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The endocannabinoid system in the visual process

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ABSTRACT

An increasing number of articles have been published in recent years on the role of the endocannabinoid system (ECS) in different cellular processes. Here we review and discuss findings on the ECS in visual processing and present the structure of the retina. We focus on the photoreceptor cell and the events that occur in the phototransduction process, considering the conformational light-induced changes in rhodopsin and in particular its chromophore (11-*cis* retinal). Advances in the distribution and function of the endocannabinoid system in the retina with special reference to its function in the physiological light process are also addressed, as is the relationship between rhodopsin, retinal pathologies and the ECS.

1. Retina

1.1. Retinal structure

The visual experience is based on information processed by the neural circuits of the eye, the retina being responsible for processing and transmitting the light signal to the brain through the optic nerve [1]. The retina is composed of neuronal cells (photoreceptors, horizontal, bipolar, amacrine and ganglion) organized in layers (Fig. 1A). Light passes through these layers of retinal cells to reach the photoreceptor cells. In mammals, light is perceived by rods, cones and by a subclass of retinal ganglion cells that express the photopigment melanopsin that renders them intrinsically photosensitive (ipRGCs) [2]. These photoreceptors are distinguished by their morphology and sensitivity to light. The rods are elongated and their outer segment is cylindrical; they can signal the absorption of a single photon through the rod-specific rhodopsin with a peak absorption of ~500 nm and are responsible for vision at low light intensities (scotopic vision) such as night vision. The cones are shorter and conical in their outer segment, they operate at high light intensities (photopic vision) such as during daytime vision and are involved in color vision. They have an absorption spectrum for visible light of ~350–560 nm and contain one of three different conopsins with absorption at wavelengths of 419 nm, 531 nm and 559 nm, for blue, green and red, respectively [3–5]. ipRGCs reach a light absorption maximum for wavelengths of blue light about 480 nm [6]. The ipRGCs responses to light include the synchronization of the internal clock with the day/-night cycle, the regulation of sleep-wake cycles, the pupillary light reflex, the modulation of mood and the participation in some aspects of vision [7–10].

1.2. Photoreceptor cell structure, composition, and renewal

The human retina contains 120 million rod cells and all photoreceptors have a common structure composed of five regions: outer segment (OS), connecting cilium (CC), inner segment (IS), nuclear region and synaptic terminal (ST) (Fig. 1B). The OS is the photosensitive region where the phototransduction process occurs. The CC connects the OS with the IS, allowing for the trafficking of specific proteins to the OS. The IS contains subcellular organelles with metabolic and biosynthetic machinery. The nuclear region is continuous with the IS and houses the nucleus. The photoreceptor terminates in the ST, where the neurotransmitter glutamate is released from photoreceptors to bipolar cells and other secondary neurons.

The OS of the rod cell is responsible for initiating the vision event in response to light stimuli [11,12]. It contains approximately 1000 flattened disk membranes with more than 100 molecules of rhodopsin per disk. Disks contain the visual pigment rhodopsin (opsin + 11-cis-retinal chromophore), peripheral proteins such as transducin in its heterotrimeric state (Tαβγ), the protein complex that regulates G-protein signaling (RGS9), phosphodiesterase 6 (PDE), calcium-binding protein

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complex (GCAP-Ca2^{+}) bound to guanylyl cyclase (GC); and Na^{+} and Ca^{2+} channels triggered by cyclic nucleotides (CNG) and the ion exchangers, Na^{+}, Ca^{2+} and K^{+} (NCKX1) in the plasma membrane (see review in Molday and Moritz, 2015) [13].

The molecular components of OS are synthesized in the IS and assembled as membranous disks at its base. The OS are continuously renewed, with aged membranes removed at the distal end by phagocytosis and new membranes added at the proximal end through OS disk morphogenesis. OS are adjacent to the retinal pigment epithelium (RPE), these cells being essential for the renewal and survival of the photoreceptors. The disk membranes, where the visual pigment rhodopsin resides, are composed of mol% of phosphatidylcholine (PC) (~45), phosphatidylethanolamine (PE) (~41), phosphatidylserine (PS) (~13) and phosphatidylinositol (PI) (~2) [14].

Disk membranes have a higher PE content than plasma membranes and their lipids present a high content of polyunsaturated fatty acids such as docosahexaenoic acid (DHA) [15]. The fatty acid composition provides membrane disks with high fluidity, which is compromised by the cholesterol content (5–30 mol%) [16]. It is well established that the fluidity of the disk membrane confers an adequate environment for the correct functioning of the visual cycle (revised in O. Soubias and K. Gawrisch, 2012) [17]. In this sense, the lipids surrounding rhodopsin are critical to its function and facilitate the displacement of Metarhodopsin I (MI) to Metarhodopsin II (MII), a conformation that interacts with transducin (see next section) [18]. Cholesterol on the other hand favors MI conformation, preventing the phototransduction process [19].

The RPE, a postmitotic epithelial cell monolayer, is responsible for the renewal of the OS, engulfing the old disks and thus keeping the OS length constant. It furthermore provides nutrients from the bloodstream, stores vitamin A and recycles the all-trans retinal chromophore [20]. Several studies have shown a circadian control of OS discs phagocytosis, observing a peak 2 hrs after light onset which persists in constant darkness [21,22], independently of the brain circadian clock [23] and possibly regulated by the RPE circadian clock [24,25].

2. Phototransduction

2.1. Rhodopsins

Since rhodopsin is a key player in the visual process, some fundamental aspects of this receptor protein will be discussed before referring to phototransduction.

In general terms, rhodopsins transduce light energy [26,27]. Microbial rhodopsins use light energy to transport ions across the membrane [28]. Animal rhodopsins carry out visual and non-visual functions, maintain circadian rhythm, and act as isomerases [29–32].

