REVIEW ARTICLE

Role of Endocannabinoids in Glaucoma: A Review

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Received on: 09 December 2024; *Accepted on:* 19 February 2025; *Published on:* 24 March 2025

Abstract

Aims: A review of the published literature was done to understand the role of endocannabinoids in glaucoma.

Background: As evidence mounts that intraocular pressure (IOP) is not the only factor in the pathogenesis and progression of glaucoma, a look into other aspects is the need of the hour. From the first instance of a drop in IOP linked to marijuana in the 1970s to the present, research has been ongoing, mostly in animals and *in vitro* models, with a scarcity of human studies, to delve into the world of the endocannabinoid system (ECS).

Methods: PubMed, ScienceDirect, and Google Scholar were searched for studies relating to endocannabinoids and their role in glaucoma.

Results: The ECS comprises ligands, receptors, and the synthesizing and degrading enzymes and is ubiquitous throughout the human body, including the visual system, from the eye to the occipital lobe. Apart from the IOP-lowering effect of the system, another property being investigated and implicated as an attribute of its receptors is neuroprotection. This neuroprotection seems to be mediated by excitotoxicity reduction and changes in vascular tone by acting on cannabinoid receptors.

Conclusion: The possibilities are indeed immense, and further research into the complex relationship between ECS and glaucoma is imperative to enable us to develop therapies for this otherwise chronic, progressive neuropathy, where the only armament in our hands is early diagnosis and maintenance therapy.

Clinical significance: We still do not have drugs for the prevention of retinal ganglion cell loss and for neuroprotection in glaucoma. Drugs that target cannabinoid receptors can revolutionize glaucoma management owing to their IOP-lowering action and neuroprotective effects. Based on the findings, we argue that further studies on the ECS and its implications in glaucoma are warranted to develop newer, effective, and better-targeted treatment strategies.

Keywords: Cannabinoid enzymes, Cannabinoid ligands, Cannabinoid receptors, Cannabinoid receptor 1, Cannabinoid receptor 2, Endocannabinoid system, Glaucoma, Neuroprotection.

Journal of Current Glaucoma Practice (2025): 10.5005/jp-journals-10078-1467

Introduction

Glaucoma, an optic neuropathy that is irreversible and progressive, has a prevalence of 3.54% worldwide. Globally, the cases of this disease in 2013 were 64.3 million in the age-group of 40–80 years, with a sharp increase expected to 111.8 million by 2040.[1] Most glaucoma patients progress despite good maintenance of target intraocular pressure (IOP), proving that there are other factors besides IOP for glaucoma and its progression. A few patients have intolerable side effects or develop tolerance to the present glaucoma medications.

The endocannabinoid system (ECS) is an intricate system comprising synthetic and degrading enzymes for their ligands and receptors for their actions. Predominant receptors are G protein-coupled, which trigger multiple signal transduction cascades. A multitude of insults befall the central nervous system (CNS), but the ECS provides protection against these by maintaining the precise amounts of endocannabinoids. This is achieved by a delicate balance between their biosynthesis and degradation by the respective enzymes.[2]

In the 1970s, Hepler and Frank noted a reduction in IOP after smoking marijuana.[3] This fueled research into cannabinoids, and the ECS has been incriminated in the pathogenesis of glaucoma, age-related macular degeneration (ARMD), and diabetic retinopathy (DR).[4,5] An excellent understanding of the ECS has been achieved to date through animal and *in vitro* models and a select few human studies, but thus far, there is still no drug available and licensed in the market that is capable of modulating the ECS in the eye because of their psychoactive side effects, poor long-term stability, and their lipophilic property.

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How to cite this article: Warjri GB, Gowtham L, Venkatraman V, *et al.* Role of Endocannabinoids in Glaucoma: A Review. J Curr Glaucoma Pract 2025;19(1):28–37.

Source of support: Nil

Conflict of interest: Dr Tanuj Dada is associated as Editor-in-Chief of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of the Editor-in-Chief and his research group.

Therefore, we aim to analyze and scrutinize the literature regarding the ECS and its relation to the pathogenesis of glaucoma and to pave the way for future research into this latent field with immense possibilities, capable of altering our very understanding of the pathophysiology of this disease.

Methods

PubMed, ScienceDirect, and Google Scholar were searched for relevant keywords. The search string included one or a combination of the terms below: endocannabinoids, ECS, cannabinoids, cannabinoid ligands, cannabinoid receptors, cannabinoid enzymes, glaucoma, 2-arachidonoylglycerol (2-AG), anandamide, N-arachidonoylethanolamine (AEA), palmitoylethanolamide (PEA), noladin ether, neuroprotection, cannabinoid receptor 1 (CB1) receptor, cannabinoid receptor 2 (CB2), animal model, pharmacology, pharmacodynamics. Furthermore, we performed a manual search of the references of a few selected articles. The publication years of the articles ranged from 1971 to 2024. Articles that were not in English and articles where the full text was not available, even after a trial of contacting the corresponding authors, were excluded.

The initial part of the review deals with the location of the different components of the ECS in the eye. Then, we reviewed studies that investigated the ECS's role in glaucoma, relating to IOP and neuroprotection. Studies that involved ocular drug delivery of cannabinoids were also assessed. Based on the current knowledge, we argue that additional studies on the ECS and its implications for glaucoma are warranted to develop newer, effective, and better-targeted treatment strategies.

Results

Cannabinoid Receptors

Most eye tissues express various endocannabinoid receptors, ligands, and enzymes except the crystalline lens.[6] They are a group of transmembrane "G protein-coupled receptors (GPCRs)" that belong to the "rhodopsin-like receptor" class.[7] They include CB1 and CB2 receptors. Additionally, there are a few "nonclassical" cannabinoid receptors, like G-protein-coupled receptor 18 (GPR18), G-protein coupled receptor 55 (GPR55), transient receptor potential vanilloid 1 (TRPV1), and peroxisome proliferator-activated receptors (PPARs) α, δ/β, and γ.

Cannabinoid Receptor 1 Receptors

Cannabinoid receptor 1 receptors were first characterized in the brain of the mouse[8] and later cloned in 1990.[9] Table 1 enlists the location of the CB1 receptors in the eye.[9] There are orthosteric and allosteric binding sites on these receptors. The actions of a direct agonist can be modulated here.[10]

Cannabinoid Receptor 2 Receptors

In 1993, the second set of receptors was identified, now referred to as CB2 receptors.[11] They share around 44% amino acids analogous to CB1 receptors and similar binding characteristics. CB2 receptors' location on the trabecular meshwork points to their possible contribution in aqueous humor dynamics.[10] CB2 receptors are present in the cornea as well as proven in a study of corneal wound healing in an *in vivo* murine model, which has demonstrated an upregulation of CB2 receptors in the cornea during the process of wound healing.[12] CB2 mRNA expression has been discovered in various parts of the retina of several species,[13] but in humans, they have been found to be expressed only in retinal pigment epithelial cells.[14]

Both CB1 and CB2 receptors are coupled positively to "mitogen-activated protein kinase (MAPK)," as shown in Figure 1A, and negatively to adenylyl cyclase, through Gi/o proteins, as illustrated in Figure 1B.[7] In turn, they modulate various signal transduction pathways, like activation of "protein kinase RNA-like endoplasmic reticulum kinase (PERK)," G protein-coupled inward rectifying K^+ channels (GIRKs), inhibition of "cyclic adenosine monophosphate (cAMP)" production, and recruitment of ß-arrestin.[15]

G-protein-coupled Receptor 18

"G-protein-coupled receptor 18" expression was prominent and isolated in the cornea, iris, trabecular meshwork, ciliary epithelium, and retina.[16] It gets activated by a downstream metabolite of anandamide (AEA), N-arachidonoyl glycine (NAGly).[17]

G-protein Coupled Receptor 55

Evidence suggests that "GPR55" mediates the increased drainage of aqueous *via* the trabecular meshwork caused by PEA in a porcine organ culture model.[18] This is indirect evidence of the location of GPR55 in the drainage facility of the eye, and there is evidence that it is expressed in the retina as well.[13]

Transient Receptor Potential Vanilloid 1

"Transient receptor potential vanilloid 1," with AEA as the ligand, has been isolated in the retinal pigment epithelium.[19] Its presence has also been seen in retinal microglia and RGCs.[20]

