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REVIEW ARTICLE

Neuroprotection by (Endo)Cannabinoids in Glaucoma and Retinal Neurodegenerative Diseases

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Abstract: ***Background*:** Emerging neuroprotective strategies are being explored to preserve the retina from degeneration, that occurs in eye pathologies like glaucoma, diabetic retinopathy, age-related macular degeneration, and retinitis pigmentosa. Incidentally, neuroprotection of retina is a defending mechanism designed to prevent or delay neuronal cell death, and to maintain neural function following an initial insult, thus avoiding loss of vision.

***Methods*:** Numerous studies have investigated potential neuroprotective properties of plant-derived phytocannabinoids, as well as of their endogenous counterparts collectively termed endocannabinoids (eCBs), in several degenerative diseases of the retina. eCBs are a group of neuromodulators that, mainly by activating G protein-coupled type-1 and type-2 cannabinoid (CB1 and CB2) receptors, trigger multiple signal transduction cascades that modulate central and peripheral cell functions. A fine balance between biosynthetic and degrading enzymes that control the right concentration of eCBs has been shown to provide neuroprotection in traumatic, ischemic, inflammatory and neurotoxic damage of the brain.

***Results*:** Since the existence of eCBs and their binding receptors was documented in the retina of numerous species (from fishes to primates), their involvement in the visual processing has been demonstrated, more recently with a focus on retinal neurodegeneration and neuroprotection.

***Conclusion*:** The aim of this review is to present a modern view of the endocannabinoid system, in order to discuss in a better perspective available data from preclinical studies on the use of eCBs as new neuroprotective agents, potentially useful to prevent glaucoma and retinal neurodegenerative diseases.

Keywords: Neuroprotection, glaucoma, retinal diseases, retinal ganglion cells, endocannabinoids, phytocannabinoids.

1. INTRODUCTION: GLAUCOMA AND RETINAL NEURODEGENERATION

Glaucoma comprises a group of eye disorders that can lead to progressive and/or irreversible blindness. It affects the elderly but is becoming more widespread also among younger people and even children [1, 2]. Glaucoma is generally caused by increased intraocular pressure (IOP), although other factors are involved such as progressive damage of retinal ganglion cells (RGCs), known as "the messengers of retina", leading to optic nerve degeneration [3-5]. These conditions cause distinct visual field defects, and eventually complete vision loss [6]. In turn, apoptotic death of RGCs in glaucoma is due to different defects in the connection between central nervous system (CNS) and retina, including faults of reactive glia, synaptic connectivity and axonal transport, neurotrophic factor deprivation, pro-apoptotic signaling activation of neurotransmitters and neuromodulators, as well as excitotoxicity and oxidative stress [7, 8]. Besides glaucoma, RGC neurodegeneration occurs in several other ocular pathologies such as diabetic retinopathy (DR), age-related macular degeneration (AMD) and some inherited retinal disorders as well as in Alzheimer's disease and Parkinson's disease, where the retina appears to be an early site of damage [9-11]. Yet, signs of pigmentary retinopathy and degeneration of retinal nerve fibers have been identified in another form of neurodegenerative disorder known as autosomal dominant cerebellar ataxias [12, 13]. Other areas potentially affected are retinal microvessels, in DR [14], and retinal pigment epithelium (RPE) and photoreceptors, together with vascular and RGC damages, in AMD [15, 16].

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So far the most effective intervention used to block glaucoma progression is the administration of drugs capable of lowering IOP, although many patients have IOP within the normal range and disease progression can continue even when IOP is effectively lowered [17, 18]. Moreover, glaucomatous damage is not limited to the eye, but it also involves central visual pathways and vascular diseases of the CNS [19]. Indeed, neurodegeneration in glaucoma shares many pathway components with other retinal and non-retinal neurodegenerative diseases, so that an innovative therapeutic approach is now to keep RGCs and photoreceptors alive to avoid irreversible damage of optic nerve, as well as synaptic connectivity and retinal microvascular alterations [20, 21]. Interestingly, the five most common classes of drugs used topically to lower IOP (α2-agonists, β-antagonists/blockers, prostaglandin analogs, carbonic anhydrase and cholinergic agents) possess an indirect neuroprotective action on the retina and/or optic nerve, by triggering mechanisms that include neuronal, glial and vascular pathways [22-24]. On the other hand, many potential biochemical pathways are activated in a receptor-dependent or -independent manner by several natural and synthetic compounds, that directly provide neuroprotection: antioxidants, N-methyl-D-aspartate (NMDA) receptor antagonists, calcium channel blockers, acetylcholinesterase inhibitors like galantamine, acetylsalicylic acid, *Ginkgo biloba* extracts, resveratrol, fish oil and ω-3 (n-3) fatty acids, stem cells, as well as neurotrophic factors such as brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), glial cell-line derived neurotrophic factor (GDNF) and nerve growth factor (NGF) [25-34]. To this list other natural compounds can be added, namely phytocannabinoids (pCBs) and endogenous cannabinoids (eCBs), based on independent studies that documented their neuroprotective effects in ocular tissues [35-44]. In this review, we summarize the main outcomes of preclinical studies that support the potential benefits of pCBs and eCBs as new neuroprotective agents, potentially useful to prevent, slow down or even cure glaucoma and retinal neurodegenerative diseases.

