



Neurotrophic factors and nerve growth factor in ocular allergy

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Purpose of review

During allergic reaction, nervous and immune systems mutually interact through release of mediators, including neurotrophic factors and nerve growth factor (NGF). These mediators modulate allergic reaction through binding their receptors expressed by immune and structural cells and by stimulating neuropeptide release by nerves. The role of neuropeptides and NGF has been demonstrated in allergic asthma and rhinitis, and, to a lesser extent, in allergic conjunctivitis. The aim of this review are to elucidate the evidence of the role of NGF and neuropeptides in the pathogenesis of allergic conjunctivitis.

Recent findings

NGF modulates allergic reaction by stimulating release of cytokines, inflammatory mediators and neuropeptides by immune and structural cells and nerve endings at the site of inflammation. Evidence showed that local and systemic NGF levels increase in patients with allergic conjunctivitis, including allergic rhinoconjunctivitis, vernal keratoconjunctivitis and atopic keratoconjunctivitis. We recently described an increase of conjunctival p75NTR expression in patients with allergic rhinoconjunctivitis, and an increase of tear levels of NGF after conjunctival provocation test with allergen.

Summary

NGF modulates ocular allergic reaction. Increasing understanding of the role of neuropeptides in allergic conjunctivitis may pave the way to the development of novel therapeutic approaches and improvement of patients' management.

Keywords

allergic conjunctivitis, nerve growth factor, neuropeptides, substance P, vernal keratoconjunctivitis

INTRODUCTION

In the recent years, a mutual interaction between immune and nervous systems has been described, and the concept of neuroinflammation has been established [1,2]. In fact, an interplay between nerves and immune cells has been demonstrated in physiologic state and pathologic conditions, including allergic diseases [3].

The main actors of this neuroimmune reaction are neurotrophins, which play a role in the pathogenesis and development of allergic diseases [1,4,5]. In fact, it has been showed that peripheral nervous system through the release of neuromediators influences most of the clinical manifestations of allergic diseases, such as redness, itching, mucous secretion, airways hyper-reactivity and bronchospasm [3].

Among the neurotrophins involved in the allergic reaction, nerve growth factor (NGF) is the most characterized [5]. NGF is the founder of the neurotrophin family, including brain-derived neurotrophic factor (BDNF) and neurotrophin (NT)-3, NT4 and NT5 [6]. Several evidence demonstrated that

NGF plays a key role in allergic inflammation and experimental evidence suggested that inhibiting NGF is effective in controlling allergic reaction [7,8]. Neurotrophic factors are released by immune cells and mucosal structural cells at the site of allergic reaction and exert their effects by inducing secretions of cytokines, inflammatory mediators and neuropeptides by immune cells and nerve endings [6,8,9].

As the role of neuromediators and neuropeptides has been well characterized in allergic airways diseases, more recently, increasing evidence showed that neuroinflammation plays a role also in ocular surface inflammatory conditions, including allergic

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KEY POINTS

- NGF and neurotrophic factors play an active role in the pathogenesis of allergic conjunctivitis.
- Tear and conjunctival levels of NGF and its receptors are increased in patients with allergic conjunctivitis.
- During allergic inflammation, NGF acts by binding its receptors expressed by immune and structural cells and nerves.
- NGF modulates allergic inflammation by inducing secretion of neuropeptides, such as substance P and CGRP by nerve terminals.

conjunctivitis [8[•],10]. In fact, experimental and preliminary clinical studies showed changes of systemic and local levels of NGF and neuropeptides in ocular allergic conditions, including allergic rhinoconjunctivitis (ARC), atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC) [11,12,13^{••},14]. Specifically, increased levels of neurotrophins were described in sera, tears and conjunctiva of patients with allergic diseases, which were further increased after conjunctival allergen provocation [13^{••},15,16^{••}]. These mediators, including NGF, BDNF, substance P (SP), calcitonin gene-related peptide (CGRP), and vasoactive intestinal peptide (VIP) are believed to be responsible for at least some of the symptoms of allergic conjunctivitis, such as itching, vasodilatation and extravasation [11,13^{••},17].

The aim of this review is to elucidate the evidence of the roles played by NGF, other neurotrophic factors and neuropeptides in the onset and development of allergic conjunctivitis.

