Acta Ophthalmologica

Acta Ophthalmologica 2018

Review Article

Role of corneal nerves in ocular surface homeostasis and disease

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ABSTRACT.

Corneal nerves are key components of the physiological system that controls ocular surface homeostasis. The cornea is primarily innervated by the ophthalmic branch of the trigeminal nerves (cranial nerve V), which distend bilaterally from the pons. The nasociliary branch (afferent) of the ophthalmic nerve is sensory for cornea, eyelid and conjunctiva. These nerve fibres play a role in sensing temperature, chemical and mechanical stimuli, and pain, whereas, branches of the facial nerve (cranial nerve VII) contain motor nerves that control blinking and autonomic (sympathetic and a paucity of parasympathetic) fibres that stimulate tear production and secretion via feedback loops between the ocular surface, lacrimal glands and brain. Disruption of these nerves with interruption of neural feedback loops between the ocular surface and lacrimal glands can lead to corneal diseases such as dry eye disease (DED) and neurotrophic keratopathy (NK). Inversely, hypersensitivity of the nerve fibres and/or dysregulation of pain-controlling nervous centres may lead to neuropathic pain. Recently, medications that specifically target regeneration of corneal nerves have started to become available – and considering the high prevalence of diseases associated with corneal nerve dysfunction, these agents promise to fulfil a hitherto important unmet need. In this review, we explore the physiology of corneal nerves, the pathology of corneal nerve diseases and how these relate to neuropathic pain, NK and DED. We also discuss what novel treatments may be useful against diseases involving corneal nerves.

Key words: corneal nerves – dry eye disease – nerve growth factor – neuropathic pain – neurotrophic keratopathy

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Acta Ophthalmol.

doi: 10.1111/aos.13844

Introduction

In 2017, 10 years after the first TFOS International Dry Eye WorkShop (DEWS) report (Dry Eye WorkShop 2007), the follow-up DEWS II was published including a new, updated definition of dry eye disease (DED) (Craig et al. 2017). This new definition of DED was designed to reflect increasing clinician awareness that, on the one hand, DED is a multifactorial condition characterized by loss of normal homeostatic mechanisms on the ocular surface, and on the other, that

neurosensory abnormalities play an aetiologic role in its development (Craig et al. 2017). The acknowledgement that DED results from derangement of tear film homeostasis – that is, an upset of the normal state of equilibrium observed in healthy functioning tissues – focuses the definition of DED on the observation that many changes can occur in the tear film and ocular surface to result in the condition. Moreover, alterations in the neurons innervating the cornea certainly underlie many aspects of ocular surface diseases. Indeed, these neurons appear to play a significant role in maintaining ocular homeostasis as well as in sensory-discriminative aspects of eye pain (Belmonte et al. 2017). Dry eye disease (DED), for example, may derive from loss of neuronal endings, often as a consequence of inflammation. In this aetiology, advanced DED may eventually evolve towards an overt form of neurotrophic keratopathy (NK), although rarely severe. On the other side of this spectrum, the cornea's neuronal network can become disturbed in the direction of hypersensitivity, either peripherally in the neuronal endings or in the central pathways that drive and compute pain. This form of pain is termed neuropathic pain.

During the last two decades, novel technologies such as *in vivo* confocal microscopy (IVCM) have enabled detailed investigations of the fine structure of human corneal nerves in states of health, disease and postsurgical injury, as well as of the treatment of pathological states affecting the ocular surface (Marfurt et al. 2010). Prior to the availability of the current noninvasive microscopic imaging modalities, most knowledge of the neuronal architecture of mammalian corneas was derived from photomicrographs of stained cadaveric donor specimens (Cruzat et al. 2010) and studies in rats, rabbits and dogs (Al-Aqaba et al. 2010). Nowadays, however, an increased understanding of living human corneal nerves and their functions as well as disruptions to these have opened new areas of research into a number of disease states in which corneal nerves have been implicated.

Damage to nerves supplying the cornea, arising anywhere from their cell bodies located in the CNS and trigeminal ganglia to their nerve fibre endings embedded in the corneal stroma and epithelium, is thought to underlie a number of ocular diseases such as NK (Bonini et al. 2003; Sacchetti & Lambiase 2014; Semeraro et al. 2014), neuropathic pain (Belmonte et al. 2004, 2015) and, if neurogenic inflammation arises, DED (Meng & Kurose 2013). This review summarizes current views on the physiology of corneal nerves and their incrimination in various more or less common ocular diseases. Also introduced are some novel therapeutic agents that may become effective interventions against corneal nerve-related pathologies.

