

Review article

Idiopathic rhinitis, the ongoing quest

The term rhinitis in daily practice is used for nasal dysfunction causing symptoms-like nasal itching, sneezing, rhinorrhea and or nasal blockage. Chronic rhinitis can roughly be classified into allergic, infectious or nonallergic/noninfectious. When allergy, mechanical obstruction and infections have been excluded as the cause of rhinitis, a number of poorly defined nasal conditions of partly unknown aetiology and pathophysiology remain. The differential diagnosis of nonallergic noninfectious rhinitis is extensive. Although the percentage of patients with nonallergic noninfectious rhinitis with a known cause has increased the last decades, still about 50% of the patients with nonallergic noninfectious rhinitis has to be classified as suffering from idiopathic rhinitis (IR), or rather *e causa ignota*. Specific immunological, clinical and sometimes radiological and functional tests are required to distinguish known causes. Research to the underlying pathophysiology of IR has moved from autonomic neural dysbalans to inflammatory disorders (local allergy), the nonadrenergic noncholinergic (NANC) sensory peptidergic neural system and central neural hyperaesthesia, still without solid ground or proof. This review summarizes the currently known causes for nonallergic noninfectious rhinitis and possible treatments. Also possible pathophysiological mechanisms of IR are discussed.

**J. B. van Rijswijk^{1,2}, H. M. Blom^{1,3},
W. J. Fokkens⁴**

¹Department of Otorhinolaryngology and Head and Neck Surgery, Erasmus MC, Rotterdam;

²Department of Otorhinolaryngology, Head and Neck Surgery and Facial Plastics, Van Weel-Bethesda Hospital, Dirksland; ³Department of ENT and Paediatric ENT, Haga Hospital, The Hague;

⁴Department of Otorhinolaryngology, Amsterdam Medical Centre, Amsterdam, the Netherlands

Key words: capsaicin; idiopathic rhinitis; nasal hyperreactivity; pathophysiology; treatment.

J. B. van Rijswijk
Westzeedijk 230
3016 AN Rotterdam
the Netherlands

Accepted for publication 29 July 2005

Rhinitis is a very common disorder known to all of us. Most people suffer from an infectious viral rhinitis, or common cold, at least once a year. It generally proves to be a self-limiting disease disappearing in 1 or 2 weeks without specific treatment. This in contrast to chronic rhinitis, affecting up to 20% of the general population (1).

Chronic rhinitis can be due to common factors such as allergy, smoking or less common factors such as xylometazoline abuse or cystic fibrosis. Rhinitis means inflammation of the nasal mucosal membrane. However, markers of inflammation are not examined in routine clinical work. Therefore, the term rhinitis in daily practice is used for nasal dysfunction causing symptoms-like nasal itching, sneezing, rhinorrhea and or nasal blockage (1).

Abbreviations: CDA, cold dry air; CNS, central nervous system; CGRP, calcitonin gene-related peptide; CGRP-Li, calcitonin gene-related peptide immuno reactivity; DRC, daily record chart; IR, idiopathic rhinitis; NANC, nonadrenergic noncholinergic; NANI-PER, nonallergic noninfectious perennial rhinitis; NARES, non-allergic rhinitis with eosinophilia syndrome; NINAR, noninfectious, nonallergic rhinitis; SP, substance P; VAS, visual analogue scale; VIP, vasoactive intestinal peptide.

Rhinitis classification

Chronic rhinitis can roughly be classified into allergic, infectious or nonallergic/noninfectious (Fig. 1) (1–3). The exact figures are unknown but most ear nose and throat (ENT) clinics report a 50–50% division between allergic and nonallergic patients in perennial rhinitis (4).

Allergic rhinitis is clinically defined as a symptomatic disorder of the nose induced by an immunoglobulin E (IgE)-mediated inflammation after allergen exposure of the nasal mucosa. The diagnosis of allergy is based on diagnostic tests for allergy, like skin prick tests and or measurement of specific serum IgE. The disease is nonallergic when allergy has not been proven by proper allergy examination (history, skin prick testing, measurement of serum-specific IgE antibodies).

Rhinitis is called noninfectious when the nasal discharge is clear and watery, and not purulent. Detection of micro-organisms (viruses, bacteria, fungi) is generally not used as a diagnostic criterion.

When allergy, mechanical obstruction and infections have been excluded as the cause of rhinitis, a number of poorly defined nasal conditions of partly unknown aetiology and pathophysiology remain. The differential diagnosis of nonallergic noninfectious rhinitis is extensive

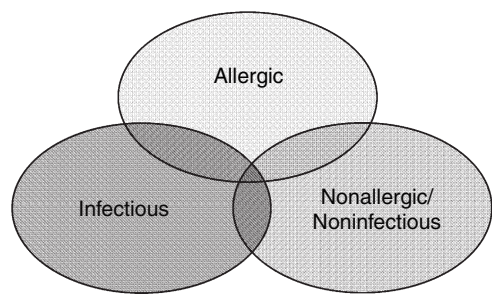


Figure 1. Schematic representation of allergic, infectious and nonallergic/noninfectious rhinitis.

Table 1. The differential diagnosis of nonallergic noninfectious rhinitis

Occupational (irritant)
Drug induced
Rhinitis medicamentosa (topical vasoconstrictive α -adrenoceptor agonists)
Other drugs
Hormonal
Rhinitis of the elderly
Nonallergic rhinitis with eosinophilia syndrome (NARES)
Smoking
Idiopathic rhinitis (e causa ignota)

(5) (Table 1). The mechanisms are only partly unravelled. If the pathophysiology is unknown, the term idiopathic rhinitis (IR) is used.

Nonallergic noninfectious perennial rhinitis

Nonallergic noninfectious perennial rhinitis (NANIPER) can be divided in disorders with known and in disorders with unknown pathology.

Occupational nonallergic rhinitis

Occupational rhinitis arises in response to an airborne agent present in the workplace. Many occupational agents are irritant and nonallergic hyper-responsiveness may occur.

Most occupational agents inducing nonallergic rhinitis are small molecular weight compounds such as isocyanates, aldehydes, ninhydrin and pharmaceutical compounds (6, 7). More than 250 different chemical entities have been identified. Although these can act as reactive haptens, nonimmunological mechanisms are common. Some compounds, like chlorine, can induce irritant rhinitis in 30–50% of the exposed workers (8, 9).

Rhinitis medicamentosa

Long-term use of topical nasal vasoconstrictors (like xylometazoline hydrochloride and other α -adrenoceptor

agonists) often results in rhinitis medicamentosa with possible histological mucosa changes and drug addiction. Rhinitis medicamentosa can be defined as a condition of nasal hyperreactivity, mucosal swelling, rebound nasal congestion and tolerance that is induced, or aggravated, by the overuse of topical vasoconstrictors with or without a preservative (10). In the Netherlands, this pathology is regularly seen in the second echelon because the over-the-counter availability of these medicines. Generally, these patients can be adequately treated by lucid exposition, vasoconstrictor withdrawal and a topical corticosteriod spray to alleviate the withdrawal process (11). After a successful vasoconstrictor withdrawal a possible remaining nasal disorder (if any) can be treated.

