Nerves and Sensations from the Eye Surface

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ABSTRACT **Because vision plays a critical role in obtaining information from the external world, evolutionary development has provided the structures that sustain this function with special protection against injury. Thus, the cornea possesses the richest sensory innervation of the body to detect noxious stimuli. The trigeminal sensory neurons that innervate the eye vary in their chemical composition and electrophysiological properties, and can be classified according to the stimuli that activate them preferentially: mechanical forces, temperature, or irritant chemicals. Different classes of noxious stimuli (mechanical injuries, heat, extreme cold) activate to a different degree the various populations of sensory fibers of the ocular surface and evoke unpleasant sensations of distinct quality. When injured either accidentally or following ocular surgery, sensory nerve fibers of the ocular surface may form neuromas that develop abnormal activity and become the source of unpleasant sensations, such as pain, dryness, grittiness, etc. In parallel, their response to natural stimuli is diminished. The possibility of hypesthesia and dysaesthesias must be considered in the assessment of the risks of therapeutic procedures that involve damage to ocular sensory nerves.**

KEYWORDS **conjunctival innervation, conjunctival sensitivity, corneal innervation, corneal sensitivity, esthesiometry, ocular dryness, ocular sensory neurons, neuropeptides, nociceptors, photorefractive surgery, surgical wounds**

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Abbreviations are printed in **boldface** where they first appear with their definitions.

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I. OCULAR SENSORY INNERVATION PLAYS A PROTECTIVE ROLE

Living organisms are continuously exposed to environmental challenges. Some of these, such as mechanical trauma, extreme temperatures, or contact with irritant gases or poisonous substances produced by plants or animals, may be dangerous and a threat to survival. Therefore, in parallel to the specific neural mechanisms that recognize innocuous elements of the environment, evolutionary development has provided other neural mechanisms to detect potential noxious stimuli and provide appropriate defensive behaviors. In higher vertebrates, neural pathways devoted to this task comprise a particular set of peripheral nociceptive neurons that innervate the body surface and internal organs; these pathways are specialized in transducing noxious stimuli into a discharge of nerve impulses that encode the intensity, as well as the spatial and temporal characteristics, of the stimulating force.

In many mammals, including humans, vision plays a critical role in obtaining information from the external world, and, thus, the structures that sustain this important function are specially protected against injury. Not surprisingly, some of the exposed areas of the eye, like the cornea, possess the richest sensory innervation of the body, predominantly dedicated to detecting noxious stimuli.[1,2] Compared with other areas of the face, the structures of the eye surface are exquisitely sensitive to potentially injurious physical and chemical stimuli, while the number of sensory fibers devoted to obtaining information about innocuous environmental changes is comparatively small. (See review by Belmonte and Gallar, 1996.[3])

II. OCULAR SENSORY NEURONS ARE FUNCTIONALLY HETEROGENEOUS

The peripheral nerve endings of primary sensory neurons located in sensory ganglia are the transducing elements responsible for the detection of external stimuli. The eye and periocular structures are innervated by the peripheral axons of neurons located in the trigeminal ganglion (**TG**) that travel to the eye through the trigeminal ophthalmic nerve and its distal branches. Within the eye, single nerve fibers branch out extensively and reach periocular tissues and the various structures of the eyeball, with the exception of the retina and the lens. (See review by Belmonte et al, 1997.[4])

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OUTLINE

I. Ocular surface innervation plays a protective role
II. Ocular sensory neurons are functionally heterogeneous
III. Physical and chemical stimuli of the ocular surface activate different populations of ocular nociceptors
IV. Sensations arising at the eye surface depend on the variable activation of different classes of ocular nociceptors
V. Injured sensory fibers do not properly transduce external stimuli and may cause pain
VI. Conclusion

The morphological appearance of ocular TG neurons is quite simple. Most of them are medium or small neurons having thin myelinated (A-delta) or unmyelinated (C) axons that terminate peripherally as naked nerve endings called *nociceptors*. Only a small group of neurons that innervate the limbus and conjunctiva have thick myelinated axons and present specialized cell structures surrounding the nerve terminals.[5] However, ocular neurons are not homogeneous in chemical composition or electrophysiological properties. Ocular neurons may contain several neuropeptides, in particular, calcitonin gene-related peptide (**CGRP**, 60%) and substance P (**SP**, 20%),[6] and they express to a variable degree a number of membrane proteins that act as receptor molecules for neurotransmitters, neuromodulators, cytokines, and growth factors, as well as ion channel proteins that regulate neuronal excitability. The transduction properties of peripheral terminals of neurons innervating the ocular structures are also different, possibly reflecting the above-mentioned variability in protein expression. The same is true for the electrophysiological properties of the cell soma.[7,8]

