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FROM PHYTOCANNABINOIDS TO CANNABINOID RECEPTORS AND ENDOCANNABINOIDS: PLEIOTROPIC PHYSIOLOGICAL AND PATHOLOGICAL ROLES THROUGH COMPLEX PHARMACOLOGY

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Ligresti A, De Petrocellis L, Di Marzo V. From Phytocannabinoids to Cannabinoid Receptors and Endocannabinoids: Pleiotropic Physiological and Pathological Roles Through Complex Pharmacology. *Physiol Rev* 96: 1593–1659, 2016. Published September 14, 2016; doi:10.1152/physrev.00002.2016.—Apart from having been used and misused for at least four millennia for, among others, recreational and medicinal purposes, the cannabis plant and its most peculiar chemical components, the plant cannabinoids (phytocannabinoids), have the merit to have led humanity to discover one of the most intriguing and pleiotropic endogenous signaling systems, the endocannabinoid system (ECS). This review article aims to describe and critically discuss, in the most comprehensive possible manner, the multifaceted aspects of *1*) the pharmacology and potential impact on mammalian physiology of all major phytocannabinoids, and not only of the most famous one Δ^9-tetrahydrocannabinol, and *2*) the adaptive pro-homeostatic physiological, or maladaptive pathological, roles of the ECS in mammalian cells, tissues, and organs. In doing so, we have respected the chronological order of the milestones of the millennial route from medicinal/recreational cannabis to the ECS and beyond, as it is now clear that some of the early steps in this long path, which were originally neglected, are becoming important again. The emerging picture is rather complex, but still supports the belief that more important discoveries on human physiology, and new therapies, might come in the future from new knowledge in this field.

I. INTRODUCTION: CANNABIS AND CANNABINOIDS, ANCIENT DRUGS BETWEEN ANECDOTES AND FACTS

The plant *Cannabis sativa* and its many preparations (for example, marijuana and hashish) have been used for millennia for recreation and medicine. In ancient China, cannabis was indicated for numerous diseases, but when taken in excess, it was described to "take away the mind." Emperor Shen-Nung allegedly prescribed cannabis in the 28th century B.C. for many ailments. The oldest written description of medicinal cannabis dates back to around 2350 B.C., on a stone from the Pyramids Texts from the Old Kingdom in Memphis, Egypt. As a drug, it has remained in active use during pharaonic times and subsequently in a succession of medical papyri. In Assyria (about 800 B.C.) it was named gan-zi-gun-nu ("the drug that takes away the mind") or azallu (when used as a therapeutic), suggesting the duality of its activity and its biphasic effects on many symptoms. It was used to treat nocturnal epilepsy (918), in agreement with the current knowledge of the anticonvulsant effects of its major components, cannabidiol (CBD) (670) and Δ^9-tetrahydrocannabinol (Δ^9-THC) (895). In India, ancient Persia, and medieval Arab societies, cannabis use proceeded as both medicinal and recreational (560), but its pharmacological effects in humans were more accurately described only in the mid-19th century, when O'Shaughnessy (635) noted the capability of cannabis peparations to afford survival in tetanus in India in 1839, and hence its use as muscle relaxant and antispasmodic in Britain and North America.

These "millennial" anecdotal and medical observations led to attempts to isolate the active constituents of cannabis in the 19th century, when the first "cannabinoid," named cannabinol (CBN), was isolated. However, the chemical structure of this compound was not elucidated until the 1930s. In the attempt to understand the molecular basis of cannabis psychotropic activity, a CBN analog, $\Delta^{6a,10a}$-tetrahydrocannabinol ($\Delta^{6a,10a}$-THC), was synthesized in a racemic mixture and shown to possess pharmacological activity similar to that of marijuana (489). Thus it was hypothesized that the psychoactive compound(s) of the plant was chemically related to $\Delta^{6a,10a}$-THC, which is now known to be much less potent than the true psychotropic constituent of cannabis Δ^9-THC. A derivative of synthetic $\Delta^{6a,10a}$-THC was administered to a small number of children with epilepsy and showed positive results (560).

To date, more than 100 chemically and biosynthetically related cannabinoids have been identified in cannabis flowers, as such or after dessication, in relative amounts depending on the plant variety. They were difficult to purify until the 1960s, when many cannabinoids, including CBD (567) and Δ^9-THC (282), were isolated, their chemical synthesis initiated, and their pharmacological and physiological significance investigated (207). These characteristic compounds are lipophilic metabolites of resorcinol and are defined as "phytocannabinoids" to distinguish them from often structurally dissimilar but pharmacologically analogous endocannabinoids and synthetic cannabinoids (678).

Loewe (488) found that cannabis extracts induce catalepsy in mice and that CBN (now known to be an artifact) reproduces this effect, albeit much less potently. These findings prompted the development by Pertwee in 1972 of a quantitative in vivo assay for psychotropic cannabinoids, known as the "ring test," in which cataleptic activity is determined (676). Martin later used this assay along with three others, measuring cannabinoid-induced hypokinesia in an open field, rectal hypothermia, and antinociception assessed with tail flick or hot plate tests; together, this is known as the "mouse tetrad" of cannabimimetic actions (535). Δ^9-THC is the only phytocannabinoid to be fully active and very potent in all four tests, due to its activity at the cannabinoid type 1 (CB1) receptor (671).

Studies on Δ^9-THC led to the discovery of CB1 receptors in 1988 (204), and of *N*-arachidonoyl-ethanolamine (AEA), or anandamide (from the Sankrit word *ananda* for "bliss"), the first endogenous ligand for such receptors (or "endocannabinoid") in 1992 (205). Thanks to investigations on Δ^9-THC, we now know that *1*) the physiological signaling system composed of cannabinoid CB1 and cannabinoid type 2 (CB2) receptors, endocannabinoids and the biochemical machinery to produce and degrade these lipids, known as the "endocannabinoid system" (ECS), is involved in most, if not all, aspects of mammalian physiology and pathology (209); *2*) ECS-based molecules are potential drugs for more than one disease, despite the emerging complexity of this system; and *3*) endocannabinoid synthetic and degrading enzymes also participate in the regulation of the levels of other endogenous signals and influence the activity also of noncannabinoid receptors (191). Nevertheless, from the point of view of the development of new therapies for the plethora of pathological conditions in which the ECS is involved (see sects. VII-X), other phytocannabinoids, which are not fully capable of interacting with this system, are emerging as being not less important than Δ^9-THC (or synthetic ECS-based drugs), and possibly less problematic in terms of safety/efficacy. For this reason, we decided to review here first our current knowledge of the phytocannabinoids, and the physiological mechanisms they regulate, by starting with CBD, the first natural phytocannabinoid the structure of which was elucidated; and then to focus on Δ^9-THC, and its best known physiological substrate, the ECS, in the second part of the article.

While addressing these topics, we have tried to be as comprehensive as possible and to tone down our personal ideas on what is more or less important in the pharmacology of phytocannabinoids and the physiology of endocannabinoids. Indeed, in only 10 years, our views, and those of many others, on what to make of the rapidly evolving knowledge in this field have changed considerably, as have the approaches aiming to develop new therapies from *Cannabis* components and the ECS. Similar turns are likely to occur again in the near future, since our understanding of the implications of these issues is yet to be settled. Nevertheless, what look presently as the best-defined aspects have been highlighted here and there in the text, and summarized in the two tables.

II. CANNABIDIOL

A. Molecular Pharmacology

CBD is the major nonpsychotropic component of *Cannabis sativa* and has attracted interest for its therapeutic potential in a number of disease states investigated in animal models (673). It is anxiolytic, antidepressant, antipsychotic, anticonvulsant, antinausea, antioxidant, anti-inflammatory, antiarthritic, and antineoplastic. Within the central nervous system (CNS), CBD is protective in animal models of epilepsy, anxiety, psychosis, and diseases of the basal ganglia, such as Parkinson's and Huntington's diseases.

CBD does not elicit the classic CB1-mediated "tetrad" of hypolocomotion, analgesia, catalepsy, and hypothermia (490), in agreement with its low affinity for CB1 receptors: K_i = 1.5 μM in humans; 4.9 and 4.8 μM in mice; 4.3 and 2.3 μM to displace [^{3}H]CP-55,940 binding to rat brain membranes; 1.3 and 1.8 μM to displace [^{3}H]SR141716A in rat brain membrane binding assays; and even >10 μM to

displace [^{3}H]HU243 binding to rat brain membranes (see Ref. 556 for a meta-analysis).

CBD functional actvity at CB1 receptors, assessed using [^{35}S]GTPγS binding assays, was not measurable in the mouse (854) and very low, if any, in the rat (100, 682). Mouse vas deferens experiments showed that CBD produces weak antagonism of CB1 receptor agonists (IC_{50} = 3.35 μM) (680). A recent study, yet to be confirmed by further investigations, points to CBD as a negative allosteric modulator of CB1 (454).

CBD displays weak inverse agonism at CB2, an action that might be responsible for its antagonism of CP55940 at the human CB2 receptor with a K_i = 4.2 ± 2.4 μM in human CB2 CHO cell membranes and 0.75 ± 0.30 μM in human CB2 HEK293 cell membranes (556).

CBD may act as "indirect" CB1/CB2 agonist by weakly inhibiting AEA enzymatic hydrolysis [IC_{50} 28 μM in mouse cell membranes (73, 478); and 10–15 μM in rat brain membranes (193, 472)] and the putative AEA transporter in rodents (IC_{50} 11–25 μM) (73, 712). CBD can increase also the levels of the other endocannabinoid, 2-arachidonoylglycerol (2-AG), as seen in the mouse periaqueductal grey (519), or colorectal cancer cells (24). Accordingly, some CBD effects are blocked by CB1 or CB2 receptor inverse agonists (79, 113, 115, 124, 183, 464, 519, 715), or are absent in CB1 receptor knockout mice (922).

CBD modulates the activity of orphan G protein-coupled receptors (GPCRs) suggested to be activated by endocannabinoids and related lipids (see below). At GPR18, CBD acts as a partial agonist and antagonizes Δ^9-THC (550); furthermore, it can antagonize GPR55 (142, 147, 475, 763, 837, 914).

CBD exhibits activity in functional assays of several channels belonging to the transient receptor potential (TRP) family, namely, rat and human TRPV1 (73, 193), rat TRPV2 (193, 702), and rat TRPA1 (193, 196, 702), whereas it antagonizes rat TRPM8 (193, 196). It has affinity for TRPV1 in binding assays (EC_{50} 1.0 ± 0.1 μM) (73), and its direct activity at TRPV1, TRPV2, and TRPA1 was confirmed by patch-clamp electrophysiology (377). Through activation/desensitization of TRPV1, it modulates anxiety (111) and pain (155). CBD modulates $[Ca^{2+}]_i$ also via T-type (743) or L-type (10, 231) channels, or by using mitochondria as source of Ca^{2+} in a manner prevented by a Na^+/Ca^{2+} exchange inhibitor but not by a mitochondrial permeability transition pore inhibitor (762).

CBD exhibits positive allosteric modulation of α1 and $\alpha1\beta$ glycine receptors in the low micromolar range (7). NMR analysis revealed a direct interaction between CBD and S296 in the third transmembrane domain of purified α3 Gly receptor, which mediates its suppression of chronic pain (926).

CBD activates PPARγ receptors (633), the blockade of which attenuates CBD inhibitory effects on reactive gliosis and subsequent neuronal damage (248), Aβ-triggered neurodegeneration (783), and tumor progression (713).

CBD inhibits the equilibrative nucleoside (both thymidine and adenosine) transporter (122) and adenosine, dopamine, and glutamate uptake in rat striatal nerve terminals (656). In animal models of inflammation, its effects are often blocked by adenosine receptor antagonists (122, 126, 482, 515, 519, 534, 559, 640, 725).

CBD has slight affinity for the 5-HT_{1A} receptor (760), and some of its effects are at least in part inhibited by 5-HT_{1A} receptor antagonists (112, 244, 297, 529, 572, 667, 807, 907, 938). Scant evidence exists for its modulation of α1-adrenergic (679) and dopamine D2 (900) receptors and its long-term increase of $GABA_A$ receptor binding (491) or allosterically modulation of μ- and δ-opioid receptors (425).

CBD mobilizes arachidonic acid (AA) by stimulating phospholipase A_2 activity (103, 722) and inhibits the metabolism of AA to leukotriene B_4 by 5-lipoxygenase (541). It dampens nitric oxide (NO) production in animal models of acute and chronic inflammation (24, 152, 162, 247, 267, 600, 654, 758), the expression of inflammatory cytokines and transcription factors [interleukin (IL)-1β, IL-2, IL-6, IL-8, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, CCL3, CCL4, NF-κB] (39, 419), and reactive oxygen species (ROS) production (320, 767). However, in many types of cancer cells, CBD is capable of generating ROS, thereby inducing cytotoxicity or apoptosis and autophagy (478, 540, 543, 547, 552, 610, 862). CBD also improves mithochondrial function and enhances mithochondrial biogenesis in vivo under pathological conditions (327).

Finally, CBD increases DNA methylation of the keratin 10 gene, thereby reducing keratin 10 mRNA levels by a CB1-dependent mechanism. In this system, CBD behaves as a transcriptional repressor controlling cell proliferation and differentiation (698).

In summary, CBD exhibits moderate activity on a wide array of molecular targets, which allows its potential use in a range of pathological conditions. This multitarget nature has been recently predicted to fit with the etiopathological prerequisites of diseases as diverse as epilepsy and ulcerative colitis, with a favorable benefit-to-risk ratio (101).

Particularly with multitarget compounds such as CBD, when discussing the potential pharmacological relevance in vivo of activities observed in vitro at different targets with

different ranges of concentrations, one should always ask two questions: *1*) Assuming equal efficacy, what is the lowest potency in vitro at a given target, necessary for a compound selective at that target to produce an effect in vivo that is due uniquely to the interaction with that target (as shown through the use of selective pharmacological or genetic tools)? *2*) Does low potency at a given target, when combined with equally not so potent activities at other targets, allow a multitarget compound to exert in vivo effects that are mediated also by that target (because of synergistic effects among the targets)? To answer the first question, one needs to test various single-target compounds and identify what is the "minimum requisite potency in vitro" to see activity in vivo that is blocked by an antagonist, or absent in a knockout, for that target. What one usually finds is that this minimum requisite potency usually varies, also by orders of magnitude, depending on the target (enzymes vs. receptors vs. channels) and type of assay (affinity vs. functional) used. For TRPV1 channel agonists or inhibitors of AEA hydrolysis/reuptake, for example, activities in the low micromolar range have been shown to be sufficient to produce direct TRPV1-mediated or indirect cannabinoid receptor-mediated effects in vivo, whereas for CB1 or CB2 direct agonists, binding affinity must be in the low-medium nanomolar range. Thus it is possible that, e.g., a full TRPV1 agonist with EC_{50} of 500 nM in a Ca^{2+} imaging assay behaves as a "selective" TRPV1 agonist in vivo even though it also exhibits a K_i of 500 nM in a binding assay for CB1. The answer to the second question is usually positive if the activity monitored in vivo is influenced by all the various targets of the compound under study, as elegantly detailed in Reference 657. Therefore, the minimum requisite potency in vitro at a given target, necessary to see activity in vivo mediated also by that target, may decrease sensibly if a compound is capable of interacting with also other targets.

B. Therapeutic Use

1. Psychosis

Psychotic symptoms can be treated with CBD. For example, *1*) a female schizophrenia patient orally treated with CBD for 26 days exhibited an improvement of symptomatology not achieved with haloperidol (946). *2*) CBD treatment significantly decreased symptomatology without any adverse effects in six patients (945). *3*) A double-blind, randomized clinical trial with CBD produced a significant clinical improvement similar to the antipsychotic amisulpride, but with less side effects (472).

Although the mode of action of CBD is not fully understood, there are clues that it may *1*) reverse the sensorimotor gating that is deficient in patients with psychotic disorders, as found in rats in a TRPV1-mediated manner (492), and *2*) inhibit the cellular uptake and enzymatic hydrolysis of AEA, thereby enhancing the levels of this potentially antipsychotic endocannabinoid (see below) (73, 472).

CBD is protective also against the acute psychotic effects of either Δ^9-THC or ketamine in healthy volunteers (423), perhaps the first indication of its potential antipsychotic activity. Oral CBD before Δ^9-THC (600 mg, administered 3.5 h before 1.5 mg Δ^9-THC iv) inhibited both paranoia and impairment of episodic memory (243). It was hypothesized that CBD in combination with a CB1 receptor antagonist could target the metabolic, inflammatory, and stress-related components of the schizophrenia phenotype (731). Indeed, CBD may attenuate immune responses associated with psychotic disorders (182), as it inhibits both the production of proinflammatory cytokines and microglia activation (534).

2. Epilepsy

CBD attenuates convulsions induced in animals (347, 670). It produces antiepileptiform and anticonvulsant effects in in vitro and in vivo models (406, 407). CBD regulation of Ca^{2+} homeostasis via several mechanisms may contribute to these actions, particularly for partial or generalized seizures. However, the exact molecular mechanism(s) remain(s) to be elucidated. CBD might inhibit seizure spread in the CNS by an action on GABA but is ineffective against strychnine-induced convulsions (157). Activation/desensitization of TRPV1 and TRPV2, which are expressed to a varying extent in the hippocampus and are suggested to participate in epilepsy, might be involved in CBD reduction of neuronal hyperactivity in epilepsy (377).

Among children with treatment-resistant epilepsy, those with early-onset and severe epilepsies such as Dravet's syndrome and Lennox-Gastaut's syndrome, have the greatest neurodevelopmental problems and, due to the high rate of seizure frequency, are in need of more effective therapies (636). Preclinical testing in recently developed murine models of Dravet's syndrome suggests the efficacy of CBD in this context (206). Preliminary expanded-access open trials in several forms of untreatable pediatric epilepsy (www.gwpharm.com/GWPandGovNewSouthWales271015.aspx) show promising results. Placebo-controlled trials are ongoing, one of which has just been reported in a press release and confirms cannabidiol efficacy in Dravet's syndrome (www.gwpharm.com/GW%20Pharmaceuticals%20Announces%20Positive%20Phase%203%20Pivotal%20Study-%20Results%20for%20Epidiolex%20cannabidiol.aspx).

3. Anxiety

The anxiolytic-like properties of CBD in different animal models (11, 587) are at least in part mediated by postsynaptic 5-HT_{1A} receptors (112, 938). Accordingly, CBD attenuates the acute autonomic responses associated to stress in rats by facilitating 5-HT_{1A} receptor-mediated neurotrasmission (266, 724). It also reduces the anxiogenic effects of stress and facilitates the extinction of fear memories in rats, in this case through indirect activation of CB1 receptors (79).

In healthy humans, CBD reverses the anxiogenic effects of Δ^9-THC and reduces anxiety in a simulated public-speaking task (65). Moreover, it enhances consolidation of explicit fear extinction (180).

4. Sleep

CBD modulates the sleep-wake cycle (for a review, see Ref. 614). However, contradictory evidence on the effect of this cannabinoid on sleep exists, including both improvement (118) and diminution after systemic administration (584). Systemic administration to male rats during the light period enhances the total percentage of sleep (133), whereas enhancement of alertness is observed following injection into the lateral hypothalamus or dorsal raphe nuclei (612, 613).

5. Neuroprotection and neurodegenerative diseases

CBD is a potent antioxidant and hence may be a neuroprotectant for the treatment of neurological disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), in which ROS play a role (262). It shows efficacy against brain damage produced by different types of insults, and in a model of neonatal ischemia its neuroprotective effects are due to multiple receptor activation (126). During inflammatory conditions, CBD alters the expression of ~1,200 genes, many of which controlled by nuclear factors involved in the regulation of stress responses and inflammation (411). The anti-inflammatory effects of CBD were related also to the control of microglial cell migration (898), the subsequent production of pro-inflammatory mediators and the inhibitory control of NF-κB signaling and inducible NO synthase (246). Other mechanisms include *1*) 5-HT_{1A} receptor activation in stroke (335); *2*) inhibition of adenosine uptake (122); and *3*) inhibition of neuronal damage induced by the β-amyloid peptide (Aβ), an effect mediated by the Wnt-β-catenin signaling pathway, playing a role in β-amyloid-induced GSK-3β activation and *tau* hyperphosphorylation in AD (247).

CBD is effective in an experimental model of parkinsonism (6-hydroxydopamine-lesioned rats) by acting through antioxidant mechanisms independently of cannabinoid receptors (283), and attenuates PD-related dystonia, but not tremor (159), in agreement with a positive correlation between the *N*-acetylaspartate-to-total creatine ratio and CBD levels measured in the putamen/globus pallidus of recreational users of cannabis (342).

In rats lesioned with 3-nitropropionic acid, a toxin inhibitor of the mitochondrial citric acid cycle resulting in a progressive locomotor deterioration resembling that of HD patients, CBD reduces rat striatal atrophy (767), in a manner independent of the activation of cannabinoid, TRPV1, and adenosine A2A receptors. In rats lesioned with malonate, instead, CBD alone does not provide protection (766). Clinical studies have shown that CBD, at an average daily dose of ~700 mg/day for 6 wk, is not effective in HD patients (158).