ROLE OF NERVE GROWTH FACTOR IN ALLERGIC DISEASES

During allergic reaction, the interplay between nervous and immune cells depends upon several factors including neurotrophic factors and neuropeptides, which interact with both immune and structural cells and modulate the immune responses [9,18]. The most studied neurotrophic factor in allergic disease is NGF, the first identified and best characterized member of the neurotrophin family [5]. Neurotrophins exert their function by binding their respective high-affinity tropomyosin receptor kinases (trk), TrkA for NGF, TrkB for BDNF and NT-4 and TrkC for NT-3 and the low-affinity pan-neurotrophin receptor p75NTR, which binds all neurotrophins [6,19]. NGF is a pleiotropic factor, essential for the survival, differentiation, and

function of peripheral and central nervous system, and extends its biologic action to cells of the immune and endocrine systems [5].

An involvement of NGF in allergic disease was firstly supposed by the evidence of high levels of serum NGF in a parachutist who had an allergy attack the day before parachute jumping [20]. Subsequent studies demonstrated increased levels of serum NGF in patients with allergic disease, and that serum NGF levels correlated with the number of mast cells in the conjunctiva of patients with VKC [15,16^{••}]. In addition, NGF levels were found increased in bronchoalveolar lavage fluid (BALF) in patients with asthma and in nasal lavage fluids in patients with allergic rhinitis, in which NGF was further increased after allergen provocation [21–24]. An increase of serum BDNF levels was also described in patients with asthma, in which NGF, BDNF and NT-3 levels in BALF were increased after allergen challenge [25,26].

The role of neurotrophins in the pathogenesis of allergic reaction is supported by experimental evidence showing that NGF is released by a variety of cells, including neurons, immune cells, such as lymphocytes and mast cells, and structural cells, such as epithelial cells, fibroblasts and smooth muscle cells [27,28]. Furthermore, NGF receptors are expressed by mucosal epithelial and immune cells, including mast cells, eosinophils, and lymphocytes [29]. NGF directly exerts several effects on immune cells, including stimulation of mast cell degranulation, granulocytes and macrophage differentiation, lymphocytes B-cell and T-cell proliferation, and differentiation [6]. In addition, an in-vitro study showed that PHA activation induces NGF secretion in human lymphocyte-T-helper (Th) type 0 (Th0) clones and Th2, but not in Th1 supporting the role of NGF in the allergic reaction [27].

In animal models of allergic asthma, it has been demonstrated that allergic airway inflammation is associated with increase of local NGF and BDNF production and that NGF acts as an amplifier for Th2 effector functions [30–32]. Furthermore, the administration of anti-NGF antibodies in animal models of allergic asthma showed to reduce bronchial constriction and allergic airway inflammation, by up-regulating Th1 and Tregs mediators (IFN γ , IL-10, TGF β , T-bet and Foxp3), and down-regulating Th2 and Th17 mediators (IL-4, TNF α , IL-17A, ROR γ T and GATA-3) [33[•]]. An experimental study demonstrated that *p75*-gene deficient mice, showed inhibition of airway eosinophilia, hyper-responsiveness and IL-4 and IL-5 in BALF following OVA challenge [34]. Similarly, treatment with anti-NGF antibodies of animal models of atopic dermatitis significantly inhibited the development of skin lesions and inhibited scratching [35].

Several evidence showed that neurotrophins modulate allergic reaction also by inducing production and release of neurotrophins in the local environment of nerve endings [4,6,36]. Neurotrophins, binding their receptors on nerve terminals, stimulate the production of tachykinins, such as substance P, neurokinin A (NK) and CGRP [37,38]. These sensory neuropeptides released from the sensory nerves act through binding their specific receptors, neurokinin 1 receptor (NK1R), NK2 and 3 receptors for tachykinins and receptor activity-modifying protein (RAMP) 1, RAMP2 and RAMP-3 for CGRP on immune cells and structural cells and are able to induce vasodilation, plasma extravasation, bronchoconstriction and mucus production [9,10,39]. Several evidence demonstrated an increase of neuropeptides at the site of allergic reaction [40–43]. In-vitro studies demonstrated that neuropeptides, including SP, CGRP and neuropeptide Y (NPY), stimulate mast cells degranulation, act as chemoattractant for eosinophils, induce lymphocytes T cells secretion of cytokines (IL-2, IFN- γ , IL-4, and IL-10) and are able to influence Th1 and Th2 populations [10,43–50].

