Up-date on neuro-immune mechanisms involved in allergic and non-allergic rhinitis*

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Abstract

Non-allergic rhinitis (NAR) is a common disorder, which can be defined as chronic nasal inflammation, independent of systemic IgE-mediated mechanisms. Symptoms of NAR patients mimic those of allergic rhinitis (AR) patients. However, AR patients can easily be diagnosed with skin prick test or allergen-specific IgE measurements in the serum, whereas NAR patients form a heterogeneous group and are difficult to diagnose because of an extensive list of different phenotypes, all varying in severity, underlying etiology and type of inflammation. Characterization of those phenotypes, mechanisms and management of NAR represents one of the major unmet needs in the field of allergic and non-allergic diseases. This review aims at providing a comprehensive overview of the state of the art in classifying the NAR patients and focuses on the neuro-immune mechanisms involved in allergic and non-allergic rhinitis, including reflections on the pathophysiology and the currently available treatment options.

Key words: non-allergic rhinitis, idiopathic rhinitis, capsaicin, neuro-immune mechanisms, nasal hyperreactivity, treatment, pathophysiology

Introduction

Chronic rhinitis represents a common condition affecting up to 30% of the Western population [1,2]. Patients with persistent rhinitis form a heterogeneous group when it comes to severity of symptoms, underlying etiology and inflammation [2]. In an attempt to take into consideration the pathophysiological mechanisms, rhinitis can be classified simplistically into allergic rhinitis, infectious rhinitis and non-allergic non-infectious rhinitis, comprising a large group with rhinitis of known and unknown origin. Indeed, up to 50% of patients with non-allergic non-infectious rhinitis do not have a clear etiology underlying their symptoms and are defined as idiopathic rhinitis (IR). In addition, combined phenotypes may occur, referred to as 'mixed' rhinitis [3]. According to the ARIA document, terms like 'vasomotor rhinitis' should be replaced by IR, as vasomotor mechanisms are ill defined and not always involved in this disease.

The definition of IR in a subgroup of non-allergic non-infectious rhinitis is largely based on exclusion criteria, i.e. the absence of clinical signs of infection and sensitization to inhalant allergens demonstrated by skin prick test (SPT) results or blood analysis of allergen-specific IgE. Symptoms of IR include nasal secretions, nasal obstruction, sneezing and nasal itching, and therefore mimic allergic rhinitis (AR). However, the majority of these patients do not respond well to anti-allergic treatment. Research on the underlying pathophysiology of IR has moved from autonomic neural disbalance with involvement of the unmyelinated sensory C-fibers containing various neuropeptides to a local inflammatory disorder with inflammation limited to the nasal mucosa with local IgE but without positive SPT and allergen-specific IgE in the blood, called 'entopy'. So far, entopy can only be demonstrated either by measuring allergen-specific IgE in the nasal cavity or by performing specific allergen provocations [4]. A subgroup of patients (30%) with persistent rhinitis symptoms and negative SPT and blood analysis, showed a positive nasal response to specific allergen provocation.

This review aims at providing a comprehensive overview of the state of the art in neuro-immune mechanisms involved in allergic and non-allergic rhinitis, including reflections on the pathophysiology and the currently available treatment options.

Rhinitis classification

Chronic rhinitis can clinically be classified into allergic, infectious and non-allergic non-infectious rhinitis [2].

The diagnosis of allergic rhinitis is based on clinical symptoms with suspicion of allergy in combination with a positive skin prick test result or the presence of allergen-specific IgE in the serum. Rhinitis is defined as infectious rhinitis on a clinical base, i.e. when the nasal discharge is discolored and/or purulent. Microbiological detection of microorganisms is not mandatory for a diagnosis of infectious rhinitis. Infectious rhinitis is discriminated from rhinosinusitis (RS) on the basis of typical clinical features of RS like headache, facial pain, smell disorder on the one hand and mucosal pathology at the level of the osteomeatal unit on the other hand [5].

