be the fact that a Dutch rhinitis patient will not be sent to the ENT department before being treated with local corticosteriods by his or her general practitioner (Lundblad et al., 2001). In addition, as might be expected, it seems that NARES patients and or patients with an occult local allergy form an IR subgroup which responds well to nasal corticosteroids (Small et al., 1982).

The data presented concurs with the data from Sanico, who was unable to find an increased responsiveness to capsaicin in a group of 8 non-allergic rhinitis patients. He therefore argued against a central role for capsaicin sensitive nerves (pivotal in the concept of neurogenic inflammation) in the pathophysiology of IR (Sanico et al., 1998).

The question then arises as to whether this immunohistochemical evaluation method is sensitive enough to detect significant differences between the groups. The calculated ratios between the geometric means of both groups indicating threshold significance at the 5% level are within the range found in patients with chronic allergic rhinitis (Fokkens et al., 1990; Godthelp et al., 1996). In these studies, which compare symptomatic allergic patients to asymptomatic controls, cellular differences between patients and controls were indeed found, while the distribution of the number of immunocompetent cells/mm^2 was in the same order of magnitude as in this IR study. We therefore think it is justified to assume that if significant mucosal inflammation was present, we would have detected it. The lack of differences in cell numbers does not exclude a functional cellular involvement. However, in two other studies, we failed to ascertain a relation between the number of immunocompetent cells and nasal complaints in IR patients (Blom et al., 1997a; Blom et al., 1998). A significant reduction of immunocompetent cells in the nasal mucosa of IR patients treated with nasal steroids (fluticasone aqueous nasal spray) was not accompanied by a reduction in nasal complaints (Blom et al., 1997a) and, inversely, a significant reduction in nasal complaints in a group of IR patients treated with topical capsaicin aqueous nasal spray was not accompanied by a change in inflammatory mediators (Blom et al., 1997b) or a reduction in the numbers of inflammatory cells (Blom et al., 1998).
Given the above, we conclude that inflammatory cells do not seem to play an important role in this meticulously characterised group of IR patients.

REFERENCES

1. Baraniuk JN (1992) Sensory, parasympathetic, and sympathetic neural influences in the nasal mucosa. J Allergy Clin Immunol 90: 1045-1050.
2. Bentley AM, Jacobson MR, Cumberworth V, Barkans JR, Moqbel R, Schwartz LB, Irani AM, Kay AB, Durham SR (1992) Immunohistology of the nasal mucosa in seasonal allergic rhinitis: increases in activated eosinophils and epithelial mast cells. J Allergy Clin Immunol 89: 877-883.
3. Blom HM, Godthelp T, Fokkens WJ, KleinJan A, Mulder PGM, Rijntjes E (1997a) The effect of nasal steroid aqueous spray on nasal complaint scores and cellular infiltrates in the nasal mucosa of patients with a non-allergic non-infectious perennial rhinitis. J Allergy Clin Immunol 100: 739-747.
4. Blom HM, Godthelp T, Fokkens WJ, Klein Jan A, Holm AF, Vroom TM, Rijntjes E (1995) Mast cells, eosinophils and IgE-positive cells in the nasal mucosa of patients with vasomotor rhinitis. An immunohistochemical study. Eur Arch Otorhinolaryngol Suppl. 1: S33-39.
5. Blom HM, Severijnen LA, Van Rijswijk JB, Mulder PG, Van Wijk RG, Fokkens WJ (1998) The long-term effects of capsaicin aqueous spray on the nasal mucosa. Clin Exp Allergy 28: 1351-1358.
6. Blom HM, Van Rijswijk JB, Garrelds IM, Mulder PG, Timmermans T, Gerth van Wijk R (1997b) Intranasal capsaicin is efficacious in non-allergic, non-infectious perennial rhinitis. A placebo-controlled study. Clin Exp Allergy 27: 796-801.

