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Topical tetrodotoxin attenuates photophobia induced by corneal injury in the rat

Paul G. Green^{1,2,4}, Pedro Alvarez^{1,4}, and Jon D. Levine^{*,1,3,4}

¹Department of Oral & Maxillofacial Surgery, University of California at San Francisco, San Francisco CA 94143-0440

²Department of Preventative & Restorative, University of California at San Francisco, San Francisco CA 94143-0440

³Department of Dental Science and Medicine, University of California at San Francisco, San Francisco CA 94143-0440

⁴Division of Neuroscience, University of California at San Francisco, San Francisco CA 94143-0440

Abstract

Corneal injury can produce an aversive sensitivity to light, photophobia. Using topical application of lidocaine, a local anesthetic, and tetrodotoxin (TTX), a selective voltage-sensitive sodium channel blocker, we assessed whether enhanced aversiveness to light induced by corneal injury was due to the enhanced activity in corneal afferents. Eye closure induced by 30 s exposure to bright light (460–485 nm) was increased 24 h after corneal injury induced by de-epithelialization. While the topical application of lidocaine did not affect the baseline eye closure response to bright light in control rats, it eliminated the enhancement of the response to the light stimulus following corneal injury (photophobia). Similarly, topical application of TTX had no effect on the eye closure response to bright light in rats with intact corneas, but markedly attenuated photophobia in rats with corneal injury. Given the well-established corneal toxicity of local anesthetics, we suggest TTX as a therapeutic option to treat photophobia, and possibly other symptoms that occur in clinical diseases that involve corneal nociceptor sensitization.

Keywords

Eye pain; photophobia; tetrodotoxin; lidocaine; corneal nociceptor

*Corresponding author Jon Levine: Phone (415) 476-5108, Jon.Levine@ucsf.edu.

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Introduction

Photophobia, an aversive sensation induced by bright visual stimuli ²⁶, is markedly enhanced in many patients that experience corneal injury, such as occurs following corneal refractive surgery ⁴, corneal abrasion ³², chemical injury ¹³, Dry Eye Syndrome (DES) ³³ or in long-term contact lens wearers ²⁹. While even bright light does not activate corneal afferents, it does excite photosensitive melanopsin-containing retinal ganglion cells that activate neurons in the superficial laminae of trigeminal subnucleus caudalis (Vc/C1) (possibly by increasing ocular blood flow ²⁶), a site in the central nervous system that is involved in transmitting pain signals. The melanopsin-containing retinal ganglion cells also project to the thalamic relay nuclei that also receive nociceptive inputs ^{19, 24}. Since the cornea is innervated by nociceptors that encode mechanical, thermal and chemical stimuli ¹, which also project to Vc/C1 ^{14, 27}, as well as to the rostral ventrolateral pole of the trigeminal interpolaris/caudalis, the convergence could occur proximally either in the trigeminal nuclear complex and/or at higher levels (e.g. in thalamic relay nuclei).

Tetrodotoxin (TTX) inhibits a subset of voltage-gated sodium channels that play a key role in inflammatory and neuropathic pain, in particular Na(V) 1.7 ⁹, which is inhibited by an extremely low, sub-nanomolar concentration of TTX ¹⁶. Of note, we have observed that TTX can reverse mechanical hyperalgesia in sensitized muscle nociceptors without eliminating protective nociceptive behaviors (P. Alvarez, unpublished observations). This is important with respect to treatment of corneal symptoms, as elimination of protective nociceptive reflexes (e.g. eyelid closure) in response to noxious stimulation of the corneal surface, allows continued corneal injury. Chronic use of local anesthetics to treat ocular pain is contraindicated due to major dose- and time-dependent corneal toxicity ^{11, 28}. Since TTX has a much lower corneal toxicity, it might be useful for symptoms that are dependent on enhanced input from nociceptive corneal afferents ³⁶. Therefore, in the present study we evaluated if topical application of TTX attenuates photophobia in the setting of nociceptor sensitization induced by traumatic injury to the cornea.

