Iancu R et al
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Nepal J Ophthalmol 2018; Vol 10 (20): 168-175
DOI: https://doi.org/10.3126/nepjoph.v10i2.20464

Review Article

Endocannabinoid System and Ocular Vascularization

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Abstract

The focus of this review is the role of endocannabinoid system in ocular and systemic circulation. By critically examining preclinical and clinical research, we explore the cannabinoid receptors localization and vascular implications as well as their interaction with other anti-inflammatory drugs. The objective is to transfer knowledge on the use of cannabinoids, specifically their effect on ocular circulation and intra-ocular pressure, and provide a better understanding of the endocannabinoid system complexity in modulating local and systemic circulations in order to identify potential uses and limitations of cannabinoid-based therapeutics.

Key words: Cannabinoids, endocannabinoid system, ocular vascularization, vasorelaxation, glaucoma.

The endocannabinoid system

The endocannabinoid system consists of the endogenous cannabinoids (endocannabinoids), cannabinoid receptors and the enzymes that synthesize and degrade endocannabinoids (Mackie, 2008).

The endocannabinoid system is a highly relevant mark for new drug development due to the its purpose in the regulation of many cellular and physiological functions (VVan der Stelt et al, 2002). The fact that they were first identified as activating the same receptors as cannabinoids, which are the primary psychoactive components of cannabis, is what gives endocannabinoids their name (Mackie, 2008). Endocannabinoids (eCBs) are endogenous lipids that activate cannabinoid receptors (Maccarrone, 2016).

The first identified endocannabinoid was anandamide (arachidonoyl ethanolamide) (even though pharmacological experiments with single cannabinoids were first carried out in the 1940s and 1950s it was only around 1988 that Anandamide - the first of five endocannabinoid receptors agonists - was discovered). The second one was 2-arachidonoyl glycerol (2-AG). These are only two examples of a large family of related bioactive acylethanolamides. (Mackie, 2008),]- Cannabinoid pharmacology: the first 66 years (Pertwee, 2009)

Conflicts of Interest: Nil
Financial Interest: Nil
Received: 15/01/18 Accepted: 7/05/18

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A feature that distinguishes eCBs from many other neuromodulators is that they are not synthesized in advance and stored in vesicles. Rather, their precursors exist in cell membranes and are cleaved by specific enzymes. This form of synthesis is often referred to as "on demand" (Mackie, 2008).

The transport of endocannabinoids into cells is managed by a specific uptake system, while their degradation is carried out by two well-characterized enzymes, the fatty acid amide hydrolase (FAAH) - the primary degradative enzyme of the endocannabinoid anandamide - and the monoacylglycerol lipase (MAGL). FAAH is widely distributed throughout the body, with high concentrations in the brain and liver. FAAH can degrade many fatty acid amides, including acylethanolamides, such as anandamide and, the sleep factor, oleamide (Rodríguez de Fonseca et al, 2005), (Lichtman et al, 2011).

Cannabinoid receptors localization and vascular implications

According to International Union of Basic and Clinical Pharmacology classification (IUPHAR), the endocannabinoid system constitutes the endogenous lipids anandamide, noladin ether and 2-arachidonoyl glycerol, and the cannabinoid CB1 and CB2 receptors as well as the proteins for their inactivation (G-protein coupled receptors). CB1 receptors are mainly

