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Review

Endocannabinoids and endocannabinoid-related mediators: Targets, metabolism and role in neurological disorders

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ABSTRACT

The endocannabinoid system (ECS) is composed of two G protein-coupled receptors (GPCRs), the cannabinoid CB1 and CB2 receptors, and the two main endogenous lipid ligands of such receptors (also known as the "endocannabinoids"), anandamide and 2-arachidonoyl-glycerol. The ECS is a pleiotropic signalling system involved in all aspects of mammalian physiology and pathology, and for this reason it represents a potential target for the design and development of new therapeutic drugs. However, the endocannabinoids as well as some of their congeners also interact with a much wider range of receptors, including members of the Transient Receptor Potential (TRP) channels, Peroxisome Proliferator-Activated Receptors (PPARs), and other GPCRs. Indeed, following the discovery of the endocannabinoids, endocannabinoid-related lipid mediators, which often share the same metabolic pathways of the endocannabinoids, have also been identified or rediscovered. In this review article, we discuss the role of endocannabinoids and related lipids during physiological functions, as well as their involvement in some of the most common neurological disorders.

Contents

Abbreviations: 2-AG, 2-arachidonoyl-glycerol; 2-MAGs, monoacylglycerols; 2-OG, 2-oleoyl-glycerol; Abhd4, α/β-hydrolase domain type-4; ABHD6 and 12, α/β-Hydrolase Domain Containing Protein 6 and 12; AC, adenylyl cyclase; AD, Alzheimer's disease; AEA, *N*-arachidonoyl-ethanolamine (anandamide); ALIA, Autacoid Local Inflammation Antagonism; Aβ, amyloid β-protein; BDNF, brain-derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; CB1 and CB2, cannabinoid receptors of type-1 and -2; CBD, cannabidiol; COX-2, cyclooxygenase-2; DAG, diacylglycerols; DAGL-α and –β, diacylglycerol lipase-α or -β; ECS, endocannabinoid system; ERK, Extracellular signal-regulated kinases; FAAH, fatty acid amide hydrolase; GABA, gamma aminobutyric acid; GDE1, glycerophosphodiesterase; GPCRs, G-protein coupled receptors; HD, Huntington's disease; IP3, inositol 1,4,5-trisphosphate; LEA, *N*-linoleoyl-ethanolamine; MAGL, monoacylglycerol lipase; MAPK, mitogen-activated protein kinase; MPTP, *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, Multiple sclerosis; NAAA, *N*-acylethanolamine acid amidase; NADA, *N*-arachidonoyl-dopamine; NAEs, *N*-acylethanolamines; NAGly, *N*-arachidonoyl glycine; NAPE-PLD, *N*-acyl-phosphatidylethanolamine-specific phospholipase D; OEA, oleoylethanolamide; OLDA, *N*-oleoyl-dopamine; PD, Parkinson's disease; PEA, palmitoylethanolamide; PG-EAs, prostaglandin ethanolamides (prostamides); PG-GEs, Prostaglandin glyceryl esters; PIP2, sn-2-arachidonoyl- phosphatidylinositol-4,5-bisphosphate; PKC, protein kinase C; PLC, phospholipase C; PPAR, peroxisome proliferator-activated receptor; PTPN22, protein tyrosine phosphatase; PTZ, pentylenetetrazol; TRPV1, transient receptor potential vanilloid type-1 channel; Δ^9-THC, tetrahydrocannabinol.

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1. The endocannabinoid system: from its early definition to the latest discoveries

The discovery of Δ^9-tetrahydrocannabinol (Δ^9-THC), the main psychoactive compound of *Cannabis sativa* [1], led to ground-breaking insights into a new class of molecules present in this plant, as well as their potential use as a therapy. From this discovery, more than eighty plant cannabinoids have been identified, each with a unique chemical structure and a different pharmacological profile, although only few, and particularly Δ^9-THC, interact with the endocannabinoid system (ECS).

1.1. The endocannabinoids

The first evidence suggesting that Δ^9-THC could bind to specific receptors in mammals was provided twenty years after its discovery, when Allyn Howlett's group showed that in murine neuroblastoma cells (N18TG2) exposure to this compound or some of its synthetic analogues inhibited the activity of adenylate cyclase in an enantioselective manner [2]. One year later, the cell membrane G-protein-coupled receptor (GPCR) responsive to Δ^9-THC was cloned and named cannabinoid receptor of type 1 (CB1) [3]. Few years later, a second GPCR for Δ^9-THC was cloned from human promyelocytic leukaemia cells, and named cannabinoid receptor of type 2 (CB2) [4]. The discovery of these two receptors immediately put forward the hypothesis of the existence of their endogenous ligands, or, as defined later, "endocannabinoids" [5]. Thus, in 1992, the first endogenous agonist of both cannabinoid receptors was isolated from the pig brain, identified as *N*-arachidonoyl-ethanolamine (AEA) and named *anandamide* from the Sanskrit word *ananda* for "bliss" [6]. Three years later, a second ligand of both cannabinoid receptors was isolated from the canine gut and turned out to be a common intermediate in phospholipid and triglyceride metabolism, i.e. 2-arachidonoyl-glycerol (2-AG) [7,8].

