

REVIEW

Mechanisms and mediators of nasal symptoms in non-allergic rhinitis

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Clinical and Experimental Allergy

Summary

Non-allergic rhinitis may be a contributing factor in up to 60% of rhinitis patients and a sole contributor in a quarter. It is a highly heterogeneous condition with poorly understood pathophysiological mechanisms. Compelling evidence is emerging of a localized nasal mucosal allergic response in some non-allergic rhinitic subjects in the absence of systemic atopy. While the inflammatory disease pathway in non-allergic rhinitis may share some of the features of its allergic counterpart, overall the mechanisms remain unclear, and there are likely to be differences. In particular, symptoms of nasal congestion and rhinorrhoea tend to be more prominent and persistent in non-allergic rhinitic patients compared with allergic rhinitis. Our aim is to review the literature relating to mechanisms and mediators of nasal symptoms in non-allergic rhinitis. Better understanding of the underlying pathophysiological basis should enable the development of more accurate testing, and better targeted therapeutic options in the future.

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Introduction

Rhinitis represents a global health problem affecting between 10% and 25% of the world population. The impact of the disease is often under-appreciated with afflicted patients having a significantly impaired quality of life (QOL). Furthermore, the disease has a profound socio-economic impact with direct medical costs, and considerable indirect costs relating both to absence from work and schools, and reduced productivity. The current classification system is based on the recent document on allergic rhinitis and its impact on asthma (ARIA) [1]. Based on the presence or absence of IgE, two broad categories are recognized: an allergic form comprising individuals with an allergy to an identifiable allergen; and a non-allergic group comprising a heterogeneous collection of subjects, some with a known cause and others with an unknown aetiology. It is thought that non-allergic rhinitis may account for up to 25% of all rhinitis patients and constitute a contributing factor in up to 60% [2–4], yet little is known about its pathophysiology till the present day. Epidemiological studies have indicated that it is more common in women than men, and that its disease severity with respect to nasal blockage and rhinorrhoea, is at least

as severe as in allergic rhinitis [4]. Compared with its allergic counterpart, few research studies have so far been undertaken in non-allergic rhinitis and as such this disease entity remains poorly defined. Various factors have contributed to this state of affairs. The heterogeneous nature of the non-allergic group has certainly led to confusion regarding its classification. Furthermore, the absence of specific laboratory tests result in the diagnosis being made through a process of exclusion, based on subjective clinical symptoms with no independent means of confirmation. Consequently, this disease is a poorly understood pathophysiological entity, comprising a very heterogeneous group of conditions in patients with a spectrum of different underlying aetiologies and disease pathways. Terminological inconsistencies have certainly impacted negatively on research efforts in this area, particularly in view of the difficulty in ensuring the comparability of patient study groups, and ultimately the validity of reported findings.

By definition, non-allergic subjects are skin prick test negative. A classification system for the non-allergic rhinitis group is shown in Table 1. Another system proposed by Settupane and Lieberman (Table 2) was based on immunological/nasal cytological features and on

aetiology/systemic disease association [5]. Various terms have been coined to further qualify non-allergic rhinitis including non-infectious non-allergic rhinitis (NINAR), non-allergic non-infective perennial eosinophilic rhinitis (NANIPER), non-allergic rhinitis with eosinophilic syndrome (NARES), idiopathic and intrinsic rhinitis [6, 7]. Both NANIPER and NARES conditions are characterized by eosinophilia, and thus the distinction between NARES and NANIPER is probably an artificial one, particularly as neither has a known aetiology and would thus be classified as idiopathic/intrinsic rhinitis. Even more confusion exists concerning the vasomotor rhinitis sub-division of non-allergic rhinitis as it has been used synonymously to encompass all forms of non-allergic rhinitis including idiopathic rhinitis (IR). Autonomic rhinitis is probably a better term as it implies a neurogenic dysfunction. A number of mechanisms have been proposed, including an imbalance between the nasal sympathetic and parasympathetic systems, based on the appreciation that the nasal response to stimuli such as isometric exercise [8], and head submersion (the diving reflex) [9] is different between subjects with vasomotor rhinitis and healthy con-

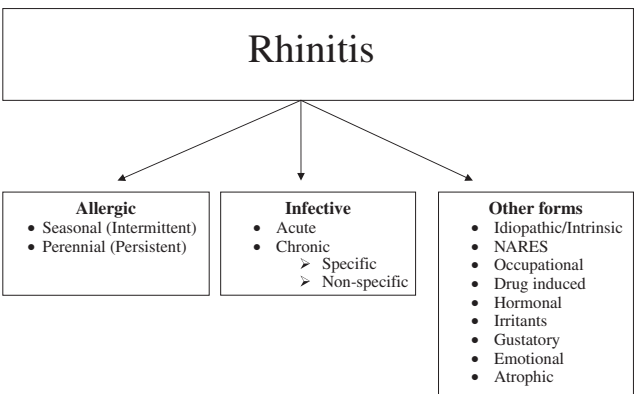
trols. Thus while aetiological mechanisms have been identified for some forms of non-allergic rhinitis e.g. (hormonal, gustatory, etc.), in many others the cause remains unknown. This latter group is defined as having idiopathic/intrinsic rhinitis encompassing a heterogeneous disease category, which by definition, does not exhibit systemic atopy and lack an IgE-mediated aetiology. This definition can be further qualified by exclusion of acute viral and bacterial infective causes.

