

Retinal Cannabinoids[☆]

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Glossary

Age-related macular degeneration (AMD) It comprises a variety of diseases, mainly of the elderly, that involves loss of vision in the central region of the retina.

Endocannabinoids Endogenous ligands of cannabinoid receptors.

Monoamine oxidase An enzyme that degrades monoamines such as dopamine, noradrenaline, adrenaline, and serotonin.

Snellen acuity A test of visual acuity that uses 11 lines of block letters with the first line consisting of one very large

letter and subsequent rows having increasing numbers of letters that decrease in size.

Transient receptor potential vanilloid 1 (TRPV1) An ionotropic receptor that increases intracellular calcium either by entry through the plasma membrane or from intracellular stores. It is activated by noxious heat, capsaicin, and the endocannabinoid, anandamide.

Vernier acuity A test of visual acuity that measures the ability to detect amalignment among two line segments or gratings.

Marijuana and the Endocannabinoids

The active component of the marijuana plant *Cannabis sativa*, Δ^9 -tetrahydrocannabinol (THC), mimics endogenous chemicals, named endocannabinoids (eCBs), that activate membrane receptors. eCBs include a variety of amide, ester, and ether derivatives of arachidonic acid. The most widely studied of these are arachidonoyl ethanolamide (anandamide, AEA) and *sn*-2 arachidonoyl glycerol (2-AG) (Fig. 1). Other eCBs have been identified with varying degrees of affinity for cannabinoid receptors, and also compete with AEA and 2-AG for metabolizing enzymes. In this way, they modulate activity by competition at the receptors or by affecting substrate availability for metabolism.

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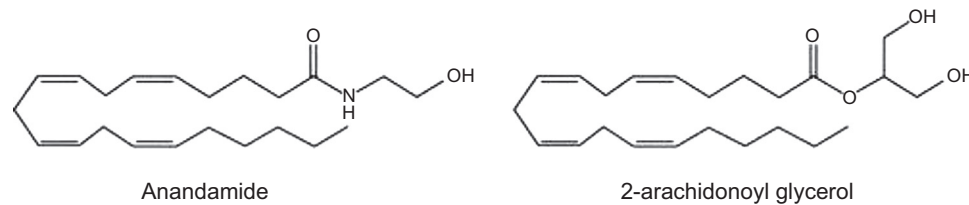


Figure 1 Chemical structures of endocannabinoids: arachidonoyl-ethanolamide (anandamide, AEA) and 2-arachidonoyl glycerol (2-AG).

Synthesis and Release

Unlike water-soluble neurotransmitters, AEA and 2-AG are lipophilic and not stored in synaptic vesicles. Rather, membrane phospholipids are metabolized on demand to liberate AEA and 2-AG by calcium-dependent phospholipases. The precursor of AEA is *N*-arachidonoylphosphatidylethanolamine (NAPE), formed by calcium-dependent transfer of arachidonic acid from arachidonoylphosphatidylcholine to phosphatidylethanolamine (PE). There are multiple pathways for AEA liberation from the membrane. First, NAPE is hydrolyzed by phospholipase D (PLD) to release AEA and phosphatidic acid. Second, NAPE is hydrolyzed to *N*-acyl-lysophospholipase A₁/A₂; then, AEA is released by lysophospholipase D. Third, phospholipase C (PLC) cleaves NAPE to generate phosphoanandamide, which is dephosphorylated to liberate AEA. The PLC pathway may be involved in the on-demand synthesis of AEA rather than in maintaining basal tissue levels of AEA.

The primary pathway for 2-AG synthesis involves hydrolysis of diacylglycerol (DAG) by DAG lipase isozymes, DAGL α and DAGL β . DAG may be produced by the PLC β -catalyzed hydrolysis of phosphatidylinositol or hydrolysis of phosphatidic acid by a phosphohydrolase. AEA and 2-AG freely diffuse within the membrane where they interact with the active sites of degradative enzymes and receptors. AEA binds reversibly to serum albumin, and it is likely that such binding is critical for the movement of AEA and 2-AG in blood, the extracellular matrix, and the cytoplasm. The presence and localization of AEA and 2-AG are inferred from the distribution of receptors, synthesizing and inactivating enzymes as well as physiological effects on identified cells.