Physiology of Corneal Nerves

The human cornea is densely supplied by nerve fibres (Al-Aqaba et al. 2010), most of which are sensory and largely originate from the ophthalmic branch of the trigeminal nerves (cranial nerve V distending bilaterally from the pons) with their free (unmyelinated) nerve endings terminating in the corneal epithelium (Müller et al. 2003; Shaheen et al. 2014). Nerve fibres from trigeminal ganglion neurons extend suprachoroidally and branch, forming a plexus at the corneoscleral limbus (Shaheen et al. 2014). Only approximately 40 thick nerve bundles penetrate into the cornea, equally distributed around the limbus (Al-Aqaba et al. 2010). From the limbal plexus, nerve trunks, which mostly do not feature a myelin sheath so as to maintain transparency, enter the corneal stroma radially then travel anteriorly, terminating as free nerve endings that serve as mechanical, chemical and thermal 'nociceptors' delivering sensory information of touch, temperature and pain on the ocular surface to the brain (Marfurt et al. 2010; Müller et al. 2003). Most corneal nociceptors are polymodal, that is, sensory to thermal, mechanical and chemical stimulation. Apart from sensory nerves, a small proportion of corneal nerve fibres are sympathetic nerves whose cell bodies originate in the superior cervical ganglion (Shaheen et al. 2014).

Ocular neural regulation plays an integral role in maintaining tear volume and composition by tightly controlling lacrimal gland secretion of the aqueous layer of tear film containing water, electrolytes and a variety of proteins (Dartt 2009). Stimulation of corneal sensory nerves promotes lacrimal gland secretion by a trigeminal–parasympathetic reflex. In normal homeostasis, low-level sensory information from corneal and conjunctival nerves is conducted dromic (afferent) to the brain's lacrimal nucleus. This in turn stimulates efferent sympathetic and parasympathetic fibres of the facial nerve (cranial nerve VII) that innervate the lacrimal gland to signal this exocrine organ to secrete sufficient lacrimal fluid to cover the ocular surface with a protective layer of tear film. More intense stimulation from sensory afferents, for example if foreign bodies enter the eye and stimulate mechano-nociceptors on the ocular surface, and input from other centres such as emotional input, cause production of overflow tears that wash away deleterious materials. It has been proposed that basal tear flow is amplified up to 100-fold in response to irritation (Bron 1988). Hence, sensory nerve endings in corneal surface epithelia are able to rapidly respond to a variety of environmental changes by altering volume of tear production (Fig. 1).

Autonomic (sympathetic and a paucity of parasympathetic) innervation of the cornea and the eye's surrounding structures is involved in regulation of secretions of various tear film components by goblet cells, lacrimal glands and meibomian glands. Thus, maintenance of tear quality and quantity to establish a healthy cornea with a smooth refractory surface is tightly controlled by rapid-acting neural response mechanisms. However, further investigation is needed to truly elucidate the intricacies of each type of innervation (McDougal & Gamlin 2015). It has been shown that the ratio of sensory vs. sympathetic nerves after inflammation, for example after herpes keratitis, changes. This supports the hypothesis that sympathetic corneal innervation and the secretion of different neurotrophic factors might have certain functions, different from sensory nerves, at least in experimental (animal) models in which sympathetic corneal innervation is significant.

Disruption of these vital neural circuits may contribute to pathologic ocular conditions such as NK, characterized by diffuse or localized corneal