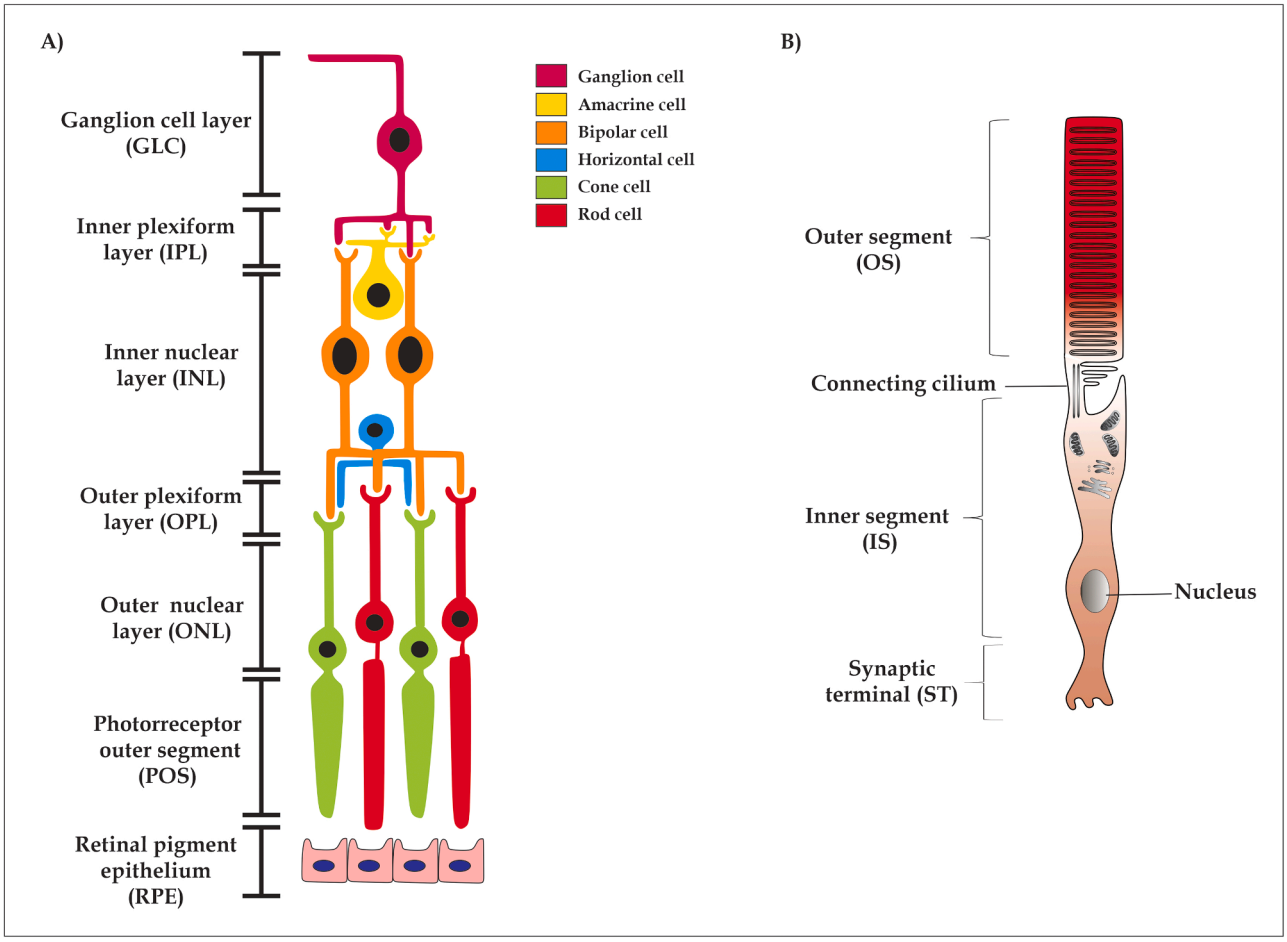

Fig. 1. Retina organization (A) and rod photoreceptor cell structure (B) Panel A shows the layers that make up the retina (left) and its different cell types (right). The retina is a complex structure comprising several types of cells distributed in layers: the outer nuclear layer, the inner nuclear layer and the ganglion cells, each in turn separated by two layers, the external and internal plexiforms. Photoreceptors are located in the posterior retina in contact with the pigment epithelium. The light information captured by rod cells is processed and transferred through the different retinal layers and sent to the visual cortex by the optic nerve, comprising the axons of the ganglion cells. Panel B shows a scheme of the rod photoreceptor cell, comprising five regions: outer segment (OS), connecting cilium (CC), inner segment (IS), nuclear region and synaptic terminal (ST). OS is where the phototransduction process occurs. OS and IS connect through the CC. IS is the site where outer segment lipids and proteins are synthesized. The nuclear region is continuous with the IS and houses the nucleus. ST releases neurotransmitter glutamate from photoreceptors to bipolar cells and other secondary neurons.

Rhodopsins are made up of an apoprotein to which a chromophore is attached by covalent bonding, such as retinal in the case of retinylidene proteins, bilin in biliproteins, and flavin in flavoproteins [33]. Microbial- and animal rhodopsins have a common structure consisting of seven transmembrane α-helices (TM) [34]. Retinal is linked by a Schiff base to a lysine of the TM7 segment [35,36]. The Schiff base changes from a protonated to an unprotonated state as rhodopsin fulfills its function. Although all rhodopsins undergo a photocycle directly related to their function [37], there is a difference between microbial and animal rhodopsins: light induces retinal isomerization from all-trans to 13-*cis* in microbial rhodopsins and from 11-*cis* to all-trans in animal rhodopsins [38]. Animal rhodopsin photoisomerization generates a series of intermediates that produce opsin release from its chromophore which is then reisomerized [39,40].

Rod outer segment rhodopsin is synthesized in the endoplasmic reticulum and further modified in the Golgi, both organelles located in the IS, far from the OS. Rhodopsin is delivered to the OS by vesicular transport within the connecting cilium, and these intracellular vesicles then directly coalesce into the disk endomembranes [41–48]. Rhodopsin's terminal carboxyl sequence plays a fundamental role in this transport, the V(valine)XP(proline)X-COOH sequence interacting with the light chain of the molecular motor cytoplasmic dynein [49–51]. It has been reported that mutations in this sequence drive rhodopsin to regions other than the OS, such as the IS or the ST [52–56]. Accumulation of mutant rhodopsin leads to apoptotic photoreceptor cell death and retinal degeneration [57]. Although the carboxyl-terminal sequence is important in terms of rhodopsin's final destination, amino terminal glicosylation [58,59], its palmitoylation [60] and the TM3 and TM5 connection help maintain the rhodopsin structure in its correct conformation [61]; this favors a Meta II state and consequently transducin activation [62,63].

2.2. Visual process

In the rod photoactivation state, a photon of energy is absorbed by the rhodopsin chromophore in its 11-cis-retinal configuration, undergoing a conformational change to all-trans-retinal (activated rhodopsin, R*) [64].11-cis-retinal acts as an inverse agonist suppressing the constitutive activity of the receptor [65] while all-trans-retinal acts as full agonist [66]. This change in the chromophore involves photoreceptor transition from the inactive Meta I state to the active Meta II state, (see review in Ernst et al., 2014) [67]. Meta II binds and activates transducin and triggers a series of reactions, converting the light signal into an electrical signal, a process called phototransduction. The decay of the Meta II state of rhodopsin is accompanied by the release of all-trans retinal, which leaves the receptor in the inactive apoprotein (opsin) form [68,69]. Meta II activates GDP for GTP exchange in the alpha subunit (Tα) of transducin. GTP-bound Tα dissociates from Tβγ subunits and activates PDE [70]. The reduction in cGMP levels causes the closure of the CNG channels on the plasmatic membrane, suppressing the flow of Na^+ and Ca^{2+}. This hyperpolarizes the rod membrane, leading to reduced release of the neurotransmitter glutamate from the ST, thus initiating a neural signal [13]. This signal is transferred to the bipolar cells and from these to the ganglion cells, whose axons form the optic nerve responsible for transferring visual information to the brain [1].

Temporal resolution of vision requires rapid inactivation of components of the phototransduction cascade so that the cell can respond quickly to the next light event [70]. Different processes lead to termination of the response to light. One such process is the decrease in the cytoplasmic Ca^{2+} concentration of the rod OS [13]. Another fundamental aspect is the deactivation of R*, process in which participate proteins such as rhodopsin kinase (RK), arrestin and recoverin [71–74]. The hydrolysis of GTP bound to Tα helps to complete the light process, allowing the assembly of the four PDE subunits and the return to its inactive state [75]. cGMP levels are restored by the action of GC [76–78]. Finally, when cGMP levels are restored, CNG channels open and the rod returns to a depolarized state [13]. An interesting mechanism by which rod cells adapt to light is the massive and reversible translocation between the OS and the rest of the cell of three key proteins in the visual process: transducin, arrestin and recoverin [79–81].

2.3. Retinoid cycle

Despite being a GPCR, rhodopsin differs from diffusible ligand-activated GPCRs by its covalently linked retinal and because unlike many GPCRs, rhodopsin is not recycled by endocytosis. Instead, as described in previous sections, new rhodopsin is synthesized in IS and incorporated into nascent disks at the base of the OS while old disks are phagocytosed by the RPE.

