CBD / THC: Corneal pain and Inflammation

The Cannabinoids Δ^8THC, CBD, and HU-308 Act via Distinct Receptors to Reduce Corneal Pain and Inflammation.

Cannabis Cannabinoid Res. 2018 Feb 1;3(1):11-20. doi: 10.1089/can.2017.0041. eCollection 2018. **Author information**

Abstract Background and Purpose: Corneal injury can result in dysfunction of corneal nociceptive signaling and corneal sensitization. Activation of the endocannabinoid system has been reported to be analgesic and anti-inflammatory. The purpose of this research was to investigate the antinociceptive and anti-inflammatory effects of cannabinoids with reported actions at cannabinoid 1 (CB_1R) and cannabinoid 2 (CB_2R) receptors and/or non cannabinoid receptors in an experimental model of corneal hyperalgesia. **Methods:** Corneal hyperalgesia (increased pain response) was generated using chemical cauterization of the corneal epithelium in wild-type (WT) and CB_2R knockout ($CB_2R^{-/-}$) mice. Cauterized eyes were treated topically with the phytocannabinoids Δ^8-tetrahydrocannabinol (Δ^8THC) or cannabidiol (CBD), or the CBD derivative HU-308, in the presence or absence of the CB_1R antagonist AM251 (2.0 mg/kg i.p.), or the 5-HT_{1A} receptor antagonist WAY100635 (1 mg/kg i.p.). Behavioral pain responses to a topical capsaicin challenge at 6 h postinjury were quantified from video recordings. Mice were euthanized at 6 and 12 h post corneal injury for immunohistochemical analysis to quantify corneal neutrophil infiltration. **Results:** Corneal cauterization resulted in hyperalgesia to capsaicin at 6 h postinjury compared to sham control eyes. Neutrophil infiltration, indicative of inflammation, was apparent at 6 and 12 h postinjury in WT mice. Application of Δ^8THC, CBD, and HU-308 reduced the pain score and neutrophil infiltration in WT mice. The antinociceptive and anti-inflammatory actions of Δ^8THC, but not CBD, were blocked by the CB_1R antagonist AM251, but were still apparent, for both cannabinoids, in $CB_2R^{-/-}$ mice. However, the antinociceptive and anti-inflammatory actions of HU-308 were absent in the $CB_2R^{-/-}$ mice. The antinociceptive and anti-inflammatory effects of CBD were blocked by the 5-HT_{1A} antagonist WAY100635. **Conclusion:** Topical cannabinoids reduce corneal hyperalgesia and inflammation. The antinociceptive and anti-inflammatory effects of Δ^8THC are mediated primarily via CB_1R, whereas that of the cannabinoids CBD and HU-308, involve activation of 5-HT_{1A} receptors and CB_2Rs, respectively. Cannabinoids could be a novel clinical therapy for corneal pain and inflammation resulting from ocular surface injury.

Endocannabinoid System in the Eye

Neural Plast. 2016;2016:2916732. doi: 10.1155/2016/2916732. Epub 2016 Jan 6.

The Endocannabinoid System in the Retina: From Physiology to Practical and Therapeutic Applications.

Schwitzer T[1], Schwan R[2], Angioi-Duprez K[3], Giersch A[4], Laprevote V[2].

Abstract

Cannabis is one of the most prevalent drugs used in industrialized countries. The main effects of Cannabis are mediated by two major exogenous cannabinoids: ∆9-tetrahydroxycannabinol and cannabidiol. They act on specific endocannabinoid receptors, especially types 1 and 2. Mammals are endowed with a functional cannabinoid system including cannabinoid receptors, ligands, and enzymes. This endocannabinoid signaling pathway is involved in both physiological and pathophysiological conditions with a main role in the biology of the central nervous system. As the retina is a part of the central nervous system due to its embryonic origin, we aim at providing the relevance of studying the endocannabinoid system in the retina. Here, we review the distribution of the cannabinoid receptors, ligands, and enzymes in the retina and focus on the role of the cannabinoid system in retinal neurobiology. This review describes the presence of the cannabinoid system in critical stages of retinal processing and its broad involvement in retinal neurotransmission, neuroplasticity, and neuroprotection. Accordingly, we support the use of synthetic cannabinoids as new neuroprotective drugs to prevent and treat retinal diseases. Finally, we argue for the relevance of functional retinal measures in cannabis users to evaluate the impact of cannabis use on human retinal processing.