6. Ischemia

CBD reverses brain damage caused by cerebral ischemia in mice and gerbils (565). The protective effect of CBD does not produce tolerance and is cannabinoid receptor-independent, long-lasting, and observed both when administered pre- and post-ischemia (333). In newborn piglets with post hypoxia-ischemia caused by temporary occlusion of both carotid arteries, CBD counteracts the cerebral hemodynamic impairment and improves brain metabolic activity, whilst reducing brain edema and seizures associated with this condition, and producing beneficial cardiac, hemodynamic, and ventilatory effects (13).

In brain ischemic conditions, CBD produces anti-inflammatory effects such as inhibition of monocyte/macrophage cells expressing high-mobility group box1 (HMGB1, a DNA-binding protein that is translocated from the nucleus to the cell cytoplasm inducing activation of microglia in the brain after ischemia), and reduction of the number of Iba1-positive cells in the striatum (333). CBD beneficial effects against excitotoxicity, oxidative stress, and inflammation are partly mediated by CB2 and 5-HT_{1A} receptors (667).

CBD produces antinecrotic effects in ischemic hearts (815) and reduces infarct size in models of ischemia-reperfusion in rats (233) and rabbits (255). It decreases myocardial inflammation by attenuating lipid peroxidation and reduced glutathione levels and by decreasing iNOS expression in the myocardium (327). CBD attenuates iNOS expression also in a model of liver ischemia-reperfusion injury (600) and in diabetic hearts and in human cardiomyocytes, and reduces high glucose-induced ROS generation (709). CBD shows benefical effects in rodent models of myocardial infarction and diabetic complications (365). Finally, a single acute dose of CBD (50 mg/kg iv) causes antiarrhythmic effects against ischemia-induced ventricular arrhythmias (896), seemingly via adenosine A1 receptors (300).

7. Pain, inflammation, autoimmunity, and retinal diseases

CBD is effective in neuropathic and inflammatory pain in rodents (162), through actions at targets involved in the control of nociception, including inhibition of AEA enzymatic hydrolysis and indirect activation of cannabinoid receptors; activation/desensitization of TRPV1 and TRPA1 channels (162); activation of the 5-HT_{1A} receptor; and inhibition of equilibrative nucleoside transporters, which causes elevation of adenosine signaling, analgesia, and inhibition of inflammation. All these targets are implicated, for example, in CBD activation of descending antinocicep-

tion (519). Activation of glycine receptors underlies part of CBD effects in acute and chronic pain models (925, 926).

The anti-inflammatory and cytokine modulatory properties of CBD (336, 419, 551) are such that its administration results in attenuation of various autoimmune conditions in animal models, including experimental autoimmune encephalomyelitis (447), rheumatoid arthritis (524), colitis (89), diabetes (912), and psoriasis (916). Indeed, CBD has been suggested as a promising treatment also for autoimmune myocarditis and possibly other autoimmune disorders, and it might be useful for organ transplantation (466). Very recently, the positive results of a phase II study that assessed the safety and efficacy of CBD in the prevention of acute graft-versus-host-disease were reported (931).

CBD may be beneficial for neurodegenerative retinal diseases such as diabetic retinopathy and glaucoma. CBD provides neuroprotection, blood-brain barrier preservation, and anti-inflammatory actions in the streptozotocin model of type 1 diabetes (237). The protective effect against diabetes-induced retinal damage may be due to inhibition of adenosine uptake (482).

8. Emesis

CBD is effective in animal models of anticipatory or conditioned gaping nausea and vomiting. These antinausea/antiemetic effects are mediated by activation of somatodendritic 5-HT_{1A} receptors in the dorsal raphe nucleus (662, 732).

9. Bone formation and fracture healing

CBD exerts beneficial effects on bone formation and fracture healing (443) and reduces bone resorption in vivo in mice. Antagonism of GPR55, which suppresses osteoclast formation but stimulates osteoclast function, seems to underlie CBD negative effects on osteoclast function (914). Migration and differentiation of mesenchymal stem cells (MSCs) are known to play a central role in bone formation and fracture healing, and CBD promotes the migration of MSCs to sites of calcifying tissue regeneration via activation of CB2 receptors, and to induce osteoblastic differentiation by inhibiting GPR55 (780). CBD also controls bone resorption during the progression of experimental periodontitis in rats (617).

10. Cancer

CBD exerts antiproliferative/proapoptotic effects (IC_{50} in the 5–25 μM range) in several tumor cell lines, including human breast, prostate and colorectal carcinoma, gastric adenocarcinoma, and rat glioma and transformed thyroid cells (478). In human prostate carcinoma cells, CBD induces apoptosis and expression of PUMA and CHOP, two markers of intrinsic apoptotic pathways (194). The production of ROS is at least in part responsible for the antitumor activity of the phytocannabinoid both in vitro (194, 478, 539, 547) and in vivo (800).

The ability of CBD to inhibit cancer cell viability and proliferation can be reversed in vitro in the presence of blockers of either CB2, TRPV1, TRPM8, cyclooxygenase-2 (COX-2), or PPARγ (reviewed in Ref. 548), and in vivo in the presence of a PPARγ antagonist (713). Furthermore, CBD is able to inhibit cancer cell invasion and metastasis (478, 548, 715). These actions, in highly aggressive human breast cancer cells, are in part mediated by inhibition of epidermal growth factor (EGF), NF-κB, ERK/AKT, and matrix metalloproteinase 2 and 9 signaling pathways (238). CBD also reduces angiogenesis through actions on both tumor and endothelial cells (809) **(FIGURE 1)**.

III. Δ^9-TETRAHYDROCANNABINOL

A. Pharmacology

Δ^9-THC is a high-affinity (K_i values in the low nanomolar range), partial agonist (efficacies lower than those of some synthetic agonists) at CB1 and CB2 receptors, the two G protein-coupled receptors identified for this compound in many higher vertebrates and mammalian organisms (544, 609). CB1 and CB2 are known as the "cannabinoid receptors" although, among the many phytocannabinoids, they are activated only by Δ^9-THC and, to a lesser extent, CBN. The multifaceted physiological and pathological importance of CB1 and CB2 receptors, and of the signaling pathways therewith associated, will be discussed in subsequent sections of this article. Prior to the molecular characterization of these receptors, Δ^9-THC was shown to inhibit cAMP accumulation in neuronal cells in an entiospecific manner, indicating a specific site of action (369, 562). By using a potent synthetic cannabinoid analog, this binding site was identified in the brain in 1988 (204), and two years later shown to be identical to a previously cloned orphan GPCR, later named CB1 (544). CB2 was cloned by homology with CB1, and shown to be abundant in the immune system (609). We now know that low levels of CB2 are present in the brain, much in the same way lower expression of CB1 is found in most peripheral tissues.

Of the two enantiomers, only the natural (−)-*trans*-Δ^9-THC binds to the cloned cannabinoid receptors with nanomolar K_i values. It produces most of its central effects in healthy animals by activating CB1 receptors, including the "tetrad" of cannabimimetic effects mentioned above (671). When a CB1 receptor antagonist and CB1 null mice were developed, it was shown that these effects are absent when CB1 is either pharmacologically or genetically inactivated (535, 943). Δ^9-THC and other CB1 receptor agonists act in the brain through neuronal presynaptic CB1 receptors to

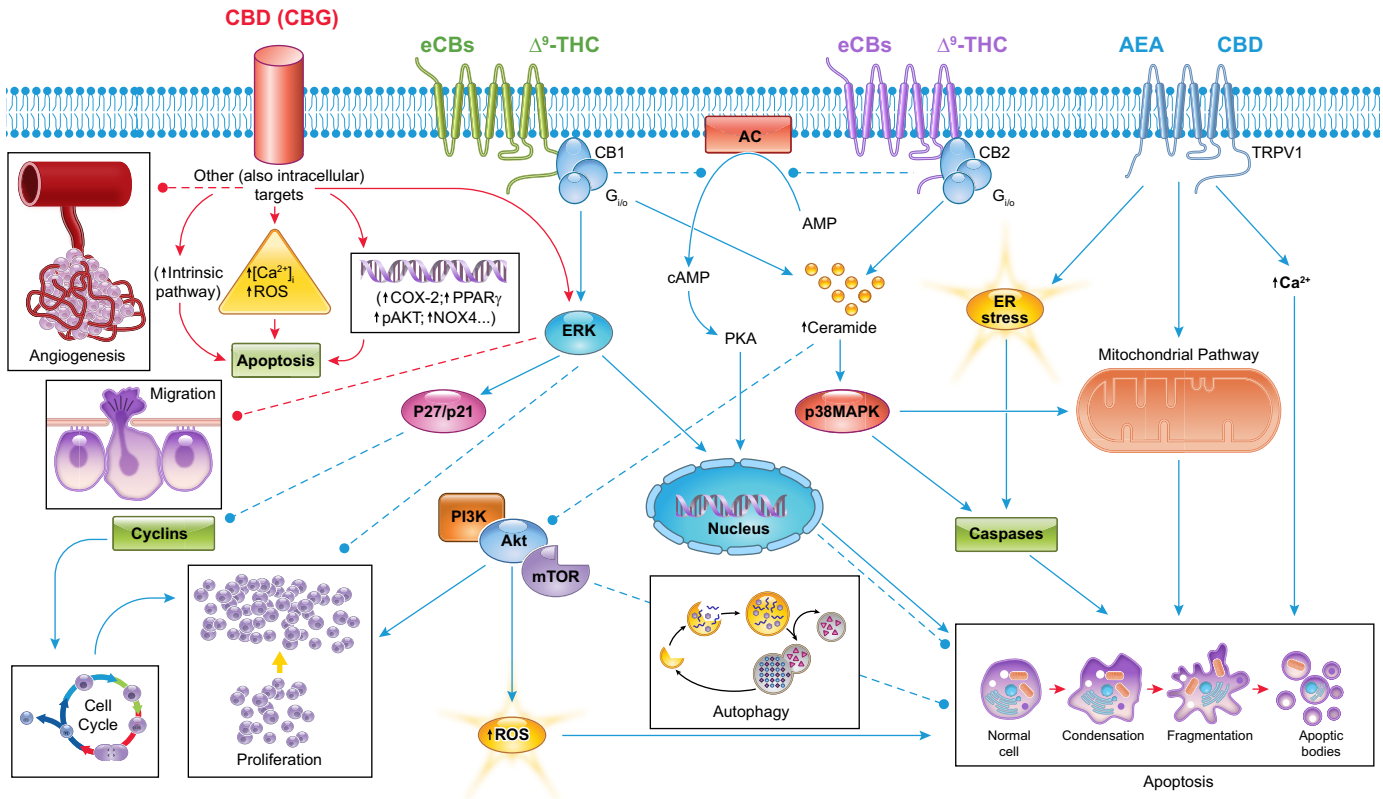

FIGURE 1. Schematic representation of the main signaling pathways through which (endo)cannabinoids impact proliferation, apoptosis, migration, and angiogenesis in cancer. Blue arrows indicate pathways initiated by cannabinoid/vanilloid receptor-mediated mechanisms, and red arrows indicate non-cannabinoid/vanilloid receptor-mediated mechanisms. Continuous lines indicate stimulation, and dotted lines indicate inhibition. AC, adenylyl cyclase; CBD, cannabidiol; CBG, cannabigerol; eCBs, endocannabinoids; ER, endoplasmic reticulum; Δ^9-THC, Δ^9-tetrahydrocannabinol; PKA, protein kinase A; AKT, protein kinase B; PI3K, phosphatidylinositol 3-kinase; ERK, extracellular regulated kinase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; ROS, reactive oxygen species; p27/p21, cyclin-dependent kinase inhibitor proteins.

inhibit ongoing neurotransmitter release, an effect shared by endogenously released endocannabinoids (838). In fact, when Δ^9-THC is acutely administered in vivo, it exhibits both "excitatory" and "inhibitory" actions in behavioral bioassays. These dual actions are due to many factors. *1*) By being a partial agonist, Δ^9-THC either directly activates CB1 receptors or attenuates the "tone" of endocannabinoid full agonists, and hence both mimics and blocks endocannabinoid-mediated neuromodulatory actions. *2*) Again, because of its relatively low efficacy, the density and G protein coupling efficiencies of CB1 receptors in different brain areas influence the potency of Δ^9-THC. In the rat, CB1 density is much higher in the cerebellum, substantia nigra pars reticulata, globus pallidus, lateral caudate-putamen, and hippocampus than in amygdala, thalamus, hypothalamus, and brain stem, yet CB1 coupling to G proteins is markedly more efficient in the hypothalamus than in cortex, cerebellum, or hippocampus (144). *3*) CB1 receptors are expressed on both inhibitory GABAergic and excitatory glutamatergic terminals in the brain, and although the former population is more abundant than the latter, "glutamatergic-CB1" appears to be activated by lower concentrations of Δ^9-THC than "GABAergic-CB1." Thus Δ^9-THC may repress glutamate release at lower concentrations than those needed to inhibit GABA release, often leading to bell-shaped "inhibitory" dose responses (578). Finally, multisynaptic mechanisms may account for CB1-mediated "excitatory" effects of Δ^9-THC, such as the activation of descending antinociceptive pathways (517).

Despite its nanomolar affinity for cannabinoid receptors, other targets have been occasionally suggested to participate in the pharmacological effects of Δ^9-THC. Controversy exists with regard to its affinity and efficacy for the orphan GPCR, GPR55, for which EC_{50} values of 8 nM in a [^{35}S]GTPγS binding assay (763) and 5 μM for increases in $[Ca^{2+}]_i$ in both mouse and human GPR55-expressing HEK293 cells as well as in mouse dorsal root ganglia (460), were reported. Instead, with the use of internalization and β-arrestin assays, no sign of Δ^9-THC activation of GPR55 was detected (420). Δ^9-THC activates GPR18 in migration (550) and β-arrestin (723) assays, and increases both $[Ca^{2+}]_i$ and MAPK in HEK cells stably expressing this receptor (156). Much more work is needed to support the claim that GPR55 and GPR18 are true cannabinoid receptors.

Δ^9-THC directly inhibits currents through recombinant human 5-HT_{3A} receptors independently of cannabinoid receptors (IC_{50} = 38 nM), acting allosterically at a modulatory site of these receptors (33). The effect is independent of 5-HT_{3A} agonist concentration, suggesting a noncompetitive inhibition, and varies with receptor density at the cell membrane surface (927). Accordingly, Δ^9-THC decreases 5-HT neurotransmission and glutamate release in the nucleus accumbens, inducing catalepsy-like immobilization (772). Inhibition of 5-HT_3 receptors may contribute to the pharmacological actions in nociception, emesis, and other neurological disorders of the phytocannabinoid. Evidence points also to Δ^9-THC modulation of behaviors typically mediated by 5-HT_{2A} receptor activation (178, 305). Both in vitro and in vivo CB1 and 5-HT_{2A} receptors seem to form functionally active heteromers in specific brain regions, which seem to be required for some cognitive and anxiolitic effects of Δ^9-THC, but not for antinociception and hypolocomotion (884).

Δ^9-THC directly potentiates glycine receptors through an allosteric and concentration-dependent mechanism, with EC_{50} values of 86 ± 9 nM for human homomeric α1 receptors, 73 ± 8 nM for heteromeric $\alpha1\beta1$ subunits in *Xenopus laevis* oocytes expressing human glycine receptors, and 115 ± 13 for isolated neurons from rat ventral tegmental area (337). The hydroxyl groups of Δ^9-THC and S296 in the glycine receptors are critical for this interaction. Some Δ^9-THC analgesic effects were absent in mice lacking α3 glycine receptors but not in those lacking cannabinoid receptors (928).

Strong evidence exists for a weak interaction of Δ^9-THC with TRPV2, as suggested by measuring elevation of intracellular Ca^{2+} in HEK293 cells transfected with recombinant TRPV2 cDNA (EC_{50} 43 μM for human TRPV2; EC_{50} 16 μM and 0.65 ± 0.05 μM for rat TRPV2) (193, 623). Because TRPV2, like other TRPs, is desensitized by its agonists [with IC_{50} 0.8 ± 0.1 μM for Δ^9-THC desensitization to the effect of lysophosphatidylcholine at rat TRPV2 (193)], these findings might explain some of the anti-inflammatory and analgesic properties of the cannabinoid. Also, TRPA1 is activated by Δ^9-THC (EC_{50} 12 ± 2 μM), an effect responsible for its CB1/CB2-independent vasodilation of rat mesenteric arteries (409). Data on rat recombinant TRPA1 confirmed that Δ^9-THC activates the channel [with EC_{50} 32.3 μM (702) or 0.23 μM (196) depending on the functional assay used]. Of note, also the endocannabinoid AEA stimulates TRPA1 (EC_{50} 4.9 μM) (192). Finally, Δ^9-THC antagonizes the stimulatory effect of menthol and icilin, two TRPM8 agonists, on intracellular Ca^{2+} elevation in HEK293 cells transfected with rat recombinant TRPM8 [IC_{50} 0.15 ± 0.02 μM against menthol and 0.16 ± 0.01 μM against icilin (196)]. In general, Δ^9-THC seems to be less efficacious than CBD and other phytocannabinoids at modulating thermo-sensitive TRP channels.

Δ^9-THC inhibits all the three human subtypes of recombinant Ca_V3 channels (IC_{50} $Ca_V3.1$, 1.6 μM; IC_{50} $Ca_V3.2$, 1.3 μM; IC_{50} $Ca_V3.3$, 4.3 μM) and the native mouse T-type currents in acutely isolated trigeminal ganglion sensory neurons (743) and NG-108-15 neuroblastoma cells (129). T-type channels are involved in a wide variety of physiological processes (reviewed in Ref. 668), which Δ^9-THC also affects, including nociception, sleep, epilepsy, and modulation of neuronal excitability. Δ^9-THC also inhibits (IC_{50} 2.4 μM) $K_v1.2$ channels through a CB1- and pertussis toxin-insensitive mechanism (689). Another observed effect with potential relevance for analgesia is its modulation of voltage-gated sodium channels (859). Finally, there have also been reports that Δ^9-THC inhibits some enzymes at micromolar concentrations: 15-lipoxygenase (IC_{50} 2.42 μM) (840); Na^+-K^+-ATPase; monoamine oxidase (IC_{50} 24.7 μM) (265); cytochrome *P*-450 enzymes CYP1A1, CYP1A2, CYP2B6, and CYP2C9 (825); and Mg^{2+}-ATPase (677).

In summary, many targets seem to be modulated in vitro by Δ^9-THC at micromolar concentrations. However, considering that only low doses of this compound are tolerated per se in both preclinical and clinical settings, it remains unlikely that targets other than CB1 and CB2 participate in the in vivo pharmacology of Δ^9-THC.

B. Therapeutic Use and Side Effects

A synthetic analog of Δ^9-THC, nabilone (Cesamet; Valeant Pharmaceuticals North America), was approved in 1981 for the suppression of the nausea and vomiting produced by chemotherapy (674). Synthetic Δ^9-THC, dronabinol (Marinol; Solvay Pharmaceuticals), was subsequently licensed in 1985 as an antiemetic and in 1992 as appetite stimulant (674). Δ^9-THC capability of stimulating the CB1 receptor is paradoxically both the main reason for, and drawback against, its therapeutic use. In fact, as discussed below, psychotropic effects, and the potential risk of cardiac side effects, tolerance, and dependence, limit the application of Δ^9-THC in therapy.

1. Diseases of energy metabolism

As will be discussed in detail in a following section, the ECS has been implicated in the physiological regulation of appetite following early observations on the ability of CB1 receptor agonists, including Δ^9-THC, to induce hyperphagia (917). It is widely accepted that administration of Δ^9-THC increases the incentive value of food and the motivation to ingest palatable food, while antagonists/inverse agonists of CB1 receptors produce opposite effects (220).

Δ^9-THC increases sucrose-induced hedonic activity and dopamine release into the nucleus accumbens (185), whereas CB1 antagonism reduces the increase of dopamine release

(569). However, although acute Δ^9-THC produces hyperphagic effects in rats (393) and mice (34), chronic administration of the compound does not result in increased body weight. This might be due to *1*) the capability of Δ^9-THC to desensitize CB1 receptors, to induce aversive responses, or to act as a partial agonist/antagonist in vivo (212); *2*) the different contribution of CB1 on glutamatergic or GABAergic terminals to produce hyperphagic or hypophagic effects, respectively, as shown through the use of conditional CB1 knockout mice lacking CB1 in either population of neurons (55); and *3*) the recent finding that CB2 receptor activation instead reduces body weight and fat mass in obese mice (881).

Peripheral effects were also described. Chronic Δ^9-THC might induce a differential decrease of subcutaneous versus intra-abdominal adipose tissue. A set of molecular mechanisms involved in fat accumulation in adipocytes influenced by Δ^9-THC was outlined (208), including adipogenesis and decreased lipolysis (852). Recently, chronic Δ^9-THC was shown to prevent body weight gain induced by a high-fat diet via effects on the gut microbiota (150).

2. Cachexia and anorexia

Some of the symptomatologies usually related to a negative energy balance often observed in cancer or AIDS (i.e., reduced appetite and food intake and augmented energy expenditure) can be associated also with other pathological conditions such as aging, anorexia nervosa, or various forms of dementia including AD (644). As mentioned above, there is clinical evidence documenting the therapeutic effectiveness of synthetic Δ^9-THC in some of these conditions (54, 688). In particular, a few studies reported the effectiveness of Δ^9-THC in stimulating appetite and weight gain in cancer and in AIDS patients (435), or in AD patients with anorexia (889).