Other drugs inducing nonallergic rhinitis

A range of medications is known to cause nasal symptoms. angiotensin converting enzyme (ACE) inhibitors, reserpine, hydralazine, guanethidine, methyldopa, α -adrenoceptor antagonists such as prazosin and phenolomine, β -blockers, immunosuppresives, oral contraceptives, aspirin and other nonsteroidal anti-inflammatory agents have all been associated with nasal symptoms, as have intraocular ophthalmic preparations (β -blockers) (1, 12). Also psychotropic agents-like thioridazine, chlor-diazepoxide, chlorpromazine, perphenazine, amitriptyline and alprazolam can have nasal side-effects (13) (Table 2).

Hormonal rhinitis

Changes in the nose are known to occur during the menstrual cycle, puberty, pregnancy and in specific endocrine disorders such as hypothyroidism and acromegaly (14–16). Hormonal imbalance may also be

Table 2. Drugs influencing nasal function

Medicin group	Examples
Nasal vasoconstrictors	Oxymetazoline, xylometazoline, epherine
ACE inhibitors	Benazepril, captopril, cilazapril, nalapril, fosinopril, lisinopril, perindopril, ramipril, quinapril, trandolapril
Antihypertensiva	Guanfacine, reserpine, hydralazine, methyldopa, guanethidine
α -Adrenoceptor antagonists	Prazosin, phenolomine
β -Blockers (also intraocular)	Carvedilol, propranolol, sotalol, tertatolol, timolol, alprenolol, oxprenolol, pindolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, nebivolol, acebutolol, celiprolol
Oral contraceptives	
Aspirin and other NSAIDs	
Psychotropics	Chlorpromazine, thioridazine, chlordiazepoxide, amitriptyline, perphenazine, alprazolam
Immunosuppresives	Cyclosporin, mycophenolic acid

NSAIDs, nonsteroidal anti-inflammatory drugs.

responsible for the atrophic nasal change in postmenopausal women. A persistent hormonal rhinitis or rhinosinusitis may develop during pregnancy in otherwise healthy women. Its severity parallels the blood oestrogen level. The symptoms usually quickly disappear after delivery.

Rhinitis of the elderly

Rhinitis of the elderly, or senile rhinitis as it is called in the Netherlands, is a characteristic clinical picture of the elderly patient suffering from a persistent clear rhinorrhea without nasal obstruction or other nasal symptoms. Patients often complain of the classical drop on the tip of the nose. The first treatment option is intranasal ipratropium bromide (up to six times a day) generally with a good clinical result, suggesting an overactivity of the parasympathetic neural system (17, 18).

Nonallergic rhinitis with eosinophilia syndrome

The nonallergic rhinitis with eosinophilia syndrome (NARES) was originally described in 1981 by Jacobs et al. (19). He described patients with perennial nasal symptoms of sneezing paroxysms, profuse watery rhinorrhea and pruritus of the nasopharyngeal mucosa in an 'on-again-off-again' symptomatic pattern with a profound eosinophilia in the nasal smear [a nasal smear with more than 25% eosinophils (20)] and no signs of allergy as tested by skin prick testing and measurement of total and specific IgE in the nasal secretion. Trigger factors associated by the patients with the acute onset of nasal symptoms were none or unknown in 42%, weather changes in 31%, odours in 15% and noxious or irritating substances in 12%. The same sort of patient group, with perennial symptoms of nasal hyperreactivity involving sneezing, rhinorrhea, nasal obstruction, pruritus and frequent hyposmia was later described by others (21, 22). Moneret-Vautrin et al. (21) suggested that NARES is a precursor of aspirin sensitivity. Other groups were not able to find eosinophilia in their population of nonallergic rhinitis patients (23, 24). This in contrast with a recent article of Powe et al. (25) describing nasal mucosa eosinophilia in IR patients comparable with perennial allergic rhinitis patients. He suggests that NARES is a local IgE-mediated response (local allergy) which does not result in systemic Th2 responses. Although local IgE production has been made plausible already in the 1980s by Platts-Mills and others (26), the final proof came recently. It has been proven by at least two groups now that local IgE production takes place in the nasal mucosa of allergic patients (27, 28). However, it remains to be proven that the same mechanism also occurs in IR patients and whether this situation is stable over time or that these patients, like has been shown in small children, develop allergic rhinitis in due time.

The definition of NARES as a subgroup of nonallergic noninfectious rhinitis is relevant for therapy because they seem to respond well to nasal corticosteroids (29). This in contrast to some other subgroups of nonallergic noninfectious rhinitis.

Smoking rhinitis

Smoke, in particular cigarette smoke, is known for its irritative effect on the mucosa of the respiratory tract. In passive smoking nonallergic children and in smoking adults a mucosal cellular infiltration with Th2-like profile including eosinophils, increased IgE-positive cells and increased interleukin (IL)-4 is found (30–32). Because smoking results in many individuals in the same clinical picture of rhinitis with rhinorrhea and nasal obstruction it has to be viewed as a cause of rhinitis in its own right. It might even be that (part of the) NARES type of nonallergic rhinitis is caused by (passive) smoking inducing an 'allergy like' inflammatory response (30, 31, 33).

Idiopathic rhinitis

If all the possible causes are excluded, a significant part of the nonallergic noninfectious rhinitis patients group persist. Syndromes of chronic rhinitis with an unknown aetiology were formerly referred to by us as NANIPER. Other terms-like noninfectious, nonallergic rhinitis (NINAR) are also purely descriptive (34, 35).

In accordance with the 'World Health Organization Initiative, Allergic Rhinitis and its Impact on Asthma' (ARIA) (1), henceforth we will be using the term IR to describe this pathology. The IR, formerly also called vasomotor rhinitis, is a diagnosis of exclusion and is given to patients suffering from perennial nasal congestion, rhinorrhea and or sneezing with no identifiable aetiology. The IR is unrelated to allergy, infection, structural lesions, polyposis and other systemic diseases (as mentioned above).

IR, being a diagnosis per exclusionem, is solely diagnosed on patient complaints. The first question therefore may be whether this disease really exists. Occasional sneezing, rhinorrhea in the morning and upon exposure to cold and polluted air can be considered a normal nasal response. Some persons consider even slight nasal symptoms to be abnormal and seek medical advice for that reason. Inquiry about the hours with daily symptoms may help to make a distinction between a normal physiological response and disease. Also the use of a daily record card (DRC; Table 3) to score symptom duration and intensity, possibly combined with peak nasal inspiratory flow measurements, can give the doctor more insight in the severity of the disease. Marked discrepancies between description of the problem at the first visit and data from these daily measurements can be found (36).

