The influence of neuropathy in dry eye symptoms: a review of corneal pain pathways and potential changes in nervous system

Ane Murueta-Goyena Larrañaga, OD, MSc¹; Javier Tomás-Juan, OD, MSc²,³

ABSTRACT: Dry eye disease is a troublesome ocular condition due to its multifactorial nature and the lack of association between signs and symptoms. This fact has led researchers to look beyond tear quality and stability, and hyperosmolarity and inflammation have lately been the focus of interest. Both are considered to have an impact on corneal nerve structure and function, although their role is still unclear. In this review, we will explore the peripheral and central nervous system mechanisms that contribute to the perception of dry eye symptoms and the possible changes in corneal pain pathways after long-standing tear deficiency and LASIK surgery that could result in corneal sensitivity or enhanced pain perception.

J Emmetropia 2014; 5: 39-50

Dry eye disease (DED) is a multifactorial disorder that results in ocular surface damage, especially in subjects over the age of 45-50. Dry eye symptoms such as burning, stinging or itchiness have little association with individual clinical tests such as meibomian gland assessment, tear break-up time, fluorescein staining or Schirmer test. Therefore, clinicians must rely on a constellation of signs and symptoms for diagnosis. Some combinations of tests may improve predictability, but there is no consensus on which combination is best. High incidence and a lack of consistency between signs and symptoms make DED diagnosis challenging. This discrepancy led Rosenthal & Borsook, together with Sullivan, to suggest that different ocular surface disorders are included in DED. Based on that assumption, alterations in the corneal pain system could cause dry eye-like symptoms without a deficient tear layer or altered meibomian glands.

Several conditions are known to cause functional and anatomical changes in corneal innervation, such as diabetes mellitus, contact lens use, LASIK, or fibromyalgia, and all are associated with dry eye-like symptoms. Nevertheless, nervous changes can also arise in the central nervous system, a factor that is seldom considered in the clinical setting. In this paper, we will review peripheral and central mechanisms that can increase sensitivity of the ocular pain pathway, and thus cause dry eye symptoms. These mechanisms could cause the discrepancy between signs and symptoms in DED.

CORNEAL NERVE TYPES

The cornea is a highly innervated area. Corneal innervation is estimated to be around 20-40 times greater than that of dental pulp. Corneal nerves fundamentally derive from the ophthalmic branch of the ipsilateral trigeminal nerve. Recent studies have described a more holistic picture of the three-dimensional distribution and spatial arrangement...
of the nerve bundles. It is now thought that limbal plexus nerves penetrate the stroma radially at a depth of 293 ± 106 μm, and nerve bundles are evenly distributed around the limbus. However, the total number of bundles is still unclear, mainly because of imaging and counting differences between studies, but there are estimated to be between 33 and 90 in the human cornea. The stromal nerves, derived from scleral and ciliary nerves, start to divide soon after entering the cornea. They run towards the centre, where they connect and form the stromal nerve network. Nerves located in the most anterior part of the stroma penetrate Bowman’s layer perpendicularly. These perforations are more abundant in the mid-periphery (125-160 perforations) than in the central cornea (25-30 perforations), and terminate as bulb-like thickenings in the sub-basal plane. Other scientists claim that stromal nerves mainly enter the epithelium in the peripheral region. Nevertheless, none are able to specify the exact distance from the limbus where the nerves perforate Bowman’s layer, and different authors might be referring to the same region under different terms. Once in the subbasal plane, stromal nerves give rise to multiple sub-basal nerves that run towards the centre of the cornea. Along their length, they divide into interconnected smaller branches that create a network within the epithelium. Subbasal nerves converge either in the inferior quadrant of the central region, or inferio-rally to the corneal apex in a whorl-like pattern. Another epithelial nerve supply comes from the Limbal Superficial Nerve Network (LSNN), which innervates the limbal area and the peripheral region of the cornea.

