

The role of neuromediators in ocular allergy

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Purpose of review

To describe and highlight the critical role of neuromediators in ocular allergy, in view of the recent findings indicating that particularly neuropeptides and neurotrophins exert a pivotal role in the complex network of neurogenic inflammation occurring in ocular allergy.

Recent findings

Neuropeptides and neurotrophins represent an interesting group of neuromediators actively taking place in allergic response. Mainly released at the neuronal edge or from immune and/or structural cells, neuropeptides and neurotrophins might either upregulate or downregulate inflammatory processes. These mediators contribute to ocular allergy by acting directly on cells responsible for both early and late phase reactions as well as on epithelial cells and fibroblasts, leading to either self-limiting or chronicity states.

Summary

This short review surveys our current knowledge on the functional activity showed by substance P, calcitonin gene-related peptide, vasoactive intestinal peptide, neuropeptide Y and nerve growth factor and integrates their opposing effects in the context of neuroimmune interactions during ocular allergy. In addition, the review will provide implications for the clinical situation and/or future strategies for treating the most severe chronic forms of ocular allergy.

Keywords

neurogenic inflammation, neuropeptides, neurotrophins, ocular allergy

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Introduction

During allergic inflammation, a bidirectional regulation of neuronal stimulation and allergic response has been prospected. Neuromediators represent the key factor of this process, working on either immune or structural cells and exerting neuroimmunomodulatory functions in retaining homeostasis and inflammatory/tissue remodeling process. According to recent findings, some modulatory aspects of substance P, calcitonin-gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), neuropeptide Y (NPY) and nerve growth factor (NGF) will be herein summarized and discussed. Understanding of the complex interactions between immune/structural cells and neuromediators might be relevant for a new generation of therapeutic approaches for treating ocular allergy.

The ocular allergy

The ocular allergy is a common disorder affecting 20% of the population in the developing countries. Ocular allergy comprises the acute (self-limiting) type-I hypersensitivity seasonal and perennial allergic conjunctivitis

(SAC and PAC) and the more complex, chronic and severe forms of atopic (AKC) and vernal keratoconjunctivitis (VKC), and giant papillary conjunctivitis (GPC) [1]. Disease severity can range from mild itching and redness (SAC and PAC) to the more serious vision-threatening forms affecting the cornea (AKC and VKC) [1].

As first contact to allergens, antigen presenting cells (dendritic cells) share processed allergens to CD4⁺ T-helper (Th) precursor cells and depending on the binding affinity, either a Th1 or a Th2 phenotype is amplified. Th2 phenotype implies a genetic predisposition, and selective cytokine release regulates IgG–IgE switching in B cells. The early phase reaction is IgE-mediated and due to FcεRI-dependent mast cell activation/degranulation, with the release of proinflammatory, immunoregulatory and tissue regulatory mediators [2]. Some mediators are preformed and granule-associated (histamine, proteoglycans such as heparin and chondroitin sulfate, and neutral proteases such as tryptase and chymase), whereas others are newly generated lipid mediators (prostaglandins and leukotriens), cytokines and chemokines [2]. The late phase reaction is mainly dependent on the recruitment/

activation of eosinophils and T cells [2], which are able to release and respond to soluble mediators and cytokines. IgE, histamine, eosinophil cationic protein (ECP), tryptase and some cytokines (IL-4/IL-13) are detected in tears and conjunctiva of allergic patients, representing useful indicator of allergic mechanisms and possible therapeutic targets [2,3]. Besides a clear-cut pathological role of mast cells, also eosinophils, T-cells, epithelial cells and fibroblast/myofibroblasts contribute to the pathogenesis of ocular allergy and all together are responsible for the more severe symptoms (fibrosis and corneal damage), whenever present [2].

A cross-talk between mast cells, eosinophils and fibroblasts might take part during chronic stages, regulating either perpetuation of allergic inflammation and tissue fibrosis and/or remodeling [4,5]. Understanding the complex interactions between cells, cytokines and other mediators might be relevant as basis for new therapeutic approaches.