3. Pain and inflammation

Δ^9-THC strongly reduces nociception in animal models of acute, visceral, inflammatory, and chronic pain (367). Six trials that included overall 325 patients examined chronic pain, and 6 trials that included 396 patients investigated neuropathic pain. Marijuana or cannabinoids produced positive results in several of these trials (349). Accordingly, Δ^9-THC exerts antinociceptive effects in preclinical tests of acute nociception (87) and of chronic pain of both neuropathic (197) and inflammatory origin (163). The antinociceptive activity of Δ^9-THC in acute pain is mediated only by the CB1 receptor, and by both CB1 and CB2 in chronic pain (163). Δ^9-THC is very effective at reducing muscular pain when administered locally, where only CB2 receptors appeared to be targeted, thus avoiding the well-known undesirable central side effect (29).

In agreement with the important role of the ECS in the regulation of immune function and inflammation (reviewed below and in Ref. 104), Δ^9-THC modulates cytokine (e.g., TNF-α, IL-1β, IL-6, IL-12, and IL-10) and chemokine production, the expression of adhesion molecules, and the migration, proliferation, and apoptosis of inflammatory cells (439, 899).

4. CNS

Cognitive impairments, apparently associated with alterations in synaptic transmission and functional expression of glutamate receptor subunits, may be observed with high doses of Δ^9-THC (251, 324, 577). Δ^9-THC causes downregulation, internalization, and endocytosis of glutamate receptors or increases synaptic and astrocytic release of glutamate, thereby elevating extracellular glutamate levels (251, 324). Interestingly, the reduced expression of glutamate transporters in Δ^9-THC-exposed animals is attenuated by COX-2 inhibitors (138).

A) NEUROPROTECTION. Δ^9-THC protects the brain from various acute neuronal insults and improves the signs of neurodegeneration in animal models of multiple sclerosis (MS), PD, HD, amyotrophic lateral sclerosis (ALS), and AD (258). Possible mechanisms underlying these protective effects involve activation of cannabinoid receptors, while others are receptor independent. In some cases, protection is due to a direct effect on neuronal cells, while in others, it results from effects on nonneuronal elements within the brain. Mechanisms include modulation of excitatory glutamatergic transmissions and synaptic plasticity (288, 358, 772, 788); modulation of immune responses and the release of inflammatory mediators (104); modulation of excitability, *N*-methyl-D-aspartate (NMDA) receptors, gap junctions, and $[Ca^{2+}]_i$ (321, 919); and antioxidant properties (323). Δ^9-THC protects primary cultured neurons against kainate-mediated toxicity in a CB1-dependent manner (2) and exerts neuroprotective effects in an ouabain-induced rat model of in vivo excitotoxicity (870). However, it was suggested that the neuroprotective effects against ischemia of Δ^9-THC are mediated almost uniquely by its CB1-mediated hypothermic effects (334).

B) MULTIPLE SCLEROSIS. MS patients are known to self-medicate with cannabis to alleviate MS symptoms, such as muscle spasticity. *Cannabis*-based medicines were approved for the treatment of pain and spasticity in MS (reviewed in Ref. 693). Accordingly, in a mouse model of chronic relapsing experimental autoimmune encephalomyelitis (EAE), which models MS spasticity, administration of Δ^9-THC ameliorates, whereas CB1 antagonism exacerbates, spasticity and tremors (31). Furthermore, in rats with EAE, Δ^9-THC reduces CNS inflammation, improves neurological outcome, and prolongs survival (498). Although a 3-yr, phase III clinical trial did not detect a beneficial effect of oral Δ^9-THC in progressive MS, people with less disability showed slowing of progression compared with placebo (695). The 15-wk treatment of MS patients with a tolerated dose of

Δ^9-THC ameliorated urinary incontinence but did not modify spasticity, measured using the Ashworth scale, although the 12 month follow-up to this trial evidenced a significant antispasticity effect (273, 936, 937). Subsequent clinical trials could not demonstrate any effect on disease progression following long-term treatment with Δ^9-THC (935).

C) HUNTINGTON'S DISEASE. Δ^9-THC (or its synthetic analog nabilone) showed no efficacy or even increased choreic movements in HD (606). The lack of efficacy despite the clear locomotor inhibitory actions of the compound might be due to the fact that CB1 expression is significantly reduced in post mortem human HD tissue (293), and in a chemically induced model of HD (458) impairment of both CB1 levels and signaling were observed in the basal ganglia as one of the earliest changes of the disease.

D) GILLES DE LA TOURETTE'S SYNDROME. Δ^9-THC was suggested to be effective in the treatment of both tics and behavioral problems in Gilles de la Tourette's syndrome (for a review, see Ref. 604). However, only two controlled trials have investigated its efficacy in the treatment of this syndrome (605, 607), and they reported effectiveness against tics but no improvement of neuropsychological performance.

E) ALZHEIMER'S DISEASE. Several studies produced new perspectives on the possible role of the ECS in neurodegenerative processes associated with inflammation (899), including AD (72) (see below), characterized by the formation of neuritic plaques rich in Aβ peptide. In an animal model of AD, treatment with Δ^9-THC (3 mg/kg) once daily for 4 wk reduced the number of β-amyloid plaques and degenerated neurons, although this effect required the presence of a COX-2 inhibitor (138). Δ^9-THC preserves memory in mice when chronically administered during the early symptomatic stage in a transgenic mouse model of AD, and coadministration with CBD reduced learning impairment and the levels of soluble Aβ-42 peptide, the most neurotoxic form of Aβ (23).

The only available clinical studies with Δ^9-THC in AD have addressed its possible use to control some of the symptoms rather than the progress of this disorder. Treatment with 2.5 mg dronabinol daily for 2 wk significantly improved the Neuropsychiatric Inventory total score for agitation and aberrant motor and nighttime behaviors (901), and six other small studies showed significant benefits from synthetic Δ^9-THC on agitation and aggression in AD (484).

F) EPILEPSY. Several groups investigated the potential antiepileptic effects of Δ^9-THC (reviewed in Refs. 200, 497). However, although originally believed to be an anticonvulsant, Δ^9-THC has a variety of effects depending on the dose, experimental model, and animal species used (497). Single administration of Δ^9-THC results in a rebound hyperexcitability in the CNS in mice, with enhanced neuronal excitability and increased sensitivity to convulsions (422). Thus current evidence argues against the use of Δ^9-THC as an anticonvulsant because of its often unpredictable and bell-shaped dose-response curves in animal models of seizures and epilepsy.

G) SCHIZOPHRENIA. It appears that hypoglutamatergic and hypodopaminergic transmission in the prefrontal cortex is involved in the negative symptoms, whereas hyperactivity of dopamine neurotransmission in the mesencephalic projections to the nucleus accumbens in the positive symptoms of schizophrenia. Thus the use of high amounts of marijuana and Δ^9-THC may produce psychotic symptoms in healthy individuals, including anxiety, hallucinations, and cognitive deficits, which resemble schizophrenia (174), and transiently exacerbate psychotic and cognitive deficits in schizophrenia patients (173). Δ^9-THC can cause acute transient psychotic symptoms in both healthy individuals and schizophrenia patients (593), which may be related to dopamine release in the striatum as shown in humans (68, 94) and in the nucleus accumbens and prefrontal cortex in animal models (847). Yet, schizophrenic patients often self-medicate with marijuana. It is likely that systemic activation of CB1 receptors of different neuronal populations in the brain by exogenous Δ^9-THC produces effects that can be overall different from those caused by local and more specific "endogenous" activation of such receptors by AEA, which instead was suggested to be protective against psychosis (see below). The CB1 inverse agonist rimonabant (20 mg/day for 16 wk) did not improve global cognitive functioning in lean patients (85), but it did ameliorate several symptoms in obese schizophrenic subjects (427). These results together with the improvement of symptoms observed in a small group of patients who instead received dronabinol (781), confirm that the role of Δ^9-THC and CB1 receptors in psychosis is quite complex.

H) ANXIETY AND FEAR. The anxiolytic properties of the synthetic Δ^9-THC analog nabilone were first demonstrated in a clinical trial in 1981 (250). After the discovery of CB1 receptors, it was suggested that the mechanisms mediating the anxiolytic effects of Δ^9-THC involve both CB1 and non-CB1 receptors [e.g., 5-HT_{1A} receptors (98)]. Through a CB1-mediated mechanism, low doses of Δ^9-THC increased the time spent on open arms, an index of anxiolytic-like effects, in rats, and, concomitantly, lowered the amounts of c-Fos in prefrontal cortex and amygdala and the increases in phosphorylated CREB in the prefrontal cortex and hippocampus (755). The response is species-specific because, in mice, Δ^9-THC produces instead a dose-dependent reduction of time spent in the open arm (664). These differences could be due to the different responsiveness of GABAergic and glutamatergic neurons to CB1 activation in rats and mice, as well as to different expression/distribution of CB1 receptors (319). Accordingly, in rats, a low dose of Δ^9-THC injected in the prefrontal cortex elicits anxiolytic effects,

whereas in the basolateral amygdala it produces an anxiogenic response (752). High doses usually induce anxiogenic-like responses in rodents (490, 755). Chronic exposure to Δ^9-THC in adolescent rats induces a depressive-like phenotype in adulthood (720, 756). In humans, the interindividual variability in the responses to cannabis may depend on a wide spectrum of factors, such as the relative concentrations of Δ^9-THC and other phytocannabinoids (846).

CB1 receptors mediate the extinction of aversive memories as shown by the finding that their genetic or pharmacological impairment in mice leads to impaired extinction in a fear-conditioning test (533). Even before these data were published, and then again afterwards, it was found that Δ^9-THC facilitates fear extinction (21, 310). Administration of Δ^9-THC during extinction learning facilitates extinction by preventing recovery of extinguished fear in rats. The compound disrupts the reconsolidation of a contextual fear memory in a manner dependent on activation of CB1 located in prelimbic subregions of the medial prefrontal cortex and on memory retrieval/reactivation (823). In humans, oral dronabinol prevents the recovery of fear (706).

In summary, Δ^9-THC holds promise for the treatment of some anxiety-related conditions, in particular posttraumatic stress disorders and phobias, for which clinical trials are ongoing in Israel (808).

I) SLEEP. Insomnia is the most common sleep disorder, and its cause is often unknown, although it may often be a consequence of a chronic disease associated with stress, pain, or depression. Experimental evidence shows that the administration of Δ^9-THC promotes sleep in both humans and animals. CB1 activation leads to induction of sleep in a manner blocked by a selective CB1 antagonist (for a review, see Ref. 611), which instead per se enhances arousal (774). However, a double-blind and placebo-controlled study on eight volunteers showed that there were no effects on nocturnal sleep of 15 mg Δ^9-THC, which only produced sedation (625).

J) EMESIS. Nausea and vomiting may present as symptoms of different diseases or as secondary consequences of chemotherapy or radiotherapy of cancer. For the latter indication, Δ^9-THC is an efficacious therapeutic agent (317, 662). Δ^9-THC inhibits 5-HT_3 receptors, whose activation appears to play a dominant role in acute emesis (930). CB1 and 5-HT_3 receptors colocalize on GABAergic neurons with opposite effects on GABA release (586). Interestingly, Δ^9-THC in combination with a TRPV1 agonist completely abolishes cisplatin-induced emesis in an additive manner (179). The superiority of the anti-emetic efficacy of cannabinoids (nabilone, Δ^9-THC, or levonantradol), compared with conventional drugs and placebo, was demonstrated through a meta-analysis (508).

5. Gastrointestinal disorders

Cannabis has a millennial use in diarrhea. Δ^9-THC causes decrease in gastric motor function partially due to activation of CB1 receptors in the dorsal medulla and vagal nerves (450). In the 2,4,6-trinitrobenzene sulfonic acid model of acute colitis in rats, Δ^9-THC reduces both markers of inflammation and colonic motility (387). An interesting recent report showed that chronic treatment of rhesus macaques with Δ^9-THC induces intestinal anti-inflammatory microRNA expression during acute simian immunodeficiency virus syndrome (135).

In a clinical trial, 10 of 11 patients with active Crohn's disease who smoked marijuana exhibited reduced inflammation without side effects (615). Improvement of pain and diarrheal symptoms in inflammatory bowel disease was also reported, although cannabis use in patients with Crohn's disease is associated with higher risk of surgery (824).

6. Cardiovascular disorders

The concerns related to the potential toxicity of *Cannabis* preparations have focused mainly on the risk of their neuropsychiatric effects, and little attention has been given instead to cardiovascular complications. Indeed, in a variety of pathological states (ranging from endotoxic, hemorrhagic, and cardiogenic shock, advanced liver cirrhosis, and cirrhotic cardiomyopathy) the activation of cardiovascular CB1 receptors contributes to hypotension and compromised cardiovascular function (644). Additionally, in cardiomyocytes, CB1-triggered signaling can lead to cardiotoxicity by promoting the reactive oxygen/nitrogen species-MAPK activation-cell death pathway (599). Yet, Δ^9-THC important effects on blood pressure and heart rate (408) might be also exploited therapeutically. Intravenous injection of this compound causes an initial bradycardic response and prolonged hypotension (452, 893), these effects being absent in mice lacking CB1 (392, 463). To explore the complex underlying molecular mechanisms of their hypotensive effects, cannabinoids have been often investigated for their vasorelaxation effects in the rat mesenteric artery. The vasodilatory effects of Δ^9-THC are complex and involve many cellular and molecular mechanisms, including CB1- and CB2-independent pathways, such as activation of TRPA1 channels (409), PPARγ (634), and K^+ channels as well as inhibition of Ca^{2+} channels (632). The potential use of Δ^9-THC to treat hypertension has been suggested (876), but the development of rapid tolerance to the hypotensive and bradycardic effects (4), and its neurobehavioral effects, remain problems to be solved.

Pretreatment with a CB2 antagonist abolishes the cardioprotective effect of Δ^9-THC in isolated hearts from rats pretreated with LPS (451). Also Δ^9-THC benefical action in hypoxic isolated neonatal cardiomyocytes, which is medi-

ated by NO production, is sensitive to CB2, but not CB1, antagonism (791). Pretreatment with Δ^9-THC, administered before myocardial infarction in mice in vivo, is cardioprotective and inhibits $ERK_{1/2}$ phosphorylation following infarct (894).

Orally administered Δ^9-THC modulates immune functions and inhibits atherosclerotic plaque progression with a CB2 receptor-dependent mechanism in the $apoE^{-/-}$ mouse model of atherosclerosis, through modulatory effects on lymphoid and myeloid cells (819). Δ^9-THC inhibits (IC_{50} = 2.42 μM) 15-lipoxygenase, an enzyme responsible for the formation of oxidized low-density lipoprotein, a causal factor for atherosclerosis (840).

7. Asthma

Smoked marijuana containing 3–7 mg/kg Δ^9-THC results in an acute bronchodilator response and potential therapeutic benefit on airway function (849). Pure Δ^9-THC produces bronchodilation in asthmatic patients (329) and may have therapeutic value in asthma also by virtue of its anti-inflammatory effects (933). Indeed, in allergic airway disease induced in mice by aerosolized ovalbumin, pretreatment with Δ^9-THC inhibits the expression of T-cell cytokines elicited by ovalbumin in the lungs and the associated inflammatory response (389). In LPS-induced bronchopulmonary inflammation in mice, intranasal Δ^9-THC decreases the levels of the proinflammatory cytokine TNF-α in a manner partly mediated by CB2 (63). Recently, the effects of Δ^9-THC and a potent synthetic CB1/CB2 agonist on bronchoconstriction in vitro in the guinea pig trachea and on airway inflammation and cough were investigated in anesthetized guinea pigs following exposure to TNF-α. In vitro, the two compounds inhibited TNF-α-enhanced nerve-evoked contractions in a manner antagonized by both CB1 and CB2 antagonists. In vivo, only Δ^9-THC inhibited TNF-α-enhanced vagal-induced bronchoconstriction, neutrophil recruitment to the airways, and citric acid-induced cough responses, whereas both compounds inhibited TNF-α-enhanced acetylcholine release, and hence contraction and bronchoconstriction, again through activation of CB1 and CB2 receptors (520).

8. Glaucoma

Glaucoma is characterized by an increase in intraocular pressure, a cause of vision loss and blindness. A serendipitous finding, i.e., the decrease in intraocular pressure in healthy marijuana smokers (340), was subsequently confirmed in a placebo-controlled, double-blind study (339). Δ^9-THC decreases intraocular pressure whether administered orally, topically, or intravenously, in both animals and humans (394). Accordingly, endocannabinoids play an important role in the regulation of intraocular pressure, are present in ocular tissues including the retina (71, 826), and their levels significantly decrease in patients with glaucoma (137).

9. Cancer

Numerous preclinical studies suggest that Δ^9-THC might directly inhibit cancer growth (269). The mechanisms are complex and involve induction of apoptosis, antiproliferative, antimetastatic, and antiangiogenic actions (665) **(FIGURE 1)**.

Treatment with Δ^9-THC inhibits the growth of various types of tumor cell in vitro or tumor cell xenografts in vivo, including lung carcinoma (692), glioma (280), and lymphoma (553). The pro-apoptotic effect of Δ^9-THC in tumor cells is complex and involves increased synthesis of the pro-apoptotic sphingolipid ceramide (280), in glioma cells; ceramide-dependent upregulation of the stress protein p8 resulting in upregulation of the endoplasmic reticulum (ER) stress-related genes ATF-4, CHOP, and TRB3 (121); p38 MAPK signaling, in human leukemia cells (343); downregulated Raf-1/mitogen-activated protein kinase/ERK kinase pathway leading to translocation of BAD to mitochondria, in leukemia T cells (400); inhibition of RAS-MAPK/ERK and PI3K-AKT survival signaling cascades, accompanied by activation of the pro-apoptotic BAD, in colorectal cancer cells (306); and rapid activation of ERK and c-Jun NH_2-terminal kinase, in human U373MG astrocytoma cells (915). Furthermore, Δ^9-THC promotes autophagy-mediated apoptosis by inducing ceramide accumulation and eukaryotic translation initiation factor 2α phosphorylation, thereby activating an ER stress response that promotes autophagy via the tribbles homolog 3-dependent inhibition of the Akt/mammalian target of mTORC1 complex axis in human glioma (768) and in hepatocellular carcinoma (875) cells. Enhancement of autophagy by the combined administration of Δ^9-THC and temozolomide exerts a strong antitumoral action in glioma xenografts (857).

Also the antiproliferative actions of Δ^9-THC seem to occur through various mechanisms in different tumor cells, i.e., by activating CB2 receptors with subsequent arrest of the cell cycle in G_2-M via downregulation of Cdc2 (108), or modulation of JunD, a member of the AP-1 transcription factor family, resulting in inhibition of cell cycle progression, in human breast cancer cells (107); upregulating PPARγ-dependent pathways in hepatocellular carcinoma cells (874); promoting the expression of the intercellular adhesion molecule 1, with subsequent enhancement of cancer cell adhesion to lymphokine-activated killer cells and lysis, in lung cancer (332). It was suggested that CB2 receptors form heteromers with tumor-promoting GPR55 in cancer cells, which might influence the action of Δ^9-THC against tumor growth. The heteromers displayed a cross-talk and cross-antagonism at the level of the cAMP and p-ERK-1/2 pathways. Δ^9-THC was shown to antagonize GPR55, both at the single receptor level and within the CB2-GPR55 hetero-

mer (592). The variability of the antitumor effects of Δ^9-THC may be related also to the differential expression of receptor targets (554).

In addition to its proapoptotic and antiproliferative effects, Δ^9-THC also inhibits the expression of proangiogenic mediators or their receptors (e.g., vascular endothelial growth factor), thereby reducing endothelial cell migration in vitro and in vivo (80). Increased expression of tissue inhibitor of matrix metalloproteinases-1 (714) and downregulation expression of matrix metalloproteinase-2 in gliomas in mice (83) also mediate the anti-invasive effects of Δ^9-THC.

IV. LESS STUDIED PHYTOCANNABINOIDS

Of the other more than 100 phytocannabinoids present in varying amounts and percent composition in the several varieties of the cannabis plant, little more than a handful have been investigated so far from the pharmacological standpoint, and these are cannabichromene (CBC), cannabigerol (CBG), cannabidivarin (CBDV), Δ^9-tetrahydrocannabivarin (THCV), Δ^9-tetrahydrocannabinolic acid (THCA), and cannabidiolic acid (CBDA). Yet, these compouds, whose abundance in cannabis flowers depends on the variety of the plant, may also be responsible for the anecdotal therapeutic actions of its preparations.

CBC may cause hypothermia, sedation, and hypoactivity in mice (860). It exerts anti-inflammatory and modest analgesic actions (181, 860) as well as antibacterial activity (19). It is a weak AEA reuptake inhibitor (193, 478) and a very weak inhibitor of the hydrolysis of 2-AG (193), whereas it is the most potent cannabinoid TRPA1 agonist in a $[Ca^{2+}]_i$ functional assay (EC_{50} = 90 nM) (193, 196).