The differential diagnosis of non-allergic non-infectious rhinitis is extensive, including non-allergic rhinitis with eosinophilia syndrome (NARES), also known as local allergy, rhinitis of the elderly, occupational rhinitis, drug induced rhinitis and hormonal rhinitis [6,7] (Table 1). The NARES group probably represents those patients with an allergen-specific immune response confined to the nasal mucosa and negative SPT [6,8]. The term 'entopy' has been proposed by Powe et al., to describe local allergy in individuals that are considered to be non-allergic [9]. The concept of local allergy in IR patients is both intriguing and controversial [10]. Some studies have demonstrated the presence of allergen-specific IgE in the nose [9], a positive nasal allergen provocation test (NAPT) [4] and inflammatory cells in a subset of IR patients [11]. Other studies do not confirm the involvement of inflammatory cells [12] or the presence of a positive NAPT [13]. These seemingly conflicting observations may be the result of differences in nasal challenge techniques and more likely patient selection criteria. Whatsoever, Rondon et al., [4] suggest that 35% of IR patients with a positive NAPT result have evidence of localized nasal specific IgE. Similar percentages are reported by Powe et al. [9], demonstrating that 30% of IR patients have evidence of local allergy. As a consequence, approximately 70% of IR patients may present with symptoms originating from other mechanisms than allergen-driven initiation of an inflammatory cascade.

So far, IR remains a diagnosis per exclusionem in patients with mucosal nasal symptoms for which no explanation can be found. Clinical examination with rhinoscopia anterior and nasal endoscopy does not allow the discrimination between the different forms of non-allergic, non-infectious rhinitis.

Nasal hyperreactivity

Nasal hyperreactivity to various nonspecific stimuli like smoke, strong odours and other irritants is a common and characteristic feature of patients with persistent rhinitis, irrespective of an infectious, allergic or other etiology [14].
Patients with allergic rhinitis usually complain of airway hyperreactivity to non-allergic stimuli both in upper as well as lower airways, generally considered to be a direct result of allergic airway inflammation [15]. Histologically, nasal hyperreactivity in AR has been shown to be associated with hyperinnervation of the nasal mucosa with increased expression of the neuropeptides calcitonin gene related peptide (CGRP) and Substance P (SP) in periglandular nerve fibers (a sign of neuronal hyperactivity) [16]. Interestingly, AR and IR patients show the same level of mucosal hyperinnervation, suggesting a neuro-inflammatory involvement in both inflammatory nasal conditions. In a study of Braat et al. on pollutional and meteorological factors, IR patients seemed to be more sensitive to minor fluctuations in weather conditions compared to controls [17]. In contrast to cold temperatures, humidity or humidity changes was surprisingly less important in the induction of nasal symptoms [17].

Until recently, the most common diagnostic test for measuring nasal hyperreactivity was the nasal histamine provocation, similar to the routinely performed bronchial histamine challenge for evaluation of bronchial hyperreactivity [18]. During nasal histamine provocation, increasing doses of histamine (0.125, 0.25, 0.5, 1, 2 and 4 mg/ml) are applied on the nasal mucosa and measurements of nasal cross-sectional diameter or flow start after 1 minute of provocation and continue for 4 minutes. In addition to nasal histamine provocation, Cold Dry Air (CDA) nasal provocation has proven to be an effective tool in quantifying nasal hyperreactivity [19]. In 1998, Van Rijswijk et al. demonstrated that CDA provocations were superior to nasal histamine provocations in discriminating IR patients from healthy controls [18]. Sensitivity for CDA was 87% compared with 100% for histamine, but, specificity was 71% for CDA and 0% for histamine. However, more studies on CDA nasal provocation studies are warranted in order to confirm the validity of this technique and elaborate it as a novel diagnostic tool in rhinology clinic. At present, there is no commercially available CDA device that can be used in clinical practice or for experimental purposes, and the reported studies on CDA have utilized home-made devices. There is now growing consensus about the usefulness of such a technique in daily practice, as nasal hyperreactivity often remains undiagnosed and cannot be taken into account in clinical trials evaluating the effects of current treatments of rhinitis.