Corneal nerve receptors are classified by their function. The vast majority (70%) are polymodal nociceptors, and as their name suggests, are sensitive to a wide range of stimuli such as heat, noxious stimuli, and chemicals (endogenous or not). They are mostly C-fiber type - un-myelinated, slow conduction fibers (< 2 m/sec). Another 20% are considered mechanonociceptors, responsible for the first acute pain. They are A-delta fibers, slightly myelinated axons with conduction velocities ranging from 3 m/sec to 120 m/sec. The remaining 10%-15% are cold nociceptors, which are thought to be responsible for lacrimal secretion maintenance. It has been suggested that there might also be some “silent nociceptors” that are exclusively activated in the presence of local inflammation. All axons lose their myelin sheath and perineurium 1 mm after penetrating the stroma in order to maintain corneal transparency. Corneal nerve populations can also be distinguished by their neuropeptidic content. The presence of substance P (SP) and Calcitonin Gene-Related Protein (CGRP) has been demonstrated in human corneal nerves, these being the most abundant neuropeptides, 20% and 60%, respectively. Others are pituitary adenylate cyclase-activating peptides (PACP) and galanin (GAL).

The activation of corneal polymodal nociceptor endings with different stimuli is perceived as an irritation, although with different qualities and thermal components. However, cold pulses between 1-3 °C almost exclusively evoke cooling sensation, but the lower the temperature, the more irritating it becomes. All these sensations are necessary for the maintenance of ocular surface integrity. Nonetheless, any disturbance of this delicate environment, whatever the cause, can activate corneal nociceptors, and consequently evoke the sensations normally attributed to corneal pain: burning, sand-like sensation, ocular dryness, foreign body sensation or even pain.

CHANGES IN CORNEAL AFFERENT FIBERS

In 2007, the Definition and Classification Subcommittee (DEWS) re-defined DED on the basis of existing research. In that new schema they introduced increased osmolarity of the tear film and inflammation of the ocular surface into their etiopathogenic classification, with visual function disturbance as a common symptom. Hyperosmolarity is reportedly the most reliable biomarker of DED (> 305 mOsmol), and can be used to classify DED patients according to severity. However, other studies demonstrate that high osmolarity is not an infallible biomarker. Fernandez et al. had a small sample size (18 patients) and no control groups, and poor eligibility criteria (previous use of, and p = 0.38, respectively), nor any correlation between clinical signs and osmolarity (p = 0.21 and p = 0.80, respectively). These studies however, have design flaws. Fernandez et al. had a small sample size (18 patients) and no control groups, and poor eligibility criteria (previous diagnosis of DED) were used in both studies. In fact, hyperosmolarity has been proposed as the main mechanism of pathogenesis in DED. Hyperosmolarity is a known trigger for corneal epithelial inflammation, and can potentially change the activity of corneal sensory fibers. A corneal insult, such as hyperosmolarity, triggers an immune response, where immune cells (e.g. macrophages and mast cells or neutrophils) infiltrate the area. Macrophages begin releasing proinflammatory cytokines such as interleukin 1-beta (IL-1β) and tumor necrosis factor (TNF-α), which are known to increase DED. IL-1β and TNF-α stimulate the production of matrix metalloproteinases (MMPs), particularly MMP-9, used as a biomarker for DED. Inflammatory cytokines and osmotic stress can activate different Mitogen-Activated Protein Kinase (MAPK) signaling pathways, and via Jun N-terminal Kinase (JNK) and p38 MAPK cascades will cause tissue inflammation and the release of pro-inflammatory cytokines and osmotic stress.
IL-6 and the chemoattractant IL-8. Moreover, many of the endogenous inflammatory mediators released by immune cells (e.g., ATP, bradykinin, protons, histamine, and prostaglandin) can have an impact on the free nerve endings of first order nociceptive axons and on nearby vasculature. Inflammatory mediators interact with membrane receptors and modulate their activity, enhancing the open probability of ion channels. As a result, all these mediators have the potential to increase the current that flows through TRP channels, and thereby increase the sensitivity of free nerve endings. Two endogenous inflammatory mediators have been tested on the cornea to cause augmented sensitivity: bradykinin and prostaglandin.

The free nerve ending itself, meanwhile, can release neuroactive peptides when depolarized. The most abundant neuropeptides in the trigeminal ganglion are SP and CGRP, and the neurotrophic character of these neuropeptides has been demonstrated. They stimulate epithelial growth and differentiation, which in turn causes epithelial cells to produce nerve growth factor (NGF) and glial-derived neurotrophic factor (GDNF). Released neuropeptides interact with immune cells or vasculature, and provoke neurogenic inflammation. Substance P is the most powerful inflammatory mediator neuropeptide. It triggers mast cell degranulation, and consequently, the release of histamine, which can bind to its specific nerve membrane receptor. It produces impulse propagation centripetally through the sensory nerve, and an antidromic impulse down the axons, causing the release of neuropeptides in adjacent nerve terminals and further inflammation, a phenomenon known as “axon reflex.” Bidirectional signaling, therefore, takes place in the inflamed tissue and the free nerve ending. These interactions can heighten the sensitivity of the free nerve ending to the signals that are translated into pain (Figure 1).