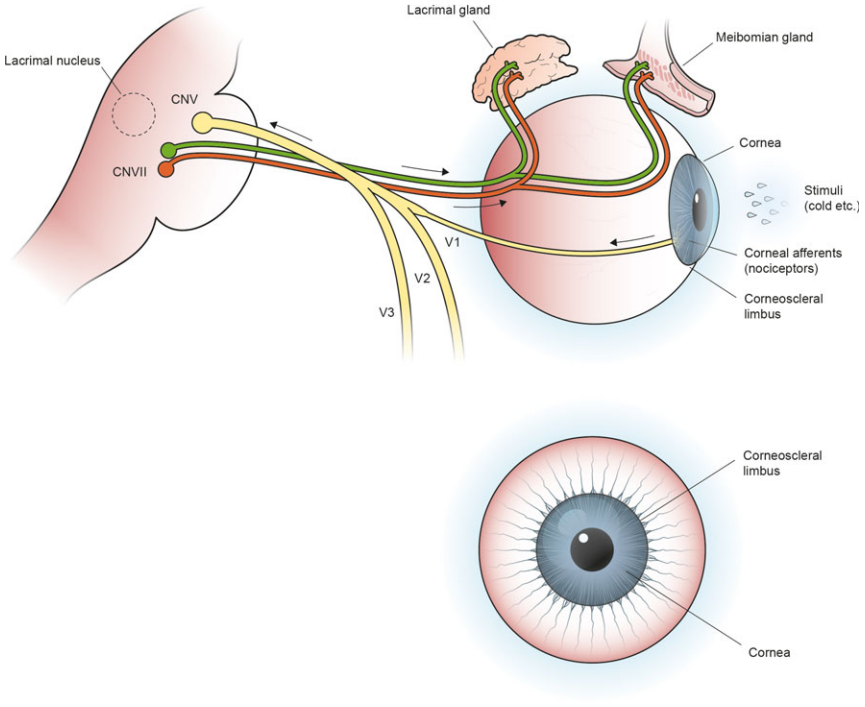

Fig. 1. Neural aspects of tear production. Stimulation of corneal afferent nerves (nociceptors forming a plexus at corneoscleral limbus and penetrating into the cornea) by environmental and noxious factors promotes lacrimal gland secretion by a trigeminal (cranial nerve V; CNV)–parasympathetic reflex looping in the brain's lacrimal nucleus. In response, efferents of the facial nerve (CNVII) stimulate lacrimal and meibomian glands and conjunctival goblet cells to secrete aqueous, lipids and mucin contents in natural tears.

anaesthesia, and conversely, DED-related symptoms of discomfort or irritation, or in more severe cases, neuropathic pain (Belmonte et al. 2017).

Dry Eye Disease

Dry eye disease (DED), which may affect between 5% and 30% of the population aged over 50 years (Spierer et al. 2016), is a multifactorial disorder of tears and the ocular surface of varying severity (Dry Eye WorkShop (DEWS) 2007; Craig et al. 2017; Bartlett et al. 2015). According to DEWS II, DED may be classified as predominantly either aqueous deficient or evaporative, although manifestations of both presenting features may emerge as DED progresses (Craig et al. 2017). Dry eye disease (DED) may be caused by dysfunction in the tear secreting glands, meibomian glands or in the neuronal circuits regulating these glands (Meng & Kurose 2013). Regardless, neurosensory abnormalities and reduced corneal sensitivity are now recognized as common features (Craig et al. 2017). Disturbance to corneal innervation has been implicated in DED associated with diabetes and use of contact lenses (Benítez-Del-Castillo et al. 2007), and DED is the most frequent complication of refractive surgery such as photorefractive keratectomy (PRK) or laser in situ keratomileusis (LASIK), and cataract surgery (Ram et al. 1998, 2002), procedures that cause alteration of corneal nerves (Fig. 2). For instance, DED affects more than 50% of patients immediately following LASIK surgery (Ambrósio et al. 2008) and may persist in 20–55% at 6 months (Levitt et al. 2015). LASIK-induced nerve transection has been speculated as the most likely aetiology in these cases (Chao et al. 2014, 2015), and new procedures that cause lesser nerve alterations such as small incision lenticule extraction have been shown to reduce the risk of DED (Denoyer et al. 2015). Almost 60% reductions in sub-basal corneal nerve density have been observed following PRK (Erie et al. 2005), and the incidence of chronic DED after this modality was estimated as 5% at 1 year postoperatively (Bower et al. 2015).

Structural and functional alterations of sub-basal corneal nerves have been reported in patients with primary (non-Sjögren's syndrome) DED, with lower nerve density and greater tortuosity, number of beadings and width compared with normal eyes. These changes were related to the severity of DED (Benítez-Del-Castillo et al. 2007; Labbé et al. 2013). A similar picture was noted in patients with severe DED of ocular chronic graft-versus-host disease (Steger et al. 2015). There is also evidence that the densely innervated meibomian glands, which secrete lipids that form the outer, anti-evaporation and pro-stabilizing layer of the tear film, and mucus-secreting conjunctival goblet cells, are activated by parasympathetic/sympathetic neurotransmitters and hence that the nervous system is involved in maintaining the tear film lipid layer and protecting the conjunctival epithelium (Aragona et al. 2006; Kam & Sullivan 2011). Because in response to trigeminal input parasympathetic and sympathetic fibres regulate both aqueous and lipid components of the tear film, disruption of trigeminal pathways may lead to complete disorganization of tear production and stability.