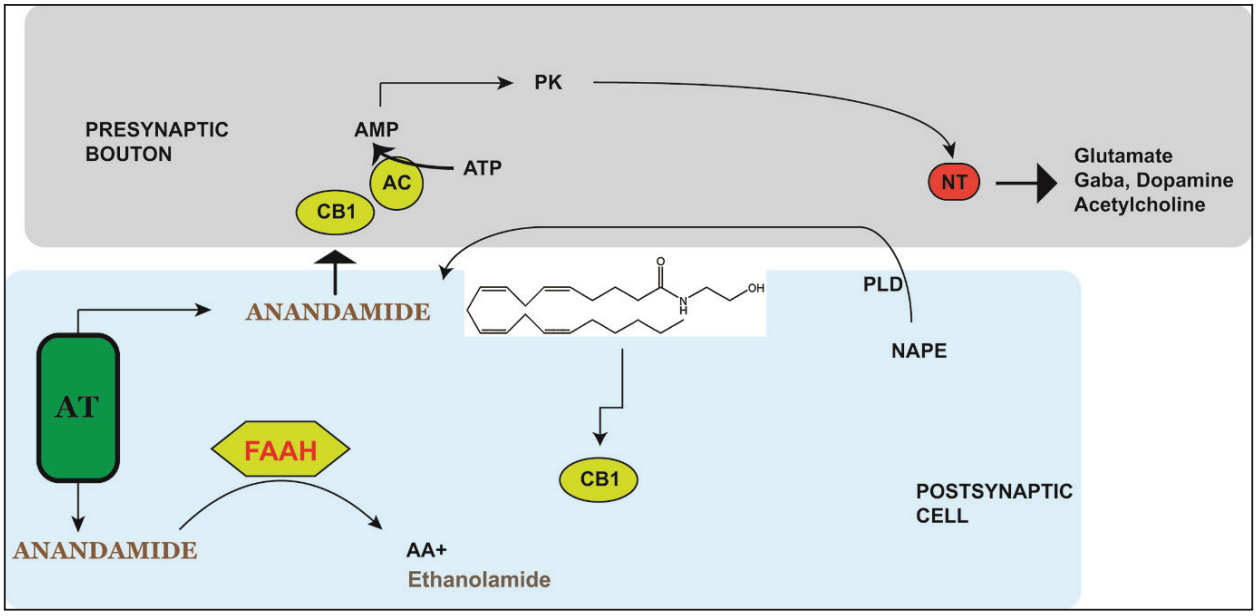

Figure 1: Overview of the biochemical pathways leading to anandamide synthesis, degradation and emerging cellular functions. Anandamide is released from N-arachidonoyl-phosphatidylethanolamine (NAPE) via a specific enzyme phospholipase D (PLD), selective for NAPEs (NAPE-PLD), with low affinity for some other membrane phospholipids, activated by depolarization or G-protein-coupled receptor (GPCR) stimulation. NAPE synthesis is catalyzed by N-acyltransferase (NAT) activated by calcium (Ca2+) and cAMP. Anandamide (AEA) acts as a reverse messenger at presynaptic cannabinoid receptors (CB1), where it regulates neurotransmitter release (NT) through its second transduction systems. Anandamide also serves a purpose as a neuromodulator of Dopamine, among other major transmitter systems, at the level of postsynaptic cells, balancing and controlling excitability and synaptic plasticity through its modulation of potassium (K+) channels, and also the adjustment of a broad spectrum of protein kinases (Dawson et al, 1977), (Flom et al, 1975).

expressed in central and peripheral (both sensory and autonomic) neuronal cells, but it can also be found in a number of other types, including: immune cells, gametes and reproductive tissue cells, astrocytes, endothelial cells from renal and vascular tissues, various epithelial cell types s(Van der Stelt et al, 2002)(Petrocellis et all, 2004). In the nerve cell, the CB1 receptor is often found in axon terminals and it is involved in inhibition of neurotransmission via a presynaptic mechanism. Inhibition of glutamatergic, GABAergic, glycinergic, cholinergic, noradrenergic and serotonergic neurotransmission has been observed in many regions of the central nervous system (Szabo B. and Schlicker E, 2005). Also, it is worth mentioning that in this territory CB1 receptors are one of the most well represented G-protein coupled receptors (Russo E. B, 2016).

The CB2 receptors were initially found in cells involved in immune and inflammatory reactions in both central and peripheral nervous system, being primarily expressed on immune cells such as B cells, T cells, macrophages, dendritic cells and microglia (Van der Stelt et al, 2002) (Schmöle A.-C.et al, 2015). CB2 receptors are described in the literature as playing an important role in the function of the immune system, but they are not described as having vasomotor functions.

In the vascular territory, anandamide (AEA) acts through CB1-dependent and CB1-independent mechanisms; the latter could suggest that AEA-binding vanilloid receptor (TRPV1) is the primary mechanism implicated in AEA-induced vasorelaxation. Another cannabinoid that leads to vasorelaxation through TRPV1 activation is methanandamide (Stanley and O'Sullivan, 2014).

