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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.

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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, cyclo-oxygenase-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

with other GPCRs including the adenosine A2, dopamine D2 or orexin type-1 receptors [29–31]. To what extent these structures occur in vivo and confer to the receptor a different pharmacology and structure activity relationship towards ligands is not yet clear. Finally, CB1 is also found in non-neuronal cells of the brain, particularly in astrocytes, where its activation promotes the release of neurotransmitters [32,33]. Surprisingly, once activated in these cells, CB1 receptors seem to induce intracellular Ca^{2+} elevations, which trigger the release of glutamate and the subsequent activation of presynaptic metabotropic glutamate receptors [34].

The intracellular region of CB1 is most frequently coupled to Gi/o proteins [27]. Therefore, the stimulation of CB1 by endogenous or exogenous ligands inhibits adenylate cyclase activity with subsequent reduction of intracellular levels of cyclic adenosine monophosphate (cAMP), or promotes mitogen-activated protein kinase (MAPK) activity [2,27]. Some studies have shown that CB1 in certain cell types can regulate adenylyl cyclase (AC) also via Gs or Gq [27], or be coupled, via Gi/o or Gq/11, to other types of intracellular signals, such as the protein kinase B (Akt/PKB), phosphoinositide 3-kinase (PI3K) and phospholipase C/inositol 1,4,5-trisphosphate/protein kinase C (PLCβ/IP3/PKC) pathways [34,35].

The AC/cAMP cascade is a key intracellular mechanism controlling the activity of a variety of cell functions including cell survival, differentiation, and proliferation. Moreover, cAMP regulates the activity of many class of ion channels, including voltage-gated K^+ and Ca^{2+} channels [36–39], and, in neurons, CB1 activation of Gi/o can also directly inhibit voltage-activated Ca^{2+} channels. Therefore, it is clear that the CB1 receptor acts as a key element controlling cell fate and function in general, and in particular neuronal electrical activity and neurotransmitter release [28]. In particular, it has been shown that, following neuronal depolarization, the synthesis of endocannabinoids at postsynaptic sites is rapidly triggered; once synthetized, AEA and, particularly, 2-AG travel backwards to stimulate CB1 receptors on presynaptic terminals to be then inactivated by hydrolytic enzymes (Fig. 1). Therefore, the "on demand" production of endocannabinoids acting as retrograde signals [40], together with CB1-mediated activation of K^+ and inhibition of Ca^{2+} channels, by controlling both excitatory and inhibitory neurotransmitter release, finely tunes the duration of synaptic activity and, subsequently, several forms of short- and long-term synaptic plasticity (Fig. 1) [41,42].

In addition to the brain, CB1 is also expressed in the peripheral nervous system and in almost all mammal tissues and organs including the

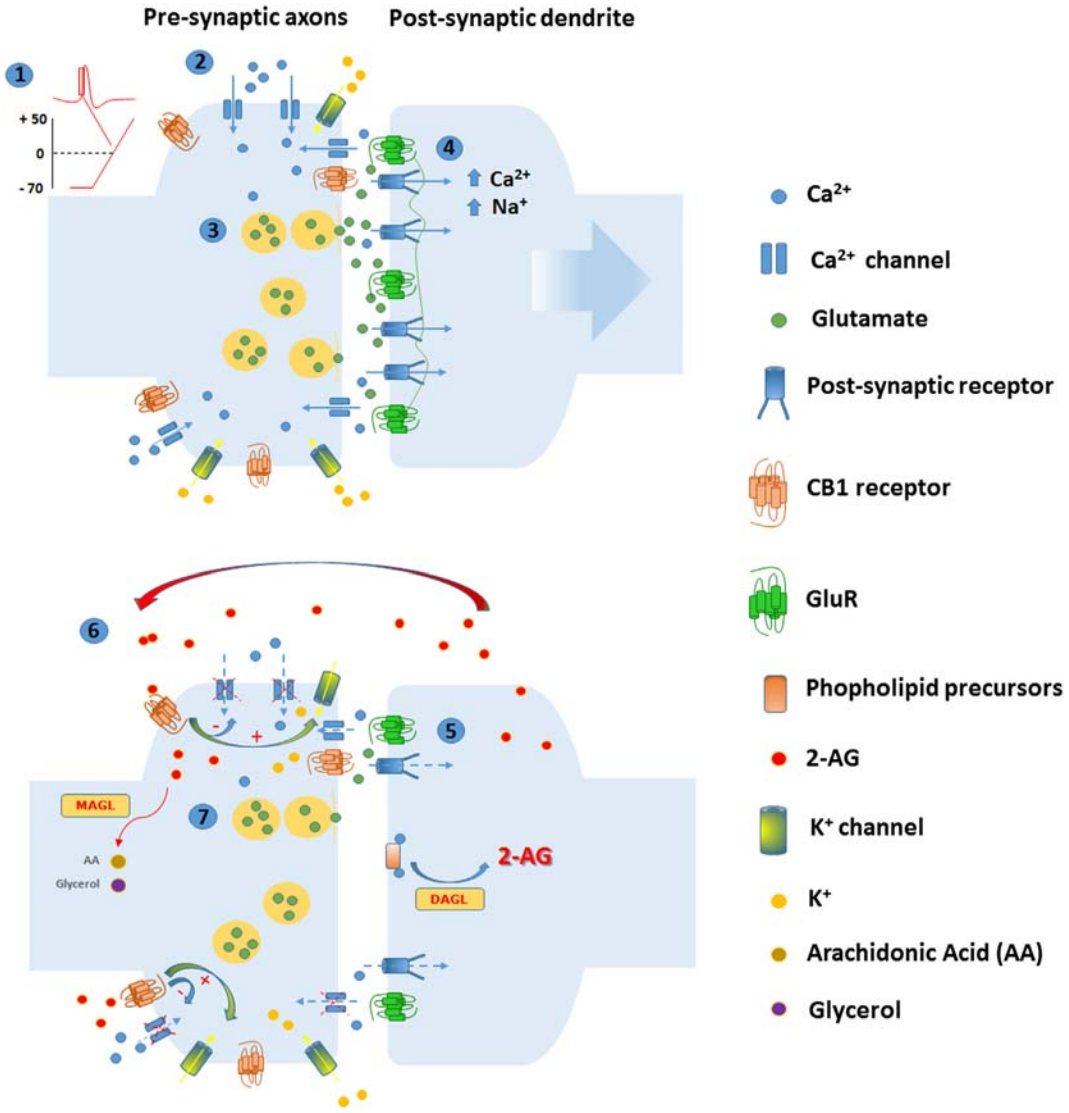

Fig. 1. An example of the "retrograde" mechanism of action of 2-AG at neuronal synapses. Following neuronal depolarization (1), the Ca^{2+}-dependent release of glutamate from presynaptic vesicles (2–3) activates NMDA receptors at the post-synaptic level (4) thereby causing excitatory postsynaptic currents (EPSCs). This change of membrane excitability rapidly triggers the synthesis of AEA and, particularly, 2-AG (5). The 2-AG travels backwards (6) to stimulate CB1 receptors on presynaptic terminals, which in turn activate K^+ channels and inversely inhibit Ca^{2+} channels, thus inhibiting excitatory neurotransmitter release (7).

gastrointestinal tract, heart, liver, adipose tissue, lungs, adrenal glands, smooth and skeletal muscle, male and female reproductive systems, bone and skin [43–47]. The crucial role of this receptor in the maintenance of homeostasis during several mammalian functions has been demonstrated by the use of both pharmacological and genetic tools (such as "global" and conditional $CB1^{-/-}$ mice). In fact, many studies have reported that the loss of CB1 receptor function may be associated with disorders affecting both central and peripheral organs [47,48].

The function of the CB2 receptor is often related to that of CB1 receptor, even though its protein sequence shows only 44% homology to that of its cognate receptor [4]. Similar to CB1, CB2 is a GPCR and is coupled to Gi/Go α proteins. Thus, its stimulation inhibits AC activity and activates MAPK [49]. In contrast to CB1, CB2 levels in the brain are very low, and emerging studies have shown that its expression is restricted to specific neuronal cells and becomes abundant in activated microglia and astrocytes [50,32]. Overexpression of CB2 in neurons and subsequent activation by agonists causes inhibition of voltage activated Ca^{2+} channels [50], and $CB2^{-/-}$ mice do exhibit a phenotype in terms of their response to anxiogenic stimuli and consumption of substances of abuse [51–53]. Xi and colleagues using $CB2^{-/-}$ mice have recently suggested that stimulation of CB2 receptors in the brain, by regulating the levels of dopamine, plays a key role in cocaine rewarding and locomotor-stimulating effects [54]. However, the role of CB2 in the brain is still controversial, and whether or not such receptor participates in affective behavior remains to be conclusively established.

In contrast, it appears clear that CB2 receptors are abundantly expressed in cells belonging to the immune system such as monocytes, macrophages, and B- and T-cells [55,56]. In these cells, CB2 receptor activation, among others, reduces the release of pro-inflammatory cytokines or lymphoangiogenic factors [55–57]. Moreover, CB2 receptors are also present in other peripheral organs and cell types playing a role in the immune response, including the spleen, tonsils, thymus gland, mast cells and keratinocytes [58–61,46], as well as in the gastrointestinal system [62,63]. Finally, in many studies utilizing drugs selective for CB2 or $CB2^{-/-}$ mice it appeared clear that CB2 receptors have the ability to control the activation and migration of immune cells, and represent key regulators of inflammatory and nociceptive responses [64,65].

1.3. Other putative endocannabinoid receptors: TRPV1 and GPR55

The transient receptor potential vanilloid type-1 (TRPV1) channel, also known as the capsaicin receptor or vanilloid receptor 1, was the first member of the TRPV channel subfamily to be discovered and cloned [66]. By homology with other TRP members, the structure of TRPV1 possesses six transmembrane domains with an additional intramembrane loop connecting the fifth and sixth transmembrane domains and forming the pore channel region [66]. This subclass of ion channels is characterized by weak voltage sensitivity and a nonselective permeability to monovalent and divalent cations including Mg^{2+}, Ca^{2+}, and Na^{+}. TRPV1 channels are activated by a plethora of both exogenous and endogenous chemical agents, such as capsaicin and its analogues, some phytocannabinoids, AEA, PEA, *N*-oleyl-dopamine, NADA, and some lipoxygenase derivatives, including leukotriene B4 and 12-hydroperoxy-eicosatetraenoic acid [66–75]. Physical or mechanical stimuli, such as high temperatures (>43 °C), low pH and osmotic changes, also activate TRPV1 [76,77].

TRPV1 function is closely dependent on the binding of key regulatory proteins that induce changes in its phosphorylation state. In particular, the phosphorylation induced by adenosine triphosphate (ATP), protein kinase A (PKA), PKC, phosphoinositide-binding protein (PIRT) and phosphatidylinositol 4,5-bisphosphate (PIP2), was shown to be required for TRPV1 activation/sensitization and cation gating. TRPV1 activation contributes to pain transmission, neurogenic inflammation and, as suggested by more recent studies, also synaptic plasticity, neuronal overexcitability and neurotoxicity [76–79,69]. On the other hand, the rise of intracellular Ca^{2+} following TRPV1 stimulation activates: i) proteins, such as calmodulin, that stabilize the channel in a closed conformational state, or ii) Ca^{2+}-dependent phosphatases, such as calcineurin, which dephosphorylate TRPV1 and again inactivate it [80–82,78]. This fast process of inactivation of TRPV1 is known as "desensitization", and is thought to underlie the paradoxical analgesic, anti-inflammatory and anti-convulsant effects of TRPV1 agonists [83,84,69].