Physiological basis of rhinitic symptoms

Nasal blockage and rhinorrhoea are very common and troublesome complaints associated with rhinitis. Furthermore, QOL evaluation has clearly shown a significant impact of rhinitis on well-being beyond the presence of nasal symptoms. An appreciation of the underlying mechanisms of nasal symptoms in non-allergic rhinitis is dependent upon an understanding of the normal nasal neurovascular anatomy and physiology.

The nasal vascular anatomy is complex with both resistance and capacitance vessels (Fig. 1). The resistance vessels are predominantly small arteries, arterioles and arteriovenous anastomoses. Blood flow to the nasal mucosa is regulated by constriction and dilatation of these vessels [10]. This is under sympathetic control, with stimulation inducing vasoconstriction with a reduction in nasal mucosal blood flow [11]. Arterial blood reaches the venous drainage system either via superficial capillaries or via arteriovenous anastomoses. The venous system is composed of a labyrinth of valveless venous sinusoids within the lamina propria, particularly prominent within the nasal turbinates [12]. Vascular congestion of the venous sinusoids results in engorgement of the turbinates and an increase in nasal airways resistance with a consequent reduction in nasal airflow. The venous engorgement is under sympathetic regulation and is determined by the tone of the arteriolar, arteriovenous anastomotic and muscular venous draining vessels. An

Table 1. Classification of rhinitis



NARES, non-allergic rhinitis with eosinophilic syndrome.

Table 2. Classification of non-allergic rhinitis based on immunological and cytological features

Perennial non-allergic rhinitis (inflammatory)	Non-inflammatory non-allergic rhinitis	Structurally related rhinitis
Eosinophilic nasal diseases	Rhinitis medicamentosa	Anatomical (septal deviation, turbinate deformity, nasal valve dysfunction)
Basophilic/metachromatic nasal disease	Reflex-induced rhinitis (bright light or other physical modalities)	Benign and malignant tumours
Infectious	Vasomotor rhinitis	Miscellaneous (choanal atresia/stenosis, trauma, foreign body, cleft palate, adenoid hypertrophy)
Nasal polyps	Irritant rhinitis	
Atrophic rhinitis	Cold air rhinitis	
Immunological disease	Gustatory rhinitis	
	Atrophic rhinitis	
	Metabolic (hormonal or thyroid related)	

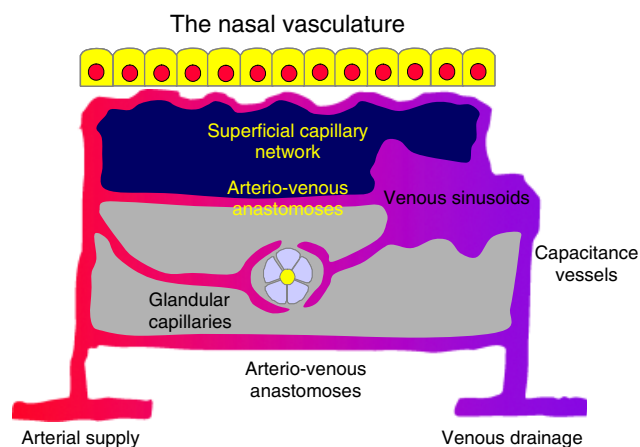


Fig. 1. Diagrammatic illustration of the nasal vasculature, identifying the resistance and capacitance vessels as well as the differing layers of arterio-venous anastomoses. Alterations in the distribution of blood flow will modify the most superficial capillary blood flow important in the transfer of heat to the inspired air. Alterations in the tone of the capacitance vessels and the arterial supply influence the state of engorgement of the venous sinusoids, which regulate the size of the turbinates, and hence air flow through the nostril.

increase in sympathetic tone decreases nasal congestion by reducing flow and facilitating sinus emptying. The vascular tone is also regulated locally by neuropeptides and in response to locally released mediators. The innervation of the nasal mucosa is well defined [13–15]. The olfactory and trigeminal nerves predominantly supply the sensory innervation of the nose. The ophthalmic and maxillary branches of the trigeminal nerve contain sensory nerves from the nasal mucosa and vestibule, and supply the sensations of touch, pain, temperature and itch as well as the appreciation of nasal airflow. These sensory nerves which consist of both myelinated and non-myelinated fibres, and contain non-adrenergic non-cholinergic peptidergic nerves, are also responsive to chemical stimuli and account for the initiation of sneezing and nasal hypersecretion through reflex pathways. The unmyelinated fibres are slow conducting and, in the vast majority, belong to the nociceptor, C-fibre type. Some of the thinnest among the myelinated ones belong to the A δ category, which may also have nociceptive functions. Sensory neural responses are conducted centrally on afferent pathways and give rise to the recognition of the sensory neural response as, for example, pain or itch. In addition, an important aspect of the non-myelinated C fibres is that their dendrites can be antidromically stimulated by action potentials that originate at different terminals of the same neuron. This results in the release of inflammatory neuropeptides from peripheral neurosecretory varicosities. Sensory C fibres from the trigeminal ganglion contain the tachykinins, substance P (SP), neurokinin A (NKA), as well as calcitonin gene-related peptide (CGRP). In addition, gastrin-releasing peptide has also