2. PHYTOCANNABINOIDS AND ENDOCANNABINOIDS: SYNTHESIS AND PRODUCTION

The pCBs family is best represented by the active ingredient of cannabis (*Cannabis sativa* or *Cannabis indica*), Δ^9-tetrahydrocannabinol (THC). Yet, it should be recalled that cannabis contains more than 480 different compounds, of which ~65 have been identified as pCBs [45]. The latter are terpenophenolic substances, that include also abundant (*e.g.*, cannabidiol [CBD]) or minor (*e.g.*, cannabidivarin [CBDV] and Δ^9-tetrahydrocannabivarin [THCV]) THC-like molecules able to interact with G protein-coupled type-1 and type-2 cannabinoid receptors (CB_1 and CB_2), that are the most relevant eCB-binding targets within the so-called "endocannabinoid system (ECS)" [46]. CB_1 and CB_2 are present in the CNS (apparently CB_2 only upon (a)biotic insults) and at the periphery [47-49]. Both receptors modulate various signal transduction pathways, such as inhibition of cAMP production, activation of pERK and G protein-coupled inward rectifying K^+-channels (GIRKs), and recruitment of β-arrestin [50]. CB_1 and CB_2 are activated by the two most active eCBs, *N*-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG) [51]. AEA and 2-AG also bind to other receptors, like GPR55 [52], transient receptor potential vanilloid 1 (TRPV1) ion channel [53], and nuclear peroxisome proliferator-activated receptors (PPAR) α and γ [54]. Also pCBs may engage ECS receptors, as well as metabolic enzymes of eCBs [45, 46]. Among them, *N*-acyl-phosphatidylethanolamine-selective phospholipase D (NAPE-PLD) and diacylglycerol lipases (DAGL) α and β synthesize AEA and 2-AG, respectively, whereas fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) degrade them, respectively [55-57]. ECS is involved throughout the body in several physiological and pathological processes, visual processing included [35-37, 41, 58].

3. PRESENCE OF ECS ELEMENTS IN RETINA AND OCULAR TISSUES

The presence of the major ECS elements has been demonstrated in ocular tissues of different species, from fishes to primates [35-37, 41, 44, 59-61]. Most studies on ECS localization have been focused on retina, that represents the key area of visual information processing [37, 41, 43, 62-65]. In particular, the presence of CB_1 and CB_2 was investigated in the different layers of retina (inner and outer plexiform layer, INL and ONL respectively) as well as in amacrine, RGCs, photoreceptors, rod bipolar, horizontal, retinal pigment epithelial cells by using different methodological approaches, such as immunohistochemistry, mRNA and protein analysis, and radioligand binding studies [62, 64, 66-69]. Incidentally, CB_1 was also found in brain areas like thalamus and cortex, known to influence visual output [70-72], as well as in trabecular meshwork, Schlemm's canal and ciliary body, where also CB_2 is expressed [66, 73-75]. Numerous studies demonstrated the presence of TRPV1 and other TRP subunits at mRNA and protein level in mammalian and non-mammalian retina, and in a variety of neuronal and glial cells of this area; yet, results remained controversial, possibly because of the use of different antibodies and staining protocols [35, 63, 76-81]. Interestingly, TRPV1 may play a major functional role in the inner retina, since it was not detected in photoreceptors and bipolar cells [63]. As for GPR55, its presence has been documented only in the inner segments of rod photoreceptors of monkey retina, suggesting a function role in scotopic vision [65, 69]. Indeed, retinal function has been assessed by several flash electroretinogram (ERG) measurements in the presence of selective antagonists of CB_1 and CB_2, suggesting the involvement of eCB signaling in the modulation of retinal response. ECS is also involved in neurotransmission within the retina. Indeed, by acting on ionic currents and electrical potentials, it may modulate the release of several neurotransmitters such as dopamine, noradrenaline, GABA and glutamate, that control synaptic activity in retinal ganglion cells and consequently modulate visual response [82-87]. In addition, AEA, 2-AG and their congener *N*-palmitoylethanolamine (PEA) have been measured by gas chromatography-mass spectrometry in human ocular tissues, demonstrating an overall higher content of 2-AG compared to AEA in human retina, and a content change upon retinal degenerative diseases [75, 88, 89]. 2-AG and AEA levels are high in retina with DR and age-related macular degeneration [89], whereas glaucoma patients have reduced levels of 2-