Inactivation

AEA and 2-AG are inactivated following intracellular accumulation by fatty acid amide hydrolase (FAAH), monoacylglycerol lipase (MAGL), cyclooxygenase-2 (COX-2), and lipoxygenase (LOX). AEA and 2-AG are hydrolyzed by FAAH into AA and ethanolamine or glycerol, respectively. 2-AG, but not AEA, is hydrolyzed by MAGL. Following hydrolysis of AEA or 2-AG, AA is incorporated into membrane phospholipids. COX-2 oxidizes arachidonic acid, AEA, and 2-AG to prostamides or prostaglandin glyceryl esters, leading to prostaglandins. In addition, oxidation of AA by LOX produces 12-(*S*)-hydroperoxyeicosatetraenoic acid (15-(*S*)-HPETE), 5-(*S*)-HETE, and leukotriene B₄, all of which are agonists of TRPV1 receptors (Fig. 2). The effects of AEA and 2-AG are modulated by the balance of metabolic enzymes that is specific to each cell type.

Receptors

Effects of cannabinoids are mediated by metabotropic (G-protein-coupled receptors (GPCRs)) and ionotropic (ion channel) receptors. In general, activation of cannabinoid 1 receptors (CB1Rs), via heterotrimeric guanosine-5'-triphosphate (GTP)-binding proteins G_{i/o} (G_{i/o}), modulates voltage-gated K⁺ and Ca²⁺ conductances, resulting in a reduction of neurotransmitter release, particularly γ -aminobutyric acid (GABA) and glutamate. CB2 receptors, which also signal through G_{i/o}, are expressed in cells of the immune system and the central nervous system (CNS), particularly in astrocytes and microglia. There is evidence for additional cannabinoid receptors, such as GPR55 and GPR18. AEA, but not 2-AG, activates the ionotropic transient receptor potential vanilloid 1 (TRPV1) that increases intracellular calcium either by entry through the plasma membrane or from intracellular stores. Prostamides and prostaglandin glycerol esters, produced by eCB oxidation by COX-2, bind to a variety of prostaglandin receptors. eCBs are ligands for peroxisome proliferator-activated receptors (PPARs), members of the nuclear receptor superfamily that are involved in lipid metabolism, insulin sensitivity, regulation of inflammation, and cell proliferation.

Distribution and Function

Cannabinoid receptors are considered to be the most numerous GPCRs in the brain. eCBs, their receptors, and synthesizing and metabolizing enzymes are expressed in several brain regions. AEA and 2-AG have short and long-term effects on synaptic plasticity and neuroprotection. The effects depend largely on retrograde transmission in which postsynaptic dendrites release an eCB that binds to presynaptic CB1Rs to reduce transmitter release. Retrograde release of eCBs is evoked by two mechanisms. In a voltage-dependent mechanism, depolarization of postsynaptic dendrites by L-glutamate opens voltage-gated calcium channels. The increase in intracellular Ca²⁺ activates Ca-dependent PLD to release an eCB. A second mechanism involves activation of heterotrimeric GTP-binding protein G_{q/11} (G_{q/11}) coupled metabotropic receptors, usually group I metabotropic glutamate receptors (mGluRs), mGluR1 and mGluR5, and muscarinic receptors (M1 and M3). eCBs are released from the plasma membrane by enzymatic cascades that may or may not release calcium from intracellular stores. The eCB-induced reduction of presynaptic glutamate and GABA release contributes to synaptic plasticity, while the reduction of glutamate release inhibits excitotoxicity following ischemia.

