

The role of neurotrophins in the pathophysiology of allergic rhinitis

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Purpose of review

Allergic rhinitis is characterized by allergic airway inflammation and a hyperresponsiveness to nonspecific stimuli which is partly neurally controlled. In this regard, neurotrophins are prime candidates as mediators of neuronal and immunological plasticity and they will be the focus of the current review.

Recent findings

Neurotrophins including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are expressed in the nasal mucosa. The majority of NGF expression has been found in eosinophil granulocytes, the glandular apparatus and peripheral nerves. As shown recently, nasal allergen provocation upregulates BDNF expression in nasal mucosa and NGF expression on peripheral nerves and nasal lavage in patients with allergic rhinitis. In this regard, increased BDNF expression positively correlates with the maximum increase in total nasal symptom score. The neurotrophin receptors including pan-neurotrophin receptor p75^{NTR}, tyrosine kinase A (trkA) and trkB are expressed in nasal tissue. TrkA is expressed on endothelial, p75^{NTR} on peripheral nerves and trkB on nasal mucosa mast cells that decreases after allergen provocation. The expression of these neurotrophin receptors is increased on peripheral blood eosinophils in allergic rhinitis compared with nonatopic controls. Further, BDNF and NGF exert immunomodulatory functions on eosinophils of patients with allergic rhinitis. Finally, eosinophils of patients with allergic rhinitis are capable of BDNF and NGF production.

Summary

Neurotrophins represent prime candidates in upper airway pathophysiology in allergic rhinitis. Research on neurotrophins in allergic rhinitis is thus becoming a progressively more exciting field and may reveal new and promising therapeutic options for the future.

Keywords

allergic rhinitis, brain-derived neurotrophic factor, eosinophil granulocytes, mast cells, nasal allergen provocation, nerve growth factor, pan-neurotrophin receptor p75^{NTR}, tyrosine kinase A

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Introduction

Allergic rhinitis is the most frequent manifestation of the atopic syndrome affecting the airways. The contribution of genetic, environmental and immunological factors on the development of allergic rhinitis has been well established [1]. In addition, it has been suggested that neural pathways play a role in the pathophysiology of allergic rhinitis [2]. Main characteristics of allergic rhinitis are nasal itching, sneezing and a hyperresponsiveness to nonspecific stimuli possibly due to enhanced neuronal reflex circuits controlling airway function [3[•]]. Changes in the structure and function of the nerves themselves – a phenomenon known as neuronal plasticity – may contribute to the pathophysiology of allergic rhinitis, as well as the response to exogenous irritants and to endogenous mediators [4]. In this regard, neurotrophins present prime

candidates for the activation of both sensory nerves and main target effector cells within the inflammatory response [5–8] in upper airway inflammation which are highlighted in the current review.

Biology of neurotrophins and receptors

Neurotrophins were initially known for their primary activity, the growth of peripheral and central nerves [9]. In the mean time, it has become evident that neurotrophins exert a variety of immunomodulatory effects on nonneuronal cells including eosinophils and mast cells, which also produce neurotrophins [7,10,11].

Nerve growth factor (NGF) represents the first discovered protein belonging to the neurotrophin family. Meanwhile, further neurotrophins including BDNF