The ocular innervation: a physiopathological point of view

The sensory as well as the autonomic sympathetic and parasympathetic pathways innervate the ocular surface. The cornea is densely innervated by sensory fibers and, to a less extent, by sympathetic and parasympathetic ones [6,7]. In the conjunctiva, a sensory and sympathetic/parasympathetic network occurs within the stroma and surround the epithelium. Epithelial layer express some specific muscarinic/adrenergic receptors that regulate tear homeostasis and mucin production [8,9]. Under physiological conditions, the lid motion, epithelium and the immune defense work together to gain appropriate wetting and corneal clarity/visual function preservation. Particularly, acetylcholine (ACh), from both parasympathetic neurons and epithelial cells, regulates tear fluid and aqueous humor production [10]. Corneal/conjunctival insults are detected by afferent sensory neurons; the information is relayed to the central nervous system and via the efferent sympathetic/parasympathetic nerves to reflexive movements (eye protection) and to the lacrimal gland, resulting in the local release of neuromediators. When tear film breaks down exposing the ocular surface to the external environment (low humidity, wind, contact lens, etc.), nerve stimulation drives blinking and secretion of proteins, mucins, lipids and water to retain tear film stability and/or repair injured surface. Any dysfunction in neuronal signals can lead to disorders (neurotrophic keratitis and dry-eye disease) [11], due to altered balance of tear film components or inability to reflex tear. As well, herpetic keratitis, diabetes, prolonged contact lens wearing and advanced age may lead to desensitized nerves and associated neural dysfunctions [11]. In line, previous chemical-sensory denervation and

chemical/surgical experimental sympathectomy inhibited vascular permeability or plasma extravasation. The interaction between nervous, immune and endocrine systems plays a key role not only in maintaining a healthy ocular surface but also in contributing to the local regulation at the site of inflammation [12,13]. The concept of neurogenic inflammation was conceived several years ago, after the discovery that inflammatory effects – such as blood–ocular barrier breakdown, vasodilatation, plasma-extravasation, smooth muscle contractility, mast cell degranulation, increased fibroblasts/leukocytes activities – are mediated by antidromic sensory nerve stimulation and followed autonomic activation [13,14]. Neurogenic inflammation and innate immunity work together to protect ocular surface from either pathogen, chemical and/or mechanical insults. Neurogenic network shows little activity under physiological conditions, whereas neuromediators are quickly released by either stimulated nerves or inflammatory cells upon pathological states [15]. These mediators comprise neurotransmitters, neuropeptides and neurotrophins [12–15]. Herein, our interest is devoted to the immunoregulatory role of substance P (SP), CGRP, VIP, NPY and NGF.

The neuropeptides as central mediators of neurogenic inflammation

Neuropeptides represent the key mediators between nerve and immune cells. Neuropeptides play an important role in the creation of an intraocular immunosuppressive microenvironment (ocular immune tolerance) as well as in limiting the occurrence of exacerbated inflammatory and autoimmune conditions [16••]. Neuropeptides are detected mainly in aqueous humor. Each neuropeptide contributes to suppress induction of delayed-type hypersensitivity (Th1-cells) and cytokine production, and to induce regulatory immunity. Besides nerve ending, some neuropeptides are also released by nerve-associated or inflammatory cells [11–15]. Their G-protein-coupled receptors might be present on different neuronal and nonneuronal cell types (mast cells, eosinophils, epithelial cells and fibroblasts) [15].

SP and CGRP are classic sensory neuropeptides, mainly involved in the transmission of pain [13,15,17••,18]. SP and CGRP take part in the pathogenesis of allergic response, contributing to tissue damage and/or chronicity [16••,19••]. SP and CGRP modulate recruitment, activation and functional activity of neutrophils, monocytes/macrophages, T cells, mast cells and eosinophils, and contributes to further release of histamine from mast cells [20••,21]. SP and CGRP influence Th1/Th2 phenotype switching as well as immunoglobulin isotype switching in B cells [22,23•]. SP and CGRP play an important role in wound-healing process, according to the reduced rate of wound closure in an experimental model of sensory

denervation [19^{••}]. In-vitro SP-stimulated fibroblasts triggered epithelial cell migration, a phenomenon not observed with CGRP-stimulated fibroblasts [20^{••}].

VIP is released by parasympathetic nerves and immune cells (mainly Th2 subtype), in response to either inflammatory/autoimmune or allergic conditions [24^{••}]. VIP elicits a broad spectrum of immunomodulating functions: VIP participates in maintaining immune tolerance by either regulating the balance between proinflammatory or anti-inflammatory factors; VIP triggers development of the functional regulatory T (Treg) cell phenotype (which in turn suppress primarily Th1 responses, interfering directly with the IL-12/Jak2/STAT4 signaling pathway); and finally, VIP shifts Th1/Th2 balance, promoting directly the differentiation/survival of Th2 cells and downregulating Th1 effectors [25,26^{••},27,28]. Binding to VIP receptors may lead to activation of mast cells via IgE/anti-IgE upregulated surface expression [28]. VIP effects are cAMP-dependent and through the activation of protein tyrosine phosphatases, with SHP-2 as a potential target [29[•]]. VIP regulates mucin secretion as well as stimulates the release of growth factors from corneal epithelial cells [30[•]].