TRPV1 channels are largely expressed in dorsal root ganglia, and sensory nerve fibers of the Aδ and C-type, but also in non-neuronal cells and tissues such as keratinocytes and skeletal muscle [85,77,61,47]. In sensory neurons, TRPV1 channels work as molecular integrators for multiple types of sensory inputs that contribute to generate and transmit pain. In central neurons, lower amounts of TRPV1 channels are expressed both pre- and post-synaptically, where they act to regulate synaptic strength [85–87] and participate in pain, anxiety, depression, emesis, and nicotine and alcohol self-administration, usually by inducing effects opposite to those exerted by CB1 receptors in the same context [88–90]. Moreover, again in conjunction with endocannabinoid signalling, TRPV1 might also participate in retinal ganglion cell (RGC) axonal transport and excitability, cytokine release from microglial cells and regulation of retinal vasculature cells [91].

GPR55 also belongs to the large family of GPCRs and is currently considered a potential cannabinoid receptor. The endogenous ligand of this receptor is lysophosphatidylinositol (LPI) [92–94], but GPR55 seems to be activated by Δ^9-THC as well as by some synthetic inverse agonists of CB1 receptors, and antagonized by the other major, non-psychotropic phytocannabinoid, cannabidiol (CBD). Contrasting data exist regarding the possibility that low concentrations of AEA, 2-AG, virodhamine, noladin ether and PEA also activate GPR55 [94,95], and such controversies might be due either to biased signalling of these molecules at this receptor, depending on the cell type and conditions used for the assay, or to the recently discovered formation of heteromers between GPR55 and CB1 [96,97]. Indeed, GPR55 is linked to a range of downstream signalling events including Ca^{2+} release, nuclear factor of activated T cells (NFAT)-, cAMP response element-binding protein (CREB)- and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)-induced transcription, and extracellular signal-regulated kinases (ERK)-1/2 phosphorylation [95]. In the mouse brain, GPR55 is expressed in the striatum, hippocampus, forebrain, cortex, and cerebellum [98], while at the peripheral level, it is found abundantly in the gastrointestinal tract [99]. It is present also in both osteoblast and osteoclast cells, where it regulates bone mass plasticity [100], as well as in metabolically active cells such as adipocytes [101]. However, the exact function of GPR55 is not fully clear yet, and the difficulties in reaching a firm conclusion on this issue are also due to the fact that $GPR55^{-/-}$ mice do not show a clear phenotype [102]. Recent findings suggested that activation of GPR55 might play an opposite role to CB1 by boosting neurotransmitter release [58], and a similar one in obesity by increasing the expression of lipogenic genes in visceral adipose tissue [101]. Furthermore, while pharmacological stimulation of CB1 and CB2 receptors by endocannabinoids or synthetic cannabinoid-based compounds appears to inhibit the aggressiveness of several types of cancer such as skin and breast carcinoma or glioma and lymphoma [103–105], the stimulation of GPR55 by LPI exerts opposite effects by promoting cancer cell proliferation [106,107].

1.4. Biosynthetic and catabolic pathways of the two major endocannabinoids, AEA and 2-AG

As also mentioned above, the ECS encompasses a growing number of lipid mediators. However, among these mediators, AEA and 2-AG are the only ones whose metabolism and pharmacology have been thoroughly investigated. For this reason, these two compounds are still considered as two "major endocannabinoids".

1.4.1. Biosynthesis of endocannabinoids

The biosynthesis of AEA, similar to that of other long chain *N*-acylethanolamines (NAEs), can occur via at least three distinct biosynthetic routes: a) directly, through the hydrolysis of *N*-arachidonoyl-phosphatidyl-ethanolamines (NArPE) by the action of NAPE-PLD; b) in three steps, via the sequential deacylation of NArPE by ABHD4 and the hydrolysis of glycerophosphoethanolamine by GDE1; and c) in two steps, via PLC-mediated hydrolysis of NArPEs to yield phosphoanandamide, which is in turn dephosphorylated to AEA by a phosphatase, such as PTPN22 [108] (Fig. 2). Recent studies suggested that the choice of one pathway instead of another might depend also on precursor's availability and/or the cell or tissue type [109]. Interestingly, at least in the brain, the different pathways seem to be able to compensate for the lack of one of them, since neither NAPE-PLD nor GDE1 null mice exhibit lower AEA levels, whereas the brain of double NAPE-PLD/GDE1 null mice only show reduced levels of the endocannabinoid and other NAEs in cell free experiments or following the treatment of the animals with an inhibitor of *N*-acylethanolamine enzymatic hydrolysis [110].

The other endocannabinoid, 2-AG is synthesized from the hydrolysis of 2-arachidonoyl-containing diacylglycerols (DAG) by either of two enzymes known as *sn*-1-specific DAGL α or β [111]. Mice lacking either DAGL-α or -β revealed that DAGL-α plays a primary role for 2-AG synthesis in the brain; conversely, DAGL-β is often active at the peripheral level, although its expression in the brain has been reported [111–113]. The DAG precursors for 2-AG biosynthesis are in turn the product of the hydrolysis of membrane phospholipids, and particularly of *sn*-2-arachidonoyl-PIP2 species by PLCβ [114,115]. However, DAG precursors for 2-AG have also been suggested to originate also from phosphatidic acid hydrolysis [116] (Fig. 2).

1.4.2. AEA and 2-AG enzymatic hydrolysis

AEA and 2-AG are hydrolysed mainly by two serine hydrolases: FAAH and MAGL, respectively (Fig. 2). The crucial role of these enzymes in the catabolism of AEA and 2-AG was confirmed in several studies by the use of selective FAAH or MAGL inhibitors and/or mice lacking FAAH ($FAAH^{-/-}$ mice) or MAGL ($MAGL^{-/-}$ mice) [117–120]. In particular, FAAH (or FAAH-1) is an integral membrane serine hydrolase protein largely expressed throughout the mammalian body, with the highest density in the brain and liver, whereas FAAH-2 is not expressed in rodents [121]. Although AEA represents its preferential substrate, FAAH is also active at hydrolysing other long-chain *N*-acylethanolamine (NAEs) such as PEA and OEA [122], and fatty acid amides (FAAs), including *N*-acyltaurines [123] and *N*-acyl-glycines [17]. Nevertheless, there is both in vitro and in vivo evidence that FAAH is also active towards 2-AG [124–126], and therefore its contribution to 2-AG inactivation in the brain under certain conditions or in particular brain areas and cells cannot be ruled out. However, MAGL is responsible for ~85% of 2-AG-hydrolyzing activity in mouse brain homogenates [127]. As a consequence, in mice lacking this enzyme, the endogenous levels of 2-AG are significantly increased in all the tissues and organs taken under analysis [119].

Over the last decades many specific FAAH or MAGL inhibitors have been developed such as URB597 [128], OL-135 [129], PF-3845 [130] and PF-04457845 [131] for FAAH; and URB602 [132], CAY10499 [133],

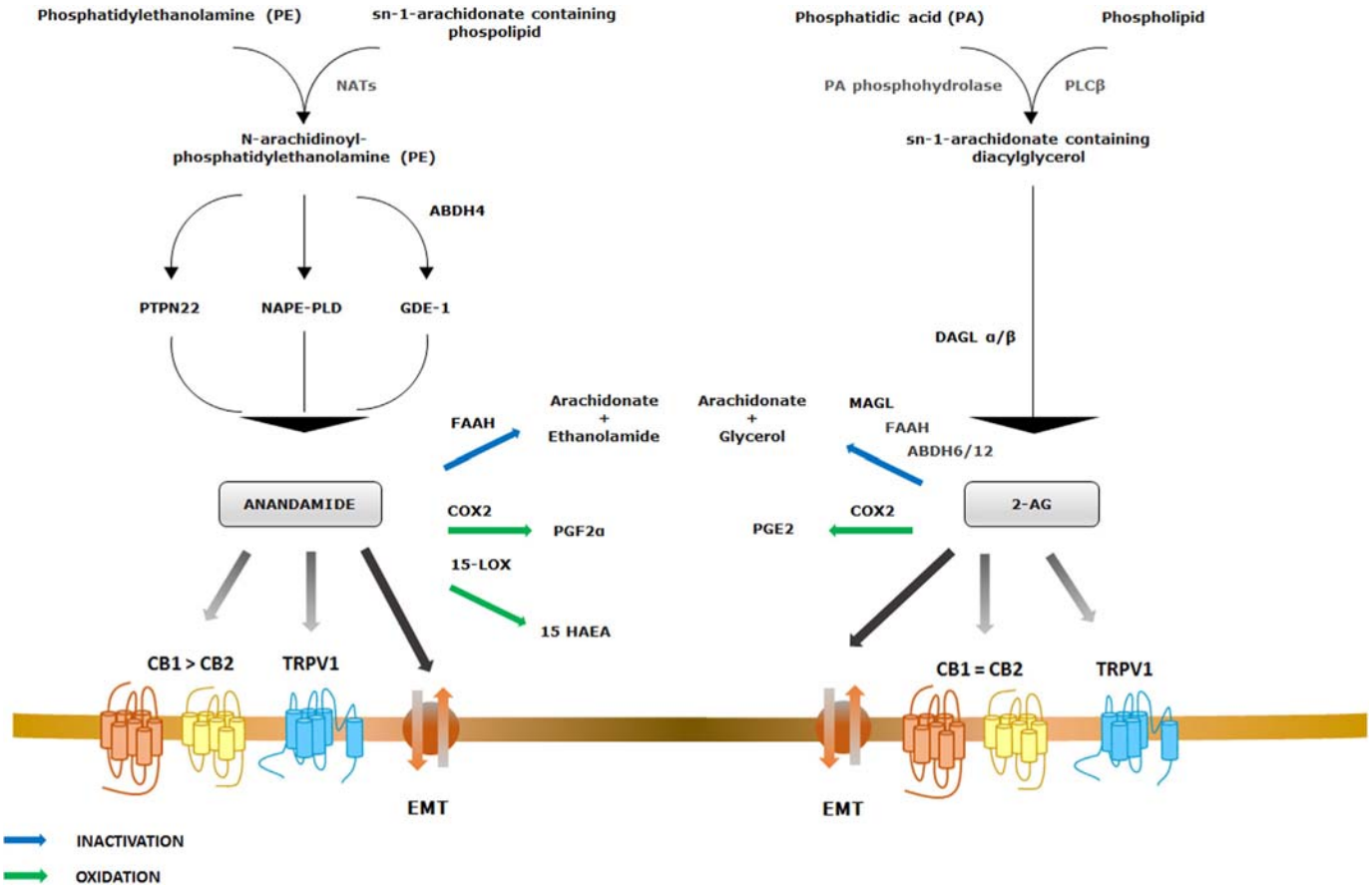

Fig. 2. Synthesis, inactivation and oxidation of AEA and 2-AG. Thick arrows denote the biochemical reactions that from the precursor membrane lead to the synthesis of the two endocannabinoids anandamide and 2AG. Abbreviations: ABDH6/12, αβ-hydrolase 4/6/12; CB1/2, cannabinoid receptor 1/2; COX2, cyclooxygenase 2; DAG, diacylglycerol; EMT, endocannabinoid membrane transporter; FAAH, fatty acid amide hydrolase; GDE1, glycerophosphodiester phosphodiesterase 1; MAGL, monoacylglycerol lipase; NAPE-PLD, *N*-acyl-phosphatidylethanolamine-specific phospholipase D; NATs, *N*-acyltransferases; PA, phosphatidic acid; PLCβ, phospholipase Cβ; PLD, phospholipase D; 15-LOX, 15-lipoxygenase; PTPN22, protein tyrosine phosphatase non-receptor type 22; PGF2α, Prostaglandin F2alpha-ethanolamide; 15 HAEA, 15(S)-HETE Ethanolamide; PGE2, Prostaglandin E2-glycerol ester; TRPV1, transient receptor potential vanilloid type-1 channel.

