# Neuropathic Pain and Itch Mechanisms Underlying Allergic Conjunctivitis

Kuruvilla M[1], Kalangara J[2], Eun-Hyung Lee F[3]

[1]Assistant Professor, Allergy/Immunology, Emory University
[2]Assistant Professor, Interventional Pain Management, Emory University
[3]Associate Professor, Pulmonology, Emory University

**Corresponding Author Contact Information:**
Merin Elizabeth Kuruvilla, MD
Address: 1365 Clifton Rd NE, Bldg A, 3rd Flr
Atlanta, GA-30322
E-mail: merin.ek1@gmail.com

**Financial support: None**

**Trial registration: Not applicable**

**Conflict(s) of Interest: None**



This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0320

## Abstract

**Objective:** Among the symptom constellation that characterizes allergic conjunctivitis, many such as burning and stinging can be attributed to chronic neuropathic pain. There is accumulating data to support that these hallmark symptoms might be linked to the effects of allergen induced neuromodulation. This review will emphasize the key characteristics of neuropathic itch and pain in allergic conjunctivitis and its pathologic mechanisms.
**Methods:** A literature review was conducted using a PubMed search focusing on allergic conjunctivitis, allergic conjunctivitis, neurogenic inflammation, neuropathic itch, 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 associated with neuropathologic changes (peripheral and central sensitization), neuronal dysfunction, and spontaneous ocular pain.
**Conclusion:** Current management goals of allergic conjunctivitis aim to minimize the inflammatory cascade associated with allergic response in the initial stages of the pathological 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.

**Key words:** Allergic Conjunctivitis,Neuropathic Pain,Neuronal Dysfunction,Dry Eye,Sensitization, Transient Receptor Potential Vanilloid 1 (TRPV1),Transient Receptor Potential Ankyrin 1 (TRPA1),Substance P (SP), Nerve Growth Factor (NGF)

## 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 realizando 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 inflamación. 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 estadíos iniciales fisiopatológicos. Sin embargo, y 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.

**Palabras clave:** Conjuntivitis Alérgica, Dolor Neuropático, Disfunción Neuronal, Ojo Seco, Sensibilización, Receptor De Potencial Transitorio Vaniloide 1 (TRPV1), Receptor De Potencial Transitorio Anquirina 1 (TRPA1), Sustancia P (SP), Factor De Crecimiento Neuronal (NGF)



doi: 10.18176/jiaci.0320

## Background

A recent hypothesis has implicated neuronal inflammation as a novel mechanisms of allergy pathogenesis. Several allergy symptoms are a direct consequence of nervous system alterations [1], including rhinorrhea, nasal congestion, and cough. Allergic inflammation can trigger complex neurogenic signaling mechanisms, manifesting as neuropathic itch (NI). NI 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 pain. This differentiates it from classic itch in inflammatory skin diseases as NI 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. The delineation of these molecular pathways underlying AC neuronal inflammation may be critical to identify 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 the English language and conducted 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, clinical and pathophysiologic aspects of AC

- **Prevalence and impact**

There is scarce epidemiological data on AC 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 sufferers in one study [4]. In another recent survey, over 50% of nasal allergy sufferers 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]. This underscores the need to explore the underlying mechanisms of AC further.

Seasonal (SAC) and perennial allergic conjunctivitis (PAC) represent the most common form and benign end of the spectrum constituting ocular allergy, and are increasing in prevalence [6]. Vernal keratoconjunctivitis (VKC), and atopic keratoconjunctivitis (AKC), while representing only 2% of ocular allergy cases, are even more severe with a greater impact on quality of life.