In a modified Belmonte aesthesiometer study conducted in a cohort of 129 US veterans, DED symptom severity was significantly ($p < 0.05$) and negatively correlated with corneal detection of mechanical stimuli and pain thresholds but not ocular surface evaluations of signs traditionally thought indicative of DED, suggesting a contributory role of corneal somatosensory dysfunction in the condition (Spierer et al. 2016). It has also been shown that patients reporting DED-related ocular pain had an incomplete subjective response to treatment with artificial tears; it was speculated that these patients may benefit from multimodal therapy including agents that alter the perception of nociceptive neurons innervating the ocular surface (Galor et al. 2016). Together, the above data imply an independent contribution of neural pathology to DED beyond tear dysfunction.

Meibomian gland dysfunction, and its related tear film instability, is a common cause of DED (Baudouin et al. 2016). Reduced tear flow and increased tear evaporation cause hyperosmolarity, initiating apoptosis of conjunctival and corneal cells, inflammation and loss of goblet cells

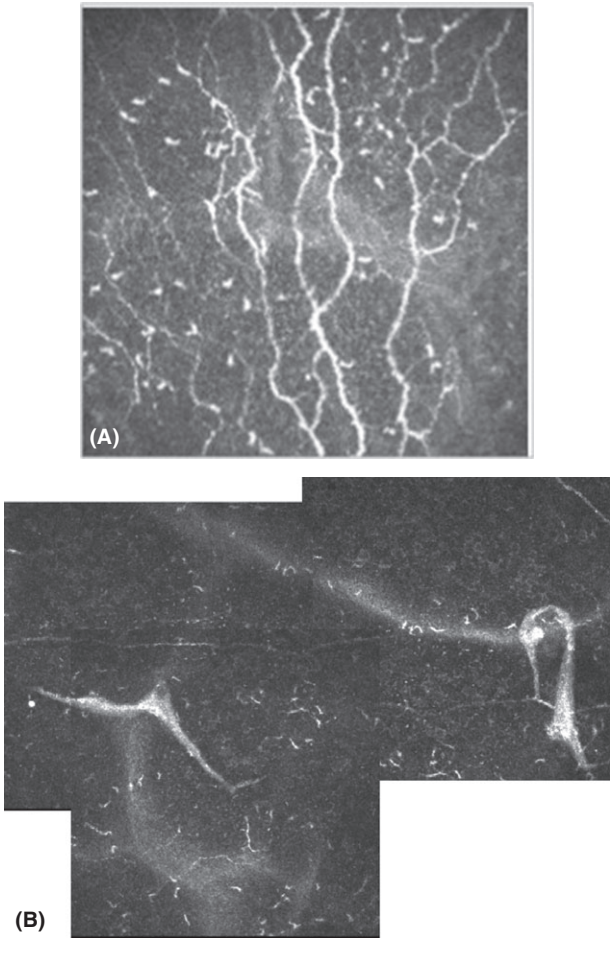

Fig. 2. *In vivo* confocal microscopy (IVCM) images revealing (A) corneal nerves with dendritiform inflammatory cells in a case of severe DED and (B) abnormal nerve regrowth 1 year after LASIK, associated with chronic dry eye and pain. The nerves are sparse and permeated by inflammatory cells. (Source: C.B.)

(Baudouin et al. 2013, 2016). This in turn causes further disruption of the tear film and perpetuates a vicious circle of DED (Baudouin et al. 2013, 2016). Hyperosmolarity may also have a peripheral neural link (Pan et al. 2011; Aragona et al. 2013; Parra et al. 2014; Quallo et al. 2015). Increases in osmolarity at steady background temperature increase the nerve terminal impulse activity of cold thermoreceptors and alter the firing pattern of polymodal nerve fibres. Hence, the subjective sensation of dryness in DED could be at least partly due to enhanced activity of corneal cold thermoreceptors that are excited by hyperosmolarity (Parra et al. 2014).

Neuropathic Pain

Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system. In contrast to nociceptive pain, which is normal and detected in response to potentially tissue-damaging noxious stimuli, neuropathic pain is caused by a functional disturbance of the neuroaxis that is not due to tissue damage or peripheral alterations (Belmonte et al. 2017). Neuropathic pain may be considered as part of a continuum of insults starting with a DED-like symptomatology. Indeed, as Galor et al. (2018) point out, the natural histories of dry eye and neuropathic pain are similar, and both conditions are associated with abnormalities on quantitative sensory testing. In people with aqueous tear deficiency of any aetiology, mechanical stress of blinking over a thinned ocular film likely induces damage and sustained overstimulation of underlying nerve terminal branches. Such damage to sensory nerve endings may be accompanied by sensitization to ongoing electrochemical activity in injured nerve fibres, trigeminal neurons and higher order neurons leading to neuropathic pain symptoms (Belmonte et al. 2017).