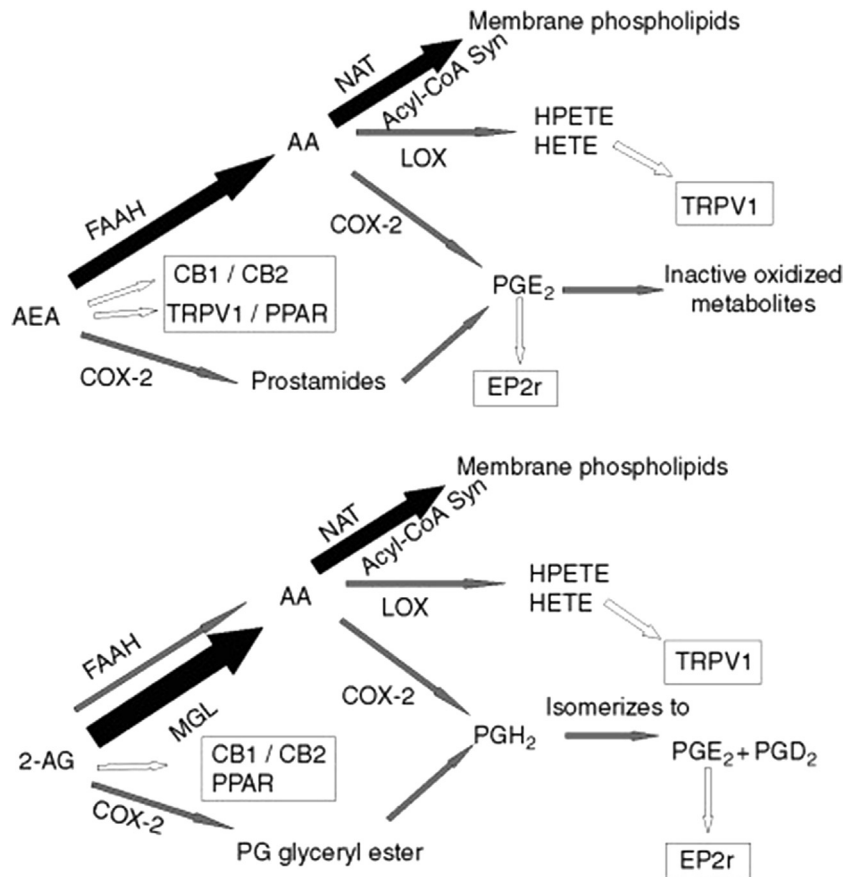


Figure 2 This schematic illustrates some of the metabolic pathways for the degradation of AEA and 2-AG. In the dominant pathways (*bold arrows*), AEA and 2-AG are hydrolyzed to arachidonic acid (AA), and then rapidly incorporated into membrane phospholipids via *N*-acyltransferase (NAT) and acyl-Coenzyme A synthetase. Lesser pathways (*shaded arrows*) involve oxidation by cyclooxygenase-2 (COX-2) of AEA, 2-AG, and AA to prostaglandins (PGE₂ and PGD₂). Additionally, AA may be oxidized by lipoxygenase (LOX) to 12-(S)- and 15-(S)-HPETE and 5-(S)-HETE. *Hollow arrows* show that AEA and 2-AG are endoligands for CB₁, CB₂, and PPAR receptors, while AEA also activates TRPV₁ receptors. Metabolites of COX-2 oxidation activate EP₂ receptors, and metabolites of LOX oxidation activate TRPV₁ receptors.

Cannabinoids and Ocular Tissues

Marijuana induces conjunctival vasodilation and reduces intraocular pressure (IOP). These effects are mediated locally by eCBs as demonstrated in the ciliary body, iris, choroid, and trabecular meshwork in mammalian tissues. THC, as low as 10^{-12} M, increases monoamine oxidase activity in the bovine trabecular meshwork, choroid, and ciliary processes but not in the iris. Hydrolysis of AEA has been measured in the porcine iris, choroid, lacrimal gland, and optic nerve. CB₁ receptor has been detected in the ciliary body, trabecular meshwork, and conjunctival epithelium of rat, mouse, bovine, and human. The bovine corneal epithelial cells express CB₁R, MAGL, α/β hydrolase domain 6 (ABHD6), α/β hydrolase domain 12 (ABHD12) and NAPE-PLD mRNA. AEA and 2-AG have been measured by gas chromatography in human ocular tissues.

