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Editorial

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Corneal Endocannabinoid System: A Promising Target for a New Class of Topical Corneal Pain Relief Medications

Ella G. Faktorovich, MD*

Director, Pacific Vision Institute, The Science of Eyesight, Foundation, Diplomat, American Board of Ophthalmology, One Daniel Burnham Court, San Francisco, CA 94109, USA, Tel: 415-922-9500/415-518-7965

Editorial

Corneal pain is complex and potentially debilitating condition caused by processes that disrupt corneal surface, such as abrasion, trauma, surgery, infection, and inflammation. Acute corneal pain arises when corneal disruption leads to release of inflammatory mediators that activate corneal nociceptors of the ophthalmic division of the trigeminal nerve. The signal is then transmitted to central nervous system where it travels through several relay centers, ending up in the somatosensory complex, where it is perceived as pain. If acute corneal injury fails to heal or corneal inflammation fails to resolve, it can precipitate abnormal regrowth of neurons or excessive neuronal sensitization which can lead to the development of chronic neuropathic pain. While many treatment options exist, safe and effective management of corneal pain remains a challenge. Over the past 30 years, an intricate signaling system, called Endocannabinoid System (ECS), has been identified throughout the body, including the cornea [1]. A wide range of potential therapeutic benefits of ECS modulation have been observed in multiple disorders, including both acute and chronic corneal pain and inflammation [2]. Exploring new therapeutic targets with topical cannabinoids and other modulators of corneal ECS is an exciting new field that offers potential to treat even refractory corneal pain safely and effectively.

Current treatment options for corneal pain

Acute corneal pain may occur in a setting of trauma, surgery, infection, or inflammation. Current topical analgesics for acute corneal pain include anesthetics, NSAIDs, anticholinergics, and steroids. Systemic analgesics are NSAIDs, acetaminophen, opioids, and gabapentinoids. While both topical and systemic analgesics can effectively relieve acute corneal pain, their safety may be a concern [3]. Topical anesthetics and NSAIDs, for example, may delay epithelial healing. Systemic opioids and gabapentinoids may lead to sedation and respiratory depression. Treatment of chronic corneal pain may present an even greater challenge. Chronic pain may accompany a chronic disease state,

such as dry eye disease, for example. While treatment of the underlying disease is essential, neuronal sensitization may, nevertheless, occur and result in chronic pain that persists even when the disease is treated or under control. Neuronal sensitization may also occur during acute infection or inflammation and result in persistent chronic pain such as post-herpetic neuralgia, for example. Treatment options for chronic neuropathic pain are typically systemic medications and they include oral gabapententinoids, opioids, and tricyclic antidepressants. Their efficacy is limited and side effects may not be acceptable. Chronic neuropathic pain is a difficult condition to treat and may adversely impact patient's quality of life.

Corneal endocannabinoid system (ECS)

An ideal corneal analgesic would target the pain locally, effectively, and with minimal side effects. Our endocannabinoid system may provide such targets and present an opportunity for development of a novel class of pain relief medications. ECS is a complex system that regulates many functions ranging from our immune response to pain signaling to various metabolic and cardiovascular functions. Components of the ECS have been identified in nearly all tissues of the body, including the cornea **[3]**. There are three essential components of the corneal ECS: receptors, endogenous cannabinoids, and enzymes responsible for synthesis and degradation of receptors and cannabinoids. Cannabinoid 1 receptor (CB1R) has been identified on corneal epithelium, stroma, and edothelium and it acts to regulate pain transmission. The cannabinoid 2 receptor (CB2R) is primarily localized to the surface of immune cells, and its activation leads to anti-inflammatory actions. Since corneal inflammation can result in both acute and chronic pain, anti-inflammatory actions of CB2R modulation can have indirect effect on improving ocular comfort. Reducing release of noxious inflammatory mediators helps to ameliorate acute pain. Prevention of neuronal sensitization by these mediators reduces the possibility of developing chronic neuropathic pain.

Topical ECS modulators for treatment of corneal pain

The use of topical ECS modulators has been explored in pre-clinical studies of corneal trauma and inflammation. The results support therapeutic potential of this novel class of analgesics and anti-inflammatories **[4]**. Recent study by Thapa D et al. **[5]**, for example, has demonstrated that topical administration of both naturally-occurring and synthetic cannabinoids activates CB1R and CB2R receptors in the cornea and on inflammatory cells and reduces pain and inflammation following corneal injury. Topical cannabinoids may be an important therapeutic approach to Dry Eye Disease (DED) since pain and inflammation often accompany this condition. Desiccated epithelium may be a source of both acute and chronic pain. Since CB1R is present on corneal epithelium, topical cannabinoids can easily access it, thereby providing pain relief. Interestingly, CB1R is also expressed in neurons innervating the lacrimal gland. Usually the expression is low, but it increases during DED-associated inflammation. McDowell et al. **[6]** showed that CB1R activation reduces sensitization of lacrimal gland nerves, thereby possibly reducing chronic neurotrophic pain. Additionally, Tran BN et al. **[7]** demonstrated improvement in corneal fluorescence and reduction of corneal and conjunctival inflammation after topical application of cannabinoids in experimentally induced dry eye model.