been identified in the human nasal mucosa [16], and more recently urocortin, a member of the corticotropin releasing factor (CRF) neuropeptide family [17]. Immunohistochemical analysis reveals that these neuropeptide-containing nerves are present in nerve endings around the sphenopalatine ganglion cells, around blood vessels, and beneath or within the epithelium. Receptors for these neuropeptides are also found in a similar distribution, co-localized to neural ganglia, glands as well as arterial and venous blood vessels [18, 19]. It is probable that in the normal nose these neuropeptides exert a fine-tuning role in the regulation of glandular secretion and vascular tone. Activation of sensory neurones by irritants and locally released inflammatory mediators induces both vasodilatation and micro-vascular leakage. This is considered to occur through stimulation of local axonal reflexes and modification of ganglionic neurotransmission. Nasal insufflation with SP and also NKA, but not CGRP, has been shown to cause nasal blockage and increase vascular permeability in subjects with rhinitis but to have little effect in the normal nose [20–22]. Urocortin may act as a locally expressed pro-inflammatory factor and induce mast cell degranulation, cytokine secretion, and trigger vascular permeability. These effects are mediated through CRF receptors in peripheral tissues [17]. Activation of the sensory nerves, in addition to a vasodilator action through axonal reflexes, leads to vasodilatation by modification of intrinsic sympathetic tone, through down-regulation of ganglionic neurotransmission at the trigeminal and sphenopalatine ganglia.

Both parasympathetic and sympathetic nerve fibres supply the efferent neural pathways to the nasal mucosa. The parasympathetic system largely regulates nasal glandular secretion, while sympathetic fibres regulate nasal flow and the state of engorgement of the venous erectile tissue. The primary parasympathetic postganglionic neurotransmitter is acetylcholine, which acts on the muscarinic (M) receptors. There are now recognized to be five different sub-types that are distributed on glands, arteries, veins and epithelial cells. The M3 subtype is the most abundant, and the predominant effect of physiologically released acetylcholine is to stimulate glandular secretion through action on M3 receptors. The cholinergic nerves also contain and release vasoactive intestinal peptide (VIP) and peptide histidine isoleucine [23]. VIP has vasodilatory properties and has also been shown to stimulate serous, but not mucous, cell secretion in human nasal mucosal explants [23]. The role of VIP in parasympathetic reflexes within the normal nose may, however, be minimal as atropine pre-treatment is very effective in inhibiting reflex-mediated nasal secretion *in vivo* [24]. The sympathetic nerves reach the nasal mucosa via the superior cervical ganglion and are distributed to the nasal blood vessels via the nerves of the pterygoid canal (vidian nerve) and by branches of the trigeminal nerve. The

primary neurotransmitter is noradrenaline [25]. This has vasoconstrictor actions through actions on α -adrenergic receptors. Although the primary sympathetic response in vasoconstrictor, it has been suggested from animal models that β_1 - and β_2 -adrenergic receptors are also present on the vasculature of the nasal mucosa, and that their stimulation results in vasodilatation of resistance vessels and thereby an increase in blood flow [11, 26]. In addition, it has been indicated that β -adrenoreceptors have an influence on glandular activity [27]. Sympathetic nerves also contain the vasoconstrictor peptide, neuropeptide Y (NPY). NPY nerve fibres are present in the walls of arterioles, arteriovenous anastomoses and other vessels within the nasal mucosa, and NPY receptors have been co-localized to these vascular sites, suggestive of the relevance of NPY to the regulation of vascular tone [28, 29].

Principally therefore, rhinitic symptoms are a reflection of the local neurohumoral environment. Many mediators stimulate either the sensory nerves or can act directly on the nasal vasculature (Fig. 2).

Mediators of nasal symptoms

In view of the heterogeneous nature of the non-allergic rhinitis group and the impending uncertainty in classifi-

cation, this section will in its first part examine the pathophysiological mechanisms underlying symptom expression in the non-allergic rhinitis group in whom a known precipitating factor or stimulus has been demonstrated. The second part will look at the group of conditions where no relevant stimulus has yet been determined.