The content of eCBs varies in certain disease states, suggesting the importance of eCBs in maintaining ocular homeostasis. For example, 2-AG levels are lower in the ciliary body of patients with glaucoma. However, in diabetic retinopathy, there are higher levels of 2-AG only in the iris, and increased levels of AEA in the retina, ciliary body, and cornea. Eyes of patients with age-related macular degeneration (AMD) also show increases of AEA in the retina, choroid, ciliary body, and cornea. Topically applied AEA reduces IOP by activation of CB₁R and activation of the prostaglandin E₂ receptor after conversion of AEA to prostamides. Administration of either AEA or THC to human nonpigmented epithelium (NPE) cells induces COX-2 expression, indicating a relationship among prostaglandins, COX-2, and eCBs in lowering IOP. In addition, EP₂ receptors have been localized in the NPE of mouse, porcine, and human ciliary body.

Cannabinoids—Retinal Anatomy

Early studies of the effects of cannabis on vision were performed in concert with the effects of alcohol in order to examine the influence on visual motor behaviors as they related to driving. Anecdotal reports showed that Jamaican and Moroccan fishermen smoke

marijuana to improve dim light vision when fishing at night. Indeed, an increased night vision was measured and it was suggested that these effects occurred at the retinal level. Acute effects on vision are subtle and include blurred and double vision, a reduction in Vernier and Snellen acuity, alterations in color discrimination, an increase in photosensitivity and an increase in recovery from foveal glare. It is unlikely that all of these effects of marijuana are due to cortical or preretinal sites because processes of light-dark adaptation take place in the retina. Knockout mice that lack CB2R exhibit increased a-wave amplitudes under scotopic conditions of electroretinogram recordings. Since the a-wave originates from the activity of photoreceptors, the stimulation of CB2R could affect these cells. The absence of CB2R also produced a different light adaptation pattern in photopic conditions. The lack of CB1R did not affect the retinal response.

Furthermore, vervet monkeys had their retinal function affected by the intravitreal injection of specific inverse agonists of CB1R and CB2R. For instance, the injection of AM251 increased the photopic a-wave amplitude at high flash intensities, whereas AM630 increased the amplitude of both photopic a- and b-waves. In scotopic conditions, both drugs increased the amplitude of the b-wave while not altering the a-wave amplitude.

On the other hand, the injection of selective GPR55 agonist and antagonist caused opposite effects compared to those of CB1R and CB2R. The intravitreal administration of the GPR55 agonist lysophosphatidylglucoside (LPG) increased the amplitude of the scotopic b-wave while the injection of the antagonist CID16020046 decreased it.

Localization—Cannabinoid Receptors

CB1R was extensively studied in the retina of various species using techniques such as in situ hybridization, reverse transcription polymerase chain reaction (RT-PCR), western blot or immunohistochemistry. CB1R was first localized in the ganglion cell layer (GCL) and inner nuclear layer (INL) of the rat retina. Since then, CB1R expression was detected in the retinas of human, monkey, mouse, rat, chick, salamander and goldfish with a similar labeling in the outer plexiform layer (OPL), inner plexiform layer (IPL) and GCL. Briefly, CB1R is expressed in the inner and outer segments of photoreceptors with a strong labeling in the cone pedicles; in the membrane but not in dendrites of horizontal cells; in the dendrites, cell body axons of rod bipolar cells; in GABAergic and other amacrine cells; in the synapses of rod and cone bipolar cells; in the cell body and fibers of ganglion cells. CB1R is also expressed in Müller cells but only for the goldfish.

The localization of CB2R in the retina has been less extensively studied than CB1R. It was first believed that CB2R was not expressed in the embryonic and adult retina. Then, CB2R mRNA localization was shown in photoreceptors, INL and GCL of the rat retina. Subsequent studies confirmed the presence of CB2R in the retina, but with a differential expression between species. CB2R is expressed in the inner and outer segments of photoreceptors, with an absence of labeling in the cone pedicles; in the membrane of the soma and in the dendrites of horizontal cells; in the membrane of the some of cone and rod bipolar cells, and in axons of rod bipolar cells; in unspecified subtypes of amacrine cells; in the soma of ganglion cells. CB2R is absent from Müller cells for most species, while in the vervet monkey it is exclusively present in these cells.

