How does chronic dry eye shape peripheral and central nociceptive systems?

Adrian Guerrero-Moreno, Darine Fakih, Stéphane Melik Parsadaniantz, Annabelle Réaux-Le Goazigo

Dry eye disease (DED) is a multifactorial disease characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (Belmonte et al., 2017).

Interestingly, DED shares common characteristics with neuropathic pain, which is defined as pain caused by damage or disease affecting the somatosensory nervous system. Ocular pain, more commonly called corneal pain, has gained recognition due to its increasing prevalence, morbidity, and resulting social burden (Belmonte et al., 2017). To date, the management of chronic corneal pain still represents a therapeutic challenge. A better understanding of the molecular and cellular mechanisms participating in the transition from acute to chronic pain are crucial issues for developing the effective management and a therapeutic strategy to alleviate this debilitating condition. Today, much of the knowledge of neuroinflammation-neuropathic pain processing comes from data from the spinal cord, but a comparatively small number of investigations have been carried out in the corneal trigeminal pain pathway.

Corneal nociceptive pathway: from the cornea to the brain: The cornea is the most densely innervated tissue in the body, with 300–600 times the sensory innervation density of the skin (7000 nociceptors/mm²). The sensory innervation of the cornea is provided by ciliary nerves, a subdivision of the nasociliary branch, which originates from the ophthalmic branch of the trigeminal ganglion (TG) (Belmonte et al., 2017). Sensory inputs from the cornea are conveyed to the ophthalmic branch of the TG by first-order neurons, which only represent 1% to 3% of the total population of trigeminal neurons (Launay et al., 2015). Then, the central axons of corneal sensory neurons make synapses in two discrete regions of the trigeminal brainstem sensory complex: the transition region between the subnucleus interpolaris (VI) and caudalis (Vc) and the TG, which constitutes the first relay of somatosensory information.

Corneal nerve damage, inflammation and peripheral sensitization after chronic dry eye: Understanding the pathophysiology of corneal neuropathic pain observed in patients suffering from DED is essential for the development of new therapeutic strategies and implies the development of relevant preclinical models that best mimic the human disease. In that context, we recently developed a model of chronic dry eye in mice, consisting of the excision of the extraorbital lachrymal gland (responsible for the aqueous constituent of the tear film) and Harderian gland (which produces lipids of the tear film). Glands removal markedly reduced tear production over time and induced corneal nerve abnormalities in the superficial epithelium (Fakih et al., 2019). The reduced number of intra-epithelial corneal nerve endings in DED mice 3 weeks after the surgery was consistent with previous animal (Kovacs et al., 2016) and clinical studies (Labbe et al., 2012; Hamrah et al., 2017). In addition to corneal nerve abnormalities, a mechanical allodynia (decreased mechanical threshold) and inflammatory responses also developed at the cornea level.

Several lines of evidence support the idea that neuroimmune and neuronal-glial interactions play a major role in the chronification of pain at both spinal and trigeminal levels (Grace et al., 2014). Indeed, the activation of immune cells participates in the peripheral sensitization mechanism, which is characterized by a change in the excitability of nociceptors (decreased threshold); an increase in spontaneous stimuli evoked the firing rate of the sensory neurons, leading to spontaneous pain and hyperalgesia. Considering that, we further evaluated changes in the spontaneous corneal nerve fiber activity of the ciliary nerve in our preclinical model of persistent dry eye. Electrophysiological recordings of the ciliary nerve fibers revealed a 100% increase of action potential frequency between sham and dry eye mice on day 21. These data confirm that corneal inflammation and nerve damage are able to modify the characteristics of trigeminal afferent neurons, resulting in their hyperexcitability and increased ongoing activity (Acosta et al., 2013; Kovacs et al., 2016; Fakih et al., 2019) (Figure 1). These results are of importance because they link corneal nerve abnormalities, the upregulation of the ongoing activity of the corneal nerve and persistent pain. Such morphological and functional alterations of the corneal nerve may indeed explain the painful state of patients suffering from chronic DED.