AG and PEA without changes in AEA in the same patients [88]. Furthermore, FAAH expression is remarkable in different layers of retina, from OPL to GCL (ganglion cell layer) in rats, zebrafishes, gold fishes, monkeys and humans [64, 90, 91], and FAAH activity can be measured in the same species and particularly in mice and rats, where it is higher in rods, bipolar cells, horizontal cells, amacrine cells, Muller cells and ganglion cells. Moreover, NAPE-PLD was identified in the retina of rodents and other mammals [90], and recently the presence of DAGL and MAGL mRNAs was documented in rat retina [41], extending previous data on their localization during postnatal development [62]. More specifically, DAGL was found to be expressed in the postsynaptic terminals of cone bipolar cells, whereas MAGL in the IPL and OPL [92]. Localization of ECS components in retina is schematically depicted in Fig. (**1**).

4. PHYTOCANNABINOIDS, IOP REDUCTION AND RETINAL PROTECTION

The first evidence for a positive role of pCBs in retina protection dates back to the '70s, when smoking marijuana was found to lower IOP in a small number of subjects [93]. Then, several experimental findings demonstrated that oral or intravenous administration of THC to human subjects with glaucoma reduces IOP, though with development of tolerance and significant education of systemic blood pressure and tachycardia [94-97]. Instead, single sublingual administration of THC temporarily reduced IOP in a well-tolerated manner in most patients, whereas 40 mg of CBD, a non-psychotropic pCB, produced a transient increase of IOP [98]. In this context, the use of animal models pretreated with the CB_1 antagonist SR141716A allowed to demonstrate that THC and other pCBs can lower IOP by directly activating ocular CB_1 [99], and also by modulating production and drainage of aqueous humor [99, 100]. However, independent studies have shown that *N*-arachidonoylglycine (NAGly) and abnormal cannabidiol (Abn-CBD), two agonists of GPR18 (a recently deorphanized G protein-coupled receptor related to eCB-binding targets), are able to reduce IOP in a murine model of disease [101]. Many additional preclinical and clinical studies have interrogated the effects of THC and CBD on IOP modulation, establishing beneficial effects in patients with glaucoma although it is just a relief of symptoms and, moreover, tolerance, short duration of these compounds as well as peripheral and CNS side-effects did not allow their use in ophthalmic clinic [98, 102-107]. More recently, scientific interest towards these compounds has been focused on their neuroprotective action that results in a greater long-term efficacy in treating glaucoma and retinal neurodegenerative diseases. In this context, different animal models of ocular diseases have represented suitable tools to dissect the mechanisms by which pCBs and/or eCBs can exert neuroprotective effects: NMDA-induced retinal cell

