REVIEWS

Neuropathic Pain and Itch Mechanisms Underlying Allergic Conjunctivitis

Kuruvilla M, Kalangara J, Eun-Hyung Lee F
Emory University, Atlanta, USA

Abstract

Objective: Among the constellation of symptoms that characterizes allergic conjunctivitis, many (eg, burning and stinging) can be attributed to chronic neuropathic pain. Cumulative data support that these hallmark symptoms might be linked to the effects of allergen-induced neuromodulation. This review investigates the key characteristics of neuropathic itch and pain in allergic conjunctivitis and their underlying pathogenic mechanisms.

Methods: A literature review was conducted using a PubMed search focusing on allergic conjunctivitis, neurogenic inflammation, neuropathic itch, and neuropathic pain. Articles were reviewed, and those discussing clinical course, pathophysiology, and neuronal regulation of chronic neuropathic symptoms as related to allergic disease were summarized.

Results: Recent evidence suggests that some symptoms of allergic conjunctivitis may be better represented as a chronic neuropathic disorder. We found that neurogenic mechanisms may have a significant role in chronic ocular surface inflammation from allergic inflammation. Manifestations may be associated with repeated ocular sensory nerve injury leading to an acute-to-chronic transition, which is in turn associated with neuropathologic changes (peripheral and central sensitization), neuronal dysfunction, and spontaneous ocular pain.

Conclusion: Current goals in the management of allergic conjunctivitis aim to minimize the inflammatory cascade associated with the allergic response in the initial stages of the pathogenic mechanism. Based on the mechanistic data reviewed herein, the recognition that neuronal inflammation explains many of the symptoms in allergic conjunctivitis opens new frontiers for drug discovery.


Resumen

Objetivo: Entre la constelación de síntomas que caracteriza la conjuntivitis alérgica, muchos, como la sensación de ardor y escozor, pueden ser fundamentados en el dolor neuropático crónico. Cada vez disponemos de más datos para respaldar que estos síntomas característicos podrían estar relacionados con los efectos de la neuromodulación inducida por alérgenos. En esta revisión se enfatizarán las características clave del dolor y el prurito neuropático en la conjuntivitis alérgica y sus mecanismos patológicos.

Métodos: Se realizó una revisión de la literatura utilizando una búsqueda bibliográfica en la base PubMed utilizando, como palabras clave, conjuntivitis alérgica, inflamación neurogénica, prurito neuropático, dolor neuropático. Se revisaron los artículos y se resumieron aquellos que se centraban en el curso clínico, la fisiopatología y la regulación neuronal de los síntomas neuropáticos crónicos en relación con la enfermedad alérgica.

Resultados: La literatura científica reciente sugiere que algunos síntomas de la conjuntivitis alérgica se representan mejor como un trastorno neuropático crónico. Los mecanismos neurogénicos parecen tener un papel significativo en la inflamación crónica de la superficie ocular inducida por las reacciones alérgicas. Las manifestaciones pueden estar asociadas con la lesión del nervio sensorial ocular repetida que conlleva una transición de aguda a crónica y se asocia con cambios neuropatológicos (sensibilización periférica y central), disfunción neuronal y dolor ocular espontáneo.

Conclusión: Los objetivos actuales de manejo de la conjuntivitis alérgica se centran en minimizar la cascada inflamatoria asociada con la respuesta alérgica en los estados iniciales fisiopatológicos. Sin embargo, en relación con los datos mecanísticos revisados en este documento, el reconocimiento de que la inflamación neuronal explica muchos de los síntomas en la conjuntivitis alérgica abre nuevas fronteras para el descubrimiento de nuevas opciones terapéuticas.