The most meaningful criterion to functionally classify ocular sensory neurons is the modality of stimulus by which they are preferentially activated. This is determined by the transduction properties of the peripheral terminals and is closely associated with the quality of sensation evoked by each type of neuron.[9] Studies on ocular sensory neurons have focused mainly on the cornea and bulbar conjunctiva, although studies of uveal and scleral nociceptors have shown that all ocular sensory neurons appear to be functionally similar.[10-12]

About 15% of corneal fibers, all of them the relatively fast-conducting A-delta type, are activated exclusively by mechanical forces. Thresholds for mechanical stimuli of corneal mechano-nociceptors are low in comparison with mechano-nociceptors of the skin; however, corneal mechano-nociceptive endings are only a few microns away from the unkeratinized corneal surface, and, conceivably, the actual forces exciting mechano-nociceptive endings in both locations are quite similar. Mechano-nociceptors are rapidly-adapting receptors, because they produce a short-lasting impulse discharge in response to sustained stimuli; thus, they serve mainly to signal the presence and velocity of change of the stimulus, rather than its absolute intensity.[13-15]

Most of the corneal sensory fibers (about 70%) are polymodal nociceptors, which are activated by mechanical energy near or above noxious levels. They also respond to heat (temperatures over 39°C) or noxious cold; to exogenous chemical irritants; and to a large variety of endogenous chemical mediators released by damaged corneal tissue or resident inflammatory cells, or originating from the plasma leaking from limbal vessels (protons, potassium ions, ATP, prostaglandins and other arachidonic acid metabolites, amino acids, amines, cytokines, kynins, growth factors).[16,17] A fraction of polymodal fibers also increase their firing rate when corneal temperature is reduced below 29°C.[9,13] Some of the polymodal nociceptor fibers belong to the thin myelinated group, but most of them are of the slow-conducting C type. Sustained mechanical, thermal, or chemical stimuli produce an irregular, continuous discharge in polymodal nociceptors that is roughly proportional to the intensity of the stimulating force and, hence, serves to encode the magnitude of the stimulus.

Another category of corneal nerve fibers (10-15% of the

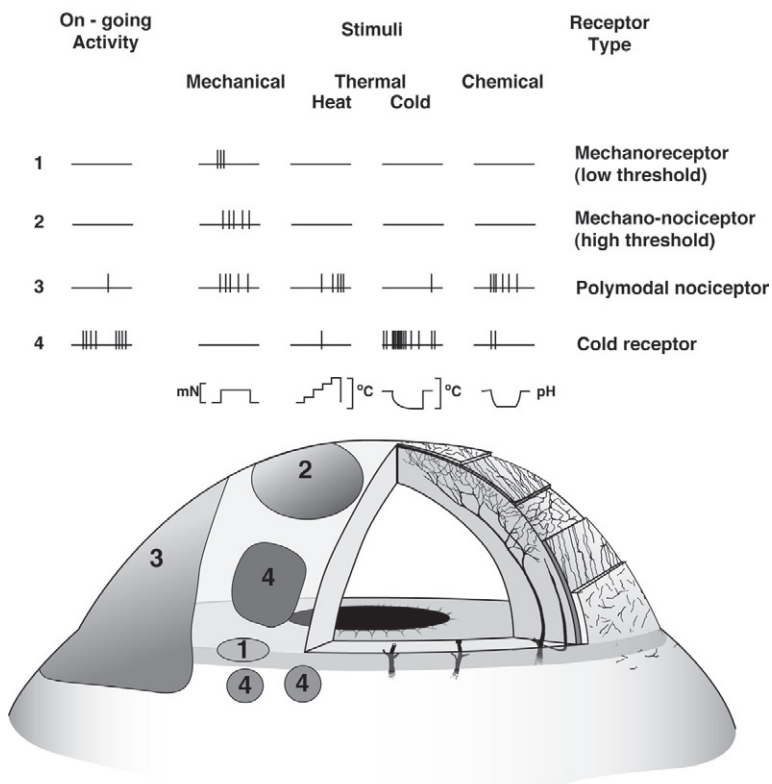

Figure 1. Functional types of sensory neurons innervating the ocular surface. The upper part of the figure shows the nerve impulse activity of the various populations of ocular sensory fibers at rest and after application of stimuli of different quality. In the lower part, a schematic diagram of the anterior segment of the eye shows the location and receptive field size of the various functional types of ocular sensory fibers. (Modified from Belmonte C, et al.[4])