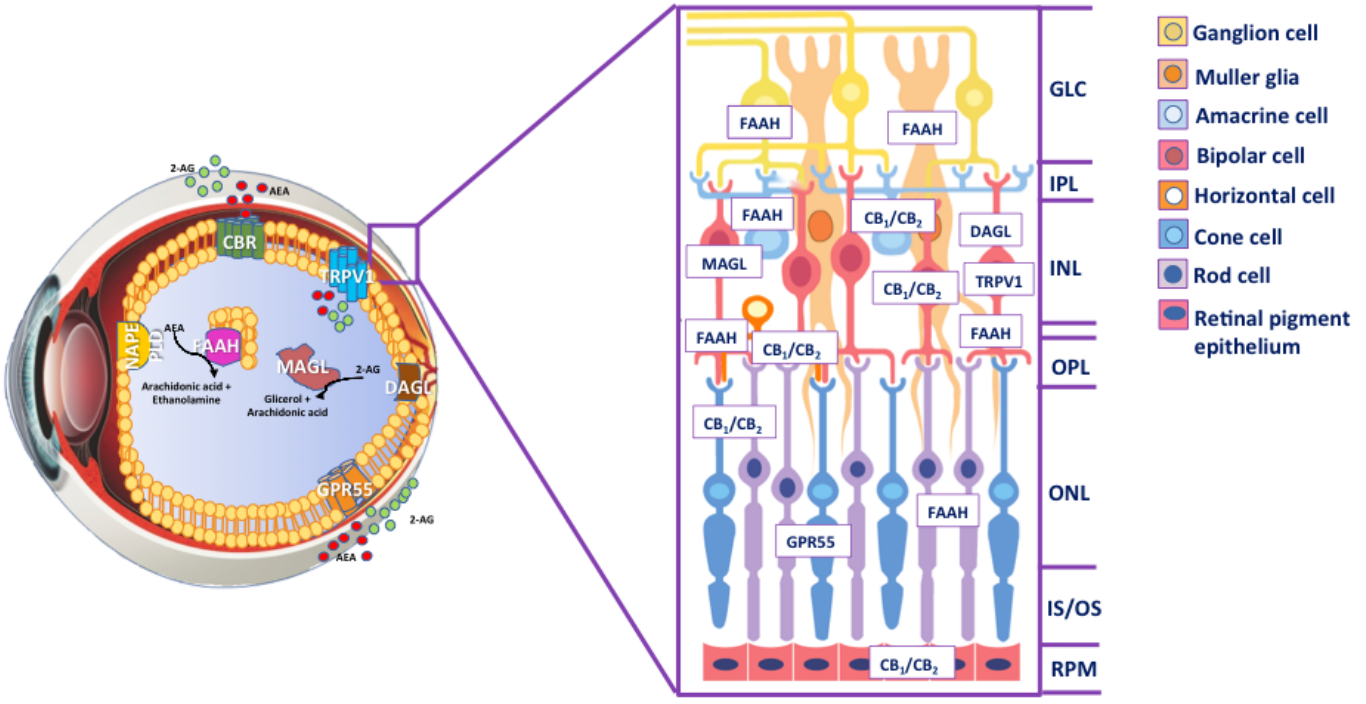

Fig. (1). Inside the eye. Schematic representation of the human eye with an overview of ECS distribution. AEA is manly synthesized by NAPE-PLD, whereas DAGL is the most important enzyme for the biosynthesis of 2-AG. AEA and 2-AG signalling pathways are terminated by enzymatic hydrolysis, mediated primarily by the serine hydrolases FAAH and MAGL, respectively. In the cross-section, the presence of ECS element in different layers of the retina is shown. *Abbreviations*: AEA, anandamide; 2-AG, 2-arachidonoylglycerol; NAPE-PLD, *N*-arachidonoylphosphatidylethanolamine-specific phospholipase D; DAGL, diacylglycerol lipase; FAAH; fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; CBR, cannabinoid receptors; GPR55, G protein-coupled receptor 55; TRPV1, transient receptor potential vanilloid type 1; GLC, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; IS/OS photoreceptor layer; RPE, retinal pigment epithelium.

degeneration, AMPA (amino-3hydroxy-5-methyl-4-isoxazole-propionic acid)-induced or light-induced transient ischemia, IOP-reperfusion (glaucoma) and the streptozotocin (STZ)-induced diabetic retinopathy [35, 38, 39, 41, 43, 105, 108-110].