Only when administered at high doses (~100 mg/kg) does CBC produce significant pharmacological "tetrad" effects in vivo, in a manner insensitive to CB1 antagonism, indicating a non-CB1 receptor mechanism of action, in agreement with its very low affinity for the CB1 receptor [K_i >10,000 nM (87); K_i 714 nM (742)]. CBC dose-dependently decreases LPS-induced inflammation in paw edema assay with a noncannabinoid receptor mechanism of action (198). It inhibits nitric oxide production, IL-10, and IFN-γ levels in LPS-activated macrophages (740), reduces inflammation-induced gut hypermotility in vivo in mice (384), and produces antidepressant-like activity in rodents (236). CBC is analgesic by stimulating the descending pathway of antinociception in the ventrolateral periaqueductal grey, through activation of TRPA1, inhibition of endocannabinoid inactivation, and subsequent elevation of local endocannabinoid levels, and potentiation of adenosine signaling (519). CBC positively influences the viability of the Nestin-positive stem cell population in differentiating adult neural stem progenitor cells through the upregulation of ERK phosphorylation, an effect mediated by the adenosine A1 receptor and leading to inhibition of astroglial differentiation, suggesting a possible proneurogenic/antineuroinflammatory action through the suppression of reactive astrocytes (790).

CBG was first detected in cannabis preparations and synthesized in 1964 (282), and subsequently found not to induce Δ^9-THC-like psychopharmacological effects in vivo (566). In its acid form is the biosynthetic precursor of the acid forms of Δ^9-THC, CBD and CBC in the cannabis plant. CBG is a potent TRPM8 antagonist (193, 196), and it activates both TRPV1 and, particularly, TRPA1, whilst showing low affinity for cannabinoid receptors (CB1, K_i 897 nM; CB2, K_i 372 nM; Ref. 742). In the low micromolar range, it acts as an AEA reuptake inhibitor (193, 478). Finally, CBG is a α2-adrenoceptor agonist and a 5-HT_{1A} receptor antagonist (125). The former activity leads to analgesia (290), whereas its action as a 5-HT_{1A} antagonist explains its blockade of the antiemetic and antinausea effects of CBD (733).

Studies on its effects in models of HD showed that CBG is neuroprotective in mice intoxicated with 3-nitropropionate through counteraction of proinflammatory induced markers and improvement of antioxidant defenses. In CBG-treated animals, an increase in the gene expression for brain-derived neurotrophic factor (BDNF), insulin-like growth factor I (IGF-I), and PPARγ, and a small reduction in the aggregation of mutant huntingtin, were observed, thus opening the possibility of it being used for the treatment of HD (863).

CBG decreases the contractions induced by acetylcholine in bladder, this effect being unaffected by CB1 or CB2 receptor antagonists (648), whereas it counteracts experimental inflammatory bowel disease by reducing macrophage NO production through activation of CB2 (90).

CBG, like CBD, inhibits human keratinocyte proliferation and differentiation via non-CB1, non-CB2-dependent epigenetic mechanisms (698, 916), and these effects may suggest its use against psoriasis and acne. CBG also shows antitumor activity in vitro (478). It inhibits prostate carcinoma growth in vitro and in vivo, with TRPM8 antagonism and activation of intrinsic apoptotic pathways as possible mechanisms (194). It inhibits the growth of xenograft tumors as well as chemically induced colon carcinogenesis, and the proliferation of colorectal cancer cells in vitro, an effect shared by other TRPM8 antagonists. CBG should be considered in colorectal cancer prevention and cure (91).

Δ^9-Tetrahydrocannbivarin (Δ^9-THCV) is the propyl-tailed analog of Δ^9-THC and the most studied phytocannabinoid after its homolog and CBD. At low doses (<3 mg/kg) it antagonizes the effects of Δ^9-THC, but acts as a CB1 agonist at higher doses (10 mg/kg) in mice (673, 681). It ex-

presses the pharmacological profile of a neutral CB1 antagonist in vitro (673, 681, 855) as it antagonizes CB1 agonist-induced [^{35}S]GTPγS binding to mouse whole brain, cerebellar, and piriform cortical membranes with no activity in the absence of agonist (199, 855). Δ^9-THCV antagonizes the ability of Δ^9-THC and other agonists to inhibit electrically evoked mouse vas deferens contractions (855). However, it is also a potent, albeit partial, agonist at CB2 receptors in vitro when the measured response is the inhibition of forskolin-induced stimulation of cAMP or the stimulation of [^{35}S]GTPγS binding to membranes obtained from either cells transfected with human CB2 or mouse spleen (86). This is a very attractive feature because, as described above and in the following sections, a combined activation of CB2 receptors and blockade of CB1 receptors might ameliorate several disorders. Δ^9-THCV suppresses carrageenan-induced hindpaw edema and formalin-induced hyperalgesia in mice, both effects being attenuated by a CB2-selective antagonist (86). Δ^9-THCV also stimulates the recruitment of quiescent mesenchymal stem cell present in bone marrow, resulting in increased formation of fibroblastic colonies in a manner blocked by a CB2 specific antagonist, thus potentially exerting beneficial effects on bone formation and fracture healing (784).

Δ^9-THCV acts as an agonist at TRPA1 (EC_{50} = 1.5 μM), which explains its pronociceptive effect on the first phase of the formalin test and desensitizes this channel to subsequent stimulation by allyisothiocyanate (IC_{50} = 3.1 μM). However, the compound also stimulates human TRPV1 (EC_{50} = 1.5 μM) and rat TRPV2 (EC_{50} = 4.1 μM) and is an antagonist at rat TRPM8 (IC_{50} = 0.9 μM) (193).

As expected from a CB1 antagonist, Δ^9-THCV attenuates Δ^9-THC-induced hypothermia and antinociception (673) and reverses some of the cognitive and physiological effects of Δ^9-THC, such as delayed verbal recall and increased heart rate, in human volunteers (242). Nine out of 10 participants also reported that, under Δ^9-THCV treatment (compared with placebo), Δ^9-THC was subjectively felt to be weaker or less intense. However, Δ^9-THCV also significantly increased memory intrusions induced by Δ^9-THC (242).

Δ^9-THCV suppresses saccharin palatability and the appetite for sweet taste (736) and, at doses as low as 3 mg/kg, shares the ability of synthetic CB1 antagonists to reduce food intake and body weight gain in mice (726), with potential use in the treatment of obesity (673). However, chronic administration of Δ^9-THCV in animal models of obesity does not modify food intake but produces an early and transient increase in energy expenditure, reduces glucose intolerance in *ob/ob* mice, and improves insulin resistance in mice with high-fat diet-induced obesity, without consistently affecting plasma lipids. Δ^9-THCV also restores insulin signaling in insulin-resistant hepatocytes and myotubes (908). All these effects were suggested to be due to non-CB1-mediated mechanisms. Additionally, like CBD, Δ^9-THCV is very efficacious at inhibiting liver lipid accumulation in in vitro and in vivo models of steatosis, seemingly by stimulating lipolysis in hepatocytes via non-CB1, non-CB2-mediated mechanisms, and reduces lipid accumulation in white adipocytes (797). These results could have relevance on the future clinical development of Δ^9-THCV for the treatment of hepatosteatosis and type 2 diabetes (556).

In human volunteers, Δ^9-THCV increases neural responding to rewarding stimuli in the midbrain, anterior cingulate cortex, caudate, and putamen, but also to aversive stimuli in the amygdala, insula, mid orbitofrontal cortex, caudate, and putamen (858). In a randomized double-blind design, 10 mg oral dose of Δ^9-THCV decreases resting state functional connectivity and increased connectivity in the cognitive control network and dorsal visual stream network. This suggests therapeutic efficacy in obesity, where functional connectivity is altered, but also indicates lower risk of depressive side effects compared with CB1 inverse agonists (764).

Δ^9-THCV increases inhibitory neurotransmission (199) by increasing, in a $GABA_A$ antagonist-sensitive manner, the inhibitory postsynaptic currents at interneuron-Purkinje cell synapses, and decreases Purkinje's cell spike firing in the mouse cerebellum in vitro (500). These effects could be useful in spinocerebellar ataxias, a pharmacologically untreatable group of hyperexcitability disorders, although preclinical in vivo animal studies in this specific therapeutic area have yet to be undertaken (347). The inhibitory effects of the compound could also be useful in epilepsy, and indeed, Δ^9-THCV produces antiepileptiform and anticonvulsant properties (346). Administered daily for 14 days to 6-hydroxydopamine-lesioned rats, it alleviates the symptoms associated with PD by blocking CB1 receptors at low doses, and induces neuroprotection (284). Δ^9-THCV improves the motor inhibition produced by 6-hydroxydopamine, as already seen with the CB1 inverse agonist rimonabant (304). On the other hand, Δ^9-THCV, via CB2 receptor activation, affords neuroprotection in the LPS-lesioned mouse model of PD, where dopaminergic cell death is caused predominantly by inflammatory events. Finally, Δ^9-THCV antipsychotic effects against some of the negative, cognitive, and positive symptoms in an animal model of schizophrenia (where CB1 antagonists also produce beneficial effects) depend on the enhancement of 5-HT_{1A} receptor activity (125).

In summary, the bulk of evidence on Δ^9-THCV pharmacology indicates a predominant action as a neutral CB1 antagonist in vitro, but a much wider spectrum of molecular targets for its actions in vivo (556).

CBDV, the propyl analog of CBD, has virtually no affinity for the CB1 receptor (K_i = 15 μM) and low affinity for CB2 (K_i = 0.6 μM) (742), but is a good agonist at TRPA1 (EC_{50} = 0.4 μM), a moderate agonist at TRPV1 (EC_{50} = 3.6 μM) channels, and a good antagonist at TRPM8 (IC_{50} = 0.90 μM) channels. It weakly inhibits 2-AG biosynthesis in preparations from cells overexpressing one of the enzymes catalyzing the production of the endocannabinoid (IC_{50} = 16.6 μM), but also counteracts the cellular uptake of AEA (IC_{50} = 21.3 μM) (193). CBDV significantly reduces the maximal stimulatory effect of L-α-lysophosphatidylinositol on ERK1/2 phosphorylation, suggesting that this compound might be an inhibitor of GPR55 signaling (18).

CBDV, as well as CBDV-rich cannabis extracts, exert significant anticonvulsant effects in models of seizure in rodents (353). Responders exhibited suppression of epilepsy-induced increased expression of several epilepsy-related genes (e.g., *Fos, Egr1, Arc, Ccl4*, and *Bdnf*) (14). When tested on epileptiform neuronal spike activity in hippocampal brain slices, CBDV reduces both epileptiform burst amplitude and duration by acting in part via TRPV1 activation/desensitization (377). These data support the clinical development of CBDV for the treatment of epilepsy.

CBDA is a weak TRPA1 (EC_{50} 5.3 μM) agonist and TRPM8 (IC_{50} 4.8 μM) antagonist (193, 196). It is a selective COX-2 inhibitor according to some authors (841) and exerts antiproliferative actions in some cancer cell lines (478). Per se or combined with Δ^9-THC is particularly effective for acute and anticipatory nausea (734, 735).

Δ^9-Tetrahydrocannabinolic acid (Δ^9-THCA) was recently reported to have moderate affinity for human CB1 (K_i 23 nM) and CB2 (K_i 56 nM) receptors (742), although previous data (6, 879) strongly contradict this finding. Δ^9-THCA is a weak TRPA1 agonist (EC_{50} 2.7 μM) and a good TRPM8 antagonist (IC_{50} 0.15 μM) (193), and is antiproliferative against cancer cells (478) and antispasmodic (860). Coadmistered with CBDA, it reduces anticipatory nausea in a manner counteracted by either a CB1 or a 5-HT_{1A} receptor antagonist (734).

V. SATIVEX

Sativex (GW Pharmaceuticals, UK) is composed of two cannabis extracts enriched in Δ^9-THC and CBD in an approximate ratio of 1:1 and was licensed as a medicine in 2005 in Canada for the relief of pain experienced by adults suffering from advanced cancer and to ameliorate spasticity caused by MS (761). CBD may potentiate the psychoactive and physiological effects of Δ^9-THC via pharmacokinetic mechanisms, by delaying the metabolism and elimination of THC (438). Furthermore, CBD weakly inhibits FAAH and the putative AEA transporter, thereby increasing the endogenous levels of AEA, which may synergize with Δ^9-THC at producing CB1 agonism. Additionally, CBD reduces peripheral hyperalgesia via TRPV1 desensitization (161), and Sativex provides better antinociception than Δ^9-THC given alone (155). CBD reduces inflammation and inflammatory cytokines through TRPV1-, adenosine receptor-, and PPARγ-mediated mechanisms, while Δ^9-THC reduces inflammation through CB1 and CB2 receptor-mediated mechanisms. CBD suppression of ROS, TNF-α, and IL-1β reduces NF-κB activity, which is induced by these stimuli, whereas Δ^9-THC may dampen NF-κB through a CB2-mediated mechanism (398). CBD inhibits cancer growth and induces apoptosis by generating ROS and upregulating caspase proteases by inducing endoplasmic reticulum and mitochondrial stress, whereas Δ^9-THC inhibition of cancer is CB1 and CB2 receptor-mediated and leads to the activation of MAPK/ERK pathways and ceramide accumulation. Thus, combining these mechanisms by using together CBD and Δ^9-THC is likely to produce synergistic effects in several diseases (527). Indeed, in an animal model of MS spasticity, the indication for which Sativex is approved in more than 26 countries, this botanical drug is more efficacious at reducing limb spasticity than Δ^9-THC alone, even though CBD is inactive in this test (356).

On the other hand, as suggested also by epidemiological studies showing that the abuse of cannabis preparations with higher relative amounts of CBD produces less central effects (342, 759, 856), coadministration of CBD with Δ^9-THC reduces several psychoactive and psychotic-like actions of the latter compound, thus widening its therapeutic window.

Apart from MS spasticity (263), Sativex is effective against neuropathic pain in MS patients, with no evidence of tolerance up to 2 yr of treatment (739). Positive results of the first phase III placebo-controlled study of the efficacy of the Sativex to alleviate neuropathic pain in MS patients were reported (453). Furthermore, in patients with advanced cancer, the Δ^9-THC:CBD extract, unlike Δ^9-THC extract only, produced significantly stronger relief of pain than placebo (404). Sativex was well tolerated, and there was no loss of effect with long-term use (405). A randomized, placebo-controlled study shows that low dose (1–4 sprays/day) and medium dose (6–10 sprays/day) of Sativex is more efficacious than high dose (11–16 sprays/day) against pain (690). In two recently reported phase 3 placebo-controlled studies against cancer pain, Sativex did not meet the primary end point. However, a prespecified pooled analysis of patients across the two trials to involve only clinical sites in the United States showed a statistically significant improvement for Sativex compared with placebo (P = 0.024), with several secondary efficacy end points exhibiting P values of <0.05 (www.gwpharm.com/GWPOtsukaResults271015.aspx).

Finally, a Sativex-like combination of Δ^9-THC:CBD is neuroprotective in the malonate-lesioned rat inflammatory model of HD (865) and improves dopamine neurotransmission and tau and amyloid pathology in a mouse model of tauopathies (123).

VI. CONCLUSIONS: ARE PHYTOCANNABINOIDS STILL TO BE CONSIDERED PROMISING THERAPEUTIC DRUGS?

Despite the wealth of preclinical studies showing the efficacy of both Δ^9-THC and several nonpsychotropic phytocannabinoids (with CBD in the frontline), still relatively few new phase 2 and 3 clinical trials with these compounds have been carried out. Nevertheless, we believe that it is reasonable to conclude that Δ^9-THC is still a useful tool at least against emesis and cachexia, while CBD is emerging as a very promising and safe therapy to treat schizophrenia and pediatric epilepsies. New indications may come in the near future from the ongoing trials of Δ^9-THCV against type 2 diabetes, and Sativex in high-grade glioblastoma multiforme. The proven efficacy of this latter botanical drug in disorders where Δ^9-THC alone is not always useful, such as spasticity in MS and, possibly, cancer pain, points to a new strategy for the development of therapies from phytocannabinoids through the combination of two or more such compounds, as either pure entities or standardized extracts from controlled varieties of the *Cannabis* plant. Indeed, some noncannabinoid components present in *Cannabis* extracts used for therapeutic purposes, including Sativex, may interact with the ECS, the best known example being β-caryophyllen. This compound is now emerging as a natural agonist of CB2 receptors, with potential beneficial effects on several disorders, such as nephrotoxicity (366).

VII. THE ENDOCANNABINOID SYSTEM

A. From Δ^9-THC to CB1 and CB2 Receptors

As highlighted in the above sections, Δ^9-THC and its main targets, the cannabinoid receptors, may be only some of the biochemical entities responsible for the manyfold pharmacological effects of cannabis. Although the anecdotal therapeutic uses of cannabis might be the product of several cannabinoids and their many targets, the psychotropic activity of, e.g., marijuana, is uniquely due to activation of CB1 receptors by Δ^9-THC. The existence of specific targets activated by this plant-derived substance was not an intuitive assumption as its lipophilic nature led for a long time to the belief that it acted by influencing membrane fluidity. Only after the identification of the exact chemical structure of Δ^9-THC (282) and the elucidation of its stereochemistry-bioactivity relationship (563), the paradigm that this compound acted via a nonspecific membrane perturbation was abandoned. Convincing evidence about the existence of specific cannabinoid receptors was reached with the availability of the synthetic tritium-labeled cannabinoid [^{3}H]CP-55,940. The presence in mouse brain plasma membranes of high-affinity, saturable, stereospecific binding sites for this radioligand, which correlated with both its in vitro inhibition of adenylate cyclase and in vivo analgesic activity, provided conclusive validation for the existence of pharmacologically selective targets for Δ^9-THC-like drugs (368). Soon thereafter, the mapping of the receptors in several mammalian species, including humans, revealed that their overall central nervous system distribution differed from any known neurotransmitter receptor pattern (341). The inhibition of [^{3}H]CP-55,940 binding by a GTP analog indicated that the receptor was functionally coupled to a guanine nucleotide-binding regulatory (G) protein (369). All these findings led to the subsequent cloning and identification of the endogenous G_i protein-coupled and Δ^9-THC-responsive brain receptor, later named CB1, out of a screening of several orphan GPCRs (544). Three years later a second GPCR, expressed in cells of the immune and hematopoietic systems, was cloned and named CB2 (609).

The simplistic assumption that the two main receptors of Δ^9-THC and of the ECS had segregated anatomical localizations, with "central" CB1 and "peripheral" CB2, endured for about a decade. We are now aware that these receptors are widely distributed throughout the body of mammals, birds, reptiles, and fish (555). CB1 expression is very dense in the brain, but is also present at much lower, and yet functionally relevant concentrations in various peripheral tissues. Within the brain, CB1 is noted in all those sensory and motor regions related with movement and cognition such as the basal ganglia, substantia nigra, globus pallidus, cerebellum, hippocampus, and brain stem (564). At the cortical level, CB1 controls neuronal activity by modulating both excitatory and inhibitory neurotransmitter release; therefore, this receptor is highly expressed on GABAergic as well as glutamatergic neurons (348). At the subcortical level, CB1 influences energy balance by modulating both food intake and energy expenditure. Although hypothalamic expression of CB1 is among the lowest in the brain (99), its activation is considered a powerful orexigenic signal to the extent that CB1 antagonists achieved the pharmaceutical market for the treatment of obesity and related metabolic diseases. However, the development of these drugs was halted by concern due to neuropsychiatric side effects, including anxiety, depression, and suicidal ideation, which may be observed after the blockade at central level of the CB1 receptor. These observations brought back many academic researchers to reconsider and reanalyze the crucial role of "central" CB1 in key brain functions, which will be discussed in the following sections. From a pharmacological perspective, and due to the unwanted side effects of both agonists and antagonists of CB1, the identification of

peripheral and often nonneuronal CB1 gave a new breath to the advance of cannabinoid drugs.

CB1 acts both at the peripheral (although still neuronal) and central (spinal and supraspinal) level in the pain pathway. In the rat spinal cord, a double band (due probably to different posttranslational modifications) of CB1 immunoreactivity is found in the dorsolateral funiculus, the superficial dorsal horn (laminae I and II inner/III transition), and lamina X (253). Indeed, CB1 is located on the axons of intrinsic interneurons (253) and synthesized in neurons of the rat dorsal root ganglia, where it is transported both centrally, reaching superficial dorsal horn terminals (360), and peripherally towards peripheral nerve terminals of sensory nerves (359). Interestingly, CB1 is well distributed in the periphery and expressed in several nonneuronal tissues (including the gastrointestinal system, reproductive system, cardiovascular system, adipocytes, liver, skeletal muscle cells, and pancreas) where, as will be described in this article, its activation contributes to the regulation of intestinal motility (672), fertility (902), protective response to circulatory shock and myocardial infarction (578), obesity-related metabolic or hormonal abnormalities (796), and myoblast differentiation (378).

