

# Pathophysiology of itching and sneezing in allergic rhinitis

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## Summary

Itching and sneezing represent two of the main bothersome symptoms, apart from nasal obstruction and rhinorrhea in allergic rhinitis. Apparently, activation of the central and peripheral nervous system plays a major role in the pathophysiology of this process. Sensory nerves of the afferent trigeminal system including myelinated A $\delta$ -fibres and thin, non-myelinated C-fibres of the nasal mucosa transmit signals generating sensations, including itching and motor reflexes, such as sneezing. These nerves can be stimulated by products of allergic reactions and by external physical and chemical irritants. Via axon reflex inflammatory neuropeptides including the tachykinins substance P (SP) and neurokinin A (NKA) and the calcitonin gene related peptide are released, leading to vasodilatation, increased vas-

cular permeability (concept of “neurogenic inflammation”), glandular activation, leukocyte recruitment and differentiation of immune cells including mast cells, eosinophils, lymphocytes and macrophages.

The present paper describes nasal (micro-) anatomy and innervation and explains the central and peripheral mechanisms initiating itching and sneezing in allergic rhinitis. Further, the role of neuropeptides and neurotrophins with regard to neuronal and immune cell activation which might play a key role in the future treatment of allergic rhinitis are discussed.

*Key words: itching; sneezing; allergic rhinitis; trigeminal nerve; neuropeptides; neurogenic inflammation*

## Introduction

Nasal itching and sneezing represent main characteristic symptoms besides nasal obstruction and rhinorrhea in allergic rhinitis. The nasal mucosa is innervated by sensory, sympathetic and parasympathetic nerves. Sensory nerves transmit signals generating sensations including itching and motor reflexes such as sneezing whereas parasympathetic and sympathetic reflexes regulate the glandular and vascular system [49].

In the nose sensory nerves monitor the conditions of the mucosal microenvironment and initiate protective mucosal responses immediately via axon response mechanisms [21]. However, in al-

lergic rhinitis parasympathetic and sympathetic reflexes are co-opted, leading to symptom generation.

In the following, a short overview is presented on nasal anatomy and nasal innervation. Further, the generation of itching and sneezing due to trigeminal activation and liberation of neuropeptides and neurotrophins in allergic airway inflammation is explained. The pathophysiology of itching and sneezing is furthermore discussed in the alternating inducement between the nervous and the immune system in allergic rhinitis.

## Specific (micro-) anatomy of the nose

The largest part of the nasal cavity and the paranasal sinuses are covered by a multilayered ciliated epithelium in the respiratory region. Ol-

factory cells, sustentacular cells and submucosal adenoids are located in the roof of the nose including areas of the medial and upper nasal

concha and upper septum in the olfactory region [12, 22, 30].

The nasal mucosa is covered by a bilayered secretion film which is produced by submucosal adenoidal and goblet cells. This secretion film includes a low viscous sol film in which cilia move, and an apical, highly viscous gel film. This specific assembly serves the physiological cleaning of respiratory air through the mucociliary apparatus. Cholinergic input causes an increased secretion of

the submucosal cells. However, goblet cell stimulation has also been shown by SP releasing sensory nerves in a rat model [26]. The cavernous tissue of the nasal concha consists of venous sinusoids and regulates the respiratory resistance. Filling of these sinusoids is regulated by sympathetic stimulation as adrenergic fibres are distributed around arteries, arterioles and veins of the human nasal mucosa [22].

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## Trigeminal activation as the central aspect for the formation of nasal itching and sneezing

The trigeminal nerve is important for the nociceptive sensory supply of the nasal mucosa in addition to the face, oral mucosa, cornea and conjunctiva. The nerve arises in the anterior distribution of the nasociliary nerve (nervus ophthalmicus) and in the posterior area due to the nasopalatine nerve (nervus maxillaris) [2]. These parts unite in the trigeminal ganglion with the mandibular branch of the trigeminal nerve, the fifth cranial nerve. It reaches the medulla oblongata via the nucleus of the trigeminal nerve and runs via the lateral spinothalamic tract to the ascending thalamic nuclei and finally ends in the somatosensory cortex [20].