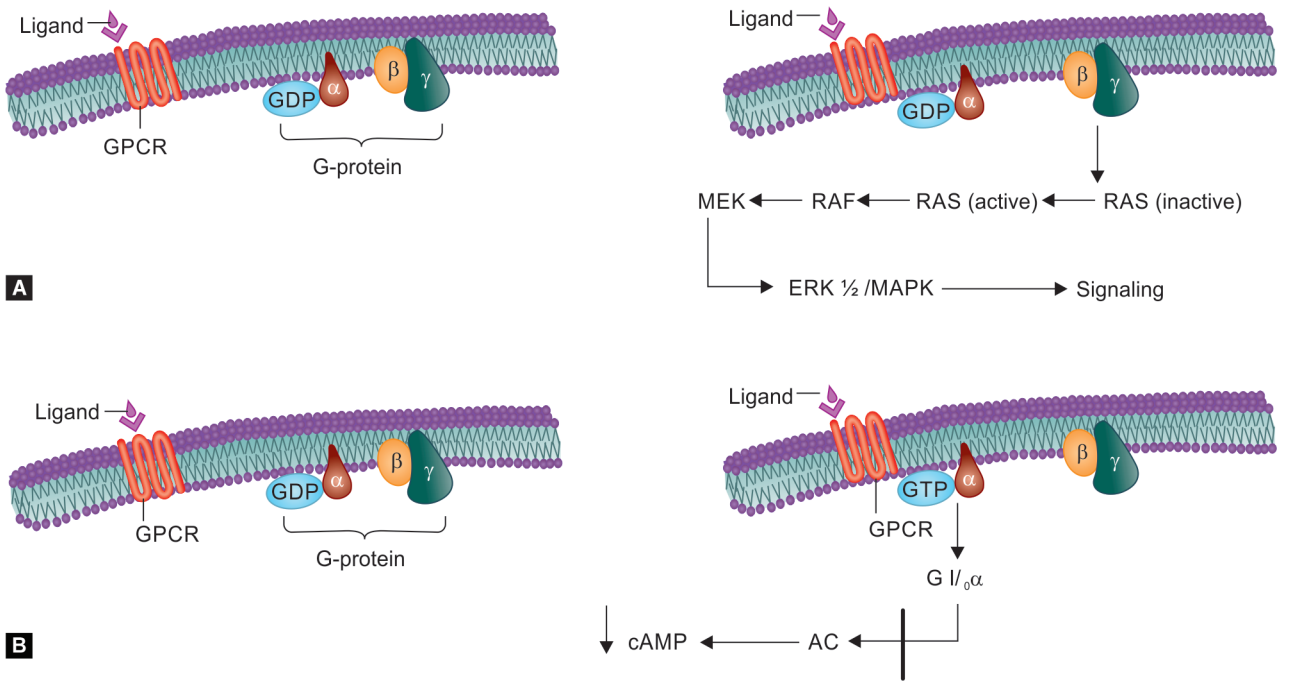
Peroxisome Proliferator-activated Receptors α

Indirect evidence shows that "PPARα" exists in the trabecular meshwork. The study was conducted using PEA, a "fatty acid amide analog" of AEA, which "fatty acid amide hydrolase (FAAH)" also degrades.[18]

Table 1: Classical and nonclassical receptors of endocannabinoids in the eye

	Iris	*Trabecular meshwork*	*Schlemm's canal*	*Ciliary body*	*Choroid*	*Retina*	*Species*
CB1	✓	✓	✓	✓	✓	✓	Rat, mouse, guinea pig, monkey, pig, human
CB2		✓				✓	Rat, pig, monkey
GPR18	✓	✓	✓	✓	✓	✓	Rat, mouse
GPR55		✓				✓	Pig, monkey
TRPV1						✓	Rat, cat, monkey
PPARα		✓				✓	Pig, cow

CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; GPR18, G protein-coupled receptor 18; GPR55, G protein-coupled receptor 55; PPAR α, peroxisome proliferator-activated receptor alpha; TRPV1, transient receptor potential cation channel subfamily V member 1



Figs 1A and B: (A) MAPK signaling pathway; (B) Adenylyl cyclase signaling pathway; AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; ERK, extracellular signal regulated kinase; GDP, guanosine diphosphate; Gi/oα are a family of G proteins of the α subunit; αßγ are subunits of G proteins; GPCR, G protein coupled receptor; GTP, guanosine triphosphate; MAPK, mitogen activated protein kinase; MEK, mitogen activated protein kinase; RAF, rapidly accelerated fibrosarcoma; RAS are a group of proteins which are regulators of signal transduction; αßγ are subunits of G proteins

Table 2: Endocannabinoid ligands in the eye

	Iris	*Trabecular meshwork*	*Schlemm's canal*	*Ciliary body*	*Choroid*	*Retina*	*Species*
2-AG	✓			✓	✓	✓	Rat, cow, human
AEA	✓	✓		✓	✓	✓	Rat, pig, cow, human
PEA	✓			✓	✓	✓	Rat, cow, human

2-AG, 2-arachidonoylglycerol; AEA, anandamide; PEA, palmitoylethanolamide

Endocannabinoid Ligands

2-arachidonoylglycerol

A monoacylglycerol, it is involved in numerous lipid metabolic pathways, where it is a precursor in some pathways and an end product in others.[21] Like AEA, its formation is also activated by a build-up in intracellular Ca^{2+}. 2-AG levels are higher than AEA, as in other parts of the CNS.[5]

N-arachidonoylethanolamine

Its synthesis is started by GPCRs or by an increase of intracellular Ca^{2+}. Table 2 enlists the location of AEA in the eye.[22–24]

N-palmitoylethanolamine

An analog of AEA, PEA is a bioactive endogenous fatty acid amide, and it is found as an active component in foods and quite a few living organisms. Its prominent roles have been identified in inflammatory processes and chronic pain.[25] Its presence in ocular tissues has also been detected.[5]

Noladin Ether

A novel putative endocannabinoid, "noladin ether (2-arachidonyl glyceryl ether)," was identified in the rat[26] and porcine brains.[27] It resembles 2-AG in structure; its ether-linked analog and chemically is 2-glyceryl ether.[27]

Synthetic Cannabinoids

A multitude of synthetic cannabinoids are well known now.[28] The most well-known are WIN-, CP-, UR-, PB-, HU-, JWH-, and AM-series.[29]

Enzymes

Both 2-AG and AEA are derived from "arachidonic acid-containing phospholipids."

Diacylglycerol Lipase-α and Lipase-ß

2-arachidonoylglycerol is synthesized from the diacylglycerols (DAG) substrates by two enzymes (isozymes), diacylglycerol lipase-α (DGLα) and diacylglycerol lipase-ß (DGLß).[30]

Monoacylglycerol Lipase and α,ß-hydrolase Domain-containing 6

Monoacylglycerol lipase (MAGL) and α,ß-hydrolase domain-containing 6 (ABHD6) are the metabolizing enzymes for 2-AG. Degradation involves two steps, the first being transportation of the substrate into the cells, followed by its hydrolysis.[31]

N-acyl Phosphatidylethanolamine-phospholipase D

N-arachidonoylethanolamine is synthesized from NAPE by the enzyme N-acyl phosphatidylethanolamine-phospholipase D (NAPE-PLD). It is a Ca^{2+}-dependent process, and the production

of both AEA and NAPE occur in parallel, albeit being mediated by separate enzymes.[32] PEA is also synthesized by NAPE-PLD.[33]

Fatty Acid Amide Hydrolase and N-acylethanolamine-hydrolyzing Acid Amidase

N-arachidonoylethanolamine is metabolized by two enzymes, FAAH and N-acylethanolamine-hydrolyzing acid amidase (NAAA).[34] The degradation follows the same two-step process as 2-AG.[35] This transport into the cell seems to be supported by many molecules, like fatty acid-binding protein 5 (FABP-5) and albumin.[36] AEA and 2-AG seem to have the same carrier for internalization and compete for it.[37] Once inside the cell, FAAH, an integral membrane protein, targets the amide bonds in various fatty acyl amides but does not degrade 2-AG. It can, however, degrade endocannabinoid and paracannabinoid fatty acid ethanolamides (FAEs). Both these facts should be considered when considering studies and experiments focusing on the removal of FAAH, pharmacologically or genetically. PEA is majorly degraded by NAAA and partly by FAAH.[33] The localization of the enzymes is depicted in Table 3.