Non-allergic rhinitis with known trigger

Cold air-induced rhinitis. Affected individuals in this condition have been shown to develop nasal symptoms following a nasal cold dry air inhalation challenge [30]. The work of Togias and colleagues [30, 31] in this area has shown evidence of release of mast cell mediators in nasal secretions, with a unilateral challenge leading to a bilateral secretory response, suggestive of the involvement of a neural reflex [32]. The associated rhinorrhoea appears to be largely the result of glandular parasympathetic stimulation as it is partially blocked by atropine [33]. While the inflammatory mediators may play a role in the subsequent hypersecretory glandular response in these cases, they are probably more important in mediating nasal congestion. An increase in both the osmolarity of nasal secretions and in histamine release, has been identified following nasal

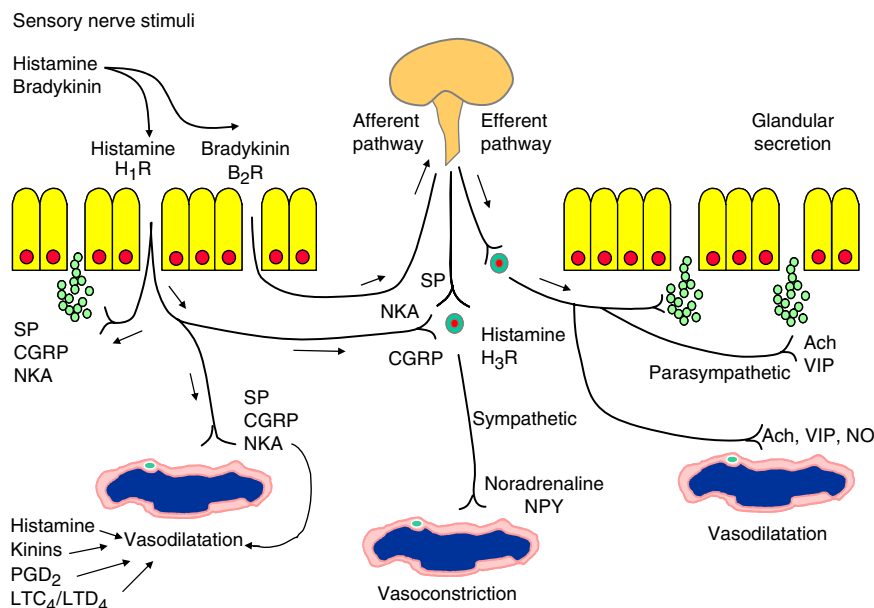


Fig. 2. Diagrammatic illustration of the neural effector mechanisms within the nose following sensory stimulation and the indirect and direct effects of mediators on the nasal vasculature. Sensory stimulation is illustrated via the histamine H₁ receptor and the bradykinin B₂ receptor leading both to the potential for antidromic release of the tachykinins substance P (SP), calcitonin gene-related peptide (CGRP) and neurokinin A (NKA), the regulation of sympathetic ganglionic neurotransmission by the tachykinins and the central stimulation of efferent pathways. Histamine, via the H₃ receptor, may also modify ganglionic sympathetic neurotransmission. The sympathetic nervous supply within the nose promotes venous sinusoidal constriction by limiting blood flow, via the release of noradrenaline and neuropeptide Y (NPY). Inhibition of ganglionic neurotransmission would lead to nasal vascular engorgement and nasal obstruction. Efferent pathways involving the parasympathetic nervous supply influence primarily glandular secretion, through the release of acetylcholine (Ach) and to a much lesser extent vasoactive intestinal polypeptide (VIP). The release of these mediators and the neural generation of nitric oxide (NO) will also influence vascular tone, leading to vasodilatation. The local generation of histamine, kinins, prostaglandin (PG) D₂ and leukotrienes (LT) C₄ and D₄, acting through their specific receptors will also lead to nasal vascular engorgement and nasal obstruction.

provocation with a hyperosmolar stimulus in these individuals [34, 35]. Interestingly, however, with regard to non-specific nasal reactivity, as tested by intranasal histamine challenge, these individuals do not appear to differ from nasal controls [35]. Nasal lavage studies have shown a significant degree of epithelial cell shedding following cold dry air challenge compared with controls [36]. It is feasible that a defect in humidifying inhaled air at extreme temperature exists within the nasal mucosa of cold dry-air rhinitic patients with a resultant increase in osmolarity of the epithelial-lining fluid and consequent epithelial shedding. Perhaps in an attempt to restore homeostasis of the tissue, a mucosal reaction ensues with an associated activation of mast cells and irritant sensory nerves. It has been well demonstrated that hyperosmolarity is indeed a trigger for mast cell mediator release *in vitro* [37] and *in vivo* [38], as well as activation of nasal sensory nerve endings [39].

Undoubtedly, the mechanisms mediating cold air-induced rhinitis are complex. There is, however, emerging evidence to support a state of neural hyperresponsiveness mediated through capsaicin-sensitive sensory nerves [40]. Other theories that have been put forward include an over-interpretation by the central nervous system of an otherwise normally innocuous irritant signal (central hyperresponsiveness), or a state of autonomic dysfunction with resulting symptomatology dependent on the dominant system (sympathetic vs. parasympathetic) [40]. The current knowledge regarding the role of the nervous system in the generation of rhinitic symptoms, and its likely interactions with the immune system, has been elegantly presented in a recent comprehensive review of the subject [40].