Other mechanisms involved in vasorelaxation include nitric oxide release, metabolism to vasoactive arachidonic metabolites, prostanoid involvement, endothelium-derived hyperpolarising factor (EDHF) release, and inhibition of calcium channels (in these cases, we refer to large-conductance calcium-activated K+ channels and voltage-sensitive K+ channels), as well as a mechanism which implies GPR-55 and GPR 18 receptors; the final two items could represent the well-known CBe receptor as described in the first published articles in the literature (Pratt et al,1998), (O'Sullivan S.E, Kendall D. A. and Randall M. D, 2004).

The biological activity of endocannabinoids like anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) is subjected in vivo to a 'metabolic control', exerted mainly by catabolic enzymes. AMT (a selective AEA membrane transporter) facilitates the transport of AEA into cells; afterwards, AEA is inactivated by fatty acid amide hydrolase (FAAH)(Amadio et al, 2010).

However, AEA is catalyzed by COX-2 at a significantly lower rate compared to arachidonic acid (AA). Also, COX-2 selectively metabolizes 2-AG at a much higher rate than AEA, the products of its oxygenation being closely parallel to those of AA oxygenation (Li G. et al, 2016) (Hamza M. and Dionne R. A, 2009).

Profound coronary and cerebral vasodilation is accomplished in vivo by cannabinoids via direct activation of vascular cannabinoid CB (1) receptors, rather than through auto regulation; cannabinoinds also cause a decrease in sympathetic tone. Differences between the hemodynamic profile of various cannabinoids may reflect quantitative differences in cannabinoid CB (1) receptor expression in different tissues and/or the involvement of as-yet-unidentified receptors (Wagner et al., 2001). The possible mechanisms for these effects are inhibition of transmitter release from sympathetic nerve terminals, direct effects on vascular smooth muscle cells, and effects on endothelial cell function (Hillard, 2000).

One of the first studies regarding the effects of Anandamide on cerebral circulation has shown that the vasodilator response can be completely blocked by indomethacin, a non-selective cyclooxygenase inhibitor (Ellis et al, 1995).

The obvious implication of this discovery was that AEA promotes vasodilation through an indirect mechanism related to arachidonic acid synthesis and its secondary COX-induced metabolism (Pacher et al, 2005).

Since the first study demonstrating that anandamide caused indomethacin-related vasodilation in rat cerebral arterioles, further reports have stipulated that the group of arachidonic acid and its COX-related metabolism is not considered a major mechanism involved in the direct vasodilation mediated by cannabinoids (Mendizábal and Adler-Graschinsky, 2007).

In a previous report it has been shown that the local analgesic interaction between anandamide and ibuprofen (a non-specific COX inhibitor) was synergistic for the acute and inflammatory phases of the formalin test (Guindon et al, 2006).

The vasorelaxant effect of anandamide displays tissue and interspecies differences (Mendizábal and Adler-Graschinsky, 2007).

The rising of cannabinoids levels after non-opioid drugs treatment could be explained by multiple mechanisms:

1. The inhibition of cannabinoids metabolism by FAAH; a part of non-opioids, including indomethacin and ibuprofen, inhibit the action of FAAH, notably at low pH, often a particularity of the site of inflammation (Hamza and Dionne, 2009),(Bari et al, 2016).
2. Inhibition of cannabinoids aerobic metabolism by COX-2; it has been stipulated that COX-2 can metabolize AEA in vitro (Hamza and Dionne, 2009); increased endocannabinoid synthesis correspondingly to shunting of free AA away from prostaglandins (PG) synthesis (Hamza and Dionne, 2009),(Holt et al, 2001)
3. In case of acetaminophen after metabolization into N-acylphenolamine (AM-404) at the brain level and spinal cord, inhibition of the cellular uptake of AEA therefore preventing its action (inactivation) and increasing its potency (Hamza and Dionne, 2009); inhibition of NO synthesis and therefore inactivating the endocannabinoid transporter. (Hamza and Dionne, 2009),(Maccarrone et al, 2000)

These studies showed that local activity of FAAH, MGL and COX, widely present at the endothelium level, limits the vasodilator mechanism of endocannabinoids in rat small mesenteric arteries. Despite the differential roles played by these enzymes on relaxation to anandamide versus 2-AG, the results suggested that inhibitors of these enzymes increase the vascular influence of endocannabinoids (Ho and Randall, 2007).

The combination anandamide/ibuprofen induced synergistic antinociceptive effects implicating both cannabinoid receptors (CB1 and CB2). Further investigations are required on the mechanisms involved.