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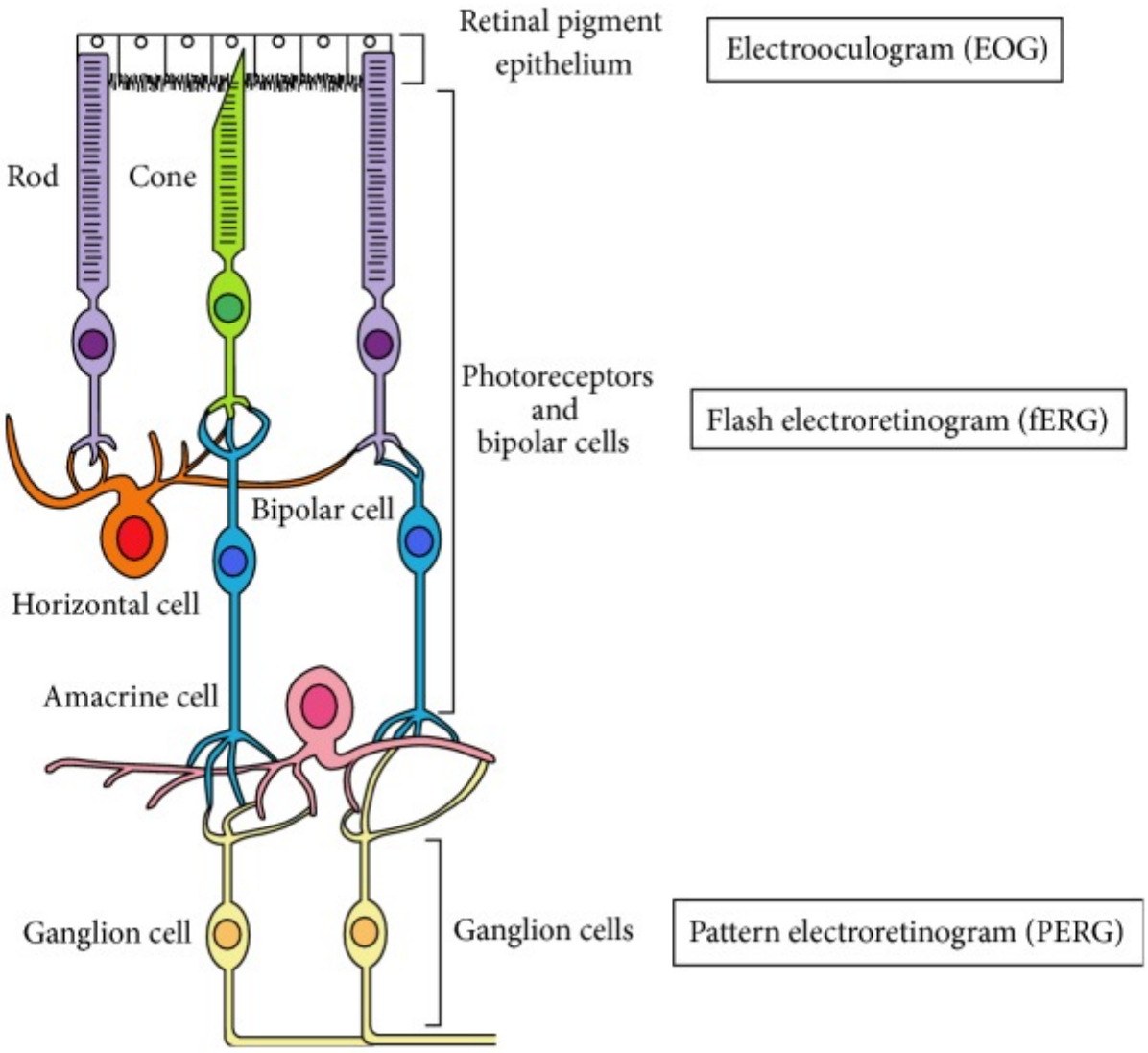
Retinal pigment epithelium
Electrooculogram (EOG)
Rod
Cone
Photoreceptors and bipolar cells
Flash electroretinogram (fERG)
Bipolar cell
Horizontal cell
Amacrine cell
Ganglion cell
Ganglion cells
Pattern electroretinogram (PERG)

CBD: Neuronal growth in retina

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Role of GPR55 during Axon Growth and Target Innervation.

Cherif H[1], Argaw A[2], Cécyre B[1], Bouchard A[1], Gagnon J[1], Javadi P[1], Desgent S[3], Mackie K[4], Bouchard JF[1].