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total) are cold-sensitive receptors. They are endings of A-delta and C nerve fibers that discharge spontaneously at rest and increase their firing rate when the normal temperature of the corneal surface (around 33°C) decreases, being sensitive to temperature reductions of 0.1°C or less. They are transiently silenced upon warming. Cooling of the corneal surface following evaporation or application of cold solutions or cold air also increases the firing rate of corneal cold receptor fibers.[15,18] Figure 1 summarizes the response characteristics of the different types of sensory fibers found in the ocular surface.

III. PHYSICAL AND CHEMICAL STIMULI OF THE OCULAR SURFACE ACTIVATE DIFFERENT POPULATIONS OF OCULAR NOCICEPTORS

Mechanical stimuli commonly acting on the surface of the eye include contact with external objects, presence of foreign bodies of variable size, and air pressure. Drying of the ocular surface also produces a mechanical distortion of epithelium layers and possibly a deformation of the intercellular spaces where nerve endings are located, leading to their mechanical stimulation. Brief touching of the ocular surface, particularly by a moving object, activates mainly mechanonociceptors and, weakly, polymodal nociceptors. They cause the sensation of acute, sharp pain, sometimes followed by transient after-sensations of irritation attributable to polymodal nociceptors. When the stimulus persists, and particularly if it leads to tissue injury, the discharge of polymodal nociceptors becomes more pronounced and continuous. This is possibly the cause of the sustained sensation of irritation and pain that occurs when a foreign body remains in contact with the cornea and/or the conjunctiva and produces local tissue damage.

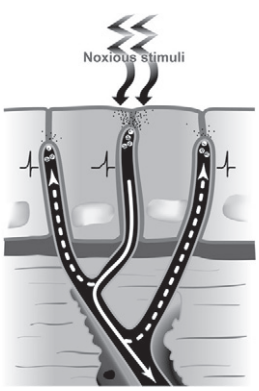

Figure 2. Schematic representation showing how direct activation of polymodal corneal sensory nerve terminals by a noxious stimuli evokes the centripetal propagation of nerve impulses along the parent axon, and also antidromically to other, non-stimulated peripheral branches (arrows). This mechanism permits the local release of the neuropeptide content of the ending (dots), not only at the injured point but also in surrounding areas that were not directly affected by the stimulus.

Irritant liquid or gaseous substances of various types that make contact with the eye surface act as chemical stimuli. They are detected primarily by polymodal nociceptors (for reviews, see Belmonte et al. 1997,[4] and Belmonte et al, 2004[19]), although they may also be signaled by a separate subclass of nociceptors called *silent* or *sleepy* nociceptors—so-called because they become responsive only when local inflammation occurs.[20] Their presence in the cornea remains to be proved experimentally.[21] Polymodal nociceptors of the A-delta type contribute to the "fast," immediate pain produced by the arrival of the stimulus,

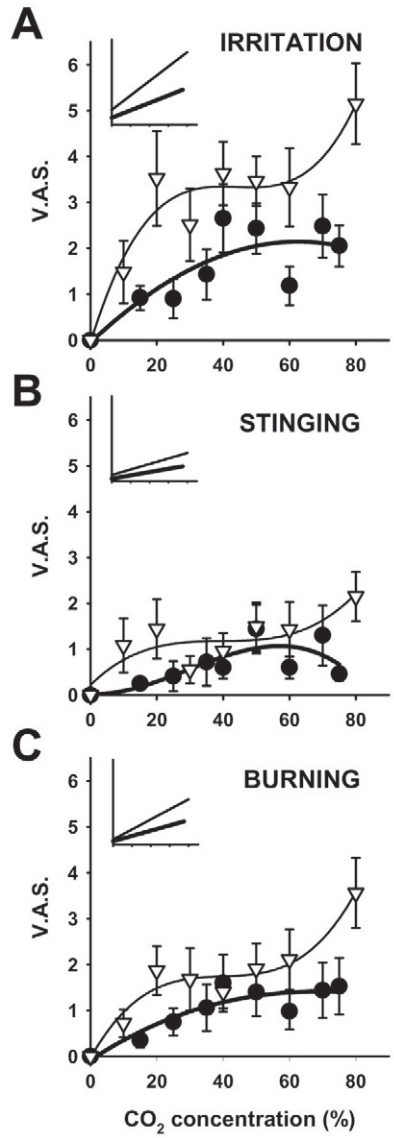

Figure 3. Intensity-response curves of the sensations of irritation, stinging and burning pain evoked by chemical stimulation of the cornea (open triangles) and conjunctiva (closed circles) with 2-sec gas jets containing increasing concentrations of CO2 (that cause proportionally larger pH drops) applied on the human cornea by means of a gas esthesiometer. (Modified from Acosta MC et al.[34])