Itching and sneezing are generated by the activation of trigeminal afferent nerve terminals in the nasal mucosa [5, 56]. These nociceptive nerve fibres consist mainly of two types of fibres [14] including the thin A $\delta$ -fibres that mediate acute perceptions with a quick adaptation and activation only during the actual irritation [5, 17, 54] and the non-myelinated C-fibres which adapt slowly and communicate dull burning, difficult to locate perceptions, which outlast acute pain [38].

In the skin slow conducting non-myelinated C-nerve fibres are involved in the development of dermal itchiness [33, 59]. The C-fibres connect the posterior horn of the spinal cord and the information reaches the brain via the spinothalamic tract. These afferents are characterised by a relatively slow conducting velocity of only 0.5 m/s [50].

Pain is also encoded via non-myelinated, slowly conducting C-fibres. However, nociception and itching are senses clearly distinguishable from

each other [32]. The itching sensing nociceptors differ from the pain sensing nociceptors mainly because they have very thin axons with distinctive branching of the terminals. This terminal branching is the basis for relatively large receptive fields to sense itching, for example, of approximately 85 mm in the lower leg [50]. Opioids inhibit nociceptive input but may amplify itching [25].

On a behavioural level, pain typically produces an escape reaction while itching leads to scratching. The fact that increased quantities of cutaneous itching stimulation also result in an intensification of itch, but not in that of pain, clearly indicates that the two sensory qualities are functionally different [8]. Interestingly, the activation of these fibres shows a greater emotional aspect than the activation of A $\delta$ -fibres. Repetitive activation of A $\delta$ -fibres gives rise to increased levels of pain. Because the nerve conduction velocity of non-myelinated nerve fibres decreases by increasing the frequency of irritation and suspends at frequencies of more than 1 Hz [46], the increasing intensity is not a result of more frequent sequences of action potentials but is probably caused by a summation process in the central nervous system [16].

It is to be expected that in simultaneous activation of A $\delta$ - and C-fibres both types of fibres will functionally influence each other [16, 32]. In allergic rhinitis, immunologically triggered inflammation results in the recruitment and activation of both types of fibres that results clinically in itching and sneezing [5, 23].

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## Scratching and rubbing

Scratching and rubbing usually bring relief of itchiness. Supposedly this effect is due to the curtailing of superficial mucosal nociceptors and to stimulation of fast conducting A-fibres [33]. Through electrical stimulation of afferent pain fibres, the histamine triggered itching can be de-

creased in cutaneous field stimulation [35]. The mechanical irritation caused by scratching results in the release of pro-inflammatory mediators which may amplify the itching-scratching-circulation [11].