Food-induced rhinitis (gustatory rhinitis). In affected individuals, excessive rhinorrhoea develops following ingestion of certain foods, particularly spicy ones. The reaction is thought to be purely neurogenic with overstimulation of the parasympathetic system and is as such partially blocked by treatment with atropine [41] or ipratropium bromide [42]. Spicy foods, such as peppers, cause symptoms probably via their related capsaicin content, which stimulates sensory nerve fibres inducing neuropeptide release [43, 44].

Drug-induced rhinitis

Aspirin-sensitive rhinitis. Aspirin-sensitive rhinitis is a non-infectious non-allergic perennial rhinitis often in association with nasal polyps, and intrinsic asthma (also known as ASA or Samter's triad). Studies involving this group of patients have shown evidence of increased sulphidopeptide leukotriene (LT) levels in nasal lavage fluid following oral aspirin challenge [45]. A key finding in these patients is the alteration in the LT pathway for

arachidonic acid metabolism, resulting in increased release of leukotrienes LTC₄, LTD₄ and LTE₄ [46]. Furthermore, it has been shown that respiratory reactions to aspirin are attenuated by 5-lipoxygenase inhibitors and sulphidopeptide LT receptor antagonists [47, 48]. This is indicative of the significant role of the LT pathway of arachidonic acid and metabolism in the aspirin hypersensitivity syndrome [49]. It is, however, appreciated that aspirin-sensitive rhinitis is not as simple as arachidonic acid metabolism being redirected down the lipoxygenase pathway, on account of the aspirin-related cyclo-oxygenase inhibition. It is evident that there also are co-existent alterations in the E-prostanoid receptor (EP) balance within the tissue. Nasal biopsy studies have revealed an increase in both EP1 and EP2 receptors predominantly on tubulin+ epithelial cells and on mucin 5 subtypes A and B (Muc-5AC+) goblet cells in aspirin-sensitive rhinosinusitis, but not aspirin-insensitive disease, as well as a decrease in EP2 receptor expression on nasal inflammatory cells [50]. As EP2 is the receptor through which prostaglandin (PG) E₂ exerts its anti-inflammatory effects, this defect may be one factor contributing to the abnormal mucosal inflammatory cell profile in this disease. An apparent inhibition of eosinophil apoptosis has also been noted in aspirin-sensitive patients [46].

Rhinitis medicamentosa. The prolonged use of topical nasal decongestant medication can be associated with rebound congestion. The underlying mechanism is believed to be secondary to α -adrenergic receptor down-regulation due to constant stimulation [51], leading to development of tolerance and an increased dosage requirement for an equivalent pharmacological effect. This ultimately results in a vicious circle of events. There are, in addition, pathological inflammatory and structural cell changes in the nasal mucosa [52, 53]. Rhinitis medicamentosa appears to be associated with prolonged abuse of topical decongestants over many months [54], although symptoms can occur after a much shorter period of treatment [55, 56]. Adverse effects are very unusual when these agents are used over the normal treatment period of up to 1 week [57, 58]. The development of rhinitis medicamentosa may also be related to the formulation of nasal decongestant sprays, particularly the concentrations and combination of anti-bacterials, preservatives, stabilizers and pH of vehicle solutions [59, 60]. Other drugs which can cause nasal blockage include anti-hypertensives, particularly β -blockers. Exogenous oestrogen and chlorpromazine can also induce rhinitis [61].

Hormonal rhinitis

Hormonal rhinitis occurs most commonly in association with pregnancy, onset of puberty, and during the

menstrual cycle. Hypothyroidism and acromegaly can also give rise to chronic nasal congestion [61].

Atrophic rhinitis. Characterized by atrophy of the nasal mucosa and underlying bone, patients typically present with a widely patent nose and symptoms of nasal blockage with crusting and foul smelling discharge. Infection with *Klebsiellae ozaenae* has been reported [62], but it is not clear whether this constitutes the primary insult. Secondary atrophy can occur following excessive nasal surgery, irradiation therapy, chronic granulomatous disease and malignancy [61].

Miscellaneous causes. Various physical and chemical stimuli can induce rhinitis including exposure to air pollutants and occupational irritants. Emotion such as stress and sexual arousal also affect the nose via the autonomic nervous system. In children, gastro-oesophageal reflux has been linked with rhinitis [63].

Idiopathic rhinitis (non-allergic rhinitis of undefined aetiology)

This is the most heterogeneous of the rhinitis subgroups with unknown pathophysiology and is likely to include patients with a spectrum of different aetiologies and disease pathways. While some studies have made a distinction between patients with NARES and NANIPER, this distinction is probably an artificial one and in this section they will both be included under the idiopathic group as they have an unknown aetiology. The main dilemma we faced here was whether we were justified in including the 'vasomotor rhinitis' subgroup within this category. To date, considerable uncertainty exists in relation to this group, which has been used synonymously in numerous studies to include all forms of non-allergic rhinitis. It is a vague category with the term 'vasomotor' implying vascular and neurological components to the disease, but in fact we now know that the disease is probably a manifestation of an autonomic nervous system imbalance in favour of the parasympathetic system [64]. While an argument exists in favour of excluding this group from this section in view of the patient heterogeneity, strictly speaking, however, this group has an unknown aetiology. Furthermore, excluding this group would leave us realistically with few studies to reference, as a significant part of the available body of work in the area of non-allergic rhinitis has involved 'vasomotor rhinitis' patients of one description or another. Again, for the purpose of conformity, one term idiopathic rhinitis 'IR' will be used throughout this section to denote patients with non-allergic rhinitis of undefined aetiology.