OMDM169 [134], JZL184 [135] and KML29 [136] for MAGL. To date, the beneficial effects of these inhibitors have been investigated in a variety of diseases including pain, inflammation, analgesia, cancer and sleeping disorders [137–139,128,129]. Moreover, the administration to mice of dual inhibitors of FAAH and MAGL, by producing more than 10-fold increases in the brain levels of both anandamide and 2-AG, leads to CB1-dependent behavioral responses in the "tetrad" of Δ^9-THC-like effects (analgesia, hypomotility, hypothermia and catalepsy) [140]. This spectrum of cannabimimetic activities was not observed upon inhibition of FAAH only. For example, JZL195 is a selective and efficacious dual FAAH/MAGL inhibitor and mimics the pharmacological activities of a "direct" CB1 receptor agonist in vivo [135], although it also shows signs of CB1 desensitization when given chronically, similar to the effects of congenital deletion of MAGL. Indeed, a recent study showed that MAGL null mice exhibit high levels of co-localization between CB1 and β-arrestin-1, a protein involved, among others, in GPCR internalization, in several brain areas, but not in the cerebellum. This results in impaired CB1-mediated signalling via MAPK, altered GABA and glutamate release and anxiety-like, depression-like and obsessive/compulsive-like behaviors [141]. Hence, caution is needed when analysing the phenotype of $MAGL^{-/-}$ mice as this may resemble that of $CB1^{-/-}$ mice rather than that expected from enhanced CB1 signalling. Conversely, it was also reported that the genetic deletion of FAAH or repeated URB597 treatment could exacerbate the inflammatory response in several models of inflammation [142–144].

Two other enzymes named ABHD6 and ABDH12 can catalyse the hydrolysis of 2-AG [145] (Fig. 2). Additionally, 2-AG can be also phosphorylated to lysophophosphatidic acid by MAG kinase [146] or acylated to DAG by MAG acyltransferase using acyl-CoA as acyl donor [147]. Finally, both anandamide and 2-AG can be oxygenated to: 1) the corresponding prostaglandin-ethanolamides (or prostamides) and glycerol esters by the sequential action of COX-2 and prostaglandin synthases, 2) hydroperoxy derivatives by 5-, 11- and 12-lipoxygenases, and 3) various oxygenated metabolites by cytochrome P450 enzymes [148–151] (Fig. 2).

Despite the extensive knowledge on the metabolism of AEA and 2-AG by the several intracellular enzymes described so far, it remains unclear how these endocannabinoids move across the plasma membrane. Several distinct mechanisms have been proposed for AEA cellular uptake (recently reviewed by Nicolussi and colleague) [152], including: 1) its simple diffusion across the membrane driven by intracellular breakdown of AEA mediated by FAAH, or by AEA sequestration by more or less selective intracellular binding proteins, and: 2) a specific carrier-facilitated mechanism, which may involve caveolae-mediated endocytosis or other "transporters" and may recognize also 2-AG [153,154]. The current prevalent hypothesis, mainly based on pharmacological evidence, is that the transport of endocannabinoids across the plasma membrane is somehow facilitated by one or more "endocannabinoid membrane transporters" (EMT). However, the molecular identity of such carrier proteins remains to be clarified and their existence is therefore subject to ongoing controversy.

In summary, although the pathways and enzymes responsible for the regulation of the tissue levels of the two major endocannabinoids have been identified, there is still a gap in our understanding of what factors and conditions determine whether AEA or 2-AG are produced and degraded by one metabolic pathway instead of another or transported across cell membranes in a facilitated manner. This knowledge will enable us to manage the intricate relationships between these metabolic pathways and their pharmacological exploitation for the treatment of human disorders associated with malfunctioning endocannabinoid signalling.

2. Anandamide congeners: palmitoylethanolamide

Of the several long chain fatty acid amides and esters that have been revisited following the discovery of AEA and 2-AG, the NAEs, and in particular OEA and PEA, are certainly the most studied ones. In this section, we review their metabolism and pharmacological mode of action, as they exemplify to a large extent what is emerging also for other endocannabinoid-like mediators.

2.1. PEA

PEA, like endocannabinoids, is an endogenous bioactive lipid, and, more specifically, the ethanolamide of palmitic acid, which is produced "on demand" from membrane phospholipids and considered since the 1950s to play an important role in various processes, from anti-inflammatory and analgesic activities to neuroprotective actions [155–159]. PEA was initially described as a compound of natural origin because it was isolated from purified lipid fractions of soybeans, egg yolk and peanut meal following the discovery of the anti-allergic and anti-inflammatory activity observed by supplementing the diet of food-deprived children with these products [160–162]. Later, PEA was defined as an endogenous mediator because it was found in most cells, tissues and body fluids of both animal and human subjects. In particular, in the periphery, PEA is produced in the liver and muscle [163], heart [164], skin [61,165–167], spinal cord [168,169], gastrointestinal tract [170–172], eye [173,174], subcutaneous adipose tissue [175], and blood [176–178]. PEA is also abundant in the central nervous system, in the brain [179–181,169] and in several brain cell types such as neurons [182], astrocytes [183] and microglia [184].

The discovery of the ECS and of the endocannabinoids, AEA and 2-arachidonoylglycerol (2-AG) [6,7], led us to classify PEA as an endocannabinoid-like molecule, since this compound, apart from belonging to the same class as AEA, i.e. the NAEs, shares biosynthetic and metabolic pathways, but only in part the same mechanisms of action, with the endocannabinoid.

2.1.1. Biosynthetic and metabolic pathways of PEA

PEA is biosynthesized from its direct phospholipid precursors, the *N*-palmitoyl-phosphatidyl-ethanolamines (NAPE), through the catalytic action of NAPE-PLD [185], and inactivated by two different hydrolytic enzymes: 1) FAAH [186] and, more specifically 2) NAAA [187], which metabolize PEA to palmitic acid and ethanolamine (Fig. 3). While FAAH belongs to the serine hydrolase family, and amidase subfamily, of enzymes, is active at alkaline pH and exhibits the highest reactivity with AEA [186,188], NAAA belongs to the cysteine hydrolase family, is active at acidic pH (and localizes to lysosomes) and hydrolyzes preferentially PEA [187]. NAAA is activated by self-catalyzed proteolysis involving a catalytic triad constituted of Cys126-Arg142-Asp145, with Cys126 acting as the catalytic nucleophile [189,190].

PEA is produced in mammalian cells and its tissue concentrations are often altered during several pathological conditions, in particular during pain and inflammatory conditions (as will be discussed below) [156,56,159]. Therefore, the existence of a specific inactivating enzyme for this lipid mediator, i.e. NAAA, highly expressed in macrophages and the lungs, as well as in various rat tissues including the brain [191,192], allowed the development of selective inhibitors able to inhibit this protein and selectively increase the endogenous levels of PEA, with subsequent anti-inflammatory and analgesic actions (Fig. 3). Several compounds have been reported to be selective NAAA inhibitors, the first having been discovered from the screening of different esters, retroesters and retroamides of palmitic acid, i.e. cyclohexylhexadecanoate, with an IC_{50} value of 19 μM [193], and cyclopentylhexadecanoate, with an IC_{50} value of 10 μM [194,13]. The latter compound showed an inhibition of a competitive nature and the ability to increase endogenous PEA levels in intact cells [194,13]. Later a series of cyclohexylhexadecanoate and 1-pentadecanyl-carbonyl pyrrolidine derivatives were synthetized, of which *N*-pentadecylcyclohexanecarboxamide and 1-(2-biphenyl-4-yl)ethyl-carbonyl pyrrolidine showed strongest inhibitory activity, with IC_{50} values of 4.5 μM and 2.1 μM, respectively, and a mechanism of action of a non-competitive and competitive nature, respectively [195,196].

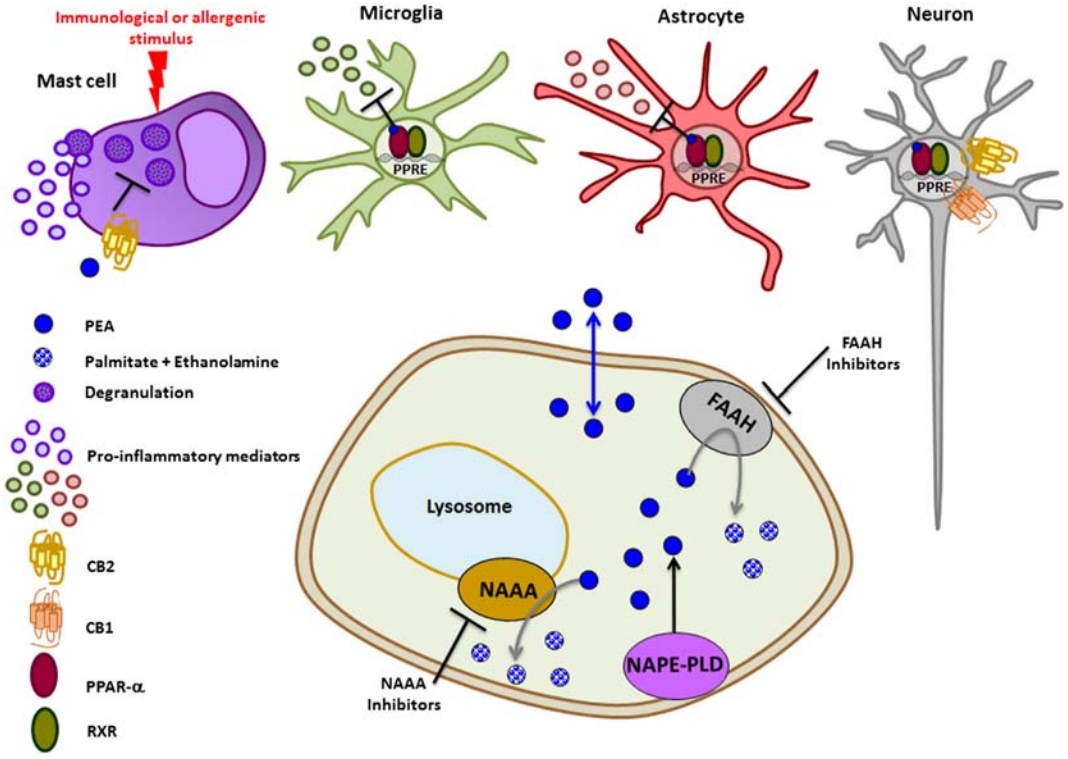

Fig. 3. Biosynthesis, degradation and cellular targets of PEA. PEA is synthetized, among others, by NAPE-PLD and hydrolyzed to palmitic acid and ethanolamine by FAAH and NAAA [13]. The degradation of PEA could be blocked by the use of specific FAAH and NAAH inhibitors [10,194,197,205]. In mast cells, PEA exerts anti-inflammatory effects by inhibiting the degranulation and the release of pro-inflammatory mediators through indirect activation of CB2 receptors [206]. PEA reduces the activation of microglia and astrocytes through a PPAR-α-mediated mechanism [181,328]. In neuronal cells, PEA exerts: 1) neuroprotective effects through a PPAR-α-mediated mechanism [333]; and 2) antiepileptic and anti-convulsive effects through a direct activation of PPAR-α receptors and an indirect activation of CB1 or CB2 receptors [336,337]. In other conditions, PEA was suggested to act also via GPR55 activation [16], although the target cell type for these actions has not been identified yet. Abbreviations: PEA, palmitoylethanolamide; CB1/2, cannabinoid receptor 1/2; PPAR-α, peroxisome proliferator-activated receptor-α; RXR, retinoid X receptor; PPRE, peroxisome proliferator–response elements; FAAH, fatty acid amide hydrolase; NAPE-PLD, *N*-acyl-phosphatidylethanolamine-specific phospholipase D; NAAA, N-acylethanolamine acid amidase.