Table 3. Design of the daily record chart for defining nasal symptoms in idiopathic rhinitis (IR) patients

Possible scores on the daily record chart	
Nasal blockage (not being able to breathe freely through the nose)	0 = absent 1 = between 0 and 1 h per half day
Clear nasal discharge (runny nose)	2 = between 1 and 2 h per half day 3 = more than 2 h per half day
Sneezing	0 = absent
Coughing	1 = <5 periods per half day 2 = between 5 and 10 periods per half day 3 = more than 10 periods per half day
Green/yellow mucus production	0 = absent 1 = present

Diagnostic criteria for idiopathic rhinitis

To exclude all known prevailing causes of chronic rhinitis one should at least take a proper history (medication, smoking in previous 6 months, occupation, etc.), adequately exclude commonly occurring inhalation allergies (skin prick test and or specific serum IgE measurement) and perform rhinoscopia anterior and nasendoscopy to exclude gross anatomical aberrations and nasal polyps.

The mucosa of the nose and sinus are contiguous and thus chronic nasal complaints can also be induced by a (accompanying) chronic sinusitis. When in doubt of a possible chronic sinusitis one should not hesitate to perform computerized tomography (CT)-scan imaging. However, if the history and the nasendoscopy lack criteria pointing at possible sinus problems, CT-scan imaging is, in our opinion, not obligatory for diagnosing IR.

Nasal complaints as a IR selection criterion

After having excluded all known causes of chronic rhinitis one is left with a group of patients with nasal complaints of unknown pathology (IR; Table 4). This means that the studied patient group is probably a melting pot of patients suffering from nasal complaints, with presumably variable pathogenesis. To study, select and define a

Table 4. Exclusion criteria for IR

Positive allergy test (specific serum IgE, skin prick test, etc.)
Smoking (in the previous 6 months)
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
Inability of the patient to stop taking medication affecting nasal function
Beneficial effect of nasal corticosteroid spray (probably NARES patient)

IR, idiopathic rhinitis; IgE, immunoglobulin E; NARES, nonallergic rhinitis with eosinophilia syndrome.

group of patients, and more, measure the effects of interventions, positive criteria are needed to make the group as homogeneous as possible. As IR is solely diagnosed on patients complaints we use (and have used in all our previous studies to IR) a DRC (Table 3) on which patients have to reach a minimum symptom score to be classified as IR patient. The minimum is set using as a basis the definition of rhinitis put forward by Mygind and Weeke (37). In affected patients, periods of nasal discharge, sneezing and/or congestion have to persist for an average of at least 1 h/day on at least 5 days during a period of 14 days.

Nasal hyperreactivity as a IR selection criterion

Various stimuli have been used to try to discriminate IR patients from normal controls. Nasal hyperreactivity to nonspecific stimuli is a common and characteristic feature of patients with chronic rhinitis. Hyperreactivity only describes the increased reactivity of the nasal mucosa to ‘nonspecific’ stimuli such as smoke, strong odours and other irritants but does not point to any cause of the disease. In addition, patients with allergic rhinitis usually complain of hyperreactivity to nonallergic stimuli, obviously as a direct result of allergic inflammation. Until now, the most common diagnostic test for measuring nasal hyperreactivity was intranasal histamine provocation (38). Histamine provocations in allergic rhinitis and asthma are proven to be a good test for hyperreactivity.

Histamine provocation, however, fails to differentiate between patients with IR and control subjects (39, 40). It has been shown that methacholine is able to discriminate IR patients with persistent rhinorrhea from controls but not IR patients with blockage as their main symptom (38). Also IR patients cannot be characterized by increased responsiveness to capsaicin provocation (41).

Cold dry air (CDA) provocation as an effective tool in quantifying the secretory response of hyperreactivity in persons susceptible to CDA was first published by the Baltimore group (39, 42). The Rotterdam group subsequently proposed a new standardized intranasal CDA provocation method, which is able to make a reasonable distinction between IR patients and controls (40). This new standardized intranasal CDA provocation resulted in increased mucus production and nasal blockage in a dose-dependent manner in patients with IR but not in control subjects; sneezing did not occur. The reproducibility, sensitivity and specificity of this CDA provocation give us a useful diagnostic tool in IR patients and the possibility to monitor treatment effect (40).

Considerations on possible pathophysiological mechanisms

In spite of trying to form a IR patient group as homogenous and uniform possible it still has to be anticipated that IR is a cumulation of different pathophysiological

entities. With the limited data available at the moment, we will speculate which pathophysiological mechanisms might play a role in IR. Whether the roles of these mechanisms are major or minor and which are important for many or few patients with IR has to be further elucidated.

Chronic inflammatory disorder

The proposed pathophysiological mechanisms for IR include a chronic inflammatory disorder of antigenic (local allergy) or neurogenic nature (43–46). A pivotal characteristic in the pathophysiological concept of inflammation is an influx of inflammatory cells in the affected tissue. In symptomatic allergic rhinitis patients, an increase of inflammatory cells has been observed in the nasal mucosa and this increase is positively correlated to nasal complaints (47–49).

In two recent nasal biopsy studies (36, 50) we did not find any significant difference for nasal mucosal lymphocytes, antigen-presenting cells, eosinophils, macrophages, monocytes, mast cells and other IgE-positive cells between IR patients and controls. This contrasts with a recent study of Powe et al. (25) who found significantly more nasal mucosa mast cells and eosinophils in a group of IR (and allergic rhinitis) patients compared with 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. (25) warranting total turbinectomy. Another explanation could be the difference in biopsy size (average surface area of 1.6 mm² in the present studies). Nasal cellular infiltrates show a focal localization 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 (two of the 65) compared with the patient group studied by Powe et al. (25). 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 corticosteroids by his or her general practitioner (51). 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 (29).

In two other studies, we failed to ascertain a relation between the number of immunocompetent cells and nasal complaints in IR patients (23, 52). 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 (23) 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 (35) or a reduction in the numbers of inflammatory cells (52).

In a placebo-controlled study, Gerth van Wijk et al. (53) did not find a therapeutic effect for capsaicin in a group of perennial allergic rhinitis patients allergic to house dust mite. The capsaicin treatment protocol in this study was identical to the one used by Blom et al. (35) showing a significant and long-term reduction of symptoms in a group of IR patients. It was speculated that allergic rhinitis was not affected by capsaicin through domination of nasal inflammation, whereas the efficacy of capsaicin in IR may be due to domination of the peptidergic system in the absence of nasal inflammation (53).

Given the above, it is our opinion that inflammatory cells do not seem to play an important role in the vast majority of IR patients.

Neurogenic mechanisms

The neural regulation of the upper airways is complex and consists of a number of interacting nervous systems. Sensory, parasympathetic and sympathetic nerves regulate epithelial, vascular and glandular processes in the nasal mucosa. The anatomically defined sensory parasympathetic and sympathetic neural systems contain heterogeneous populations of nerve fibres often containing unique combinations of neurotransmitters and neuropeptides (34, 54).

Parasympathetic/sympathetic neural dysbalans

In 1959, Malcomson (55) stated that IR was caused by an autonomic dysbalans. Normally, base line sympathetic tone provides a constant α - and β -adrenergic receptor stimulation (56). The marked α -1 predominance in nasal blood vessels leads to vasoconstriction (57). Underactivity of the sympathetic nervous system leads to nasal obstruction (58). Parasympathetic effects on blood vessels are minimal under basal conditions. Stimulation of cholinergic nerves leads to hypersecretion and dilatation of mainly resistance vessels (increase in nasal blood flow) and to some extent capacitance vessels (decrease in nasal patency). Overactivity of the parasympathetic system leads to rhinorrhea (58).