CB2 was initially identified in cells and tissues of the immune system, such as the marginal zone of the spleen, cortex of the lymph nodes, and nodular corona of Peyer's patches (499). Further studies confirmed its key role in immune tissues and corresponding cell lines, indicating that among immune cell subpopulations, B rather than NK cells exhibit particularly high levels of its mRNA (278). The rank order of CB2 mRNA levels in the immune tissues examined (tonsils > spleen > PBMC > thymus) correlates with their B cell content and agrees with the low expression in other non-immune-related peripheral tissues (i.e., adrenal gland, heart, lung, prostate, uterus, pancreas, and testis) (278). Originally, the discovery of CB2 in the CNS was controversial. On the one hand, the dogma of having two receptor subtypes that split their actions based on the anatomical level (with the therapeutic implications that this distribution might contemplate) was difficult to repudiate. On the other hand, technical problems, such as the scarce selectivity of antibodies against CB2 receptors and the fact that CB2 knockout mice in some genetic backgrounds did conserve a nonfunctional portion of the protein, complicated the validation of CB2 finding in the brain. In fact, initially, many authors failed to confirm the presence of CB2 in the healthy CNS (134, 308, 778, 831), while others confined its expression to rat microglial (119), cerebellar granule cells (801), primary mouse astrocytes (576), human astrocytes (789), and the adult retina (495), particularly during inflammatory conditions. Some pharmacological data suggested, and molecular and immunocytochemical studies later confirmed, the presence of very low levels of CB2 in both peripheral and CNS neurons (232, 302, 641, 675, 814, 872), for example, following axonal lesions (886). It is still controversial, however, whether or not CB2 is functionally active in the CNS (641, 822, 872). For example, a pharmacological study showed that CB2 is not active under physiological conditions (145), although a more recent report highlighted the potential functional significance of this receptor in hippocampal plasticity (822). In summary, the neuronal expression of functional CB2 receptors is still being debated (see Ref. 647 for a comprehensive review) and, possibly as a consequence of this controversy, the role of CB2 in the healthy brain is less characterized than that of the CB1 receptor.

Independently from their anatomical distribution, one thing that CB1 and CB2 definitely share is their belonging to the rhodopsin subfamily of GPCRs and their ability to activate multiple signaling pathways. This multiplicity of intracellular transduction mechanisms entails that receptor activation finely regulates several cellular and systemic functions. Once again, the majority of these mechanisms have been characterized for CB1 (93). Orthosteric ligands activate the receptor by interacting within the pore formed within the transmembrane helical cluster (602); the presence of a palmitoylated juxtamembrane COOH-terminal region allows for the orthosteric activation of G proteins, while the distal COOH-terminal tail domain modulates the magnitude and kinetics of signal transduction (628). Both CB1 and CB2 were originally thought to be exclusively associated with G_i or G_o (only in the case of CB1) dependent inhibition of adenylyl cyclase activity and activation of different MAPK cascades (53, 95–97, 369). CB1, mostly via G_o, also modulates voltage-dependent ion channels and, in particular, it inhibits voltage-gated Ca^{2+} channels (primarily N- and P/Q-type) and activates inwardly rectifying K^+ channels (511, 512, 787, 830). Additional complexity is afforded by the fact that the same effector regulates the interconnectivity of signaling cascades. For example, the inhibition of intracellular cAMP concentration, and the resulting decrease in PKA activity, affects not only gene expression by blocking the initiation of gene transcription through reduced cAMP response binding element (CREB) activation (93), but also another series of intracellular events. Less known examples of cellular responses under the control of CB1 and CB2 are the activation of cell survival/death decision, the modulation of cell excitability and neurotransmitter release, and the regulation of synaptic plasticity that can be, among others, a consequence of the following effector actions: *1*) decrease in constitutive inhibitory phosphorylation of c-Raf (with consecutive activation of ERK1/2); *2*) direct activation of voltage-dependent K^+ A-currents via the reduction of channel phosphorylation; and *3*) activation of focal-adhesion kinase (pp125 FAK and FRNK), through the inhibition of their phosphorylation (368).

In addition to the classical $G\alpha_{i/o}$ coupling, both $G\alpha_s$ and $G\alpha_q$ coupling can occur for CB1, but not CB2, e.g., in rat cultured striatal or hippocampal neurons, in response to micromolar concentrations of agonist, under conditions of pertussis toxin (PTX) inactivation of $G\alpha_{i/o}$-type G proteins (294, 459). The physiological relevance of these alternative couplings might be to provide a compensatory mechanism preventing, e.g., excessive cell excitability upon robust receptor activation. $G\alpha_{i/o}$ and then $G\alpha_s$ activation by increasing concentrations of CB1 agonists may explain biphasic concentration-response profiles for these drugs (i.e., biphasic regulation of voltage-gated Ca^{2+} currents or GABA release) (252, 303). Finally, further emphasizing the complexity of its signaling cascade, CB1 may recruit intracellular effectors via G protein-independent mechanisms. In primary astrocytes, but not in other cells, such as primary neurons, U373-MG astrocytoma cells, and Chinese hamster ovary cells transfected with the CB1 receptor cDNA, CB1 activation leads to sphingomyelin breakdown via the adaptor protein FAN independently from $G\alpha_{i/o}$ signaling (771). The fact that CB2 does not induce ceramide generation via sphingomyelin hydrolysis (280) and does not couple in alternative ways to G proteins, supports the idea that, in cannabinoid-mediated signaling, the downstream mediators are subtype specific. Therefore, the preferential activation of different intracellular effectors by each G protein contributes to the diversity and the selectivity of the responses regulated by cannabinoid receptors. This, together with ligand-dependent biased signaling (556), makes CB2 and, particularly, CB1 agonists very flexible, but often difficult to fully control, tools to regulate a plethora of physiological and pathological conditions.

With respect to the many cellular events triggered by CB1 and CB2, it is noteworthy that their signaling repertoire has been recently enriched by important evidence (sustained by the latest and most advanced methodologies) on the occurrence of GPCR multimerization. In particular, CB1 receptors were shown to form homodimers by using a "dimer antibody" as well as classical immunoprecipitation techniques, and were also reported to make heterodimers with D2 dopamine, A_{2a} adenosine, OX-1 orexin, 5-HT_{2a} serotonin, μ opioid, AT1 angiotensin II, and GPR55 receptors, the latter of which form heterodimers also with CB2 receptors (373, 509, 592, 669). Interestingly, there is also a report of the occurrence in the brain of CB1/CB2 heterodimers, the coactivation of which results in a negative crosstalk over Akt phosphorylation and neurite outgrowth (110).

Additional factors influencing the functional responses associated with cannabinoid receptor signaling are membrane microdomains and, particularly, cholesterol-enriched lipid rafts, which can modulate accessibility and mode of ligand binding (175). In human breast cancer cells, CB1 is physically associated with lipid rafts in a cholesterol-dependent manner, and this association can be dynamically modified by AEA binding (775). This spatial and functional coupling between CB1 and lipid rafts was also shown in an ex vivo model of striatal neurons, where raft disruption by cholesterol depletion causes a marked increase of CB1 binding and activity (503). Cholesterol depletion, by increasing membrane fluidity, improves ligand recognition by the CB1 receptor. Similar effects were shown in isolated rat C6 glioma cells, where lipid raft perturbation doubles the binding efficiency (i.e., the ratio between maximum binding and dissociation constant) and changes receptor trafficking by driving it almost entirely towards caveolin-1-enriched membrane fractions (35, 37). Therefore, removal of cholesterol can interfere with the constitutive endocytosis of CB1, leading to increased amounts of receptor associated with the plasma membrane. Interestingly, membrane cholesterol is known to modulate some conditions [i.e., Alzheimer's disease (254), neurotoxicity by immunodeficiency virus type 1 (HIV-1) glycoprotein gp120 (505), and the plasticity and efficiency of synapses (573) in which endocannabinoids are involved via CB1-dependent mechanisms (190)]. In contrast, the CB2 receptor is not under the control of lipid rafts in either immune or neuronal cells, where the cholesterol depletor methyl-β-cyclodextrin does not affect its binding to endocannabinoids (38). Indeed, CB2 displays a different compartmentalization, by being associated with non-raft fractions in dorsal root ganglion and neuroblastoma cells (727). The substantial dissimilarities in membrane microdomains-mediated modulation of the two-cannabinoid receptors indicates that cell-specific differences, or different physiological and pathological conditions, could alter the ratio of cannabinoid receptor signaling via different pathways.

B. Other Receptors for Endocannabinoids

As mentioned above, CB1 and CB2 are not the exclusive targets through which cannabinoids and endocannabinoids [despite the definition of the latter as endogenous agonists of cannabinoid receptors (217)] exert their actions. The ability of these small molecules to modulate non-CB1, non-CB2 receptors was suggested to underlie some of their behavioral effects, which may occur via synergistic actions at different signal transduction pathways. The first target that must be mentioned in this context is TRPV1, a nonselective cation channel that integrates multiple noxious stimuli activated by the naturally occurring vanilloids, capsaicin and resiniferatoxin (RTX), noxious heat, and acid (839). This channel is widely expressed in dorsal root ganglia, and sensory neurons, where its gating leads to Ca^{2+} influx and algogenic/vasodilating neurotransmitter release. By exhibiting an intracellular binding site for capsaicin and the major endocannabinoid AEA, TRPV1 has emerged as an "ionotropic receptor" counterpart for CB1 and CB2, a concept strengthened by the subsequent finding that both long chain *N*-acylethanolamine congeners of AEA (as well as

long-chain *N*-acyldopamines) and non-Δ^9-THC phytocannabinoids activate this channel. Thus AEA was not only the first endocannabinoid but also the first "endovanilloid" to be discovered (189, 210). The intrinsic potency of AEA at TRPV1 is low compared with that observed at the CB1 receptor (679) and, as a result, the physiological relevance of AEA as an endovanilloid was initially controversial. However, there is ample evidence that the interaction of AEA with TRPV1 receptors is specific (AEA is able to displace radiolabeled RTX from recombinant TRPV1) and enhanced by a plethora of physical and chemical stimuli interacting with these channels. Indeed, TRPV1 antagonism, knockout, and/or desensitization via capsaicin pretreatment abrogate several pharmacological effects of AEA and so does neonatal capsaicin treatment (744). Recently, also the other major endocannabinoid, 2-AG, was suggested to activate TRPV1, although less potently than AEA (213).

The second receptor claimed as an additional cannabinoid receptor subtype is the GPR55, originally identified as an orphan GPCR, extremely abundant in the brain and later reported as highly expressed in tissues known to respond to cannabinoids (513, 776). A wide range of phytocannabinoids, endocannabinoids, and congeners stimulate GTPγS binding with EC_{50} values in the low nanomolar range in cells overexpressing GPR55. However, pretreatment with either PTX or cholera toxin did not alter cannabinoid stimulation of GTPγS binding, excluding a mechanism through G_i, G_o, and G_s proteins (513). This indicates that this receptor possesses not only amino acid sequence but also ligand binding and signaling profiles different from those of CB1 and CB2. Indeed, there is controversy regarding the effects of endocannabinoids and congeners at GRP55, due to the different results obtained with different functional assays in various biological systems (786). It is possible that different biased signaling properties of these ligands, and tissue and cell-dependent coupling of GPR55 with different G proteins and effector systems, or with CB1 or CB2 in heteromers, all contribute to this heterogeneity of results (110, 537, 592).

Lastly, a recent discovery has pointed to the major ionotropic inhibitory neurotransmitter receptor $GABA_A$ as a novel target for 2-AG, which synergizes with the endogenous neurosteroid 3α,21-dihydroxy-5α-pregnan-20-one (THDOC) and modulates δ-subunit-containing receptors, known to be located extrasynaptically and to respond to neurosteroids (794). 2-AG directly interacts with $GABA_A$ by allosteric potentiation via a binding site located in transmembrane segment M4 of the β2 subunit (52). The identification of a functional binding site for 2-AG in the $GABA_A$ receptor may have important consequences for the study of locomotion and sedation.

C. Endocannabinoid Biosynthesis and Degradation

By definition, the ECS includes also proteins responsible for the biosynthesis, transport, and the inactivation of endocannabinoids. The first two identified and most studied endocannabinoids are AEA and 2-AG. The former compound was discovered in the pig brain in 1992 (205) and the latter one in the canine gut after 3 years (561). Subsequent research led to the identification of the major enzymes responsible for the main metabolic pathways for AEA and 2-AG, and, later, to the partial identification of alternative pathways for the biosynthesis and degradation of these compounds and their bioactive congeners. In fact, it was realized that the two endocannabinoids occur in tissues together with other long-chain *N*-acylethanolamines (NAEs) and 2-acylglycerols, which were later found to produce their effects mostly via noncannabinoid receptors (176, 779). Nevertheless, palmitoylethanolamide (PEA) and oleylethanolamide (OEA), as well as 2-palmitoyl- and 2-linoleoyl-glycerol (58), can enhance endocannabinoid activity/levels by the so-called "entourage" effect (719, 737). Other endogenous lipids that bind cannabinoid receptors were identified, i.e., 2-arachidonyl-glyceryl-ether (noladin ether) (326), *N*-arachidonoyl-dopamine (NADA) (76), and *O*-arachidonoyl-ethanolamine (virodhamine) (691). However, despite some efforts by the scientific community to characterize the metabolism of these molecules, their role as endocannabinoids is still controversial, and yet, the picture of the ECS has become more and more complicated over the years (222, 371, 432, 494). Additional key players (i.e., endocannabinoid-like molecules, putative orphan receptors, and alternative metabolic pathways) are being proposed to be part of this evolutionarily conserved and finely regulated lipid signaling system, whose number of additional potential components is predicted to raise even further in the future. Below, only the best-characterized metabolic pathways for the two major endocannabinoids, AEA and 2-AG, are described.

Differently from classical neurotransmitters, endocannabinoid production is believed to be de novo and "on demand," in most cases following elevation of $[Ca^{2+}]_i$. Only recently a storage system also for these mediators has been proposed, according to which endocannabinoids are secreted from microglial cells through extracellular membrane vesicles (known as exosomes) (275). In initial studies, two direct biosynthetic precursors were identified: *1*) AEA originates from the phospholipid *N*-arachidonoyl-phosphatidylethanolamine (NArPE), which in turn is formed from the *N*-arachidonoylation of phosphatidylethanolamine via yet to be characterized Ca^{2+}-dependent *N*-acyltransferases (NATs) (see NOTE ADDED IN PROOF); *2*) 2-AG originates from diacylglycerols (DAGs) with AA esterified on the 2-position, which are produced, in turn, mostly from the phospholipase Cβ-catalyzed hydrolysis of phosphatidylinositol, and in some cases from the hydrolysis of phos-

phatidic acid (77, 78, 106, 215, 218). The subsequent transformation of NArPE into AEA can occur via four possible alternative pathways, the most investigated of which is the direct conversion, catalyzed by an *N*-acyl-phosphatidylethanolamine-selective phospholipase D (NAPE-PLD). However, AEA biosynthesis occurs via additional pathways as indicated by the fact that no reduction in AEA levels was found in NAPE-PLD$^{-/-}$ mice (470). One possibility is the formation of a phospho-AEA precursor achieved after the hydrolysis of NArPE from an as yet unidentified phospholipase C (PLC)-like enzyme, such as the protein tyrosine phosphatase PTPN22 (485, 486). Alternatively, AEA can be formed through the sequential cleavage of the two *sn*-1 and -2 acyl groups of NArPE via the catalysis of α/β-hydrolase domain type-4 (ABHD4), followed by the hydrolysis of glycerophospho-AEA to AEA by glycerophosphodiesterase E1 (GDE1) (799). An additional route was proposed in cell-free brain homogenates and is the conversion of NArPE into 2-lyso-NArPE by a soluble form of phospholipase A_2, followed by the action of a lyso-phospholipase D (833). The prevalence of either pathway might depend also on precursor availability and cell type. An elegant study demonstrated the crosstalk between GDE1 and NAPE-PLD pathways for the regulation of NAE production (798). In brain homogenates, neither NAPE-PLD nor GDE1 null mice exhibit lower levels of AEA, whereas double NAPE-PLD/GDE1 null mice only show a partial disruption of NAE biosynthesis. Intact neurons from these double knockout animals were still capable of converting NArPE congeners to NAEs, suggesting that in situ different NAPE-converting pathways are likely to exist. However, when treated with a FAAH inhibitor, whole brain and testis from GDE1$^{-/-}$/NAPE-PLD$^{-/-}$ mice displayed significant reductions in several NAEs including AEA, suggesting that both enzymes, together, contribute to NAE biosynthesis (798).

The biosynthesis of 2-AG appears to occur almost exclusively via DAG hydrolysis by either of two *sn*-1-specific diacylglycerol lipases (DAGL) α or β (74), the α-isoform being more important in the adult brain, whereas the β-isoform was proposed to be more involved at the peripheral level (although there are exceptions to this rule). DAG precursors for 2-AG biosynthesis are mostly produced from the hydrolysis of *sn*-2-arachidonoyl-phosphatidylinositol-4,5-bisphosphate (PIP_2) species by the PIP_2-selective PLCβ (331). However, studies in PLC$\beta^{-/-}$ mice suggest the existence of a PLCβ-DAG-DAGL independent pathways for 2-AG formation (221).

In the developing brain, DAGLα is localized in terminal axons, while in the adult brain the enzyme is postsynaptic to allow the retrograde neuromodulatory action of 2-AG (74). The development of DAGLα or -β knockout mice enabled to tease out the role of DAGLα in 2-AG biosynthesis in the CNS, since a massive reduction in 2-AG levels was observed in the brain (both in whole tissue and in specific areas) of DAGL$\alpha^{-/-}$, and much less so in DAGL$\beta^{-/-}$, mice (1). A similar reduction, accompanied by corresponding reduction in AA, was reported in the liver of mice lacking DAGLβ (281). A significant reduction also in brain AEA levels was observed in DAGL$\alpha^{-/-}$ but not DAGL$\beta^{-/-}$ mice, indicating that DAGLα might indirectly contribute to AEA biosynthesis (1). The comparison of the effects of acute (with DAGL inhibitors with no selectivity for either the α or β isoform) and congenital (with DAGL$\alpha^{-/-}$) blockade of DAGLα on 2-AG "retrograde" signaling, measured by using electrophysiological techniques (see below) in slices from various brain areas, opened a discussion on whether preexisting pools of 2-AG may exist in neurons, which would differ from the conventional "on demand" production concept (848, 939).

The enzymatic hydrolysis of the AEA and 2-AG amide and ester bonds is responsible for their inactivation and subsequent release of degradation products (AA and ethanolamine or glycerol, respectively), which are rapidly incorporated into membrane phospholipids. This signal termination appears to be mediated by a two-step process, which includes membrane trafficking prior to the processing by intracellular catabolic enzymes. The specific process through which endocannabinoids are bidirectionally moved across the plasma membrane is still controversial. Early investigations suggested a temperature- and time-dependent carrier-mediated uptake process specific for AEA versus other NAEs, and independent from ATP or ion gradients (57, 201, 218, 354). The primary characteristic of such a mechanism is that chemical probes can block it. Indeed, several inhibitors of AEA cellular uptake were developed and provided indirect evidence of the existence of the putative membrane transporter (188, 226, 271, 585, 626, 627, 642). In one case, nanotechnologies and the AEA cytosolic binding site on TRPV1 channels were exploited to detect AEA entry into cells. This study demonstrated how uptake inhibitors lose their efficacy when AEA is prevented from interacting directly with plasma membrane proteins because masked into nanoparticles, thus arguing in favor of the existence of membrane carrier (476). Different models of AEA cellular uptake and transport have been proposed and argued over. The first envisages a simple diffusion across plasma membrane driven by an inward concentration gradient created by AEA enzymatic degradation (202, 291). However, this concept was challenged by biochemical studies with selective uptake inhibitors (416) and by the evidence of a saturable and fast AEA uptake in mouse brain synaptosomes from mice lacking the major AEA degrading enzyme (477). A second model proposed describes a caveolae-related endocytosis-mediated uptake for AEA with intracellular sequestration (40). Although this model supports the existence of a plasma membrane-localized AEA-binding protein, it cannot explain why uptake inhibitors also affect AEA efflux. Right after the identification of several cytosolic AEA "chaperone" proteins, such as FABP5,

FABP7, Hsp70, albumin, and the more controversial FLAT (274, 415, 637, 773), a revised version of the simple diffusion model was proposed. According to this model, the passive diffusion process of AEA across the membrane is followed by intracellulaer carrier-mediated transport to effector proteins, catabolic enzymes, and sequestration sites (268, 270). The identification of intracellular carriers for AEA explained how lipophilic molecules such as the endocannabinoids manage to cross a hydrophilic barrier such as the cytosol. However, these findings did not cast light on the molecular mechanism of transport across the membrane. In addition, selective pharmacological inhibition, bidirectional transport across the plasma membrane, and the identification of a high-affinity membrane-binding site distinct from degrading enzymes are all findings that cannot be explained only with intracellular carrier proteins. Recently, an integrated model taking into account all the evidence so far reported was suggested. According to this model, AEA associates with the plasma membrane and accumulates in specific domains where it binds to specific membrane transporter protein(s), which biridectionally translocate AEA across the lipid bilayer and eventually present AEA to intracellular shuttles that translocate the endocannabinoid to its target or degradation sites (502). Evidence also suggests the existence of a 2-AG transport process, which was inhibited by AEA cellular uptake inhibitors (143). Moreover, two independent groups, by means of fluorescence polarization and crystallography, showed that some of the AEA shuttles also bind 2-AG (627), thus suggesting the existence of one endocannabinoid membrane transporter (EMT), rather than a AEA specific one.