Background

A recent hypothesis has implicated neuronal inflammation as a novel mechanism in the pathogenesis of allergy. Several allergy symptoms, including rhinorrhea, nasal congestion, and cough, are a direct consequence of nervous system alterations [1]. Allergic inflammation can trigger complex neurogenic signaling mechanisms to manifest as neuropathic itch. Neuropathic itch is a chronic condition caused by neuronal dysregulation that typically presents with pruritus but can also present with characteristic neuropathic pain symptoms such as burning and stinging. This differentiates it from classic itch in inflammatory skin diseases, as neuropathic itch is often described as burning in quality. Although pain is not typically considered a significant symptom in allergic conditions, it is a common feature of allergic conjunctivitis (AC). Sensations of irritation and pain of varying intensity frequently accompany AC, including burning, dryness, and grittiness. Neuronal mechanisms underlying these sensations of irritation, discomfort, and itch have yet to be investigated. Delineation of the molecular pathways underlying neuronal inflammation in AC may play a key role in identifying potential therapeutic targets.

Methods

A comprehensive literature review was performed using a PubMed search with the following terms (in order of relevance): allergic conjunctivitis, neurogenic inflammation, neuropathic itch, neuropathic pain, substance P (SP), calcitonin-gene related peptide (CGRP), nerve growth factor (NGF), transient receptor potential vanilloid 1 (TRPV1), allergic rhinitis, asthma, chronic cough, and gabapentinoids. All searches were conducted in English back to 2000. Articles were reviewed, and those discussing clinical course, pathophysiology, and neuronal regulation of ocular symptoms as related to chronic allergic conjunctivitis were summarized.

Epidemiologic, Pathophysiologic, and Clinical Aspects of AC

Prevalence and Impact

Epidemiological data on AC are scarce, likely due to underdiagnosis and the fact that this disease is often linked with allergic rhinitis (AR). It is estimated that 20% of the US population reports ocular symptoms consistent with AC [2], and approximately 70%-80% of seasonal AR patients have severe ocular symptoms [3]. Ocular symptoms were as severe or more severe than nasal symptoms in approximately 70% of over 500 hay fever patients in one study [4]. In another recent survey, over 50% of nasal allergy patients stated that AC symptoms were moderately to extremely bothersome, and for 15% of these patients, the ocular component of their reactions was the most troublesome [5]. The underlying mechanisms of AC warrant further investigation.

Seasonal AC and perennial AC, which are the most common forms and the benign end of the spectrum of ocular allergy, are increasing in prevalence [6]. Vernal keratoconjunctivitis and atopic keratoconjunctivitis represent only 2% of ocular allergy cases, yet are even more severe and have a greater impact on quality of life.

Pathophysiologic

Since the discovery of 2 functionally distinct CD4+ T-cell subpopulations (T_{h1} and T_{h2}) about 30 years ago, it quickly became evident that T_{h2} cells play a crucial role in the development of allergic airway inflammation. It has been commonly assumed that a T_{h2} immune response and type I hypersensitivity form the basis of AC. The allergic response is elicited by ocular exposure to an allergen, such as pollen, that cross-links membrane-bound IgE and triggers mast cell degranulation. This release a cascade of mediators including histamine, leukotrienes, proteases, prostaglandins, and cytokines. The main contributors to the severity of AC are thought to be the allergen load on the ocular surface and locally produced specific IgE. Furthermore, there is a highly significant correlation between the presence of allergen-specific IgE in tears and ocular allergy symptoms [7]. This continued histamine release, along with increasing allergen load, leads to an expanding population of resident mast cells in conjunctival tissue, thus perpetuating the allergic response [8].

With seasonal AC, the immediate response is predominantly mast cell–mediated. However, little is known about the pathogenesis of the late phase allergic reaction corresponding to the persistent clinical inflammation that typifies ocular signs and symptoms in chronic allergic diseases. Vernal keratoconjunctivitis and atopic keratoconjunctivitis in particular are characterized by a severe late-phase reaction comprising mucosal infiltration by eosinophils, neutrophils, basophils, and T lymphocytes. Mediators released by conjunctival mast cells during the early-phase reactions also contribute to the development of late-phase inflammation during IgE-mediated AC in vivo. There is a general correlation between the degree of cellular infiltration and the severity of disease. Moreover, products from infiltrating cells are known to promote conjunctival irritation. In addition, conjunctival and corneal epithelial cells and fibroblasts mount the allergic response by producing cytokines and other factors that maintain local inflammation and lead to tissue remodeling.