However, van Megen (59), in a group of four patients, was unable to show significant differences in α -2, α -1 and β -adrenoreceptors between controls and vasomotor rhinitis patients.

On the contrary, some data suggesting a sympathetic involvement in IR has recently been published by the Liverpool group. Although the magnitude between patients with IR and controls were small, patients with IR were found to have an abnormal nasal response compared with controls after isometric exercise (60) and after axillary pressure (61). The specificity of these findings compared with other forms of rhinitis however, has to be confirmed.

Nonadrenergic noncholinergic or peptidergic neural system

Because of extensive research in the 1970s and 1980s it was discovered that perivascular and intraepithelial nonadrenergic noncholinergic (NANC), sensory nerve fibres contain neuropeptides [including vasoactive intestinal peptide (VIP), substance P (SP), calcitonin gene-related peptide (CGRP), etc.], which were demonstrated in the nasal mucosa of various mammals including man (62, 63). The actions of these neuropeptides are limited by degradation by neutral endopeptidase (64). These neuropeptides are locally released from peptidergic neurones (antidromic release), mainly unmyelinated sensory C-fibres, in the nasal mucosa after activation by unspecific stimuli, and can be responsible for the symptoms of IR (65–67). Stimulation can be induced by inflammatory mediators-like histamine and bradykinin but also by a number of inhaled irritants-like nicotine, cigarette smoke, formaldehyde and capsaicin (68–70).

The unmyelinated sensory C-fibres or 'pain receptors' are specifically sensitive to capsaicin (8-methyl-*N*-vanillyl-6-nonenamide), the pungent agent of hot red pepper (71, 72). Nasal capsaicin provocation results in rhinorrhea, nasal blockage and sneezing (54). This sensory neural stimulation may produce these effects either through an orthodromic, central neural reflex, associated with efferent, predominantly parasympathetic, neurotransmission, and or via an antidromic, afferent, local release of neuropeptides from sensory neurones (73) (Fig. 2). Repeated applications of capsaicin, however, lead to desensitization and even degeneration of peptidergic unmyelinated sensory C-fibres (74, 75).

Therefore the hypothesis, suggested among others by Wolf (76) that a hyperactive NANC peptidergic neural system is the underlying pathophysiology in IR may offer an explanation for the beneficial effect of intranasal capsaicin with these patients.

This hypothesis was corroborated by Lacroix et al. (67), who reported an increased concentration of neuropeptides in a group of chronic IR patients, improvement of symptoms by local treatment of capsaicin giving a 50% reduction in CGRP-Li content in nasal biopsies (77), and a correlation between symptom intensity and CGRP-Li concentration in nasal mucosa (78). Several studies have been published showing a therapeutic effect in IR patients for repeated topical applications of capsaicin (79–81). In recent studies, we showed that repeated administration of capsaicin in a double-blind placebo-controlled trial led to a significant and long-term reduction of symptoms (35, 82).

However, the mechanism explaining this therapeutic effect remains for the greater part unclear. In spite of the CGRP-Li reduction found by Lacroix et al. (67) we did not find any significant difference in pan-neurogenic staining of nasal mucosa using neurofilament and synaptophysine between capsaicin- and placebo-treated

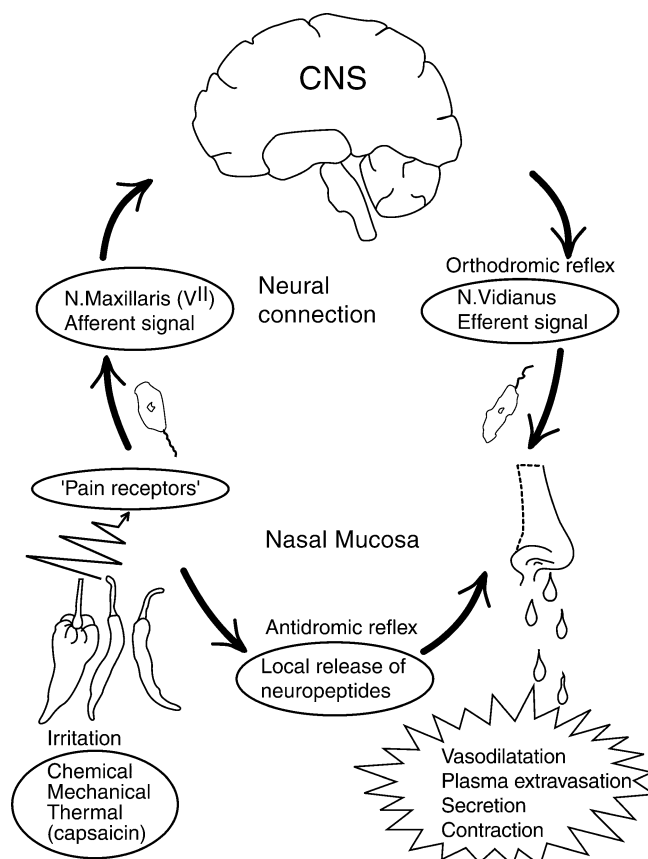


Figure 2. Simplified scheme of autonomic and peptidergic innervation of the nasal mucosa. Irritation initiates an afferent, sensory signal. After central processing this will lead to an efferent, predominantly parasympathetic signal giving rise to increased secretion and vasodilatation – the orthodromic reflex. The initial irritation also induces the local release of neuropeptides [substance P (SP), calcitonin gene-related peptide (CGRP), etc.] from sensory nerves in the nasal mucosa also resulting in increased vasodilatation, vascular permeability and secretion – the antidromic reflex.

patients 2 weeks, 3 months and 9 months after therapy although there was a significant therapeutic effect measured with visual analogue scale (VAS) (52). Also Wolf et al. (79) was unable to show a reduction of NANC-fibres in the nasal mucosa in IR patients after successful capsaicin treatment. He suggested capsaicin receptor blockage as a possible explanation for the capsaicin treatment effect. Although sounding attractive it seems improbable that capsaicin receptor blockage alone can result in the long-lasting therapeutic effect observed in IR patients.

These findings, however, do not discard the hypothesis of a hyperactive NANC peptidergic system, as the activity of this system was not measured. A functional hyperactivity of this system, not captured by histological changes, could still be the underlying pathophysiological process in IR.

Hyperesthesia or dysesthesia at the CNS level

Another possibility, raised by Sanico and Togias (34), is a hyperesthesia or dysesthesia at the central nervous system (CNS) level as an explanation for IR (Fig. 2). This would explain the lack of changes/differences in cell counts and neurogenic staining in the several studies mentioned above. According to this theory a functional or numerical downregulation of the unmyelinated peptidergic sensory C-fibres would also explain the therapeutic effect of intranasal capsaicin application (34). One might speculate that CNS hyperesthesia is induced by a vicious circle of environmental irritants and changes in atmospheric conditions, perceived as an ever irritating stimulans at the CNS level, and the protective responses hereupon-like rhinorrhea, vascular congestion and sneezing. Although sounding attractive it will be hardly impossible to prove due to the key role allocated to the CNS in this theory.