Localization—Synthesizing and Catabolic Enzymes

The synthesizing enzyme DAGL α is present in the synaptic layers of the mouse retina. Indeed, DAGL α is localized in postsynaptic terminals of type 1 OFF cone bipolar cells as well as in the dendrites of unidentified bipolar cells. DAGL α expression was recently found in the rat retina, as its presence was detected in cone and rod photoreceptors, horizontal cells' processes, some cone bipolar cells' axonal connections, amacrine cells, and ganglion cells. DAGL β is exclusively expressed in retinal blood vessels.

The hydrolyzing enzyme FAAH is localized in the retina of mice, rats and primates. It was expressed in cone photoreceptors, axon terminals of rods, horizontal cells, rod and cone bipolar cells, dopamine amacrine cells, dendrites of starburst amacrine cells and some ganglion cells of the rat retina.

The metabolizing enzyme MAGL is expressed in the mouse and rat retina. In the OPL, MAGL is found in rod spherules and cone pedicles. MAGL is mainly expressed in rod spherules, cone pedicles, amacrine cells, Müller cells and in the axonal connections of type 2 cone bipolar cells.

The expression of the metabolizing ABHD6, a serine hydrolase, was reported in the mouse retina. It is localized in GABAergic amacrine cells, ganglion cells, and in the dendrites of ganglion cells or displaced amacrine cells.

As for the synthesizing enzyme NAPE-PLD, a major synthesizing enzyme of AEA and OEA from lipids, its retinal expression was shown but not its distribution.

Cannabinoids—Retinal Physiology

Effects on Transmitter Release

In the retina, cannabinoids inhibit the release of various neurotransmitters. Stimulation of CB1Rs via G_{i/o} reduces voltage- and Ca²⁺-evoked release of noradrenaline and dopamine in guinea pig retina. A first proof of concept for the importance of CB1R-mediated modulation of glutamate release came from the inhibition by agonists of CB1R, but not CB2R of [³H] D-aspartate (a substitute of L-glutamate for high-affinity uptake sites) release following ischemia or K⁺ channel activation in isolated bovine retina. Uptake of [³H] D-aspartate identifies high-affinity uptake sites for L-glutamate and L-aspartate in photoreceptors, a small

percentage of ganglion cells and Müller's cells. Some evidence also suggests a regulatory effect on GABA_A receptor-mediated inward currents from WIN55,212-2, a synthetic cannabinoid with similar affinity to both CB1R and CB2R, on low spontaneous transmission in embryonic chick amacrine cells. The effect of WIN55,212-2 is not mediated by CB1R.

Effects on Ganglion Cells

An in vitro study showed that CB1R/CB2R activation with WIN55,212-2 causes a partial inhibition of high-voltage activated Ca²⁺ channels and thus decreasing the excitability of cultured rat RGCs. Another report revealed that activation of cannabinoid receptors with the same agonist caused a significant reversible reduction in the frequency of spontaneous postsynaptic currents (sPSCs) in RGCs of adult and young mice. WIN55,212-2, AEA, the selective CB1R agonist arachidonoyl-2-chloroethylamide (ACEA), and the CB2R agonist CB65 inhibit I_K via the tetraethylammonium (TEA)-sensitive K(+) current component in rat RGCs. These effects could not be reversed by the CB1R inverse agonists AM251/SR141716A nor by the CB2R inverse agonist AM630 although both CB1Rs and CB2Rs are present on ganglion cells. The authors suggest that eCBs modulate potassium channels in rat RGCs in a receptor-independent manner, as demonstrated in other cells.

Effects on Amacrine Cells

The neuroprotective effects of endogenous and synthetic cannabinoids on the viability of amacrine cells were studied using an in vivo AMPA excitotoxicity model of retinal neurodegeneration. AEA, HU-210 and methanandamide (a stable synthetic chiral analogue of AEA) afforded partial recovery following the AMPA-induced excitotoxicity of both bNOS-positive and cholinergic amacrine cells. This neuroprotection is mediated by a mechanism involving CB1R but not CB2R, and PI3K/Akt and/or MEK/ERK_{1/2} signaling pathways.