- **Pathophysiology**

Two functionally distinct CD4+ T-cell subpopulations called Th1 and Th2 cells were discovered about 30 years ago. Since then, it became quickly evident rather quickly that Th2 cells play a crucial role in development of allergic airway inflammation. It has been commonly assumed that a Th2 immune response and type I hypersensitivity forms the basis of AC. The allergic response is elicited by ocular exposure to an allergen, such as pollen, that cross-links membrane-bound Immunoglobulin E (IgE) and triggers mast cell (MC) degranulation. This releases a cascade of mediators including histamine, leukotrienes, proteases, prostaglandins and cytokines. The largest contributor to the severity of AC is thought to be the allergen load on the ocular surface and locally produced specific IgE. Further, 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 SAC, the immediate response is predominantly MC-mediated. However, little is known about the pathogenesis of the late phase allergic reaction which corresponds to the persistent clinical inflammation that typifies the ocular signs and symptoms in chronic allergic diseases. VKC and AKC are especially characterized by a severe late-phase reaction. It is characterized by the mucosal infiltration of 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. Also, products from infiltrating cells are known to promote conjunctival



doi: 10.18176/jiaci.0320

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, conjunctival and eyelid swelling and redness. These are reflected in the total ocular symptom score (TOSS) questionnaire used to measure symptoms of AC. However, AC subjects 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 sign of papillae on 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 non-allergic and mixed rhinitis [11]. This is akin to hyperreactivity to heat, sunlight and wind during the active phase of VKC which may be reflective of neural involvement [12], as does 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 described as trigger factors 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**

Ocular surface innervation is provided by primary sensory neurons located in the trigeminal ganglion (TG), the majority 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 two among these 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 pro-inflammatory exogenous and endogenous agents. It is also stimulated by several mediators relevant to the allergic reaction such as histamine and bradykinin. As with TRPV1, TRPA1 is activated by inflammatory mediators including those germane to 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, exemplified by nerve growth factor (NGF), act directly on peptidergic C fiber nociceptors to potentiate TRPV1 receptors and also increase the expression of SP 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 ocular 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 allergic 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:**



doi: 10.18176/jiaci.0320

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]. TRPV1 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 SP levels were found to be significantly higher in patients with non-allergic rhinitis [19] and asthma, especially refractory cases [20]. Further, histamine sensitizes the nociceptor TRPV1 and has been shown to contribute to visceral hypersensitivity in animals [21]. In addition, certain other endogenous inflammatory allergy mediators (e.g., prostaglandin E2, bradykinin, etc.) can markedly enhance the sensitivity of TRPV1 and lower its threshold for activation of sensory nerves [22].

Inhalation of allergen also up-regulates the expression of genes involved in the production of SP and CGRP which both act as itch sensation-enhancing neuropeptides [23, 24]. Allergen exposure also enhances the release of SP and CGRP from sensory nerve endings (antidromic pathway). SP and CGRP cause nociceptor antidromic stimulation which results in C-fiber activation and synergistically augments the allergic inflammatory reaction [24, 25]. Most recently, Azimi et al described the role of SP–mediated activation of MC receptors in inducing itching in a mouse model [26].

Allergic reactions can also lead directly to the release of neurotrophic factors especially nerve growth factor (NGF), from MCs and also from other cells, such as the airway epithelium [27]. NGF is a complex regulator of neural plasticity and further sensitizes afferent nerves. It has been found in eosinophils and peripheral nerves [25, 28] and is upregulated by nasal allergen provocation. Endogenous NGF levels are not only elevated 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 BAL fluids and nasal lavage 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, consequently 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 human subjects. The overall changes in firing of corneal sensory fibers correlated with the foreign body and itching sensations reported by AC patients [30]. These results suggest a possible TRPV1-dependent pathway in the sensitization stage but requires further studies for confirmation.

The consequent 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 where ocular TG neurons project. Amplification of responses occur in the central nervous system (CNS) 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 caused phenotypic changes in intrinsic membrane properties of CNS 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 the 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.



doi: 10.18176/jiaci.0320

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 non-allergic stimuli, thus translating the degree of inflammation into severity of neural hyperreactivity.

Figure 2 outlines neural involvement in allergic conjunctivitis.