Abstract

Guidance molecules regulate the navigation of retinal ganglion cell (RGC) projections toward targets in the visual thalamus. In this study, we demonstrate that the G-protein-coupled receptor 55 (GPR55) is expressed in the retina during development, and regulates growth cone (GC) morphology and axon growth. In vitro, neurons obtained from gpr55 knock-out (gpr55(-/-)) mouse embryos have smaller GCs, less GC filopodia, and have a decreased outgrowth compared with gpr55(+/+) neurons. When gpr55(+/+) neurons were treated with GPR55 agonists, lysophosphatidylinositol (LPI) and O-1602, we observed a chemo-attractive effect and an increase in GC size and filopodia number. In contrast, cannabidiol (CBD) decreased the GC size and filopodia number inducing chemo-repulsion. In absence of the receptor (gpr55(-/-)), no pharmacologic effects of the GPR55 ligands were observed. In vivo, compared to their wild-type (WT) littermates, gpr55(-/-) mice revealed a decreased branching in the dorsal terminal nucleus (DTN) and a lower level of eye-specific segregation of retinal projections in the superior colliculus (SC) and in the dorsal lateral geniculate nucleus (dLGN). Moreover, a single intraocular injection of LPI increased branching in the DTN, whereas treatment with CBD, an antagonist of GPR55, decreased it. These results indicate that GPR55 modulates the growth rate and the targets innervation of retinal projections and highlight, for the first time, an important role of GPR55 in axon refinement during development.

KEYWORDS:
GPR55 receptor; axon guidance; development; growth cone; retinal ganglion cell; vision
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PMCID:PMC4699829
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CBD: how it protects the retina

Invest Ophthalmol Vis Sci. 2008 Dec;49(12):5526-31. doi: 10.1167/iovs.08-2196. Epub 2008 Jul 18.

Mediation of cannabidiol anti-inflammation in the retina by equilibrative nucleoside transporter and A2A adenosine receptor.

Liou GI[1], Auchampach JA, Hillard CJ, Zhu G, Yousufzai B, Mian S, Khan S, Khalifa Y.

Abstract

PURPOSE:
Cannabidiol (CBD), a nonpsychotropic, nontoxic compound has been shown to block diabetes- and endotoxin-induced retinal damage. However, the protective mechanism of this anti-inflammatory cannabinoid is not completely understood. The goal of this study is to determine the role of adenosine signaling in retinal inflammation and its potential modulation by CBD.

METHODS:
The adenosine receptor (AR) subtypes expressed in rat retinal microglial cells were assessed by quantitative real-time RT-PCR. AR function was determined via in vitro and in vivo inflammatory models. Microglial cells or rats were treated with or without lipopolysaccharide (LPS) in the presence or absence of adenosine, adenosine receptor agonists/antagonists, or CBD. Adenosine uptake and tumor necrosis factor (TNF)-alpha release in cells or in retinas were determined.

RESULTS:
The results showed that A(2A)ARs are abundantly expressed in rat retinal microglial cells. When the cells or rats were treated with LPS, activation of the A(2A)AR was the most efficient in mediating AR agonist- or CBD-induced TNF-alpha inhibition. CBD inhibited adenosine uptake via equilibrative nucleoside transporter 1 and synergistically enhanced adenosine's TNF-alpha suppression after treatment with LPS.

CONCLUSIONS:
These results suggest that the activated A(2A)AR in the retinal microglial cells plays a major anti-inflammatory role in the retina and that CBD's anti-inflammatory effects are linked to the inhibition of adenosine uptake.
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CBD: protects against uveitis

Mol Vis. 2008;14:2190-203. Epub 2008 Dec 3.

Neuroprotective effects of cannabidiol in endotoxin-induced uveitis: critical role of p38 MAPK activation.

El-Remessy AB[1], Tang Y, Zhu G, Matragoon S, Khalifa Y, Liu EK, Liu JY, Hanson E, Mian S, Fatteh N, Liou GI.

Abstract

PURPOSE:
Degenerative retinal diseases are characterized by inflammation and microglial activation. The nonpsychoactive cannabinoid, cannabidiol (CBD), is an anti-inflammatory in models of diabetes and glaucoma. However, the cellular and molecular mechanisms are largely unknown. We tested the hypothesis that retinal inflammation and microglia activation are initiated and sustained by oxidative stress and p38 mitogen-activated protein kinase (MAPK) activation, and that CBD reduces inflammation by blocking these processes. **METHODS:** Microglial cells were isolated from retinas of newborn rats. Tumor necrosis factor (TNF)-alpha levels were estimated with ELISA. Nitric oxide (NO) was determined with a NO analyzer. Superoxide anion levels were determined by the chemiluminescence of luminol derivative. Reactive oxygen species (ROS) was estimated by measuring the cellular oxidation products of 2', 7'-dichlorofluorescin diacetate. **RESULTS:** In retinal microglial cells, treatment with lipopolysaccharide (LPS) induced immediate NADPH oxidase-generated ROS. This was followed by p38 MAPK activation and resulted in a time-dependent increase in TNF-alpha production. At a later phase, LPS induced NO, ROS, and p38 MAPK activation that peaked at 2-6 h and was accompanied by morphological change of microglia. Treatment with 1 microM CBD inhibited ROS formation and p38 MAPK activation, NO and TNF-alpha formation, and maintained cell morphology. In addition, LPS-treated rat retinas showed an accumulation of macrophages and activated microglia, significant levels of ROS and nitrotyrosine, activation of p38 MAPK, and neuronal apoptosis. These effects were blocked by treatment with 5 mg/kg CBD. **CONCLUSIONS:** Retinal inflammation and degeneration in uveitis are caused by oxidative stress. CBD exerts anti-inflammatory and neuroprotective effects by a mechanism that involves blocking oxidative stress and activation of p38 MAPK and microglia.