Nitric oxide synthase

Recently, Ruffoli et al. (83) reported a strong localization of nitric oxide synthase (using NADPH-diaphorase cytochemistry) in the vascular smooth muscle cells of the cavernous sinuses in seven IR patients compared with the nitric oxide synthase localization in unaffected subjects. In the present study, they hypothesize that local, antidromic neuropeptide release of sensory fibres in the nasal mucosa of IR patients could cause nitric oxide synthase induction in vascular smooth muscle cells through a cAMP-dependent mechanism, giving nasal congestion. However, no significant differences were found in endothelial nitric oxide synthase localization between IR patients and unaffected subjects. Although interesting, it is too early for definitive conclusions about a possible role for nitric oxide synthase in the pathophysiology of IR.

Treatment modalities

In general one can state that the less is known about a disease (and its underlying pathophysiology) the more treatment options there are available. This in particular counts for IR with a wide range of available therapies, surgical as well as pharmacotherapeutical, all claiming partial success. With the exception of rhinitis of the elderly where ipratropium bromid is the obvious first treatment of choice (see above), there is no obvious best treatment or first treatment to start with in nonallergic noninfectious rhinitis.

Topical or systemic sympathicomimetica

A topical sympathicomimeticum provides instant relief but only for a short period. It should not be used for more than 1 week in view of the risk for developing

rhinitis medicamentosa (see above). Considering this it only has a very limited role in the therapeutic arsenal of chronic IR. Systemic sympathicomimetica, although widely used in some countries, seem to have many considerable side-effects (84).

Topical steroids

In our view, a topical steroid aqueous spray once or twice daily, preferably combined with nasal 0.9% saline douches, is the treatment of first choice in IR (85). It should be tried for a minimum period of 6 weeks before treatment evaluation should take place, for it can take a few weeks to reach the maximum treatment effect (86, 87). Often IR patients, referred by the general practitioner to the second or third echelon because of treatment failure after short time use of a topical steroid spray, react as yet favourable to topical steroid spray using it for a longer period.

However, with the exception of NARES patients who in general respond well to a topical steroid spray (see above) we feel that for the rest of the nonallergic noninfectious rhinitis patients topical steroids often do not provide the same relief as they do in allergic rhinitis (23, 44).

Antihistamines

Sneezing as a predominant complaint in nonallergic noninfectious rhinitis is rare, but if present antihistamines can be prescribed, sometimes with good results (1). Also in the case of extreme hyperreactivity antihistamines are sometimes helpful, possibly because of a pathophysiological role for mast cell degranulation releasing histamine in these patients. Two double-blind placebo-controlled trials have been published showing a therapeutic effect for azelastine nasal spray in IR patients with nasal obstruction and or rhinorrhea (88, 89). The precise mode of action (antihistaminic, anti-inflammation, or otherwise) remains to be elucidated (90).

The older antihistamines often also have some anticholinergic action possibly contributing to the therapeutic effect.

Ipratropium bromid

Ipratropium bromid is an anticholinergic drug used mainly in the treatment of asthma. Clinical studies using this drug as a nasal spray have shown it to be effective in reducing the severity and duration of the rhinorrhea in nonallergic noninfectious rhinitis (17, 91). It is therefore the first treatment option in rhinitis of the elderly (see above).

Capsaicin

As mentioned before several studies have been published showing a therapeutic effect in IR patients for repeated

topical applications of capsaicin (79–81). In recent studies, we showed that repeated administration of capsaicin in a double-blind placebo-controlled trial led to a significant and long-term reduction of symptoms (35, 82). Although direct observations explaining the efficacy and working mechanisms of capsaicin are lacking, it is the therapy of choice in IR patients in our institutes when a minimum period of 6 weeks of treatment with a topical steroid spray has proven unbeneficial in relieving symptoms. As we have recently shown that five treatments of intranasal capsaicin on a single day at 1-h intervals (after local anaesthesia) is at least as effective as five treatments of capsaicin in 2 weeks we are now provided with a patient and doctor-friendly therapy (82). Of course, as with other therapies for IR, not all patients will be cured but a great percentage of patients (we feel approximately 75%) will show a long-lasting (more than 1 year) relieve of symptoms. When IR symptoms return after a symptom-free period upon capsaicin therapy it is very worthwhile to treat these patients (after careful examination excluding again all known causes of rhinitis) for a second (or sometimes third) time with capsaicin for the favourable reaction to capsaicin will most probably repeat itself (unpublished data). This was also reported by Wolf et al. (79).

Surgery

Most authors feel that surgical therapy should only be considered for those patients who fail to obtain symptomatic relief with medical therapy (20, 58, 85). Surgical procedures for nonallergic noninfectious rhinitis aim to either modify the size of the inferior turbinate or to denervate the nose of its autonomic supply. Turbinate reduction can be a valuable alternative when medical therapy fails. The surgical scalpel, chemical sclerosing solutions, electrocautery, cryosurgery, snake venom and laser surgery have all been reported to diminish obstruction complaints (92–96). The duration of effectiveness reported varies from 6 months to several years (57).

Golding-Wood (97, 98) described the effect of vidian neurectomy. This procedure is effective in relieving excessive secretion but not so much the obstruction. Both preganglionic parasympathetic and sympathetic fibres are interrupted. Grote (99) concluded that vidian neurectomy was not the panacea it was claimed to be, because reinnervation would occur. This was corroborated by several authors (100, 101).

Conclusion

Although the percentage of patients with nonallergic noninfectious rhinitis with a known cause has increased the last decades, still about 50% of the patients with a nonallergic noninfectious rhinitis has to be classified as suffering from IR. Specific immunological, clinical and sometimes radiological and functional tests are required to distinguish known causes. Research to the underlying pathophysiology of IR has moved from autonomic neural dysbalans to inflammatory disorders (local allergy), the NANC peptidergic neural system (with or without nitric oxide synthase induction in vascular smooth muscle cells) and central neural hyperesthesia, still without convincing solid ground or proof. It can be expected that in the next future some more explanatory pathophysiological mechanisms for nonallergic noninfectious rhinitis will be found, doing justice to the idea that the diagnosis IR is still a 'melting pot' of several pathophysiological conditions. Hopefully the future unravelling of this intriguing disease will lead to more specific and maybe better treatment options (such as IL antagonists, for example). However, recent progression has been made in the therapy of IR patients not reacting to topical steroids, with the improved and patient (and doctor) friendly treatment of five intranasal capsaicin applications on a single day at 1-h intervals (after local anaesthesia). We hope these findings will be corroborated by others in the near future.