## Central processing of itching

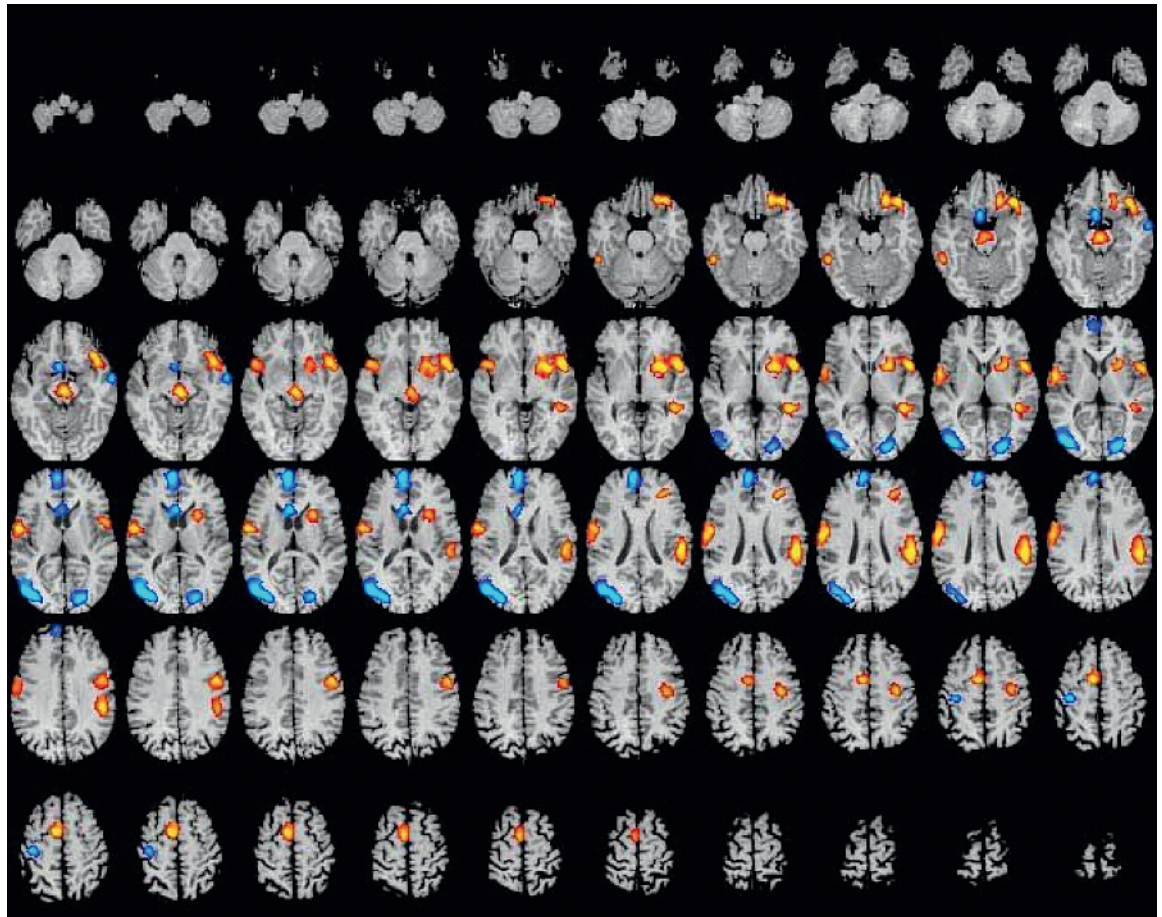
Clinical studies using Positron Emission Tomography (PET) indicate that there is no isolated itching centre in the brain but that there are different cortical centres which are involved in the processing of the itch [13].

Activation of the anterior gyrus cinguli, the supplementary motor cortex and the inferior parietal lobe partly explains the connection between itching and the related reflex of scratching [50]. Using functional MRI, the activation of

corresponding cortical units following painful trigeminal stimulation has been shown [15] (fig. 1). In this regard, neuropeptides produced in the cell body of C-fibre neurons can also be transported in granule structures within the cytoplasm to nerve terminals in the central nervous system. This leads to “central sensitisation” a phenomenon associated with activation of nociceptive C-fibres [49].

**Figure 1**

Activation (yellow-red areas) of brain structures assessed by means of functional MRI following nasal chemosensory trigeminal stimulation (from [15] with permission: Oxford University Press).



## Relationship between the nervous and immune system

In recent years, the existence of a close functional relationship between the nervous and immune system has been clearly demonstrated [1]. This interaction partially explains the clinical observation that psychological influences may modulate the course of allergic reactions. Allergic reactions may be amplified by psychological stress [43, 45, 57]. Looking at a picture of a rye field may even cause allergic symptoms, such as nasal itching and sneezing, in a sensitive patient [29].

Apart from its sensory capacity the nervous system plays an important role in the local regulation of allergic inflammation and thereby the generation of itching [36]. The concept of neurogenic inflammation was suggested in the fifties and the nature and the distribution of afferent fibres in-

involved in the axon reflex arrangement was described [3]. Direct evidence for this neurogenic inflammation was demonstrated by the effect of denervation and by pre-treatment with capsaicin, the pungent component of hot pepper [19, 36].

