Cannabineyed

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The word *cannabineyed* refers to endocannabinoid system (ECS) physiology, dysregulation and modulation in the context of ocular and periocular tissues and structures. It derives by placing the word *eye* into the original one, *cannabinoid.*

Specifically, the endocannabinoid system (ECS) is a complex regulatory system, highly conserved among vertebrates. It has been widely described in nearly all human tissues. In the eye, the ECS expression has been demonstrated both in the anterior and in the posterior segment. In this context, the ECS is believed to play a pivotal role in the modulation of the local inflammatory state as well as in the regulation of tissue repair and fibrosis, neo-angiogenesis, pain perception, intraocular pressure (IOP) control and neuroprotection.

Keywords: CannabinEYEds ; Endocannabinoids ; endocannabinoid system

1. Introduction

The endocannabinoids (ECB) are endogenous lipid mediators able to bind to and to activate cannabinoid (CB) and non-cannabinoid receptors (e.g., transient receptor potential cation channel subfamily V member 1 (TRPV1) and peroxisome proliferator-activated receptors (PPARs) [1], which constitute the primary molecular targets responsible for the biological effects of the Δ^9-tetrahydrocannabinol (Δ^9-THC) [2][3]. The ECB system (ECS) has been widely described in nearly all human tissues.

Among other functions, the ECS acts to regulate inflammation and immune response. For instance, both 2-arachidonoylglycerol (2-AG) and N-arachidonoylethanolamine or anandamide (the primary mediators of the ECS) have been shown to inhibit cyclooxygenase activity [4][5]. In addition, ECB have been found to prevent NFκB activation and its downstream pro-inflammatory cascade, via direct inhibition on I-kB kinase [6][7]. Nonetheless, anandamide (AEA) demonstrated the ability to reduce mitogen-induced T- and B-lymphocyte proliferation, probably because of increased apoptosis [8]. Moreover, as shown in a number of studies, both 2-AG and anandamide are able to induce nitric oxide release through binding to their specific receptor [9][10][11].

Even in the eye, the ECS is thought to play a pivotal role in the modulation of the local inflammatory state as well as in the regulation of tissue repair and fibrosis, neo-angiogenesis, pain perception, intraocular pressure (IOP) control and neuroprotection [12].

2. ECS modulation in Dry Eye Syndrome

The evidence of the strong functional role in mediating nociception, innate immune responses and wound healing has promoted the ECS as a novel therapeutic target for the management of both acute and chronic ocular surface inflammatory disorders [12]. Among the others, dry eye disease (DED) is one of the most investigated condition.

Dry eye is defined as a multifactorial disease of the tear fluid and ocular surface that results in symptoms of discomfort, visual disturbance and tear film instability, with potential damage to the ocular surface as per the local, dysregulated inflammatory response [12].

The first data promoting a link between the ECS modulation and DED comes from Chen et al., in 2014. In a mouse model, they proved that high levels of inflammatory cytokines, including TNFα and IL-1β, were associated with the downregulation of PPARγ expression on the ocular surface (i.e., their expression was inversely proportional) [12].

Even the modulation of TRPV1 was shown to be promising for the management of DED symptoms. Bereiter et al. demonstrated that the application of TRPV1 antagonists was able to reduce orbicularis oculi muscle activity, a marker for nocifensive behavior, in a rat model of DED [12]. These results not only promoted TRPV1 as an important mediator of nociception in DED, but also suggested a novel target for the control of ocular pain in moderate to severe cases of DED.

Based on this evidence, Di Zazzo et al. conducted a pilot, single-masked, prospective cohort study to evaluate the effect on the ocular surface of topical application of PEA eye drops (Defluxa, Medivis, Tremestieri Etneo, Catania, Italy), in patients under glaucoma treatment and suffering from DED symptoms. PEA is an endocannabinoid mimetic amide functioning as a direct agonist of PPARα and as an indirect agonist of CB1. It plays a well-known anti-inflammatory and analgesic activity. PEA eye drops treatment was shown to be effective in improving tear break up time, Schirmer test type 1 and conjunctival hyperemia without inducing any major or minor adverse event [12].

3. ECS modulation and glaucoma

Glaucoma is a chronic, progressive neurodegenerative disease characterized by retinal ganglion cells loss (RGC) . The mechanisms responsible for RGC loss are not yet fully understood. The IOP represents the only modifiable risk factor; hence, it is the primary therapeutic target for the management of the disease .

The modulation of the ECS during the course of glaucoma has been shown to be promising. In fact, it has been demonstrated that the phytocannabinoid, Δ9-tetrahydrocannabinol, and the synthetic cannabinoid, WIN 55,212-2, are able to determine a reduction in IOP levels by a CB1-mediated mechanism dependent on β-adrenergic receptor activity .

Nonetheless, WIN 55,212-2 showed a significant neuroprotective effect on RGC mediated by a CB1-mediated intracellular signaling .

4. Conclusions

While the exact mechanisms underlying ocular surface inflammatory disorders are still unclear, evidence to date overwhelmingly promotes the endocannabinoid system as an important regulator and as a promising therapeutic target for the management of local immune response, wound healing, nociception, intraocular pressure (IOP) control and neuroprotection [12]. However, a number of issues must be solved.

First of all, further investigation determining how the ECBS dysregulation might affect ocular surface functionality and which cellular and molecular targets should be modulated in order to restore the local homeostasis should be carried out.

Moreover, it should be noted that there are challenges in formulation of these very lipophilic compounds. Their use may, in fact, either not be able to penetrate the target organs or result in dose-dependent ocular and systemic toxicity with chronic use [12]. Thus, future research should explore novel cannabinoid drug combinations, appropriate routes of local delivery and evaluate both acute and chronic dosing in representative models of ocular diseases.

Furthermore, it must be noted that there is evidence suggesting that cannabinoids have similar and, in some cases, superior efficacy and fewer side-effects as compared to traditional immunosuppressive therapeutics commonly used in clinical practice [12]. Clinical trials attesting that cannabinoids benefits outweigh health hazards would allow them to be legally and safely use as therapeutic devices for ocular surface diseases.

Finally, we found the word cannabineyed as useful when referred to the analysis of the ECS physiology, pathophysiology and modulation in the context of ocular and periocular structures. We hence propose its widespread adoption in both research and clinical practice.

References

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