Prostaglandin-ethanolamides (prostamides) are the degradation product of AEA and prostaglandin glyceryl esters for 2-AG.[38] There is evidence that both AEA and 2-AG can be directly metabolized by cyclooxygenase-2 (COX-2). COX-2 is nonselective between arachidonic acid and 2-AG, emphasizing the association and close connection between the eicosanoid system and the ECS.[7] Figures 2 and 3 depict the flow chart diagrams of the synthesis and breakdown products of endocannabinoids.

Discussion

Intraocular Pressure and the Endocannabinoid System

The effects and sites of action of endocannabinoids for ocular hypotension were thoroughly studied through the years. The beneficial effect of marijuana causing ocular hypotension initially seemed to outweigh the adverse effects. On the other side of this same coin, marijuana did not seem to be more effective or safer than the drugs or surgical procedures already available for the management of glaucoma.[39] The effect of the ECS on IOP can be

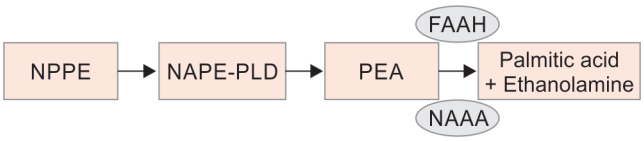


Fig. 3: Production and metabolism of PEA. FAAH, fatty acid amide hydrolase; NAAA, N-acylethanolamine-hydrolyzing acid amidase; NAPE-PLD, N-acyl phosphatidylethanolamine-phospholipase D; NPPE, N-palmitoyl phosphatidylethanolamine PEA, palmitoylethanolamide

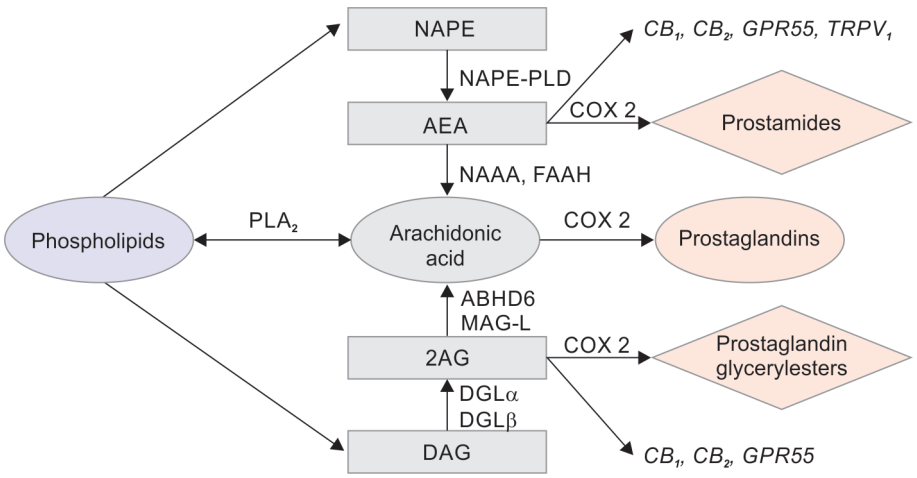


Fig. 2: Production and metabolism of endocannabinoids. 2-AG, 2-arachidonoylglycerol; ABHD6, α,ß-hydrolase domain-containing 6; AEA, anandamide; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; COX-2, cycloosygenase-2; DAG, diacylglycerol; DGL α/ß, diacylglycerol lipase α/ß; FAAH, fatty acid amide hydrolase; GPR55, G protein-coupled receptor 55; MAGL, monoacylglycerol lipase; NAAA, N-acylethanolamine-hydrolyzing acid amidase; NAPE, N-acyl phosphatidylethanolamine; NAPE-PLD, N-acyl phosphatidylethanolamine-phospholipase D; PLA2, phospholipase A2; PPAR α, peroxisome proliferator-activated receptor alpha; TRPV1, transient receptor potential cation channel subfamily V member 1

Table 3: Enzymes (synthesis and metabolizing) of endocannabinoids in the eye

	Iris	*Trabecular meshwork*	*Schlemm's canal*	*Ciliary body*	*Choroid*	*Retina*	*Species*
DGLα/ß						✓	Rat, mouse
MAGL		✓				✓	Rat, mouse
ABHD6						✓	Rat
NAPE-PLD						✓	Rat, mouse
FAAH		✓				✓	Rat, mouse, cow, monkey
NAAA						✓	Mouse

ABHD6, α,ß-hydrolase domain-containing 6; DGLα/ß, diacylglycerol lipaseα/ß; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; NAAA, N-acylethanolamine-hydrolyzing acid amidase; NAPE-PLD, N-acyl phosphatidylethanolamine-phospholipase D

seen mainly by its actions on the CB1 receptors[40] by various ligands as follows:

Delta-9-tetrahydrocannabinol

The topical application of delta-9-tetrahydrocannabinol (Δ-9-THC) was linked with a remarkable drop in IOP in the treated and contralateral eyes. There were no manifestations of psychotropic effects in the glaucoma patients.[41]

WIN55,212-2

Synthetic cannabinoids and their antagonists then came into play. Their use further consolidates the role of endocannabinoids. Porcella et al. demonstrated that the topical application of WIN55,212-2, a synthetic cannabinoid, reduced IOP in patients in the first 60 minutes.[42] Nevertheless, these effects of lowering IOP in cannabinoids seem mainly due to actions at the CB1 receptors.[42,43] There is no CB2 involvement, as demonstrated by Szczesniak et al.[44] Their study found that the effect of WIN55,212-2 was not blocked by AM630, a CB2 antagonist, but by a CB1 antagonist AM251, which blocked it. This was further consolidated by the use of CB2 knockout mice, where it was shown that the difference in reduction of IOP was similar to in controls.[44]

As already elaborated, CB1 receptors have been localized to the trabecular meshwork[24,45] and the ciliary body.[46] Contraction of ciliary muscles is well known to cause an increase in the drainage through the trabecular meshwork.[46]

While all of the above proves the involvement of the outflow facility, a study by Chien et al.[43] demonstrated that WIN55,212-2 resulted in an 18% reduction of aqueous humor production in monkeys. The outflow facility remained unchanged in these monkeys, and IOP was reduced in both control eyes and eyes with glaucoma of the monkeys after the application of WIN55,212-2.[43] Therefore, we can state that CB1-mediated modulation of IOP is both at the production and outflow levels. It was found that WIN55,212-2 causes a decrease of IOP by 47% in experimentally induced glaucoma in rats. Another important point noted was that this effect was maintained for 4 weeks with no symptoms or signs of local or systemic toxicity.[47]

Noladin Ether

Noladin ether, a cannabinoid ligand, was shown to produce a reduction in IOP in rabbits by action on CB1 receptors, as the effect was diminished by "AM251," a CB1 receptor antagonist.[48] In yet another study of an organ culture model, an increase in outflow in trabecular meshwork cells was noted after addition of noladin ether, and this effect was stopped when the cells were treated with SR141716A, a selective CB1 antagonist, consolidating the role of noladin ether and its site of action as the CB1 receptor.[49]

N-arachidonoylethanolamine and 2-arachidonoylglycerol

Coming to the main ligands, AEA and 2-AG, it was shown in a porcine ocular perfusion model that AEA heightened the outflow of aqueous for 30 minutes. This effect was lengthened to 5 hours on administration of a FAAH inhibitor, URB 597.[50] This study also demonstrated that FAAH exists and has activity at trabecular meshwork.[51] Applying this same model, a nonselective MGL/FAAH/ABHD6 inhibitor had the same effect of prolonging the increase in outflow facility to a comparable level.[52] These studies support the evidence that the above enzymes have been localized to the trabecular meshwork. Applying AEA or CP55,940, a synthetic cannabinoid, led to a constricting of bovine ciliary muscle by activating CB1 receptors. In a study of normotensive mice, topical 2-AG was shown to lower IOP by action at CB1 receptors in MAGL knockout mice.[53] Inhibitor 2, an inhibitor of MAGL, was used in another murine model and it was able to reduce IOP by ~4.5 mm Hg in a sustained manner for 12 hours after a single dose ocular application.[54]