After light response, opsin must bind to 11-*cis* retinal to regenerate rhodopsin and thus be available for a new visual cycle. RPE and rod OS participate in the canonical visual cycle [82,83]. A group of enzymes are responsible for regenerating 11-*cis* retinal from all-trans retinal. All-trans-retinal is reduced to retinol by retinol dehydrogenase 8 (RDH8) and transported out of the OS to RPE, where reisomerization takes place [82–84]. The Retinoid-Binding Protein (RBP) transfers all-trans-retinol from OS to the RPE, where it can be converted back to 11-cis-retinal by the following enzymes: retinol:lecithin acyltransferase (LRAT), RPE-specific 65 kDa protein (RPE65), 11-cis-retinol dehydrogenases 5 (RDH5) and 11(RDH11). Regenerated 11-cis-retinal is then again available to bind opsin and form the visual pigment for a new phototransduction cycle [40,85]. RPE has a different source of 11-cis-retinal: a retinal G protein-coupled receptor (RGR), homologue to rhodopsin, interacts with all-trans-retinal and responds to the light, converting the chromophore to 11-cis-retinal [86].

3. Endocannabinoid system

3.1. Endocannabinoids and their metabolism

The endocannabinoid system (ECS) is composed of membrane receptors, endogenous ligands (endocannabinoids, ECs), which include amides, esters, and other derivatives of arachidonic acid, and the enzymes responsible for the metabolism of these ligands. ECs are molecules of a lipid nature, 2-arachidonoylglycerol (2-AG) and arachidonoyl ethanolamide (anandamide, AEA) being the most studied.

The principal 2-AG synthesis pathway involves diacylglycerol (DAG) hydrolysis by the diacylglycerol lipase (DAGL) enzyme. This enzyme presents two isoforms, DAGLα and DAGLβ, of which DAGLα is the main enzyme involved in the synthesis of this EC [87]. DAG, the substrate that gives rise to 2-AG, derives from the hydrolysis of phosphatidylinositol 4, 5-bisphosphate (PIP_2) by the phospholipase C (PLCβ1) action. This is the most accepted synthesis mechanism because the activation of metabotropic receptors is coupled to the PLC and DAGL pathways [88]. The production of 2-AG can also occur through alternative pathways such as the action of lysophosphatidate phosphohydrolase (LPAP) on 2-arachidonoyl lysophosphatidate (2-arachidonoyl-LPA) [89]; the use of a DAG from phosphatidic acid (PA) hydrolysis by the action of a calcium- and magnesium-dependent PA phosphohydrolase [90,91]; and by the concerted action of phosphatidylinositol (PI) specific- phospholipase A type 1 (PLA1)/ lysophospholipase C (lyso-PLC) enzymes [92,93].The main route of AEA synthesis is by the action of a phospholipase D (PLD) called N-arachidonoyl-phosphatidylethanolamine phospholipase D (NAPE-PLD) on the phospholipid precursor N-arachidonoyl-phosphatidylethanolamine (NAPE) [94–96]. However, other, less important enzymatic routes for AEA synthesis exist [97–99].

2-AG catabolism can occur through two different pathways, one of which is by hydrolysis, generating arachidonic acid and glycerol. This action is carried out mainly by monoacylglycerol lipase (MAGL), which hydrolyzes 2-AG by 85% in the nervous system [100,101]. Other enzymes involved in this catalytic activity are the serine hydrolases 6

(ABHD6) and 12 (ABHD12), and fatty acid amido hydrolase (FAAH). In the nervous system, ABHD6 and ABHD12 contribute ~10% to the hydrolysis of 2-AG [101–105], while FAAH contributes between 15% and 25% [100,101]. Oxidation through cyclooxygenase 2 (COX-2) and/or 12-lipooxygenase (12-LOX) enzymes is a secondary pathway by which 2-AG can be catabolized [106,107]. AEA is mainly degraded by FAAH, producing arachidonic acid and ethanolamine [108]. Like 2-AG, AEA can also be metabolized by COX-2 [109]. The synthesis and catabolism pathways of the main endocannabinoids, 2-AG and AEA, are presented in Fig. 2.

3.2. Endocannabinoid receptors

ECs can act on the receptors of the same cell in which they were formed or can be released into the extracellular space where they bind to specific transport proteins and are carried to more distant targets [110]. The receptors to which ECs can bind with higher affinity are called cannabinoid receptors 1 (CB1) and 2 (CB2), which are also activated by Δ9-tetrahydrocannabinol (THC), the main psychotropic component of the flowers of the Cannabis sativa plant. CB1 and CB2 belong to the A-GPCRs family, which also includes the rhodopsin receptor [67, 111–115]. CB1 was the first cannabinoid receptor to be discovered in the brain [116] and is abundant in the central nervous system (CNS), particularly in the cortex, basal ganglia, hippocampus, and cerebellum [117]. The CB2 was characterized in the immune system [118]. CB1 and CB2 receptors are members of the seven transmembrane segment receptor superfamily and possess domains that can associate with G proteins of the Gi/o family. These receptors are involved in different signal transduction pathways. One of the most studied pathways in tissues and cells includes the activation of Gi with the consequent inhibition of adenylyl cyclase (AC). The inhibition in the cyclic adenosine monophosphate (cAMP) production is a characteristic response of cannabinoid agonists on the CB1 in brain tissue [119,120] and in cell lines expressing this receptor [121]. However, cannabinoid receptors can stimulate AC via the Gs signaling pathway in some experimental models [122–124]. There is evidence linking cannabinoid receptors with the flow of Ca^{2+} ions and with increased phospholipase A and C activity. In addition, stimulation of these receptors leads to phosphorylation and consequent activation of the mitogen-activated protein kinase p42/ p44 (MAPK) and Jun N-terminal kinase (JNK) as signaling pathways that regulate nuclear transcription factors. It has been reported that CB1 can regulate channels that permeate Ca^{2+} and K^{+}, probably by activation of the Go protein [125]. As with other GPCRs [126,127] the involvement of β-arrestin-1 and β-arrestin-2 in CB1 and CB2 signaling has also been demonstrated [128]. The β-arrestin-2 recruitment by the activation of both receptors could participate in their desensitization and internalization [129,130].

ECs can activate receptors other than CB1 and CB2. Transient receptor potential vanilloid type 1 (TRPV1) was the first ionotropic cannabinoid receptor identified and can be activated by AEA and 2-AG [131,132]. This receptor is a cation channel belonging to the transient receptor potential (TRP) family involved in Ca^{2+} homeostasis in cells [133]. TRPV1 is homologous to TRP channels described in Drosophila photoreceptors which are activated by light [134–136].

Other receptors that also interact with synthetic cannabinoid ligands, ECs, and phytocannabinoids are the GPR55 receptor and the nuclear peroxisome proliferator activated receptor (PPAR) [137,138]. GPR55 forms heterodimers with CB1 and CB2 receptors expressed in specific regions of the CNS [139–141]. A large body of papers in the literature holds that many A-GPCRs family members can form dimers and oligomers [142]. In this respect, rhodopsin receptor is organized as rows of dimers, the ordering of two protomers being necessary for the formation of these structures [143]. Furthermore, the high rhodopsin density in disk membranes would favor the formation of dimeric structures at low concentrations [144,145]. Although the monomeric GPCR form triggers signaling correctly [146,147], dimers and oligomers offer an alternative way of regulating the activity of these receptors [148].

One of the most studied aspects of ECs is their ability to act as retrograde messengers by binding to presynaptic receptors, modulating the release of a wide variety of neurotransmitters [149,150]. ECs are synthesized and released into the extracellular medium from postsynaptic neurons and exert most of their action by binding to the CB1 present in the presynaptic terminal [150]. The EC release is triggered by stimuli that depolarize the postsynaptic membrane, involving the participation of Ca^{2+} channels, Gq protein-coupled receptors and Ca^{2+}-assisted receptors, among others [149]. It is currently considered that the retrograde regulation exerted by ECs as modulators of neurotransmission is preferentially mediated by 2-AG [151]. Although the main mechanism by which ECs regulate synaptic function is by retrograde signaling, there is evidence indicating its autocrine signaling by binding to TRPV1 receptors or by astrocytic modulation of pre- and postsynaptic functions [152].