The total tear suppression observed following the excision of the extraorbital lachrymal gland and Harderian gland could be considered as a severe dry eye model. Other mild and moderate preclinical models through reducing tear volume have been developed. For example, controlled environment chamber model using exposure to low humidity and constant airflow, as well as its combination with lachrymal gland insufficiency generated by systemic application of scopolamine, are well established murine models of DED mimicking the human pathology.

Concomitant corneal inflammation: how inflammatory responses and peripheral sensitization are interacting? Corneal inflammation is characterized by a 100% increase of action potential frequency in the spontaneous corneal nerve fiber activity of the ciliary nerve in our preclinical model of persistent dry eye. Electrophysiological recordings of the ciliary nerve fibers revealed a 100% increase of action potential frequency between sham and dry eye mice on day 21. These data confirm that corneal inflammation and nerve damage are able to modify the characteristics of trigeminal afferent neurons, resulting in their hyperexcitability and increased ongoing activity (Acosta et al., 2013; Kovacs et al., 2016; Fakih et al., 2019) (Figure 1). These results are of importance because they link corneal nerve abnormalities, the upregulation of the ongoing activity of the corneal nerve and persistent pain. Such morphological and functional alterations of the corneal nerve may indeed explain the painful state of patients suffering from chronic DED.

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neurotrophic factors and chemokines, contribute to neuronal excitability and central sensitization mechanism during chronic pain states (Melik Parsadaniantz et al., 2015). We found higher Iba1-immunopositive cells and CD68 and Itgam mRNA levels in the trigeminal brainstem complex, confirming the activation of microglial cells in acute (7 days) and persistent (21 days) ocular pain (Launay et al., 2016; Fakih et al., 2019). Aside from immune cell activation, astrocyte activation (astrogliosis) was also confirmed by a robust astrocyte reaction (higher levels of GFAP immunoreactivity) and the upregulation of GFAP mRNA expression in the ipsilateral trigeminal brainstem sensory complex. Proinflammatory responses occurred in this brain structure three weeks after gland excisions; proinflammatory cytokines (IL-6 and IL-1β), oxidative stress enzyme (iNOS2) and neuronal (ATF3 and FOS) markers were increased, confirming a dysregulation in glial cells activation in the central nervous system (Fakih et al., 2019; Figure 1). Overall, this study highlights neuronal–glial and neuroinflammatory interactions which may account for the development and persistence of the ocular pain reported in DED patients.

Accumulating evidence has also suggested that chronic changes of activity in primary afferent neurons induce synaptic rearrangements in the central nervous system and lead to the functional remodeling of presynaptic sites. With regard to the synaptic mechanisms of chronic inflammatory and neuropathic pain, it has been proposed that changes in presynaptic function play an essential role; however, until now, nothing has been known about the possible presynaptic changes during a persistent ocular pain state. Piccolo, one of the components of the presynaptic zone, plays a key role in synaptic plasticity by facilitating/managing the secretion of synaptic vesicles. A significant finding in our study was the increased levels of Piccolo immunoreactivity in the trigeminal brainstem complex, confirming the activation of the presynaptic zone, plays a key role in synaptic plasticity by facilitating/managing the secretion of synaptic vesicles. A significant finding in our study was the increased levels of Piccolo immunoreactivity in the trigeminal brainstem complex, confirming the activation of the presynaptic zone.

In summary, the cellular modifications we reported in the context of chronic corneal pain include changes in proinflammatory gene expression, changes in cell morphology (cell activation), and a reorganization of neuronal nociceptive networks in the central nervous system. Many experiments are still required to further characterize the precise nature of this central neuronal plasticity linked to pain.

To conclude, a better understanding of the sequence and nature of the events that drive these neurobiological mechanisms will offer significant promise for the discovery of new approaches and targets for the management of chronic ocular pain. We predict that this will be an exciting area of new investigations. Further fundamental and clinical studies using functional and morphological magnetic resonance imaging studies may help to depict how chronic corneal pain can shape the brain and identify the morphological changes that may occur during persistent corneal pain. An elegant in vivo magnetic resonance imaging study has already reported macrophage infiltration in the TG after corneal alkali burn in mice (Ferrari et al., 2014). Although our knowledge of the mechanisms involved in corneal pain has progressed over the last decade, our efforts must be continued for the identification and validation of new therapeutic targets, which are currently sorely lacking.