Clinical Manifestations

Ocular symptoms of AC are frequently underreported. The pathognomonic symptoms of ocular allergy include itching, tearing, and conjunctival and eyelid swelling and redness. These are reflected in the Total Ocular Symptom Score questionnaire, which is used to measure symptoms of AC. However, AC patients have multiple distinguishing symptoms beyond itch including grittiness, burning and stinging (65%), and soreness (75%) [9]. They may also complain of a foreign body sensation, blurring, and photophobia if there is corneal involvement. Conjunctival hyperemia and papillae on the tarsal conjunctiva may be observed on examination. Local symptoms are often
accompanied by irritability and fatigue [3] and patients with AC have a poor quality of life, irrespective of the severity of associated nasal symptoms [10].

Neuronal dysregulation is likely to be responsible for at least some of these symptoms. Exaggerated hyperreactivity to nonspecific stimuli such as temperature changes, strong odors, and irritants is known to be a manifestation of neuronal inflammation in nonallergic and mixed rhinitis [11]. This is akin to hyperreactivity to heat, sunlight, and wind during the active phase of vernal keratoconjunctivitis, which may be reflective of neural involvement [12], as is the nonspecific increase in reactivity in the conjunctival response to histamine in AC patients [13]. In addition, exposure to nonspecific environmental stimuli, pollutants, and cigarette smoke were reported to be triggers in a substantial proportion of AC patients [14] and may be similarly attributable to neural hypersensitivity. The term vasomotor conjunctivitis has been used to describe this phenomenon [15].

Mechanisms of AC-Induced Neuropathic Pain

Sensory Nociceptive Innervation of the Ocular Surface

Peripheral origin: The ocular surface is innervated by primary sensory neurons located in the trigeminal ganglion, most of which (70%) are polymodal nociceptors [16]. The afferent C fibers express transient receptor potential (TRP) channels that play a role in many diseases. Pain and itch also employ largely overlapping transduction machinery. Transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1) are 2 such TRP channels that appear to be important in allergic responses. TRPV1 is known as a capsaicin responder, but also reacts to a host of other proinflammatory exogenous and endogenous agents. In addition, it is stimulated by several mediators that are relevant to the allergic reaction, such as histamine and bradykinin. As with TRPV1, TRPA1 is activated by inflammatory mediators including those involved in allergic disease.

TRPV1/TRPA1 receptor activation in the eye induces the release of neuropeptides such as neurokinins, calcitonin gene-related peptide (CGRP), and substance P (SP). Furthermore, activated sensory neurons can themselves directly release proinflammatory peptides into surrounding tissue (antidromic release). Other molecules known as neurotrophins (eg, nerve growth factor (NGF)), act directly on peptidergic C fiber nociceptors to potentiate TRPV1 receptors and increase the expression of substance P and TRPV1. This ultimately translates into nociception and pain [16].

Central representation: The cell bodies of sensory neurons innervating the ocular surface are located in the trigeminal ganglion and terminate in the trigeminal brainstem complex. There, they establish contact with second-order oculars neurons that project to the somatosensory cortex, where the original noxious signal is perceived as pain.

A schematic representation of the pathogenesis of ocular pain and itch is outlined in Figure 1.

Allergen-Induced Neuromodulation of Sensory Nerves

Under pathological and chronic conditions, dysfunction of the nervous system itself can generate chronic neuropathic pain and itch. This is secondary to neural plastic changes in primary sensory neurons of the peripheral nervous system (peripheral sensitization) and spinal cord, brainstem, and cortical neurons in the central nervous system (central sensitization). A significant body of physiological data suggests that allergy symptoms may be significantly modulated by the nervous system. This neural plasticity may be responsible for symptoms of neuropathic pain and itch in AC. Reflex neural activity is upregulated in the presence of allergic inflammation and further amplifies the histamine-mediated immunopathological response in the conjunctiva.

Peripheral sensitization in allergic inflammation: During chronic inflammation, including allergic inflammation, long-lasting changes develop in the expression and function of stimulus-transducing ion channels such as TRPV1 and TRPA1. This results in abnormal hyperexcitability of neurons and may evoke chronic neuropathic pain.