Another trial involving human subjects was conducted to assess the effectivity of sublingual Δ-9-THC, where it was noted that IOP was reduced temporarily for a period of 4 hours and was well tolerated by patients.[55]

A study by Angmo et al. has also revealed that plasma AEA and 2-AG are significantly higher in normal individuals as compared to glaucoma patients. Also, the glaucoma patients had significantly higher levels of cortisol in aqueous humor and in plasma and exhibited poorer quality of life scores.[56] They also assessed the levels of tear endocannabinoids, which have never been estimated before in any other study. However, they did not find significant differences in the tear endocannabinoid levels between normal individuals and glaucoma patients.[56]

The ligands AEA and 2-AG, if administered externally, however, have an extremely short-lived duration of action, thereby making their therapeutic potential very limited.[57] Clinical trials studying the use of cannabinoids for the treatment of ocular hypertension demonstrate a lack of success, mainly due to the limited duration of action of the cannabinoids, in addition to behavioral side effects. Other issues like potential receptor desensitization and variable efficacy are also noteworthy.[58] Newer pharmacological techniques tried to overcome the above limitations are allosteric modulators or degradative enzyme inhibitors.[38]

Palmitoylethanolamide

A few trials have been conducted on the association between PEA and glaucoma. A randomized clinical trial on POAG patients and ocular hypertension showed that IOP was significantly decreased when they were administered oral PEA.[59] Pretreatment with PEA in patients undergoing bilateral laser iridotomy was found to be effective in counteracting the rise of IOP after the procedure.[60] A study was conducted on patients with normal-tension glaucoma to gauge the effect of oral PEA on IOP and visual field worsening. It was established that IOP was significantly reduced and visual field variables were improved.[61] To concur with these findings, Chen et al. showed that the amount of PEA in the uveal tissue of donor's glaucomatous eyes was lower than the nonglaucomatous ones.[23] The above effects of PEA are due to an enhancement in the aqueous humor outflow being mediated by GPR55 and PPARα receptors.[18] These two receptors have been isolated in the trabecular meshwork.[13,18,45]

ß-adrenergic Receptors and Other Receptors

Apart from these CB1 receptor-independent factors, others at play, namely the ß-adrenergic receptors (ßARs).[44,57] Application of cannabinoid agonists, ßAR agonists, and antagonists in wild-type and CB2 knockout mice models has shown a reduction in IOP but failed in CB1 knockout and ßAR knockout mice models. Depletion of catecholamines also failed to lead to a reduction in IOP after incorporation of a CB1 agonist. This clearly proves that ßARs have a major role in regulating IOP and cannabinoids.[57] As we had stated earlier, GPR18 has been isolated in mice' ciliary epithelium and trabecular meshwork.[16] All of this direct or indirect evidence proves that all these receptors have a role in the regulation of IOP. A recent concept by Miller et al.[50] explored the potential of blocking

transport molecules to raise endocannabinoid levels. These molecules would prevent the reuptake of endocannabinoids and lead to a rise in their levels. A FABP blocker SBFI-26 was used in an animal study, and it was found that IOP was lowered and the effect was not demonstrated in mice that had been made CB1 knockout.[50]

Cannabinoids and Neuroprotection

Being initially studied only for their property of reduction of IOP, evidence now also demonstrates their neuroprotective property.[62] The mechanisms for RGC loss have been studied and revealed that they die by apoptosis, which is triggered by glutamate receptors activation [N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)], resulting in the accumulation of excessive calcium inside the cells, which activates nitric oxide synthase and caspases with the release of toxic "reactive oxygen species (ROS)."[63] Excitotoxicity seems to be the basis of this cell death. Therefore, it would stand to reason that molecules which inhibit inflammation along with causing a reduction of ROS and calcium channel activation would ameliorate glaucomatous optic neuropathy. A study on glaucoma patients has already proven that molecules involved in stress like ROS, cortisol, and interleukin-6 levels were elevated and their levels decreased after intervention in the form of mindfulness meditation.[64] Elevated glutamate levels have been observed in experimental models of glaucoma in humans with glaucoma.[63,65] In line with this observation is the fact that antagonists of NMDA, a glutamate receptor, have provided neuroprotection to RGCs in experimental and animal models.[66] Even slight elevation of glutamate causes damage to the RGCs, mainly the large ones.[67] Irreversible retinal damage occurs once caspases are activated. Strategies to combat this apoptosis should be directed to pathways before activation of caspases and before late-phase apoptosis sets in; otherwise, cellular function becomes irreversibly lost.[68]

Excitotoxicity Reduction

Apart from glutamate, there is a release of nitric oxide and tumor necrosis factor from astrocytes, microglia, and Muller cells in the experimental models of glaucoma.[69] To further substantiate the above hypothesis about experimental models of glaucoma, it has been revealed in models of CNS diseases that CB1 and CB2 receptor stimulation triggers microglial cells and reduces nitric oxide and pro-inflammatory cytokines.[70] Quite a few studies on human subjects have already been done linking a reduction in inflammatory biomarkers, reduction in IOP, yoga/meditation, and increase in endocannabinoids.[64,71]

Numerous experimental studies have been published on the neuroprotective aspect of cannabinoids. One such study was performed on rats with ocular hypertension, where it was noted that there was an increase in the number of surviving RGCs after weekly administration of Δ-9-THC.[72] The authors argue that the most probable reason would be the property of THC in reestablishing the blood flow and diminishing ischemia in the retina. The other probable mechanisms are the moderation of ROS by decreasing formation or scavenging the ROS, mediated through CB1 receptors[73] or the suppression of calcium influx.[74]

WIN55,212-2, besides its IOP-lowering properties, has shown promising neuroprotective properties in rat high IOP models. There was a decrease in the RGC loss in rats receiving the cannabinoid, and this action was blocked by AM251, a CB1 antagonist, indicating the role of CB1 receptors in neuroprotection.[75] CB1 receptors are involved in neuroprotection, as revealed in another study where Δ-9-THC administration prevented NMDA (intravitreal injection in rats)-induced RGC death. This effect was partially attenuated when SR141716A, a CB1 antagonist, was coadministered, thereby consolidating the partial role of CB1 in neuroprotection.[76]

Kokona et al. studied the AMPA excitotoxicity model where 2-AG was intravitreally injected with AMPA in "wild-type," "CB1 knockout, and CB2 knockout mice." 2-AG provided neuroprotection to amacrine cells in the wild-type and CB2 knockout mice but did not do so in the CB1 knockout mice.[77] 2-AG was studied in an inflammation model that used lipopolysaccharide (LPS) in Müller glial cultures. It was noted that there was an increase in the anti-inflammatory cytokines and a decrease in the pro-inflammatory ones. As the effects were attenuated by CB1 and CB2 receptor antagonists, this strengthens the hypothesis of receptor-mediated activity.[78] Evidence for PEA-mediated neuroprotection after traumatic CNS injury exists, unlike neuroprotection in the retina, which is yet to be proven. It reduces cell necrosis and apoptosis, reduces pro-inflammatory cytokines, and attenuates edema.[79]

Fatty Acid Amide Hydrolase Inhibition

In a study related to AEA, it was seen that in a transient "high IOP-induced ischemia model in rats," URB597, a FAAH inhibitor, was shown to reduce RGC loss.[80] CB1 and TRPV1 seemed to be the action targets here.[80] Apart from the classical cannabinoid receptors, the survival and function of RGCs are mediated by TRPV1.[81] Nucci et al. noted in their experimental model that ocular hypertension followed by retinal ischemia was accompanied by a one-fourth decrease in the levels of AEA in the rat retina. This was found to be due to an upregulation of the activity of FAAH, the degradation enzyme of AEA. URB597 was seen to prevent this increase in FAAH activity. This supports the hypothesis that AEA's role in neuroprotection against ocular hypertension.[62] Rats that had undergone optic nerve axotomy were studied for the neuroprotective effect of AEA. URB597, by increasing AEA, was shown to be neuroprotective, thereby proving that these actions of AEA have, in part, a mechanism independent of IOP.[82]