Long-term inflammation further changes neuronal membrane receptor sensitivity. NGF and GDNF can also activate some MAPK pathways (ERK and p38), giving rise to synaptic plasticity. This plasticity leads to changes in the channel open probability and expression of new receptors in the nerve terminal membrane. In this situation, the nerve fiber is more prone to excitation: the activation threshold of transducers diminishes and they become more responsive to stimuli. In fact, activity is often spontaneous. The capacity of polymodal nociceptors to undergo these anatomical changes is called “peripheral sensitization,” and it is the underlying cause of hyperalgesia. Belmonte & Giráldez demonstrated the sensitization of polymodal nociceptor fibers with electrophysiological studies. When polymodal nociceptors were stimulated twice with stepwise increments in temperature at an interval of 3 minutes, the second (higher) temperature stimulus caused them to fire more rapidly, and increased the average frequency to 52. When corneal nociceptors are sensitized because of inflammation (also considered subclinical inflammation), even normal thinning of the tear layer, and consequent cooling of the ocular surface and activation of cold nociceptors, might evoke unpleasant sensations on the ocular surface. Corneal hyperalgesia can explain in part dry eye symptoms without evident clinical signs.

Prior to development of the non-contact gas esthesiometer, the Cochet-Bonnet esthesiometer was the only device capable of measuring corneal sensitivity. The Cochet-Bonnet esthesiometer only stimulates mechanosensitive fibers, whereas the gas esthesiometer uses controlled mechanical, thermal and chemical impulses to measure corneal nociceptor response. In recent years, both types of esthesiometers have been used to compare corneal sensitivity between dry eye patients and normal subjects (Table 1). Using a non-contact gas esthesiometer, Tuisku et al., found hypersensitivity in moderate DED patients due to chronic epithelial inflammation secondary to ocular surface dryness in 20 Sjögren Syndrome patients and 40 post-LASIK patients compared to controls. However, several studies found a reduction in corneal sensitivity in both Sjögren and non-Sjögren dry eyes. Using the Cochet-Bonnet esthesiometer, Xu et al. found a significant decrease in corneal sensitivity in dry-eye patients (p < 0.001 and p < 0.01, respectively). Bourcier et al. and Benítez-del-Castillo et al. obtained similar results using a non-contact gas esthesiometer (p < 0.001 and p < 0.001, respectively). All studies had age-matched control groups. A functional alteration or a pathological nerve-switch, i.e. neuropathy, may underlie corneal hyposensitivity.
Neuropathy in Dry Eye Disease

Confocal microscopy is becoming a powerful means of studying corneal nerves. In-vivo confocal microscopy gives information about corneal nerve density, number, width, tortuosity, and reflectivity. Several studies have shown a reduced sub-basal nerve density in dry eye patients compared to controls, and this is correlated with corneal sensitivity. Benítez del Castillo et al. found a negative correlation between subbasal nerve density and activation threshold ($r = -0.791$, $p < 0.001$), similar to Labbé et al., who found a positive correlation between nerve density and corneal sensation in Sjögren Syndrome (SS) patients ($r = 0.644$; $p = 0.0045$), as well as in non-SS subjects ($r = 0.383$, $P = 0.041$). Moreover, authors such as Benítez del Castillo et al. ($p = 0.004$), Labbé et al. ($p < 0.0001$), or Labbé et al. ($p < 0.001$) agree that subbasal nerve density was lower in dry eye patients, while others failed to demonstrate any change in nerve density. The variability of results in regard to sub-basal nerve density and its correlation with corneal sensitivity might be due to differences in patient characteristics, quantification methods and small sample sizes. Nonetheless, Villani et al., and Cruzat et al. agree that nerve tortuosity is increased, and this might be linked to hypoesthesia as well as to dry eye nerve alterations. NGF over-expression is known to lead to peripheral nervous system hypertrophy, suggesting that NGF can also be the culprit behind nerve tortuosity.

Table 1. Corneal sensitivity in DED (Mean ± Standard Deviation).