The nonsteroidal antiinflammatory drug (NSAID) Ibuprofen has recently been shown to inhibit the hydrolysis of anandamide at pharmacologically relevant concentrations, whereas acetylsalicylic acid and acetaminophen were without effect. Also, ibuprofen, ketorolac, and flurbiprofen are optically active compounds, therefore allowing an examination of the steric conditions of the inhibition. The two enantiomers of Ibuprofen inhibit AEA hydrolysis by a slightly different potency, as it has already been shown (Fowler et al, 1999).

WIN55212-2 is a strong agonist of CB1 and CB2 receptors. Despite the evidence

which implies the action of CB1 receptors in endocannabinoid-vascular response, many studies failed to demonstrate the role of CB1 receptors, although the same agonist and the same territory have been studied in case of the same species. The vasodilator effect of WIN 55212-2, as well as the vasodilator effect of anandamide, differ between tissue and species (Reis et al, 2011). It still seems unusual that, even though CB1 receptors are present and capable to induce vasorelaxation, this effect would not be revealed for all CB1 receptors agonists; WIN55212-2 did not induce vasorelaxation of mesenteric vascular flow or aorta in rabbits (Randall et al, 2004),(Mukhopadhyay et al., 2010). Also, WIN 55212-2 induced arterial vasodilation of medial cerebral artery (Rademacher et al, 2008) and aorta in rats (Dannert et al, 2007), both being very sensitive to CB1 receptors antagonism. Several factors could lead to the discrepancy in these results. It is certain that they will depend on the presence or absence of CB1 receptors in a certain arterial segment; another possibility is that the substances (antagonists) used for these studies could operate on other receptors than CB1. We also have to consider that endocannabinoids can exert their actions via multiple pathways; blocking of one may be offset by others. Such behavior has been observed in terms of CB2 receptors: only certain CB2 ligands (2-AG, JWH-015) but not others (WIN55212-2) inhibited the calcium channels by activating CB2(Mackie, 2008).

In terms of CBe receptors, some studies showed no influence on the vasorelaxant effect of WIN 55212-2, 2-AG or CP55,940 (Stanley and O'Sullivan, 2014),(Nagarkatti et al, 2009),(White and Hiley, 1997).

It was widely recognized by now that Δ9-THC, the main psychoactive constituent of cannabis, produces numerous effects by acting via cannabinoid receptors. A previous study on the effect of smoked marijuana strongly suggested the probability of tolerance (Tomida, 2004). Therefore, the reduction of IOP and the duration of marijuana use seemed inversely related (Tomida, 2004),(Flom et al, 1975). In contrast with this study came another research that reported the ophthalmological findings by comparing patients that were not users with long term users of marijuana (for a minimum of 10 years); after applying the water loading test to both groups, the IOP reduction related to marijuana treatment was comparable between both groups(Tomida, 2004),(Dawson et al, 1977). Since these early findings numerous reports have been conducted approving that systemic and topic administration of different types of cannabinoids, including cannabidiol, cannabigerol, endogenous cannabinoids, and some synthetic cannabinoids, induce the IOP reduction (Tomida, 2004). The role of CB1 receptors in reducing IOP in normotensive rabbits, after topical application of the endogenous ligand arachidonylethanolamide, was called into question by the absence of action of systemically administered WIN55212-2 (Porcella et al, 2001),(Landa et al, 2016).

Still, very recently, it was demonstrated that, in rabbits, local application of WIN55212-2 was able to reduce IOP in a time and dose dependent manner (Porcella et al, 2001). Also, results stipulated that topical administration of WIN55212-2 lowers IOP in glaucoma patients, and that these effects are, most likely, directly mediated through a CB1 cannabinoid receptor(Porcella et al, 2001).

The mechanism of action of cannabinoids in the human eye is not completely known or understood. Until recently, the effect of cannabinoids on IOP was considered to be mediated through Central Nervous System (CNS). Some reports involving unilateral topical administration of cannabinoids have shown a significant difference between the treated and the untreated eye, suggesting a local mechanism of action (Tomida, 2004),(Liu and Dacus, 1987).

Hopefully, these current data will encourage further clinical research and development of CB receptors agonists- CB1 receptor agonists in particular- as potential antiglaucomatous agents.

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