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NK1R Inhibition: a Novel Ocular Pain Management Strategy Following Mechanical Corneal Injury

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Abstract

Purpose : Extensive corneal axotomy induced by keratorefractive surgery or injury is often followed by corneal pain. Ocular pain represents a leading cause of patients' quality of life impairment, and remains challenging to treat when it becomes chronic. Substance P (SP) is a neuropeptide that has been implicated in mediating the nociception of the ocular surface primarily by activating the neurokinin 1 receptor (NK1R). The purpose of this pre-clinical study was to determine the role of SP signaling in nociception following mechanical corneal injury.

Methods : Mice were injured by removing corneal epithelium and partial anterior stroma using Algerbrush II. SP expression in the injured corneas and ipsilateral trigeminal ganglions (TG) was measured by ELISA. Eye wiping test was performed by instillation of hypertonic saline (2M NaCl) on days 0, 4, 7, 14, and 21 to evaluate hyperalgesia. At the same time, an automated video analysis was used to assess allodynia by quantifying palpebral ratio (PR) of the animals' eyes after instillation of iso-osmolar saline (0.9 % NaCl) as innocuous stimulus. L-733,060 (1µg/µl), an NK1R antagonist, or PBS was administered topically twice daily immediately after injury until 21 days. One-way ANOVA followed by Tukey's post hoc test or student t-test was used to evaluate the difference among experimental groups.

Results : Corneal SP expression levels persistently increased from 7,921 ± 703 pg/mg before injury to 13,040 ± 2,027 pg/mg on day 14 ($P<0.05$) and 12,927 ± 1,383 pg/mg on day 21 ($P<0.05$) after the injury. No major changes were observed in the TG. Injured mice developed worsening hyperalgesia ($P<0.01$) and allodynia ($P<0.05$). Both

hyperalgesia and allodynia were significantly reduced in L-733,060 treated group compared to the vehicle group on days 7 ($P<0.05$) and 14 ($P<0.05$). On day 21, SP levels in the L-733,060 treated group were reduced locally in the cornea (-25.7%) but not centrally in the TG, compared to the vehicle group.

Conclusions : Our data suggest that SP is a key mediator of nociception after corneal injury. Suppression of its function via inhibition of NK1R signaling reduces hyperalgesia and allodynia in the mechanical injury model.

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