The two major enzymes responsible for the inactivation of AEA and 2-AG are two intracellular serine hydrolases: fatty acid amide hydrolase (FAAH) and monoacylglycerol hydrolase (MAGL), respectively (164, 227). In human, but not rodent, tissues, another isoform of FAAH, named FAAH-2, was identified (910). However, this enzyme recognizes with higher affinity other NAEs. Although 2-AG can be directly esterified into neutral lipids (214), the portion of this compound acting as endocannabinoid appears to be inactivated by MAGL (44). Two additional enzymes, α/β-hydrolase domain types 6 and 12 (ABHD6, ABDH12), with different subcellular distributions, were also suggested to regulate the hydrolysis of distinct pools of 2-AG in the nervous system and its efficacy at cannabinoid receptors (621). In some cell types, under certain experimental conditions, FAAH inhibition leads to elevated 2-AG, which is in fact good substrate for FAAH (184, 517).

Other enzymes, belonging to the AA cascade (i.e., COX-2, LOX-12, LOX-15, as well as Cyt*P*-450), can oxidize both endocannabinoids (446). The COX-2-mediated oxidation of AEA eventually produces the prostaglandin-ethanolamides (prostamides) and that of 2-AG the prostaglandin-glycerol esters (glyceroprostaglandins). These oxidative derivatives are not recognized by, or are very poor substrates for, FAAH or MAGL, and act via non-CB1, non-CB2, non-TRPV1 receptors that have been characterized only in part (923). The oxygenation of AEA or 2-AG by LOX or Cyt*P*-450 enxymes produces hydroperoxy/hyroxy- or epoxyeicosatetraenoyl derivatives (88, 806). In most cases, these latter metabolites, whose presence in living tissues is yet to be demonstrated, are still able to activate cannabinoid (or TRP) receptors (687, 817), and hence their biological relevance is still under dispute.

D. Endogenous Allosteric Modulators of CB1 Receptors

Endogenous allosteric modulators of CB1 receptors have been identified. This new class of molecules includes the anti-inflammatory lipid lipoxin A4, which, by enhancing AEA-induced CB1 activation, displays a protective effect against β-amyloid (1–40)-induced spatial memory impairment in mice (653). Negative modulators are the α-hemoglobin-derived small peptide endocannabinoids (or pepcans), and the neurosteroid pregnenolone (51, 867). The latter compound seems to protect the brain from Δ^9-THC-induced CB1 receptor overactivation, reinforcing the concept that these modulators may play an important role in the regulation of endocannabinoid signaling. More studies are needed from independent research groups to substantiate the physiological importance of these discoveries.

VIII. PHYSIOLOGICAL ROLE OF THE ECS

A. CNS

1. Synaptic plasticity

Perhaps the most important role of endocannabinoids in the adult brain is their function as "retrograde" signals at central synapses (448, 514, 920) **(FIGURE 2)**. This function fits with the lipophilic nature of these compounds, their "on demand" and Ca^{2+}-dependent modality of biosynthesis, and the anatomical distribution of most of their biosynthetic and degrading enzymes and CB1 receptors. In fact, after being produced from the postsynaptic neuron, endocannabinoids, and 2-AG in particular, travel "backwards" to activate CB1 receptors very often located on presynaptic nerve terminals (510), and inhibit the release of either glutamate or GABA, thus participating in both short- and long-term synaptic plasticity, including depolarization-induced inhibition of excitatory (DSE) or inhibitory (DSI) currents, long-term depression (LTD) of both excitatory and inhibitory signaling (127, 638, 721). With the use of pharmacological approaches and genetically altered mice, it was shown that retrograde endocannabinoid signaling is critical, e.g., for LTD in the striatum (288) and nucleus accumbens (729). Various forms of endocannabinoid-mediated

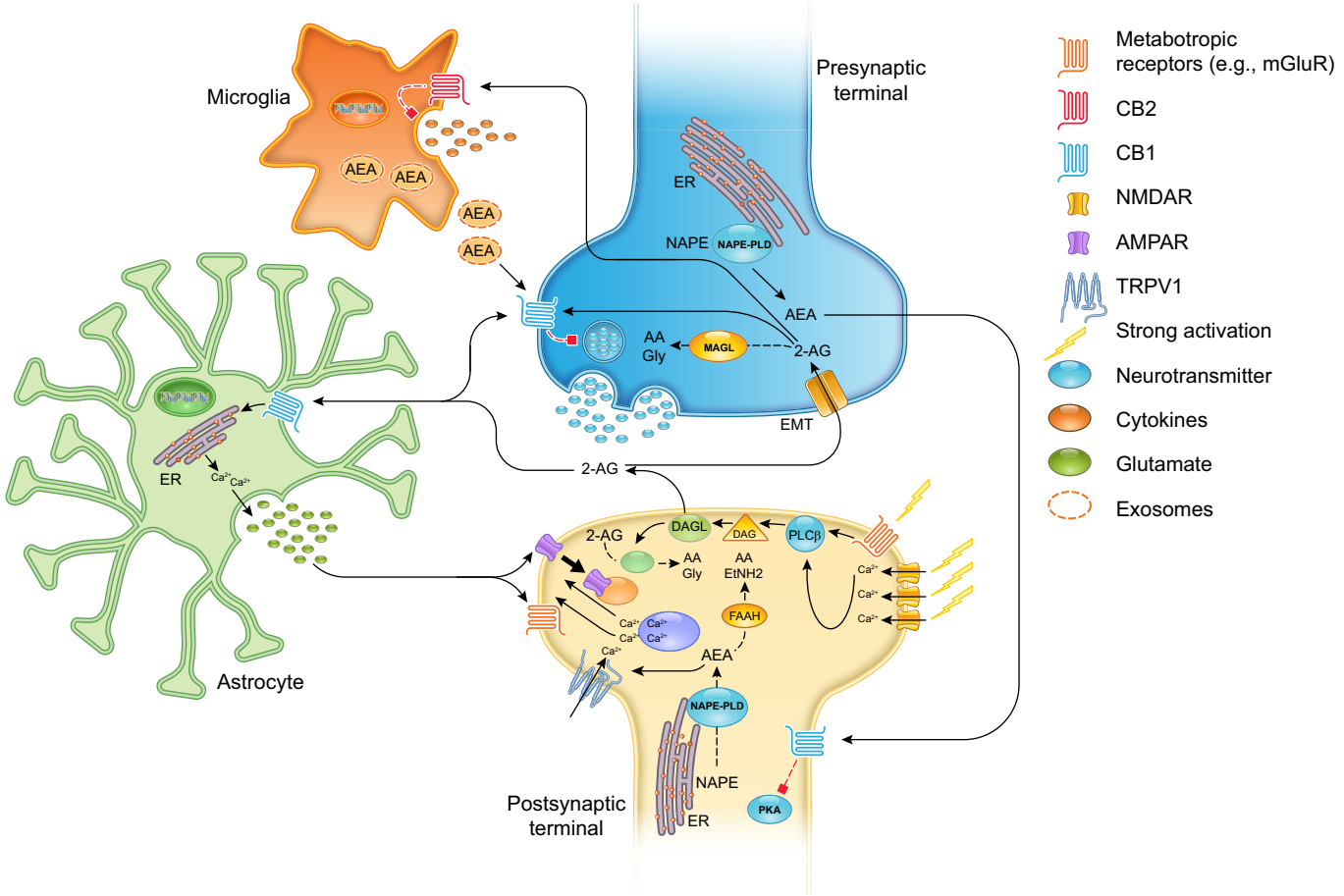

FIGURE 2. Physiological role of the endocannabinoid system in modulating synaptic plasticity through retrograde and anterograde signaling at the tripartite synapse. Exosome-mediated release of anandamide (AEA), which might regulate dendritic spine pruning, and CB2-mediated attenuation of inflammatory mediators, in microglia are also depicted. In astrocytes, retrograde modulation of glutamate release via $G_{q/11}$-coupled and intracellular Ca^{2+} mobilization by CB1 receptors is shown. Black arrows indicate stimulation, and red blunted arrows indicate inhibition. Dotted black arrows indicate enzymatic transformation. The green empty oval in the postsynaptic terminal denotes α,β-hydrolase-6. Gly is glycerol.

short-term depression and LTD occur in different brain regions (418).

Glutamate, via metabotropic glutamate receptors, or acetylcholine, via muscarinic M1/M3 receptors, directly generate endocannabinoids (430, 514), as do numerous other neurotransmitters that by acting at postsynaptic $G_{q/11}$-coupled GPCRs cause intracellular Ca^{2+} mobilization and DAG production, both necessary for 2-AG biosynthesis (418). Thus endocannabinoid-mediated retrograde signaling is a negative-feedback mechanism through which the activity of postsynaptic GPCRs is regulated when excessive neurotransmitter release activates the postsynpatic biosynthesis of endocannabinoids, which then inhibit the release of the same neurotransmitters via CB1 activation.

At first sight, the release mechanism of AEA seems incompatible with endocannabinoid-mediated retrograde signaling, due to spatial and temporal constraints (127). AEA generated in postsynaptic cells by synaptic activation of metabotropic glutamate receptors in the nucleus accumbens can instead modulate synaptic strength via postsynaptic TRPV1 channels (700), to trigger a form of LTD (311). In this case, AEA may activate also presynaptic CB1, suggesting its function as both endocannabinoid and endovanilloid (311). TRPV1 suppresses excitatory transmission in rat and mouse dentate gyrus by regulating postsynaptic function through a Ca^{2+}-dependent internalization of AMPA receptors, again triggering a form of LTD mediated by AEA in a CB1-independent manner (136). It is noteworthy that, in the dentate gyrus, hippocampus, or some other areas, the AEA biosynthetic enzyme, NAPE-PLD, occurs in presynaptic nerve endings (235), which would suggest an anterograde signaling role for AEA. However, it is not still clear whether this protein, which has also been found postsynaptically (168), is the main biosynthetic enzyme for AEA production in neurons (see above). The ECS can allow the diversification of synaptic plasticity in a single neuron so that, in the amygdala, LTD is mediated or by postsynaptic mGluR5-dependent release of AEA acting on postsynaptic

TRPV1, or by 2-AG acting on presynaptic CB1 (699). In this case, NAPE-PLD is postsynaptic (in dendrites and dendritic spines) like FAAH (in mitochondrial membranes and other intracellular organelles), suggesting that AEA acts as endovanilloid in an autocrine manner. Instead, MAGL is always found in presynaptic terminals, in agreement with 2-AG role as retrograde mediator (316).

Studies with mice in which either of the two 2-AG biosynthetic enzymes, DAGLα or -β, was knocked out suggest that 2-AG, and not AEA, and DAGLα, and not DAGLβ, mediate retrograde signaling at synapses (281, 848). The existence of an anatomically defined structure, the "2-AG signalosome," dedicated to the production and release of this endocannabinoid, was suggested. This structure was first identified in dendritic spines of excitatory synapses of the ventral striatum and prefrontal cortex and links metabotropic glutamate receptor-5 to DAGLα and PLCβ (414), but is likely present in other regions of the mammalian CNS and involved in retrograde signaling at most glutamatergic synapses (545, 631). In this "superstructure," when glutamate secreted by excitatory axon terminals binds to mGluR5, PLCβ and DAGLα produce 2-AG, which crosses the synaptic cleft, binds CB1 on axon terminals, reducing calcium channel activity and suppressing glutamate release. This action is then terminated presynaptically by MAGL (316), whereas the 2-AG that remains in the dendritic spine is probably cleared by postsynaptic ABHD-6 (531). When examining the effects of acute pharmacological inhibition of DAGLα, it was demonstrated that 2-AG for synaptic retrograde signaling is supplied as a result of "on demand" biosynthesis by DAGLα rather than mobilization from presumptive preformed pools (330). In summary, endocannabinoids are "retrograde" signals, despite some examples of "autocrine" (see above but also Ref. 28), or anterograde action. AEA appears to mediate CB1-dependent retrograde signaling only in some situations (311, 429), whereas 2-AG mediates most forms of CB1-mediated retrograde regulation of synaptic transmission. Interestingly, in the striatum, AEA inhibits the production of 2-AG by activating TRPV1 (506), whereas DAGLα knockout mice exhibit lower basal levels of AEA, thus suggesting the existence of possible positive and negative cross-talks between the two compounds, and their distinct roles in synaptic plasticity, during physiological and/or pathological conditions. For example, in the mouse hippocampus, AEA signaling at postsynaptic TRPV1 receptors antagonizes tonic 2-AG signaling at CB1, thereby affecting the tonic control over GABA release by the latter compound. A selective inhibitor of MAGL elicited a robust increase in 2-AG levels and decreased GABAergic transmission, whereas FAAH inhibitors, by enhancing "endovanilloid" signaling, attenuated this synaptic effect of 2-AG (465).

It is now widely accepted that glial cells, i.e., astrocytes and microglia, play a major role in synaptic plasticity. Production and inactivation of endocannabinoids by these cells were shown in many studies (821, 897). There is bidirectional signaling communication between astrocytes and neurons. Fluorescence techniques revealed that cultured astrocytes respond to glutamate with an elevation of $[Ca^{2+}]_i$ from the endoplasmic reticulum (160). Synaptic neurotransmitters activate astroglial GPCRs with production of inositol 1,4,5-trisphosphate (IP_3) and Ca^{2+} release from the endoplasmic reticulum (880). Therefore, astrocytes are able to respond to activity of single synapses (655). The elevated Ca^{2+} may then act as a cellular signal triggering chemical transmitters release, modulating in turn neuronal excitability and synaptic function, exchanging information with pre- and postsynaptic neurons, and leading to the concept of "the tripartite synapse" (20). Recent evidence shows that endocannabinoids and astroglial CB1 are new players in the tripartite synapse (619). CB1 in hippocampal astrocytes is activated by endocannabinoids released by neurons, with elevation of $[Ca^{2+}]_i$ through CB1-$G_{q/11}$ signaling, and stimulation of astrocytic glutamate release and participation in synaptic plasticity (618). Accordingly, acute Δ^9-THC-induced LTD of glutamate transmission in hippocampal synapses in vivo is abolished in conditional mutant mice lacking CB1 in astrocytes, unlike mice lacking neuronal CB1 (324). Astroglial CB1 can also modulate a short-term type of synaptic plasticity, i.e., long-term potentiation (LTP) (299). Astrocytes are able to synthesize endocannabinoids (820) and participate in endocannabinoid turnover in the brain (56). Biosynthetic enzymes as well as FAAH and MAGL are expressed in astrocytes (827, 861). A recent study genetically dissected the cellular anatomy of MAGL-mediated 2-AG metabolism in the brain and showed that neurons and astrocytes coordinately regulate 2-AG levels and CB1-mediated synaptic plasticity and behavior, and that astrocytic MAGL converts 2-AG to neuroinflammatory prostaglandins (882).

Also, microglia participate in the regulation of synaptic strength, for example, by regulating the pruning of synapses (30). Interestingly, AEA produced by microglia and released in exosomes was recently shown to inhibit presynaptic transmission in target GABAergic neurons via CB1 activation (275).

The neuromodulatory and synaptic plasticity strengthening actions of endocannabinoids play important roles in various aspects of CNS physiology and pathology, which will be the subject of the following sections.

2. Brain development in utero, postnatally, and in adolescence

The role of the ECS in the programming of neural cells and in the developing nervous system, since the early stages of embryo development and implantation (661) and until nervous system development (328) and adult neurogenesis (301), is recognized as extremely important. Endocannabi-

noids are much more spatially widespread in the fetal brain, and during embryo development the distribution of CB1 and endocannabinoids change (66). AEA prevails in the early embryonic stages, being essential for implantation and the maintenance of pregnancy. Then 2-AG levels increase during differentiation to control neural progenitor cells and their commitment versus astroglia or neurons. Following commitment, CB1 levels become upregulated while CB2 levels, high in progenitor cells, are lowered, as demonstrated in vitro and in vivo (650). Thus endocannabinoids may modulate cell proliferation, cell fate, and migration, as well as synaptogenesis of postmitotic neurons by allowing neuron migration and axon targeting. Molecular details of these functions can be found in a very recent and elegant review (504).

In the light of these arguments, perinatal pharmacological manipulation of CB1 may deeply alter development (12). Also in adolescence, the impact of exposure to Δ^9-THC on maturational events mediated by the ECS that might occur in the brain has been pointed out (753) so that heavy adolescent exposure to marijuana might represent a risk factor for developing subsequent disorders at adulthood (757).

3. Spatial memory

Several studies provide evidence that CB1 agonists produce spatial memory deficits (322, 877). Conversely, genetic and pharmacological blockade of CB1 leads to deficits in extinction processes (877), whereas the selective inactivation of hippocampal CB1 may enhance memory (730). Pharmacologically elevated AEA levels through FAAH inhibition impair hippocampal-dependent learning and memory tasks (45), and blockade of 2-AG hydrolysis interferes with memory performance (307). On the other hand, 2-AG in the hippocampus selectively mediates the beneficial impact of stress on spatial memory retrieval, since rats trained under high stress display increased hippocampal levels of 2-AG, but not AEA, and improved memory (589).

4. Aversive memories and conditioned behaviors

The ECS has a pivotal function in extinction of aversive memories. CB1 knockout mice show impaired short- and long-term extinction in fear-conditioning tests, while memory acquisition and consolidation are not affected. CB1 is required at the moment of memory extinction, with levels of endocannabinoids being higher in the basolateral amygdala following fear conditioning trials (533). In fact, contextual conditioning is strongly based on the activity of the basolateral amygdala and is enforced via stress hormones (741). Stress-induced ECS activation seems to be necessary for processing of aversive memories at the level of the amygdala and hippocampus (590). Accordingly, systemic administration of the CB1 inverse agonist rimonabant blocks the extinction but not the reconsolidation of memory (835), and impairs the extinction in rats when administered just before trials; administration of the AEA transport inhibitor AM404 produces the opposite effect (140). Other studies reported improved extinction after treatment with AM404 (652), which is also a strong TRPV1 agonist (188). It was suggested that an increase of AEA influences aversive memory extinction with an action on either CB1 or TRPV1: while the block of CB1 prevents short- and long-term extinction, TRPV1 blockade anticipates extinction (455). In the hippocampus, endovanilloids and endocannabinoids play complementary roles also in memory consolidation, but only in strong shock and post-strong training protocols the administration of the TRPV1 antagonist capsazepine disrupts memory consolidation (187, 287). Stress may result in endocannabinoid levels increasing in the hypothalamus after glucocorticoid administration (224), continuous electric foot shock (361), or emotional memories (417).

Intact extinction of eye-blink conditioning, a model of cerebellum-dependent discrete motor learning, was reported instead in CB1 knockout mice and mice treated with a CB1 antagonist (437). However, the treated animals as well as CB1-knockout mice exhibited impaired acquisition of this conditioning, which was dependent on the deficiency in cerebellar LTD at parallel fiber-Purkinje cell synapses, which in turn is dependent on CB1 (765). Accordingly, many animal models with deficient cerebellar LTD display impairment of delay eyeblink conditioning (418).

5. Mood and emotions

Experimental animal and human studies using CB1 antagonists and knockout mice have shown the involvement of the ECS in the regulation of anxious states (887). Rimonabant produces anxiogenic effects (549, 620), and CB1-knockout mice exhibit an anxiogenic-like behavioral phenoype (318, 536), thus evidencing the presence of an anxiolytic CB1-mediated tone. AEA might be generated in the amygdala during anxiety to contribute to the regulation of emotion and anxiety. Accordingly, FAAH inhibitors produce anxiolytic-like effects in rats in a CB1-mediated manner (426). The anxiolytic properties of the AEA uptake inhibitor AM404 in three rat models of anxiety were also reported (92), and since this compound is also a TRPV1 ligand, its effects might be TRPV1-mediated. However, there is evidence that high doses of intracranially administered TRPV1 agonists, including AEA, produce TRPV1-mediated anxiogenic effects (754), although in a recent study AEA-induced anxiogenic-like effects observed in the open field were not blocked by the TRPV1 antagonist capsazepine (660). Nevertheless, several reports have shown anxiolytic effects of TRPV1 antagonists infused in brain regions involved in mood control, suggesting that overactivity of TRPV1 channels may participate in anxiety (588), and possibly explaining why TRPV1-knockout mice show anxiolytic behavior in the elevated plus maze and dark-light tasks (532). *N*-arachidonoyl-serotonin, a dual FAAH/

TRPV1 inhibitor (518), is more efficatious at producing anxiolytic-like effects than two more potent and selective single inhibitors of FAAH and TRPV1 (403, 570).

Also, 2-AG seems to play a key protective role in the tonic modulation of emotion and anxiety. Pharmacological blockade of its hydrolyzing enzyme MAGL produces anxiolytic-like effects (479, 782, 941). Genetic modification by adeno-associated virus-mediated overexpression of MAGL in hippocampal glutamatergic neurons of the mouse resulted in a 50% decrease in 2-AG tissue levels without affecting the content of AEA, and led to increased anxiety-like behavior (312). Also MAGL knockout was accompanied by anxiety-like behaviour and elevation of glutamate release to the prefrontal cortex, although these appeared to be the consequences of chronic CB1 stimulation and internalization by elevated 2-AG levels in prefrontal cortex, amygdala, and hippocampus (382). Accordingly, genetic deletion of DAGLα and the subsequent impaired 2-AG biosynthesis in the brain results in an anxiety-like phenotype and impaired endocannabinoid retrograde signaling at amygdala glutamatergic synapses (397, 793). Chronically stressed mice show decreased 2-AG production in glutamatergic neurons of the basolateral amygdala and subsequent anxiety. This is due to an increased activity of protein tyrosine phosphatase 1B (PTP1B) and enhanced inhibition of mGluR5 phosphorylation, resulting in decreased DAGLα activity (703).