**Ocular symptoms deriving from neurogenic inflammation:**

The importance of neurogenic inflammation in the ocular surface is suggested by its large trigeminal sensory innervation. MC 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 performed with TRPV1 and TRPA1 activators induced immediate as well as more prolonged pain; and during 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 demonstrated 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, such as IL-31 induced itch, also directly activate TRPV1/TRPA1 sensory nerves in mouse models of dermatitis [35]. Further, 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 SP levels are increased in tears of patients with AC compared with healthy individuals, suggesting that SP may contribute to the pathogenesis and severity of AC [37]. The concentration of SP in tears has also been found to be elevated at baseline in patients with seasonal AC and VKC [38], with further increases in SP 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 higher 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.

**Implications of AC neurogenic mechanisms for management approaches**

The current mainstay of AC therapy includes topical MC stabilizers and antihistamines, with variable and limited clinical success possibly because other factors, besides MCs and histamine, play important roles in AC. Therefore, investigating 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 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 skin denervation of sensory nerves demonstrated dampened inflammatory responses after induction of anaphylaxis and MC activation. Similar responses were obtained following pretreatment with selective SP 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. TRPV1 vagal sensory neurons 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



doi: 10.18176/jiaci.0320

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, 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 when combined with fluticasone propionate did not improve allergen-induced symptoms [49]. Similarly, symptoms after cold dry air exposure in patients with non-allergic rhinitis (NAR) did not Improve with this therapy either [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 the TRPA1, might be involved in their development.

On the other hand, a recent study among NAR patients found an overexpression of TRPV1 in the nasal mucosa and increased SP levels in nasal secretions at baseline, with reduced symptoms and reduced levels of nasal hyper-reactivity following topical capsaicin treatment [19]. The authors suggest that the ablation of the TRPV1-SP nociceptive signaling pathway by capsaicin in the nasal mucosa was responsible for this therapeutic effect. Several trials of topical capsaicin in non-allergic rhinitis patients have demonstrated reduction in symptoms and nasal hyperreactivity [51-53].

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

Table 1 summarizes trials of neuromodulation to date for allergic and non-allergic upper airway diseases presumed to be related to neuroplasticity.

**Future directions:**

Thus, despite substantial advances in our understanding of AC pathophysiology, the exact correlates between targeted therapy and successful responses remain controversial and present a roadblock to translating these findings to the clinic. 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 symptom constellation that characterizes AC, many such as burning and stinging can be attributed to chronic neuropathic pain. There is accumulating data 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 of allergic conjunctivitis aim to minimize the inflammatory cascade associated with allergic response in the early stages of the pathological 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.