In another *in vivo* rat model, AEA, MethAEA, and HU-210 (a synthetic cannabinoid) were injected intravitreally with AMPA to assess the AMPA-induced amacrine cell loss. It was uncovered that the neuroprotection offered by the cannabinoids was reversed by AM251, a CB1 receptor-selective antagonist.[83] Another molecule, HU-211, a nonpsychotropic cannabinoid, is also neuroprotective, as described in another optic nerve axotomy model.[84]

Vascular Tone and Other Mechanisms

Optic disk perfusion is involved in the patho-mechanism of glaucoma, with various studies revealing that the perfusion is reduced in glaucoma.[85,86] This perfusion can also be enhanced post adjunctive intervention (mindfulness meditation), as evidenced on optical coherence tomography angiography (OCTA).[87]

Endocannabinoids also seem to have the ability to affect vascular tone. Vasospastic stimuli seem to cause an increase in plasma endothelin-1 in cases of open-angle glaucoma.[88] It has been demonstrated that AEA causes bovine ophthalmic artery dilation.[89] Dronabinol is an appetite stimulant used in cases of AIDS-related anorexia and an antiemetic in chemotherapy-related nausea, and it is a synthetic Δ-9-THC. Retinal perfusion is increased and IOP decreases after its administration.[90] Inhibition of endothelin-1, a vasoconstrictor, seems to cause this vasodilation.[91]

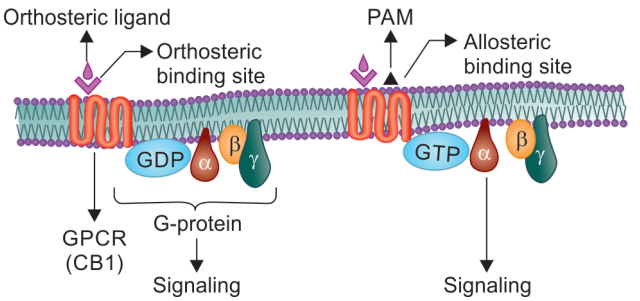


Fig. 4: Allosteric modulator and binding site. CB1, cannabinoid receptor 1; GDP, guanosine diphosphate; GPCR, G protein coupled receptor; GTP, guanosine triphosphate; PAM, positive allosteric modulator; αßγ are subunits of G proteins

Evidence suggests that CBD, HU-211, and Δ-9-THC may act independently of CB1 receptors to provide neuroprotection, most probably by reducing oxygen free radicals derived from excitotoxicity through glutamate,[55] or by cannabinoids acting on thromboxane receptor agonists.[92]

Cyclooxygenase-2 and the Endocannabinoid System

As COX-2 metabolizes endocannabinoid to produce prostamides, we can expect endocannabinoids to be part of an important pathway in IOP dynamics. In line with the above statement, a study showed that there was a reduction in COX-2 and lower levels of prostaglandin E2 (PGE2) in the aqueous humor of glaucomatous eyes compared to controls.[93] A synthetic prostamide analog, bimatoprost, decreases IOP by increasing both the trabecular and uveoscleral aqueous humor outflow.[94] It binds to a prostaglandin receptor (FP/altFP receptor), leading to ciliary muscle remodeling.[95] COX-2 by-products, such as PGE2 and matrix metalloproteinases, are responsible for the remodeling of the ciliary muscle and trabecular meshwork.[96] It has been demonstrated that AEA, methanandamide, or Δ-9-THC increases COX-2 expression in cell cultures in nonpigmented epithelium cells of the ciliary body.[97] All this evidence strengthens the hypothesis that endocannabinoids and eicosanoids play a role in increasing the outflow of aqueous humor.

Drug Delivery

A cannabinoid drug has not been developed to date due to a few inherent problems, such as behavioral side effects, persistent receptor activation/blockade, and receptor desensitization.[98] Swelling of the eyelids and irritation of the ocular surface were reported when light mineral oil was tried as a vehicle.[99] High lipophilicity and lower aqueous solubility of natural and synthetic cannabinoids make them impermeable through the cornea. Microemulsions, surfactants, and cyclodextrins (macrocyclic oligosaccharides) have been tried to enhance ocular penetration.[100] WIN-55,212-2 has been applied as eye drops to glaucoma patients with a cyclodextrin vehicle, and a significant drop in IOP was noted in patients whose IOP was not controlled on their current drugs.[42] There have been attempts to develop a stable formulation for Δ-9-THC. One study showed promise owing to the increased aqueous solubility of the formulation, but it failed in solid-state stability, pH stability, and sensitivity to oxygen.[101] In another study, fast-gelling films and solid lipid nanoparticles were used in rabbits topically. It was found that Δ-8-THC levels were high in the cornea, aqueous, and sclera, except for the vitreous.[102] Allosteric modulators have also been described, with a reported decrease in receptor desensitization (Fig. 4).[103]

The arrival of urea-based FAAH inhibitors seemed to enhance solubility and make them more appropriate for instillation into the eye. However, they were highly metabolized by cytochrome P450 (CYP) enzymes.[104] A recent concept of "biased agonism" or "functional selectivity" has gained popularity. The concept describes how an agonist can have a predilection to activate a particular signaling pathway, which can be applied to both orthosteric and allosteric ligands. This new approach has led to studies of new biased allosteric modulators of CB1 receptors, having a prolonged effect without undesirable psychotropic effects.[105] Other modalities being studied include soluble prodrugs, nanoemulsions, and nanoparticles.[106]

Conclusion

The future of endocannabinoids in the medical field, particularly in glaucoma, seems promising. Evidence of their IOP-lowering properties and neuroprotective capabilities in the literature is plentiful. Targeted management of glaucoma, therefore, seems very plausible, but we are still far from a breakthrough in this field. A collective endeavor from the scientific community is the need of the hour.

Clinical Significance

Currently, no drugs can target the loss of RGCs in glaucoma. Therefore, drugs that can target CB1 receptors can change the course of glaucoma treatment, as they can exert hypotensive and neuroprotective effects in conjunction. Further studies in the form of experimental models and clinical studies are necessary to appreciate and understand the complex ECS and its relation to glaucoma and other ocular pathologies to allow the development of stable, effective, and better-targeted therapies.

Acknowledgment

The authors wish to acknowledge Miss Tanisha Phanbuh for the illustrations.

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References

1. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology 2014;121(11):2081–2090. DOI: 10.1016/j.ophtha.2014.05.013
2. Di Marzo V. Endocannabinoid signaling in the brain: biosynthetic mechanisms in the limelight. Nat Neurosci 2011;14(1):9–15. DOI: 10.1038/nn.2720
3. Hepler RS, Frank IR. Marihuana smoking and intraocular pressure. JAMA 1971;217(10):1392.
4. Cairns EA, Baldridge WH, Kelly MEM. The endocannabinoid system as a therapeutic target in glaucoma. Neural Plast 2016;2016:9364091. DOI: 10.1155/2016/9364091
5. Matias I, Wang JW, Moriello AS, et al. Changes in endocannabinoid and palmitoylethanolamide levels in eye tissues of patients with diabetic retinopathy and age-related macular degeneration.