Autonomic neural dysfunction. Parasympathetic innervation of the nasal mucosa is thought to play an important

part in the pathogenesis of symptoms in a significant number of IR sufferers. A tentative link between the cholinergic nervous system and histamine stores has been established since the demonstration that vagal stimulation leads to the release of gastric histamine [65–67]. In addition, the stimulation of cholinergic nerves causes a significant depletion of histamine stores in the submaxillary and parotid glands of cats and dogs [68]. Some studies have demonstrated that the stimulation of parasympathetic nerve endings through the vidian nerve (nerve of pterygoid canal) which provides the main parasympathetic nerve supply to nasal respiratory and maxillary sinus mucosa, is associated with a significant increase in histamine release from mucosal mast cells in patients with vasomotor rhinitis. Furthermore, this condition has been shown to be associated with a net increase, in comparison to normal controls, of histamine content in nasal mucosal samples and of mast cell secretory activity [69–71]. A cholinergic link between vidian nerve stimulation and the observed release of histamine is further suggested by the reported inhibitory effect of atropine, and the potentiating effect of eserine on histamine release [68]. Vidian nerve section, as well as inducing a reduction in the secretory activity of the glands and vasoconstriction of the venous plexuses [72, 73], also appears to induce a significant decrease in histamine tissue levels and histidine decarboxylase activity [70]. This is associated with a reduction in density and in the degranulation index of mast cells [70]. In this context, histamine released from mucosal mast cells by cholinergic stimulation could enhance the parasympathetic response of glands and vessels. Essentially, there appears to be a functional relationship between parasympathetic innervation, tissue histamine synthesis and stores, and mast cell degranulation. It would appear that mast cell histamine regulation via the parasympathetic system constitutes an important pathophysiological mechanism in symptom initiation in a number of IR sufferers. With the introduction of various medical therapies including topical steroids, second generation non-sedating H₁-antagonists, and topical anticholinergics, the need for surgery in the form of vidian neurectomy is nowadays confined to cases of intractable rhinorrhoea significantly impacting on the patient's QOL, and where medical treatment has clearly failed. This is particularly so when one considers that symptomatic improvement following such surgery may be short-lived, probably due to reinnervation, in addition to the risks posed by the surgery itself. Surgical treatment including reduction of the bulk of the inferior turbinates (resection, diathermy, powered endoscopic turbinoplasty, etc.) nowadays would be advocated in medically resistant cases where nasal blockage is the main symptom, but are unlikely to be of any significant benefit for the treatment of rhinorrhoea.

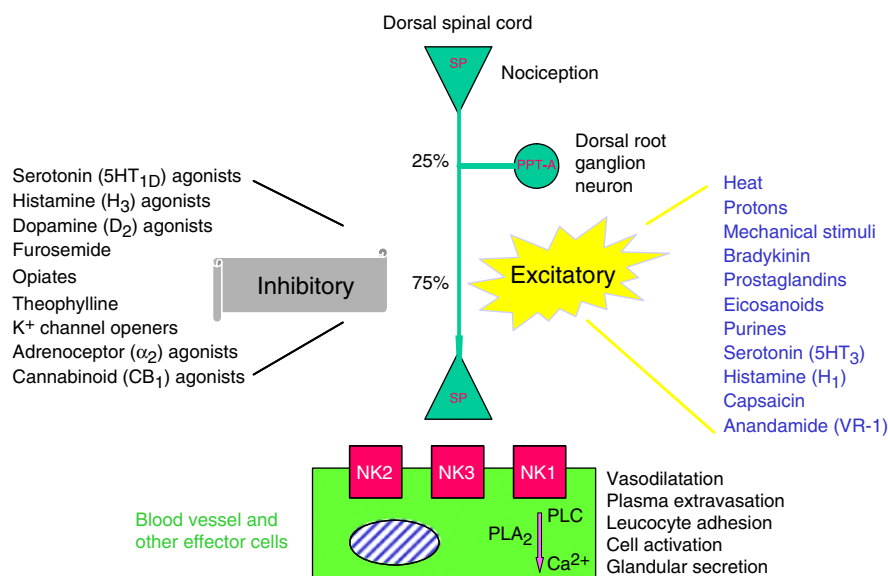


Fig. 3. Diagrammatic illustration of the potential excitatory and inhibitory stimuli that influence substance P (SP) release and its ability to act on the different neurokinin (NK) receptors NK1, NK2 and NK3, whose stimulation is mediated by calcium (Ca^{2+}) flux within cells, with involvement of phospholipase C (PLC) and phospholipase A₂ (PLA₂) (PPT-A, preprotachykinin A).