TRPV1 is believed to be a major cause of neuropathic pain [17]. It also has a proven role in itch and, in particular, histamine-induced itch. Chronic allergic inflammation is known to mediate plasticity of TRPV1 in airway diseases. Inhalation of allergen by rats or guinea pigs leads to the expression of TRPV1 in Aδ cough nerves [18]. TRPV1 expression and substance P levels were found to be significantly higher in patients with nonallergic rhinitis [19] and asthma, especially refractory cases [20]. Furthermore, histamine sensitizes the nociceptor TRPV1 and has been shown to contribute to visceral hypersensitivity in animals [21]. In addition, other endogenous inflammatory allergy mediators such as prostaglandin E2 and bradykinin can markedly enhance the sensitivity of TRPV1 and lower its threshold for activation of sensory nerves [22].
Inhalation of allergen also upregulates the expression of genes involved in the production of substance P and CGRP, both of which act as itch sensation-enhancing neuropeptides [23,24]. Allergen exposure also enhances the release of substance P and CGRP from sensory nerve endings (antidromic pathway). Substance P and CGRP cause antidromic stimulation of nociceptive fibers, which results in C-fiber activation and synergistically augments the allergic inflammatory reaction [24,25]. In 2017, Azimi et al [26] described the role of substance P–mediated activation of MC receptors in inducing itching in a mouse model.

Allergic reactions can also lead directly to the release of neurotrophic factors, especially NGF, from mast cells and other cells, such as the airway epithelium [27]. NGF is a complex regulator of neural plasticity that further sensitizes afferent nerves. It has been found in eosinophils and other cells, such as the airway epithelium [27]. NGF is a complex regulator of neural plasticity that further sensitizes afferent nerves. It has been found in eosinophils and other cells, such as the airway epithelium [27]. NGF levels are elevated not only in certain chronic pain conditions, but NGF serum levels have also been found to be increased in allergic diseases and asthma [29], as well as in bronchoalveolar lavage and nasal lavage fluids from these patients.

All of these factors further stimulate the vascular endothelial cells or mast cells to release even more chemical mediators such as histamine, thus producing a vicious circle of disease exacerbation.

This concept of peripheral sensitization was supported by a guinea pig model of AC, which demonstrated a reduced threshold for activation of polymodal nociceptors, as well as an augmented response to noxious chemical stimuli. The authors suggested the operation of a comparable pathway in humans. The overall changes in firing of corneal sensory fibers correlate with the foreign body and itching sensations reported by AC patients [30], thus suggesting a possible TRPV1-dependent pathway in the sensitization stage. However, further studies must be performed to confirm this finding.

The sensitization of sensory nerves results in augmented pain sensations and may be responsible for the burning quality of AC symptoms. Chronic inflammation may also damage sensory nerve fibers of the ocular surface leading to formation of neuromas that spontaneously discharge and cause unpleasant sensations, such as pain, dryness, and grittiness [16].

Central sensitization in allergic inflammation: Neuropathic pain may also result from abnormal function of higher brain structures, from where ocular trigeminal ganglion neurons project. Amplification of responses occur in the central nervous system through sensitization of central pathways, failure of inhibitory control mechanisms, or both. Central sensitization can cause secondary hyperalgesia and allodynia, thus contributing to enhanced inflammatory pain.

Central neural mechanisms are also thought to be involved in allergic inflammation. Extended exposure to allergen in a primate model of allergic asthma causes phenotypic changes in the intrinsic membrane properties of central nervous system neurons, resulting in their increased excitability [31]. This is analogous to the increased excitability of spinal neurons during prolonged neuropathic or inflammatory pain.

Other consequences of central sensitization include changes in autonomic nerve activity. Allergic inflammation may enhance autonomic tone, which has been directly observed in an allergen-sensitized guinea pig model [32].

Loss of inhibitory synaptic transmission (disinhibition) in the spinal cord has also been attributed to both chronic pain and chronic itch. This disinhibition of the central nervous system and, therefore, hyperactivity of trigeminal nociceptive pathways can produce a much more intense response to irritants.