doi: 10.18176/jiaci.0320

**References:**


1. Undem BJ, Taylor-Clark T. Mechanisms underlying the neuronal-based symptoms of allergy. J Allergy Clin Immunol. 2014;133(6):1521-34.
2. Gomes PJ. Trends in prevalence and treatment of ocular allergy. Curr Opin Allergy Clin Immunol. 2014;14(5):451-6.
3. Katelaris CH, Bielory L. Evidence-based study design in ocular allergy trials. Curr Opin Allergy Clin Immunol. 2008;8(5):484-8.
4. Wuthrich B, Brignoli R, Canevascini M, Gerber M. Epidemiological survey in hay fever patients: symptom prevalence and severity and influence on patient management. Schweiz Med Wochenschr. 1998;128(5):139-43.
5. Blaiss MS. Allergic rhinoconjunctivitis: burden of disease. Allergy Asthma Proc. 2007;28(4):393-7.
6. Ono SJ, Abelson MB. Allergic conjunctivitis: update on pathophysiology and prospects for future treatment. J Allergy Clin Immunol. 2005;115(1):118-22.
7. Hoffmann-Sommergruber K, Ferreira ED, Ebner C, Barisani T, Korninger L, Kraft D, et al. Detection of allergen-specific IgE in tears of grass pollen-allergic patients with allergic rhinoconjunctivitis. Clin Exp Allergy. 1996;26(1):79-87.
8. Anderson DF, MacLeod JD, Baddeley SM, Bacon AS, McGill JI, Holgate ST, et al. Seasonal allergic conjunctivitis is accompanied by increased mast cell numbers in the absence of leucocyte infiltration. Clin Exp Allergy. 1997;27(9):1060-6.
9. Katelaris CH. Ocular allergy in the Asia Pacific region. Asia Pac Allergy. 2011;1(3):108-14.
10. Virchow JC, Kay S, Demoly P, Mullol J, Canonica W, Higgins V. Impact of ocular symptoms on quality of life (QoL), work productivity and resource utilisation in allergic rhinitis patients--an observational, cross sectional study in four countries in Europe. J Med Econ. 2011;14(3):305-14.
11. Bernstein JA, Singh U. Neural Abnormalities in Nonallergic Rhinitis. Curr Allergy Asthma Rep. 2015;15(4):18.
12. Bonini S, Bonini S, Schiavone M, Centofanti M, Allansmith MR, Bucci MG. Conjunctival hyperresponsiveness to ocular histamine challenge in patients with vernal conjunctivitis. J Allergy Clin Immunol. 1992;89(1 Pt 1):103-7.
13. Ciprandi G, Buscaglia S, Pesce GP, Bagnasco M, Canonica GW. Ocular challenge and hyperresponsiveness to histamine in patients with allergic conjunctivitis. J Allergy Clin Immunol. 1993;91(6):1227-30.
14. Leonardi A, Piliego F, Castegnaro A, Lazzarini D, La Gloria Valerio A, Mattana P, et al. Allergic conjunctivitis: a cross-sectional study. Clin Exp Allergy. 2015;45(6):1118-25.
15. Bielory L. Vasomotor (perennial chronic) conjunctivitis. Curr Opin Allergy Clin Immunol. 2006;6(5):355-60.
16. Belmonte C, Aracil A, Acosta MC, Luna C, Gallar J. Nerves and sensations from the eye surface. Ocul Surf. 2004;2(4):248-53.
17. Sukhotinsky I, Ben-Dor E, Raber P, Devor M. Key role of the dorsal root ganglion in neuropathic tactile hypersensibility. Eur J Pain. 2004;8(2):135-43.
18. Lieu TM, Myers AC, Meeker S, Undem BJ. TRPV1 induction in airway vagal low-threshold mechanosensory neurons by allergen challenge and neurotrophic factors. Am J Physiol Lung Cell Mol Physiol. 2012;302(9):L941-8.
19. Van Gerven L, Alpizar YA, Wouters MM, Hox V, Hauben E, Jorissen M, et al. Capsaicin treatment reduces nasal hyperreactivity and transient receptor potential cation channel subfamily V, receptor 1 (TRPV1) overexpression in patients with idiopathic rhinitis. J Allergy Clin Immunol. 2014;133(5):1332-9, 9 e1-3.
20. McGarvey LP, Butler CA, Stokesberry S, Polley L, McQuaid S, Abdullah H, et al. Increased expression of bronchial epithelial transient receptor potential vanilloid 1 channels in patients with severe asthma. J Allergy Clin Immunol. 2014;133(3):704-12 e4.
21. Wouters MM, Balemans D, Van Wanrooy S, Dooley J, Cibert-Goton V, Alpizar YA, et al. Histamine Receptor H1-Mediated Sensitization of TRPV1 Mediates Visceral Hypersensitivity and Symptoms in Patients With Irritable Bowel Syndrome. Gastroenterology. 2016;150(4):875-87 e9.
22. Raemdonck K, de Alba J, Birrell MA, Grace M, Maher SA, Irvin CG, et al. A role for sensory nerves in the late asthmatic response. Thorax. 2012;67(1):19-25.
23. O'Hanlon S, Facer P, Simpson KD, Sandhu G, Saleh HA, Anand P. Neuronal markers in allergic rhinitis: expression and correlation with sensory testing. Laryngoscope. 2007;117(9):1519-27.
24. Sarin S, Undem B, Sanico A, Togias A. The role of the nervous system in rhinitis. J Allergy Clin Immunol. 2006;118(5):999-1016.
25. Rogerio AP, Andrade EL, Calixto JB. C-fibers, but not the transient potential receptor vanilloid 1 (TRPV1), play a role in experimental allergic airway inflammation. Eur J Pharmacol. 2011;662(1-3):55-62.
26. Azimi E, Reddy VB, Pereira PJS, Talbot S, Woolf CJ, Lerner EA. Substance P activates Mas-related G protein-coupled receptors to induce itch. J Allergy Clin Immunol. 2017;140(2):447-53 e3.
27. Bresciani M, Laliberte F, Laliberte MF, Gramiccioni C, Bonini S. Nerve growth factor localization in the nasal mucosa of patients with persistent allergic rhinitis. Allergy. 2009;64(1):112-7.