Recent studies [31] indicate that NPY is produced by sympathetic nerves as well as immune cells, during physiological and pathological states. Upon nerve stimulation, NPY is quickly released by terminals and exerts pleiotropic effects on both the innate and adaptive response, with effects ranging from modulation of Natural killer cells, macrophage and T-cell migration/distribution as well as immunoglobulin production from B-cells [32] to cytokine/mediator release (neurotransmitter included) [33]. Besides the major role in the regulation of Th1 responses, NPY exact role is still an enigma. Recent studies [34] provide step forwards demonstrating that NPY has a bimodal role: a negative regulator of T-cells and an activator of antigen presenting cells function.

The neurotrophins and the neurogenic inflammation

Neurotrophins are actively released by both nervous termini and inflammatory cells and take part in the neurogenic inflammation process [35,36]. The findings achieved until now demonstrate that the neurotrophin definition for NGF, mainly based to NGF discovery occurred in the early 1950s, does not fit actually with the real NGF concern in both physiological and pathological conditions. First identified for its ability to stimulate growth, differentiation, survival and maintenance of peripheral sensory and sympathetic as well as central neurons, to date NGF appears to be able to modulate endocrine and immune systems, as well as embryogenesis

and angiogenesis [35]. This pleiotrophic factor represent the prototype of the neurotrophin gene family, which includes neurotrophin 3 and 4/5 and brain-derived neurotrophic factor [36]. These neurotrophins are widely expressed in both anterior and posterior eye segments and are significantly increased upon damage [37]. A tidy NGF contribution has been also provided in the visual system during physiological conditions [38]. A consistent contribution of NGF has been also observed in the neurogenic inflammation that develops during allergic states [39–41], even though the meaning of NGF contribution is actually a site of debate. Autocrine NGF modulates T/B cell proliferation and stimulates Th and B cells after specific activation [42]. NGF appears a communicating factor, being produced by monocyte/macrophages, neutrophils, granulocytes and lymphocytes (Th0/1/2 and B) [42]. NGF enhances the functional activity of both mast cells and eosinophils, as well as NGF appears a modulating factor for fibroblasts/myofibroblasts [39].

Neuromediators in ocular allergy: the basis for future therapies

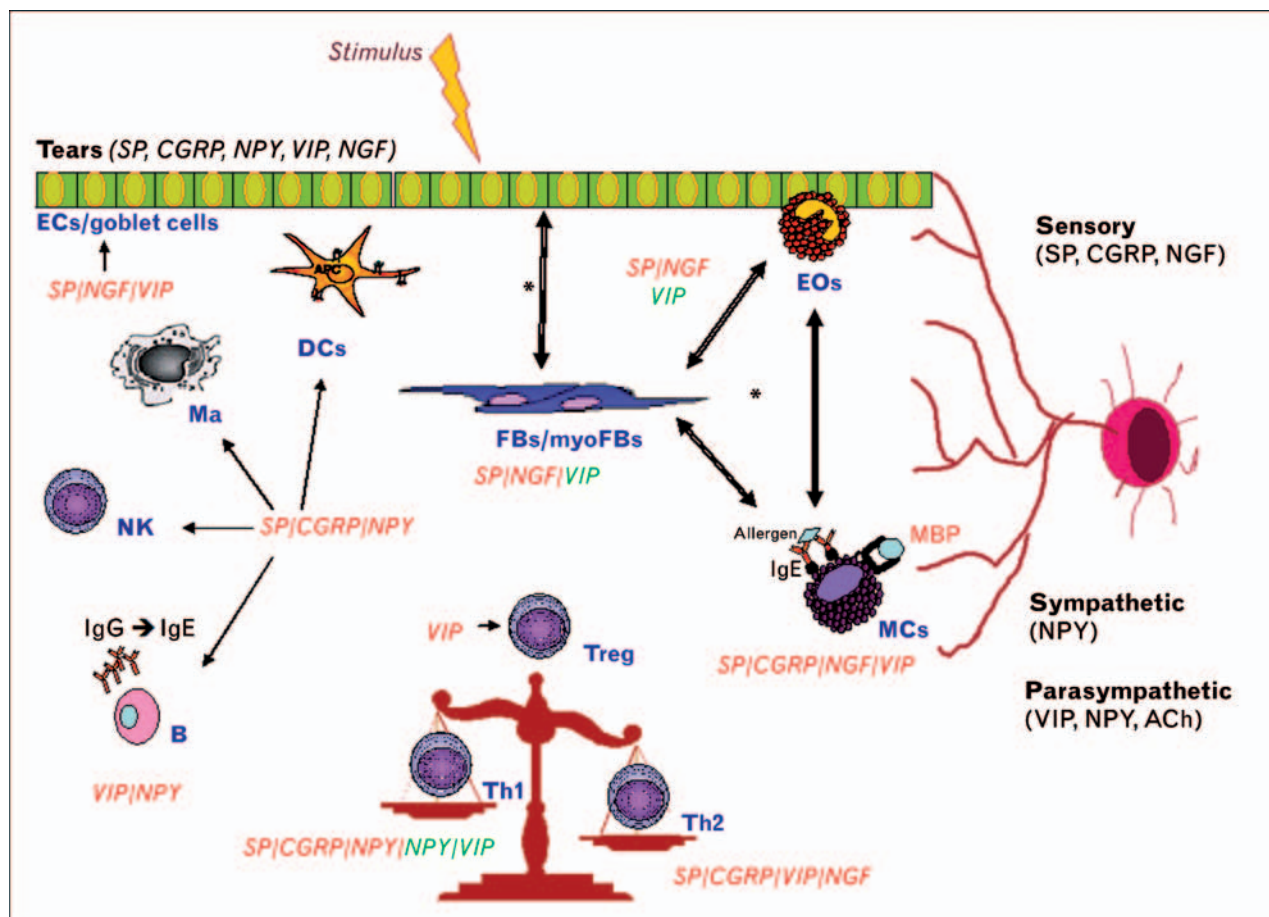
Allergic patients are characterized by increased levels of neuropeptides and neurotrophins in comparison with healthy individuals [39–41]. Particularly, SP, VIP, CGRP, NPY and NGF plasma levels are changed in asthmatic patients during disease exacerbation [39–41], implying that neuromediators may play important roles in asthma and allergic disorders. Actually the contribution of neurogenic inflammation during allergic disorders represents an open debate: it could be either specific or nonspecific response to inflammation [40].