The importance of ECS in the regulation of neurotransmission in the CNS has been widely demonstrated [153]. Many recent studies on this system in ocular tissue report the existence of ECS components in this tissue. Furthermore, since the retina is an extension of the CNS, it is proper to infer that ECS is involved in the visual response.

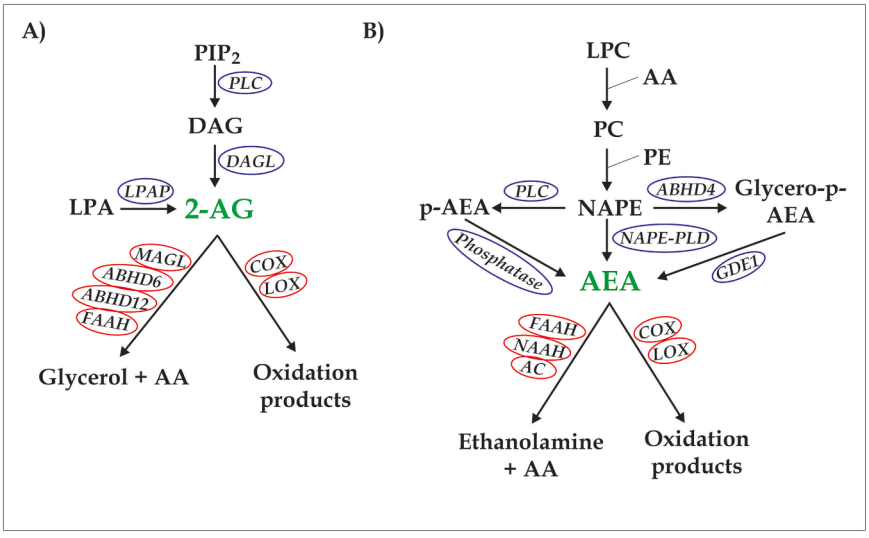

Fig. 2. 2-Arachidonoil glycerol (2-AG) and anandamide (AEA) metabolism The main pathway of 2-AG synthesis is through phosphatidylinositol-(4,5)-bisphosphate (PIP2) hydrolysis, by sequential action of phospholipase C (PLC) and diacylglycerol lipase (DAGL). 2-AG can also be generated from lysophosphatidic acid (LPA) by lysophosphatidate phosphohydrolase (LPAP) activity. 2-AG is mainly hydrolyzed by MAGL and to a lesser extent by alpha/beta-hydrolase 6 and 12 (ABHD6 and ABHD12), and fatty acid amide hydrolase (FAAH) enzymes (A). AEA can be formed from N-arachidonoyl-phosphatidylethanolamine (NAPE) through three enzymatic pathways: 1) N-arachidonoyl-phosphatidylethanolamine phospholipase D (NAPE-PLD), 2) alpha/beta-hydrolase 4 (ABHD4)/ glycerophosphodiester phosphodiesterase 1 (GDE1), and 3) phospholipase C (PLC)/phosphatase. AEA is hydrolyzed by FAAH, N-acylethanolamine acid amide hydrolase (NAAA) and acid ceramidase (AC) (B). Both endocannabinoids are also able to be oxidized by lypoxigenase (LOX) or cyclooxigenase (COX) action.

4. Endocannabinoid system in the retina

4.1. Expression and function of ECS in retinal neurons

The presence of ECS elements has been demonstrated in the ocular tissue of different species, from fish to primates [154–157]. The level of 2-AG was found to be significantly higher than that of AEA in human and bovine retinas [90,158]. DAGL and MAGL expression was observed in rat and mouse retinas, which are the main enzymes responsible for the synthesis and hydrolysis of 2-AG [159–161]. In mice retina, DAGLα was detected in OFF bipolar cells type 1 contiguous with cone synaptic terminals which express CB1, while DAGLβ was only found in retinal blood vessels. The presence of MAGL was described in rod cells and in OS cones (COS), in the outer plexiform layer (OPL), and in the inner plexiform layer (IPL) [160]. ECS have been shown to play a role in brain development, with exposure to cannabinoids generating neurofunctional alterations during the process [162]. In this sense, Cécyre et al. (2014) show that DAGLα is highly expressed in photoreceptor, horizontal, amacrine and ganglion cells throughout development; while MAGL appears in late development stages and its presence is limited to amacrine and Müller cells [159]. Retinal ganglionar cells (RGCs) express both the AEA synthetic (NAPE-PLD) and hydrolytic (FAAH) enzymes [163,164], suggesting they could also be a source of ECs.

Cannabinoid receptors are also expressed in retinal layers of different species [164–167]. CB1 was found in retinas of rhesus monkey, mouse, rat, chicken, goldfish, and salamander. This receptor was located in COS and ROS (rod OS) at the OPL, and also in amacrine and ganglion cells. A low CB1 expression was observed in OS and IS of retinal photoreceptor cells from monkey, rat, mouse, and chicken [167]. Other findings indicate widespread CB1 distribution in bipolar cells, in a subtype of GABAergic amacrine cells, in horizontal cells and in IPL [164]. Likewise, studies employing retinas from vervet monkey demonstrated CB1 expression in photoreceptors, OPL, inner nuclear layer (INL), IPL, and retinal ganglion cell layer (RGCL). Furthermore, preferential CB1 localization in central retina cones was observed and a slight expression in COS and ROS of the OPL [165]. CB2 distribution was studied in the adult rat retina and its presence was detected in RPE, IS from photoreceptors, amacrine and horizontal cells, as well as in RGCL and IPL [166]. The expression of other receptors that also respond to cannabinoids, such as GPR55 and TRPV1, has been described in the retina [168,169]. In vervet monkey retinas, the GPR55 receptor was observed in the photoreceptor layer, with a greater predominance in the IS and colocalizing with rhodopsin in rods [168]. Studies in Zebrafish and Goldfish retinas demonstrated that TRPV1 locates only in rod and cone ST [169].

Different approaches have been used to clarify the role of ECS in the visual process. The main findings arise from analyzing electroretinographic records (ERG) in response to light stimulus. ERGs are mainly generated by the responses of photoreceptors (rods and cones), ON bipolar cells and Müller cells. ERGs evaluate two conditions: the photopic (light) and the scotopic (darkness) adaptation mediated by cones and rods, respectively [170]. Two main components are observed in an ERG: an electronegative component, called a-wave, generated by photoreceptor hyperpolarization, followed by an electropositive component, called b-wave, that reflects the depolarization of ON bipolar and Müller cells [171]. The vervet monkey was one of the species used to study the role of cannabinoid receptors in normal retinal function. For this purpose, ERGs administering CB1 and CB2 antagonists by intravitreal injection to vervet monkey were evaluated. The CB1 antagonist increased the amplitude of a-wave under photopic conditions, while the CB2 antagonist increased the amplitude of both a- and b-waves. Under scotopic conditions, both antagonists increased the b-wave amplitude without changes in the a-wave. These observations indicate that both receptors play a role in retinal functionality [172]. Other studies in CB1 or CB2-knocked out mice revealed that in the absence of CB2 and under photopic conditions a longer adaptation time to light was required, while under scotopic conditions the amplitude of the a-wave was increased. These results indicate CB2 to be particularly involved in the response to light, and that the two receptors could have different roles in visual processing [173].