Innervation of the nasal mucosa

Neural regulation in the upper airways is maintained by the sympathetic (adrenergic) and the parasympathetic (cholinergic) ner-

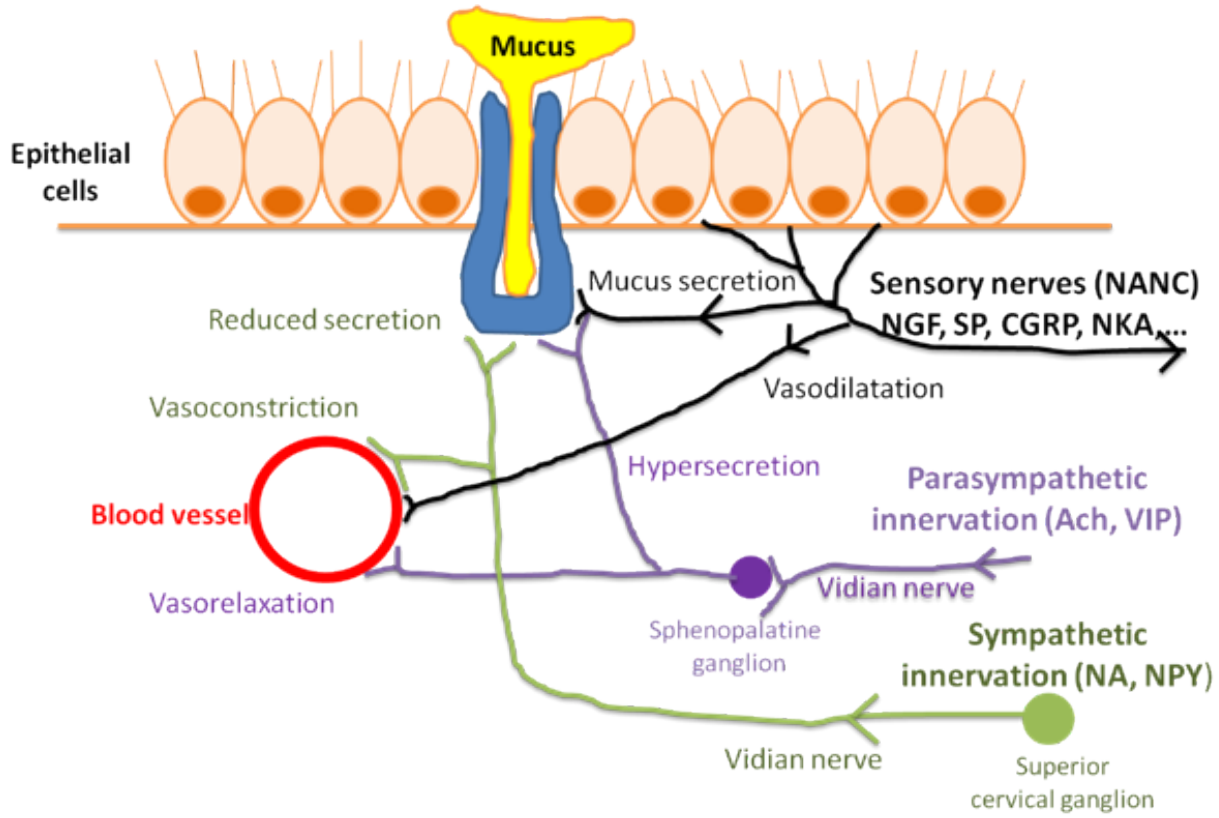

Figure 1. Innervation of the nasal mucosa.

vous systems (Figure 1), which innervate and interact in the nasal mucosa to regulate epithelial, vascular and glandular processes in particular. The sympathetic nerve fibers innervate mainly the vascular structures and to a lesser extent the secretory glands, where they release norepinephrine and neuropeptide Y (NPY) to cause predominantly vasoconstriction and a decrease in nasal secretion [20,21]. Parasympathetic fibers innervate both the blood vessels and the exocrine (seromucous and serous) glands of the nasal mucosa, of which glands appear to be more densely innervated. Those nerve fibers release predominantly acetylcholine and neuropeptide transmitters such as vasoactive intestinal peptide (VIP), which increase nasal secretion and induce vasorelaxation leading to nasal congestion under extreme conditions [22]. VIP mainly acts through VPAC1 and VPAC2 receptors leading to glandular secretion. Under normal conditions the sympathetic nervous system is dominant ensuring vascular tone.