Injury to the corneal surface caused by physical or chemical insults induces damaged cells and locally infiltrating immune cells to release large numbers of signalling molecules including prostaglandins and leukotrienes, cytokines such as chemokines, interleukins and tumour necrosis factor, and the neurotrophic protein nerve growth factor (NGF) (Belmonte et al. 2015; Launay et al. 2016). These released molecules provoke sustained firing of nociceptors as well as a lowered stimulatory threshold and stronger impulse transmission following suprathreshold stimulation, collectively contributing to peripheral sensitization experienced as persistent irritation or pain and allodynia (pain that is exaggerated in relation to a normally innocuous insult) or hyperalgesia (pain that is felt more severely than it should) (Belmonte et al. 2004, 2015). If the underlying ocular surface damage persists, the affected individual may go on to develop central sensitization. This 'centralized' sensitization, as opposed to nociceptive pain resulting from transient external stimuli, may persist as chronic neuropathic pain irrespective of ocular surface findings –the experienced pain is disconnected from ongoing peripheral pathology, and may become permanent, thus resisting aetiologic treatments (Galor et al. 2015).

Neurotrophic Keratopathy

Neurotrophic keratopathy (NK) is a rare but likely much underestimated and misdiagnosed corneal disease. There are three stages of severity according to the Mackie classification (Table 1) (Mackie 1995; Sacchetti & Lambiase 2014). Clinically, stage 1 NK is rather similar to moderate-to-severe DED or many other epitheliopathies, and an assessment of the corneal sensitivity is required to reach a differential diagnosis. The disease is caused by partial or total impairment of trigeminal innervation, resulting in decreased or absent corneal sensation (hypoaesthesia/anaesthesia) (Bonini et al. 2003; Sacchetti & Lambiase 2014) accompanied by reduction in growth factor-mediated trophic support (Mantelli et al. 2015). The most common underlying mechanisms leading to trigeminal

Table 1. Clinical grading of neurotrophic keratopathy (Sacchetti & Lambiase 2014).

Stage	Clinical findings
I	• Corneal epithelial hyperplasia and irregularity • Scattered small facets of dried epithelium (Gaule spots) • Superficial punctate keratopathy • Rose bengal staining of the inferior conjunctiva • Increased viscosity of tear mucus • Decreased break-up time • Superficial neovascularization • Stromal scarring • Dellen
II	• Persistent corneal epithelial defect with smooth and rolled edges • Descemet's membrane folds and stromal swelling • Anterior chamber inflammatory reaction with hypopyon (rare)
III	• Corneal ulcer • Corneal perforation • Corneal stromal melting

nerve (including endings) injuries are viral infection (herpes simplex/herpes zoster keratoconjunctivitis), chemical burns, physical injuries and unwanted iatrogenic effect of ocular or brain surgery (Sacchetti & Lambiase 2014) or preservative use over the long term (Baudouin et al. 2010). The trigeminal nerve or ganglion may also become compressed by intracranial space-occupying lesions such as neuroma, meningioma and aneurysms, whereas systemic diseases including diabetes and multiple sclerosis can impair sensory fibres (Bonini et al. 2003; Sacchetti & Lambiase 2014; Semeraro et al. 2014). All these nerve impairments lead to an insufficient supply of neural factors to the ocular surface. Damage to the trigeminal nerve also results in diminished lacrimal gland reflex and reduced tear production, further injuring the corneal epithelium (Bonini et al. 2003; Sacchetti & Lambiase 2014). In turn, chronic DED per se may reduce corneal sensitivity (Bourcier et al. 2005) and thus likely further contribute to aggravating NK or preventing persistent corneal defects from healing properly.

Diagnostic rationales and tools for investigating NK have been described in detail elsewhere (Sacchetti & Lambiase 2014; Semeraro et al. 2014). In practice, NK diagnosis is mainly based on recording characteristic medical history and completing a careful eye examination. It is important to differentiate NK from other clinical entities that mimic the condition, including DED and active local infections (Sacchetti & Lambiase 2014). Past history of herpetic infections and surgical trauma to the head should be carefully investigated. Patients often complain of a red eye and reduction in visual acuity (Semeraro et al. 2014). Interestingly, although the hallmark of NK is hypoaesthesia and the lesion area is hypoaesthetic/anaesthetic, other areas of the cornea and conjunctiva may present normal sensitivity and develop inflammatory responses and tissue damage that stimulate these unaffected nerves to signal pain or irritation. Hence, even though NK is usually painless, the presence of ocular symptoms, even intense, should not exclude diagnosis.