GPR55 functionality in visual processing has also been studied. It was observed that the stimulation of this receptor under scotopic conditions in vervet monkeys produces an increase in the amplitude of the ERG b-wave, while its blocking decreases the amplitude of this wave. On the contrary, under photopic conditions, the ERG was not affected by GPR55 modulation. The above suggests a GPR55 functional role in scotopic vision [172].

Cannabinoid receptors are also involved in the regulation of ion channels in retinal cells [174,175]. It has been reported that the cannabinoid receptor agonist WIN 55,212–1 (WIN) modulates voltage-dependent Ca^{2+}, K^{+}, and Cl^{-} - currents in the IS cones of goldfish. WIN concentrations less than 1 μM increased all ionic currents, an effect that could be mediated by the Gs protein; and WIN concentrations above 1 μM suppressed these currents, an action related to a Gi/o protein. All these WIN effects were blocked by the CB1 antagonist SR141716A [174]. The effects of cannabinoids on voltage-gated currents in the retinal cones may occur at the first synapse in the visual pathway. This regulates transmitter release and consequently cone responses to light, suggesting effects of cannabis on visual abilities. The changes in K^{+}-current would regulate the recovery time of the photoreceptors to light stimulation, this would affect the transmission from cone photoreceptors to second-order neurons. On the other hand, the modulation of Cl^{-}-current would modify not only the membrane potential but also the Ca^{2+}-current, which would affect the tone and/or glutamate release [176–178].

In the same model it was observed that CB1 agonists inhibited K^{+}-current in ON bipolar cells, an effect that was blocked by antagonizing CB1. This finding is consistent with the abundant CB1 expression in ON bipolar cells ST [179]. Other reports indicate that CB1 activation in the photoreceptor ST and in the bipolar cells of the salamander differentially modulates Ca^{2+} and K^{+}-currents [167,175]. It was observed that WIN increased the Ca^{2+} current in rods and decreased it in cones and suppressed the K^{+}-current in both photoreceptors [175]. On the other hand, Ca^{2+} and K^{+}-currents were inhibited in bipolar and ganglion cells [167,180,181], an effect mediated by CB1 and CB2 for the Ca^{2+}-current in both type cells, and CB-independent for the K^{+}-current in ganglion cells [181]. Fig. 3 summarizes the distribution of the main ECS components, enzymes and receptors in the different retinal neurons. It also highlights the expression of receptors that respond to cannabinoids and the enzymes involved in 2-AG metabolism in OS of rod cells, described for the first time by our research group [182].

4.2. ECS under physiological light stimulus

This section presents and discusses the main findings of our research group, focusing on ECS behavior in response to light stimuli and its participation in the light adaptation process.

As described in the previous section, the presence and location of ECS (ECs, receptors and enzymes) has mainly been studied by immunohistochemical techniques in the retina of various species [159,167,172,173,175,183]. These studies suggest the participation of the ECS in the visual process but do not elucidate how EC availability and the receptors to which they bind respond to light stimulation. Fig. 4 shows how the level of receptors that respond to cannabinoids and the 2-AG-related enzymes in ROS are modified by light, the physiological stimulus of the retina [182]. Light stimulus (3000 lx for 30 min) on bovine retina produced increased CB1 and CB2 expression and a diminished GPR55, DAGL and MAGL level in ROS. Results regarding 2-AG metabolism and its regulation by light, are also presented (Fig. 5). In this case, light was applied to the retina (rLROS) or directly to ROS (LROS) from dark-adapted retinas. In both lighting models, the greater availability of 2-AG was favored by the stimulatory effect of light on DAGL activity (Fig. 5) [182].

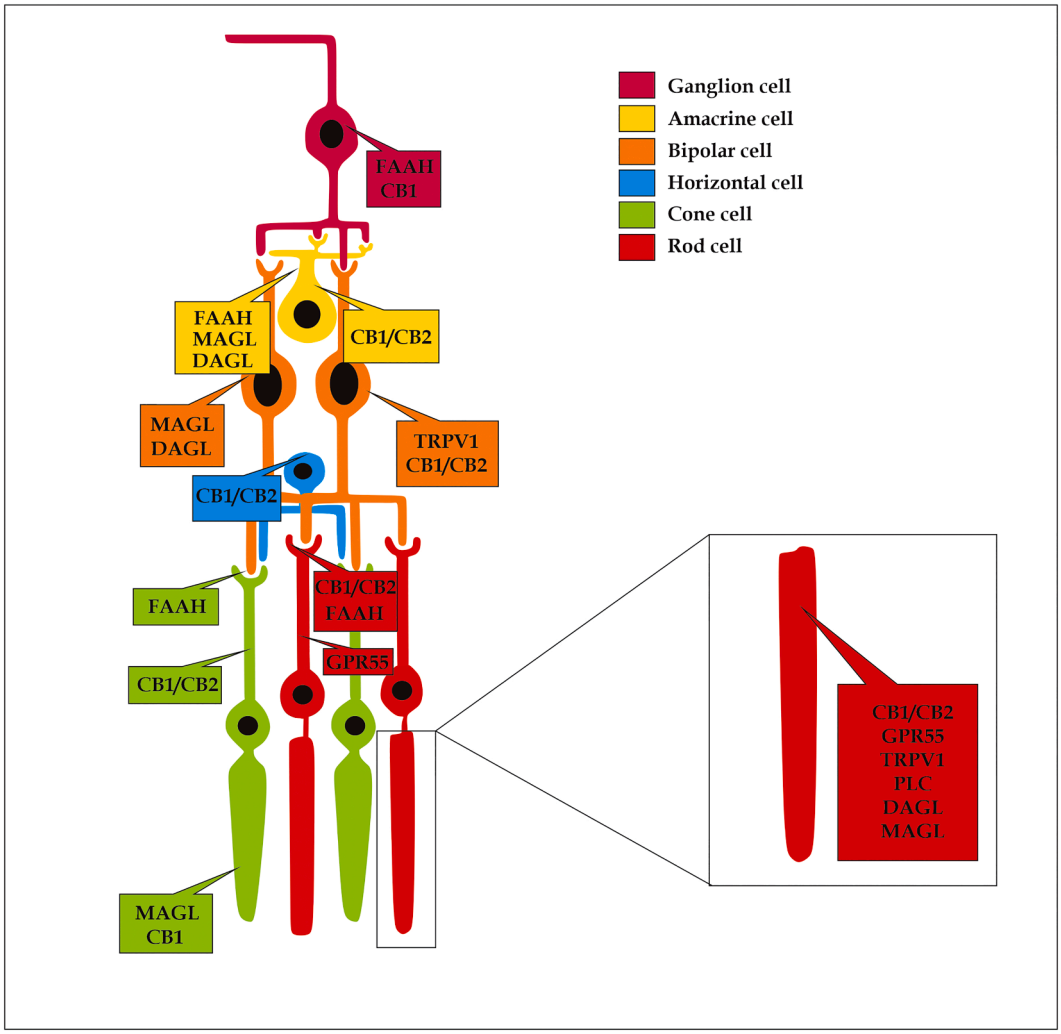

Fig. 3. Distribution of ECS components in the retina. The presence of ECS components (enzymes and receptors) has been demonstrated in the ocular tissue of different species. This figure shows how cannabinoid-related enzymes and receptors are distributed in the different retinal cells. EC metabolism enzymes have been described in ganglion, amacrine, bipolar, and cone (OS and ST) cells. Cannabinoid-responsive receptors were found in ganglion, amacrine, bipolar, horizontal, and cone (IS and OS) cells. The presence of the ECS was reported in rod cells (Chamorro-Aguirre et al., 2019) and the enzymes involved in the synthesis (PLC and DAGL) and hydrolysis (MAGL) of 2-AG as well as CB1, CB2, GPR55 and TRPV1 receptor expression described. These findings are highlighted in the same figure. CB1 and CB2: cannabinoid receptors 1 and 2, GPR55: G protein–coupled receptor 55, TRPV1: transient receptor potential cation channel. Other references are indicated in Fig. 2.