but also to the dull, long-lasting pain that develops afterward, which is mainly due to the activity of C-polymodal nociceptor fibers. A prominent feature of polymodal nociceptors is "sensitization," i.e., a decrease in threshold and an increase in the firing frequency of the nociceptors in response to the stimulus, often accompanied by the development of ongoing activity.[22]

Sensitization is produced by inflammatory mediators originating from the injured cells, the resident and blood-borne inflammatory cells, or the extravased plasma, all of which interact with membrane receptor proteins of the nociceptor ending membrane.[23] These, in turn, activate intracellular second- and higher order messenger systems, leading ultimately to the opening of ion channels, which depolarizes the nerve endings, increasing their excitabil-

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ity.[24,25] Some of these channels, like the TRPV1 (also called the capsaicin receptor), can be also gated directly by extracellular chemicals and possibly act as the "final pathway" for the excitatory effect of a variety of endogenous and exogenous chemicals.[26,27]

In recent years, great progress has been made in the identification and understanding of the molecular mechanism of action of a large number of inflammatory substances that contribute to nociceptor sensitization. (See review by Handwerker and Reeh, 1991.[23]) Furthermore, there is growing evidence that nociceptive neurons change the expression of some membrane receptor proteins and ion channels in response to inflammatory mediators, cytokines, and growth factors released by injured tissues, leading to more permanent and long-lasting changes in their excitability.[28] This explains at the peripheral level the enhanced pain sensibility to stimuli and the spontaneous sensations of pain felt at the inflamed tissues.[29]

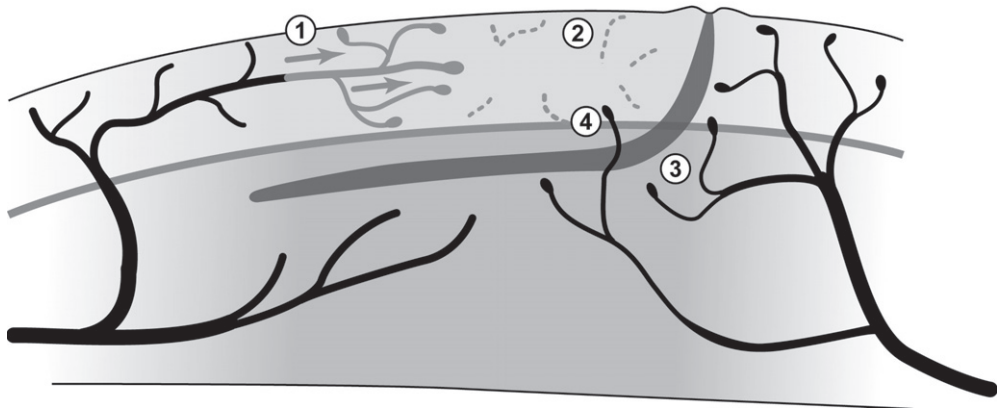

Figure 4. Schematic representation of the changes that occur in corneal sensory nerves following LASIK. The injured area is invaded by sprouts of intact nerves from the periphery of the lesion (1), while the peripheral ends of the damaged axons degenerate (2). Central stumps of injured nerves form neuromas at the periphery of the wound (3). Weeks afterwards, sprouts of the injured sensory nerves begin to penetrate the denervated area (4) and contribute to partial restoration of the sensitivity of the cornea.

Another important feature of polymodal nociceptor neurons is that, when depolarized, they release their neuropeptide content at the peripheral nerve terminals.[30,31] This process is extended to branches of the parent axon that were not directly exposed to the stimulus but are invaded by the propagated nerve impulse that travels to the central nervous system and also invades antidromically all the peripheral branches (Figure 2).[32] Released neuropeptides (in particular, SP and CGRP) act as pro-inflammatory substances, promoting the release of other mediators, cell chemotaxis, plasma extravasation, etc., giving rise to the "neurogenic inflammation" that develops immediately after noxious stimulation of peripheral tissues. It has also been suggested that these neuropeptides contribute to the trophic maintenance of the cornea. (See review by Müller et al, 2003.[44])