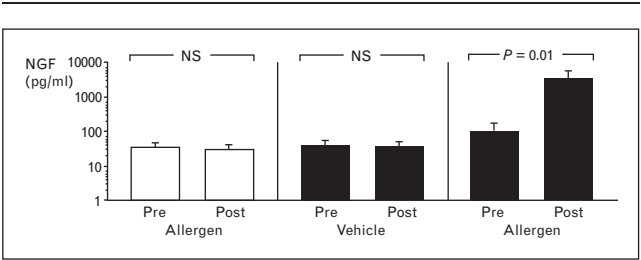
and neurotrophin-3 and neurotrophin-4/neurotrophin-5 have been discovered. Neurotrophins belong to a family of homologous proteins that exert their effects primarily as target-derived paracrine or autocrine neurotrophic factors. NGF targets nociceptor fibres, leading to upregulated activity, increased substance P content and dendrite sprouting [12]. The biological effects of neurotrophins are mediated by binding either to the tyrosine kinase (trk) receptors to which mature neurotrophins bind with high-affinity and specificity. TrkA has been identified as the preferred receptor for NGF, trkB for BDNF and neurotrophin-4 and trkC for neurotrophin-3 [13]. In addition, there is the pan-neurotrophin receptor p75 (p75^{NTR}), a member of the tumor necrosis factor super family, to which mature neurotrophins bind with low-affinity and specificity [14]. The expression of these neurotrophin receptors is widely distributed on neurons of the peripheral and the central nervous system. In addition, trkA–C and p75^{NTR} receptors are expressed on nonneuronal cells including smooth muscle cells, epithelial cells and immune cells including eosinophils and mast cells [15,16–18,19,20**].

Neurotrophins in the peripheral blood and nasal lavage

The initial report of increased NGF production was provided by Bonini *et al.* [21] indicating that patients with allergic rhinitis display significantly higher serum levels of NGF compared with controls. In addition to allergic rhinitis, also patients with allergic asthma and atopic dermatitis are characterized by increased serum levels of NGF [21,22]. When we analyzed neurotrophin expression in the peripheral blood of patients with allergic rhinitis we found increased levels of BDNF and NGF [23**]. This is in accordance with atopic dermatitis and allergic asthma patients who are also characterized by increased serum and plasma levels of BDNF [22,24]. Possible sources of NGF production are vascular smooth muscle cells as shown recently for human umbilical veins and human iliacal arteries [20**].

In nasal lavage fluids NGF protein levels are increased compared with nonatopic controls as assessed in a study by Sanico *et al.* [25]. Nasal allergen provocation further up-regulated increased NGF expression in nasal lavage in allergic rhinitis in contrast with controls (Fig. 1). Interestingly, unlike histamine provocation, allergen provocation caused significantly increased levels of NGF protein in nasal lavage of patients, thus indicating that increased NGF levels are not an artefact of plasma leakage but the result of an active release of preformed NGF of cells in the nasal mucosa [25]. In this regard, also bronchial lavage fluids have been characterized for increased NGF, BDNF and neurotrophin-3 levels after allergen provocation in patients with allergic asthma, suggesting an endobronchially production following allergen provocation [26].

Figure 1 Nerve-growth factor in nasal lavage before and after nasal allergen provocation



Concentrations of NGF in nasal lavage fluids before and after nasal challenge with allergen or vehicle. Nasal provocation with 1000 pnu of ragweed or grass extract significantly increase nasal lavage NGF concentrations in the 20 individuals with allergic rhinitis. NGF levels were not affected by allergen in five healthy control individuals nor by the vehicle in 10 individuals with allergic rhinitis. Open bars = control individuals; solid bars = rhinitis individuals. NGF, nerve-growth factor; NS, not significant. Reproduced with permission from [25].

Expression of neurotrophins and receptors in nasal mucosa

Recently, we and others have shown that NGF is expressed in the glandular apparatus, nasal epithelium and peripheral nerves in the nasal mucosa of patients with persistent and intermittent allergic rhinitis [23**,27,28]. Using double immunofluorescence staining Wu *et al.* [27] demonstrated NGF in only 2% of mast cells, 0.2% of T cells, but in 62.2% of activated eosinophils suggesting that submucosal glands, epithelium and eosinophils represent the major sources for NGF in human nasal mucosa (Table 1). In a study including 17 patients with allergic rhinitis and 23 controls who underwent nasal surgery, epithelial immunoreactivity for NGF was significantly increased in patients [29]. Further, increased epithelial NGF expression positively correlated with increased subepithelial protein gene product (PGP) 9.5 innervation in allergic rhinitis, suggesting a role for NGF in neuronal plasticity.