Methods

Animals

Experiments were performed on adult male Sprague Dawley rats, (200–250 g; Charles River, Hollister, CA). Animals were housed 3 per cage, under a 12 h light/dark cycle, in a temperature- and humidity-controlled environment. Food and water were available *ad libitum*. All behavioral testing was performed between 10:00 AM and 4:00 PM. Rats were acclimatized to the testing environment, by bringing them to the experimental environment, in their home cages, where they were left for 30–60 min, after which they were placed in cylindrical clear acrylic restrainers for evaluation of their response to stimulation with a bright light.

All experimental protocols were approved by the University of California, San Francisco Committee on Animal Research and conformed to National Institutes of Health *Guidelines for the Care and Use of Laboratory Animals*. Efforts were designed to minimize the number of animals used and their suffering.

Measuring photophobia

Bright light stimulates eye closure even in normal control animals^{31, 38}. We measured this response to bright light in awake rats after they had been acclimated to being in a restrainer (10 min/day for 3 days). Some rats underwent corneal de-epithelialization injury, as previously described⁴¹. Briefly, in rats anesthetized with 3% isoflurane, a defect in the central part of the cornea in one eye of each rat was made by placing a ~3.5 x 3.5 mm square of filter paper (Whatman Grade 40, GE Health care, Buckinghamshire, UK), saturated with n-heptanol, on the cornea for 90 s. After removing the filter paper, the eye was irrigated with 0.9% saline, and the n-heptanol-treated epithelial surface removed with a sclerotome (Katena Products Inc., Denville, NJ, USA). 24 h after de-epithelialization, the magnitude of eye closure in response to 30-s exposure to high intensity (48 lumens), 460–485 nm wavelength (LXML-PB01-0023 Luxeon® Rebel high power LED) light²⁶ was again assessed. Of note, the maximal absorbance for melanopsin is ~480 nm² and therefore the wavelength of light we used maximally activates the intrinsically photosensitive melanopsin-containing retinal ganglion cells. Video recordings were made and played back in real-time to grade magnitude of maximal eye closure using the scale illustrated in Figure 1. Bright light induced eye closure was evaluated before and 10 min after topical corneal application of the local anesthetic, lidocaine, or TTX (5 µl volume for each) in awake, lightly restrained rats.

Drugs

Tetrodotoxin citrate (TTX) was obtained from Abcam (Cambridge, MA, USA), and lidocaine hydrochloride and n-heptanol were obtained from Sigma Chemical Co. (St. Louis, MO, USA). TTX and lidocaine were dissolved in 0.9% saline. The n-heptanol was used undiluted.

Statistical analyses

Group data are presented as mean ± SEM. Statistical significance was determined by one- or two-way repeated-measures ANOVA, followed by Dunnett's multiple comparison *post hoc* test. $P < 0.05$ was considered statistically significant.

Results

To test the hypothesis that corneal injury enhances aversion to bright light, we compared the eye closure score in response to bright light in control rats and in those that had undergone corneal de-epithelialization injury. Photophobia was significantly increased when measured 24 h following corneal injury (Figure 2). To explore the possibility that enhanced activity in nociceptors, caused by corneal injury, contributes to the enhanced response to bright light (photophobia), we evaluated the effect of the topical application of a local anesthetic to the cornea on injury-induced photophobia. Compatible with the hypothesis that enhanced activity in corneal afferents contributes to the photophobia observed in rats with de-epithelialized corneas, the enhanced closure response in rats with a corneal injury was completely eliminated 10 min after topical application of lidocaine (2%, 10 µl) to the corneal surface (Figure 2, baseline (n=18) vs. corneal injury (n=6) $P < 0.05$; corneal injury (n=6) vs. corneal injury + lidocaine (n=9), $P < 0.05$; baseline (n=18) vs. + lidocaine (n=5), $P = \text{N.S.}$,

one-way ANOVA with Dunnett's post-hoc test). Thus, our data support the hypothesis that increased activity in corneal nociceptors is responsible for the enhanced aversion to bright light observed in the setting of corneal injury.