There is a dysfunction of the ECS in patients with mood and psychiatric disorders. While a significant increase of CB1 density in the prefrontal cortex of depressed suicide victims (375) and of serum AEA levels in patients suffering from minor depression (352) were reported, decreased CB1 density in grey matter (442) and lower levels of endocannabinoids in the serum of patients with major depression and anxiety (351) were also found. Intense exercise has antidepressant effects and increases both AEA and BDNF levels (344), and enhanced endocannabinoid signaling promotes neurogenesis with both antidepressant and anxiolytic effects (350). FAAH inhibitors increasing AEA brain levels enhance the activity of serotonergic neurons in the dorsal raphe nucleus and noradrenergic neurons in the nucleus locus ceruleus, thus eliciting antidepressant effects (295). Accordingly, *1*) higher levels of FAAH in the rat frontal cortex and hippocampus may cause depressive-like disorders (885), and *2*) chronic mild unpredictable stress, a model for depression, leads to impairment of 2-AG-mediated LTD in the CA1 region of the hippocampus, an effect prevented MAGL inhibition (942), which also enhances neurogenesis and LTP in the dentate gyrus (941). Accordingly, long-term antidepressant treatments increase 2-AG levels in different brain areas (803).

In agreement with the important role of CB1 end endocannabinoids in the control of mood also in humans, daily oral administration to obese patients of 20 mg of the body weight-lowering CB1 inverse agonist rimonabant led to increased risk of anxiety, depression, and suicide (148), leading the European Medicines Agency to decide its withdrawal from the market in 2008.

6. Reward

There are a number of excellent reviews on the involvement in reward of the ECS (521, 568), which was shown to be important for the rewarding effects of most addictive compounds, including nicotine (153, 568), ethanol (904), morphine (463), and cocaine (521). Endocannabinoids modulate the activity of the mesolimbic dopaminergic pathway by strengthening, via a multisynaptic pathway in which they act as retrograde messengers at CB1, the release of dopamine in the nucleus accumbens shell, the most widely accepted neurochemical substrate of substance seeking and addictive behavior. Accordingly, elevation of extracellular dopamine levels in the nucleus accumbens shell by most rewarding as well as addictive substances is blocked in rats by CB1 pharmacological inactivation (153) and genetic invalidation (374). However, the ECS is involved also in the modulation of the behavioral consequences of drug withdrawal. Alterations of endocannabinoid-mediated plasticity in the nucleus accumbens after short-term morphine withdrawal are accompanied by increased DAGLα expression, suggesting the involvement of 2-AG (906). On the other hand, dual inhibition of MAGL and FAAH attenuates opioid withdrawal signs in mice via activation of CB1 receptors (716). In a rat model of morphine withdrawal, increased expression of CB1 was shown in nucleus accumbens (934).

Recent data suggest that also tonic TRPV1 activation by endocannabinoids/endovanilloids such as AEA could be involved in reward and addiction. In the dorsal striatum, repeated morphine treatments are able to upregulate TRPV1 gene expression, and the administration of the TRPV1 agonist capsaicin potentiates morphine reward, whereas microinjection of selective TRPV1 antagonists inhibit morphine-conditioned place preference (338). TRPV1 affects μ-opioid receptor binding, which is increased by morphine and diminished by microinjection of capsazepine. It seems that other than in dorsal striatum, TRPV1 participates in morphine reward also in the cortex, nucleus accumbens, and ventral tegmental area (338). Further experimental data suggest that TRPV1 contributes to morphine reward via adenylyl cyclase 1, p38 MAPK, and NF-κB (624). In a rat model of cocaine addiction, a TRPV1 receptor antagonist decreases cocaine-seeking behavior in the reinstatement phase, although TRPV1 seems to be unnecessary for the rewarding effect of cocaine (3). Finally, TRPV1 null mice consume more ethanol than wild-type littermates, an effect reproduced in the latter by injection of the antagonist capsazepine (84).

7. Appetite and feeding behavior

Endocannabinoids play a crucial role in feeding behavior through CB1 (220), which is widely expressed in brain areas associated with the regulation of energy homeostasis, e.g., the hypothalamus, and cortico-limbic system (166). Agonists increase food intake in a CB1-dependent manner while CB1 antagonists reduce food intake in wild-type and obese animals, but not in CB1-knockout mice (154, 219). The ECS modulates energy sensing and motivational stimuli regulating satiety and food intake, through interactions with central orexigenic (orexins, NPY, MCH, etc.) and anorexigenic (α-MSH, β-endorphin, CCK, etc.) peptides and neurotransmitters in (888), and is under the negative and positive control of peripheral signals of energy status, such as leptin, ghrelin, insulin, and cortisol. Both increasing endocannabinoid levels in the nucleus accumbens and/or hypothalamus through the use of inhibitors of degradation, and direct endocannabinoid administration in these regions, stimulate feeding behavior (388, 436, 812). The hypothalamic and limbic forebrain concentrations of endocannabinoids, particularly 2-AG, increase during short-term food deprivation and return to normal after refeeding (436), and this is possibly due to corresponding changes in peripheral hormones controlling endocannabinoid biosynthesis, such as the orexigenic ghrelin (444) or cortisol (225), and the anorexiant leptin (219), whose levels increase and decrease following food deprivation, respectively.

Leptin is a white adipose tissue-derived hormone and the primary signal through which the hypothalamus senses nutritional state and modulates food intake and energy balance. It reduces food intake by upregulating anorexigenic neuropeptides and downregulating orexigenic ones as well as the endocannabinoids (219). Accordingly, genetic deficiency of leptin signaling in *ob/ob* and *db/db* mice and Zucker rats is accompanied by increased hypothalamic endocannabinoid levels (219). The anorexiant effects of leptin depend in part on the presence of hypothalamic CB1 (117) because of leptin tonic inhibitory effect on endocannabinoid signaling. Endocannabinoid/CB1 retrograde signaling inhibits excitatory outputs on lateral hypothalamic neurons that synthesize the orexigenic peptide orexin-A, while inhibiting inhibitory outputs to neurons that synthesize another orexigenic signal, melanin-concentrating hormone (MCH) (372), thus potentially producing opposite effects on food intake. However, in murine models of obesity with leptin deficiency, such as *ob/ob* mice and mice made obese by a high-fat diet (DIO mice), orexin-A neurons undergo a shift from predominant control by CB1-expressing excitatory to CB1-expressing inhibitory inputs. This is accompanied by enhanced DAGLα expression and 2-AG overproduction in orexinergic neurons, and hence results in presynaptic CB1 overactivation, with reduced inhibition, rather than reduced stimulation, of orexinergic neurons in obese mice, and enhanced orexin-A release to target brain areas such as the nucleus accumbens, ventral tegmental area, and other hypothalamic nuclei, thus contributing to hyperphagia and increased body weight (167). According to a more recent study, in the arcuate nucleus, activation of CB1 receptors by exogenous agonists is the cause, rather than the mere effector, of another type of switch: following administration of CB1 agonists, proopiomelanocortin neurons were suggested to release β-endorphin instead of a-MSH, thus producing orexigenic rather than anorexiant effects (441). However, the issue as to whether endocannabinoids are also capable of inducing this switch was not investigated.

In the hypothalamus, endocannabinoids also act on hypothalamic-pituitary-adrenal axis by lowering glucocorticoid levels under stress conditions. In particular, stress and glucocorticoids can trigger endocannabinoid synthesis and CB1 signaling under acute conditions, whereas chronic or repeated stress leads to downregulation of CB1 signaling (169). In the paraventricular nuclei, orexigenic glucocorticoids suppress excitatory glutamatergic synaptic inputs on neurons involved in food intake inhibition through retrograde CB1 activation. Thus the ECS is likely involved in acute stress-induced food intake.

Endocannabinoids in the olfactory cortex increase odor detection and food intake in fasted mice, by decreasing, via CB1 abundantly expressed on axon terminals, the activity of cortical glutamatergic neurons that project from olfactory cortex areas to the main olfactory bulb food (811).

The role of the ECS in energy metabolism is exerted also in peripheral organs participating in the maintenance of homeostasis and controlling feeding behavior, particularly the liver, adipose tissue, skeletal muscle, and pancreas. For details on this role, the reader is referred to a recent review on this topic (796) and to some of the sections below.

8. Pain

The role of the ECS in pain has been widely reviewed (315, 684, 687). Cells in injured and inflamed tissues generate proalgesic lipid mediators and oxidative metabolites of polyunsaturated fatty acids that increase the excitability of nociceptive neurons. Endocannabinoids modulate nociception by lowering sensory neuron excitability and regulating the transmission of nociceptive signals to the CNS. Local injections of AEA are able to control pain initiation (109). This action is CB1 dependent, whereas 2-AG antinociceptive effects seem to require activation of both CB1 and CB2 (315). CB1 is localized in neurons of peripheral sensory ganglia, the dorsal horn of the spinal cord, and supraspinal brain areas involved in pain transmission, such as the periaqueductal grey (PAG), rostral ventromedial medulla (RVM), and cortex. Although there is evidence that CB2 receptors are also expressed in neurons (872), their role in pain seems to be effected mostly at the level of the inhibition

of the release of inflammatory mediators from macrophages, keratinocytes, or microglia (704).

In addition to CB1, AEA can interact with various transient TRP channels involved in nociception, including TRPV1 (8), TRPA1 (192), and TRPM8 (195). Nevertheless, studies using CB1 and CB2 knockout mice have suggested that endocannabinoids produce analgesia mostly via cannabinoid receptor-mediated mechanisms (433). In the modulation of descending antinociceptive pathways from the PAG to the RVM, however, endocannabinoids might enhance the activity of RVM OFF cells that turn off pain and reduce the activity of RVM ON cells that enhance pain. This effect seems to occur via both retrograde activation by 2-AG of presynaptic CB1 receptors on GABAergic terminals innervating the antinociceptive excitatory output neurons of the PAG, which become disinhibited, and direct TRPV1-mediated activation of these same neurons by AEA (371, 518, 816).

Inhibitors of AEA and 2-AG inactivation via FAAH, MAGL, or the putative EMT, administered locally at injury sites, produce antinociception, e.g., by differentially suppressing nociception provoked by intraplantar injections of capsaicin through peripheral cannabinoid mechanisms (813). The antinociceptive effects of systemic FAAH inhibitors were suggested to be mediated only by peripheral CB1 (813), and, indeed, a peripherally restricted FAAH inhibitor produced antinociception in models of nerve injury and inflammation (149). However, intrathecal injection of intermediate-high doses of a FAAH inhibitor also produce analgesia, and this is mediated by TRPV1 activation/desensitization due to either stronger elevation of spinal AEA or its enzymatic oxidation to compounds that still fully activate the channel (817). Indeed, endocannabinoids can be metabolized to pro-algesic and pro-inflammatory mediators acting via non-CB1, non-CB2-mediated mechanisms. For example, in an animal model of osteoarthritic pain, spinal AEA is oxidized by COX-2 and prostaglandin F synthase to prostamide $F_{2\alpha}$, which then overexcites dorsal horn nociceptive neurons, thus contributing to inflammatory hyperalgesia (286).

B. Peripheral Tissues

1. Cardiovascular system

The physiological role of the ECS in cardiovascular tissues has been actively investigated (580). The expression of CB1 and CB2 in these tissues and corresponding cell types may differ strongly among the various models. CB1 is expressed in human myocardium (278), but it has been reported to be absent in cardiomyocytes of newborn rats (791). CB1, but not CB2, is present also in the myocardium of adult rats (891). However, overall, the data in adult rats are conflicting as, while CB2 mRNA was not found in the myocardium in one study (102), another study reported that both mRNA and protein of both CB1 and CB2 are present in this tissue (911). The former receptor was observed in the arterial and capillary endothelial cells of the heart, and CB2 in cardiomyocytes and endothelial cells of larger arteries (469). In mice, both CB1 and CB2 receptors occur in the left ventricle (905). Discrepancies in different studies may reflect differences in the used models: in situ versus isolated hearts, whole hearts versus isolated myocytes, and mice versus rats.

AEA is seemingly more effective at producing hypotension and decreased cardiac contractility in mice lacking FAAH than wild-type mice, pointing to effects not due to its metabolism to AA (645). The endocannabinoid was investigated for its vasorelaxation of the rat mesenteric artery, although this effect is complex and involves many cellular and molecular mechanisms (345), including TRPV1 and possibly TRPA1 channels as well as various types of Ca^{2+} and K^+ channels, and/or as-yet-unidentified receptors. However, Δ^9-THC and synthetic agonists elicit vasodilation in vivo by direct activation of vascular CB1 receptors (892), and the hypotensive actions of AEA are completely absent in mice lacking CB1 (463). It seems that the vasodilation by 2-AG, instead, depends on its hydrolysis to AA and subsequent conversion to COX products (391), and it was suggested that cyt*P*-450 metabolites may mediate its Ca^{2+}-induced relaxation of rat mesenteric arteries (26). At any rate, mice lacking FAAH or cannabinoid receptors showed normal cardiovascular function, suggesting that this enzyme may not play a crucial role in the physiological regulation of the cardiovascular system (49, 645).

2. Gastrointestinal tract

Cannabinoid receptors are highly expressed on enteric nerves (CB1) and throughout the intestinal mucosa on enteroendocrine cells (CB1), immune cells (CB1 and CB2), and enterocytes (CB1 and CB2). The several actions of endocannabinoids, and AEA in particular, in the gastrointestinal (GI) tract, like for example inhibition of GI motility and secretion, are mostly mediated by CB1 under physiological conditions (386). At enteric synapses, CB1 inhibits the release of acetylcholine, utilizing endocannabinoids and a retrograde purine messenger working in opposite directions to control synaptic strength (363). The 2-AG biosynthetic enzyme DAGLα is expressed in the enteric nervous system, and its inhibition reverses slowed GI motility, intestinal contractility, and constipation mediated by CB1 receptor activation (46).

As mentioned above, endocannabinoids control feeding and energy balance by activating CB1 receptors. CB1 localized in enteroendocrine cells may regulate the release of enteroendocrine peptides such as cholecystokinin (836). Importantly, enteric microbiota regulate CB1 expression on enterocytes, which in turn controls gut permeability, plasma LPS levels, and adipogenesis (594). Enteric micro-

biota determine adipose tissue physiology, and blocking CB1 expression reduces obesity in part through the enhancement of intestinal barrier function. Furthermore, a specific genetic deletion of the endocannabinoid synthetic enzyme NAPE-PLD in adipocytes induces metabolism alterations and obesity mediated by a shift in gut microbiota composition (289). However, this effect does not seem to be mediated by AEA, but rather by its congeners PEA and/or OEA, which can be produced by the same enzyme.

Gut-derived AEA and 2-AG, on the one hand, and OEA, on the other hand, are key signaling molecules for the opposing control of satiety (683). Food deprivation-induced increases of the levels of AEA and 2-AG in the rat small intestine contribute to inhibit satiety and are further elevated in obese Zucker rats (385). The enhancement of 2-AG, in particular, can be prevented by surgical resection of the vagus nerve or by M3 acetylcholine receptor inhibitors (223). OEA, instead, acts as a fat-derived signal acting on enterocytes for the induction of satiety via the vagus nerve and satiety-controlling centers in the brain stem (683).

3. Kidneys

CB1 is detected in the entire kidney and in different parts of the nephron such as afferent and efferent arterioles, glomeruli, tubules, the loop of Henle, and collecting ducts, but also in various kidney cells such as podocytes, proximal and distal tubular epithelial cells, and mesangial cells (exhaustively reviewed in Ref. 842). The healthy kidney contains high basal levels of endocannabinoids, but its expression of CB2 receptors, instead, is still controversial. Very recently, in immortalized epithelial cells derived from the pig kidney proximal tubule, mRNAs encoding for enzymes of the ECS were detected together with TRPV1 channels (770). In vitro, AEA (1 μM) vasodilates via CB1 the juxtamedullary afferent arterioles; at 10 nM, it stimulates NO release from perfused renal arterial segments; and at 1 μM, it exerts neuromodulatory effects by inhibiting KCl-stimulated norepinephrine release from sympathetic nerves on isolated renal arterial segments (203). Therefore, the ECS regulates renal hemodynamics, and AEA via CB1 increases renal blood flow but also decreases the glomerular filtration rate (445). AEA has diuretic effects not mediated by either CB1 or TRPV1 but rather by the neuronal reflex of the kidney (474). Intramedullarily infused AEA increases urine volume and Na^+ and K^+ excretion, effects that are blocked by a selective COX-2 inhibitor, suggesting the involvement of its prostamide metabolites. Accordingly, prostamide E_2 administered intravenously is able to reduce mean arterial pressure (728). AEA via CB1 and TRPV1 is also able to block the Na^+/H^+ transporter and $Na^+/K^+/2Cl^-$ cotransporter activity (795), and to modulate the Na^+-K^+-ATPase pump in proximal tubule cells, a transporter that maintains extracellular fluid volume and composition (770).

4. Pancreas

A pathway that through 2-AG signaling at CB1 and focal adhesion kinase activation drives insulin release was identified in the pancreas (522), thus providing a function for the previously observed stimulatory effect of high glucose on AEA and 2-AG synthesis in β-cells in vitro, and explaining why CB1 agonists are able to increase insulin release (177, 542).

It was also shown that in mouse fetuses and human pancreatic islets, α cells produce 2-AG that through CB1 is able to recruit β cells. In the fetal pancreas, CB1 signaling is very important for regulating the spatial organization of both α and β cells, as shown by pharmacological blockade of CB1 or DAGLα (523). MAGL knockout mice show an unchanged size of pancreatic islet but an increased number of α cells per islet. The authors used an in vitro culture in suspension of "α-like" cells of mouse origin with "β-like" cells of rat origin producing "pseudoislets," which resemble the murine pancreatic islet. Extending the experiments to AEA, which efficiently activates also TRPV1, they demonstrated that the channel decreases the size of these pseudoislets, whereas its pharmacological or genetic blockade increases it, without affecting the spatial arrangements of α and β cells (523).

5. Immune system

Endocannabinoids, their metabolic enzymes, and receptors have been identified in monocytes, macrophages, basophils, lymphocytes, and dendritic cells, where they modulate immune function in an autocrine and paracrine fashion. Immune cells preponderantly express CB2, with B lymphocytes expressing the highest levels followed by macrophages, monocytes, NK cells, and polymorphonuclear cells (278, 778). The "immune-competent" CB2 distribution is not confined to peripheral tissues but is a feature also of immune cells in the CNS (261). It was suggested that 2-AG is the only functionally efficacious endocannabinoid at CB2 (831), through which it plays an immunomodulatory role (487). However, also AEA is linked to immune functions, such as the inhibition of *1*) the production of pro-inflammatory cytokines like IL-6 and IL-8 from human monocytes (64) and *2*) the release of IL-2, TNF-α, and IFN-γ from activated human peripheral T lymphocytes (130). The immunological effects of AEA may occur via cannabinoid receptor-independent mechanisms (64, 701). Endocannabinoids cooperate with other signaling molecules to modulate the functional activities of immune cells (146).

Hematopoietic stem and progenitor cells express cannabinoid receptors, and bone marrow stromal cells secrete AEA and 2-AG, whose levels increase in response to stress in vivo. Endocannabinoids induce migration and trafficking of hematopoietic stem and progenitor cells from the bone marrow to the peripheral blood. Therefore, the ECS is a

physiological regulator of hematopoiesis (401). It seems, however, that the two main endocannabinoids may play different roles in this context: AEA reduces, while 2-AG enhances, bone marrow cell migration, and both enhance the formation of granulocyte, erythrocyte, macrophage, and megakaryocyte colonies, AEA being more potent than 2-AG (666). Endocannabinoids released from stromal cells exert distinct effects on mesoderm-derived hematopoietic and mesenchymal stem cell differentiation and migration determining the formation of several cell types alone or in synergy with classical growth factors (279, 666). The effects occur through CB2 activation (666, 866). Furthermore, 2-AG is able to drive a cell line expressing surface antigens of both erythroid and megakaryocytic phenotypes towards megakaryocytic differentiation (128), thereby stimulating platelet production and release (285). Accordingly, 2-AG hydrolytic enzymes are under control of inducers of megakaryocyte differentiation (285).

6. Skeletal muscle

Muscle cells produce endocannabinoids and express cannabinoid receptors and metabolic enzymes (165, 234, 249, 483). In the skeletal muscle, CB1 activation by endocannabinoids plays a role in the development of insulin resistance, possibly by enhancing IRS-1 phosphorylation and ERK activation (234, 483). However, the ECS plays a fundamental role also in myogenesis, and 2-AG levels are decreased in vitro during myotube formation from murine myoblasts and in vivo during mouse muscle growth. A synthetic CB1 agonist and 2-AG prevent myotube formation via CB1, whereas embryos from CB1 null mice exhibit muscle fascicles with more myofibers and nuclei. This myoblast differentiation inhibitory action of 2-AG occurs through indirect inhibition of the activity of the Kv7.4 channel (378). It is noteworthy that endocannabinoids activate TRPV1, which was suggested to promote skeletal muscle mitochondrial biogenesis (496) and hypertrophy (383). Yet, there is no evidence of TRPV1 involvement in endocannabinoid myogenetic actions.