Several decades ago, the presence of intraepithelial and perivascular nonadrenergic noncholinergic (NANC) sensory nerve fibers was demonstrated in the human nasal mucosa [23]. These mainly unmyelinated sensory C-fibers contain various neuropeptides including Substance P (SP) [24], calcitonin gene related peptide (CGRP) [25], neurokinin A and B (NKA and NKB) [24] which can be released by unspecific stimuli. In conjunction with the parasympathetic neurons, sensory (NANC) nerves play an essential role in protective nasal clearing reflexes such as sneezing, mucus production and congestion in response to noxious stimuli. These sensory neurons are receiving increasing attention as they are abundantly present and considered to be responsible for the release of neuropeptides in IR [26], murine naso-bronchial [15] and human naso-ocular [2] interactions in allergic airway disease.

Neuro-immune interactions in AR

At present, the pathophysiology of allergic rhinitis is well known from an immunologic point of view. After binding of allergens to the allergen-specific IgE molecules on the surface of resident mast cells in the nasal mucosa and cross-linking of the Fcε-receptor I, mast cells degranulate and release a wide array of pro-inflammatory mediators in sensitized individuals. Mediators like histamine, proteases, prostaglandin (PG)-D2 and leukotriens (LT)-C4 initiate an immune reaction that causes an early and late immune reaction with attraction of granulocytes like eosinophils to the location of allergen deposition. Activated mast cells and other cells of the immune system release pro-inflammatory mediators such as interleukin (IL)-1, IL-4, IL-5, tumor necrosis factor (TNF)-α and interferon (INF)-γ, which all contribute to the inflammatory spectrum of AR. In addition to these immune mediators, neurogenic peptides are also involved in this process (Figure 2). Inflammatory mediators stimulate the afferent sensory nerve