Effects on Bipolar Cells

CB1R-mediated inhibition of L-type calcium (I_{Ca}) and delayed rectifier (I_K) currents has been reported for ON-bipolar cells of salamander and goldfish. As yet there are no data on OFF-bipolar cells. The agonist WIN55,212-2 reversely inhibited I_{Ca} in salamander bipolar cells. On the goldfish large ON-type bipolar cells, the activation of CB1R and CB2R inhibited I_K , and this inhibition could be reversed by using an inverse agonist for CB1R. As this inverse agonist did not cause by itself much increase in the I_K of some ON bipolar cells and no increase on others, an eCB modulating tone present in this area remains unclear. This lack of direct modulation of bipolar cells by cannabinoids does not necessarily translate into no cannabinoid-mediated mechanism for these cells. Retrograde signaling from ganglion cells is still a plausible mechanism and was first demonstrated for 2-AG.

WIN55212-2 also inhibits the enhancement in I_K seen following the activation of D1 receptors. It has thus been proposed that the cannabinoid and dopaminergic systems have opposite properties on bipolar cells. A CB1R inverse agonist and a pre-treatment with *pertussis toxin* could both block this mechanism, although WIN55,212-2 by itself did not cause an increase in conductivity on I_K . Cannabinoids effects on ON bipolar cells have thus been associated with a tonic effect whereas D1-mediated effects have been described as phasic.

Effects on Photoreceptors

Different effects on rod and cone photoreceptors have been reported for the salamander and goldfish following WIN55,212-2 addition, with a potential biphasic response based on concentration for the goldfish. Delayed rectifier currents (I_K) were suppressed by WIN55,212-2 in cones and rods, whereas Ca²⁺ currents (I_{Ca}) were enhanced in rods and suppressed in cones, which could potentially be translated to an increased transmitter release, thus reducing light sensitivity. A cannabinoid-mediated retrograde suppression of membrane currents via 2-AG release on goldfish cones in retinal slices was also tested by Fan and Yazulla. These authors found the existence of a retrograde transmission in cones, with bipolar cell dendrites as the likely source of 2-AG. Furthermore, the retrograde suppression of I_K is mediated by Ca²⁺ dependent release of 2-AG from bipolar cell dendrites.

Cannabinoids also preserved cone and rod structure, as well as function and synaptic connectivity with postsynaptic neurons in a transgenic model for autosomal dominant retinitis pigmentosa. Indeed, HU-210, a more potent and long lasting synthetic analogue of THC, increased the scotopic a- and b-wave amplitudes in treated animals, and preserved photoreceptor degeneration and synaptic contacts between photoreceptors and bipolar or horizontal cells.

Cannabinoids—Development and Neuroprotection

Development

As shown in other systems, eCBs are well known modulators of synaptic transmission and neuronal plasticity, mostly via pre-synaptic inhibitory mechanisms. The impact of the eCB system during CNS development has been documented in the last decade.

The eCB system regulates the proliferation, migration, specification and survival of neural progenitors, dictates the differentiation of neurons, and controls the establishment of synaptic connections. The importance of eCBs during neuronal development is confirmed by the demonstration that maternal marijuana smoking or cannabinoid consumption during pregnancy causes cognitive, motor and social deficit. In addition, 2-AG levels in the CNS progressively increase during embryonic development, and then peak just after birth. However, eCB-mediated changes in developmental processes are not only limited to the higher brain structures, they can also affect the development of the retina.