Prostaglandins Leukot Essent Fatty Acids 2006;75(6):413–418. DOI: 10.1016/j.plefa.2006.08.002
6. Hu SSJ, Arnold A, Hutchens JM, et al. Architecture of cannabinoid signaling in mouse retina. J Comp Neurol 2010;518(18):3848–3866. DOI: 10.1002/cne.22429
7. Howlett AC, Barth F, Bonner TI, et al. International union of pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev 2002;54(2):161–202. DOI: 10.1124/pr.54.2.161
8. Devane WA, Dysarz FA 3rd, Johnson MR, et al. Determination and characterization of a cannabinoid receptor in rat brain. Mol Pharmacol 1988;34(5):605–613.
9. Matsuda LA, Lolait SJ, Brownstein MJ, et al. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990;346(6284):561–564. DOI: 10.1038/346561a0
10. Navarro HA, Howard JL, Pollard GT, et al. Positive allosteric modulation of the human cannabinoid (CB) receptor by RTI-371, a selective inhibitor of the dopamine transporter. Br J Pharmacol 2009;156(7):1178–1184. DOI: 10.1111/j.1476-5381.2009.00124.x
11. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993;365(6441):61–65. DOI: 10.1038/365061a0
12. Murataeva N, Miller S, Dhopeshwarkar A, et al. Cannabinoid CB2R receptors are upregulated with corneal injury and regulate the course of corneal wound healing. Exp Eye Res 2019;182:74–84. DOI: 10.1016/j.exer.2019.03.011
13. Bouskila J, Javadi P, Casanova C, et al. Müller cells express the cannabinoid CB2 receptor in the vervet monkey retina. J Comp Neurol 2013;521(11):2399–2415. DOI: 10.1002/cne.23333
14. Wei Y, Wang X, Wang L. Presence and regulation of cannabinoid receptors in human retinal pigment epithelial cells. Mol Vis 2009;15:1243–1251.
15. Pertwee RG. Receptors and channels targeted by synthetic cannabinoid receptor agonists and antagonists. Curr Med Chem 2010;17(14):1360–1381. DOI: 10.2174/092986710790980050
16. Caldwell MD, Hu SSJ, Viswanathan S, et al. A GPR18-based signalling system regulates IOP in murine eye. Br J Pharmacol 2013;169(4):834–843. DOI: 10.1111/bph.12136
17. Kohno M, Hasegawa H, Inoue A, et al. Identification of N-arachidonylglycine as the endogenous ligand for orphan G-protein-coupled receptor GPR18. Biochem Biophys Res Commun 2006;347(3):827–832. DOI: 10.1016/j.bbrc.2006.06.175
18. Kumar A, Qiao Z, Kumar P, et al. Effects of palmitoylethanolamide on aqueous humor outflow. Invest Ophthalmol Vis Sci 2012;53(8):4416–4425. DOI: 10.1167/iovs.11-9294
19. Martínez-García MC, Martínez T, Pañeda C, et al. Differential expression and localization of transient receptor potential vanilloid 1 in rabbit and human eyes. Histol Histopathol 2013;28(11):1507–1516. DOI: 10.14670/HH-28.1507
20. Sappington RM, Sidorova T, Long DJ, et al. TRPV1: contribution to retinal ganglion cell apoptosis and increased intracellular Ca2+ with exposure to hydrostatic pressure. Invest Ophthalmol Vis Sci 2009;50(2):717–728. DOI: 10.1167/iovs.08-2321
21. Stella N, Schweitzer P, Piomelli D. A second endogenous cannabinoid that modulates long-term potentiation. Nature 1997;388(6644):773–778. DOI: 10.1038/42015
22. Bisogno T, Delton-Vandenbroucke I, Milone A, et al. Biosynthesis and inactivation of N-arachidonoylethanolamine (anandamide) and N-docosahexaenoylethanolamine in bovine retina. Arch Biochem Biophys 1999;370(2):300–307. DOI: 10.1006/abbi.1999.1410
23. Chen J, Matias I, Dinh T, et al. Finding of endocannabinoids in human eye tissues: implications for glaucoma. Biochem Biophys Res Commun 2005;330(4):1062–1067. DOI: 10.1016/j.bbrc.2005.03.095
24. Straiker A, Stella N, Piomelli D, et al. Cannabinoid CB1 receptors and ligands in vertebrate retina: localization and function of an endogenous signaling system. Proc Natl Acad Sci USA 1999;96(25):14565–14570. DOI: 10.1073/pnas.96.25.14565
25. Re G, Barbero R, Miolo A, et al. Palmitoylethanolamide, endocannabinoids and related cannabimimetic compounds in protection against tissue inflammation and pain: potential use in companion animals. Vet J 2007;173(1):21–30. DOI: 10.1016/j.tvjl.2005.10.003
26. Fezza F, Bisogno T, Minassi A, et al. Noladin ether, a putative novel endocannabinoid: inactivation mechanisms and a sensitive method for its quantification in rat tissues. FEBS Lett 2002;513(2–3):294–298. DOI: 10.1016/s0014-5793(02)02341-4
27. Hanus L, Abu-Lafi S, Fride E, et al. 2-arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB1 receptor. Proc Natl Acad Sci USA 2001;98(7):3662–3665. DOI: 10.1073/pnas.061029898
28. Potts AJ, Cano C, Thomas SHL, et al. Synthetic cannabinoid receptor agonists: classification and nomenclature. Clin Toxicol (Phila) 2020;58(2):82–98. DOI: 10.1080/15563650.2019.1661425
29. Tai S, Fantegrossi WE. Synthetic cannabinoids: pharmacology, behavioral effects, and abuse potential. Curr Addict Rep 2014;1(2):129–136. DOI: 10.1007/s40429-014-0014-y
30. Aretxabala X, García del Caño G, Barrondo S, et al. Endocannabinoid 2-arachidonoylglycerol synthesis and metabolism at neuronal nuclear matrix fractions derived from adult rat brain cortex. Int J Mol Sci 2023;24(4):3165. DOI: 10.3390/ijms24043165
31. Kokona D, Spyridakos D, Tzatzarakis M, et al. The endocannabinoid 2-arachidonoylglycerol and dual ABHD6/MAGL enzyme inhibitors display neuroprotective and anti-inflammatory actions in the *in vivo* retinal model of AMPA excitotoxicity. Neuropharmacology 2021;185:108450. DOI: 10.1016/j.neuropharm.2021.108450
32. Cadas H, di Tomaso E, Piomelli D. Occurrence and biosynthesis of endogenous cannabinoid precursor, N-arachidonoyl phosphatidylethanolamine, in rat brain. J Neurosci 1997;17(4):1226–1242. DOI: 10.1523/JNEUROSCI.17-04-01226.1997
33. Rahman IAS, Tsuboi K, Uyama T, et al. New players in the fatty acyl ethanolamide metabolism. Pharmacol Res 2014;86:1–10. DOI: 10.1016/j.phrs.2014.04.001
34. Tsuboi K, Sun YX, Okamoto Y, et al. Molecular characterization of N-acylethanolamine-hydrolyzing acid amidase, a novel member of the choloylglycine hydrolase family with structural and functional similarity to acid ceramidase. J Biol Chem 2005;280(12):11082–11092. DOI: 10.1074/jbc.M413473200
35. Piomelli D, Tagne AM. Endocannabinoid-based therapies. Annu Rev Pharmacol Toxicol 2022;62:483–507. DOI: 10.1146/annurev-pharmtox-052220-021800
36. Kaczocha M, Glaser ST, Deutsch DG. Identification of intracellular carriers for the endocannabinoid anandamide. Proc Natl Acad Sci USA 2009;106(15):6375–6380. DOI: 10.1073/pnas.0901515106
37. Nicolussi S, Gertsch J. Endocannabinoid transport revisited. Vitam Horm 2015;98:441–485. DOI: 10.1016/bs.vh.2014.12.011
38. Rouzer CA, Marnett LJ. Endocannabinoid oxygenation by cyclooxygenases, lipoxygenases, and cytochromes P450: cross-talk between the eicosanoid and endocannabinoid signaling pathways. Chem Rev 2011;111(10):5899–5921. DOI: 10.1021/cr2002799
39. Brown B, Adams AJ, Haegerstrom-Portnoy G, et al. Pupil size after use of marijuana and alcohol. Am J Ophthalmol 1977;83(3):350–354. DOI: 10.1016/0002-9394(77)90732-2
40. Wright NJD. A review of the direct targets of the cannabinoids cannabidiol, Δ9-tetrahydrocannabinol, N-arachidonoylethanolamine and 2-arachidonoylglycerol. AIMS Neurosci 2024;11(2):144–165. DOI: 10.3934/Neuroscience.2024009
41. Merritt JC, Perry DD, Russell DN, et al. Topical delta 9-tetrahydrocannabinol and aqueous dynamics in glaucoma. J Clin Pharmacol 1981;21(S1):467S–471S. DOI: 10.1002/j.1552-4604.1981.tb02626.x
42. Porcella A, Maxia C, Gessa GL, et al. The synthetic cannabinoid WIN55212-2 decreases the intraocular pressure in human glaucoma resistant to conventional therapies. Eur J Neurosci 2001;13(2):409–412. DOI: 10.1046/j.0953-816x.2000.01401.x
43. Chien FY, Wang RF, Mittag TW, et al. Effect of WIN 55212-2, a cannabinoid receptor agonist, on aqueous humor dynamics in monkeys. Arch Ophthalmol 2003;121(1):87–90. DOI: 10.1001/archopht.121.1.87