Tachykinin response. While the nasal hyperresponsiveness described in IR can be partially attributed to the neurovascular imbalance, it does not completely explain the exaggerated obstructive and secretory response to chemical stimuli [74]. An over-expression of the tachykinin response has been suggested to explain this hyperresponsiveness, based on the importance of these nerves to the nasal response in rodent models (Fig. 3). Many neuropeptides have been identified in peptidergic fibres in the airway including CGRP, the tachykinin SP and kinins [75–77]. These have also been localized to the lower airways in animals and man [77–80], where they have been shown to have potent bronchoconstrictive actions [79, 81, 82]. This led to therapeutic intervention, based on this paradigm, with encouraging results, despite little evidence for an exaggerated peptidergic nasal response to intranasal capsaicin challenge in non-allergic rhinitis [83], even though this is so in allergic rhinitis [21, 22]. Capsaicin, the active principle of red-hot pepper from the plant genus *Capsicum* is known to stimulate non-myelinated sensory 'C' fibres, thereby inducing neuropeptide release. Repeated capsaicin administration leads to tachyphylaxis of its effects, due to stimulation-related depletion of the sensory neuropeptides and sensory neurone degeneration. Thus repeated capsaicin application to the nasal mucosa has been used to identify whether this can improve symptom expression in non-allergic rhinitis. Several studies have now reported the clinical benefit of this approach, with improvements in symptom expression being reported for up to a year after a series of intranasal applications [43, 84–86]. The treatment is unpleasant, in that it induces an extreme burning pain, although this can

be modified by pre-treatment with local anaesthesia. Nasal biopsies up to 9 months after treatment have not identified any atrophic effects of this therapy on the nasal mucosa [87], and the effects are specific to the disease, in that topical capsaicin therapy has not been found to have any significant effect on disease expression in perennial allergic rhinitis [88]. At present this approach to therapy is the only disease-specific treatment for non-allergic rhinitis, although with the development of tachykinin-receptor antagonists there may be alternative therapies that can achieve similar effects.

Integration of neuroendocrine and immune systems. While the precise pathophysiological role of neuropeptides in the upper airways in IR remains unclear, the potent effect of these peptides on various aspects of airway function suggest that they may be involved in controlling airway tone, mucus secretion and plasma extravasation [89]. Dysfunction of neuropeptide-containing nerves might be involved in nasal hyperreactivity [81]. Release of bradykinin, a potent inflammatory mediator, has been shown in IR [90–93]. The pattern of mediator release in nasal secretions during the response to cold dry air is similar to that observed following antigen challenge, suggesting the involvement of mast cells in the pathophysiology of IR [30]. Kinin generation following methacholine nasal airway challenge in IR subjects was inhibited by pre-treatment with anticholinergic agents such as ipratropium bromide, suggesting that the response is partly mediated by a cholinergic reflex [93]. Bradykinin has also been shown to induce *in vivo* a dose-dependent plasma leakage into the nasal cavity without affecting the mast cells, while

stimulating nerve endings resulting in the release of SP in non-allergic subjects [89]. This raises the possibility that bradykinin may be acting through an IgE-independent mechanism, exerting a direct action on the release of SP as a representative of neurokinins in neurogenic inflammation [89]. This could partly explain the bradykinin-evoked clinical symptoms in the non-allergic nose. The other alternative of course, which applies in the allergic nose, is that SP release might be via an IgE-dependent mast cell degranulation leading to increased vascular permeability and plasma influx with consecutive activation of the kallikrein-kinin system and bradykinin generation [89]. Furthermore, SP has been shown to induce histamine release *in vitro* from the nasal mucosa of subjects with IR [94], and its exogenous administration has also been shown to induce nasal obstruction in a dose-dependent manner in normal subjects and patients with allergic rhinitis without classical mast cell degranulation [95]. This may represent another important mechanism in mediating nasal responses in IR subjects. SP appears to constitute an important neuro-immunological link in physiological and pathophysiological nasal conditions.

The exogenous application of β -endorphin, an endogenous peptide opiate and derivative of pro-opiomelanocortin, has been shown to induce nasal congestion in normal and allergic rhinitic subjects, without a β -endorphin-induced mediator release [96]. While mediator release could not be demonstrated, direct evidence has been provided of a β -endorphin-mast cell interaction by a significant increase in histamine concentration in nasal lavage [96]. These observations provide yet more evidence of the likely interaction of the immune system with the neuroendocrine system.

Furosemide, a powerful diuretic which inhibits sodium and potassium reabsorption in renal tubules, has been shown to exert a protective effect from bronchospasm in the lower airways [97]. A protective effect has also been noted in the upper airways in allergic rhinitis [98]. Interestingly, in patients with IR, furosemide has been shown to induce a reduction in nasal resistance measured by anterior rhinomanometry [99], although no convincing effect on mediator release has yet been demonstrated [100]. The mechanism of action of furosemide in the airways is yet to be fully elucidated but possibilities put forward have included interference with electrolyte epithelial transport, PG levels, inflammatory cell activity, vascular and neural regulation [101].