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Corneal sensitivity</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>DED</td>
</tr>
<tr>
<td><strong>COCHET-BONNET</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esthesiometer (mg/S)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labbé et al. (2013)</td>
<td>14</td>
<td>43</td>
</tr>
<tr>
<td>Labbé et al. (2012)</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Villani et al. (2007)</td>
<td>20</td>
<td>--</td>
</tr>
<tr>
<td>Xu et al. (1996)</td>
<td>26</td>
<td>44</td>
</tr>
<tr>
<td><strong>NON CONTACT GAS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esthesiometer (ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuisku et al. (2008)</td>
<td>10</td>
<td>--</td>
</tr>
<tr>
<td>Benítez-del-Castillo et al. (2007)</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Bourcier et al. (2005)</td>
<td>44</td>
<td>14</td>
</tr>
<tr>
<td>De Paiva &amp; Pflugfelder (2004)</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

DED: Dry eye disease; C: Controls; non-SS: non-Sjögren Syndrome; SS: Sjögren Syndrome

(a) Mean corneal sensitivity from 5 different areas (superior, inferior, temporal, nasal and central)
(b) Corneal sensitivity values in terms of mg/S
(c) Corneal mechanical threshold values
! Corneal hypersensitivity in DED patients.
in addition to hyperalgesia. All these studies focus on anatomical and structural changes in corneal nerve plexus, but little is known about the firing pattern of abnormal nerves in dry eye patients.

**Neuropathy in LASIK patient**

The increasing demand for refractive surgery is giving us greater insight into the mechanism involved in ocular surface sensation. Estimates suggest that half of LASIK patients have dry eye symptoms 6 months after surgery. In LASIK surgery, corneal axons are disrupted because of corneal flap formation and photoablation. This interrupts the lacrimal function unit (LFU), which consists of the main lacrimal gland, the ocular surface and the innervation, and is essential for tear film composition and secretion. After LASIK surgery, corneal sensitivity measured with the Cochet-Bonnet esthesiometer and clinical indicators of tear insufficiency such as tear volume, TFBUT, and corneal and conjunctival staining return to preoperative values within 1 year, and according to Tuisku et al. (p = 0.666), in 2 years these parameters do not differ from those found in normal subjects. Gallar et al., however, found that when corneal sensitivity was measured with a non-contact esthesiometer, it took up to 2 years to recover normal values. Despite the return of clinical signs to preoperative levels, Tuisku et al. found that symptoms continued to be significantly different from normal subjects after 2 years (p < 0.022). Post-surgical inflammation or axotomy of corneal nerves may trigger dry eye symptoms, without evident clinical signs.

Long-standing hyperosmolarity has also been documented in post-LASIK patients. Hyposecretion or tear instability secondary to LFU disturbance are likely contributors to increased tear osmolarity. As in the cascade of events discussed in the beginning of this section, hyperosmolarity will likewise lead to ocular surface and neurogenic inflammation in post-LASIK patients, and to the resulting peripheral nerve sensitization with subsequent irritation and pain symptoms, as seen in early post-operative period. Besides peripheral inflammation, corneal axon severing can also alter nerve sensitivity. The response to injury depends on the initial damage and the resulting degeneration. It starts with Wallerian degeneration that consists of axons and myelin fragmentation, removal of debris by Schwann cells, and histamine and serotonin release by mast cells. Glial cells interrupt the synaptic connections between damaged neurons and the central nervous system (CNS). Cell somas in the trigeminal ganglion (TG) receive little NGF due to nerve damage, and this triggers regeneration. In the regenerative state, major changes occur in gene expression including the upregulation of sodium channels, downregulation of potassium channels, and a lowering of the threshold of transient receptor potential (TRP) channels that appears to cause ectopic discharges; that is, a sensory inflow from non-injured hypersensitive fibers which fire spontaneously. Axonal restoration is the rule, and so is the pruning of nerve sprouts, but if the process of regeneration is interrupted, spontaneous discharges will continue to evoke sensations of burning, dysesthesia and paresthesia such as ocular dryness, foreign body sensation or sand-like feeling.