To date, an extended definition of ECS encompasses a large group of molecules including: a) the two major arachidonate-based endocannabinoids, AEA and 2-AG, and also other putative endogenous CB1 and CB2 ligands such as, for example, 2-arachidonoyl-glyceryl ether or noladin ether (2-AGE), *O*-arachidonoyl-ethanolamine (virodhamine), *N*-arachidonoyl-dopamine (NADA), and oleamide (OA); b) the two canonical G protein-coupled cannabinoid receptors, CB1 and CB2, and also other proposed targets for the endocannabinoids, such as, for example, the orphan GPCR 55 (GPR55) and the transient receptor potential vanilloid type-1 (TRPV1); c) a large number of enzymes involved in AEA and 2-AG biosynthesis [*N*-acyl-phosphatidylethanolamine-specific phospholipase D (NAPE-PLD), α/β-hydrolase domain type-4 (Abdh4), glycerophosphodiesterase-1 (GDE1), protein tyrosine phosphatase N22 (PTPN22), for AEA; and diacylglycerol lipase-α or -β (DAGLα and DAGLβ for 2-AG] or degradation [fatty acid amide hydrolase-1 (FAAH) for AEA; and monoacylglycerol lipase (MAGL), α/β-Hydrolase Domain Containing Protein 6 and 12 (ABDH6 and 12), and FAAH-1 for 2-AG] [9,10].

Two AEA-related compounds, i.e. *N*-oleoylethanolamine (OEA) and *N*-palmitoylethanolamine (PEA), are part of this "extended" ECS. Although these two latter molecules lack strong affinity for either CB1 or CB2 receptors, they are biosynthetized by the same class of enzymes mentioned above for AEA. In addition to FAAH, however, they are hydrolysed by FAAH-2, which is not expressed in rodents [11] and shows preference for OEA, and *N*-acylethanolamine hydrolysing acid amidase (NAAA), which shows preference for PEA [12–13]. In addition, OEA was also suggested to activate the orphan GPCR 119 (GPR119) [14], while PEA behaves as a GPR55 agonist in some assays [15,16]. Finally, other endocannabinoid-related lipid mediators have only recently been discovered, such as: 1) the amides between some fatty acids and certain amino acids (namely glycine and serine), also known as lipoamino acids [17–19]; 2) metabolites derived from the cyclooxygenase-2 (COX-2)-mediated oxidation of AEA and 2-AG, denoted as prostaglandin ethanolamides (or prostamides) and prostaglandin glyceryl esters [20,21]; and 3) the *N*-acyl-dopamines and the *N*-acyl serotonins [17,22–23].

In summary, research on endocannabinoids and cannabinoid receptors led to the identification of new classes of lipid mediators, together with the enzymes regulating their tissue levels and receptors potentially mediating their action. We would like to refer to this new system of small molecules, the proteins necessary for their biosynthesis, function and inactivation, and the genes encoding these proteins, as the "endocannabinoidome" [24]. Here, we provide an overview of the more recent discoveries on the role of endocannabinoids and related lipids during physiological functions, as well as their involvement in some of the most common neurological disorders.

1.2. The cannabinoid receptors: CB1 and CB2

The CB1 and CB2 cannabinoid receptors belong to the large family of GPCRs, with seven transmembrane domains connected by three extracellular and three intracellular loops, an extracellular N-terminal tail, and an intracellular C-terminal tail. CB1 and CB2 receptors are activated by three major chemical classes of ligands: 1) cannabinoids (Δ^9-THC and to a lower extent cannabinol) and their synthetic analogues; 2) eicosanoids, such as AEA and 2-AG, and 3) aminoalkylindoles. However, many other classes of synthetic compounds have been designed that are capable to bind these two receptors and act as either agonists, inverse agonists, antagonists or allosteric modulators (the latter having been found so far only for CB1) [25].

CB1 is expressed in all brain structures, and in decreasing amounts from the olfactory bulb, cerebellum, hippocampus, basal ganglia, cortex and amygdala, to the hypothalamus, thalamus and brainstem [26]. Overall, CB1 is known to be the most abundant GPCR in the mammalian brain and for this reason it used to be referred to as the "brain cannabinoid receptor" [27]. In most brain areas, CB1 is expressed in presynaptic terminals of both glutamatergic and gamma aminobutyric acid (GABA)-ergic neurons [28]. in homodimeric or heterodimeric structures. However, CB1 can also be expressed post-synaptically, and many studies have proved that it can form heterodimers in association