OCULAR SURFACE AND NEUROTROPHIC FACTORS

The ocular surface is a functional unit, composed by the tear film, cornea, conjunctiva, lacrimal gland, and their related innervation. These structures mutually interact through release of mediators, including cytokines, growth factors and neuropeptides with the common goal to maintain integrity and to protect the eye. Structural cells, nerves and immune cells of the ocular surface participate to the modulation of tear production by lacrimal glands, mucous secretion by conjunctival goblet cells and corneal epithelial proliferation [51–53]. Ocular innervation contributes to this regulation, by providing ocular surface sensation, stimulating tear reflex, and also by producing neuromediators, which promote epithelial cell proliferation and differentiation. Conversely, epithelial cells influence

nerve function and survival by releasing growth factors, such as NGF, in a mutual interaction [53].

The wide expression of neurotrophic factors and neuropeptides by posterior and anterior segment of the eye, including nerves, structural and immune cells of the ocular surface support the hypothesis of an active role of corneal and conjunctival cells in physiological state [54–57]. Specifically, in healthy subjects, NGF, BDNF, NT-3, NT-4 and their receptors TrkA, TrkB, TrkC and p75NTR are expressed by ocular surface cells, including corneal and conjunctival epithelium and stroma [51,54,58–60] (Table 1). NGF is able to stimulate corneal and conjunctival epithelial cell proliferation and differentiation, and both NGF and BDNF stimulate goblet cell secretion [51,52,61–63]. Tear film also contains NGF, BDNF, NT-3, NT-4, SP, CGRP and NPY in healthy individuals, suggesting a role of these neuropeptides in the maintenance of ocular surface homeostasis [11,13²²,55,64]. Furthermore, changes of NGF pathway at the ocular surface has been described in several pathologic conditions, such as allergic conjunctivitis, dry eye, herpetic keratitis, limbal stem cell deficiency and in corneal transplant outcomes [13²²,52,54,65–67].

ROLE OF NEUROMEDIATORS IN ALLERGIC CONJUNCTIVITIS

Allergic conjunctivitis is classified in different clinical forms, seasonal and perennial allergic rhinoconjunctivitis (ARC), or hay fever, and vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC) [68]. The latter are more severe forms, characterized by intense ocular symptoms and frequent involvement of the cornea and potential impairment of visual function [69]. Allergic reaction at the ocular surface is characterized by conjunctival infiltration of lymphocytes, mast cells and eosinophils and by lymphocyte-T-helper type 2 (Th2) immune response [68,70,71].

Allergic conjunctivitis is associated with the presence of goblet cells hyperplasia, increase of mucus secretion and conjunctival hyper-reactivity [72–74]. Advances in the understanding of allergic

Table 1. Nerve growth factor and nerve growth factor receptor expression at ocular surface structures in healthy subjects

	NGF	TrkA	P75NTR
Corneal epithelium	++ (51,59)	++ (51,54)	+ (58)
Corneal stroma	+ (Keratocytes) (51,59)	+ (51)	+ (Keratocytes, nerves) (58)
Conjunctival epithelium	+ (14)	+(13,54,60)	+(13,60)
Conjunctival stroma	+ (Fibroblasts, immune cells)	+ (Fibroblasts, immune cells) (54,60)	+ (Fibroblasts) (60)
Tears	+ (13,55)	–	–

NGF, nerve growth factor; TrkA, tropomyosin receptor kinase A.

conjunctivitis pathogenesis overcome the classic mechanism of type I hyper-sensitivity and mast cells' activation, demonstrating an involvement of neuroinflammation [10,54]. However, the mechanisms of action and the specific role of neuropeptides in the pathogenesis of allergic conjunctivitis has not yet completely understood.

The role of NGF in allergic conjunctivitis was firstly suggested by the evidence of a significant increase of circulating NGF levels in patients with VKC, when compared with healthy subject [15]. In this study, the increase of NGF plasma levels were significantly correlated with the number of mast cells in the tarsal and bulbar conjunctiva [15]. A subsequent study demonstrated that NGF plasma levels were also increased in patients with asthma, rhinoconjunctivitis, and urticaria–angioedema when compared with healthy controls [16²²]. These results further supported the hypothesis of a role of NGF in the modulation of allergic reaction. However, the evidence of an increase of NGF could be also explained as an epiphenomenon, namely the result of an increased production of NGF by

inflammatory cells involved in allergic conjunctivitis. In fact, mast cells structurally and functionally interact with nerves and are able to synthesize and release NGF [5]. To better clarify the role of NGF in allergic conjunctivitis, subsequent studies evaluated the conjunctival biopsies of patients with VKC showing that immunoreactivity for both NGF and trkA in the conjunctival stroma were increased when compared with healthy subjects [14,54]. Interestingly, conjunctival stroma of VKC patients showed an increase of immune cells, which expressed TrkA in approximately 80% of activated eosinophils and 80% of the T-helper lymphocytes (CD4 positive) [54]. These results strongly supported the hypothesis of an active role of NGF in the modulation of allergic inflammation through binding to its receptors, expressed by epithelial cells, lymphocytes, mast cell, and eosinophils.