The foregoing paresthesia, dysesthesia, negative signs such as sensorial deficiency (corneal hypoesthesia), spontaneous or evoked pain, are all characteristics of neuropathic pain. The underlying lesion or disease in somatosensory nerves must be determined in order to refer to these symptoms as neuropathic pain. To assess such changes in the cornea, in vivo confocal microscopy and esthesiometer can be used. Novel therapeutic treatments such as platelet-rich plasma have been investigated for sensory and anatomical recovery using such devices, but the results have been discouraging. Javaloy et al. studied myopic eyes receiving LASIK, with half the patients receiving topical platelet-rich plasma treatment. The results showed that both groups had similar corneal sensitivity (p > 0.05) and subbasal nerve density (p = 0.66) after 3 months of treatment. Nonetheless, studies in animal models have demonstrated increased corneal nerve regeneration with NGF plus docosahexaenoic acid (DHA) after photorefractive surgery, and with pigment epithelial-derived factor (PEDF) plus DHA after lamellar keratectomy. Corneal sensation restoration was also possible with the latter, and with naltrexone in diabetes-induced rats.

**POTENTIAL CENTRAL NERVOUS SYSTEM CHANGES**

Neuropathic pain can have a peripheral or central origin. The peripheral sources of dry-eye-like neuropathic pain have been discussed in the previous section, and we will now focus on the potential changes in CNS that can result in dry eye symptom perception or aggravation. Corneal afferents project to two different locations in the trigeminal spinal nucleus in the brainstem: the ventrolateral area of the transition between nucleus interporalis and caudalis (Vc/Vi), that we will refer to as the “rostral region”, and the superficial laminas in the transition between nucleus caudalis and upper cervical cord (Vc/C1) or the “caudal region” (Figure 2). These areas have been identified using axonal tract-tracers and c-fos immunochemistry (a marker of neuronal activation) after thermal, chemical, and mechanical corneal stimulation. Studies have shown that corneal afferents projecting to rostral and caudal regions have different features,
such as neurochemical content, electrophysiological responses, modulation by endogenous ligands, and different receptive fields. Their synaptic neurons also have different projections. Some project to regions in the thalamus, particularly to the ventral posterior medial area, posterior nucleus/zona incerta (PO/ZI), or nucleus submedius (SM), whereas others project to some brainstem nuclei: superior salivary nucleus/facial motor nucleus (SSN/VII), or the parabranchial area (PBA). Consequently, each trigeminal spinal region has been attributed with different corneal pain processing functions. It has been suggested that Vc/C1 transition regions project to higher nociceptive processing regions, such as the posterior nucleus/zona incerta of the thalamus (PO/ZI) and parabranchial complex (PBA) for sensory discrimination and autonomic reflex adjustment, whereas Vi/Vc projections to the superior salivary nucleus/facial motor nucleus area (SSN/VII) have ocular-specific functions (spontaneous lacrimation and eye blink), because they rarely send input to thalamic nuclei and have cornea-restricted receptive fields. Nevertheless, as efferent projection targets of Vi/Vc and Vc/C1 have not been fully explained, the Vi/Vc and Vc/C1 roles in corneal nociception are still unclear.

Poor knowledge of how corneal-responsive neurons connect to their targets heightens the difficulty of exploring the changes that can occur after peripheral nerve inflammation and injury. It is known that central nervous system changes can also occur elsewhere in the body, in addition to peripheral sources of modification that can lead to heightened nociceptive action potentials. This might involve an increase in the excitability of second order neurons following high levels of nociceptive activity, known as central sensitization (CS). There seem to be two forms of CS: the first is a rapidly induced (within seconds) transcription-independent form, a phenomenon called wind-up, and the second, a transcription-dependent form or long-term potentiation (LTP). Wind-up manifests following the activation of A-delta and C fibers at certain frequencies (25-100 pulses, 50Hz), and lasts for several minutes after stimulus removal. Prolonged ectopic activity of nociceptors leads to sustained depolarization of second order neurons. If there is an N-methyl-D-aspartate (NMDA) receptor-dependent mechanism in those neurons, sustained depolarization might be sufficient to remove magnesium block and the influx of calcium, changing the synaptic efficacy. As stated above, inflammation and axotomy can trigger increased firing in affected nerves and also in adjacent non-injured nerves due to a phenotypic switch. Spontaneous discharges and hypersensitivity could potentially evoke the repeated activity required for sensitization. Consequently, a wind-up phenomenon could contribute to an aggravation of dry eye symptoms.

LTP has been studied in the context of peripheral inflammation. As previously mentioned, the wind-up phenomenon allows calcium, the most important intracellular second messenger, to enter the cell. Calcium can provoke changes in gene expression, and maintain the hyperexcitable state by inserting new ion channels in the membrane. The plastic changes in the corneal units in the trigeminal nucleus following peripheral inflammation, however, are unclear, but as LTP occurs in spinal subnucleus oralis, it could also develop in Vc/C1.