As ocular surface is highly innervated and neuromediators are widespread expressed during physiological states, our hypothesis is that neuropeptides and neurotrophins might contribute to both maintaining ocular homeostasis and modulating pathogenesis of autoimmune/allergic ocular disorders. In 1995, our group described for the first time increased circulating NGF levels in VKC patients, in association with an increase of mast cells in inflamed conjunctiva [43]. Next, our group observed SP increases in VKC plasma and conjunctiva, suggesting a possible neuronal control of both pathogenesis and severity/chronicity of disease [44]. Recently, Motterle *et al.* [45] observed an alteration of cholinergic/adrenergic response as well as of VIP expression in VKC inflamed conjunctiva, extending our previous data. This would imply that changed expression of neuropeptides and neurotrophins, by either nerves or structural/immune cells, may trigger mechanism for neurogenic inflammation at least in VKC. As cholinergic muscarinic receptors play a role in water output control and mucous regulation under physiological conditions, the reduction

and irregular distribution of muscarinic receptors might explain at least in part the mucus hyper-production observed in VKC [45]. During inflammatory allergic states, some mediators appear significantly increased in tear/ocular tissue [3]. Besides inflammatory mediators and cytokines, neuromediators may contribute to changes in basal innervation [12,13]. Conversely, nerve-ending-derived neurotransmitters, neuropeptides and neurotrophins might directly influence immune cells and modulate the inflammatory process [15]. In concert, sympathetic and parasympathetic pathways, which are known to regulate fluid and mucus secretion under physiological conditions, might drive mucus hyper-secretion, goblet cell hyperplasia, conjunctival hyper-reactivity, plasma exudation, edema formation and activation of endothelial cells, upon pathological conditions. Finally, the release of neuropeptides and neurotrophins might contribute to tissue remodeling/fibrosis [19**].