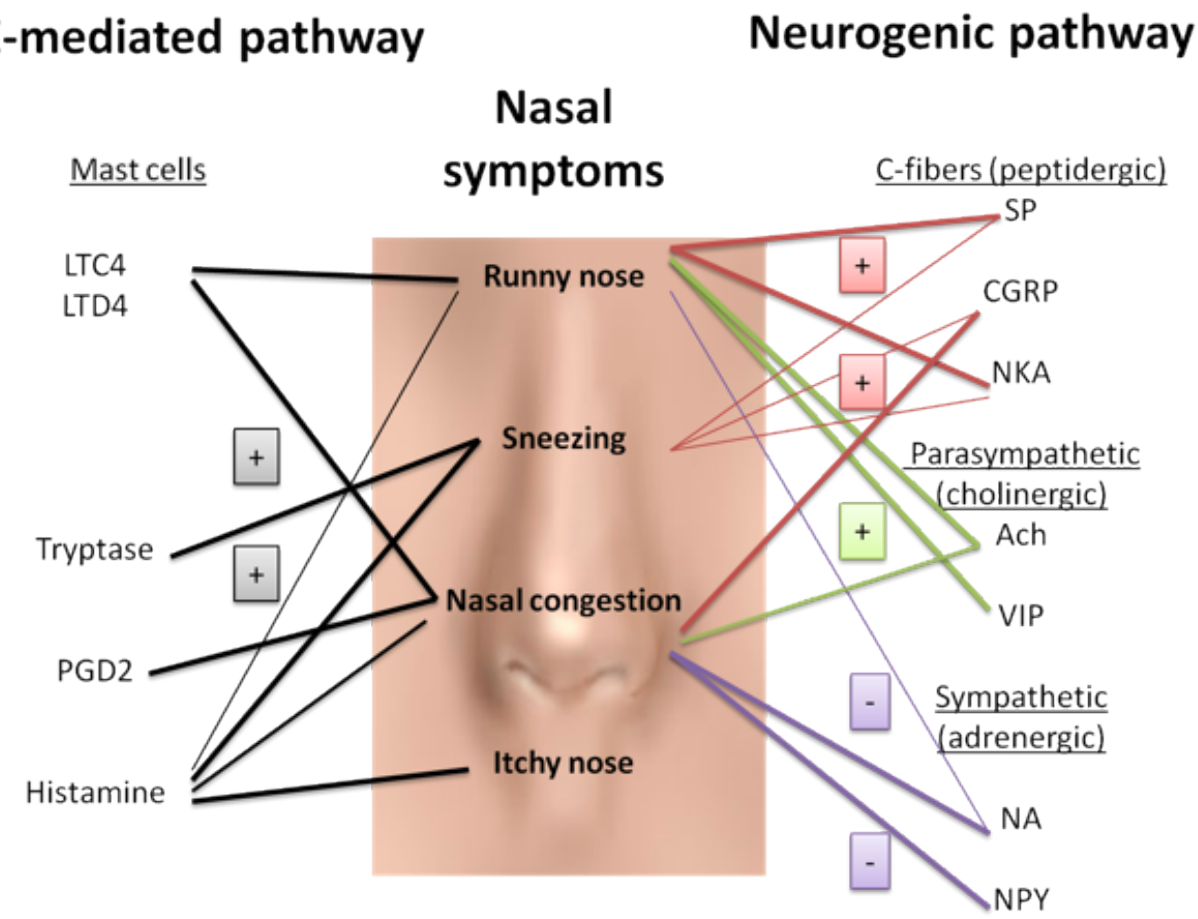

Figure 2. Pathways inducing nasal symptoms.

endings in the nasal mucosa. Activated nerve endings release neurotrophins (nerve growth factor (NGF), brain derived growth factor (BDGF) and different neuropeptides, like SP, NKA and NKB and CGRP [27]. SP and NKA/B are also called 'tachykinins'. Tachykinins are inactivated by endopeptidases (type 24.11) present in several nasal tissue cells [28,29].

Neurotrophins were initially known for their primary activity, i.e. the growth of peripheral and central nerves. In the mean time, it has become evident that neurotrophins have a variety of immunomodulatory effects on non-neuronal cells including eosinophils and mast cells (neurotrophin receptors present: trkA-C and p75), which also produce neurotrophins (neuronal feedback mechanisms) [30,31]. NGF also targets nociceptive fibers leading to increased SP content and dendrite sprouting. Increased levels of NGF have been reported both in serum as well as in nasal lavage fluid of allergic individuals [32]. Interestingly, nasal allergen provocation further up-regulated increased NGF in nasal lavage in atopic patients, but not in controls. Additionally, nasal BDNF expression was significantly increased after allergen provocation in AR [33].

The neuropeptides SP and NKA are both released by afferent nerves upon activation, and bind their NK1 and NK2 receptor respectively, present on epithelial and endothelial cells. Activation of these receptors results in glandular activation, leukocyte recruitment and activation of different immune cells. CGRP release results in vasodilatation upon binding to its receptor on endothelial cells. Besides stimulated afferent nerves, different studies have demonstrated that immune cells like eosinophils, neutrophils and dendritic cells are also a source of tachykinins such as SP [34]. Mast cells are not a source of SP, but express the NK1 receptor. Forsythe et al. demonstrated neuroimmune-interaction within the human lung [35]. The activation of mast cells, eosinophils, sensory nerve endings and epithelial cells is responsible for the entire spectrum of symptoms, characteristic for AR (Figure 3). Okamoto et al. showed that SP upregulates mRNA for the pro-inflammatory cytokines IL-1β, IL-3, IL-5, IL-6, TNF-α and IFN-α in the human nasal mucosa, which is an additional stimulus to allergic inflammation [36]. The long-term effects of SP on human mast cell expression of the Fcε-receptor I was investigated by McCary et al., who showed a SP-mediated downregulation of receptor expression [37].