7. Braunstahl GJ, Overbeek SE, Fokkens WJ, Kleinjan A, McEuen AR, Walls AF, Hoogsteden HC, Prins JB (2001) Segmental bronchoprovocation in allergic rhinitis patients affects mast cell and basophil numbers in nasal and bronchial mucosa. Am J Respir Crit Care Med 164: 858-865.
8. Braunstein G, Buvry A, Lacronique J, Desjardins N, Frossard N (1994) Do nasal mast cells release histamine on stimulation with substance P in allergic rhinitis? (see comments). Clin Exp Allergy 24: 922-929.
9. Carney AS, Hooi D, Powe DG, Huskisson RS, Jones NS (2001) Autoanti-IgE antibodies in patients with allergic and idiopathic rhinitis. Clin Otolaryngol 26: 298-301.
10. Carney AS, Jones NS (1996) Idiopathic rhinitis: idiopathic or not? Clin Otolaryngol 21: 198-202.
11. Fokkens WJ, Holm AF, Rijntjes E, Mulder PG, Vroom TM (1990) Characterization and quantification of cellular infiltrates in nasal mucosa of patients with grass pollen allergy, non-allergic patients with nasal polyps and controls. Int Arch Allergy Appl Immunol 93: 66-72.
12. Fokkens WJ, Vroom TM, Gerritsma V, Rijntjes E (1988) A biopsy method to obtain high quality specimens of nasal mucosa. Rhinology 26: 293-295.
13. Godthelp T, Holm AF, Fokkens WJ, Doornenbal P, Mulder PG, Hoefsmit EC, Kleinjan A, Prens EP, Rijntjes E (1996) Dynamics of nasal eosinophils in response to a nonnatural allergen challenge in patients with allergic rhinitis and control subjects: a biopsy and brush study. J Allergy Clin Immunol 97: 800-811.
14. Joos GF, Germonpre PR, Pauwels RA (1995) Neurogenic inflammation in human airways: is it important? Thorax 50: 217-219.
15. Lacroix JS, Buvelot JM, Polla BS, Lundberg JM (1991) Improvement of symptoms of non-allergic chronic rhinitis by local treatment with capsaicin. Clin Exp Allergy 21: 595-600.
16. Lacroix JS, Kurt AM, Pochon N, Bretton C, Lunberg JM, Deshusses J (1995) Neutral endopeptidase activity and concentration of sensory neuropeptide in the human nasal mucosa. Eur Arch Otorhinolaryngol 252: 465-468.
17. Lacroix JS, Pochon N, Lundberg JM (1992) In Secondary Increased concentration of sensory neuropeptide in the nasal mucosa from patients with non-allergic chronic rhinitis, Vol. II Monduzzi Editore S.p.A., Italy, Sorrento, Italy, pp. 59-63.
18. Lundblad L, Saria A, Lundberg JM, Anggard A (1983) Increased vascular permeability in rat nasal mucosa induced by substance P and stimulation of capsaicin-sensitive trigeminal neurons. Acta Otolaryngol 96: 479-484.
19. Lundblad L, Sipila P, Farstad T, Drozdziewicz D (2001) Mometasone furoate nasal spray in the treatment of perennial non-allergic rhinitis: a nordic, multicenter, randomized, double-blind, placebo-controlled study. Acta Otolaryngol 121: 505-509.
20. Mikaelian AJ (1989) Vasomotor rhinitis. [Review]. Ear Nose Throat J 68: 207-210.
21. Mygind N, Weeke B (1985) Allergic and vasomotor rhinitis: Clinical aspects. Munksgaard, Copenhagen.
22. Philip G, Sanico AM, Togias A (1996) Inflammatory cellular influx follows capsaicin nasal challenge. Am J Respir Crit Care Med 153: 1222-1229.
23. Philip G, Togias AG (1995) Nonallergic rhinitis. Pathophysiology and models for study. Eur Arch Otorhinolaryngol Suppl. 1: S27-S32.
24. Powe DG, Huskisson RS, Carney AS, Jenkins D, Jones NS (2001) Evidence for an inflammatory pathophysiology in idiopathic rhinitis. Clin Exp Allergy 31: 864-872.
25. Sanico AM, Philip G, Proud D, Naclerio RM, Togias A (1998) Comparison of nasal mucosal responsiveness to neuronal stimulation in non-allergic and allergic rhinitis: effects of capsaicin nasal challenge. Clin Exp Allergy 28: 92-100.
26. Shatkin JS, Delsupehe KG, Thisted RA, Corey JP (1994) Mucosal allergy in the absence of systemic allergy in nasal polyposis and rhinitis: a meta-analysis. Otolaryngol Head Neck Surg 111: 553-556.
27. Small P, Black M, Frenkiel S (1982) Effects of treatment with beclomethasone dipropionate in subpopulations of perennial rhinitis patients. J Allergy Clin Immunol 70: 178-182.
28. Wolf G (1988) [New aspects in the pathogenesis and therapy of hyperreflexive rhinopathy]. Laryngol Rhinol Otol (Stuttg) 67: 438-445.

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