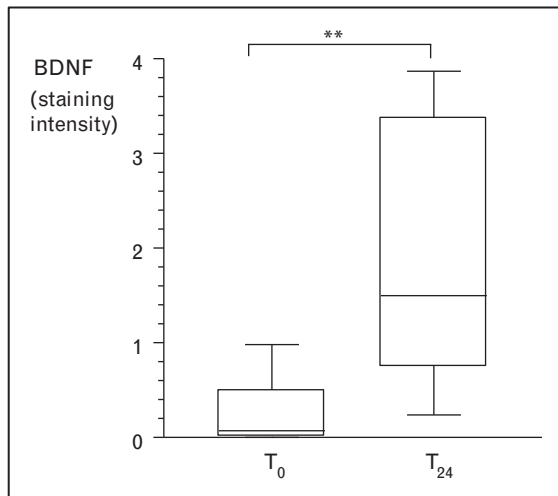
In a study performed by our group, expression of NGF positive nerves was significantly increased in nasal mucosa of patients with allergic rhinitis after allergen provocation

Table 1 Cellular sources of nerve growth factor in the human nasal mucosa

Tryptase⁺ NGF⁺	Total tryptase⁺	%*
1 (0.8, 1)	47 (42.8, 55.3)	2 (1.3, 2.3)
CD3⁺ NGF⁺	Total CD3⁺	%*
1 (0.3, 1.8)	398.5 (392.5, 411.5)	0.2 (0, 0.4)
EG2⁺ NGF⁺	Total EG2⁺	%*
15.5 (13, 21.3)	25 (21, 34.3)	62.2 (56.2, 68)

Double immunofluorescence staining in human nasal mucosa tissue of six individuals. Median numbers [25th, 75th percentiles] of cells per mm². % indicates the percentage of tryptase⁺, CD3⁺ or EG2⁺ (eosinophilic cationic protein) positive cells that also stained positive for nerve growth factor (NGF). *Kruskal–Wallis test comparing the above percentages: P = 0.001. Reproduced with permission from [27].

Figure 2 Expression of brain-derived neurotrophic factor before and after nasal allergen provocation in the nasal mucosa of allergic rhinitis



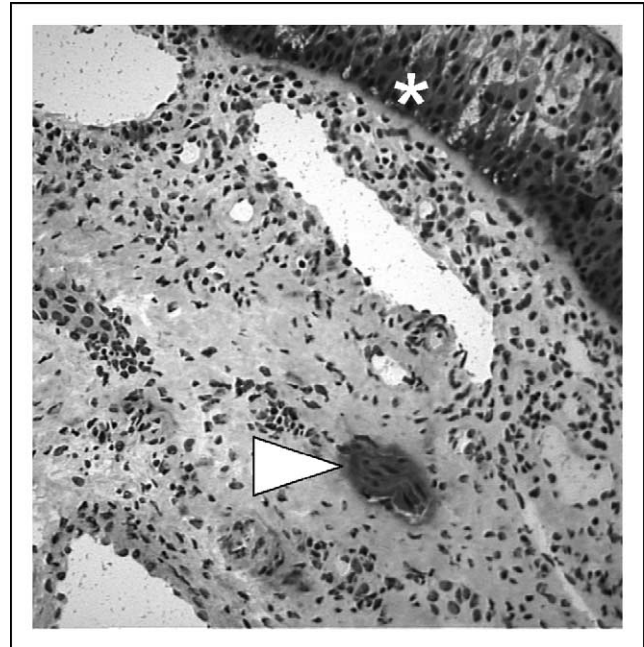
Quantitative analysis of brain-derived neurotrophic factor (BDNF) expression defined as staining intensity in nasal mucosa of allergic rhinitis at baseline (T₀) and 24 after nasal allergen provocation (T₂₄), presented as box blot graph with median (line within the box) and interquartile range (edge of box, $n = 9$; ** $P < 0.01$). Reproduced with permission from reference [23**].

[23**]. Additionally, nasal BDNF expression was significantly increased after allergen provocation but only in allergic rhinitis and not in controls (Fig. 2) [23**]. This finding is interesting, as neurotrophins may also participate in late phase reactions with special regard to remodelling activities. In this regard, NGF has been shown to exert profibrogenic effects on skin and lung fibroblasts indicating a role for NGF in tissue repair and fibrosis [30].