References

1. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic Rhinitis and its Impact on Asthma (ARIA). *J Allergy Clin Immunol* 2001;**108**(5 Pt 2):S147–334.
2. Group IRMW. International Consensus Report on the diagnosis and management of rhinitis. *Allergy* 1994;**49**(Suppl. 19):S1–34.
3. Dykewicz MS, Fineman S, Skoner DP, Nicklas R, Lee R, Blessing-Moore J et al. Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. *American Academy of Allergy, Asthma, and Immunology. Ann Allergy Asthma Immunol* 1998;**81**(5 Pt 2):478–518.
4. Fokkens WJ. Thoughts on the pathophysiology of nonallergic rhinitis. *Curr Allergy Asthma Rep* 2002;**2**:203–209.
5. Bachert C. Persistent rhinitis – allergic or nonallergic? *Allergy* 2004;**59**(Suppl. 76):11–15.
6. Slavin RG. Occupational rhinitis. *Ann Allergy Asthma Immunol* 1999;**83**(6 Pt 2):597–601.
7. Saria A. Neuroimmune interactions in the airways: implications for asthma, allergy, and other inflammatory airway diseases. *Brain Behav Immun* 1988;**2**:318–321.

8. Leroyer C, Malo JL, Girard D, Dufour JG, Gautrin D. Chronic rhinitis in workers at risk of reactive airways dysfunction syndrome due to exposure to chlorine. *Occup Environ Med* 1999;**56**:334–338.
9. Shusterman D, Balmes J. Measurement of nasal irritant sensitivity to pulsed carbon dioxide: a pilot study. *Arch Environ Health* 1997;**52**:334–340.
10. Graf P. Long-term use of oxy- and xylometazoline nasal sprays induces rebound swelling, tolerance, and nasal hyperreactivity. *Rhinology* 1996;**34**:9–13.
11. Graf P. Rhinitis medicamentosa: aspects of pathophysiology and treatment. *Allergy* 1997;**52**(Suppl. 40):28–34.
12. Kaufman HS. Timolol-induced vasomotor rhinitis: a new iatrogenic syndrome [Letter]. *Arch Ophthalmol* 1986;**104**:970.
13. Mabry RL. Nasal stuffiness due to systemic medications. *Otolaryngol Head Neck Surg* 1982;**91**:93–94.
14. Incaudo G, Schatz M. Rhinosinusitis associated with endocrine conditions: hypothyroidism and pregnancy. In: Schatz M, Settipane GA, eds. *Nasal manifestations of systemic diseases*. Providence, RI, USA: Oceanside, 1991; 54.
15. Ellegard E, Karlsson G. Nasal congestion during pregnancy. *Clin Otolaryngol* 1999;**24**:307–311.
16. Navarrete-Palacios E, Hudson R, Reyes-Guerrero G, Guevara-Guzman R. Correlation between cytological characteristics of the nasal epithelium and the menstrual cycle. *Arch Otolaryngol Head Neck Surg* 2003;**129**:460–463.
17. Malmberg H, Grahne B, Holopainen E, Binder E. Ipratropium (Atrovent) in the treatment of vasomotor rhinitis of elderly patients. *Clin Otolaryngol* 1983;**8**:273–276.
18. Dockhorn R, Aaronson D, Bronsky E, Chervinsky P, Cohen R, Ehtessabian R et al. Ipratropium bromid nasal spray 0.03% and beclomethasone nasal spray alone and in combination for the treatment of rhinorrhea in perennial rhinitis. *Ann Allergy Asthma Immunol* 1999;**82**:349–359.
19. Jacobs RL, Freedman PM, Boswell RN. Nonallergic rhinitis with eosinophilia (NARES syndrome). Clinical and immunologic presentation. *J Allergy Clin Immunol* 1981;**67**:253–262.
20. Mikaelian AJ. Vasomotor rhinitis [Review]. *Ear Nose Throat J* 1989; **68**:207–210.
21. Moneret-Vautrin DA, Hsieh V, Wayoff M, Guyot JL, Mouton C, Maria Y. Nonallergic rhinitis with eosinophilia syndrome a precursor of the triad: nasal polyposis, intrinsic asthma, and intolerance to aspirin. *Ann Allergy* 1990;**64**:513–518.
22. Ingels K, Durdurez JP, Cuvelier C, Van Cauwenberge P. Nasal biopsy is superior to nasal smear for finding eosinophils in nonallergic rhinitis. *Allergy* 1997;**52**:338–341.
23. Blom HM, Godthelp T, Fokkens WF, KleinJan A, Mulder PGM, Rijntjes E. 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* 1997;**100**:739–747.
24. Numata T, Konno A, Hasegawa S, Hanazawa T, Nagata H, Motosugi H et al. Pathophysiological features of the nasal mucosa in patients with idiopathic rhinitis compared to allergic rhinitis. *Int Arch Allergy Immunol* 1999;**119**:304–313.
25. Powe DG, Huskisson RS, Carney AS, Jenkins D, Jones NS. Evidence for an inflammatory pathophysiology in idiopathic rhinitis. *Clin Exp Allergy* 2001;**31**:864–872.
26. Platts-Mills TA. Local production of IgG, IgA and IgE antibodies in grass pollen hay fever. *J Immunol* 1979; **122**:2218–2225.
27. KleinJan A, Vinke JG, Severijnen LW, Fokkens WJ. Local production and detection of (specific) IgE in nasal B-cells and plasma cells of allergic rhinitis patients. *Eur Respir J* 2000;**15**: 491–497.
28. Durham SR, Gould HJ, Thienes CP, Jacobson MR, Masuyama K, Rak S et al. Expression of epsilon germ-line gene transcripts and mRNA for the epsilon heavy chain of IgE in nasal B cells and the effects of topical corticosteroid. *Eur J Immunol* 1997;**27**:2899–2906.
29. Small P, Black M, Frenkiel S. Effects of treatment with beclomethasone dipropionate in subpopulations of perennial rhinitis patients. *J Allergy Clin Immunol* 1982;**70**:178–182.
30. Vinke JG, KleinJan A, Severijnen LW, Fokkens WJ. Passive smoking causes an 'allergic' cell infiltrate in the nasal mucosa of non-atopic children. *Int J Pediatr Otorhinolaryngol* 1999;**51**:73–81.
31. Villar MT, Holgate ST. IgE, smoking and lung function. *Clin Exp Allergy* 1995;**25**:206–209.
32. Rennard SI, Umino T, Millatmal T, Daughton DM, Manouilova LS, Ullrich FA et al. Evaluation of sub-clinical respiratory tract inflammation in heavy smokers who switch to a cigarette-like nicotine delivery device that primarily heats tobacco. *Nicotine Tob Res* 2002;**4**:467–476.
33. Bouwhuisen ECA, Dijkstra MD, Severijnen LW, KleinJan A, Fokkens WJ. Effects of cigarette smoking on nasal mucosa inflammation. *Allergologie* 1996;**19**:56.
34. Sanico A, Togias A. Noninfectious, nonallergic rhinitis (NINAR): considerations on possible mechanisms. *Am J Rhinol* 1998;**12**:65–72.
35. Blom HM, van Rijswijk JB, Garrelds IM, Mulder PG, Timmermans T, Gerth van Wijk R. Intranasal capsaicin is efficacious in non-allergic, non-infectious perennial rhinitis. A placebo-controlled study. *Clin Exp Allergy* 1997;**27**:796–801.
36. Blom HM, Godthelp T, Fokkens WJ, KleinJan A, Holm AF, Vroom TM et al. Mast cells, eosinophils and IgE-positive cells in the nasal mucosa of patients with vasomotor rhinitis. An immunohistochemical study. *Eur Arch Otorhinolaryngol Suppl* 1995;**1**:S33–39.
37. Mygind N, Weeke B. Allergic and vasomotor rhinitis: clinical aspects. Copenhagen, Denmark: Munksgaard, 1985.
38. Gerth van Wijk R, Dieges PH. Nasal reactivity to histamine and methacholine: two different forms of upper airway responsiveness. *Rhinology* 1994;**32**:119–122.
39. Togias A, Lykens K, Kagey-Sobotka A, Eggleston PA, Proud D, Lichtenstein LM et al. Studies on the relationships between sensitivity to cold, dry air, hyperosmolar solutions, and histamine in the adult nose. *Am Rev Respir Dis* 1990;**141**:1428–1433.
40. Braat JP, Mulder PG, Fokkens WJ, Gerth van Wijk R, Rijntjes E. Intranasal cold dry air is superior to histamine challenge in determining the presence and degree of nasal hyperreactivity in nonallergic noninfectious perennial rhinitis. *Am J Respir Crit Care Med* 1998;**157**(6 Pt 1):1748–1755.
41. Sanico AM, Philip G, Proud D, Naclerio RM, Togias A. Comparison of nasal mucosal responsiveness to neuronal stimulation in non-allergic and allergic rhinitis: effects of capsaicin nasal challenge. *Clin Exp Allergy* 1998;**28**:92–100.