Moreover, 1-(2-biphenyl-4-yl)ethyl-carbonyl pyrrolidine reduced, in a dose-dependent manner, the mRNA expression levels of iNOS and IL-6 in an in vitro model of inflammation induced by lipopolysaccharide (LPS) in mouse macrophages, and this effect was also accompanied by an increase of the intracellular levels of PEA [196]. On the other hand, *N*-[(3S)-2-oxo-3-oxetanyl]-3-phenylpropanamide ([(S)-OOPP]) was discovered as a more potent NAAA inhibitor since it exhibited nanomolar IC_{50} values, 420 nM, blocked NAAA through a non-competitive mechanism, increased PEA levels in activated leukocytes, attenuated inflammation and tissue damage, and improved recovery of motor function in mice subjected to spinal cord trauma [197,198].

Later, in order to obtain even more potent inhibitors starting from the structure of (S)-OOPP, a series of β-lactones were prepared. Although (S)-*N*-(2-oxo-3-oxetanyl)biphenyl-4-carboxamide at first seemed to be more potent than (S)-OOPP with an IC_{50} value of 115 nM [198], it showed lower chemical stability. Subsequently, a derivative of this compounds, (2S,3R)-2-methyl-4-oxo-3-oxetanylcarbamic acid 5-phenylpentylester (ARN077), turned out to be the most potent NAAA inhibitor ever developed [199]. This compound, which showed enhanced chemical stability, was able to inhibit NAAA with an IC_{50} value of 50 nM [200] and with a non-competitive mechanism [201]. Moreover, topical administration of ARN077 attenuated, in a dose-dependent manner, heat hyperalgesia and mechanical allodynia elicited in mice by either carrageenan injection or sciatic nerve ligation, and reversed the decreased levels of PEA in sciatic nerve ligation, as well as the allodynia caused by ultraviolet B radiation in rats [201]. Instead, modifications of the 5-phenylpentyl side chain of ARN077 led us to identify a threonine-derived-lactone analogue of ARN077, (4-phenylphenyl)-methyl-N-[(2S,3R)-2-methyl-4-oxo-oxetan-3-yl]carbamate as the first single-digit nanomolar inhibitor of intracellular NAAA activity, with an IC_{50} value of 7 nM [200]. Recently, a new class of less potent NAAA inhibitors, the 3-aminoazetidin-2-one derivatives has been reported, of which *N*-[(S)-2-oxoazetidin-3-yl]nonanamide showed good inhibitory potency with an IC_{50} value of 340 nM [202].

Finally, EPT4900 (4,5-diacetyloxy-9,10-dioxo-anthracene-2-carboxylic acid or diacerein), already known for its anti-inflammatory effects and clinical effects against osteoarthritis [203,204], was recently reported to be a new potential inhibitor of NAAA [205]. This discovery allowed us to hypothesize that NAAA inhibition might be the mechanism through which diacerein exerts its effects, since the mechanism of action for this drug had never been reported before, and to propose that NAAA inhibition might work against inflammatory pain also in humans [205]. The compound inhibited NAAA both in cell-free preparations and intact cells with an IC_{50} value of 7.2 μM, and pre-incubation before the addition of substrate improved its inhibitory activity by 10-fold (IC_{50} = 0.7 μM) [205]. Moreover, in a model of acute inflammatory pain induced by an intraplantar injection of carrageenan in rats, EPT4900/diacerein was able to exert anti-inflammatory and anti-hyperalgesic actions, and these effects were accompanied by increased tissue levels of PEA [205]. It has emerged recently that the oxazoline intermediate of PEA, EPT4102 (2-pentadecanoyl-oxazoline) is also able to inhibit NAAA by 58% at the maximal concentration tested (50 μM) (S. Petrosino & V. Di Marzo, unpublished results).

2.1.2. Mechanisms of action of PEA

In order to explain the anti-inflammatory and analgesic actions of PEA, three mechanisms of action have been put forward and are known as: 1) the "Autacoid Local Inflammation Antagonism" (ALIA) hypothesis; 2) the direct receptor-mediated mechanism; and 3) the "entourage effect". The existence of the former mechanism does not

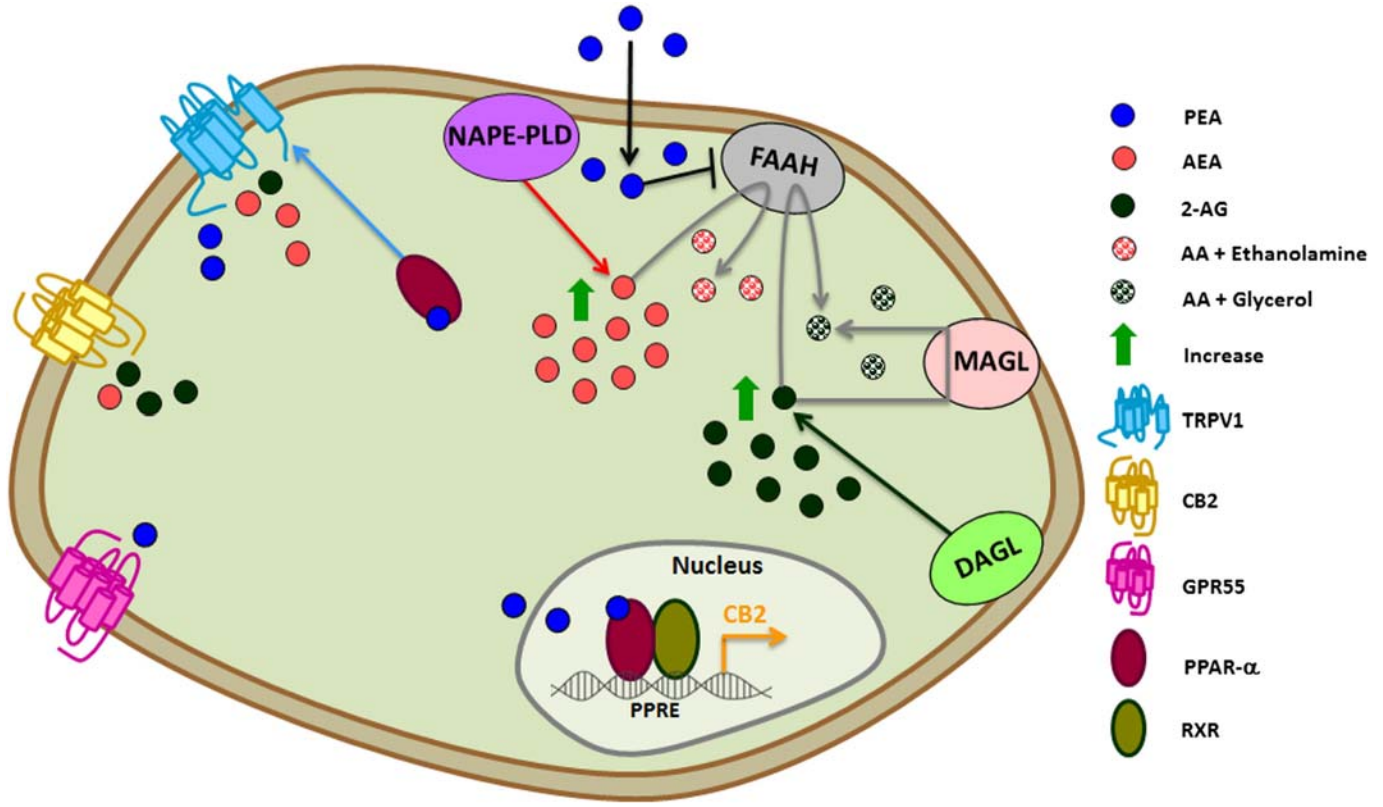

Fig. 4. Proposed mechanisms of action of PEA. PEA, through the inhibition of the activity or expression of FAAH, or via additional unknown mechanisms, increases the endogenous levels of AEA and 2-AG, which directly activate CB2 and TRPV1 receptors ("entourage effect") [210,218]. PEA, possibly through an allosteric modulation of TRPV1 receptors, potentiates the actions of AEA and 2-AG at TRPV1 receptors ("entourage effect") [70,211,218]. In keratinocytes, PEA exerts anti-inflammatory effects through this proposed mechanism [61]. PEA directly activates PPAR-α receptors [209]. In sensory neurons, PEA activates TRPV1 receptors via PPAR-α receptors [73,74]. PEA increases the expression of CB2 receptors and this effect is mediated by PPAR-α receptors (Guida F, Maione S and Di Marzo V, personal communication). PEA also seems to directly activate GPR55 receptors [99]. Abbreviations: PEA, palmitoylethanolamide; AEA, anandamide; 2-AG, 2-arachidonoyl-glycerol; AA, arachidonic acid; TRPV1, transient receptor potential vanilloid type-1 channel; CB2, cannabinoid receptor 2; GPR55, orphan G-protein coupled receptor 55; PPAR-α, peroxisome proliferator-activated receptor-α; RXR, retinoid X receptor; PPRE, peroxisome proliferator–response elements; NAPE-PLD, *N*-acyl-phosphatidylethanolamine-specific phospholipase D; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; DAGL, diacylglycerol lipase.

exclude either of the latter two, and in fact, a synergistic interaction may occur between the "receptor-mediated mechanism" or the "entourage effect" and the ALIA hypothesis.

It was originally demonstrated that systemic administration of PEA reduces mast cell degranulation induced by local injection of substance P in the ear pinna of developing rats [155]. This evidence indicated a local antagonism exerted by PEA on inflammation, and this effect was denoted as ALIA [155]. Successively, the "receptor mechanism" was proposed based on the capability of PEA to directly stimulate different receptor targets. In fact, at first PEA was described as an agonist of the cannabinoid CB2 receptor, since it was able to inhibit [^{3}H]WIN 55,212-2 binding to the CB2 receptor [206], and the administration of the CB2 antagonist, SR144528 reversed the analgesia produced by PEA [207] (Fig. 3). However, SR144528 did not impede the inhibition of inflammation by the PEA [208], and this finding, together with the lack of effect of the compound in binding assays carried out with recombinant human or mouse CB2 receptors, led to test and eventually demonstrate the hypothesis that the peroxisome proliferator-activated receptor-α (PPAR-α) could be the receptor mediating the anti-inflammatory effects of PEA (as will be discussed below) [209] (Figs. 3 and 4). Later, GPR55 was also suggested as a potential target for PEA [99,16] (Fig. 4). Finally, an indirect receptor mechanism of action for PEA was hypothesized and named "entourage effect" [210,70,211], based on the capability of PEA to increase either the levels or the actions, or both, of AEA (Fig. 4). In fact, PEA can potentiate some actions of AEA at CB1 and CB2 receptors or at TRPV1 channels, either via inhibition of the expression of FAAH [210], or through a seemingly positive allosteric modulation of TRPV1 channels [70,209] (Fig. 4). In this regard, numerous papers suggest for PEA an AEA-mediated mechanism of action following TRPV1-, CB1- or CB2-activation, in as much as it has been demonstrated that the protective effects exerted by PEA can be attenuated or prevented by specific antagonists of these receptors, i.e. 5-iodioresiniferatoxin (I-RTX) or capsazepine (CPZ) for TRPV1, AM251 or SR141716 for CB1 and SR144528 or AM630 for CB2. For example, the analgesic effects following i.p. administration of PEA in a murine model of neuropathic pain [212], as well as after injection of PEA into the ventrolateral periaqueductal grey of male rats [213], were blocked by both I-RTX and AM251. Moreover, the hypotensive response after intrathecal injection of PEA and AEA was prevented by both CPZ and SR141716 [214]. On the other hand, in a mouse model of post-inflammatory accelerated transit, I-RTX was able to increase the inhibitory effect of PEA on gastrointestinal motility, while SR141716 blocked this action [215], and likewise the anti-inflammatory effect of PEA in a murine model of colitis was increased by CPZ and blocked by AM630 [16]. These data may suggest that the capability of PEA to activate indirectly TRPV1 in some cases leads to the activation and desensitization of this channel, thus contributing to PEA anti-inflammatory actions, whereas in other cases it results only in activation, thus counteracting the inhibitory effect of the lipid mediator on inflammation, mediated by other targets (e.g. direct activation of PPAR-α or indirect activation of CB1 and CB2 receptors). However, it was demonstrated that TRPV1 blockers do antagonize the anti-inflammatory effects induced by PEA in in vitro and in vivo models of contact allergic dermatitis (CAD) [61]. In fact, I-RTX was able to reverse the inhibitory effects of PEA on the expression and release of chemokine