CB1R mRNA is expressed in the rat retina as early as embryonic age 13 (E13), which is a good indicator of its possible developmental implication. By E15 to E17, the GCL expresses CB1R mRNA and, from E20-E21, it is present in the GCL as well as in an unspecified cell layer that appears to be the INL. The CB1R is also expressed in the chick retinotectal system as soon as E4, with labeling in ganglion cells and the IPL and INL. The CB1R, FAAH, DAGL α and MAGL were also detected during postnatal development of the rat retina. The CB1R is present in ganglion cells, amacrine, horizontal and mitotic cells at P1. During retinal development, a transient expression of CB1R was reported in cones and bipolar cells. Moreover, FAAH was found at P1 in ganglion and cholinergic amacrine cells, and in the course of development, it appeared in cones, horizontal and bipolar cells. FAAH is transiently expressed in horizontal, cholinergic amacrine cells and cone bipolar cells, showing an important redistribution of the enzyme during postnatal retinal development. Additionally, at P1, DAGL α is expressed early in retinal development where it is present in cone and rod photoreceptors, horizontal, amacrine, and ganglion cells. MAGL expression is detected at low levels from P1 to P9, and then gradually increases onto adulthood. MAGL is constantly found in amacrine and Müller cells from P11 onto the adult age. Overall, the expression of DAGL α combined with the absence of MAGL expression in early postnatal development of the retina suggests that 2-AG levels could be elevated and thus play an active role in retinal development. Despite an important body of literature currently available on the involvement of eCBs in developmental functions, only few studies focused on the impact of cannabinoids in retinal development. It is to be noted that retinas from *cnr1*-KO and *cnr2*-KO animals do not show obvious changes in retinal structures, as their thickness and morphology were similar to wild-type animals. For these reasons, it is too early to hypothesize on the role of eCBs in retinal development.

The TRPV1 is also present in the rat retina from E19 onto adulthood. From E19 to P5, the TRPV1 is detected in the neuroblastic layer, in the pigment epithelium and in a few small cell bodies in the GCL. From P15 onto adulthood, TRPV1 is also present in all cell layers with prominent labeling in the IPL and GCL. The precise cellular expression of TRPV1 in the retina is still incomplete. So far, TRPV1 has been located in RGC and microglial cells.

No studies have yet reported the expression of GPR18 in the developing retina. Recent studies from our group have so far shown that GPR55 mRNA and protein are expressed in the retina of newly born mice, more specifically in RGCs.

Regeneration

The end point of several retinal degenerative diseases is the ganglion cell death by apoptosis that may be caused by a multitude of mechanisms. In addition to their effect at the level of ionic channels, eCBs show neuroprotective properties. For example, in a model of glaucoma, CB1R agonists as well as inhibition of FAAH protect ganglion cells from glutamate excitotoxicity and ischemia caused by increased IOP. In addition, blockade of FAAH produces neuroprotective effects on RGCs in a rat model of optic nerve axotomy through a CB1R-mediated mechanism.

Conclusion

eCBs are the one of the most recently described neuromodulators to be studied in neural and non-neural tissues. Their extensive expression in the nervous system and peripheral organ systems highlights the range of their actions, and their potential in therapeutic applications. Strong evidence now suggests a wide distribution of eCBs, receptors and enzymatic machinery in key structures of the visual system, including a strong presence in the retina. Although a clear picture can ascertain of the specific effects cannabinoids can have in the retina itself, or the visual system as a whole, various mechanisms in specific cellular structures of the retina have now been reported. The cannabinoid system also appears to have several roles in neuronal survival and apoptosis in the retina, and could be linked with many other ocular disorders. However, their specific mechanisms in retinal development, neuroplasticity, and neuroprotection need to be more thoroughly investigated.

Further Reading

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- Hu, S.S., Arnold, A., Hutchens, J.M., Radicke, J., Cravatt, B.F., Wager-Miller, J., Mackie, K., Straiker, A., 2010. Architecture of cannabinoid signaling in mouse retina. *J. Comp. Neurol.* 518 (18), 3848–3866.
- Yazulla, S., 2008. Endocannabinoids in the retina: from marijuana to neuroprotection. *Prog. Retin. Eye Res.* 27 (5), 501–526.

Relevant Websites

<http://cannabinoidsociety.org/> – This is the Official Website of the International Cannabinoid Research Society. It Provides Updates and Background Information on All Aspect of the Endocannabinoid Field.

<http://webvision.med.utah.edu/> – This Website From the University of Utah Provides Extensive Coverage of Retinal Anatomy and Physiology, Particularly in Mammals.