Single nasal allergen provocation however displayed no impact on bronchial BDNF and NGF expression as shown in patients with allergic rhinitis and controls [23**]. This may be related to the single allergen provocation or to the fact that different mechanisms other than neurotrophins are responsible for upper and lower airway interactions in allergic rhinitis.

The low-affinity neurotrophin receptor p75^{NTR} is expressed on basal epithelial layer and peripheral nerves in bronchial and nasal mucosa in allergic rhinitis (Fig. 3) and control individuals [23**]. This is in agreement with the finding of Ricci *et al.* [31] who assessed an expression of p75^{NTR} on neurons in human lung. Interestingly, our group found a lower number of p75^{NTR} positive nerve bundles in nasal mucosa of allergic rhinitis compared with control individuals at baseline levels. An explanation for this lower expression could be the internalization of p75^{NTR} and, thereby, the downregulation of receptor surface expression. In a mouse model it was shown that p75^{NTR} contributes to airway hyperreactivity and airway

Figure 3 Expression of p75^{NTR} in human nasal mucosa



Immunohistochemical staining of pan-neurotrophin receptor (p75^{NTR}) in nasal mucosa section of a patient with allergic rhinitis. Arrow points to p75^{NTR} positive nerve, asterisk marks p75^{NTR} positive basal epithelial layer. Magnification $\times 200$.

inflammation in the lower airways [32]. However, in our study we did not find a correlation of p75^{NTR} expression and clinical data, suggesting that other mechanisms than p75^{NTR} are functionally involved in upper airway hyper-responsiveness in humans.

Both high-affinity (trkA) and low-affinity receptors (p75^{NTR}) for NGF have been found not only on nerves, but also on nasal epithelium, submucosal glands, for trkA also on endothelial cells and for trkB on mast cells [23**,27]. The latter with a downregulation after nasal allergen provocation in patients with allergic rhinitis. Together with the finding of increased BDNF expression after nasal allergen provocation trkB downregulation may be due to receptor binding in allergic rhinitis.

The finding that neurotrophin receptors are expressed in cells other than nerves supports the notion that the role of neurotrophins is broader than simple modulation of the sensorineural system.

Eosinophils and neurotrophins in allergic rhinitis

Normal human eosinophils constitutively express mRNA for NGF and neurotrophin-3. They synthesize and store these neurotrophins intracellularly, and continuously replenish them [33]. Toyoda *et al.* [34] found that

NGF is localized in the central core of stable granules in human peripheral blood eosinophils from patients with atopic dermatitis. Proteins of BDNF, neurotrophin-3 and NGF were also detectable by Western blot and fluorescence activated cell sorting (FACS) analysis in eosinophils of allergic asthma patients and controls [35]. In this regard, NGF levels were significantly higher in lysates of eosinophil granulocytes derived from patients with asthma compared with controls. Further, stimulation with platelet-activating factor (PAF) after priming with granulocyte macrophage-colony stimulating (GM-CSF) led to a dose-dependent release of NGF and BDNF of eosinophils. This is in accordance with the finding of atopic dermatitis patients who are characterized by increased levels of NGF in freshly isolated peripheral blood eosinophils which further correlate with major basic protein (MBP) levels compared with healthy controls [34]. Functionally, NGF increases the release of IL-4 of peripheral blood eosinophils and inhibits their programmed cell death [16,36]. In addition to NGF, also neurotrophin-3/neurotrophin-4 significantly inhibited peripheral blood eosinophil apoptosis in allergic rhinitis compared with controls [15[•]]. Further, neurotrophins including BDNF and neurotrophin-3 increased the release of eosinophil protein x (EPX) of peripheral blood eosinophils of patients with allergic rhinitis [16], whereas there was no effect on eosinophil cationic protein (ECP) release [10]. Interestingly, eosinophils are releasers of BDNF as shown in atopic dermatitis suggesting autocrine stimulation mechanisms [10]. The production and release of NGF however can be down-regulated by dexamethasone in eosinophils as shown by Noga *et al.* [37] for patients with allergic asthma.