monocyte chemoattractant protein 2 (MCP-2) in polyinosinic polycytidylic-acid (poly-(I:C))-treated human keratinocytes (HaCaT) cells in vitro. Additionally, in dinitrofluorobenzene (DNFB)-sensitized mice the anti-inflammatory effects of PEA were counteracted by CPZ [61]. Finally, it was shown that these TRPV1-mediated effects of PEA could be attributed to the elevated levels of endogenous AEA and OEA observed both in poly-(I:C)-HaCaT cells and in the DNBS in vivo model of CAD [61,216].

It was originally believed that PEA could induce an "entourage effect" only on AEA endogenous levels/actions, since it seemed that TRPV1 channels could only be activated and desensitized by AEA [210, 211,70]. However, more recently, 2-AG was also shown to activate TRPV1 channels [217], and it was demonstrated that PEA is able to exert an "entourage effect" also on this endocannabinoid, by increasing its endogenous levels both in HaCaT cells in vitro and in Beagle dogs and human volunteers in vivo [218]. Importantly, it was also shown that, although PEA only slightly enhanced 2-AG activation of TRPV1, it significantly increased 2-AG-induced TRPV1 desensitization [218]. Since 2-AG is significantly more efficacious than AEA at activating CB2 receptors [37,57], the finding that PEA can enhance the levels of the former endocannabinoid might help explain initial data showing that CB2 antagonists could block some effects of PEA even though this compound cannot interact directly with CB2 receptors. Finally, providing yet another possible mechanism to its "entourage" effects and the sensitivity of its actions to CB2 antagonists, recent data indicate that PEA, at least in microglia, also upregulates CB2 receptor expression (Guida F, Maione S and Di Marzo V, personal communication).

3. Endocannabinoids and endocannabinoid congeners in major neurological disorders

In most of the physiological and pathological perturbations of the cell steady-state in which its function has been studied to date, the ECS has been shown to play a pro-homeostatic role, facilitated by the fact that endocannabinoids are local mediators that can be biosynthesized and released on demand and thus activate their targets only when and where needed. As a consequence, tissue endocannabinoid levels are very often altered, and the activity of their targets modified, in nearly all chronic disorders, as an adaptive response aimed at restoring homeostasis or as a maladaptive mechanism eventually contributing to disease symptoms or progress. Thus, pharmacological manipulation of endocannabinoid levels and/or CB1, CB2 and TRPV1 activity, in one direction or the other (i.e. with potentiation or counteraction of endocannabinoid tone), often produces beneficial effects in animal models of diseases [145] (Tables 1 and 2). It would be impossible to describe here all pathological conditions in which the ECS, and now endocannabinoid-like mediators as well, have been implicated, and therefore we elected to focus only on some chronic and degenerative neurological disorders.

3.1. The role of endocannabinoids in neurodegenerative and convulsive diseases

3.1.1. Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia, affecting over 35 million people worldwide [219]. The neuropathological hallmarks of AD include the formation of plaques caused by the abnormal accumulation of amyloid β-protein (Aβ), neurofibrillary tangles, neuropil threads, and dystrophic neurites containing hyperphosphorylated tau protein [220–223]. These alterations cause the progressive atrophy and degeneration of neurons in both cortical and subcortical regions, including the hippocampus, amygdala, temporal, parietal and frontal cortex [220].

Post-mortem analysis of brains from AD patients revealed that this disorder is associated with a significant reduction in CB1 receptor expression, whereas the expression of CB2 and FAAH in both microglia

Table 1
Experimental and potential therapeutic use of cannabinoid receptor agonists and antagonists/inverse agonists in neurological disorders.

Disease	Target	Type of drug		Effect	Type of study	Reference
Epilepsy	CB1	Antagonist	SR141716 (Rimonabant)	Pro-convulsant	Pilocarpine-induced seizure in rats	[304]
				Pro-convulsant	KA -induced seizure in mice	[306,387,388]
			AM251	Pro-convulsant	Penicillin-induced seizures in rats	[389]
		Agonist	ACEA	Anti-convulsant	PTZ-induced seizures in mice	[390]
					Penicillin-induced seizures in rats	[389,391]
			ACPA	Anti-convulsant	PTZ-induced seizures in rats	[304,392]
	CB1/CB2	Agonist	WIN 55,212 2	Anti-convulsant	Pilocarpine-induced seizure in mice	[306]
				Anti-convulsant	Low Mg^{2+}	[300]
				Anti-convulsant	PTZ-induced seizures in rats	[393,394]
	TRPV1	Agonist	Capsaicin	Pro-convulsant	PTZ-induced seizures in rats	[313]
				Pro-convulsant	KA-induced seizures in rats	[395]
			OLDA	Pro-convulsant	Pilocarpine-induced seizure in rats	[314]
		Antagonist	Capsazepine	Anti-convulsant	4AP-induced seizure in rats	[396]
Huntington's disease	CB1	Antagonist	SR141716 (Rimonabant)	Neurotoxic	Malonate-induced toxicity in rats	[266]
	CB2	Agonist	HU308	Neuroprotection	Malonate-induced toxicity in rats	[267]
		Antagonist	SR144528	Neuroprotection	Malonate-induced toxicity in rats	[267]
	CB1/CB2	Agonist	HU210	Neurotoxic	R6/1 mice	[397]
Parkinson's disease	CB1	Antagonist	SR141716 (Rimonabant)	Neuroprotection	6-OHDA lesioned rats	[398,252]
				No effect	MPTP-lesioned monkey	[249]
				No effect	24 patients	[234]
				Neuroprotection	MPTP-lesioned marmosets	[242]
	CB1/CB2	Agonist	WIN 55,212 2	Neuroprotection	6-OHDA or MPTP-lesioned rats	[399,400]
Alzheimer's disease	CB2	Agonist	JWH-133	Neuroprotection	Amyloid-β-induced toxicity in rats	[224]
	CB1/CB2	Agonist	WIN 55,212 2	Neuroprotection	Amyloid-β-induced toxicity in rats	[224–401]
			MDA7	Neuroprotection	Amyloid-β-induced toxicity in rats	[93]
			HU210	Neuroprotection	Amyloid-β-induced toxicity in rats	[224]
Multiple sclerosis	CB1	Antagonist	SR141716 (Rimonabant)	Neurodegeneration	CREAE in mice	[168]
	CB2	Agonist	JWH-133	Neuroprotection	CREAE in mice	[168]
			Gp1a	Neuroprotection	EAE in mice	[288]
	CB1/CB2	Agonist	WIN 55,212-2	Neuroprotection	EAE in mice; CREAR in mice	[402,168]

ACPA, arachidonylcyclopropylamide; KA, kainic acid; ACEA, arachidonyl-2-chloroethylamide; OLDA, N-oleoyl-dopamine; PTZ, pentylenetetrazol; 4AP, 4-aminopyridine; 6-OHDA, 6-hydroxydopamine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahyropyridine; CREAE, chronic experimental autoimmune encephalomyelitis; EAE, experimental autoimmune encephalomyelitis.

Table 2
Experimental and potential therapeutic use of endocannabinoid-related enzyme inhibitors in neurological disorders.

Disease	Target	Inhibitor	Effect	Type of study	Reference
Epilepsy	MAGL	URB602	Pro- and anti-convulsant	PTZ-induced seizures in mice	[395]
		AM404	Pro- and anti-convulsant	PTZ-induced seizures in mice	[395]
	FAAH	AM5206	Anti-convulsant	KA-induced seizures in rats	[307]
		URB597	Anti-convulsant	PTZ-induced seizures in mice	[395,394]
		AM374	Anti-convulsant	KA-induced seizures in rats	[403,308]
	MAGL and FAAH	AM6701	Anti-convulsant	KA-induced seizures in rats	[307]
Huntington's	DAGL	O-3841	Neuroprotection	Malonate-lesioned rats	[268]
	MAGL	JZL184	Neurotoxicity	Malonate-lesioned rats	[268]
		OMDM169	Neurotoxicity	Malonate-lesioned rats	[268]
Parkinson's	FAAH	URB597	No effect	6-OHDA induced lesions	[404]
Multiple sclerosis	MAGL	JZL184	Neuroprotection and reduced inflammation	EAE in mice	[405,283]
	FAAH	CAY100400	Anti-spasticity	EAE in mice	[283]
		CAY100402	Anti-spasticity	EAE in mice	[283]
		URB597	Anti-spasticity	EAE in mice	[283]

PTZ, pentylenetetrazol; KA, kainic acid; 6-OHDA, 6-hydroxydopamine; EAE, experimental autoimmune encephalomyelitis.

and astrocytes was increased [223]. Indeed, several studies carried out in experimental AD models have suggested that endocannabinoids may not only exert a neuroprotective role due to their anti-inflammatory and anti-apoptotic mechanisms, but also participate in some of the symptoms via their neuromodulatory actions [224–230]. CB2 receptor stimulation counteracts microglia activation induced by Aβ, a beneficial effect found in both in vitro and in vivo models [225,226]. CB1 receptor stimulation was reported to protect neurons by activating brain-derived neurotrophic factor (BDNF) [220], and to rescue toxicity in hippocampal CA1 pyramidal and GABAergic neurons by restoring normal neuronal excitability [229–232]. However, CB1 receptors can also participate in the symptoms in as much as their blockade was shown to reduce memory retention deficits [233] and CB1 activation by 2-AG was found to contribute to synapse silencing via prolonged depolarization-induced suppression of inhibition in the hippocampus [234] in mice treated with Aβ. Thus, it has been proposed that enhancement of endocannabinoid tone with inhibitors of endocannabinoid metabolism can produce neuroprotection and reduce memory deficits only if carried out soon after the neurotoxic insult [227].

In agreement with a protective role of endocannabinoids in human AD patients, an Aβ-dependent deficit in AEA mobilization was shown to be associated with cognitive dysfunction [235], whereas increased plasma 2-AG levels were found to correlate with white matter hyper intensity volume, as well as with memory and attention performances, thus potentially representing an adaptive mechanism modulating the impairment of cognitive performance during the disorder [236].