The metabolic pathway for 2-AG synthesis involves the combined action of the enzymes PLC and DAGL [88,184]. The level of the PLCβ1 isoform is higher in ROS from light-exposed retinas compared to those from dark-adapted retinas. Other PLC isoforms modified by light have been identified in ROS from different species [185–189]. Studies in bovine retinas describe this enzyme in ROS membrane and soluble fractions [190] and its regulation by arrestin, one of the proteins involved in shutting down the visual process [190,191]. Activation of PLC appears to play a role in photoreceptor desensitization/adaptation to light [186]. Consistent with this, it has been shown that arrestin translocation is initiated by a signaling cascade involving PLC and PKC pathways [192]. DAG, formed by the action of PLC, can be hydrolyzed by DAGL, giving rise to 2-AG, which in turn can be degraded mainly by MAGL. This would produce a decrease in DAG signaling and initiate new signaling mediated by 2-AG, which can be terminated by its hydrolysis. Two DAGL isoforms (α and β) can hydrolyze DAG at the sn-1 position [134]; however, only DAGL α isoform expression in ROS was observed (Fig. 4). DAGL isoform with a molecular weight of ~70 kDa have been described in Drosophila photoreceptors and in bovine ROS [182], suggesting them to be specific enzyme isoforms with a possible role in the visual system of both vertebrates and invertebrates. Lower DAGL and MAGL protein levels in ROS as a consequence of light exposure (Fig. 4) suggest their migration from OS to IS. In support of this possibility, it has been observed that DAGL is an integral membrane protein containing a sequence in its carboxyl terminal PPxxF (proline, proline, other amino acids and phenylalanine) that allows its binding to Homer proteins [193], which are responsible for recycling and maintaining the level of the enzyme [194].

The location and distribution of CB1 and CB2 in rod outer segments from bovine retina was unknown until Chamorro-Aguirre et al. (2019) [182]. Results of this report, reveal not only the presence of CB1 and CB2 but also their increased expression in the illuminated state of the retina (Fig. 4) [182]. As opsin molecules are transported from IS to OS [44], CB1 and CB2, which are also integral membrane proteins, could have an opsin-like mode of transport [195–197]. In support of this, it has been reported that the redistribution of arrestin and transducin between IS and OS by light (Fig. 6C) is accompanied by a flux of other proteins between these compartments [196]. The increases in the level of CB1 and CB2 proteins induced by light (Fig. 4) correlates with increased 2-AG availability under this condition (Fig. 5) [182]. It is important to

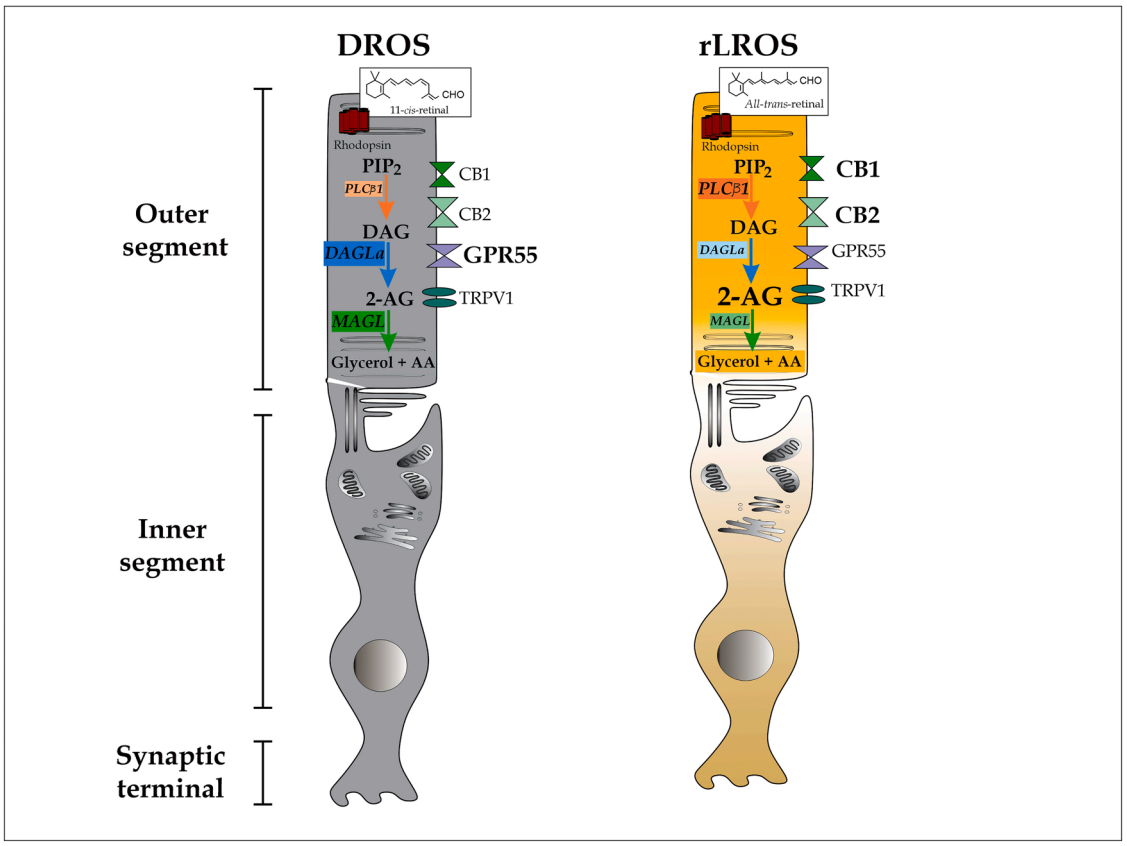

Fig. 4. Light-related changes in the enzymes involved in 2-AG metabolism and in cannabinoid receptor levels in rod outer segment. The relative size of letters indicates the level of enzymes and receptors in rod outer segment from dark-adapted (DROS) or light-exposed (rLROS) retinas. The enzyme names are indicated in blue and green rectangles. The activation of rhodopsin after applying the light stimulus on the eye cup increased the expression of CB1 and CB2, and decreased that of GPR55, DAGL and MAGL. DAG: diacylglycerol, AA: arachidonic acid. Other references are indicated in Fig. 2.

note that in the phototransduction process, the absorption of a single photon hyperpolarizes the rod plasma membrane, generating a decrease in glutamate release [13] (Fig. 6B). On the other hand, the decrease in GPR55 observed in the OS is likely a consequence of its migration towards the IS, where its activation depolarizes the membrane [172] maintaining the glutamate tone and/or completing the phototransduction process (Fig. 6C). Another receptor observed to have the ability to bind cannabinoids is TRPV1, whose level is not modified by light [182]. There is a close relationship between TRPV1, Ca^{2+} currents and the visual process, because TRPV1 is an intracellular Ca^{2+}-release channel [198]. Ca^{2+} levels are modified by light, and this cation is the main driver of the tone of neurotransmission that characterizes retinal signaling [199]. The proposed role of ECS in rod cells is summarized in Fig. 6.