Expression of neurotrophin receptors including p75^{NTR} and trkA-C has been shown on peripheral blood eosinophils of patients with allergic rhinitis [15[•],16]. Interestingly, the expression profile was lower in allergic rhinitis patients compared with atopic dermatitis but higher compared with controls [15[•]]. A similar finding has been assessed in children with asthma, revealing a higher expression of NGF receptors on peripheral blood eosinophils if they suffered from both, allergic asthma and allergic rhinitis [38].

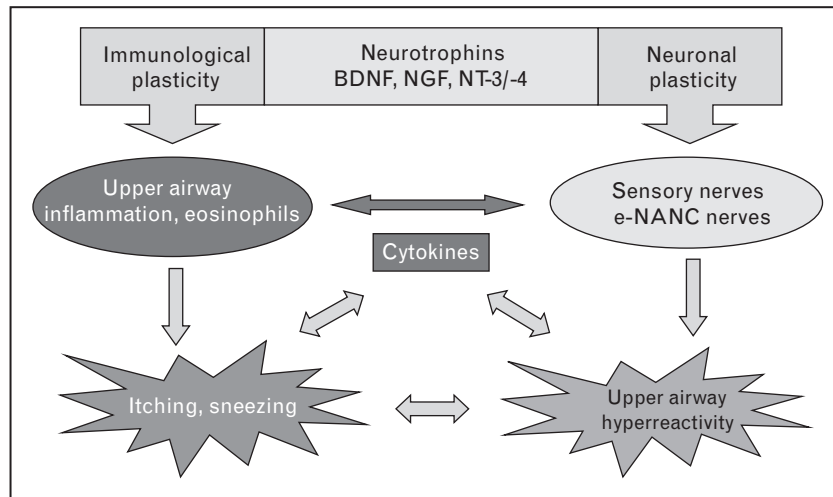
Regarding direct neuroimmune interactions between eosinophils and nerves, Kobayashi *et al.* [33] revealed a promotion of neurite extension of the PC-12 pheochromocytoma cell line by supernatants derived from human peripheral blood eosinophils stimulated with IgA immune complex and IL-5. Eosinophil supernatants contained increased levels of NGF and neurite outgrowth was abolished by pretreatment of supernatants with anti-NGF neutralizing antibody. Thus, Kobayashi *et al.* provided the first evidence for a modulation of the functional activity of nerves by eosinophils through the release of biologically active NGF.

Together, eosinophils are not only a source of neurotrophin, they are also functionally activated upon neurotrophin stimulation. Further, eosinophils are able to release neurotrophins with a functional effect on peripheral nerves. Interestingly, eosinophils can be found in close vicinity to nerves [39]. Therefore, neurotrophins serve as prime candidates for neuroimmune interactions between eosinophil granulocytes and neurons underlining their bidirectional interaction in allergic diseases including allergic rhinitis.

Neurotrophins and hyperresponsiveness

NGF has been shown to induce biochemical as well as structural changes in nerves that can lead to hyperresponsiveness [12]. In this regard, several animal studies reveal an increased airway responsiveness in mice overexpressing NGF and in guinea pigs exogenously supplied with NGF [40,41]. Treatment of sensitized and aerosol challenged BALB/c mice with blocking anti-NGF antibodies inhibited allergen-induced early-phase reaction and suppressed airway inflammation [42]. Further, sensitized and challenged transgenic mice constitutively overexpressing NGF in the airways (Clara-cell secretory protein promoter [CCSP]-NGF-tg) display an augmented early-phase reaction, airway inflammation, as well as percental relative increases in serotonin levels compared with wild-type mice. In addition, CCSP-NGF-tg mice have an increased reactivity of sensory neurons in response to inhaled capsaicin demonstrating NGF-mediated neuronal plasticity [42]. The mechanism of NGF action depends on the pan-neurotrophin receptor p75 (NTR). This receptor is expressed both in normal and asthmatic lungs and airways. Analysis of p75(NTR^{-/-}) mice, as well as in-vivo blocking of p75(NTR), revealed that airway inflammation is to a large extent dependent upon functional receptor expression, whereas neuronal hyperreactivity depends entirely on this receptor [32]. In a study of allergic mice selectively expressing p75^{NTR} in immune cells, allergen sensitization and provocation led to normal inflammation but no sensory nerve hyperreactivity, whereas mice selectively expressing p75^{NTR} in nerve cells displayed a diminished inflammation and a distinct sensory nerve hyperreactivity [18]. These data indicate that p75^{NTR} plays a dual role by promoting hyperreactivity of sensory nerves and airway inflammation, thus indicating that antagonization of p75^{NTR}-mediated signals might be a novel approach in asthma therapy. Further, treatment with the tyrosine kinase inhibitors (K252a or tyrphostin AG879) both inhibited the development of allergic hyperreactivity (AHR) in a guinea pig model for allergic airway inflammation [43].