42. Togias AG, Naclerio RM, Proud D et al. Nasal challenge with cold, dry air results in release of inflammatory mediators. Possible mast cell involvement. *J Clin Invest* 1985;**76**:1375–1381.
43. Shatkin JS, Delsupehe KG, Thisted RA, Corey JP. Mucosal allergy in the absence of systemic allergy in nasal polyposis and rhinitis: a meta-analysis. *Otolaryngol Head Neck Surg* 1994;**111**:553–556.
44. Philip G, Togias AG. Nonallergic rhinitis. Pathophysiology and models for study. *Eur Arch Otorhinolaryngol Suppl* 1995;**1**:S27–32.
45. Carney AS, Jones NS. Idiopathic rhinitis: idiopathic or not? *Clin Otolaryngol* 1996;**21**:198–202.
46. Garay R. Mechanisms of vasomotor rhinitis. *Allergy* 2004;**59**(Suppl. 76):4–10.
47. Bentley AM, Jacobson MR, Cumberworth V, Barkans JR, Moqbel R, Schwartz LB et al. Immunohistology of the nasal mucosa in seasonal allergic rhinitis: increases in activated eosinophils and epithelial mast cells. *J Allergy Clin Immunol* 1992;**89**:877–883.
48. Fokkens WJ, Holm AF, Rijntjes E, Mulder PG, Vroom TM. 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* 1990;**93**:66–72.
49. Braunstahl GJ, Overbeek SE, Fokkens WJ, KleinJan A, McEuen AR, Walls AF et al. Segmental bronchoprovocation in allergic rhinitis patients affects mast cell and basophil numbers in nasal and bronchial mucosa. *Am J Respir Crit Care Med* 2001;**164**:858–865.
50. van Rijswijk JB, Blom HM, KleinJan A, Mulder PGH, Rijntjes E, Fokkens WJ. Inflammatory cells seem not to be involved in idiopathic rhinitis. *Rhinology* 2003;**41**:25–30.
51. Lundblad L, Sipila P, Farstad T, Drozdiewicz D. Mometasone furoate nasal spray in the treatment of perennial non-allergic rhinitis: a nordic, multicenter, randomized, double-blind, placebo-controlled study. *Acta Otolaryngol* 2001;**121**:505–509.
52. Blom HM, Severijnen LA, van Rijswijk JB, Mulder PG, Gerth van Wijk R, Fokkens WJ. The long-term effects of capsaicin aqueous spray on the nasal mucosa. *Clin Exp Allergy* 1998;**28**:1351–1358.
53. Gerth Van Wijk R, Terreehorst IT, Mulder PG, Garredts IM, Blom HM, Popering S. Intranasal capsaicin is lacking therapeutic effect in perennial allergic rhinitis to house dust mite. A placebo-controlled study. *Clin Exp Allergy* 2000;**30**:1792–1798.
54. Baraniuk JN. Sensory, parasympathetic, and sympathetic neural influences in the nasal mucosa. *J Allergy Clin Immunol* 1992;**90**(6 Pt 2):1045–1050.
55. Malcomson KG. The vasomotor activities of the nasal mucous membrane. *J Laryngol* 1959;**73**:73–75.
56. Lung MA. The role of the autonomic nerves in the control of nasal circulation. *Biol Signals* 1995;**4**:179–185.
57. Kimmelman CP, Ali GH. Vasomotor rhinitis. *Otolaryngol Clin North Am* 1986;**19**:65–71.
58. Jones AS, Lancer JM. Vasomotor rhinitis [Editorial]. *Br Med J* 1987;**294**:1505–1506.
59. van Megen YJB. Neuroreceptors in nasal allergy. Nijmegen, the Netherlands: University of Nijmegen, 1989.
60. Wilde AD, Cook JA, Jones AS. The nasal response to isometric exercise in non-eosinophilic intrinsic rhinitis. *Clin Otolaryngol* 1996;**21**:84–86.
61. Wilde AD, Jones AS. The nasal response to axillary pressure. *Clin Otolaryngol* 1996;**21**:442–444.
62. Lundblad L, Lundberg JM, Brodin E, Anggard A. Origin and distribution of capsaicin-sensitive substance-P-immunoreactive nerves in the nasal mucosa. *Acta Otolaryngol* 1983;**96**:485–493.
63. Uddman R, Alumets J, Densert O, Hakansson R, Sundler F. Occurrence and distribution of VIP nerves in the nasal mucosa and the tracheobronchial wall. *Acta Otolaryngol* 1978;**85**:443–448.
64. Baraniuk JN. Neuropeptides. *Am J Rhinol* 1998;**12**:9–16.
65. Baraniuk JN, Kaliner MA. Neuropeptides and nasal secretion. *J Allergy Clin Immunol* 1990;**86**(4 Pt 2):620–627.
66. Fang SY, Shen CL. Neuropeptide innervation and neuroendocrine cells in allergic rhinitis and chronic hypertrophic rhinitis. *Clin Exp Allergy* 1998;**28**:228–232.
67. Lacroix JS, Kurt AM, Pochon N, Bretton C, Lunberg JM, Deshusses J. Neutral endopeptidase activity and concentration of sensory neuropeptide in the human nasal mucosa. *Eur Arch Otorhinolaryngol* 1995;**252**:465–468.
68. Svensson C, Andersson M, Greiff L, Persson CG. Nasal mucosal endorgan hyperresponsiveness. *Am J Rhinol* 1998;**12**:37–43.
69. Anggard A. Basic mechanisms in autonomic nervous responses in specific and nonspecific nasal hyperreactivity. *Acta Otolaryngol* 1993;**113**:394–396.
70. Sanico AM, Atsuta S, Proud D, Togias A. Dose-dependent effects of capsaicin nasal challenge: in vivo evidence of human airway neurogenic inflammation. *J Allergy Clin Immunol* 1997;**100**:632–641.
71. Jancso N, Jancso-Gabor A, Szolcsanyi J. Direct evidence of neurogenic inflammation and its prevention by denervation and pretreatment with capsaicin. *Br J Pharmacol Chemother* 1967;**31**:138–151.
72. Holzer P. Local effector functions of capsaicin sensitive nerve endings: involvement of tachykinins, calcitonin gene-related peptide and other neuropeptides. *Neuroscience* 1988;**24**:739–768.
73. Lundblad L, Saria A, Lundberg JM, Anggard A. Increased vascular permeability in rat nasal mucosa induced by substance P and stimulation of capsaicin-sensitive trigeminal neurons. *Acta Otolaryngol* 1983;**96**(5–6):479–484.
74. Holzer P. Capsaicin: cellular targets, mechanisms of action, and selectivity for thin sensory neurons. *Pharmacol Rev* 1991;**43**:143–201.
75. Kitajiri M, Kubo N, Ikeda H, Sato K, Kumazawa T. Effects of topical capsaicin on autonomic nerves in experimentally-induced nasal hypersensitivity. An immunocytochemical study. *Acta Otolaryngol Suppl* 1993;**500**:88–91.
76. Wolf G. New aspects in the pathogenesis and therapy of hyperreflexive rhinopathy. *Laryngol Rhinol Otol* (Stuttg) 1988;**67**:438–445.
77. Lacroix JS, Buvelot JM, Polla BS, Lundberg JM. Improvement of symptoms of non-allergic chronic rhinitis by local treatment with capsaicin. *Clin Exp Allergy* 1991;**21**:595–600.
78. Lacroix JS, Pochon N, Lundberg JM. Increased concentration of sensory neuropeptide in the nasal mucosa from patients with non-allergic chronic rhinitis. In: The new frontiers of otorhinolaryngology in Europe (II). Sorrento, Italy: Monduzzi Editore S.p.A., 1992:59–63.
79. Wolf G, Anderhuber W, Hauser-Kronberger C, Saria A. Treatment of nonspecific hyper-reflexory rhinopathy (vasomotor rhinitis) with capsaicin. *Laryngorhinootologie* 1995;**74**:289–293.