doi: 10.18176/jiaci.0320

28. Raap U, Braunstahl GJ. The role of neurotrophins in the pathophysiology of allergic rhinitis. Curr Opin Allergy Clin Immunol. 2010;10(1):8-13.
29. Bonini S, Lambiase A, Bonini S, Angelucci F, Magrini L, Manni L, et al. Circulating nerve growth factor levels are increased in humans with allergic diseases and asthma. Proc Natl Acad Sci U S A. 1996;93(20):10955-60.
30. Acosta MC, Luna C, Quirce S, Belmonte C, Gallar J. Changes in sensory activity of ocular surface sensory nerves during allergic keratoconjunctivitis. Pain. 2013;154(11):2353-62.
31. Chen CY, Bonham AC, Schelegle ES, Gershwin LJ, Plopper CG, Joad JP. Extended allergen exposure in asthmatic monkeys induces neuroplasticity in nucleus tractus solitarius. J Allergy Clin Immunol. 2001;108(4):557-62.
32. Undem BJ, Hubbard WC, Christian EP, Weinreich D. Mast cells in the guinea pig superior cervical ganglion: a functional and histological assessment. J Auton Nerv Syst. 1990;30(1):75-87.
33. Alenmyr L, Hogestatt ED, Zygmunt PM, Greiff L. TRPV1-mediated itch in seasonal allergic rhinitis. Allergy. 2009;64(5):807-10.
34. Gelardi M, Leo ME, Quaranta VN, Iannuzzi L, Tripodi S, Quaranta N, et al. Clinical characteristics associated with conjunctival inflammation in allergic rhinoconjunctivitis. J Allergy Clin Immunol Pract. 2015;3(3):387-91 e1.
35. Cevikbas F, Wang X, Akiyama T, Kempkes C, Savinko T, Antal A, et al. A sensory neuron-expressed IL-31 receptor mediates T helper cell-dependent itch: Involvement of TRPV1 and TRPA1. J Allergy Clin Immunol. 2014;133(2):448-60.
36. Akiyama T, Carstens E. Neural processing of itch. Neuroscience. 2013;250:697-714.
37. Mantelli F, Micera A, Sacchetti M, Bonini S. Neurogenic inflammation of the ocular surface. Curr Opin Allergy Clin Immunol. 2010;10(5):498-504.
38. Micera A, Lambiase A, Bonini S. The role of neuromediators in ocular allergy. Curr Opin Allergy Clin Immunol. 2008;8(5):466-71.
39. Sacchetti M, Micera A, Lambiase A, Speranza S, Mantelli F, Petrachi G, et al. Tear levels of neuropeptides increase after specific allergen challenge in allergic conjunctivitis. Mol Vis. 2011;17:47-52.
40. Lambiase A, Bonini S, Micera A, Rama P, Bonini S, Aloe L. Expression of nerve growth factor receptors on the ocular surface in healthy subjects and during manifestation of inflammatory diseases. Invest Ophthalmol Vis Sci. 1998;39(7):1272-5.
41. Bielory L. Ocular allergy and dry eye syndrome. Curr Opin Allergy Clin Immunol. 2004;4(5):421-4.
42. Dogru M, Gunay M, Celik G, Aktas A. Evaluation of the tear film instability in children with allergic diseases. Cutan Ocul Toxicol. 2016;35(1):49-52.