Chamorro-Aguirre et al. (2019) [182] demonstrate the existence and related enzymatic activities of 2-AG metabolism, whose balance could contribute to the greater bioavailability of this endocannabinoid in ROS. An increase in DAGL activity is observed when the retina is stimulated by light. Interestingly, light has a dual effect on DAGL activity and expression, since while the former increases, the level of enzymatic protein decreases. This could be a mechanism to regulate the enzyme, with the lower protein level helping to control its action. It is worth noting that DAGL activity increased in both illumination models: when the eye cup was exposed to light (where a protein flux between OS and IS could occur, rLROS) and when the isolated rod OS (LROS) was exposed to light. This indicates that DAGL activity is independent of visual protein flux between OS and IS. Phototransduction studies in Drosophila [134,200,201] showed that a mutation in the gene encoding DAGL was identified in flies exhibiting a defective response to light, indicating that DAGL action is necessary for the rod cell response to light [134]. The other pathway involved in 2-AG synthesis through the LPAP activity on LPA were not modified by light (Fig. 5 rLROS and LROS) [182]. MAGL activity, the main enzyme that hydrolyzes 2-AG with high efficiency [103], was observed in ROS not only using exogenous substrate, but also on the substrate (MAG) generated by DAGL activity. Although glycerol production in the latter was higher than in the former, the light stimulus was only observed when the activity was determined using the exogenous substrate. Interestingly, MAGL was only modified when the light stimulus was exerted on the retina (rLROS), which suggests that this enzyme could be regulated by some protein that migrates between the IS and OS due to the effect of light, as is the case of arrestin [81,202,203].

In summary, Chamorro-Aguirre et al. (2019) findings with respect to the 2-AG metabolic balance suggest that a greater availability of this endocannabinoid occurs in rod OS when the retina is subjected to its physiological stimulus: although light stimulates its synthesis and hydrolysis, a significantly greater effect on DAGL enzymatic activity was observed. Studies in a non-excitable cell type demonstrated that 2-AG increases intracellular Ca^{2+}concentration, an effect that was mediated by CB1 and TRPV1 action [204]. This report supports the hypothesis that increased 2-AG availability accompanied by higher CB1 and CB2 expression in ROS under light generates greater signaling via these receptors and/or a functional coupling with TRPV1, favoring Ca^{2+} entry into the ROS and thus restoring the light-modified ion current (Fig. 6C).

4.3. ECS and retinal phatologies

The retina is part of the CNS and as such can be affected by different processes leading to its neurodegeneration. With this in mind, different neuroprotective strategies have been explored to preserve the retina from degenerative processes such as glaucoma, diabetic retinopathy,

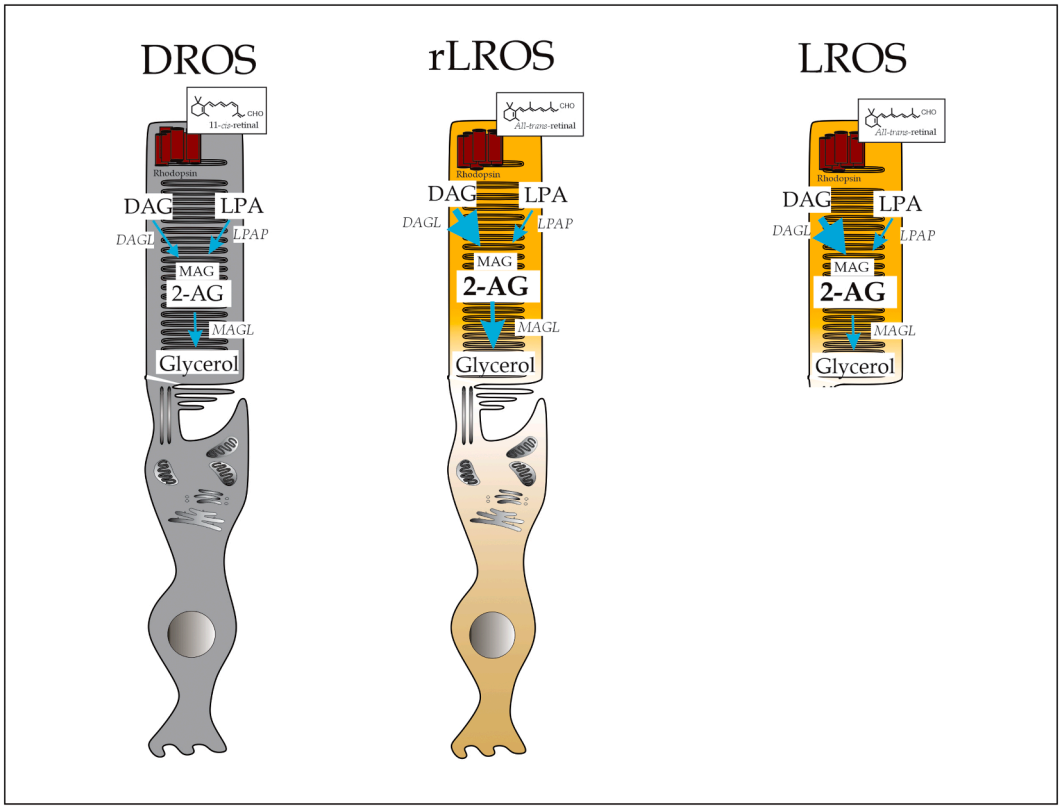

Fig. 5. Light-related changes in the activity of enzymes involved in 2-AG metabolism in rod outer segment. The relative size of arrows indicates the predominance of MAG (2-AG) synthesis and/or hydrolysis in rod outer segment (ROS) of light-exposed retina (rLROS) or ROS isolated in dark and then exposed to light (LROS) with respect to ROS from dark-adapted retina (DROS). Enzyme names are in italic. Under both forms of illumination, DAGL and MAGL activities increased while LPAP activity remained unchanged. The balance in the DAGL and MAGL enzyme activities suggests greater 2-AG bioavailability under light stimulation. References are indicated in Fig. 2.

age-related macular degeneration, and retinitis pigmentosa [205]. A significant number of mutations in visual cycle enzymes and retinoid binding proteins have been identified as the cause of some of these severe retinal diseases [84,206]. For instance, mutations in rhodopsin are associated with a classical form of retinitis pigmentosa, which causes dysfunction and death of rod and cone cells [207]. Rhodopsins with mutations G(glycine)51V(valine) and G(glycine)89D(aspartic acid) are associated with retinitis pigmentosa. The G51V mutation was able to regenerate a chromophore-like wild type rhodopsin; G89D could do so only partially. This retinal pathology presents altered photointermediates and keeps the receptor in a light-induced conformation toxic to rod cells. Alteration in the Meta I to Meta II pathway under the illumination state of the G51V and G89D mutant rhodopsins is likely one of the triggers of this pathology [208]. In age-related macular degeneration and other retinal diseases, photoreceptors are affected both in number and functionality. Animal models subjected to retinal damage by exposure to high light intensity have been used to elucidate the mechanisms underlying retinal dysfunction in various eye diseases. The role of the ECS in fulfilling neuroprotective functions has been widely described in various neurodegenerative processes affecting the CNS [209–212] and in models of retinal neurodegeneration [157,213–216]. Some data on the ECS and retinal damage are available in the literature. Studies of EC-related receptors and enzymes in albino rats subjected to light-induced retinal damage showed that both mRNA and protein levels of DAGL, NAPE-PLD, MAGL and FAAH enzymes were not modified; however, the mRNA and protein expression of CB1 and CB2 were increased. Functional studies in retinal injury models induced by light exposure demonstrated that selective blockade of CB1 and CB2 were able to reduce rod death while preserving the cellular morphology and functionality [161]. Imamura et al. (2017), employing models of light-induced damage in mice and in the 661 W cone cell line, reported an increase in CB1 expression and showed that blocking this receptor abolished the neural and functional damage generated by light [217]. The same authors reported a decrease in CB2 levels in these injury retinal models and observed that the CB2 agonist (HU-308) has a protective effect, attenuated by the CB2 antagonist (SR144528) [218]. This group's work therefore shows that CB1 promotes retinal light–induced damage and CB2 protects against it. In models where the retinal damage is generated by ischemia, a decrease in the level of AEA and in CB1 and TRPV1 expression was observed [215]. In the same work, it was reported that the inhibition of FAAH minimized the retinal damage observed in the ischemic model and that methanandamide (an analogue of AEA) reduced cell loss in RGCL, effects that were reversed by antagonizing CB1 or TRPV1 receptors [215]. Similar results were found in another model of damage generated by axotomy of the optic nerve in the rat, where the inhibition of FAAH increased the survival of RGC, an effect that was mainly mediated by CB1 [216]. This receptor was also associated with neuroprotection of rat retinal amacrine neurons when subjected to AMPA excitotoxicity in vivo [214]. Other authors argue that the neuroprotective effect of ECS in retina may be due to the possible protective role of TRPV1 ligands AEA and 2-AG against ischemic injury and excitotoxicity [215,219–221]. The presence of TRPV1 in ROS could therefore contribute to their protection against some stress factors such as an excess or prolongation of the light stimulus. The ECS exerts its neuroprotective effect on retinal neurodegenerative diseases by different mechanisms, including the reduction in intraocular pressure and the preservation of retinal cells, such as photoreceptors, through anti-inflammatory and antioxidant actions [205].