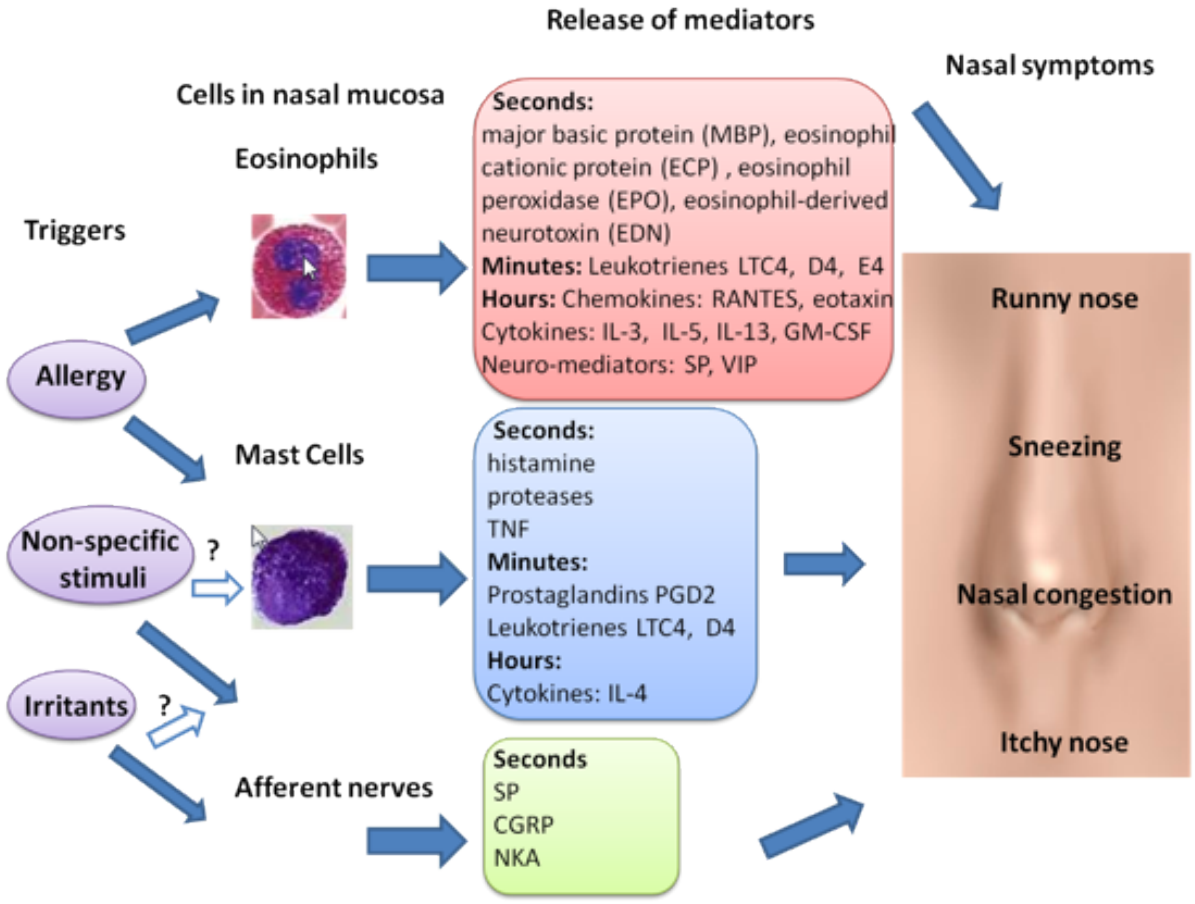

Figure 3. Triggers and cells involved in inducing rhinological symptoms in AR and IR patients.

Few reports examined the effects of anti-allergic agents on neuropeptides. Shinoda et al., showed a decrease in SP concentration in nasal lavage fluid in allergic patients with seasonal rhinitis after intake of oral antihistamines [38]. Recently, Schäper et al., showed significantly lower baseline levels of SP after intranasal Fluticasone propionate treatment (14 days treatment) in nasal lavage fluid of patients with persistent allergic rhinitis [39]. This effect was accompanied by an improvement in the clinical symptoms. Different mechanisms were proposed to contribute to this decreased release of neuropeptides caused by intranasal steroids. Corticosteroids can down-regulate tachykinin receptors and neuropeptides synthesis in neurons and in other immune cells [40]. Additionally, corticosteroids are able to up-regulate the synthesis of neuropeptide-degrading enzymes (endopeptidases type 24.11) [41]. Besides the neuropeptides, other short amino acid peptides like endothelins (21 amino acids) can play a role in the induction of symptoms in AR since the expression of endothelins is enhanced in glands and inflammatory cells in chronic inflammation and endothelin-1 induces the secretion of pro-inflammatory mediators in human nasal mucosa. However, more studies are needed in order to determine the real importance of this endothelin cascade in nasal inflammation [42].

Neuro-immune interactions in IR

As the name suggests, the etiology of IR remains largely unknown. Several mechanisms have been postulated to explain the pathophysiology of IR. The two most plausible hypotheses are non-IgE- mediated inflammatory responses and/or neurogenic responses.