43. Kalangara JP, Galor A, Levitt RC, Felix ER, Alegret R, Sarantopoulos CD. Burning Eye Syndrome: Do Neuropathic Pain Mechanisms Underlie Chronic Dry Eye? Pain Med. 2016;17(4):746-55.
44. Siebenhaar F, Magerl M, Peters EM, Hendrix S, Metz M, Maurer M. Mast cell-driven skin inflammation is impaired in the absence of sensory nerves. J Allergy Clin Immunol. 2008;121(4):955-61.
45. Quan L, He H. Treatment with olopatadine and naphazoline hydrochloride reduces allergic conjunctivitis in mice through alterations in inflammation, NGF and VEGF. Mol Med Rep. 2016;13(4):3319-25.
46. Trankner D, Hahne N, Sugino K, Hoon MA, Zuker C. Population of sensory neurons essential for asthmatic hyperreactivity of inflamed airways. Proc Natl Acad Sci U S A. 2014;111(31):11515-20.
47. Yun JW, Seo JA, Jeong YS, Bae IH, Jang WH, Lee J, et al. TRPV1 antagonist can suppress the atopic dermatitis-like symptoms by accelerating skin barrier recovery. J Dermatol Sci. 2011;62(1):8-15.
48. Huang CC, Kim YS, Olson WP, Li F, Guo C, Luo W, et al. A histamine-independent itch pathway is required for allergic ocular itch. J Allergy Clin Immunol. 2016;137(4):1267-70 e6.
49. Bareille P, Murdoch RD, Denyer J, Bentley J, Smart K, Yarnall K, et al. The effects of a TRPV1 antagonist, SB-705498, in the treatment of seasonal allergic rhinitis. Int J Clin Pharmacol Ther. 2013;51(7):576-84.
50. Murdoch RD, Bareille P, Denyer J, Newlands A, Bentley J, Smart K, et al. TRPV1 inhibition does not prevent cold dry air-elicited symptoms in non-allergic rhinitis. Int J Clin Pharmacol Ther. 2014;52(4):267-76.
51. Bernstein JA, Davis BP, Picard JK, Cooper JP, Zheng S, Levin LS. A randomized, double-blind, parallel trial comparing capsaicin nasal spray with placebo in subjects with a significant component of nonallergic rhinitis. Ann Allergy Asthma Immunol. 2011;107(2):171-8.
52. Gevorgyan A, Segboer C, Gorissen R, van Drunen CM, Fokkens W. Capsaicin for non-allergic rhinitis. Cochrane Database Syst Rev. 2015(7):CD010591.
53. Van Rijswijk JB, Boeke EL, Keizer JM, Mulder PG, Blom HM, Fokkens WJ. Intranasal capsaicin reduces nasal hyperreactivity in idiopathic rhinitis: a double-blind randomized application regimen study. Allergy. 2003;58(8):754-61.
54. Morice AH, Faruqi S, Wright CE, Thompson R, Bland JM. Cough hypersensitivity syndrome: a distinct clinical entity. Lung. 2011;189(1):73-9.
55. Ryan NM, Birring SS, Gibson PG. Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial. Lancet. 2012;380(9853):1583-9.
56. Cevikbas F, Braz JM, Wang X, Solorzano C, Sulk M, Buhl T, et al. Synergistic antipruritic effects of gamma aminobutyric acid A and B agonists in a mouse model of atopic dermatitis. J Allergy Clin Immunol. 2017;140(2):454-64 e2.