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CBD: diabetic retinopathy

Mol Vis. 2010 Aug 4;16:1487-95.

Cannabidiol protects retinal neurons by preserving glutamine synthetase activity in diabetes.

El-Remessy AB[1], Khalifa Y, Ola S, Ibrahim AS, Liou GI.

Abstract

PURPOSE: We have previously shown that non-psychotropic cannabidiol (CBD) protects retinal neurons in diabetic rats by inhibiting reactive oxygen species and blocking tyrosine nitration. Tyrosine nitration may inhibit glutamine synthetase (GS), causing glutamate accumulation and leading to further neuronal cell death. We propose to test the hypothesis that diabetes-induced glutamate accumulation in the retina is associated with tyrosine nitration of GS and that CBD treatment inhibits this process. **METHODS:** Sprague Dawley rats were made diabetic by streptozotocin injection and received either vehicle or CBD (10 mg/kg/2 days). After eight weeks, retinal cell death, Müller cell activation, GS tyrosine nitration, and GS activity were determined **RESULTS:** Diabetes causes significant increases in retinal oxidative and nitrative stress compared with controls. These effects were associated with Müller cell activation and dysfunction as well as with impaired GS activity and tyrosine nitration of GS. Cannabidiol treatment reversed these effects. Retinal neuronal death was indicated by numerous terminal deoxynucleotidyl transferase dUTP nick end-labeling (TUNEL)-labeled cells in diabetic rats compared with untreated controls or CBD-treated rats. **CONCLUSIONS:** These results suggest that diabetes-induced tyrosine nitration impairs GS activity and that CBD preserves GS activity and retinal neurons by blocking tyrosine nitration.
PMID: 20806080 PMCID: PMC2925907 [Indexed for MEDLINE] Free PMC Article

CBD: acts indirectly through endothelia

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Cannabinoid and lipid-mediated vasorelaxation in retinal microvasculature.

MacIntyre J[1], Dong A[1], Straiker A[2], Zhu J[1], Howlett SE[1], Bagher A[1], Denovan-Wright E[1], Yu DY[3], Kelly ME[4].

Abstract

The endocannabinoid system plays a role in regulation of vasoactivity in the peripheral vasculature; however, little is known about its role in regulation of the CNS microvasculature. This study investigated the pharmacology of cannabinoids and cannabimimetic lipids in the retinal microvasculature, a CNS vascular bed that is autoregulated. Vessel diameter (edge detector) and calcium transients (fura-2) were recorded from segments of retinal microvasculature isolated from adult, male Fischer 344 rats. Results showed that abnormal cannabidiol (Abn-CBD), an agonist at the putative endothelial cannabinoid receptor, CBe, inhibited endothelin 1 (ET-1) induced vasoconstriction in retinal arterioles. These actions of Abn-CBD were independent of CB1/CB2 receptors and were not mediated by agonists for GPR55 or affected by nitric oxide synthase (NOS) inhibition. However, the vasorelaxant effects of Abn-CBD were abolished when the endothelium was removed and were inhibited by the small Ca(2+)-sensitive K channel (SKCa) blocker, apamin. The effects of the endogenous endocannabinoid metabolite, N-arachidonyl glycine (NAGly), a putative agonist for GPR18, were virtually identical to those of Abn-CBD. GPR18 mRNA and protein were present in the retina, and immunohistochemistry demonstrated that GPR18 was localized to the endothelium of retinal vessels. These findings demonstrate that Abn-CBD and NAGly inhibit ET-1 induced vasoconstriction in retinal arterioles by an endothelium-dependent signaling mechanism that involves SKCa channels. The endothelial localization of GPR18 suggests that GPR18 could contribute to cannabinoid and lipid-mediated retinal vasoactivity.

KEYWORDS: Cannabinoid; GPR18; Microvasculature; Retina
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