If that were the case, corneal pain evoked by non-noxious stimuli (allodynia), spread of pain sensitivity to non-injured areas (receptive field spread or secondary hyperalgesia), and temporal summation would suggest the involvement of CS. As Vc/C1 corneal receptive fields also receive periorbital cutaneous input, determination of receptive field spread becomes difficult. Measuring temporal summation is another challenge, as adequate tools have not yet been validated. Further studies are needed to ascertain whether central changes contribute to dry eye symptoms in animal models, and new clinical assessment tools must be developed.

**Descending modulation of pain transmission**

The brainstem regulates pain-related signals. The periaqueductal gray (PAG) is a key node that allows pain modulation feedback. The PAG receives input from structures in the forebrain such as the amygdala and hypothalamus, which are involved in emotional experience and expression. Abdallah et al. have recently traced bilateral hypothalamic projections to trigeminal spinal nucleus caudalis using the retrograde tracer fluorogold (FG) in rats. They suggest that these pathways...
may play a role in sensory inflow modulation, although it is still unclear whether nociceptive input activates hypothalamic-descending neurons\textsuperscript{126}. In addition, several studies have demonstrated that disturbances in the hypothalamic-pituitary-adrenal axis contribute to long-standing alterations in pain processing\textsuperscript{127-130}. This prompted Blackburn-Munro & Blackburn-Munro to hypothesize that the hypothalamus could alternatively or concurrently influence nociceptive transmission via endocrine mechanisms\textsuperscript{131}. The PAG also receives input from cortical areas, such as the dorsolateral prefrontal cortex, somatosensory cortex, and the insular cortex\textsuperscript{123,132-134}. The information coming from the cortex, hypothalamus, and amygdala is integrated in PAG, and is involved in the modulation of pain transmission\textsuperscript{123,132,133}. PAG output goes to other areas of the brainstem. Modulatory inputs in the trigeminal spinal nucleus originating from some of the brainstem nuclei release biogenic amines neurotransmitters, such as the locus ceruleus (LC)\textsuperscript{135-137}, and nucleus raphe magnus (NRM)\textsuperscript{123,136,139}. The LC releases norepinephrine and the NRM releases serotonin. Electrophysiological studies have demonstrated that these neuromodulators can influence the excitability of the trigeminal neurons\textsuperscript{136,139}. Meng et al. excited corneal afferents electrically, and observed that NRM inhibited cornea-responsive A- and C-fibers in rostral (Vi/Vc) and caudal (Vc/C1) regions of the trigeminal spinal nucleus. The parabranchial area (PBA) similarly inhibited corneal afferents, with no statistical differences between PBA and NRM\textsuperscript{139}. Other areas of medullary reticular formation, such as the rostroventral medulla (RVM), are also involved in pain modulation and processing (Figure 3)\textsuperscript{123,125,140,141}.

There is evidence that the hypothalamus and descending inhibitory relays such as PBA receive direct input from corneal units of Vi/Vc and Vc/C1\textsuperscript{111,142}. This further suggests that these regions may control the ascending nociceptive input by feedback mechanisms, although the recruitment of descending pathways is not known. Meng et al. suggested that Vi/Vc could be involved\textsuperscript{109}, but some authors later abolished this hypothesis when they discovered that Vi/Vc projecting corneal fibers were inhibited by descending pathways\textsuperscript{139}. In the circuitry of the trigeminal nucleus caudalis there are interneurons that release neuropeptides such as enkephalins and other endogenous opioid substances\textsuperscript{143}. Descending modulators from structures such as NRM and PBA can trigger activation of these local inhibitory interneurons, hyperpolarizing second order neurons. However, they can also mediate the inhibition acting directly on the first afferent nociceptive nerve fiber or hyperpolarizing trigeminal projection neurons\textsuperscript{140}. Nevertheless, there is a growing body of evidence to show that descending pain pathways also have facilitatory effects\textsuperscript{123,140,144,145}. In fact, peripheral injury and inflammation can result in a decrease of descending inhibition or an increase in their facilitatory effects\textsuperscript{140,146,147}.Either would have a similar net effect: increased excitability with subsequent abnormal pain sensitivity. Even though corneal pathways have not been studied in depth, we imagine that if such changes in the corneal units in the trigeminal spinal nucleus occur secondary to inflammation in dry eye or corneal fiber injury after LASIK, they would manifest as increased dry eye symptoms that would not correlate with external signs\textsuperscript{2}.