Incidentally, it should be noted that an excessive extracellular glutamate stimulates NMDA receptors involved in retinal neuronal cell death, an event that is common to glaucoma, retinal ischemia, and diabetic retinopathy. For instance, in a NMDA excitotoxic rat model, THC and CBD were found to protect the retina in a CB_1/CB_2-independent manner, by decreasing peroyxnitrite levels and oxidative stress-related substances in neurons of the INL and GCL [108]. Consistently, independent studies underlined the antioxidant capacity of THC (and other pCBs) as a key feature to provide retinal neuroprotection (for a comprehensive review see [44]). In DR, retinal vascular dysfunction is associated to enhanced production of inflammatory mediators, such as vascular endothelial growth factor (VEGF) and cytokines (tumor necrosis factor TNF-α and inteleukin-6) [111, 112]. Additionally, adenosine and its receptors have been shown to possess anti-inflammatory properties in DR [113], where also CBD blocks retinal inflammation by equilibrating nucleoside transporter and A2A adenosine receptor, and suppresses lipopolysaccharide-induced TNF-α release [114, 115]. Moreover, an increase in peroxynitrite correlates with accelerated retinal endothelial damage, breakdown of the blood-retinal barrier (BRB), and accelerated neuronal cell death in experimental models of diabetes, inflammation, and neurotoxicity [108]. Yet, CBD treatment reduced neurotoxicity, inflammation, and BRB breakdown in diabetic animals through activities that may involve inhibition of p38 MAP kinase [109]. The best investigated effects of THC and CBD on retinal neurodegenerative diseases are summarized in Table **1**.

5. ENDOCANNABINOIDS AND RETINAL PROTECTION

eCBs show neuroprotective effects in different models of retinal neurodegeneration [35, 37-39,110]. Retinal ischemia models, induced by chemicals or acute elevation of IOP, affect the viability of a variety of amacrine, rod bipolar and RGC cells and lead to increased glutamate levels and activation of ionotropic glutamate (NMDA and AMPA) receptors. Consequently, intracellular calcium ions and NOS activity increase, resulting in glutamate-mediated excitotoxic retinal cell death [116, 117]. In that context, AEA produces a neuroprotective effect against retinal cell death induced by high IOP, through engagement of CB_1 and TRPV1 [35]. In particular, blocking AEA degradation with the specific FAAH inhibitor URB587, or mimicking this effect by using the non-hydrolysable analogue of AEA, methanandamide, confers retinal neuroprotection against high IOP-induced cell death [35]. Moreover, CB_1 was reported to reduce IOP *via* the β-adrenergic system, through inhibition of norepinephrine release [118]. In a rat model of optic nerve axotomy, URB587 promotes retinal ganglion cell neuroprotection through CB_1, and its efficacy declines with age and is associated to a significant increase in AEA levels. In parallel, a decrease in the AEA congener *N*-arachidonoyl-glycine is observed in young (but not in aged) animals, and 2-AG levels are not affected [38]. Furthermore, AEA and the synthetic cannabinoids HU-210 and MetAEA, injected intravitreally, protect retinal amacrine cells from AMPA excitotoxicity *via* a mechanism involving CB_1 and the PI3K/Akt and/or MEK/ERK1/2 signaling pathways [110]. Otherwise it has been shown that deletion of CB_1 or treatment of diabetic mice with CB_1 antagonist SR141716 prevented retinal cell death in a mouse model of DR, as well as in human primary retinal endothelial cells (HREC) exposed to high glucose, by reducing MAPK activation, oxidative stress and inflammatory signaling [119]. Also oral PEA given for three months seems to reduce IOP in ocular hypertensive patients [120], possibly by increasing AEA content, that is reduced in glaucomatous eyes [99], through inhibition of its degradation [121]. 2-AG was found to lower IOP in a concentration- and CB_1-dependent manner [122, 123], and indeed in a murine model of disease MAGL blockade can lower IOP by raising endogenous eCB levels [123] and consequently providing indirect neuroprotection. Interestingly, several studies re-

Table 1. Main effects of THC and CBD on retinal neurodegenerative diseases.

Source of Model	Target	Overall Effect	Phatology	References
Human	Eye	IOP reduction	Glaucoma	Hepler and Frank 1971*;* Flom *et al.,* 1975*;* Purnell and Gregg, 1975*;* Cooler and Gregg 1977*;* Flach *et al.,* 2002*;* Tomida *et al.,* 2006
Cat, Rat	Eye	IOP reduction	Glaucoma	Colasanti 1990
Mouse	Anterior Eye	IOP reduction	Glaucoma	Caldwell *et al.,* 2013
Dog	Eye	IOP reduction	Glaucoma	Fischer *et al.,* 2013
Rabbit	Cornea	IOP reduction	Glaucoma	Hingorani *et al.,* 2012
Rat	Retinal Ganglion Cells	Cell protection	Glaucoma	El-Remessy *et al.,* 2003 Crandall *et al.,* 2007
Rat	Retinal Neuronal Cells	Cell protection	Diabetic retinopathy	El-Remessy *et al.,* 2006
Chick	Retinal Section	Cell protection	Diabetic retinopathy and glaucoma	Araujoa *et al.,* 2017