Taken together, the evidence supports a model in which allergic inflammation leads to the release of proinflammatory mediators that sensitize trigeminal sensory neurons (and their processes), resulting in a decreased pain/itch threshold. This may manifest as neuropathic pain and itch. Therefore, there is a putative positive feedback loop between allergic cells and neuronal inflammation in the development and maintenance of the pathophysiology of AC. These, in turn, modulate ocular responses to allergic and nonallergic stimuli, thus translating the degree of inflammation into severity of neural hyperreactivity.

Figure 2 outlines neural involvement in allergic conjunctivitis.

**Figure 2.** Schematic representation of neural sensitization in allergic conjunctivitis. AC indicates allergic conjunctivitis; TRPV, transient receptor potential vanilloid; TRPA, transient receptor potential ankyrin; SP, substance P; CGRP, calcitonin gene-related peptide; NGF, nerve growth factor.
Ocular Symptoms Deriving From Neurogenic Inflammation

The importance of neurogenic inflammation is suggested by the large trigeminal sensory innervation of the ocular surface. Mast cell activation in AC results in overt stimulation of polymodal nociceptors, which are responsible for burning and stinging eye pain. Nasal provocation studies in AR patients showed that TRPV1 and TRPA1 activators induced immediate and more prolonged pain; during the pollen season, provocations with TRPV1 activators induced itch as well as pain [33]. In fact, in a recent series, 80% of patients with symptomatic AC had no evidence of conjunctival inflammation, while over half had nasal inflammation only. It was postulated that neurogenic mediators could explain this disconnect between ocular symptoms (especially itching) and detectable inflammatory conjunctival infiltration [34].

Emerging evidence suggests that the underlying allergic and neural inflammatory pathways can interact. Histamine-induced itching via H1 receptors on conjunctival sensory nerve fibers requires activation of TRPV1. Histamine-independent pruritic pathways, as in IL-31–induced itch, also directly activate TRPV1/TRPA1 sensory nerves in mouse models of dermatitis [35]. Furthermore, leukotriene B4 (LTB4) can activate TRPV1 and induce itching via interaction with LTB4 receptors on sensory nerves [36].

The activation of TRPV1 causes the release of proinflammatory and pruritic mediators. It has been reported that substance P levels are increased in tears of patients with AC compared with healthy individuals, suggesting that substance P may contribute to the pathogenesis and severity of AC [37]. The concentration of substance P in tears has also been found to be elevated at baseline in patients with seasonal AC and vernal keratoconjunctivitis [38], with further increases in substance P and CGRP documented after conjunctival allergen challenge [39]. On the ocular surface, NGF has been hypothesized to influence the immune response in AC [40].

A strong relationship has long been recognized between AC and dry eye, with a large symptomatic crossover that may reflect interrelated mechanistic characteristics [41]. Tear film instability, a characteristic of dry eye, was also noted to be more pronounced in children with AC [42]. Increased inflammatory allergic cytokines are also associated with goblet cell loss and tear volume insufficiency. Recent evidence has further expanded the phenotypic spectrum of patients with dry eye syndrome and implicated neuropathic pain in dry eye pathogenesis. A significant body of physiological data suggests that dry eye symptoms may be significantly modulated by the nervous system [43]. However, our understanding of neuropathic pain in dry eye remains incomplete, largely because of limited access to tests that assess the function of the ocular sensory-nociceptive apparatus.

Neurogenic Mechanisms of AC: Implications for Management Approaches

The current mainstay of AC therapy includes topical mast cell stabilizers and antihistamines, with variable and limited clinical success possibly because factors other than mast cells and histamine play important roles in AC. Therefore, research into more effective treatments is necessary. The simultaneous targeting of multiple inflammatory signaling mediators might represent a more promising treatment modality.

Addressing the neurogenic component of allergic inflammation has been an active area of study. The hyperreactivity phenotype of allergic sensitization can be physiologically dissociated from the immune component, and neural sensitization has been targeted in animal models as well as in humans.

Murine models of allergic sensitization have provided evidence of the anti-inflammatory actions induced by the depletion of neuropeptides [25]. Mice that had undergone surgical denervation of cutaneous sensory nerves demonstrated dampened inflammatory responses after induction of anaphylaxis and mast cell activation. Similar responses were obtained following pretreatment with selective substance P and CGRP antagonists [44]. Recently, treatment with olopatadine and naphazoline hydrochloride was shown to reduce conjunctivitis in mice via effects on NGF [45].