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References

Acosta MC, Luna C, Quirce S, Belmonte C, Gallaj J (2013) Changes in sensory and motoric activity of corneal sensory nerves during allergic keratoconjunctivitis. Pain 154:2353–2362.

Beltzmore C, Nicholls JJ, Cox SM, Brock JA, Begley CG, Bereiter DA, Dartt DA, Galor A, Hamrah P, Ivanusic JJ, Jacobs DS, McNamara NA, Rosenblatt MJ, Stapleton F, Wolffsohn JS (2017) TOCS DEWS II pain and vision report. Ocul Surf 15:404–437.

Fakih D, Zhao Z, Nicolle P, Rebussion E, Joubert F, Luzu J, LeCot A, Rostene W, Baudouin C, Melik Parsadaniantz S, Reaux-Le Goazigo A (2019) Chronic dry eye induced corneal hypersensitivity, neuroinflammatory responses, and synaptic plasticity in the mouse trigeminal brainstem. J Neuroinflammation 16:268.

Ferrari G, Bignami F, Giaconini C, Capitolo E, Cioni G, Chaabane L, Rama P (2014) Ocular surface injury induces inflammation in the brain: in vivo and ex vivo evidence of a corneal-trigeminal axis. Invest Ophthalmol Vis Sci 55:6289–6300.

Grace PM, Hutchinson MR, Maier SF, Watkins LR (2014) Pathological pain and the neuroimmune interface. Nat Rev Immunol 14:127–141.

Hamrah P, Qazi Y, Shaffakt B, Dastjerdi MH, Pavan-Langston D, Jacobs DS, Rosenthal P (2017) Corneal nerve and epithelial cell alterations in corneal allografting: an in vivo confocal microscopy case series. Ocul Surf 15:139–151.

Kovalov A, Luna C, Quirce S, Mizerska K, Callejo G, Riesstra A, Fernandez-Sanchez L, Meseguer VM, Cuenc a N, Merayo-Lloves J, Acosta MC, Gausa X, Belmonte C, Gallaj J (2016) Abnormal activity of corneal cold thermoreceptors underlies the unpleasant sensations in dry eye disease. Pain 157:399–417.

Labbe A, Alalawi H, Van Westen C, Brusa E, Georgescu D, Baudouin C (2012) The relationship between subbasal nerve morphology and corneal sensitivity in ocular surface disease. Invest Ophthalmol Vis Sci 53:4926–4931.

Launay PS, Godefroy D, Khabou H, Rostene W, Sahel JA, Baudouin C, Melik-Parsadaniantz S, Reaux-Le Goazigo A (2015) Combined 3D/CGC clearing method, retrograde tracer and ultramicroscopy to map corneal neurons in a whole adult mouse trigeminal ganglion. Exp Eye Res 139:136–143.

Launay PS, Rebussion E, Liang H, Kessal K, Godefroy D, Rostene W, Sahel JA, Baudouin C, Melik Parsadaniantz S, Reaux-Le Goazigo A (2016) Ocular inflammation induces trigeminal pain, peripheral and central neuroinflammatory mechanisms. Neurobiol Dis 88:16–28.

Melik Parsadaniantz S, Rivat C, Rostene W, Reaux-Le Goazigo A (2015) Opioid and chemokine receptor crossstalk: a promising target for pain therapy? Nat Rev Neurosci 16:69–78.

Rahman M, Okamoto K, Thompson R, Katagiri A, Bereiter DA, Dartt DA, Galor A, Hamrah P, Ivanusic JJ, Jacobs DS, McNamara NA, Rosenblatt MJ, Stapleton F, Wolffsohn JS (2017) TOCS DEWS II pain and vision report. Ocul Surf 15:404–437.

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