ported that TRPV1 plays a major role as a mediator of RGC function and survival [124-126]. In line with this, in an inducible mouse model of glaucoma both genetic (knock-outs) and pharmacological (antagonists) blockade of TRPV1 accelerate RGC degeneration upon exposure to elevated IOP [125]. Moreover, *in vivo* TRPV1 expression increases in monkey and human RGCs in response to elevated IOP, thus supporting enhanced excitability. Such an enhancement is likely mediated by Ca^{2+} currents, since activation of TRPV1 in RGCs increases intracellular Ca^{2+} in isolated RGCs [124, 126]. In addition to promoting RGC excitability during retinal stress, TRPV1 seems to mediate the release of neuroprotective cytokines, such as interleukin (IL) 6, from glial cells [124]. Instead, in adult retinal explants both genetic and pharmacological blockade of TRPV1 improved RGC survival upon exposure to elevated hydrostatic pressure, as did chelation of extracellular Ca^{2+} [124]. Activation of TRPV1 was found to protect retinal neurons *in vivo* from injury induced by intravitreal NMDA in rats [127]. Indeed, treatment with the TRPV1 antagonist capsazepine almost completely erased the protective effect of the TRPV1 agonist capsaicin in the same model [127]. Other studies investigated the involvement of eCB-binding receptors in cell death induced by ischemia in an avascular (chick) retina model where oxygen and glucose deprivation (OGD) was induced. They failed to demonstrate an involvement of CB_1 and CB_2 in driving cell death at the early stages of ischemia [39], despite several studies showing that these receptors have a protective role against this type of damage [110, 128-130]. Probably, such a discrepancy depends on the different models used (AMPA toxicity, ischemia/reperfusion and acute ischemia). In a cellular model of AMD the expression of CB_1 is upregulated and its pharmacological blockade and/or inhibition of CB_1 with small interfering RNA (siRNA) can ameliorate H_2O_2-induced retinal oxidative stress and production of superoxide dismutase (SOD), thus preventing RPE cell death through PI3K/Akt signaling pathway [131]. In the pathogenesis of AMD and in other retinal diseases, also photoreceptors play a pivotal role, because they represent the main actors in phototransduction. Light-damaged animal models have been widely used to investigate the mechanisms of neuroretinal dysfunction in several ocular diseases, including human AMD [132, 133]. In line with this, our group provided the first evidence that bright continuous light (BCL) selectively affects ECS gene and protein expression in the albino rat retina, where only CB_1 and CB_2 levels were increased [41]. Similarly, accumulated evidence showed that CB_1/CB_2 levels are elevated in pathological retinal conditions, sometimes in association with oxidative stress [37, 131]. Of note, the other major components of retinal ECS were not modulated by BCL [41], including TRPV1 that plays a role in retinal death induced during IOP-related disease [39]. Remarkably, the selective blockage of both CB_1 and CB_2 was able to reduce light damage-induced photoreceptor death, thus preserving morphology and visual function, with a major involvement of CB_2 compared to CB_1 [41]. Consistently with these data, an upregulation of CB_1 expression was demonstrated in a light-induced photoreceptor damage model, both *in vitro* and *in vivo*, particularly in the photoreceptor outer segment layer [43]. Here, the CB_1 antagonist rimonabant effectively and potently blocked neuronal damage, tissue loss, and functional impairment *via* suppression of oxidative stress and inflammation [43]. In this context, it has been shown that photoreceptor death can be reduced in several animal models of neurodegeneration, by using both neuroprotectants [134] and antioxidants [135], and remarkably saffron [136]. Experimental studies demonstrated that saffron (*Crocus sativus*), given as a dietary supplement, counteracts the effects of BCL exposure in the albino rat retina, preserving both morphology and function [137]. Then, a pilot clinical trial conducted on AMD patients provided the first evidence of a therapeutic benefit of saffron treatment [138], also over time [139] and in patients carrying genetic defects [140]. Multiple actions of saffron have been suggested, including modulation of gene expression in animal models of retinal degeneration [141]. In keeping with this notion, recently we demonstrated that saffron down-regulates gene and protein expression of CB_1 and CB_2 in an animal model of retinal degeneration induced by light exposure [41]. Taking into account that some retinal pathologies are associated with a decrease in the amplitude of the electroretinographic waves, the measurement of b-wave of the electroretinogram is considered a solid indicator of inner retina functionality. In rats with retinal damage the b-wave amplitude was modulated by saffron or CB_1 and CB_2 antagonists in quite a similar manner, suggesting that these molecules could trigger the same mechanism, or else that saffron might directly impinge on CB_1/CB_2-dependent signal transduction to afford retinal protection [41]. In line with these data, CB_1 and CB_2 were found to modulate the electroretinographic waves in vervet monkey [65]. In particular, under photopic conditions blockade of CB_2 increased the amplitude of the b-wave above the standard flash intensity value, whereas under scotopic conditions blockade of either CB_1 or CB_2 increased only the amplitude of the b-wave irrespective of flash intensity [65], suggesting a role of both receptors in vision and retinal protection. Recently, a novel mechanism underlying a CB_1-mediated increase in RGC intrinsic excitability through AMPK-dependent inhibition of the Na^+-K^+-$2Cl^-$ co-transporter 1 (NKCC1) has been proposed [142]. CB_1 activation markedly improved visual contrast sensitivity under low-light conditions [142], whereas the role of CB_2 in intraocular pressure, aqueous humor outflow and ocular inflammatory pathologies remains unclear [143-145]. For example, activation of CB_2 has anti-inflammatory effects on the retina in a chronic experimental model of autoimmune uveoretinitis, associated with inhibition of leukocyte trafficking *in vivo* and reduction of inflammatory mediators *in vitro* [146]. Modulation of ocular CB_2 in a model of endotoxin-induced uveitis by the synthetic agonist HU-308 attenuates leukocyte-endothelial cell adhesion in the iridial microvasculature and reduces release of pro-inflammatory mediators (TNF-α, IL-1β, IL-6, INF-γ, CCL5 and CXCL2), but also of transcription factors NF-κβ and AP-1 [147], which enhance transcription of pro-inflammatory genes [148, 149]. In addition, CB_2 activation reduces leukocyte adhesion and improves capillary perfusion in the iridial microvasculature during systemic inflammation induced by lipopolysaccharide [150]. The main functions of ECS in retinal neurodegenerative diseases are summarized in Table **2**.