A prominent candidate pathway is TRPV1, which has been described in several forms of allergic disease. Vagal sensory neurons in TRPV1 can dramatically affect airway hyperreactivity. Several trials have explored therapies that target TRPV1-expressing neurons as a strategy for the management of allergic diseases. This has been supported by murine models, where ablation of TRPV1 expressing vagal neurons abolishes airway hyperreactivity, even in the presence of a full lung inflammatory response [46]. In yet another mouse model, the use of a TRPV1 antagonist alleviated atopic dermatitis–like symptoms as evidenced by suppression of itch behavior and acceleration of skin barrier recovery [47]. In another murine model of AC, ocular itch was significantly attenuated in TRPA1 and TRPV1 knockout mice, implicating both TRPA1 and TRPV1 in the genesis of allergic ocular itch [48].

Clinical trials exploring the potential for neuronal-targeted therapies in patients with allergic inflammation are in their early stages. However, in subjects with allergic rhinitis, an intranasal TRPV1 antagonist alone or combined with fluticasone propionate did not improve allergen-induced symptoms [49]. Similarly, symptoms appearing after exposure to cold dry air in patients with nonallergic rhinitis did not improve with this therapy [50].

These findings may indicate that TRPV1 may be a facilitating ion channel—but not a key mediator—for itch and other allergic symptoms, suggesting that other receptors expressed in C fibers, such as TRPA1, might be involved in their development.

On the other hand, a recent study of patients with nonallergic rhinitis revealed overexpression of TRPV1 in the nasal mucosa and increased substance P levels in nasal secretions at baseline, with reduced symptoms and reduced levels of nasal hyperreactivity following topical capsaicin treatment [19]. The authors suggest that the ablation of the TRPV1–substance P nociceptive signaling pathway...
by capsaicin in the nasal mucosa was responsible for this therapeutic effect. Several trials of topical capsaicin in patients with nonallergic rhinitis have demonstrated relief of symptoms and nasal hyperreactivity [51-53].

Systemic neuromodulating agents may constitute another approach to the management of neuropathic symptoms in allergic disease. With the recognition that chronic cough is similar to other hypersensitivity neuropathic syndromes such as chronic pain [54], gabapentin, a common treatment for neuropathic pain, has proven clearly efficacious for refractory cough [55]. The clinical relevance of neuroinflammation and sensitization has also been extrapolated to chronic itch. Cevikbas et al [56] described a synergistic role for γ-aminobutyric acid A and B agonists for addressing symptoms of itching in murine atopic dermatitis. The utility of gabapentin has also been demonstrated in this setting [57].

The Table summarizes trials examining neuromodulation to date for allergic and nonallergic upper airway diseases presumed to be related to neuroplasticity.

### Future Directions

Despite substantial advances in our understanding of the pathophysiology of AC, the exact association between targeted therapy and successful responses remains controversial and prevents these findings being applied in clinical practice. However, targeting neuronal inflammation remains a potential novel strategy for the treatment of AC. The definition of these pain-relevant neural circuits may facilitate future development of targeted therapies.

### Conclusions

Among the constellation of symptoms that characterizes AC, many, such as burning and stinging, can be attributed to chronic neuropathic pain. There is evidence to support that these hallmark symptoms might be linked to the effects of allergen-induced neuromodulation. Thus, neurogenic mechanisms may have a significant role in chronic ocular surface inflammation. Current management goals in allergic conjunctivitis aim to minimize the inflammatory cascade associated with allergic response in the early stages of the pathogenic mechanism. Based on the mechanistic data reviewed herein, the recognition that neuronal inflammation explains many of the symptoms in AC opens new frontiers for drug discovery.

### Funding

The authors declare that no funding was received for the present study.

### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Neuropathic Pain/Itch in Allergic Conjunctivitis


Manuscript received June 20, 2018; accepted for publication September 11, 2018.

Merin Elizabeth Kuruvilla
1365 Clifton Rd NE, Bldg A, 3rd Flr
Atlanta, GA-30322
USA
E-mail: merin.ek1@gmail.com