80. Riechelmann H, Davris S, Bader D. Treatment of perennial non-allergic rhinopathy with capsaicin. *HNO* 1993;**41**:475–479.
81. Marabini S, Ciabatti PG, Polli G, Fusco BM, Geppetti P. Beneficial effects of intranasal applications of capsaicin in patients with vasomotor rhinitis. *Eur Arch Otorhinolaryngol* 1991;**248**:191–194.
82. van Rijswijk JB, Boeke EL, Keizer JM, Mulder PGH, Blom HM, Fokkens WJ. Intranasal capsaicin reduces nasal hyperreactivity in idiopathic rhinitis: a double-blind randomised application regimen study. *Allergy* 2003;**58**:754–761.
83. Ruffoli R, Fattori B, Giambelluca MA, Soldani P, Giannessi F. Ultracytochemical localization of the NADPH-d activity in the human nasal respiratory mucosa in vasomotor rhinitis. *Laryngoscope* 2000;**110**:1361–1365.
84. Broms P, Malm L. Oral vasoconstrictors in perennial non-allergic rhinitis. *Allergy* 1982;**37**:67–74.
85. Lieberman P. Treatment update: non-allergic rhinitis. *Allergy Asthma Proc* 2001;**22**:199–202.
86. Wight RG, Jones AS, Beckingham E, Andersson B, Ek L. A double blind comparison of intranasal budesonide 400 micrograms and 800 micrograms in perennial rhinitis. *Clin Otolaryngol* 1992;**17**:354–358.
87. Scadding GK, Lund VJ, Jacques LA, Richards DH. A placebo-controlled study of fluticasone propionate aqueous nasal spray and beclomethasone dipropionate in perennial rhinitis: efficacy in allergic and non-allergic perennial rhinitis. *Clin Exp Allergy* 1995;**25**:737–743.
88. Banov CH, Lieberman P. Efficacy of azelastine nasal spray in the treatment of vasomotor (perennial nonallergic) rhinitis. *Ann Allergy Asthma Immunol* 2001;**86**:28–35.
89. Gehanno P, Deschamps E, Garay E, Baehre M, Garay RP. Vasomotor rhinitis: clinical efficacy of azelastine nasal spray in comparison with placebo. *ORL J Otorhinolaryngol Relat Spec* 2001;**63**:76–81.
90. Ciprandi G. Treatment of nonallergic perennial rhinitis. *Allergy* 2004;**59**(Suppl. 76):16–23.
91. Tan R, Corren J. Optimum treatment of rhinitis in the elderly. *Drugs Aging* 1995;**7**:168–175.
92. Jones AS, Lancer JM, Moir AA, Stevens JC. The effect of submucosal diathermy to the inferior turbinates on nasal resistance to airflow in allergic and vasomotor rhinitis. *Clin Otolaryngol* 1985;**10**:249–252.
93. McCombe AW, Cook J, Jones AS. A comparison of laser cautery and submucosal diathermy for rhinitis. *Clin Otolaryngol* 1992;**17**:297–299.
94. Moore JR, Bicknell PG. A comparison of cryosurgery and submucous diathermy in vasomotor rhinitis. *J Laryngol Otol* 1980;**94**:1411–1413.
95. al-Samarrae SM. Treatment of 'vasomotor rhinitis' by the local application of silver nitrate. *J Laryngol Otol* 1991;**105**:285–287.
96. Ibragimov GT, Rasunova AK. Treatment of patients with vasomotor rhinitis using snake venom [Russian]. *Vestn Otorinolaringol* 1987;**1**:39–41.
97. Golding-Wood PH. Vidian neurectomy and other trans-antral surgery – 1970. *Laryngoscope* 1970;**80**:1179–1189.
98. Golding-Wood PH. Vidian neurectomy: its results and complications. *Laryngoscope* 1973;**83**:1673–1683.
99. Grote JJ. The autonomic innervation of the nasal mucosa. Nijmegen, the Netherlands: University of Nijmegen, 1974.
100. Krajina Z. Critical review of vidian neurectomy [Review]. *Rhinology* 1989;**27**:271–276.
101. Krant JN, Wildervanck de Blecourt P, Dieges PH, de Heer LJ. Long-term results of vidian neurectomy. *Rhinology* 1979;**17**:231–235.