Table 2. Main effects of ECS on retinal neuroprotection.

Animal/Human/Cell Model	Target	Molecular Effect	Effect on eCB-Binding Receptors	Overall Effect	References
Retinal ischemia mice model	Retinal Ganglion Cells	FAAH inhibition	↓ CB_1, TRPV1	IOP reduction	Nucci *et al.,* 2007
Knockout mice (-/-) for β_1 AR, β_2 AR, CB_1, or CB_2	Anterior Eye	NE release Inhibition	↑ CB_1	IOP reduction	Hudson *et al.,* 2011
Rat model of axotomy	Retinal Ganglion Cells	FAAH inhibition	↑ CB_1	Cell protection	Slusar *et al.,* 2013
AMPA excitotoxicity animal model	Amacrine Cells	PI3K/AKT and MEK/ ERK1/2 signalling pathway	↑ CB_1	Cell protection	Kokona *et al.,* 2015
Ocular hypertensive subjects	Vascular Endothelium	Inhibition of AEA degradation (?)	Receptor-independent	IOP reduction	Strobbe *et al.,* 2013
Knockout (-/-) mice for CB_1, CB_2, or MAGL	Nonpigmented Ciliary Epithelium	MAGL blockage	↑ CB_1	IOP reduction	Miller *et al.,* 2016
Knockout (-/-) mice for TRPV1	Retinal Ganglion Cells	Enhanced Ca^{2+} excitability by efflux	↑ TRPV1	Cell protection	Sappington *et al.,* 2015
Streptozotocin-induced diabetics rat model Human retinal endothelial cell	Retinal Endothelial Cells	Suppression of oxidative stress and inflammation	↑ CB_1	Cell protection	El-Remessy *et al.,* 2008
Animal/Human/Cell Model	Target	Molecular Effect	Effect on eCB-binding Receptors	Overall Effect	References
NMDA excitotoxicity rat model	Retinal Ganglion Cells	Activation of CGRP and tachykinin NK1 receptors	↑ TRPV1	Cell protection	Sakamoto *et al.,* 2014
Xenopus leavis	Retinal Ganglion Cells	Enhanced excitability by chloride channel current	↑ CB_1	Visual response protection	Miracourt *et al.,* 2016
Light-induced damage mice model	Murine Retinal Cone Cells	Suppression of oxidative stress and inflammation	↑ CB_1	Photoreceptor protection	Inamura *et al.,* 2017
Human retinal pigmental epithelial cells	Retinal Pigment Epithelium	Downregulation oxidative stress	↑ CB_1	Cell protection	Wei *et al.,* 2013
Light-induced photoreceptor damage rat model	Retinal Section	Mediated by saffron	↓ CB_1, CB_2	Photoreceptor protection	Maccarone *et al.,* 2016