3.1.2. Parkinson's disease (PD)

The pathology of Parkinson's disease (PD) results from an abnormal accumulation of alpha-synuclein protein in the dopaminergic neurons of substantia nigra which leads to progressive and irreversible cell toxicity of nigrostriatal afferents. The subsequent deficit of dopamine in the striatum is responsible for both primary and secondary symptoms such as muscle rigidity, tremors, slowing of physical movements (bradykinesia), cognitive dysfunction and subtle language problems [237].

Many studies have demonstrated that the ECS works as a key modulator of dopaminergic neurotransmission [238,239], and that, vice versa, dopamine depletion can cause significant alterations in the ECS [240–242]. Interestingly, in rat or non-human primate models of PD an over-activity of endocannabinoid signalling was found in the basal ganglia, for example after the administration of reserpine [243], 6-hydroxydopamine [244–246] or *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [247]. Likewise, in non-human primates treated with MPTP, elevation of 2-AG and anandamide levels in the striatum, and of 2-AG in the substantia nigra, was reported [242]. These changes are consistent with the previously suggested role for endocannabinoids in mechanisms attempting to compensate for loss of dopamine in untreated experimental parkinsonism. In the human brain, post-mortem analysis revealed that the transcript levels of CB_1 receptors was decreased in the caudate nucleus, anterior dorsal putamen and external segment of the globus pallidus, but remained unchanged in other brain areas [248]. These changes could be due to chronically enhanced endocannabinoid levels in the basal ganglia described in the animal models, which might therefore contribute to motor dysfunction in PD. For these reasons, the ECS has raised interest as a potential pharmacological target to treat neurological disorders caused by alteration in dopamine neurotransmission. However, in both in vivo models and human studies of PD, selective pharmacological blockage of CB1 receptors with rimonabant yielded controversial results [243,249–251]. More recent results suggested that the dose of CB1 antagonist, the type and severity of dopaminergic injury, and the stages of the disease all together may represent critical factors for determining the efficacy of the drug treatment [252,253].

In addition to CB1, in vivo studies have shown that the pharmacological activation of CB2 receptors dampens microglial activation, thus reducing the neuroinflammation and degeneration occurring in PD [254]. In particular, CB2 receptors are elevated in microglial cells recruited to, and activated at, lesioned sites in the substantia nigra of PD patients compared to control subjects. Using experimental models, CB2 expression was found particularly pronounced in the inflammation-driven models of PD (MPTP- or LPS lesioned mice) than in the neurotoxic model (6-hydroxydopamine lesioned rats [254,255]. In the same study, it was reported that the genetic inactivation of CB2 receptors aggravates LPS-induced inflammation. The neuroprotective role of 2-AG was experimentally demonstrated in mice lesioned with MPTP, where the treatment with JZL184, a selective MAGL inhibitor, reduces neurodegeneration [256]. Instead, in vitro, Aymerich and colleagues showed that JZL184 increases cell survival in neuron-like cells SH-SY5Y cells treated with 1-methyl-4-phenylpyridinium iodide (MPP+), in a manner blocked by AM630, a CB2 receptor antagonist, and mimicked by JWH133, a CB2 receptor agonist [257]. Collectively, these data indicate the involvement of CB2 receptors in the protection against inflammation-induced neurogeneration. Accordingly, $CB2^{-/-}$ mice show more vulnerability to LPS than 6-hydroxydopamine [255], although, in a previous study CB2 overexpression was found to protect the brain of mice lesioned with 6-hydroxydopamine [258]. Interestingly, the phytocannabinoid Δ^9-tetrahydrocannabivarin, which differs from Δ^9-THC because it bears a n-propyl instead of an n-pentyl side chain, showed promising activity at delaying disease progression in PD and ameliorating parkinsonian symptoms, possibly due to its well documented antioxidant properties and ability to activate CB2 and antagonize CB1 receptors [255]. In summary, although there has been great progress in our understanding of ECS and phytocannabinoid role in neurodegenerative disorders, there has been so far little effort to translate this knowledge into clinical trials.

3.1.3. Huntington's disease (HD)

Huntington's disease (HD) is characterized by progressive abnormal involuntary writhing movements known as chorea. The cause of HD is an autosomal dominant mutation in either of an individual's two copies of the gene encoding for the corresponding protein called huntingtin. In particular, an abnormal expansion of a CAG (cytosine–adenine–guanine) triplet repeat stretch within the Huntingtin gene results in various non-functional forms of huntingtin protein. These mutant versions of the protein prevent the normal cellular processes of protein turnover, producing abnormal aggregates within the neurons of HD brain regions [237].

In the brain tissue of patients with HD, post mortem analysis revealed a loss of cannabinoid CB1 receptor and dopamine receptor D2 expression in the globus pallidus and substantia nigra [259]. This finding has been supported by subsequent studies revealing a prominent loss of both CB1/GABA/enkephalin and CB1/GABA/substance P positive neurons within the globus pallidus [260], whereas, in microglia, CB2 receptor expression is up-regulated [261].

Interestingly, the activity of FAAH is reduced in HD patients with respect to non-HD patients [262].

In 12 week old R6/1 mice, a common genetic animal model of HD, 2-AG levels are significantly increased in the cortex, whereas AEA levels are decreased in the hippocampus, when compared to littermate controls. However, in this case, CB1 expression in the brain did not undergo significant changes, except for a slight decrease in the substantia nigra [263]. In the brain of R6/2 mice, an alternative animal model of HD, Bisogno and colleagues found that endocannabinoid levels change in a disease phase- and region-specific way, suggesting that the impairment of the ECS represents a hallmark of HD [264]. More recently, it has been reported that, in the brain of R6/2 mice, the loss of CB1 receptor expression and its dependent activation of the downstream effector BDNF is associated with the damage observed in dorsolateral striatum neurons [265].

In murine models of HD pharmacologically induced by malonate, which causes striatal neuron degeneration, the selective CB1 blocker SR141716 enhanced the magnitude of striatal degeneration [266]. A greater sensitivity to malonate, was also found in $CB2^{-/-}$ mice [267]. Interestingly, however, the pharmacological inhibition of 2-AG biosynthesis in rats lesioned with malonate reduced, instead of exacerbating, neuronal loss, possibly through the counteraction of the formation of pro-neuroinflammatory PGE2-glycerol ester formed from the COX-2-mediated oxygenation of 2-AG [268].

The current therapy used to treat HD uses antibiotic and/or antioxidant agents (i.e. minocycline, coenzyme Q10, unsaturated fatty acids, inhibitors of histone deacetylases) or tetrabenazine, which is the first drug approved by FDA in 2008 to treat choreic symptoms [269]. These drugs relieve the symptoms of HD, but are not able to prevent the cause of the disease. Therefore, it is important to find new treatments that prevent the initiation of HD [247,248]. One possible way to accelerate the finding of new drugs is to use compounds that have already been tested in humans, such as the plant cannabinoids. Recent studies have showed that Δ^9-THC, alone or in combination with CBD, the other major plant cannabinoid with little activity at CB1 and CB2 receptors, provides significant beneficial effects in distinct genetic or drug-induced animal models of HD [270–274]. Δ^9-THC also showed a neuroprotective effect in R6/2 mice [275]. Moreover, Valdeolivas and colleagues found that the combination of Δ^9-THC with CBD, prevented acute brain damage in malonate treated animals in a manner at least in part dependent on CB1 and CB2 receptor activation [275].

To date, only a few human clinical trials have been performed with pure cannabinoids in HD. In particular, in two uncontrolled single-patient and in one double-blind placebo-controlled study, nabilone, a structural analogue of Δ^9-THC, yielded conflicting results. Some patients treated with nabilone in fact claimed an amelioration of motor and cognitive functions [276,277], while other patients experienced a worsening of symptoms [278]. In conclusion, although the potential benefits of CB1 or CB2 activation has not been proved yet in patients affected by HD, the robustness of the beneficial effects exerted by Δ^9-THC alone or in combination with CBD in HD animal models justifies further clinical studies.

3.1.4. Multiple sclerosis

Multiple sclerosis (MS) is a progressive neurological disorder characterized by the demyelination of axons in the brain and spinal cord with the subsequent impairment of nerve signal transmission between the central nervous system and peripheral tissues or organs. Wide ranges of neurological symptoms characterize MS such as spasticity, neuropathic and nociceptive pain, dysaesthesia, cognitive dysfunction, insomnia, anxiety and depression [279,280]. The cause of MS remains unclear, but is most likely due to a combination of genetic, immunological, environmental, infectious and possibly other factors including vascular dysfunction [280–282]. To date, there is no cure for MS and the treatments currently available only afford partial relief.

Early studies in the MS model of chronic-remitting experimental allergic encephalomyelitis in Biozzi mice showed that the use of selective or nonselective CB1/CB2 receptor agonists (i.e. R(+)-WIN 55,212, Δ^9-THC, methanandamide and JWH-133 or others) significantly reduce the spasticity and tremors associated with the disease, whereas the CB1 antagonist SR141716 instead exacerbated these symptoms [168]. Indeed, in this same model, AEA and 2-AG levels in both the brain and spinal cord were increased selectively during the spasticity phase of the disorder [168], and inhibitors of FAAH or MAGL reduce spasticity [283], indicating that the tone of the ECS is increased during MS spasticity to counteract this neurochemical unbalance.

Interestingly, however, in another mouse model of experimental autoimmune encephalomyelitis (EAE), the enhanced interferon (IFN)-γ activity associated with EAE lesions acts to inhibit DAGLα expression in microglia, thereby limiting 2-AG-mediated neuroprotection [284], and providing a further reason why the prevention of endocannabinoid inactivation might be a new strategy not only to reduce spasticity but also to retard the progression of the disease. Indeed, Wen and colleagues recently showed that inhibition of ABHD6 enhances 2-AG levels with subsequent activation of CB2 receptors in immune cells, and reduction of EAE-induced neuroinflammation [285]. In fact, a previous study using CB1 and CB2 knockout mice had already suggested that CB1 and CB2 play distinct roles in the control of EAE progression. While CB1 receptors in neurons, but not T cells, are required for EAE suppression, CB2 in encephalitogenic T cells is critical for controlling inflammation associated with this MS model [286]. CB2-deficient T cells in the CNS during EAE exhibited reduced levels of apoptosis, a higher rate of proliferation and increased production of inflammatory cytokines, resulting in severe clinical disease. The ECS inhibits leukocyte rolling and adhesion, which participate in leukocyte infiltration when the blood–brain barrier is disrupted [287–289], and reduces microglia activation, nitrotyrosine formation, oligodendrocyte toxicity, myelin loss and axonal damage [290]. These effects appear to be mediated by the CB1 receptor as they were abrogated by specific CB1 receptor antagonists or in $CB1^{-/-}$ mice [290,291,286]. However, in $CB2^{-/-}$ mice with EAE, T cells exhibit reduced levels of apoptosis, a higher rate of proliferation and increased production of inflammatory cytokines, resulting in increased infiltration in the brain [286].

In summary, these findings could provide the basis to treat with ECS-based drugs also the progress of MS and not only its symptoms, as it is currently done with Sativex [279]. This is an oromucosal spray containing equivalent amounts of Δ^9-THC and CBD in the form of botanical extracts, approved to date for the treatment of spasticity and pain associated to MS [291]. At the present, Sativex is approved as a treatment for MS spasticity in 27 countries, but it would be important to test the usefulness of Sativex also in MS disease progression [292]. This assessment is necessary given the immunomodulatory, anti-inflammatory and cytoprotective actions exhibited by phyocannabinoids tested in distinct preclinical models of MS [293–299,283,286].