The accumulated evidence above indicates that the modulation of the SEC, cannabinoid receptors and EC-related enzymes could be of

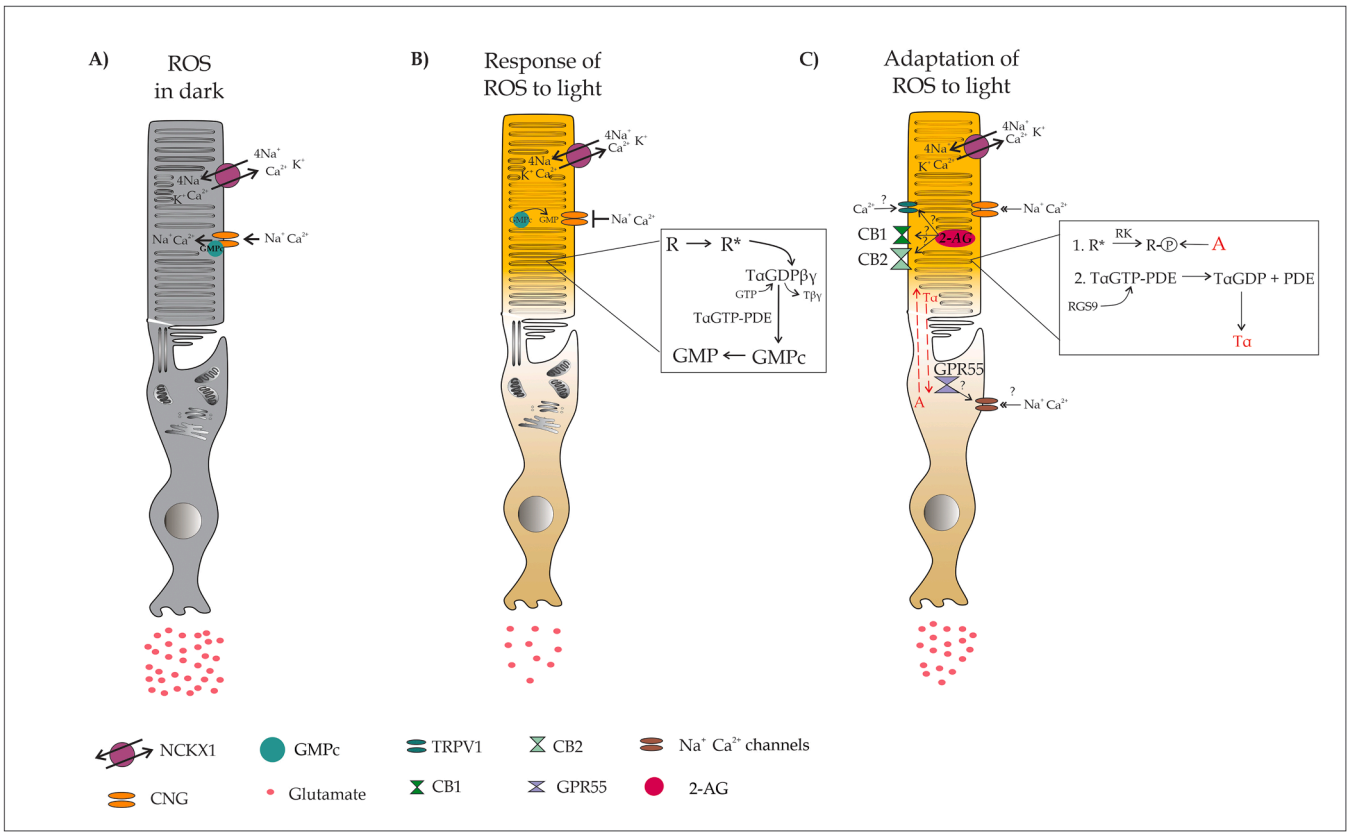

Fig. 6. Representation of the possible role of the ECS in rod cells. Under the dark condition the CNG channels (triggered by cyclic nucleotides) remain open, allowing Na+ and Ca2+ ions to enter the cell due to the presence of cGMP, that generates a partial depolarization favoring the release of glutamate (A). Light triggers the phototransduction process. In rods, rhodopsin (R) detects light and undergoes a conformational change in its chromophore (R*), favoring the dissociation of the alpha subunit of transducin from its heterotrimeric state (TαGDPβγ). The alpha subunit (TαGTP) activates phosphodiesterase (PDE), generating the hydrolysis of cGMP. The decrease in cGMP levels causes the closure of the CNG channels, producing a decrease in the release of glutamate (B). Under continuous bright light exposure, the photoreceptor has light-adaptive machinery that involves regulation of cGMP and Ca2+ levels. PDE deactivation is accelerated by TαGTP hydrolysis, facilitated by RGS9 and by phosphorylation of R* by rhodopsin kinase (RK) and subsequent binding of arrestin (A). The continuous extraction of Ca2+ ions by the exchanger NCKX1 lowers the intracellular Ca2+ level, producing the activation of guanylyl cyclase, thus increasing the cGMP level and opening the CNG channels. The increase in 2-AG, CB1 and CB2 in the OS could be involved in adaptation to light. Interestingly, TRPV1 is a Ca2+ channel possibly involved in the recovery of intracellular Ca2+ levels. It is furthermore possible that GPR55 migrates to the IS, favoring the opening of Na+ and Ca2+ channels and the release of glutamate (C). Red arrows indicate the movement of A and transducin alpha (Tα) subunits inside rods when the eye cup is exposed to light.

therapeutic potential for the treatment of ocular pathologies.

5. Conclusion and future perspectives

This review summarizes recent advances by our group and other authors in relation to the ECS and the visual process. In the retina, different publications indicate that: (a) some ECS components are regionalized in certain neuronal types; (b) the administration of exogenous cannabinoids modulates various retinal functions; (c) the expression and activity of enzymes and cannabinoid receptors in ROS are modulated by light; (d) cannabinoids modify ion channels and other membrane currents relevant to visual function; and (e) these molecules play a protective role against light-induced retinal neurodegeneration. The aforementioned suggest a substantial role played by the ECS in the physiology of the retina, as well as in the entire visual process. Findings to date open important avenues of research into ECS functionality and in particular the neuroprotective capacity of ECs in light injury processes that compromise the integrity and functionality of photoreceptors. Another interesting area of study is to assess the action of extracts derived from *Cannabis* sp. or its active components in the modulation of EC levels in pathological models, aspects poorly explored to date.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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