Signs suggestive of previous herpetic infections may include corneal opacity, recurrent episodes of persistent epithelial defect and corneal neovascularization. Corneal sensitivity may be assayed by a number of tests, most commonly using a Cochet–Bonnet aesthesiometer. *In vivo* confocal microscopy (IVCM) is a useful tool that may reveal damage to stromal and subbasal nerves (Labbé et al. 2012; Sacchetti & Lambiase 2014; Semeraro et al. 2014). A study using this device demonstrated marked reduction in corneal epithelial cell density in NK eyes, particularly those with chronic disease, and suggested that the underlying hindered innervation negatively disrupts the survival and function of this tissue (Cruzat et al. 2010). Hence, both assessment of corneal sensitivity and imaging of the corneal structures are useful in diagnosing NK (Sacchetti & Lambiase 2014).

A number of reports point to contributory roles of many neurotransmitters including substance P (SP) and acetylcholine (Ach) as well as neurotrophins such as NGF in the development of NK (Cavanagh & Colley 1989; You et al. 2000; Bonini et al. 2003; Semeraro et al. 2014). For example, injury to corneal nerves results in depletion of SP and ACh levels in the cornea (Semeraro et al. 2014), whereas coculture with SP stimulates growth of corneal epithelial cells (Reid et al. 1993). Hence, SP and ACh exert mitogenic effects on ocular surface cells. Moreover, NGF was able to facilitate recovery of chemically impaired sensory nerve fibres in rat experimental models (Donnerer et al. 1996) and was shown to upregulate proliferation of rabbit corneal cells in a cytologic colony growth assay (Kruse & Tseng 1993). These preliminary findings from animal experiments encouraged several clinical investigations of the potential therapeutic use of topical NGF in patients with ocular diseases including corneal ulcers (Lambiase et al. 1998), glaucoma (Lambiase et al. 2009) and NK (Bonini et al. 2000).

Treatment Options

Dry eye disease

The aims of treatment in DED are to reduce symptoms and inflammation, and to re-establish a normal ocular surface, tear volume and epithelial integrity (American Optometric Association). Approaches to achieving these ends include tear replacement with artificial tears, usually containing viscosity-enhancing agents, lipid supplementation, tear conservation, for instance punctal occlusion by a variety of plug devices, and other strategies including tear stimulation (Belmonte et al. 2017).

Ciclosporin is an anti-inflammatory drug that is potentially neuroprotective in DED and increases tear production (Matsuda & Koyasu 2000; Kunert et al. 2002; Donnenfeld & Pflugfelder 2009; Mantelli et al. 2013; Shaheen et al. 2014). Indeed, in a study conducted in patients with Sjögren syndrome, ciclosporin significantly increased sub-basal corneal nerve density, enhanced corneal sensitivity and improved signs and symptoms of dry eye (Levy et al. 2017). The study investigators noted that direct nerve damage occurs in DED, and speculated that ciclosporin exerts its therapeutic effects in this clinical condition by inducing direct neurotrophic effects on damaged nerve cells, which may enhance their delivery of neuropeptides to epithelial cells and thereby promote epithelial healing (Levy et al. 2017). Ciclosporin has also been shown to promote recovery from loss of corneal sensitivity at 3 months post-LASIK surgery, and this apparent nerve regeneration was postulated to arise by a nonimmunomodulatory mechanism (Peyman et al. 2008). Further evidence in support of this contention was supplied by the observation that ciclosporin induces

NGF expression in cultured human corneal cells (Lee et al. 2011). Topical application of ciclosporin in DED patients has been shown to improve comfort and enhance tear production and stability, and may prevent disease recurrence over time (Mantelli et al. 2013; Shaheen et al. 2014). Moreover, in patients undergoing LASIK or cataract surgery, ciclosporin eye drops may be useful preoperatively for the treatment of DED and postoperatively to prevent worsening of the condition due to incidental nerve damage (Shaheen et al. 2014) – although not all authors have reported beneficial effects of ciclosporin post-PRK or post-LASIK (Hessert et al. 2013). Further research is required in this area.