Since repeated use of lidocaine is toxic to corneal stroma²⁰, we next tested if the enhanced photophobia in the setting of an injured cornea can be attenuated by TTX. Bright light induced eye closure in control rats (intact corneas, n=6) was not affected by application of TTX (1 KM, 10 µl) to the cornea. In contrast, in rats with a corneal injury (n=6), photophobia was significantly attenuated by application of TTX (1 mM, 10 µl) to the corneal surface, when measured 1 and 2 hours after application of TTX (Figure 3, repeated-measures one-way ANOVA with Dunnett's post-hoc test). These results suggest that TTX-sensitive sodium channels play an important role in the photophobia observed in the setting of corneal injury.

Discussion

The topical application of TTX or lidocaine to the cornea similarly attenuated the photophobia induced by corneal injury, while neither TTX nor lidocaine affected the eye closure response to bright light in control rats, in the absence of corneal injury. Of note, the reduction in eye closure in rats with the corneal injury produced by both TTX and lidocaine was to a level similar to that observed in cornea-intact control rats, whose response to bright light was not affected by either TTX or lidocaine, supporting the suggestion that they are eliminating the sensitization state. In addition to eliciting a local inflammatory response, de-epithelialization injures corneal sensory nerve fiber terminals, decreasing neural density in the corneal epithelium within the area of the wound, but doubling it at the wound periphery⁷. Thus, abnormal activity in corneal afferents in our model may reflect neuropathic as well as inflammatory mechanisms. Injured afferent sensory fibers have altered expression of membrane ion channels, including the TTX-sensitive Na(V) 1.7 sodium channel^{22, 39}, which is upregulated by inflammation and nerve injury¹⁷. The altered expression of ion channels in the regenerating nerve terminals is believed to be the origin of the marked increase in spontaneous firing of injured corneal nociceptors¹² and the hyperalgesia that occurs following corneal injury¹. Injury-induced axotomy and sprouting of nerve terminals, and local inflammatory response in the cornea, likely also contribute to the generation of the nerve impulses that contributes to eye pain as well as to photophobia.

Corneal nociceptors stimulate neurons in Vc/C1 superficial laminae of trigeminal subnucleus caudalis^{24, 25}; and bright light, which activates intrinsically photosensitive melanopsin-containing retinal ganglion cells, also increases activity of neurons in Vc/C1 and thalamic relay nuclei, enhancing activity in central pain pathways¹⁰. Thus, the photophobia observed following de-epithelialization is likely to be due to a convergence of input from sensitized corneal afferent nociceptors with retinally connected thalamic neurons that respond to noxious stimulation as well as bright light. Similar mechanisms may explain the moderate-to-severe photophobia that can occur when nociceptors in non-corneal cranial structures may contribute, for example, migraine headache¹⁹, meningitis²¹, subarachnoid hemorrhage⁶, as well as other ophthalmological conditions such as uveitis³⁷.

While TTX produced a significant attenuation of photophobia in de-epithelialized cornea, its application to the intact cornea had no effect on eye closure in response to bright light. This difference in the effect of TTX on the response to a bright light in normal control versus injured corneas might be due to TTX only being effective in reducing firing of neurons in an inflammatory or neuropathic state. In fact, while TTX appears not to be anesthetic with thermal and mechanical stimuli in non-neuropathic rats¹⁵, it is antinociceptive in rodent neuropathic pain models, such as spinal nerve ligation¹⁸, chronic constriction injury, and spared nerve injury⁴², as well as in chemotherapy-induced neuropathy models (see Nieto et al.,²³ for review). Importantly, TTX inhibits the Na(V) 1.7 sodium channel, which is upregulated in the setting of nerve injury and inflammation^{3, 22, 39}, at low nanomolar concentrations⁹. While it is also possible that the lack of effect of TTX on the photophobia in intact corneas is related to the form of TTX used, the citrate salt that is polar and therefore may have more limited corneal penetration, in the present experiments we applied TTX at a very high (1 mM) concentration. Therefore, it is likely at high enough concentrations to reach corneal nociceptor terminals at effective (nanomolar⁹) concentrations. Furthermore, a similar distinction was seen for the effect of lidocaine in rats with control and injured corneas.