doi: 10.18176/jiaci.0320

57. Yosipovitch G, Bernhard JD. Clinical practice. Chronic pruritus. N Engl J Med. 2013;368(17):1625-34.





doi: 10.18176/jiaci.0320

**Table 1. Randomized controlled trials of neuropathic therapies for allergic/non-allergic airway inflammation**

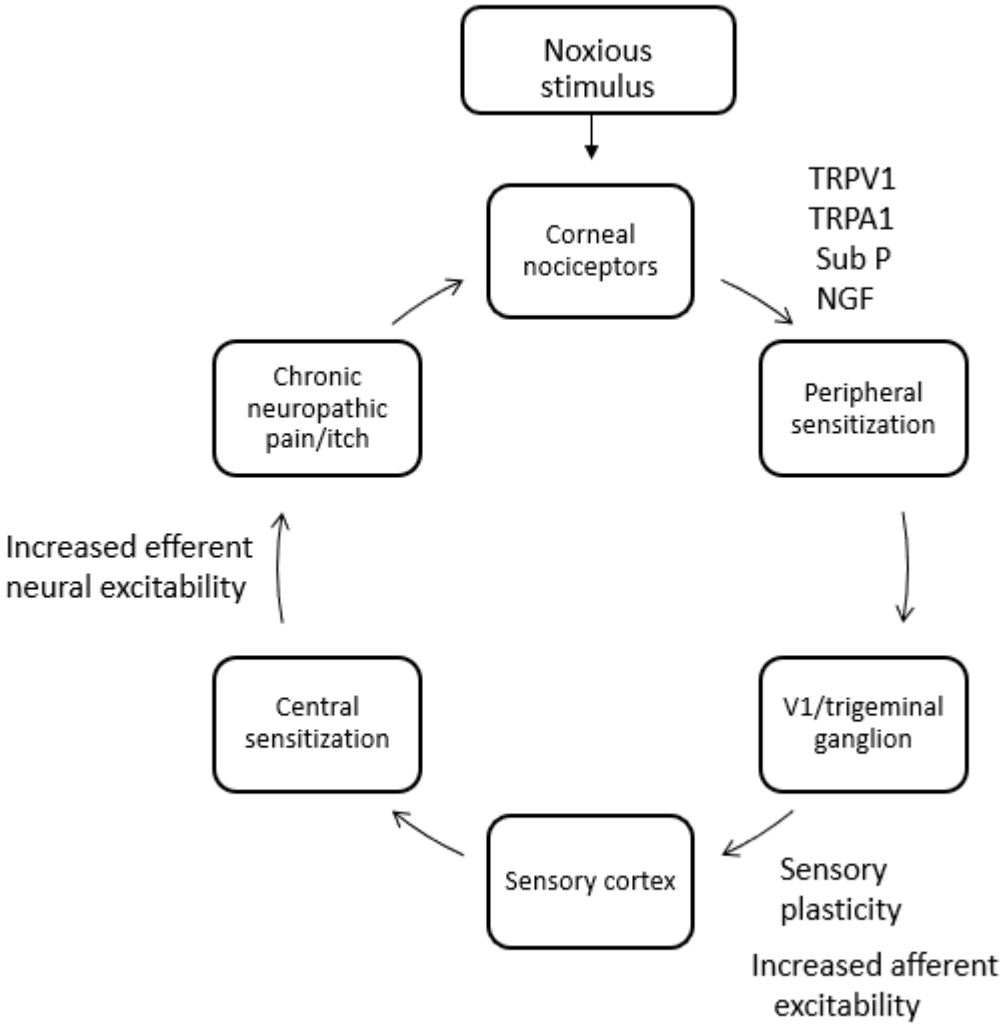
| Drug | Mechanism | Disease evaluated | Outcome assessed | Efficacy |
|---|---|---|---|---|
| SB-705498 | Intranasal TRPV1 antagonist | Allergic rhinitis | Total nasal symptom score (TNSS) - SB-705498 versus placebo, fluticasone propionate (FP), and SB-705498 + FP | No differences in allergen-induced mean TNSS between SB-705498 alone and placebo or between SB-705498 plus FP and FP alone [49] |
| SB-705498 | Intranasal TRPV1 antagonist | Non-allergic rhinitis (NAR) | Total symptom score (TSS), expressed as weighted mean over 60 minutes (WM0-60) or maximum TSS at 1 hour and 24 hours post-dosing | No differences in or maximum TSS at 1 hour and 24 hours post-dosing on days 1 or 14, relative to placebo [50] |
| Capsaicin | Intranasal TRPV1 agonist that ablates the TRPV1-SP signaling pathway | Idiopathic rhinitis (IR) | Visual analog scale (VAS) and therapeutic response evaluation (TRE) scores, and nasal hyperreactivity by means of CDA provocation | Significant decrease in VAS and TRE scores, and abrogation of nasal hyperreactivity to CDA [19] |
| Capsaicin | Intranasal TRPV1 agonist that ablates the TRPV1-SP signaling pathway | Non-allergic rhinitis (NAR) | Visual analog scale (VAS) scores, and nasal hyperreactivity by means of CDA provocation | Significant decrease in VAS scores, and abrogation of nasal hyperreactivity to CDA up to 9 months after treatment [53] |
| ICX72 (Capsicum + Eucalyptol) | Intranasal TRPV1 agonist that ablates the TRPV1-SP signalling pathway | Non-allergic rhinitis (NAR) | Total nasal symptom scores (TNSS), individual symptom scores (ISS) over 2 weeks and average time to first relief | Significant improvements in TNSS and each ISS, and average time to first relief of 52.6 seconds [51] |