A recent allergen challenge study, evaluated the involvement of TrkA and p75NTR pathway in patients with allergic rhinoconjunctivitis (ARC) before and after conjunctival provocation test (CPT) with allergen (Fig. 1). This study showed that

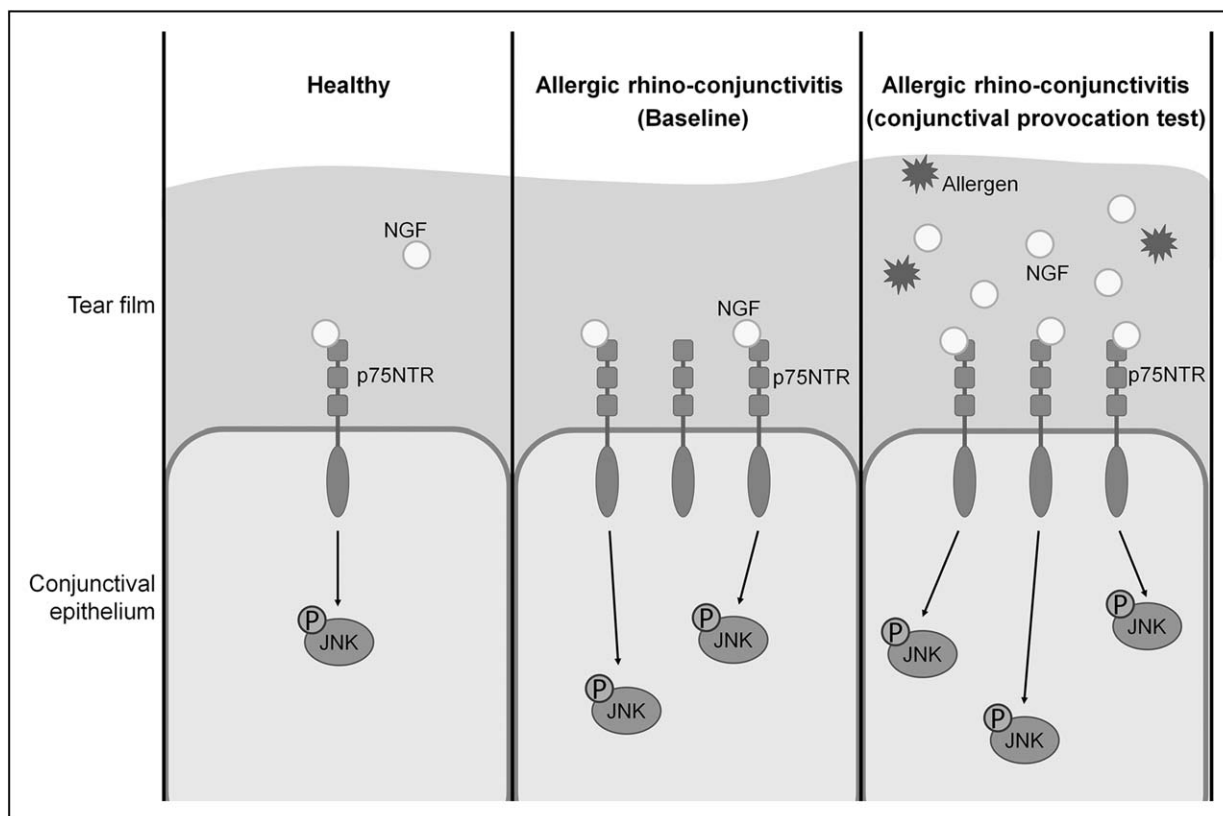


FIGURE 1. Our results showed that conjunctival epithelium of patients with allergic rhinoconjunctivitis in the quiescent phase showed significant increase of conjunctival expression of p75NTR and stress-activated protein kinase/c-Jun NH(2)-terminal kinase (SAPK/JNK), when compared with healthy subjects (a and b). Conjunctival provocation test (CPT) with allergen induced an increase of tear levels of NGF and of conjunctival SAPK/JNK activation suggesting that NGF acts through p75NTR pathway during the allergic inflammation (c). ARC, allergic rhinoconjunctivitis; NGF, nerve growth factor.