3.1.5. Epilepsy

Epilepsies represent a group of neuronal dysrhythmias caused by defects in membrane excitability, leading to aberrant synchronization of neural networks. This alteration in electrical activity is characterized by a long-term risk of recurrent seizures [69]. Interestingly, accumulating evidence suggests that alterations in ECS activity are closely associated to a wide range of in vitro and in vivo models of epilepsy [300–306]. Evidence from mice lacking CB1 in excitatory neurons, but not in inhibitory interneurons, led Marsicano and colleagues to postulate for the first time that increased levels of endocannabinoids during seizures represent, through pre-synaptic CB1 receptor stimulation and reduction of glutamate signalling, an important endogenous mechanism to counteract epileptiform discharges [306,303].

The pro-homeostatic and neuroprotective role attributed to the ECS during epilepsy have also been underpinned by other studies showing that administration of exogenous CB1 agonists or selective MAGL or FAAH inhibitors protect neurons from recurrent seizures [307,308]. In agreement with these findings, pharmacological blockade of CB1 receptor or its genetic ablation in $CB1^{-/-}$ mice cause instead a marked enhancement of the severity of seizures in several (although not all) models of epilepsy [309]. However, other studies revealed that the systemic administration of exogenous cannabinoids or drugs able to interfere with their metabolism is not a viable therapeutic strategy in all experimental models of seizing activity, since it can give rise also to pro-convulsive effects [310]. A possible explanation for this discrepancy is due to the fact that CB1 receptor expression is not restricted to glutamatergic, and also occurs in GABAergic, pre-synaptic terminals, the inhibition of which might increase neuronal excitability [310]. Indeed, in the hippocampus of epileptic patients, Ludányi and colleagues showed that 2-AG levels were reduced and associated with the loss of CB_1 expression in glutamatergic axon terminals; whereas, the expression of CB1 in GABAergic neurons was not changed. Thus, down-regulated levels of 2-AG and CB1 receptors seemingly correlates with increased excitability and neuronal damage [311].

Recent studies have shown that changes in the expression and activity of another target of endocannabinoids, the TRPV1 channel, facilitate epileptogenesis in patients affected by mesial temporal lobe epilepsy [312]. Furthermore, TRPV1 channels activated by AEA increase excitatory circuit activity in synaptically reorganized dentate gyrus [313], and are also involved in electrical and pentylenetetrazol (PTZ)-induced kindling development. In addition, PTZ-induced clonic seizures were reported to be reduced in TRPV1 knockout mice [314]. In support of a role of TRPV1 in seizures, we recently showed that these channels are strongly phosphorylated (and hence sensitized) in Mg^{2+}-free rat hippocampal slices, an in vitro model of neuronal hyperexcitability. Prolonged or repeated stimulation with the prototypical TRPV1 agonist, capsaicin, induces the rapid dephosphorylation of TRPV1, an event accompanied by reduced neuronal activity [69].

In summary, in some brain structures, including the hippocampus, CB1 and TRPV1 receptors coexist and their activation by endocannabinoids might produce opposite effect on neuronal excitability. This provides a rationale for the development of new pharmacological therapies to counteract seizures, epilepsies or related syndromes from: 1) compounds that activate CB1 only on glutamatergic terminals, as it can be the case for FAAH or MAGL inhibitors if such terminals exhibit ongoing endocannabinoid turnover during seizures; and 2) TRPV1 antagonists or rapidly desensitizing agonists. Indeed, the "dual" FAAH/TRPV1 blocker, *N*-arachidonoyl serotonin (see below), is very efficacious at reducing seizures and enhancing survival in picrotoxin-treated mice [315]. The phytocannabinoid CBD also seems to exhibit both these properties as well other potentially neuroprotective and anti-neuroinflammatory actions, thus possibly explaining in part its successful use against untreatable paediatric epilepsies, such as Dravet's syndrome, in ongoing clinical trials (Pharmaceuticals, G.W. (2015) GW Pharmaceuticals Announces New Physician Reports of Epidiolex® Treatment Effect in Children and Young Adults with Treatment-Resistant Epilepsy, GW Pharmaceuticals).

3.2. The role of other N-acylethanolamines in neurodegenerative and convulsive diseases

3.2.1. PEA

As mentioned above, PEA is also produced in the central nervous system, in particular in the brain and in several cell types during neurodegenerative diseases [316]. PEA has been proposed as a homeostatic agent aimed at counteracting the inflammatory response, and several studies report the anti-inflammatory and neuroprotective effects of this mediator (Table 3). The first evidence dates back to 1996 when it was demonstrated that PEA protects cultured mouse cerebellar granule neurons against glutamate toxicity [317]. Later, in chronic relapsing experimental autoimmune encephalomyelitis (CREAE) in mice, a model of multiple sclerosis, it was found that PEA levels were increased in areas associated with nerve damage, and when PEA was exogenously administered the spasticity was transiently ameliorated (as opposed to the effect of AEA which was more long lasting) [168]. Additionally, PEA levels were increased in a model of multiple sclerosis induced by Theiler's virus inoculation, where the exogenous administration of the compound resulted in a reduction of motor disability accompanied by an anti-inflammatory effect [318]. More recently, Rahimi and colleagues demonstrated that in a mouse EAE model induced by injecting myelin oligodendrocyte glycoprotein (MOG) in C57BL/6 mice, PEA reduced the severity of the neurobehavioral scores of EAE, and this effect was accompanied by diminished inflammation, demyelination, axonal damage and inflammatory cytokine expression [319]. PEA levels were also found to be increased in the tissue surrounding the primary ischemic lesion, in a patient with hemispheric stroke [320], and in the mouse cerebral cortex after focal cerebral ischemia [321]. Importantly, in the blood of patients who had experienced stroke, the levels of PEA on admission were directly correlated with NIHSS scores of neurological impairment [322]. Accordingly, exogenously administered PEA was able to reduce

Table 3
Experimental and potential therapeutic use of endocannabinoid-like mediators in neurological disorders.

Compound	Disease	Effect	Type of study	Reference
PEA	Multiple sclerosis	Neuroprotection	CREAE in mice	[168]
		Neuroprotection and anti-inflammation	Theiler's virus-induced EAE in mice	[318]
		Neuroprotection and anti-inflammation	EAE in mice	[319]
	Alzheimer's	Neuroprotection	Amyloid-β 25–35-induced neurotoxicity in mice	[329]
		Neuroprotection and anti-inflammation	Amyloid-β 1–42-induced neurotoxicity in rats	[330]
	Parkinson's	Neuroprotection	MPTP-induced PD in mice	[333]
	Epilepsy	Anti-convulsant	PTZ-induced seizures in mice	[334]
		Anti-convulsant	PTZ-induced seizures in rats	[337]
		Anti-epileptic	WAG/Rij rats	[336]
OEA	Parkinson's	Neuroprotection	6-OHDA-induced neurotoxicity in rats	[348]
OLDA	Epilepsy	Pro-convulsant	PTZ-induced seizures in rats	[314]

CREAE, chronic experimental autoimmune encephalomyelitis; EAE, experimental autoimmune encephalomyelitis; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahyropyridine; PD, Parkinson's disease; PTZ, pentylenetetrazol; 6-OHDA, 6-hydroxydopamine.

the risk of damage or to improve function in ischemia–reperfusion brain injury [323]. Recently, it was also demonstrated that PEA decreased oxygen-glucose deprivation (OGD)-induced increase in permeability during reperfusion, suggesting an important role of this compound against blood–brain barrier damage during ischemic stroke [324].

These results may suggest that, even though the endogenous levels of PEA, both in animal and human subjects, are up-regulated during some neurological diseases, its production may not always be sufficient to exert neuroprotection and anti-inflammatory actions. Thus, the exogenous administration of PEA might be an effective therapeutic alternative to counteract the neurological diseases [325]. In fact, several clinical studies have shown analgesic effects of PEA accompanied by a reduction in disability, and/or improvement of neurological functions and quality of life using a dietary supplement of PEA with the trade names Normast®, Pelvilen® and Glialia® [326,327]. On the other hand, selective inhibitors of PEA degradation (as discussed above), might also be useful to increase the endogenous levels of PEA under conditions when a pathological reduction of such levels is observed. Indeed, it was demonstrated that PEA (as well as endocannabinoid) levels are decreased in the striatum of symptomatic R6/2 mice, a transgenic model of Huntington's disease [264], although no data exist to date as to possible beneficial effects of exogenous PEA in this model.

In addition to these studies, the role of PEA has also been investigated in Alzheimer's disease. The first evidence was obtained in vitro, on neuroglial cultures and organotypic hippocampal slices, and showed that PEA was able to decrease the number of infiltrating astrocytes during β-amyloid challenge, and to improve neuronal survival through activation of PPAR-α [328]. Later, in an animal model of Alzheimer's disease consisting of injecting intracerebroventricularly Aβ 25–35, PEA treatment reduced the behavioral impairments, as well as the increase of lipid peroxidation, iNOS expression, and the induction of pro-apoptotic pathways induced by this peptide [329]. The effects of PEA were similar to those observed with a PPAR-α agonist, GW7647, and could not be observed in PPAR-α null mice injected with Aβ25–35 [329]. PEA was also able to reverse gliosis, amyloidogenesis and tau protein hyperphosphorylation induced by injection of Aβ 1–42 in adult male rats [330]. Also in this case, the effects of PEA seemed to be PPAR-α-mediated because reversed by GW6471, an antagonist of these nuclear receptors [330].

Potentially important neuroprotective and anti-inflammatory actions have recently been described for a new formulation of PEA, in both in vitro and ex-vivo models of Alzheimer's disease, again induced by the injection of amyloid Aβ1–42 [331]. The combination of PEA with the antioxidant flavonoid, luteolin (Lut), denoted as PEALut, subjected to an ultra-micronization process, was able to reduce iNOS, glial fibrillary acidic protein expression and neuron apoptosis, while normal nNOS and BDNF levels were restored [331]. Recently, PEALut was demonstrated to be also efficacious, at a lower dose compared with PEA alone, at counteracting the neurodegeneration and neuroinflammation induced by traumatic brain injury (TBI) [332,323].

The neuroprotective role of PEA has also been demonstrated in Parkinson's disease [333]. Chronic treatment with PEA after MPTP injection, an animal model of Parkinson's disease, protected both against MPTP-induced loss of tyrosine hydroxylase-positive neurons and the alterations of microtubule-associated proteins in the substantia nigra [333]. Moreover, PEA reduced MPTP-induced microglial activation and reversed MPTP-associated motor deficits. These protective effects of PEA seemed to be PPARα-mediated, since MPTP systemic toxicity was exacerbated in PPAR-α null mice [333].

Finally, PEA was reported to exert anticonvulsant and antiepileptic activities in convulsive diseases. After i.p. administration, PEA was effective against PTZ and 3-mercaptopropionic acid-induced convulsions in mice [334,335], and showed anti-absence properties in a genetic animal model of absence epilepsy, the WAG/Rij rat [336]. In particular, it was demonstrated that PEA was able to decrease epileptic spike–wave discharges (SWDs) in the WAG/Rij rat model, and when the compound was co-administered with CB1 or PPAR-α antagonists, SR141716 and GW6471 respectively, its effects were blocked [336]. These data suggest antiepileptic actions of PEA both through direct PPAR-α-mediated and "entourage" effects, e.g. via CB1 receptor activation by endocannabinoids [336]. Accordingly, a recent study showed that when seizures are induced by PTZ in rats, the anti-convulsive effects of PEA are antagonized not only by CB1 and but also by CB2 antagonists [337].

In summary, the potential therapeutic exploitation of PEA, and its derivatives or formulations, does not seem to be limited to the treatment of pain and inflammation, as originally believed, but extends also to several other neurological and neuroinflammatory conditions.