Neuromediators might control either cell recruitment/activation and/or mediator release. Both IgE-dependent (tyrosine-kinases mediated) and IgE-independent (G-proteins mediated) mechanisms contribute to the pathogenesis of ocular allergy, affecting lid, conjunctiva and cornea, through the release of several mediators, from mainly mast cells and eosinophils. Although some newly synthesized mediators (prostaglandin and leukotriene) represent an exclusive IgE-dependent source [20**], histamine, proteases (tryptase, chymase), growth factors and some neuropeptides/neurotrophins are common to both responses. Neuropeptides and neurotrophins may influence directly/indirectly the recruitment/infiltration, differentiation and immunological activity of cells taking actively part in the process (mast cells, eosinophils, T, macrophages), by modulating both sign and symptoms of ocular allergy. Particularly, mast cells may respond to SP, VIP or NGF by releasing histamine in a

Figure 1 Cell-site neuromediator control during ocular allergy



Allergen stimulation may lead to a bidirectional communication between nervous and immune systems, through the release of several neuromediators. The panel highlights the specific cell-type contribution of substance P (SP), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), neuropeptide Y (NPY) and nerve growth factor (NGF). Stimulatory effects are indicated in red, whereas opposite effects are shown in green. The symbol asterisk indicates the presence of a bidirectional cross-talk. Ach, acetylcholine; B, B-lymphocytes; DCs, dendritic cells; ECs, epithelial cells; EOs, eosinophils; FBs, fibroblasts; Ma, macrophages; MBP, major basic protein; MCs, mast cells; NK, natural killer cells; Th, T-helper lymphocytes; Treg, regulatory T cell.

concentration-related manner [31]. This FcεRI-independent histamine release would imply a more specialized function for mast cells (gate-keepers), in both homeostasis and pathological conditions. Interestingly enough, tryptase and chymase are capable of cleaving SP/VIP and VIP/CGRP, respectively, suggesting an additional control of neuromediator activity [46]. The observation that neuropeptides and neurotrophins might regulate their own synthesis/release, either at the end-fibers or at the level of inflammatory immune cells, would imply a further amplification pathway of neuroimmune interaction during neurogenic inflammation. Actually, the role of neurotrophins in modulating neuronimmune plasticity and neurotrophin source during local inflammation still represent an open question, especially in ocular surface where complex immunoregulation mechanisms take place. NGF can influence the intensity and duration of the local immune response, by regulating neuropeptide synthesis in lymphocytes and neuronal cells [39,40,44]. NGF stimulation drives the release of SP and CGRP from mast cells [40], whereas autocrine NGF production regulates CGRP expression in activated B cells [39].

Likewise, neuropeptides and neurotrophins might influence ocular sign and symptoms by regulating the release of several mediators from immune cells (Fig. 1). In allergic conjunctivitis, the main mediator is represented by histamine, a vasoactive peptide that drives vasodilation/vascular permeability, cell proliferation, tissue growth and repair [2]. Histamine is involved in itching, flare and redness, by H1-receptor activation on blood vessels and nociceptive nerves [47]. Histamine increases vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 expression (cell adhesion/invasion), enhances IL-8/granulocyte and macrophage-colony stimulating factor) production (chemotaxis) and IL-6 production (epithelial damages) as well as epithelial cells/fibroblasts activation [14]. Quickly released in tears [1,2,47], a prolonged exposure to increased histamine has been reported in VKC, most probably due to a reduced activity of the histaminase enzymes [47]. Particularly, SP and NGF drive histamine release from mast cells [39].

Alteration in both expression/function of cholinergic muscarinic system may be implicated in the etiopathogenesis of some ocular diseases, and its pharmacological regulation (muscarinic agonists/antagonists) may have therapeutic value. In inflamed conjunctiva, muscarinic receptor activation may result in opposing effects on histamine release by recruited mast cells. Interestingly enough, primed-eosinophils release consistent amount of major basic protein (MBP), an endogenous antagonist for muscarinic receptors, which is able to trigger Ach release and regulate epithelial and inflammatory cell function [48]. Finally, neuropeptide receptors and related protein-

ases play an important role in preserving tissue integrity, as well in the regulation of inflammatory and immune responses. In VKC, VIP role is uncertain, due to its effect on Th2 response and to its downregulation of inflammation. According to recent findings from several human disorders, 'VIP also named as a very important peptide' may be considered a new candidate for therapeutic intervention and drug development [49*,50**]. A VIP efficacy in ocular experimental uveoretinitis has been recently described [51], suggesting VIP as a novel therapeutic tool also for human ocular allergy.

Conclusion

Current therapy for ocular allergy encompasses antihistamines, mast cell stabilizer, topical steroids, cyclosporine and multi-action drugs. As a recent point of view, during allergic states, several neuromediators (SP, CGRP, VIP, NPY, NGF) are released from intracellular sites or their expression is changed, driving the common signs of ocular allergic inflammation (pain, redness, swelling, heat), in concert with the classic cell types (Fig. 1). Therefore, the need to know more about the mechanism of action of these mediators will provide future and consistent roots, for development of new nonimmunological focused therapeutic strategies for ocular allergy or ones to improve conventional treatments.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 496).

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