The adjacency of mast cells and afferent C-fibres in the skin allows the assumption that a close functional relationship exists [59]. Activation of mast cells leads to the liberation of histamine and other proinflammatory mediators including prostaglandins, leukotrienes, etc. In allergic rhinitis, histamine has an important role in producing itching, sneezing and nasal obstruction [37]. Following nasal allergen challenge histamine levels are increased in nasal lavage fluid in allergic but not in non-allergic patients [27]. Histamine acti-

vates H1 receptors on sensory nerve fibres and smooth muscle [55] and forwards itching afferences via the spinal cord to the brain [53]. In addition, histamine induces cholinergic reflexes and leads to liberation of additional neurotransmitters, including vascular intestinal polypeptide (VIP) [34]. Further, the increase in the concentration of prostaglandins and leukotrienes released by mast cells results in activation and sensitisation of nociceptors and mechanoreceptors, which may precede itching [5, 38]. With regard to neuroimmune interactions the neurotransmitters substance P (SP) and VIP induce mast cell degranulation as shown recently [28].

In the airways eosinophil granulocytes have been found in close vicinity to peripheral nerves [18]. In a mouse model of allergic airway inflammation eosinophils impaired cholinergic M2 receptor function [4]. In human nasal mucosa, SP increases allergen-induced eosinophil accumulation [6]. Together, these data provide evidence for a role of immune cells including mast cells and eosinophils in airway dysfunction in allergic inflammation with possible neuroimmune interactions [39, 44].

## Neurotransmitters, neuropeptides and neurotrophins

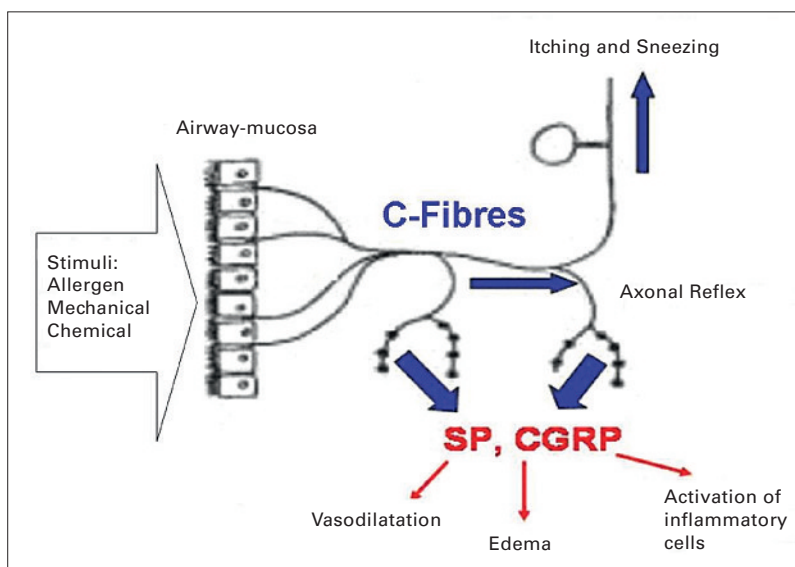
In allergy-related nasal inflammation it can be demonstrated that especially the neurotransmitter SP is released by C-fibres [1, 9, 21, 53] (fig. 2). SP acts via neurokinin (NK)-1 receptors that are expressed on human nasal glands, epithelium and immune cells including mast cells [28, 52]. SP is significantly increased in the nasal lavage of patients with allergic rhinitis, in contrast to healthy subjects, which is interpreted as a sustained stimulation of the sensory system [23, 29].

Exogenically administered SP results in a dose dependent occurrence of nasal symptoms in asymptomatic patients with allergic rhinitis and controls, without elevation of inflammatory mediators (fig. 3). However, exogenic administration of SP after nasal allergen provocation significantly increases the release of mediators in the nasal lavage in allergic patients [23, 29]. This study allows the assumption that neurokinin receptor ac-

tivation has a role in neurogenic activation that is further amplified during allergen application leading to the release of proinflammatory mediators in addition to increased clinical symptoms.