3.2.2. Other N-acylethanolamines

OEA and *N*-linoleoyl-ethanolamine (LEA), which, together with PEA, belong the family of NAEs, are also synthetized and inactivated by the action of NAPE-PLD and FAAH, respectively [338,12]. However in several species, including humans but not rodents, OEA can also be substrate for FAAH-2 [121]. Although in smaller amounts with respect to PEA, they are produced in most of the mammalian tissues, and it has also been reported that in the small intestine LEA may be present in higher concentrations than OEA [339,340]. OEA and LEA can activate both PPAR-α and the orphan GPCR, GPR119 [340–343], as well as TRPV1 channels [344]. The main function reported for OEA and LEA is the inhibition of food intake [345,340], although antiinflammatory and neuroprotective actions have also been described [346,347]. In particular, OEA induced neuroprotection in both in vitro and in vivo models of 6-hydroxydopamine (6-OHDA)-induced degeneration of substantia nigra dopamine neurons (a model of Parkinson's disease) [348] (Table 3), as well as after acute cerebral ischemic injury in mice, whereas LEA induced neuroprotection in a middle cerebral artery occlusion model of stroke [349,350].

4. Other endocannabinoid-related lipid mediators

As mentioned above, since the discovery of endocannabinoids and the "rediscovery" of NAEs, other endocannabinoid-like molecules are emerging as important modulators in the central nervous system. These molecules have usually very little affinity for CB1 and CB2 receptors but are able to activate other receptors or channels that can be or not targets of endocannabinoids and/or phytocannabinoids. Importantly, some of these mediators are biosynthesized and inactivated by the action of the same enzymes involved in the metabolism of the endocannabinoids, whereas others result from the oxidative metabolism of AEA or 2-AG.

4.1. Endogenous long chain fatty acid amides

N-acyl-dopamines congeners of NADA, and some members of the family of *N*-acyl-amino acids (also known as lipoaminoacids), have been discovered in mammalian tissues as endogenous TRPV channel activators. In particular: 1) *N*-oleoyl-dopamine (OLDA) [351] and *N*-arachidonoyl-taurine [123] activate TRPV1 channels; or 2) *N*-acyl-prolines and *N*-acyl-tyrosines mixtures activate TRPV2 channels [352]; and 3) *N*-arachidonol-taurine [123] and *N*-acyl-tryptophan and *N*-acyl-tyrosine mixtures activate TRPV4 channels [352]. OLDA, the most investigated of these lipids, has been found in the mammalian brain [351], and only recently in the plasma of patients with traumatic stress exposure and post-traumatic stress disorder (PTSD) [353]. OLDA, like capsaicin, produces hyperalgesia via TRPV1 [351]. In fact, it induces calcium influx in TRPV1-transfected human embryonic kidney (HEK)-293 cells, and reduces the latency of paw withdrawal from a radiant heat source after subcutaneous injection into the rat hind paw [351]. These effects are blocked by co-administration of a TRPV1 antagonist [351]. The effects of OLDA have also been studied on long-term potentiation (LTP) in the lateral nucleus of the amygdala (LA) in mice, and it has been observed that LA-LTP is reduced in OLDA-treated slices derived

from mice, but not in slices treated with the TRPV1 antagonist, AMG9810, or prepared from TRPV1 knockout mice [354]. On the other hand, a short period of acute stress, i.e., exposure to a forced swim test, significantly impairs LA-LTP, and OLDA enhances LA-LTP in control but not TRPV1 knockout mice, suggesting a protective effect of OLDA through a desensitization of TRPV1 receptors [354]. Finally, OLDA was very recently reported to accelerate the incidence of seizures in pentylenetetrazole and amygdala-induced kindling in male rats, and this pro-convulsant effect was reduced by TRPV1 antagonism by AMG-9810 [317] (Table 3). On the other hand, although *N*-arachidonoyl serotonin (AA-5-HT) was first synthesized as a non-competitive FAAH inhibitor [355,356], this compound was then also discovered as a TRPV1 antagonist [357,358]. AA-5-HT has only recently been found, together with other congeners (such as *N*-oleoyl-serotonin, *N*-palmitoyl-serotonin and *N*-stearoyl-serotonin), to occur in mammalian tissues, particularly in the jejunum and ileum of pigs and mice [22, 359], and in bovine and human brain samples [23,360]. These studies have also confirmed the capability of AA-5-HT to inhibit FAAH, and shown its ability to stimulate the release of GLP-1 from intestinal tissue via the orphan GPCR, GPR119 [22,23,359,360]. Importantly, an arylalkylamine *N*-acyltransferase from *Drosophila melanogaster* that catalyzes the formation of long-chain *N*-acylserotonins has been recently reported [361].

Among the lipoaminoacids thus far identified as endogenous compounds, *N*-arachidonoyl glycine (NAGly) is the most studied one. NAGly has been suggested to be produced either via direct oxidation of AEA by the action of alcohol dehydrogenase (ADH), or via the conjugation of arachidonic acid and glycine in a FAAH-dependent reaction [362], or catalysed by glycine *N*-acyltransferase [363]. It is hydrolysed again by FAAH [17]. NAGly is a potent activator of the orphan GPCR, GPR18 [364], and shows anti-inflammatory properties because its ability to reduce migration of inflammatory leukocytes in an animal model of peritonitis has recently been demonstrated. This effect might be GPR18-mediated [365]. *N*-arachidonoyl- and *N*-oleoyl-serine have also been identified in bovine brain and in mouse bone, respectively [18, 19]. *N*-arachidonoyl-L-serine shows neuroprotective effects after traumatic brain injury, and these effects seem to be reversed by CB2 and TRPV1 antagonists [366,367]. *N*-oleoyl-serine was shown to rescue bone loss by increasing bone formation and restraining bone resorption in a mouse ovariectomy model for osteoporosis [19].

4.2. Monoacylglycerols

Monoacylglycerols (2-MAGs), such as 2-oleoyl-glycerol (2-OG), 2-palmitoyl-glycerol and 2-linoleoyl-glycerol, are other endogenous 2-AG-like molecules, and were initially considered to act merely as "entourage compounds" for 2-AG [368]. Unlike 2-AG, 2-MAGs can be produced also from triacylglycerols (TAG) by the action of lipases during lipolysis [369], but like 2-AG, they are inactivated by the action of MAGL [125,370]. In particular, the role of 2-OG has recently been investigated and confined at the peripheral level, where the compound seems to be produced in the intestine and involved in anorectic effects by activating GPR119, thereby producing the release of incretin hormone GLP-1, with subsequent insulin secretion [344,371].

4.3. Cyclooxygenase-2-derived metabolites of AEA and 2-AG

Prostaglandin glyceryl esters (PG-GEs) and prostaglandin ethanolamides (PG-EAs or prostamides), such as PGE_2-GE, PGD_2-GE and $PGF_{2\alpha}$-GE, or PGE_2-EA, PGD_2-EA and $PGF_{2\alpha}$-EA, are formed via the oxygenation of 2-AG and AEA, respectively, by cyclooxygenase (COX)-2, followed by the action of prostaglandin E, D or F synthases, respectively [21,148,372–376,20]. Among these metabolites, PGE_2-GE and $PGF_{2\alpha}$-EA are among the most studied and seem to be important modulators of neurotransmission. In particular, it has been shown that PGE_2-GE induces a concentration dependent increase in the frequency of miniature inhibitory postsynaptic currents (mIPSCs) in GABAergic primary cultured hippocampal neurons, while $PGF_{2\alpha}$-EA did not increase the frequency of mIPSCs [377]. This effect is attenuated by an IP3 receptor or MAPK inhibitor [377], in agreement with previous data indicating that PGE_2-GE is able to induce Ca^{2+} mobilization, increase the levels of IP3 and activate PKC in a mouse macrophage cell line [378]. PGE_2-GE also increases miniature excitatory postsynaptic currents (mEPSCs) in glutamatergic neurons, and this effect is again mediated by ERK, p38 MAPK and IP3 but also by NF-κB [379]. Moreover, PGE_2-GE also induced neurotoxicity, which was attenuated by blocked NMDA receptors [379]. Finally, PGE_2-GE and $PGF_{2\alpha}$-EA elevated long-term potentiation in the hippocampus, and this effect was once again MAPK- and IP3-mediated [380]. Taken together, these results indicate that the oxidative metabolism of the endocannabinoids initiated by the action of COX-2 modulates synaptic plasticity in a manner opposite to that exerted by AEA and 2-AG via CB1 receptors, and that both PG-GEs and PG-EAs might contribute, among others, to inflammation-induced neurodegeneration.

In addition to these effects observed at the central level, it was also reported that PGE_2-GE and $PGF_{2\alpha}$-EA are pro-inflammatory and pro-nociceptive mediators at the peripheral level. In fact, although the local production of PGE_2-GE was unchanged in an animal model of inflammation induced by carrageenan, intraplantar administration of this compound induced mechanical allodynia and thermal hyperalgesia, and these effects were only partially blocked by a cocktail of antagonists for prostanoid receptors [373]. On the contrary, the levels of $PGF_{2\alpha}$-EA were strongly increased in the spinal cord of mice with kaolin/λ-carrageenan-induced knee inflammation [375], and, like with PGE_2-G, the direct spinal application of $PGF_{2\alpha}$-EA after the induction of knee inflammation increased the firing of nociceptive neurons and reduced the threshold of paw withdrawal latency of mice [375]. Treatment with a $PGF_{2\alpha}$-EA, but not with an FP, receptor antagonist, attenuated the effects of the mediator [375]. These results indicate that COX-2-mediated oxygenation of AEA and 2-AG might induce the activation of nociceptive neurons and subsequent pain transmission.

By contrast, a recent report has identified PGD_2-GE as an anti-inflammatory mediator. In fact, the increased levels of PGD_2-GE following the inhibition of ABHD6 in macrophages, or direct application of PGD_2-GE in lipopolysaccharide-induced inflammation in mice, produced a reduction of pro-inflammatory cytokines, and these effects were not mediated by cannabinoid, PPAR-γ or PPAR-α receptors [381].

$PGF_{2\alpha}$-EA also exerts opposing actions as compared to its precursor, AEA, in the framework of adipocyte differentiation from pre-adipocytes [382]. In fact, it was reported that AEA stimulates adipogenesis through the CB1 receptors or, at higher concentrations, PPAR-γ receptors [383, 384]. On the contrary, Silvestri and colleagues demonstrated that exposure of mouse 3T3-L1 or human preadipocytes to PGF2α-EA during early differentiation inhibits adipogenesis, and this effect is counteracted by selective antagonism of PGF2α-EA receptors [382]. Thus, these results suggest that prostamide signalling in preadipocytes could be a novel anandamide-derived antiadipogenic mechanism [382].

5. Conclusions

As if the biosynthesis, mechanism of action and inactivation of endocannabinoid signalling, with all its redundancy and promiscuity, was not complicated enough, studies on the endocannabinoids have opened a true Pandora's pot of potentially almost numberless endocannabinoid-related mediators, and of corresponding molecular targets. This "endocannabinoidome" can only be studied in a thorough and comprehensive manner by using "omic" approaches, and we are still far from fully appreciating its true importance in the control of homeostasis and its functional relationships with endocannabinoid signalling. It remains to be established, for example, if also the "endocannabinoidome" can be modulated by the several conventional and alternative clinical interventions, dietary interventions, epigenetic changes or the gut microbiota, which are already known to modulate

the ECS [383–386]. It may well be that the lessons learnt when investigating endocannabinoid regulation and function do not always apply to the plethora of endocannabinoid-related mediators. Thus, when looking at the extended ECS, one cannot help thinking that one is only looking at the tip of an iceberg.

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