Lifitegrast is a small molecule lymphocyte function-associated antigen (LFA)-1 antagonist that inhibits LFA-1 binding to intercellular adhesion molecule -1 and thereby targets T cell-mediated inflammation associated with DED (Semba et al. 2011). This drug was approved for DED by the US Food and Drug Administration (FDA) under the brand name Xiidra in 2016 and filed for approval in Europe in 2017 (PharmaTimes 2017).

Nerve growth factor (NGF), although originally developed for the treatment of NK, is also a promising therapy for DED. This neurotrophin signalling molecule is known to induce corneal healing and restore sensitivity, and modulates inflammatory reactions in the eye (Lambiase et al. 2012; Mantelli et al. 2013). It has also been shown to increase tear production and conjunctival goblet cell density (Coassin et al. 2005; Mantelli et al. 2013) and promote nerve regeneration after mechanical corneal nerve injury (Lambiase et al. 2011).

MIM-D3 (tavilermide) is a small molecule mimetic of NGF that acts as a partial agonist of tropomyosin receptor kinase A (TrkA). This agent showed early promise against DED in phase II (Meerovitch et al. 2013) and accordingly has progressed to three phase III studies (Mimetogen Pharmaceuticals USA, Inc. 2013, 2015, 2016). A further novel therapeutic opportunity for the correction of tear insufficiency in DED may be topically applied SYL1001, a short interfering (si)RNA drug that exerts its mechanism of action by silencing gene expression of transient receptor potential vanilloid type 1 channels (Jones et al. 2017), which play a role in pain sensitivity to heat (Belmonte et al. 2015). In a large, placebo-controlled clinical trial, SYL1001 demonstrated significant improvements in visual analogue scale scores and excellent tolerability (Benitez-Del-Castillo et al. 2016).

Docosahexaenoic acid (DHA) is an omega-3 fatty acid that has potent ability to inactivate proapoptotic and proinflammatory signalling, and may enhance the effects of NGF on promoting corneal nerve regeneration (Esquenazi et al. 2005). Docosahexaenoic acid (DHA) is a component of neuronal phospholipid membranes and may be converted to its derivative, neuroprotectin D1, which also exerts anti-inflammatory and neuroprotective properties (He & Bazan 2010). Future investigations are necessary to evaluate the therapeutic role of essential fatty acids, given both systemically and topically, in the management of DED (Barabino et al. 2017).

Recently, as-needed (at least twice daily) neurostimulation of acute tear production using an electric current-applying intranasal device such as TrueTear™ was successfully tested in patients with aqueous-deficient DED and demonstrated clinically and statistically significant increases in tear production and an acceptable safety profile over 180 days (TrueTear™). The prescription-only device was granted marketing approval by the FDA in 2017 (Allergan 2017).

A broader treatment approach that should also be discussed is the role of blood-derived products for the management of symptoms associated with DED. Blood-derived products, such as platelet-rich plasma, have shown promising results in clinical trials in improving symptoms in patients with moderate-to-severe chronic DED (Alio et al. 2017). However, the development of these products is often time-consuming and costly. Fingerprick autologous blood is currently under investigation as a low cost and practical alternative. Initial research in a small case series suggests that this approach is worth further investigation for the treatment of DED (Than et al. 2017).

Neuropathic pain

Neuropathic pain affecting the eye may respond to treatments that are aimed at neuropathic pain arising elsewhere in the body, such as systemic pharmacological agents traditionally used to manage pain, topical analgesics and neuromodulators, adopting antioxidant-rich diet, exercise or stimulation therapies (Belmonte et al. 2017). In this respect, Goyal & Hamrah (2016) have proposed a three-step approach to ocular neuropathic pain: managing surface disease; managing comorbidities; and finally, managing the true component of pain using regenerative, anti-inflammatory and environmental modifiers. These authors suggest that regenerative therapy may include the use of autologous serum eye drops or NGF; topical corticosteroids or ciclosporin may reduce inflammation and an omega-3-rich diet might be a valuable complementary measure (Goyal & Hamrah 2016).