IV. SENSATIONS ARISING AT THE EYE SURFACE DEPEND ON THE VARIABLE ACTIVATION OF DIFFERENT CLASSES OF OCULAR NOCICEPTORS

The discrimination capacities and threshold values for the different stimuli that may act on the ocular surface are determined by the transduction characteristics and the corresponding selective activation of the various functional classes of sensory nerve endings. These are clinically explored with use of various types of esthesiometers. Contact esthesiometers explore primarily the response of mechano-nociceptors, whereas gas esthesiometers, which additionally use CO2 as an acidic stimulus and warmed or cooled air for high and low temperature stimuli, permit the responsiveness of polymodal and thermal receptors to be evaluated also.[33]

Psychophysical studies have shown that the intensity of the stimulus, the firing frequency of nerve fibers, the number of nerve fibers that are recruited by the stimulus, and the subjective intensity of the sensation are directly correlated.[9] Classical as well as more recent studies using these instruments have provided evidence that the normal cornea possesses a remarkable sensitivity to all modalities of stimuli, a sensitivity that is always higher than that of the conjunctiva (Figure 3).[34] Regional differences exist in threshold among ocular surface areas.

Sensitivity decreases with age, probably reflecting a reduction in nerve density that seems to affect earlier polymodal nociceptors.[35] Corneal sensitivity is also greater in women, although it decreases during pregnancy and may oscillate during the menstrual cycle.[36-38]

V. INJURED SENSORY FIBERS DO NOT PROPERLY TRANSDUCE EXTERNAL STIMULI AND MAY CAUSE PAIN

Sensations of irritation and pain of variable intensity may accompany contact lens wear, as well as some pathological conditions, such as ocular surface dryness, wounds, surgical injuries, keratitis, conjunctivitis, etc. Often these conditions are accompanied by a reduced sensitivity or complete anesthesia to natural stimuli applied to the affected area. Still, various unpleasant sensations (itching, burning, dryness, foreign body sensation) are frequently experienced by these patients and projected to the eye surface. The neural basis of these processes in the eye is still incompletely understood.[19] It is well known that when corneal nerves are cut, the denervated area is first invaded by sprouts of intact nerve fibers; later, injured axons start to regenerate and microneuromas develop. Newly formed sprouts begin to appear from the microneuromas, while early branches from intact fibers degenerate (Figure 4).[39-43] (See review by Müller et al, 2003.[44])

These morphological events are accompanied by profound changes in the molecular machinery of the affected neurons.

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The over- and under-expressed genes that encode cell proteins, such as membrane receptor proteins, ion channels, etc.,[45] modify the functional behavior and the overall excitability of the axotomized and sprouting neurons, particularly in their regenerating peripheral branches. There, spontaneous activity and abnormal responses to external stimuli and to changes in the chemical microenvironment of the ending may develop.[46,47] This allows an aberrant barrage of nerve impulses to reach the central nervous system, and these will be ultimately interpreted as sensations arising from the injured area of the eye.

On the other hand, the responsiveness of damaged axons to direct mechanical, thermal, or chemical stimuli applied to their cut endings is severely impaired and, therefore, the injured area exhibits an insensitivity or a much higher threshold to natural stimuli. Thus, the apparent paradox is the presence of spontaneous pain or of pain elicited by stimuli that somehow activate abnormally the nerves of an injured area of the cornea or conjunctiva, while esthesiometry of the partially denervated corneal areas demonstrates a very low sensitivity to the applied stimuli. Moreover, chronically augmented sensory inflow to second- and higher-order nociceptive neurons in the trigeminal nuclear complex may produce plastic changes in synaptic connectivity, enhancing their excitability and giving rise to secondary hyperalgesia and allodynia typical of chronic pain states. Unpleasant sensations evoked by this neuropathic activity can be manifested as ocular pain, but also as ocular dryness or feelings of sand or foreign body in the eye, which are some of the sensations that the normal activation of these pathways evokes. These symptoms may appear after surgical interventions that damage corneal nerves, in particular after photorefractive surgery. It can be speculated, however, that they are also experienced in other conditions that may perhaps involve a more subtle injury of corneal nerve endings, such as chronic inflammation of the cornea, contact lens wear, or chronic dryness of the ocular surface.

VI. CONCLUSION

In conclusion, sensory nerves play an essential role in protecting the ocular surface from external irritants, but they may be also the source of undesired, unpleasant sensations. This possibility must be considered in the assessment of the risks of therapeutic procedures that involve damage to ocular sensory nerves.

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