44. Szczesniak AM, Maor Y, Robertson H, et al. Nonpsychotropic cannabinoids, abnormal cannabidiol and canabigerol-dimethyl heptyl, act at novel cannabinoid receptors to reduce intraocular pressure. J Ocul Pharmacol Ther 2011;27(5):427–435. DOI: 10.1089/jop.2011.0041
45. Kumar A, Song ZH. CB1 cannabinoid receptor-mediated changes of trabecular meshwork cellular properties. Mol Vis 2006;12:290–297.
46. Lograno MD, Romano MR. Cannabinoid agonists induce contractile responses through Gi/o-dependent activation of phospholipase C in the bovine ciliary muscle. Eur J Pharmacol 2004;494(1):55–62. DOI: 10.1016/j.ejphar.2004.04.039
47. Hosseini A, Lattanzio FA, Williams PB, et al. Chronic topical administration of WIN-55-212-2 maintains a reduction in IOP in a rat glaucoma model without adverse effects. Exp Eye Res 2006;82(5):753–759. DOI: 10.1016/j.exer.2005.09.017
48. Laine K, Järvinen K, Mechoulam R, et al. Comparison of the enzymatic stability and intraocular pressure effects of 2-arachidonylglycerol and noladin ether, a novel putative endocannabinoid. Invest Ophthalmol Vis Sci 2002;43(10):3216–3222.
49. Njie YF, Kumar A, Qiao Z, et al. Noladin ether acts on trabecular meshwork cannabinoid (CB1) receptors to enhance aqueous humor outflow facility. Invest Ophthalmol Vis Sci 2006;47(5):1999–2005. DOI: 10.1167/iovs.05-0729
50. Miller S, Daily L, Dharla V, et al. Endocannabinoid metabolism and transport as targets to regulate intraocular pressure. Exp Eye Res 2020;201:108266. DOI: 10.1016/j.exer.2020.108266
51. Njie YF, Qiao Z, Xiao Z, et al. N-arachidonylethanolamide-induced increase in aqueous humor outflow facility. Invest Ophthalmol Vis Sci 2008;49(10):4528–4534. DOI: 10.1167/iovs.07-1537
52. Njie YF, He F, Qiao Z, et al. Aqueous humor outflow effects of 2-arachidonylglycerol. Exp Eye Res 2008;87(2):106–114. DOI: 10.1016/j.exer.2008.05.003
53. Miller S, Leishman E, Hu SS, et al. Harnessing the endocannabinoid 2-arachidonoylglycerol to lower intraocular pressure in a murine model. Invest Ophthalmol Vis Sci 2016;57(7):3287–3296. DOI: 10.1167/iovs.16-19356
54. Alapafuja SO, Malamas MS, Shukla V, et al. Synthesis and evaluation of potent and selective MGL inhibitors as a glaucoma treatment. Bioorg Med Chem 2019;27(1):55–64. DOI: 10.1016/j.bmc.2018.11.003
55. Tomida I, Azuara-Blanco A, House H, et al. Effect of sublingual application of cannabinoids on intraocular pressure: a pilot study. J Glaucoma 2006;15(5):349–353. DOI: 10.1097/01.ijg.0000212260.04488.60
56. Angmo D, Warjri GB, Gowtham L, et al. Endocannabinoids and cortisol in plasma, aqueous and tear samples of primary angle closure glaucoma versus controls. Eur J Ophthalmol 2024;35:163–171. DOI: 10.1177/11206721241247419
57. Hudson BD, Beazley M, Szczesniak AM, et al. Indirect sympatholytic actions at β-adrenoceptors account for the ocular hypotensive actions of cannabinoid receptor agonists. J Pharmacol Exp Ther 2011;339(3):757–767. DOI: 10.1124/jpet.111.185769
58. Pinar-Sueiro S, Rodríguez-Puertas R, Vecino E. Cannabinoid applications in glaucoma. Arch Soc Esp Oftalmol 2011;86(1):16–23. DOI: 10.1016/j.oftal.2010.11.015
59. Gagliano C, Ortisi E, Pulvirenti L, et al. Ocular hypotensive effect of oral palmitoyl-ethanolamide: a clinical trial. Invest Ophthalmol Vis Sci 2011;52(9):6096–6100. DOI: 10.1167/iovs.10-7057
60. Pescosolido N, Librando A, Puzzono M, et al. Palmitoylethanolamide effects on intraocular pressure after Nd:YAG laser iridotomy: an experimental clinical study. J Ocul Pharmacol Ther 2011;27(6):629–635. DOI: 10.1089/jop.2010.0191
61. Costagliola C, Romano MR, dell'Omo R, et al. Effect of palmitoylethanolamide on visual field damage progression in normal tension glaucoma patients: results of an open-label six-month follow-up. J Med Food 2014;17(9):949–954. DOI: 10.1089/jmf.2013.0165
62. Nucci C, Bari M, Spanò A, et al. Potential roles of (endo)cannabinoids in the treatment of glaucoma: from intraocular pressure control to neuroprotection. Prog Brain Res 2008;173:451–464. DOI: 10.1016/S0079-6123(08)01131-X
63. Dreyer EB, Grosskreutz CL. Excitatory mechanisms in retinal ganglion cell death in primary open angle glaucoma (POAG). Clin Neurosci 1997;4(5):270–273.
64. Gagrani M, Faiq MA, Sidhu T, et al. Meditation enhances brain oxygenation, upregulates BDNF and improves quality of life in patients with primary open angle glaucoma: a randomized controlled trial. Restor Neurol Neurosci 2018;36(6):741–753. DOI: 10.3233/RNN-180857
65. Nucci C, Tartaglione R, Rombolà L, et al. Neurochemical evidence to implicate elevated glutamate in the mechanisms of high intraocular pressure (IOP)-induced retinal ganglion cell death in rat. Neurotoxicology 2005;26(5):935–941. DOI: 10.1016/j.neuro.2005.06.002
66. Hare WA, WoldeMussie E, Weinreb RN, et al. Efficacy and safety of memantine treatment for reduction of changes associated with experimental glaucoma in monkey, II: structural measures. Invest Ophthalmol Vis Sci 2004;45(8):2640–2651. DOI: 10.1167/iovs.03-0567
67. Glovinsky Y, Quigley HA, Pease ME. Foveal ganglion cell loss is size dependent in experimental glaucoma. Invest Ophthalmol Vis Sci 1993;34(2):395–400.
68. Hara MR, Snyder SH. Cell signaling and neuronal death. Annu Rev Pharmacol Toxicol 2007;47:117–141. DOI: 10.1146/annurev.pharmtox.47.120505.105311
69. Weinreb RN, Khaw PT. Primary open-angle glaucoma. Lancet 2004;363(9422):1711–1720. DOI: 10.1016/S0140-6736(04)16257-0
70. Jackson SJ, Diemel LT, Pryce G, et al. Cannabinoids and neuroprotection in CNS inflammatory disease. J Neurol Sci 2005;233(1–2):21–25. DOI: 10.1016/j.jns.2005.03.002
71. Sadhasivam S, Alankar S, Maturi R, et al. Inner engineering practices and advanced 4-day Isha Yoga Retreat are associated with cannabimimetic effects with increased endocannabinoids and short-term and sustained improvement in mental health: a prospective observational study of meditators. Evid Based Complement Alternat Med 2020;2020:8438272. DOI: 10.1155/2020/8438272
72. Crandall J, Matragoon S, Khalifa YM, et al. Neuroprotective and intraocular pressure-lowering effects of (–)Delta9-tetrahydrocannabinol in a rat model of glaucoma. Ophthalmic Res 2007;39(2):69–75. DOI: 10.1159/000099240
73. Caulfield MP, Brown DA. Cannabinoid receptor agonists inhibit Ca current in NG108-15 neuroblastoma cells via a pertussis toxin-sensitive mechanism. Br J Pharmacol 1992;106(2):231–232. DOI: 10.1111/j.1476-5381.1992.tb14321.x
74. Wilson RI, Nicoll RA. Endocannabinoid signaling in the brain. Science 2002;296(5568):678–682. DOI: 10.1126/science.1063545
75. Pinar-Sueiro S, Zorrilla Hurtado JÁ, Veiga-Crespo P, et al. Neuroprotective effects of topical CB1 agonist WIN 55212-2 on retinal ganglion cells after acute rise in intraocular pressure induced ischemia in rat. Exp Eye Res 2013;110:55–58. DOI: 10.1016/j.exer.2013.02.009
76. El-Remessy AB, Khalil IE, Matragoon S, et al. Neuroprotective effect of (–)Delta9-tetrahydrocannabinol and cannabidiol in N-methyl-D-aspartate-induced retinal neurotoxicity: involvement of peroxynitrite. Am J Pathol 2003;163(5):1997–2008. DOI: 10.1016/s0002-9440(10)63558-4
77. Kokona D, Zimmer A, Thermos K. 2-arachidonoylglycerol protects the retina from AMPA excitotoxicity *in vivo* via the activation of CB1 receptor. Involvement of the P13K/Akt signaling pathway. Proceedings of the Neuroscience Abstracts Washington, DC, USA. 2014.
78. Krishnan G, Chatterjee N. Endocannabinoids alleviate proinflammatory conditions by modulating innate immune response in muller glia during inflammation. Glia 2012;60(11):1629–1645. DOI: 10.1002/glia.22380