doi: 10.18176/jiaci.0320

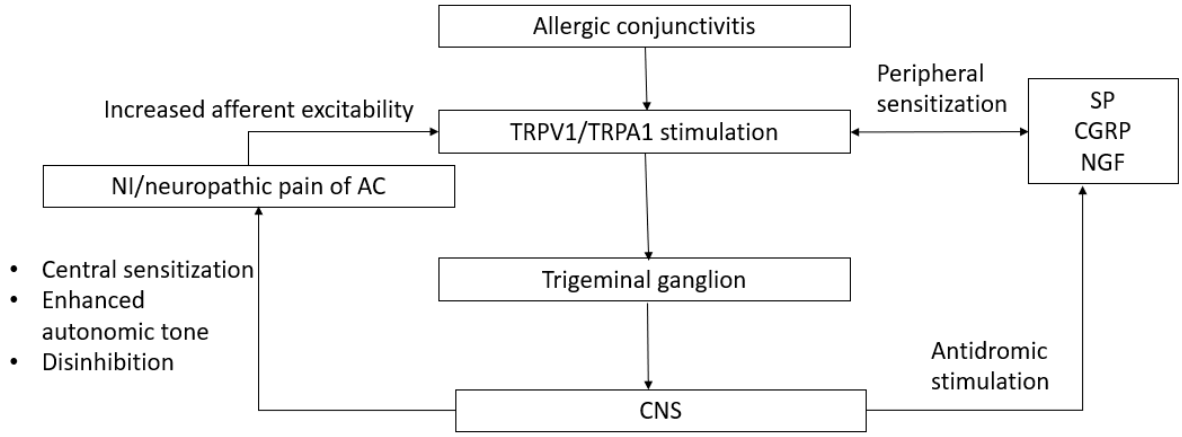
**Figure 1. Schematic representation of neuropathic pain and itch in ocular surface disease**






doi: 10.18176/jiaci.0320

**Figure 2. Schematic representation of neural sensitization in allergic conjunctivitis**








doi: 10.18176/jiaci.0320