Importance of mechanical stimuli. The role of mechanical stimuli on nasal symptoms has been investigated in a study looking at the effect of forced expiration (nose blowing) in patients with IR compared with non-rhinitic controls. A small but significant increase in nasal airways resistance, was found in the non-allergic rhinitis group compared with the non-rhinitic controls [102]. This can

have important implications during nasal challenge which involves nasal blowing in order to collect secretions and measurements of nasal patency.

Pollution and meteorological factors have also been shown to be closely related to nasal complaints in IR patients. Using a time series model, substantial changes in nasal symptoms such as nasal blockage in IR patients were induced by minor pollution and meteorological disturbances compared with non-rhinitic controls, irrespective of other factors such as allergies or infection [103].

Eicosanoids. The role of eicosanoids (PGs and LTs) in the pathophysiology of IR remains a controversial issue compounded by the fact that relatively few studies have examined this specific area. PGs and LTs are local hormones and potent inflammatory mediators and have been implicated in conditions of both the upper and lower airways. Evidence has emerged over the last decade or so of the important role of the eicosanoids particularly the cysteinyl LTs in allergic upper airway disease including chronic perennial allergic rhinitis and nasal polyposis [104, 105]. In particular, there is a significant body of work in the literature on LT receptor antagonists and LT synthesis inhibitors, which may offer new more efficacious therapies in the treatment of various forms of allergic rhinitis [106–108]. By comparison, there is a dearth of information on the profile of these mediators in IR. One study has reported increased levels of LTC₄ and PGD₂ in nasal lavage in symptomatic IR patients, compared with control subjects [109]. Other research has contradicted this with findings of significantly lower levels of PGE₂, PGD₂ and LTE₄ in untreated rhinitics compared with controls [110], although there were no changes detected in levels of LTB₄. Furthermore, this study reported that steroid treatment in these subjects apparently raised the levels of these eicosanoids apart from LTB₄ which was unaffected by the therapy [110]. These findings appear to refute the current thinking that increased levels of eicosanoids are implicated in the pathogenesis of IR. Evidently more work is required to clarify this further.

Localized mucosal inflammation. Nasal hyperreactivity is a recognized feature of IR, as demonstrated by increased methacholine and capsaicin responsiveness as previously discussed. With rhinostereometry, an optic method for detection of small changes in nasal resistance, responsiveness to histamine in IR has also been demonstrated [111]. The observation regarding nasal mucosal hyperreactivity in IR poses the question of an underlying inflammatory aetiology in association with this phenomenon. The pathophysiology of IR remains largely unknown, and the presence or absence of inflammation remains equally controversial. Studies on IR patients and comparison of data are hampered by the heterogeneity of

patients. Although some patients with IR are characterized by eosinophilic infiltration (NARES) and responsiveness to intranasal corticosteroids [112], some studies have suggested that IR is essentially a non-inflammatory disease exhibiting non-responsiveness to corticosteroids [113, 114]. Circumstantial evidence for this assumption is suggested by the effectiveness of repeated capsaicin application in attenuating nasal symptoms in IR patients [86], but not in perennial allergic rhinitis patients [115]. Furthermore, in the subgroup of IR patients which had been labelled as 'vasomotor rhinitis', two groups of investigators have failed to identify in nasal lavage or mucosal biopsies, any differences between these patients and healthy controls, with respect to cellular or biochemical inflammatory markers [113, 116, 117]. It appears therefore that in a certain proportion of patients with IR no obvious inflammatory basis is immediately identifiable. Nevertheless, an increasing body of evidence is emerging which advocates the presence of active mucosal inflammation in IR [118–120]. More recently, further evidence for an inflammatory pathophysiology in a subgroup of IR has been elegantly presented with demonstration of similarities between IR and the allergic rhinitic mucosa with respect to their inflammatory infiltrate, suggesting that both groups share a highly localized Th2, IgE-mediated cellular immunopathology [121]. Work from the same group has also demonstrated the feasibility of a localized nasal mucosal allergic response in IR subjects in the absence of systemic atopy, and coined the term 'entopy' to qualify this phenomenon [122–124]. This exciting concept will no doubt have wider implications in relation to the proposed need for testing techniques of higher sensitivity levels for allergy-associated rhinitis as well as localized allergic responses in other mucosal sites such as the eye.

Conclusions

The jury remains out as to the precise pathophysiological mechanisms and mediators underlying nasal symptoms in non-allergic rhinitis. This review has attempted to examine and appraise the available literature on the subject, but evidently more work is needed to further clarify this area. Crucially though, and in view of the heterogeneity of this group of patients, it would be far more productive to undertake such studies in the future using a standardized system which would allow accurate phenotyping of these patients. This would certainly minimize the classification confusion that has arisen previously, as well as ensuring the comparability of patient study groups. Better quality and more robust research would undoubtedly lead to better understanding of the pathophysiological basis of non-allergic rhinitis, which should hopefully translate to improved diagnostic accuracy and more effective treatments.

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