Inconsistent data have been published on the non-IgE-mediated inflammatory responses as mentioned before. Powe et al., demonstrated an increased number of epithelial activated mast cells, increased mucosal eosinophils and increased IgE^+ cells in the nasal airways of IR patients [11], which could not be confirmed by the groups of Van Rijswijk and Blom et al., [12,43]. The major difficulty in comparing the few studies published on this topic is the inconsistency in defining this patient group. NARES patients for example were not excluded in Powe's study and can explain the discrepancy between reports.
Recently, more evidence for neurogenic mechanisms involved in IR was obtained. Activation of the sensory C-fibers of peptidergic neurons can lead to local release of neuropeptides (antidromic release) in the human nasal mucosa and thus can primarily trigger symptoms of IR, similar to AR (Figure 2). This

Table 1. Differential diagnosis of non-allergic non-infectious rhinitis.

Nonallergic rhinitis with eosinophilia syndrome (NARES) / Local Allergy
Drug induced rhinitis
Hormonal rhinitis
Rhinitis of the elderly
Occupational rhinitis
Idiopathic rhinitis (e causa ignota)

hypothesis was corroborated by Lacroix et al., who reported an increased concentration of neuropeptides in a group of IR patients [44]. Similarly, Heppt et al., demonstrated a denser innervation of SP-containing sensory nerves in the nasal mucosa of IR patients [45]. Similar observations are reported in occupational rhinitis and drug induced rhinitis [46]. In some forms of drug induced rhinitis, neurogenic mechanisms have been proposed to play a crucial role [47]. For example, drugs such as guanethidine and methyldopa, principally sympatholytic agents, elicit their effects by down-regulation of the sympathetic nervous system, leading inevitably to symptoms of nasal congestion [47].

Current treatment options for IR

Intranasal corticosteroids (INS)

Today, as recommended by current guidelines, almost all patients with severe persistent rhinitis, independent of the underlying pathophysiology, are initially treated with intranasal corticosteroids (INS) [48]. Due to their potent anti-inflammatory potential, INS have a good clinical efficacy in nasal inflammation. However, clinicians will agree that not all patients with IR benefit from INS. Indeed, inconsistent results have been reported on the efficacy of INS in the treatment of IR patients, suggesting that inflammation may not be an important underlying mechanism in all patients. In studies showing a favorable effect of INS in IR patients [49], NARES patients/patients with local IgE were not excluded, possibly explaining their positive results. In contrast, Blom et al., showed only limited or no benefit of INS in IR [50].

Antihistamines

Two double-blind placebo-controlled trials have been published showing a therapeutic effect of azelastine nasal spray in IR patients with nasal obstruction and or rhinorrhea when treated for 15 or 21 days [51,52]. In spite of their efficacy, the precise mode of action remains to be elucidated. The older antihistamines often have some anticholinergic side effects possibly contributing to the therapeutic effect.

Ipratropium bromide

Ipratropium bromide (IB) is an anticholinergic drug, effective in reducing the severity and duration of the rhinorrhoea in IR [53]. IB is considered a safe molecule and is recommended for use in the elderly with bilateral nasal secretions as presenting symptom and without other endonasal pathology.

Nasal application of botulinum toxin A (BTA)

Nasal hypersecretion due to IR can often not be treated sufficiently by conventional medication [50]. In a placebo-controlled study, Rohrbach et al. showed that BTA applied with a sponge brought subjective long-lasting reduction of hypersecretion in 46% of the patients with therapy-resistant IR [54]. The fact that not all patients treated reported a subjective improvement, can be explained by the knowledge that acetylcholine does not play a major role in all patients with nasal hypersecretion. Baraniuk et al. postulated that BTA also influenced other neuropeptides in nasal secretion [26], explaining the observed reduction of nasal secretion by BTA in some of the ipratropium bromide resistant patients [25].

Capsaicin (Table 2, table of all published data)

Since 1991, several studies have demonstrated that repeated nasal applications of capsaicin have a therapeutic effect in 70% - 80% of IR patients [55-57]. Most studies reported a long-lasting relief of symptoms ranging from 6 to 9 months [43]. Capsaicin, the pungent ingredient of the plants of the genus Capsicum is known for its ability to activate/desensitize a specific subset of primary sensory C- and A-δ fibers [58]. Recently, Davies et al., showed that capsaicin can initiate TRPV1-dependent cell death in neuron-like cells [59]. This finding of an apoptosis-like process triggered by capsaicin can explain the long-lasting effects of capsaicin treatment in IR patients. Capsaicin binds the TRPV1 receptor, also known as 'pain receptor,' present on these C-fibers. TRPV1 is part of the superfamily of transient receptor potential (TRP) cation channels. TRPV1 is highly selective for capsaicin and other vanilloid-like compounds. In addition, TRPV1 is activated by acidic pH and temperatures > 42°C [60]. This intriguing receptor family appears to respond to an amazing variety of environmental stimuli, including noxious irritants, environmental pollutants and temperature. Activation of TRPV1 by capsaicin can cause release of neuropeptides (antidromic release) and subsequently rhinorrhea, nasal

Table 2. Literature on capsaicin and idiopathic rhinitis.