79. Esposito E, Cuzzocrea S. Palmitoylethanolamide in homeostatic and traumatic central nervous system injuries. CNS Neurol Disord Drug Targets 2013;12(1):55–61. DOI: 10.2174/1871527311312010010
80. Nucci C, Gasperi V, Tartaglione R, et al. Involvement of the endocannabinoid system in retinal damage after high intraocular pressure-induced ischemia in rats. Invest Ophthalmol Vis Sci 2007;48(7):2997–3004. DOI: 10.1167/iovs.06-1355
81. Sappington RM, Sidorova T, Ward NJ, et al. Activation of transient receptor potential vanilloid-1(TRPV1) influences how retinal ganglion cell neurons respond to pressure-related stress. Channels (Austin) 2015;9(2):102–113. DOI: 10.1080/19336950.2015.1009272
82. Slusar JE, Cairns EA, Szczesniak AM, et al. The fatty acid amide hydrolase inhibitor, URB597, promotes retinal ganglion cell neuroprotection in a rat model of optic nerve axotomy. Neuropharmacology 2013;72:116–125. DOI: 10.1016/j.neuropharm.2013.04.018
83. Kokona D, Thermos K. Synthetic and endogenous cannabinoids protect retinal neurons from AMPA excitotoxicity *in vivo*, via activation of CB1 receptors: involvement of PI3K/Akt and MEK/ERK signaling pathways. Exp Eye Res 2015;136:45–58. DOI: 10.1016/j.exer.2015.05.007
84. Yoles E, Belkin M, Schwartz M. HU-211, a nonpsychotropic cannabinoid, produces short- and long-term neuroprotection after optic nerve axotomy. J Neurotrauma 1996;13(1):49–57. DOI: 10.1089/neu.1996.13.49
85. Al Zoubi H, Riemer T, Simon R, et al. Optic disc blood perfusion and oxygenation in glaucoma. Graefes Arch Clin Exp Ophthalmol 2022;260(11):3587–3595. DOI: 10.1007/s00417-022-05722-6
86. Bojikian KD, Chen CL, Wen JC, et al. Optic disc perfusion in primary open angle and normal tension glaucoma eyes using optical coherence tomography-based microangiography. PLoS One 2016;11(5):e0154691. DOI: 10.1371/journal.pone.0154691
87. Dada T, Lahri B, Mahalingam K, et al. Beneficial effect of mindfulness based stress reduction on optic disc perfusion in primary open angle glaucoma: a randomized controlled trial. J Tradit Complement Med 2021;11(6):581–586. DOI: 10.1016/j.jtcme.2021.06.006
88. Nicolela MT, Ferrier SN, Morrison CA, et al. Effects of cold-induced vasospasm in glaucoma: the role of endothelin-1. Invest Ophthalmol Vis Sci 2003;44(6):2565–2572. DOI: 10.1167/iovs.02-0913
89. Romano MR, Lograno MD. Cannabinoid agonists induce relaxation in the bovine ophthalmic artery: evidences for CB1 receptors, nitric oxide and potassium channels. Br J Pharmacol 2006;147(8):917–925. DOI: 10.1038/sj.bjp.0706687
90. Plange N, Arend KO, Kaup M, et al. Dronabinol and retinal hemodynamics in humans. Am J Ophthalmol 2007;143(1):173–174. DOI: 10.1016/j.ajo.2006.07.053
91. Ronco AM, Llanos M, Tamayo D, et al. Anandamide inhibits endothelin-1 production by human cultured endothelial cells: a new vascular action of this endocannabinoid. Pharmacology 2007;79(1):12–16. DOI: 10.1159/000097072
92. Lindner T, Schmidl D, Peschorn L, et al. Therapeutic potential of cannabinoids in glaucoma. Pharmaceuticals (Basel) 2023;16(8):1149. DOI: 10.3390/ph16081149
93. Maihöfner C, Schlötzer-Schrehardt U, Gühring H, et al. Expression of cyclooxygenase-1 and -2 in normal and glaucomatous human eyes. Invest Ophthalmol Vis Sci 2001;42(11):2616–2624. DOI: 10.5167/uzh-5516
94. Woodward DF, Krauss AH, Chen J, et al. The pharmacology of bimatoprost (Lumigan). Surv Ophthalmol 2001;45(Suppl 4):S337–S345. DOI: 10.1016/s0039-6257(01)00224-7
95. Liang Y, Woodward DF, Guzman VM, et al. Identification and pharmacological characterization of the prostaglandin FP receptor and FP receptor variant complexes. Br J Pharmacol 2008;154(5):1079–1093. DOI: 10.1038/bjp.2008.142
96. Winkler NS, Fautsch MP. Effects of prostaglandin analogues on aqueous humor outflow pathways. J Ocul Pharmacol Ther 2014;30(2–3):102–109. DOI: 10.1089/jop.2013.0179
97. Rösch S, Ramer R, Brune K, et al. R(+)-methanandamide and other cannabinoids induce the expression of cyclooxygenase-2 and matrix metalloproteinases in human nonpigmented ciliary epithelial cells. J Pharmacol Exp Ther 2006;316(3):1219–1218. DOI: 10.1124/jpet.105.092858
98. Järvinen T, Pate DW, Laine K. Cannabinoids in the treatment of glaucoma. Pharmacol Ther 2002;95(2):203–220. DOI: 10.1016/s0163-7258(02)00259-0
99. Jay WM, Green K. Multiple-drop study of topically applied 1% delta 9-tetrahydrocannabinol in human eyes. Arch Ophthalmol 1983;101(4):591–593. DOI: 10.1001/archopht.1983.01040010591012
100. Hingorani T, Adelli GR, Punyamurthula N, et al. Ocular disposition of the hemiglutarate ester prodrug of Δ9-Tetrahydrocannabinol from various ophthalmic formulations. Pharm Res 2013;30(8):2146–2156. DOI: 10.1007/s11095-013-1072-x
101. Thumma S, Majumdar S, Elsohly MA, et al. Preformulation studies of a prodrug of Delta9-tetrahydrocannabinol. AAPS PharmSciTech 2008;9(3):982–990. DOI: 10.1208/s12249-008-9136-7
102. Punyamurthula NS, Adelli GR, Gul W, et al. Ocular disposition of Δ8-Tetrahydrocannabinol from various topical ophthalmic formulations. AAPS PharmSciTech 2017;18(6):1936–1945. DOI: 10.1208/s12249-016-0672-2
103. Ross RA. Allosterism and cannabinoid CB(1) receptors: the shape of things to come. Trends Pharmacol Sci 2007;28(11):567–572. DOI: 10.1016/j.tips.2007.10.006
104. Guglielmi P, Carradori S, Campestre C, et al. Novel therapies for glaucoma: a patent review (2013–2019). Expert Opin Ther Pat 2019;29(10):769–780. DOI: 10.1080/13543776.2019.1653279
105. Corelli F. Has a "chemical magic" opened up new prospects for glaucoma? J Med Chem 2021;64(12):8101–8103. DOI: 10.1021/acs.jmedchem.1c00843
106. Afflitto GG, Aiello F, Scuteri D, et al. CB1R, CB2R and TRPV1 expression and modulation in *in vivo*, animal glaucoma models: a systematic review. Biomed Pharmacother 2022;150:112981. DOI: 10.1016/j.biopha.2022.112981