The potential for systemic penetration and side effects associated with ECS modulators should be considered. Psychoactive effects are related to CB1R activation in CNS. Agents that selectively activate CB2R are not associated with these effects and may be explored for treatment of inflammation and pain. To reduce systemic

penetration of CB1R modulators, their chemical structure may be altered to restrict them from crossing blood-brain barrier. Reduction in neuropathic pain with these agents has been demonstrated in preclinical models [3]. Other methods of ECS modulation are being investigated. One method uses modulators that increase binding affinity of cannabinoids to the receptors thereby allowing for a smaller dose of cannabinoid to achieve the desired effect. Another method uses enzyme inhibitors that increase levels of endocannabinoids by inhibiting the actions of enzymes that degrade them. Treatment with enzyme inhibitors has been shown to reduce pain and inflammation in several preclinical models, including chronic neuropathic pain [3]. The ubiquitous presence of endocannabinoid system in the cornea, its role in analgesia, and its demonstrated responsiveness to topical modulators represent a unique opportunity to continue developing a novel class of corneal pain relief medications. These medications would either be used alone or in conjunction with other analgesics to optimize ocular comfort and relieve both acute and chronic pain.

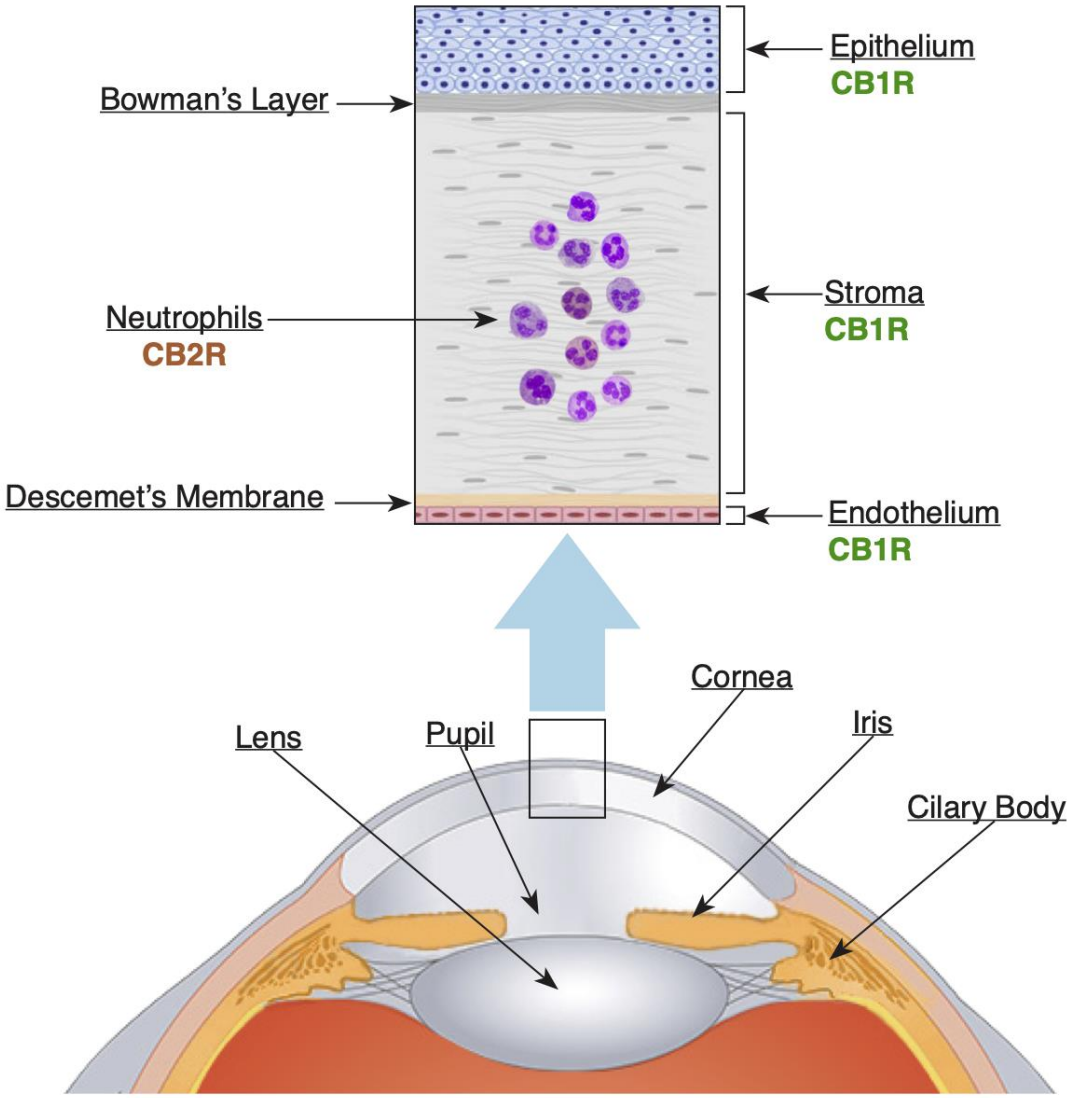

Figure: ECS localization in the cornea and on the surface of neutrophils that may infiltrate that infiltrate the stroma during inflammation.

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