Study: Capsaicin - IR	Publication	Subject	Conclusions
1. Lacroix et al.	Clinical and Experimental Allergy, 1991	Improvement of symptoms of non-allergic chronic rhinitis by local treatment with capsaicin.	- Capsaicin nasal spray is an effective treatment for IR patients
2. Riechelmann et al.	HNO, 1993 (in German)	Treatment of perennial non-allergic rhinopathy with capsaicin.	- Capsaicin is an effective treatment for IR patients
3. Blom et al.	Clinical and Experimental Allergy, 1997	Intranasal capsaicin is efficacious in non-allergic, non-infectious rhinitis. A placebo controlled study.	- Capsaicin has no effect on inflammatory mediators - Inflammatory cells do not play a major role in the pathogenesis of NANIPER
4. Sanico et al.	Clinical and Experimental Allergy, 1998	Comparison of nasal mucosa responsiveness to neural stimulation in NAR and AR: effects of capsaicin nasal challenge.	- Non-allergic rhinitis is not characterized by increased responsiveness of capsaicin-sensitive nerve fibres; while allergic rhinitis is marked by hyperresponsiveness manifested as increased albumin leakage in nasal fluids.
5. Blom et al.	Clinical and Experimental Allergy, 1998	The long-term effects of capsaicin aqueous spray on the nasal mucosa	- Capsaicin significantly improves nasal symptomatology in NANIPER patients without affecting cellular homeostasis or overall neurogenic staining
6. Van Rijswijk et al.	Allergy, 2003	Intranasal capsaicin reduces nasal hyperreactivity in IR: a double-blind randomized application regimen study.	- Intranasal capsaicin is safe - 5 applications on 1 day is as effective as 5 treatments in 2 weeks
7. Ciabatti et al.	Acta Oto-Laryngologica, 2009	Intranasal Capsicum spray in IR: a randomized prospective application regimen trial.	- Local capsicum oleous nasal spray reduces the frequency of IR symptoms vs controls. - No side effects were recorded

blockage and sneezing (Figure 2). This initial aggravation of nasal complaints is indeed reported by patients receiving nasal capsaicin application.

The hypothesis that hyperreactivity of the sensory, unmyelinated C-fibers is the underlying pathophysiology in IR can offer an explanation for the beneficial effect of this treatment. Lacroix et al., reported an increased concentration of neuropeptides in a group of IR patients, which support this hypothesis [44]. However, Blom et al., could not find reduction of those sensory C-fibers in the nasal mucosa in IR patients after successful capsaicin treatment [43].

In placebo-controlled studies, no therapeutic effect for capsaicin was found in patients with house dust mite AR patients [61,61]. This observation indirectly supports the idea that neurogenic inflammation is secondary to the IgE-mediated pathway in AR, whereas the efficacy of capsaicin in IR may be due to predominance or dysfunction of the peptidergic system in the absence of nasal inflammation.

Until know, no further research has been done on TRPV1 receptors on other structures of the nasal mucosa. Mast cells and epithelial cells in the skin of prurigo nodularis patients express TRPV1 suggesting that capsaicin is not solely interacting with sensory nerve fibers and thus other mechanism of action may be involved [63]. Better insight in the mechanism of action of capsaicin is mandatory to develop more specific and more potent agents to treat.

Conclusion

At present, we are still at the beginning of understanding the heterogeneity of the different pathophysiological mechanisms involved in NAR. The neural mechanisms involved in NAR and AR have been an underappreciated area of research so far. Understanding the role of neuropeptides is mandatory for the elaboration of novel treatment options. Following the currently available treatments for NAR, new therapeutic approaches consist of the development of substances that intervene in the neurogenic inflammatory processes and inhibit the synthesis/release of neuropeptides.

Conflict of interest

None

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