Photophobia is a common disabling symptom that can occur following corneal damage (e.g. in corneal refractive surgery⁴, corneal abrasion³² or chemical injury¹³). Corneal damage is also associated with other symptoms, most notably ocular pain, which is dependent, at least in part, on corneal nociceptor sensitization and ongoing nociceptor activity. Since the inhibition of photophobia by TTX is likely to be due to a decrease in corneal nociceptor activity, TTX may also be useful for the treatment of pain and other ocular symptoms associated with corneal injury of diverse etiologies. Although local anesthetics, such as lidocaine, can attenuate eye pain and photophobia, their corneal toxicity is well documented²⁰, impairing corneal re-epithelialization⁵ and producing caspase-dependent corneal endothelial cell apoptosis⁴³. Thus due to the dose- and time-dependent corneal epithelial toxicity lidocaine and other local anesthetic use is contraindicated for chronic treatment of persistent ocular pain^{11, 28}. This is of particular importance since ocular pain after photorefractive keratectomy is one of the most important limitations of this surgery (most patients experience moderate to severe pain), with transition from physiological to neuropathic pain occurring in ~50% of patients within 1 month post-LASIK surgery^{8, 40} (LASIK differs from photorefractive keratectomy in that the former uses a blade or laser to create a corneal flap, whereas in photorefractive keratectomy only the epithelium is removed and the layer just below the epithelium is then treated with a laser). While high dose TTX applied topically to the cornea has previously been shown to be able to produce long-lasting corneal anesthesia, in contrast to lidocaine, TTX does not produce *in vitro* cell toxicity and cell death³⁰, and *in vivo* TTX does not produce corneal or systemic toxicity at anesthetic concentrations^{35, 36}. Therefore TTX may be an effective therapeutic option to reduce the symptoms of photophobia that occurs after photorefractive keratectomy, as well as photophobia associated with other clinical diseases that involve corneal nociceptor sensitization (e.g. ocular inflammation³⁴, optic or trigeminal neuropathies³³, DES³³).

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Perspective

We show that lidocaine and tetrodotoxin (TTX) attenuate photophobia induced by corneal injury. While corneal toxicity limits use of local anesthetics, TTX may be a safer therapeutic option to reduce the symptom of photophobia associated with corneal injury.

Highlights

- Corneal injury produced an increased sensitivity to light (photophobia)
- Tetrodotoxin and lidocaine had no effect on light aversive behavior in normal control rats
- Tetrodotoxin and lidocaine both eliminated photophobia in rats with corneal injury
- Because of lidocaine corneal toxicity, topical TTX may be a safer therapeutic option

Figure 1. Scale for quantification of eye closure response to bright light in the rat

Eye closure was scored according to its magnitude: no closure = 0, ~25% closure = 1, ~50% closure = 2, ~75% closure = 3, full closure = 4.

Figure 2. Lidocaine attenuates the increase in the eye closure response induced by corneal injury Lidocaine (2%, 10 μ l) did not significantly affect the magnitude of eye closure produced by exposure to bright light (~48 lumens, 465–480 nm) for 30 s in control eyes. However, the enhanced response, photophobia, following de-epithelialization injury was significantly attenuated by lidocaine (* P <0.05 baseline vs. corneal injury and ** P <0.05, corneal injury vs. corneal injury + lidocaine).

Figure 3. TTX attenuates photophobia induced by corneal injury

The magnitude of eye closure response produced by bright light was not significantly affected by TTX (1 mM, 10 μ l) applied to rats with uninjured corneas, but was significantly attenuated 1 and 2 h after application TTX to rats with injured corneas (* P <0.001).