In humans, individuals with active allergic rhinitis were found to have a significantly greater sensitivity and reactivity of the sneezing reflex, a significantly greater

Figure 4 Concept of the neuroimmune network in allergic rhinitis

Concept of the neuroimmune network in allergic rhinitis, featuring clinical symptoms including sneezing and itching in addition to nasal hyperresponsiveness. Neurotrophins bridging the gap between neuronal and immunological plasticity of allergic rhinitis. BDNF, brain-derived neurotrophic factor; NANC, nonadrenergic noncholinergic nerve system; NGF, nerve growth factor; NT-3, neurotrophin-3. Adapted with permission from [7].

secretory responsiveness to sensory nerve stimulation and a significantly greater plasma extravasation indicated by albumin leakage following capsaicin nasal challenge compared with healthy individuals [44]. As these patients were characterized by increased levels of NGF in nasal lavage it was concluded that neurotrophins including NGF may be implicated in neural hyperresponsiveness.

A participation of neurotrophins in nasal responsiveness has been confirmed by our group [23^{••}]. In this study, nine patients with mono-allergy to grass pollen and nine age matched nonatopic controls underwent nasal allergen provocation with grass pollen. Compared with the expression of BDNF at baseline we found an increased expression 24 h after nasal allergen provocation in allergic rhinitis patients, but not in controls. Interestingly, the increased expression of nasal BDNF positively correlated with the maximal increase of total nasal symptom score in allergic rhinitis patients [23^{••}], thus underlining its pivotal role in upper airway pathophysiology.

The concept of neuroimmune interactions in allergic rhinitis

Patients with allergic rhinitis feature both airway inflammation and airway hyperresponsiveness to non-specific stimuli which is partly neurally controlled. Neurotrophins have been shown to be exceptional in supporting survival of neurons in the central and peripheral nervous system. In addition, neurotrophins including NGF and BDNF promote haematopoietic colony growth and participate in wound healing and tissue repair, contributing to airway remodelling in

inflammatory conditions. Therefore, the observations of NGF and BDNF expression in upper airways with increased expression after nasal allergen provocation and correlation with clinical symptoms reveal important implications for the pathophysiological role of neurotrophins in mucosal immunity and inflammation pointing to neuroimmune interactions. Thus, production of NGF and BDNF may represent a well integrated mechanism for maintaining and/or restoring homeostatic functions of nasal tissue during or after inflammation in allergic rhinitis. Interestingly, neurotrophins including NGF and BDNF functionally activate key effector cells as shown for eosinophils, underlining their role for the immunological plasticity. Further, eosinophils, which have been detected in close vicinity of airway nerves produce neurotrophins including NGF orchestrating neuronal feedback mechanisms. This bidirectional interaction of neurotrophins between nerves and key effector cells bridges the gap between neuronal and immunological plasticity (Fig. 4).

Conclusion

Allergic rhinitis presents a complex disease in which neurotrophins play an important role for upper airway pathophysiology. Research on neurotrophins in allergic rhinitis is thus becoming a progressively more exciting field and may reveal new and promising therapeutic options for the future.

Acknowledgement

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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