### Cortical and subcortical changes

Structural and anatomical plastic changes occur in both subcortical and cortical areas after peripheral or central nervous system injuries, which contribute to pain perception\textsuperscript{148}. However, little is known about the cortical representation of corneal pain. Therefore, the brain mechanism for corneal pain perception and synaptic changes in cortical and subcortical areas due to corneal neuropathic pain are not yet understood. Moulton et al. published the first study on the localization of corneal pain in the primary somatosensory cortex (S1)\textsuperscript{149} in which data from one subject with hard contact lens-related corneal abrasion was obtained using functional magnetic resonance imaging (fMRI), and light was used as the painful stimulus. Corneal pain activated the middle region of the contralateral S1, which corresponds to the representation of the eye in Penfield’s homunculus\textsuperscript{149}. The contralateral ventral posteromedial thalamus (VPM) and anterior cingulated cortex (ACC) were also noticeably activated during the painful state (p < 0.0001) compared to the recovered state (9 days later,

---

**Figure 3.** Schematic view of the descending modulation of pain transmission to the trigeminal spinal nucleus. Cx: Cortex; PAG: periaqueductal gray; PBA: parabranchial area; NRM: nucleus raphe magnus; LC: locus ceruleus; MRF: medullary reticular formation; BS: brainstem.
when abrasion was resolved\textsuperscript{150}. Central sensitization-like phenomena are known to emerge in ACC in neuropathic pain patients, as described by Moulton et al., as well as in the amygdala\textsuperscript{151,152}. Changes in thalamus activity have also been described in neuropathic pain elsewhere in the body, resulting in an increase in spontaneous activity\textsuperscript{153,154}. It is interesting to note that cortical reorganization and changes in somatosensory activity are absent in long-standing non-neuropathic pain, based on fMRI study of orofacial pain\textsuperscript{155}. Animal models with long-standing or intense pain states (e.g. inflammation) have altered representation of painful areas in the thalamus and the cortex. These alterations are thought to be responsible for a low pain threshold and low pain tolerance, with increased pain perception in chronic back pain syndrome and episodic headaches\textsuperscript{156}. Similar results were found by Vehof et al., in dry eye patients\textsuperscript{157}. Pain sensitivity and tolerance were tested with heat stimulus on the forearm, and dry eye symptoms were assessed using the Ocular Surface Disease Index (OSDI). The severity of dry eye symptoms was strongly associated with low pain tolerance and high pain sensitivity (p = 0.003 and p = 0.008, respectively)\textsuperscript{159}. Long-term DED has similarities with neuropathic pain syndromes, further suggesting that DED symptoms can be considered corneal neuropathic pain. Similarly, psychiatric disorders that alter the normal function of cortical networks could also be involved in the perception of dry eye symptoms or corneal pain. In fact, posttraumatic stress disorder (PTSD) and depression to better understand corneal nerve changes molecular and cellular mechanisms are not completely understood. Nevertheless, suitable tools and questionnaires are required for the assessment of neuropathic corneal pain. An appropriate nomenclature for ocular sensitivity and pain will help achieve that goal.

**REFERENCES**


**CONCLUSIONS**

Ocular pain and sensitivity are often referred to as dry eye symptoms. Tears may have a role in the pathophysiology and longevity of these symptoms, as well as in direct damage to corneal nerves after LASIK, although the molecular and cellular mechanisms are not completely understood. To better understand corneal nerve changes after such insults, improved corneal imaging technology is required. Moreover, the variety of projections from brainstem corneal units to higher nuclei makes it hard to establish their role in corneal pain processing, and consequently in the functional and anatomical central nervous system changes that occur in long-standing ocular pain and sensitization. Electrophysiological studies in animal models could explain whether central sensitization-like phenomena occur in corneal units in the trigeminal spinal nucleus. Since little is known about the descending pathways that modulate corneal pain transmission, and cortical representation of corneal pain, further study with MRI/fMRI/PET is required. A standardized clinical protocol would help to distinguish between ocular inflammation and neuropathy, which would lead to the development of new therapeutic strategies. Nevertheless, suitable tools and questionnaires are required for the assessment of neuropathic corneal pain. An appropriate nomenclature for ocular sensitivity and pain will help achieve that goal.