patients with ARC in the quiescent phase showed significant increase of conjunctival expression of p75NTR and its downstream signalling molecules stress-activated protein kinase/c-Jun NH(2)-terminal kinase (SAPK/JNK) and p53, but not of NGF and TrkA, when compared with healthy controls, suggesting a role of p75NTR in the pathogenesis of allergic conjunctivitis [13²²]. After specific allergen challenge patients with ARC showed a significant increase of tear NGF levels and of conjunctival SAPK/JNK and p53 phosphorylations as compared with baseline values. These results suggested that conjunctival epithelium plays an active role during ocular allergic inflammation and that NGF is involved through p75NTR/JNK pathway [13²²].

Few data are available on the role of the other neurotrophins in allergic conjunctivitis. However, an increase of all neurotrophins, namely NGF, BDNF, NT-3 and NT-4 were described in patients with AKC when compared with healthy subjects [75]. In this study, patients with AKC showed further increase of tear NGF, BDNF, NT-3 and NT-4 levels after exposure to passive smoking supporting the hypothesis of a role of neurotrophins in the pathogenesis of conjunctival hyperreactivity [72,74,75].

To summarize, several studies provide evidence to support the hypothesis that NGF and neurotrophins released by conjunctival epithelial and immune cells during ocular allergic reaction, modulate allergic reaction through binding with Trk and p75 expressing cells, including nerves, conjunctival epithelial cells, eosinophils and T-helper lymphocytes.

In addition, NGF modulates the allergic reaction through the induction of secretion of neuromediators by nerves' terminals, such as of substance P and CGRP [37,38]. It has been demonstrated that not only circulating NGF but also SP were increased in patients with VKC when compared with healthy subjects, and that tear and conjunctival levels of SP increased in patients with allergic conjunctivitis [41,76]. The hypothesis of a role of these mediators in allergic conjunctivitis, was further confirmed by the demonstration of a significant increase of tear levels of SP, CGRP and VIP after specific CPT with allergen in patients with allergic conjunctivitis in the quiescent phase [11]. The results of this study suggested that locally released neuromediators contribute to allergic reaction by inducing conjunctival itching, hyperemia and chemosis [11]. An experimental study with animal model of allergic conjunctivitis also showed that nasal and conjunctival levels of SP, VIP, and NGF increased 1 and 24 h after nasal challenge with ovalbumin [38].

CONCLUSION

Allergic conjunctivitis is very frequent in the young and adult population and represents a relevant social burden because of decreased quality of life and social function of patients [77]. Increasing understanding of neuroimmune interaction during allergic reaction at the ocular surface is of high interest in order to increase knowledge of allergic conjunctivitis pathogenesis and to open novel research and therapeutic perspectives. In fact, current treatments for allergic conjunctivitis only address the immunological basis of the allergic reaction and as antihistamine drugs are only partially effective in controlling allergic symptoms, corticosteroid drugs have a marked suppressive effect on the allergic inflammation, with a great control of symptoms, but their chronic use is associated with a high risk of side effects, such as cataract and glaucoma [68]. Therefore, identifying novel pharmacological targets, able in controlling allergic reaction and ameliorating clinical outcomes of patients with allergic conjunctivitis may significantly improve the management of these conditions. However, from the first evidence of a role of neurotrophins during allergic conjunctivitis, only few studies focalized on the mechanisms of action of neurotrophins on ocular allergic diseases. The evidence of an increase of NGF and its receptors' local and systemic levels in patients with ARC, VKC and AKC demonstrate that NGF plays an active role in the pathogenesis of allergic conjunctivitis [13²²,14,15,54]. In addition, experimental studies suggest that inhibiting NGF is effective in controlling allergic reaction [5,7,78]. As consequence, NGF represents an interesting candidate to be a therapeutic target in allergic diseases. To date, no well tolerated and effective NGF antagonists are available for clinical use, however, different strategies to inhibit NGF without side effects, such as small molecules and mimetic peptides are under investigation [79]. Further studies are necessary to evaluate the potential inhibition of NGF and/or its receptors as a potential therapeutic approach in allergic conjunctivitis.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
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