Neurotrophic keratopathy

Treatment of NK aims to prevent progression of corneal damage and promote healing of the corneal epithelium. Treatment decisions should reflect the clinical stage at presentation (Lambiase et al. 1999). In general, the first step is always to discontinue toxic drugs, especially those containing preservatives, antibiotics unless mandatory and nonsteroidal anti-inflammatory drugs. In cases of glaucoma, preservative-free drugs should be preferentially used or more radical options such as laser trabeculoplasty or surgery considered. For patients who do not require surgery, there are a number of pharmacologic and non-pharmacologic options available for the alleviation of NK, including preservative-free artificial tears particularly for early-stage disease (Sacchetti & Lambiase 2014; Semeraro et al. 2014), topical collagenase inhibitors (Sacchetti & Lambiase 2014) and antibiotic eye drops for prevention of infections at later stages 2 and 3 (Sacchetti & Lambiase 2014). Doxycycline may be effective as an anti-inflammatory and anticollagenolytic agent (Pflugfelder 2004; Smith & Cook 2004). Therapeutic corneal and scleral contact lenses may be used to promote epithelial healing of persistent defects, although they increase the risk of secondary infections (Sacchetti & Lambiase 2014). Autologous serum eye drops and other blood-derived products such as platelet releasate contain many growth factors and tear components

that facilitate ocular surface epithelial proliferation, migration and differentiation (Liu et al. 2006; Semeraro et al. 2014). In patients with persistent epithelial defects despite conventional therapy, a combination approach using serum eye drops plus hydrogel bandage contact lenses has been demonstrated successfully (Schrader et al. 2006).

Recently, matrix therapy using regenerating agents (RGTA) such as the heparan sulphate mimetic biopolymer (Cacicol®) (Barritault et al. 2017), has emerged as a novel approach that may prevent the onset of ulceration in inflammatory ocular surface disorders (Brignole-Baudouin et al. 2013). Cacicol® demonstrated early efficacy against corneal ulcer due to NK in a small series of 25 patients (Guerra et al. 2017) and is currently undergoing phase III investigation in that clinical setting (Laboratoires Thea).

Nerve growth factor (NGF) may play a useful role in the armamentarium against NK. This neurotrophin is essential to the development and survival of some sensory and sympathetic neurons, and is involved in repair of neuronal injuries (Semeraro et al. 2014). Nerve growth factor (NGF) stimulates production of ACh in the CNS and SP in the peripheral nervous system (Levi-Montalcini 1987; Donnerer et al. 1996; Bonini et al. 2003), and activates TrkA and p75 neurotrophin receptor [p75 (NTR)] expressed on corneal epithelial cells and sensory neurons, thereby stimulating mucin release and goblet cell differentiation (Meerovitch et al. 2013). Restoration of epithelial integrity and corneal sensitivity has been demonstrated in patients with NK following treatment with murine NGF (Bonini et al. 2000), and this neurotrophin has also been shown to promote healing of corneal ulcers (Lambiase et al. 1998, 2000). More recently, a recombinant human NGF eye drop formulation was developed and demonstrated good safety and tolerability in phase I (Ferrari et al. 2014). Thereafter, the formulation underwent clinical evaluation (Mantelli et al. 2017) and gained EU approval, under the trade name Oxervate® (cenegermin), for the treatment of moderate-to-severe NK in 2017 (European Medicines Agency 2017).

Another potentially useful treatment against NK is plasma rich in growth factors (PRGF). Teardrops formulated with PRGF were used in the care of patients with NK with good outcomes (Sanchez-Avila et al. 2017); however, it is important to note that data from the long-term use of these agents are not yet available and *in vivo* studies suggest the potential for side effects such as the risk of a proangiogenic response (Seo et al. 2001). This strategy should therefore be further evaluated in clinical trials.

Conclusion

It is becoming increasingly well known that corneal innervation plays a key role in ocular surface homeostasis and disease. As knowledge of the interplay between corneal nerves in sensing ocular damage and promoting healing in DED and other corneal diseases increases, so will the potential for new and innovative modes of treatment. Therapies that target nerve regeneration and restore nerve function may fill existing unmet needs for treating NK and conversely counteract DED-perpetuating factors such as hyperosmolarity, tear secretion and stability, and inflammation. Neuropathic pain remains a highly intractable pathology that somewhat overlaps with DED and deserves effective therapeutics. Further research on the neural contribution of ocular surface disorders is greatly merited.

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Received on January 12th, 2018.
Accepted on May 14th, 2018.

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Allergan provided funding for the author meetings and for the development of this manuscript. Alex Kahney of Synergy Medical provided editorial support, and this service was paid for by Allergan. Adrian Roots drew the original illustration, and this service was paid for by Allergan. The authors were involved in the entire process, from design to critical revision of the manuscript, and maintained complete control over its direction and content. Allergan did not have any influence on the manuscript content.

ML has acted as occasional consultant for Alcon, Allergan, Bausch & Lomb, Dompe, MSD, Novartis, Santen, Thea. CB has acted as consultant for Alcon, Allergan, Dompe, Horus Pharma, Santen, Shire, Thea.