In addition to SP, other neuropeptides, including calcitonin gene-related peptide (CGRP) and vasoactive intestinal polypeptide (VIP), are increased in nasal lavage fluids after nasal provocation in allergic rhinitis [34]. Further, phenotypic alteration of neuropeptide-containing nerve fibres including SP, VIP and NPY are characteristic features of allergic rhinitis patients in comparison to controls as shown in immunohistological studies [10]. So far NK-1 receptor antagonists have only been applied in animal models, showing an inhibition of allergen induced airway inflammation and an inhibition of allergen induced airway hyper-reactivity [51]. Allergic inflammation increases the amount of neuropeptide production by sensory nerves [7] and potentiates the release of neuropeptide transmitters as shown in animal studies. In allergic rhinitis this could be confirmed by the finding of increased neuropeptide content in nasal tissues and an increased plasma extravasation after capsaicin provocation in patients with allergic rhinitis [47, 48].

One feature of allergic rhinitis is sensorineural hyper-responsiveness influenced by products of the allergic reaction including eicosanoids, cytokines such as IL-6, IL-1 $\beta$ , TNF- $\alpha$  and, most importantly, neurotrophins including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). NGF targets nociceptor fibres, leading to up-regulated activity, increased SP content and dendrite sprouting [31]. Recently, we and others have shown that NGF is expressed in the glandular and nasal epithelium and peripheral nerves in the nasal mucosa [41, 58]. Both nasal NGF and BDNF expression significantly increased after nasal allergen provocation in patients with allergic rhinitis compared to healthy controls [41]. In addition, the allergen induced increased BDNF expression in the nasal

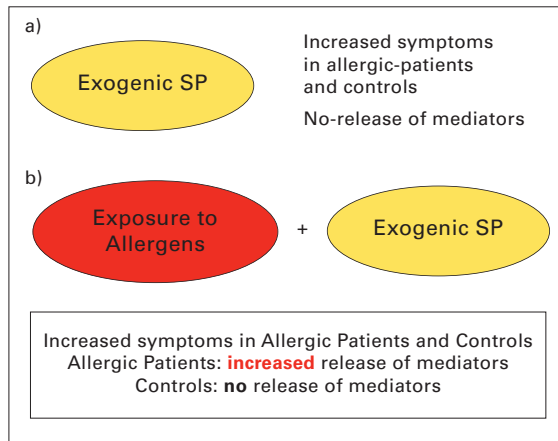


**Figure 2**

Schematic presentation of the processes involved in "neurogenic inflammation" leading to itching and sneezing. Activation of afferent trigeminal C-fibres by several stimuli including allergen contact may result in an efferent liberation of substance P (SP) and calcitonin-gene related peptide (CGRP) via axonal reflex. This further leads to vasodilatation, oedema, and recruitment/migration of inflammatory cells [1, 9, 21, 53].

**Figure 3**

Exogene administered Substance-P (SP) results in nasal symptoms without liberating mediators in both allergic and healthy people (a). After nasal allergen exposure allergic subjects show an elevated concentration of mediators in the nasal lavage fluid, while the lavage of healthy persons does not show such a response (b, [23, 29]).



mucosa significantly correlated with the maximal increase of total nasal symptom score in allergic rhinitis [41]. BDNF and NGF are both expressed and released especially by eosinophils [24, 42]. Interestingly, neurotrophins also modulate the functional activity of immune cells including eosinophil granulocytes of allergic rhinitis [40]. Therefore, neurotrophins certainly represent another pathway for the complex interplay between peripheral nerves and immune cells with regard to neuroimmune interaction.

## Conclusion

Taken together the trigeminal nerve activation of specific C- and A $\delta$ -fibres plays a major role in the cause of nasal itching and sneezing in allergic rhinitis. These trigeminal afferents may also modulate the local inflammatory process (neurogenic inflammation) through the liberation of neuropeptides, including SP.

Published reports to date allow the assumption that neuropeptides and neurotrophins play an important role in allergic inflammation. In addition, the frequent clinical observations of the influence of the psyche on the progression of allergic rhinitic discomforts may be explained in this way.

New therapeutical approaches are needed for the treatment of allergic rhinitis, especially with regard to the main symptoms including itching and sneezing. A possible approach could be the in-

hibition of the trigeminal nerve activation by modulation of appropriate neuropeptides and neurotrophins within the neurogenic inflammation.

**Acknowledgements:** We are grateful to Prof. Thomas Hummel (Dresden, Germany) and Dr. Ingo Böttcher (Wiesbaden, Germany) for their valuable support.

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