6. TOPICAL ADMINISTRATION OF CANNABINOIDS FOR RETINAL DISORDERS

Natural and synthetic cannabinoids are highly lipophilic molecules with a low aqueous solubility, which limits their application by topical administration, consequently it is very challenging determine the appropriate route for delivering these compounds. Various formulation strategies have been used to overcome this obstacle, including the use of surfactants and cyclodextrins [151, 152]. Actually, in the case of THC the use of light mineral oil, as a vehicle, improved the aqueous solubility and transcorneal permeability, but caused irritation to the human eye [153]. Also different microemulsions, such as submicron emulsion of THC, and cyclodextrins (macrocyclic oligosaccharides) have been shown to improve the corneal penetration of cannabinoids [143, 151]. Recently, prodrug strategy represents a new approach to development of molecules with high solubility, permeability and absorption in ocular drug delivery [154]. Incidentally, prodrugs are pharmacologically inactive molecules which must undergo chemical or enzymatic transformations within the body before exerting their pharmacological or therapeutic effect [154]. In this context, phosphate ester prodrugs of three cannabinoids (arachidonylethanolamide, R-methanandamide and noladin ether) have been synthesized and their physicochemical properties have been studied, showing a significantly enhanced aqueous solubility compared to their parent drugs with adequate chemical stability in buffer solutions [155]. Similarly, hemisuccinate (THC-HS) and hemiglutarate (THC-HG) ester prodrugs and WIN 55-212-2 (WIN), a synthetic cannabinoid, as well as prodrug-ion-pair complexes with l-arginine or tromethamine have been used in rabbit cornea demonstrating an improved solubility and permeability of an ion-pair complex of THC-HG [106]. In addition, use of surfactants led to a significant improvement in the aqueous solubility of THC-HG [152]. A

recent study demonstrated that combination of THC with mono and di-valine esters (THC-Val and THC-Val-Val) and amino acid (valine)-dicarboxylic acid (hemisuccinate) ester (THC-Val-HS) improve the penetration of THC into the anterior segment of the eye following topical application [156]. Lowering IOP is still the primary target of these prodrugs in the glaucoma treatment, although as discussed here, neuroprotective drugs represent a promising next-generation therapy that could employ the strategy of prodrugs to enhance the solubility and ocular penetration of eCBs.

CONCLUSION

The neuroprotective effects of pCBs and eCBs on retinal neurodegenerative diseases discussed here appear to engage different mechanisms, including IOP reduction, RGCs and photoreceptor preservation through anti- inflammatory and antioxidant actions. Interestingly, some of them are mediated by CB_1 whereas others go through non-CB receptors, especially TRPV1, and/or additional neuromodulatory systems. Therefore, CB_1 and TRPV1 agonists or antagonists, and inhibitors of distinct metabolic enzymes, like FAAH and MAGL, that extend the duration of action of eCBs, could have therapeutic potential for the treatment of glaucoma and other ocular pathologies like DR, AMD and retinal disorders associated to Alzheimer's disease and Parkinson's disease. In addition, drugs targeting CB_2 may be valuable therapeutics for ocular inflammation [146, 147, 150]. As discussed in this review, several preclinical studies underline anti-inflammatory and neuroprotective effects of CBD, a pCB devoid of unwanted psychoactive side effects. Given that CBD in combination with THC has been approved for the treatment of inflammation, pain, and spasticity associated with multiple sclerosis in humans [157, 158], it could be tested also to treat degenerative eye diseases such as glaucoma and DR. On a final note, new combined therapies where cannabinergic agents are associated with antioxidant molecules, possibly in innovative prodrug formulations that allow "smart" delivery to a distinct area of the body, could provide better efficacy to prevent neurodegeneration and death of retinal cells. For instance, topical use of CB_1 and CB_2 antagonists, in combination with saffron supplement in the diet, might hold potential to prevent, slow down or even cure retinal neurodegenerative processes.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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