7. Bone

Bone is a dynamic tissue, constantly being remodeled through the action of osteoclasts, which resorb bone, and osteoblasts, which reconstitute it. This process is coordinated by a complex system that involves endocannabinoid signaling (381, 844). The ECS is expressed in bone: CB1, CB2, and TRPV1 were identified on human osteoclasts (750); GPR55 was found in human and mouse osteoclasts and osteoblasts (914); and mouse bone expresses CB1, CB2 (381), and TRPV1 (379). AEA and 2-AG are detectable in human osteoclasts and osteoblasts in vitro (750, 914), and their biosynthetic enzymes, NAPE-PLD (750) and diacylglycerol lipases (845), and degradation enzymes, FAAH and MAGL, are found in human osteoclasts (746, 750) and murine osteoblasts (376). The role of the ECS in bone, however, is still contentious. CB2 null mice display a normal phenotype during the first 3 months but later develop an increased age-related bone loss (27). CB1-deficient mice show high (381) or low bone mass (844), depending on the genetic background, gender, and the construct used for gene ablation. CB1 null mice exhibit increased trabecular bone mass at 3 months, due to reduced number or activity of osteoclasts and normal osteoblast activity, but marrow stromal cells, the committed osteoblast precursors, show enhanced capacity for adipocyte rather than for osteoblast differentiation (380).

Synthetic cannabinoid antagonists decrease osteoblast and osteoclast functions in vitro (379, 381), whereas in vivo they reduce bone loss associated with ovariectomy (381, 810). In vitro, 2-AG treatment of rat bone marrow stromal osteoblast precursor cells increases markers of osteoblast differentiation (784); in contrast, in a murine osteoblast cell line, 2-AG decreased the production of the marker alkaline phosphatase and osteoblast cell number (845). AEA stimulates osteoclast formation in culture (381), although in another study it was found that 2-AG and AEA reduce osteoclast formation through inhibition of differentiation (914). A very recent study has investigated the effects of AEA and 2-AG on human osteoblast growth and differentiation in vitro (804). Both endocannabinoids decreased osteoblast proliferation and increased early cell differentiation, but again 2-AG decreased late osteoblast-specific markers of differentiation. AEA-induced changes in differentiation were cannabinoid receptor-independent and partially reduced by TRPV1 antagonism (804). Indeed, CB2 expression in human osteoclasts is modulated by TRPV1, which profoundly affects bone remodeling (747). In human osteoblasts in culture, CB2 and TRPV1 modulate osteogenesis in opposite ways, with CB2 enhancing and TRPV1 inhibiting it (748). The cross-talk between CB2 receptors and TRPV1 in osteoclast biology plays an important role in osteoporosis.

Endocannabinoids are important in the CNS regulation of bone remodeling because CB1 is expressed on sympathetic nerve afferents to osteoblasts (844) and its activation inhibits norepinephrine release, which in turn inhibits bone formation and stimulates bone resorption (239). Thus CB1 activation by bone-derived 2-AG may stimulate ectopic bone formation under certain pathological conditions through this retrograde mechanism (845).

In summary, endocannabinoid may modulate bone formation and resorption in complex and even opposing ways depending on the receptor involved and the starting physiopathological condition. This is typical of the pro-homeostatic role of the ECS, which can correct perturbations of most basic physiological functions in either direction. However, some conclusions, summarized in **FIGURE 3,** can be

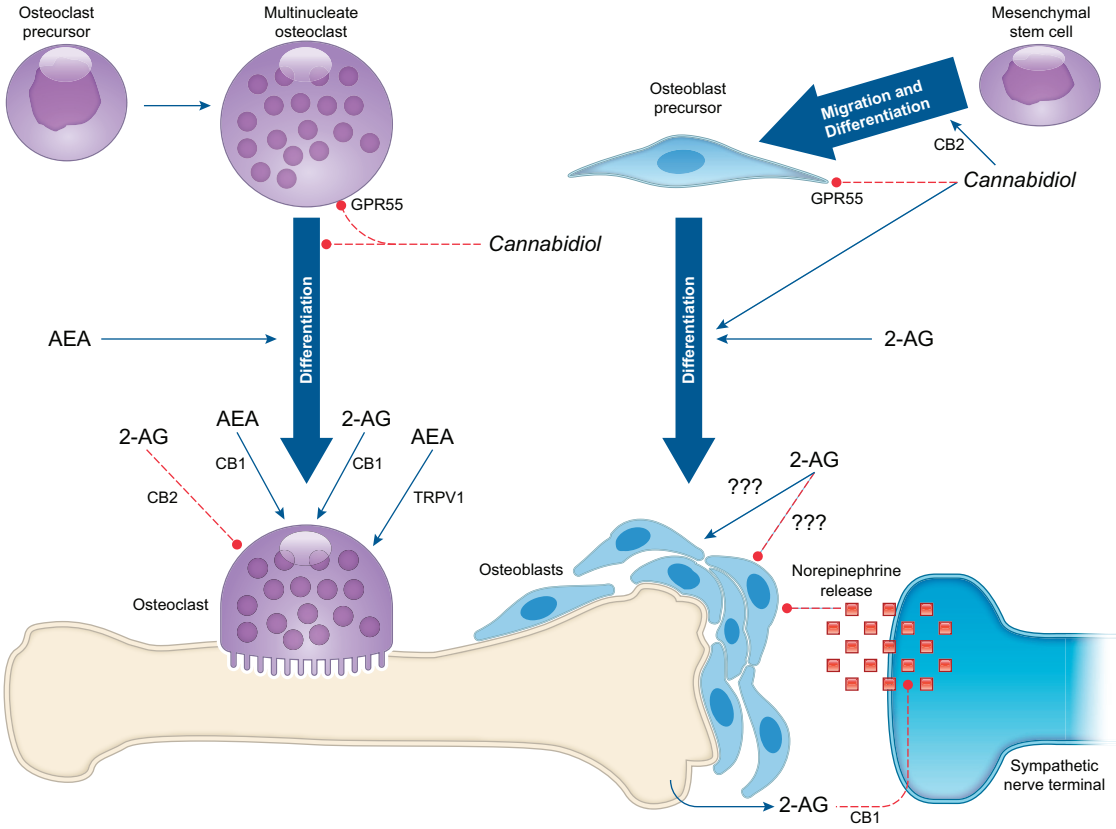

FIGURE 3. Endocannabinoid and phytocannabinoid modulation of bone formation and resorption. Blue arrows indicate stimulation, and red blunted arrows indicate inhibition. The molecular targets through which anandamide (AEA) and 2-arachidonoylglycerol (2-AG) seem to modulate osteoblast and osteoclast differentiation and activity are shown. Cannabidiol was suggested to inhibit osteoclast and stimulate osteoblast differentiation by blocking GPR55.

drawn regarding the overall effects of endo- and phytocannabinoids on bone physiology.

8. Reproductive system

The ECS interacts with sex steroid hormones and cytokines, thus indirectly regulating fertility (421). CB1 and CB2 are expressed in preimplantation mouse embryos (902). AEA in the uterus may activate CB1 and interfere with embryo development. Endocannabinoid signaling is crucial to the synchronization of preimplantation embryo development and for the preparation of the endometrium for implantation, as suggested by the the lower levels of AEA and CB1 found in receptive uteri and activated blastocysts (902). A balance between AEA synthesis and degradation in mouse embryos and oviducts determines normal embryo development and oviductal transport, and hence a correct endocannabinoid signaling is critical for female pregnancy outcome (924), also in humans (902).

Male mouse germ cells possess an active and complete ECS, which is modulated during spermatogenesis, with 2-AG levels being higher in mitotic cells and playing a pivotal role in promoting the meiotic progression of germ cells by activating CB2 (309). It was also shown that 2-AG levels are high in mouse spermatozoa isolated from the caput of the epididymis, where these cells are immotile, and decrease in spermatozoa isolated from the cauda. Thus a gradient of 2-AG levels regulates spermatozoa motility via CB1 expressed on the sperm membrane (151). Activation of CB1 by AEA in spermatozoa affects not only motility but also the acrosome reaction, which is pivotal to the fertilization capacity (902). A CB2-dependent mechanism was also suggested to mediate this process (558). In human sperm, AEA was detected at nanomolar levels (272), and CB1, CB2, TRPV1, as well as the biosynthetic and degrading enzymes NAPE-PLD and FAAH are differentially expressed, confirming a functional and physiological role of the ECS in fertilization (718). In conclusion, the maintenance of a correct endocannabinoid tone is necessary for the preservation of normal sperm function and male fertility.

9. Skin

The ECS is involved in the regulation of biological processes of the skin. Epidermal keratinocytes, hair follicles, as well as sebaceous and sweat glands all produce endocannabinoids and express CB1, CB2, and metabolic enzymes (70). In the

epidermis, AEA inhibits proliferation and reduces differentiation of human epidermal keratinocytes via CB1-coupled signaling (697). CB1 controls melanogenesis in epidermal melanocytes too (696), possibly also through intercellular communication mechanisms involving the keratinocytes (516). Interestingly, in mice, genetic ablation of CB1 delays, whereas lack of CB2 accelerates, recovery of the epidermal permeability barrier, which is keratinocyte proliferation and differentiation dependent (738). Furthermore, CB1 signaling inhibits human hair elongation, whereas CB2 stimulates lipogenesis in human sebaceous gland-derived sebocytes (70). In contrast, the inhibition of the proliferation and secretory activity of sweat gland epithelial cells by AEA occurs through non-CB1/CB2-dependent mechanisms (170).

IX. SUMMARY: IN WHAT PHYSIOLOGICAL FUNCTIONS DOES THE ECS PLAY THE MOST IMPORTANT ROLE?

Apart from (and possibly as part of) its universally accepted fundamental role in neuromodulation in the CNS, only 10 years ago researchers in the field would have bet on the control of energy balance, at the level of both food intake/satiety and peripheral metabolism, as the most important physiological function of endocannabinoids acting at CB1. In fact, pharmaceutical companies did invest heavily in this option by developing antiobesity CB1 receptor blockers that, although efficacious, were eventually suspended because of side effects. Additionally, immune modulation would have been the first choice for the most important endocannabinoid function at CB2, yet agents targeting this receptor have so far eluded clinical development. While both these options are still open, and, especially in the case of the former, have been reinforced by recent data, others, such as the multi-faceted roles of the ECS in peripheral organ function (see Ref. 501 for a recent review) and, particularly, development (see, for example, Refs. 378, 523), have made their way into the mind of the "endocannabinoid-philes." With increased knowledge in this rapidly evolving field, the old view of CB1 being most important in neurons and the nervous system and CB2 in immune cells needs to be revisited. Although new hypotheses on the crucial role of endocannabinoids might not stand the test of time, our best prediction of where the field will move to in the future is summarized in **TABLE 1**.

X. ROLE OF THE ECS IN PATHOLOGICAL CONDITIONS

A. CNS

1. Schizophrenia

The levels of AEA are markedly increased in the cerebrospinal fluid (471) and peripheral blood (186, 472) of schizophrenia patients. As successful antipsychotic therapy reversed the increased levels of AEA (186, 472), this increase might represent an adaptive reaction to overactivation of dopamine D2 receptors (472). In rats, it was suggested that AEA and 2-AG play a potentially different role (protective and counterprotective, respectively) in the schizophrenia-like cognitive and negative symptoms induced by chronic phencyclidine, and that cannabis use or CB1 antagonism and FAAH inhibition might exacerbate or improve, respectively, such symptoms by modifying endocannabinoid signaling (5, 313, 883).

Growing evidence indicates that the immune system is involved in the pathogenesis of psychotic disorders, including schizophrenia and bipolar disorder (67). CB2 mRNA levels were decreased in peripheral blood mononuclear cells of schizophrenia patients after treatment with olanzapine (186). This effect might be a consequence of reduced activity of blood leukocytes since CB2 is upregulated in activated macrophages and leukocytes (440).

2. Stroke and brain injury

The neuroprotective potential of compounds targeting the ECS is due to counteraction of excitotoxicity, oxidative stress and inflammation, and promotion of cell homeostasis and survival. Endocannabinoids are neuroprotective because of their activity on all CNS cells (neurons, astrocytes, microglia, oligodendrocytes, etc.) and the blood-brain barrier. They reduce excitotoxicity and neuroinflammation through neuronal CB1 and microglial CB2, respectively, whereas through astroglial cannabinoid receptors they enhance the trophic and metabolic support to neurons. Furthermore, their effects may involve also noncannabinoid receptors such as NF-κB, PPARs, 5-HT_{1A}, and adenosine receptors, among others (259). Endocannabinoids exert neuroprotection in a variety of in vitro and in vivo models of neurodegeneration (132, 240, 929). Inhibition of their hydrolysis by FAAH and MAGL usually recapituales these actions. However, there is evidence for cannabinoid receptor-independent anti-inflammatory effects by inhibitors of MAGL, which might be due to the fact that AA formed from 2-AG hydrolysis can act as a precursor for several proinflammatory prostaglandins (630). Thus MAGL inhibitors might be producing neuroprotection via either indirect activation of cannabinoid receptors or prevention of prostaglandin biosynthesis.

Ischemic brain damage with blood vessel occlusion is characterized by excessive release of the excitatory glutamate with a strong inflammatory response. Endocannabinoids are neuroprotective against the consequences of stroke or traumatic brain injury (241). Their benefical effects were demonstrated in different animal models, particularly for 2-AG in traumatic brain injury (659) and experimental ischemia (355), but also for AEA (357). CB1 null mice exhibit worsened neurological function in both pathologi-

Table 1. *Established and emerging aspects of the role of the endocannabinoid system in basic physiological functions*

Organ	Tissue or Cell Type	CB1	CB2	Differences Between AEA and 2-AG (if any)	Physiological Function	Reference Nos.
Central nervous system	Neural progenitor stem cells	↑ Differentiation, migration	↑ Proliferation and differentiation		Brain development, aging	279, 650, 790
	Neurons	↓ Neurotransmitter release (retrograde)		Prominent role of 2-AG	Food intake	127, 418, 448, 514, 545, 638, 699, 861, 920
		↓ ↑ Gene expression (postsynaptic)		(As above)	Reward	
		↓ ↑ Synaptic strength and plasticity		(As above)	Memory	
					Mood	
					Nociception	
					Neuroendocrine functions	
	Astrocytes and oligodendrocytes	Neuromodulation	Regulation of cytokine release and astrocyte activity		Synaptic function	
		Regulation of synaptic plasticity and myelinisation	Regulation of cytokine release and microglial phenotype		Aging	299, 618, 619
	Microglia	Dendritic spine pruning (?)				30, 275
Gastrointestinal system	Stomach	↓ Gastric emptying			Digestion and satiety	211
	Small intestine	↓ Motility		Prominent role of AEA	Digestion and food intake	385
		↑ Intestinal permeability		(As above)	Nutrient adsorption, microbiome-mediated functions	
		↓ Intestinal secretion			Energy processing	
	Colon	↓ Motility	↓ Motility (during inflammatory conditions)	Prominent role of AEA	Digestion	46, 47, 172, 289, 594
					Nutrient adsorption	
					Microbiome-mediated functions	
	Pancreas	↑ Insulin release from β-cells ↑ Langerhan's islet differentiation			Insulin function	208, 522, 523, 542
					Energy storage and utilization	
	Adipose tissue	↑ Adipogenesis and lipid metabolism in white adipocytes		Prominent role of 2-AG	Energy storage and utilization	449
		↓ Thermogenesis in brown adipocytes				
Immune system	Hematopoietic stem cells		↑ Hematopoiesis	Prominent role of 2-AG	Blood cell specification	279, 401, 666, 866
	T and B lymphocytes		↓ Th1 response	(As above)	Humoral versus cellular immune response	
			↑ Th2 response	(As above)		
Musculoskeletal system	Bone	See Figure 3	See Figure 3		Bone structure and strength	381, 844, 845
	Skeletal muscle	↓ Insulin sensitivity		Prominent role of 2-AG	Nutrient processing	234, 378, 483
		↓ Differentiation		(As above)	Muscle fiber thickness	
Reproductive system	Male	↓ Sperm motility	↑ Spermatogenesis	Prominent role of 2-AG	Control of reproduction	151, 309, 902
		↓ Capacitation and acrosome reaction		Prominent role of AEA		
	Female	↑ Oocyte maturation	↑ Oocyte maturation	Prominent role of AEA	Control of reproduction	902, 924
		↓ Embryo implantation		(As above)		
		↓ Decidualization		(As above)		

Continued

Table 1.—*Continued*

Organ	Tissue or Cell Type	CB1	CB2	Differences Between AEA and 2-AG (if any)	Physiological Function	Reference Nos.
		Placentation and parturition				
Cardiovascular system		↓ Heart rate		Prominent role of AEA	Control of hemodynamic function	452, 892
		↓ Mean artery pressure		(As above)		
Skin		↓ Keratinocyte differentiation	↑ Lipogenesis in sebocytes	Prominent role of AEA	Control of skin barrier	70, 696, 697
		↓ ↑ Melanogenesis		Prominent role of AEA		
		↓ Hair elongation				

cal conditions (658, 663). Also CB2 knockout mice show increased infarct size and neurological deficits in an induced-stroke model (940), confirming results from pharmacological experiments with selective CB2 agonists, also in traumatic brain injury (16). Of note, 2-AG levels are transiently elevated at the site of traumatic brain injury (659) to reduce brain damage and improve functional deficits, while in the neonatal rat brain, this seems to apply to AEA (325). In stroke, both CB1 and CB2 expression is upregulated (402, 873), whereas in traumatic brain injury this is true for CB2 but not CB1 (230).

3. Multiple sclerosis

Chronic relapsing EAE mice present increased levels of endocannabinoids and PEA in areas associated with nerve damage, and this, together with the inhibition of spasticity found following either pharmacological or genetic blockade of FAAH or MAGL (694), and the exacerbation observed in CB1 null mice, provides evidence for a CB1-mediated tonic control of MS spasticity by the ECS (31). However, endocannabinoids exert also neuroprotective actions in EAE models of MS, by acting via both CB1 and CB2 and through antiexcitotoxic, anti-inflammatory, and remyelinating effects (131). This is also shown by the higher or lower susceptibility to disease progression of EAE in CB1 and CB2 knockouts or FAAH knockouts, respectively (60, 909), and by the finding of altered endocannabinoid and cannabinoid receptor levels in brain of EAE mice and rats (32, 105), and, most importantly, in the blood, cerebrospinal fluid, and post mortem brain tissue of MS patients (131). Both receptors exert a direct suppression of CNS autoimmune inflammation, but in different cell types: CB1 in neurons and CB2 in autoreactive T cells (528).

4. Alzheimer's disease

In AD experimental models, endocannabinoids reduce classic neurotoxic events, such as excessive glutamatergic transmission and Ca^{2+} influx, inflammation, and oxidative stress. The selective activation of either cannabinoid receptor type is beneficial at preserving neuronal cells or preventing microglial activation induced by β-amyloid peptides (22, 717). The beneficial effects of genetic or pharmacological inactivation of endocannabinoid degradative enzymes were also investigated (61, 139, 685, 878). However, in agreement with the hypothesis that activation of CB1, particularly by 2-AG, might also contribute to some of the cognitive impairments in late stages of the disease, because of maladaptive neuromodulatory effects (603), also CB1 antagonists can produce beneficial effects (546), and a FAAH inhibitor capable of elevating 2-AG levels was shown to ameliorate memory retention loss caused by β-amyloid only when administered early after the insult (869). Instead, MAGL inhibitors afford protective actions not so much because they elevate 2-AG levels, but due to their capability of inhibiting AA production from 2-AG and inflammatory prostaglandin biosynthesis (685).

Also suggestive of a possibly different role of 2-AG and AEA in AD is the finding, in both an animal model and post mortem AD brains, of differential regulation of the levels of the two compounds, with AEA decreasing with disease progression and 2-AG first increasing and then returning to baseline (413, 869). Post mortem brain tissues from AD patients present upregulation of CB2 in reactive microglial cells surrounding neuritic plaques (59, 717), which might be related to the beneficial effects of compounds selectively targeting CB2 in animal models (22, 717). Instead, the reduction in CB1 levels observed in AD-affected areas (717, 913), together with the decrease in AEA levels (see above), may be partly responsible for, or be a consequence of, neuronal loss and cognitive problems, and due in part to elevation of FAAH levels in astrocytes associated with senile plaques in the human cortex (59, 413).

5. Parkinson's disease

CB2 activation is anti-inflammatory and neuroprotective in animal models of PD, a disease where inflammation and

oxidative stress are important pathogenic factors and lead to the death of nigrostratial neurons controlling movement. In the substantia nigra of PD patients, CB2 is elevated in microglial cells recruited and activated at lesioned sites (298). CB2 activation with selective agonists counteracts microglial activation/infiltration in PD models of mitochondrial dysfunction or LPS insult (284, 298). These findings are supported by studies with CB2 knockout mice, which are more vulnerable to LPS lesions (284), whereas CB2 overexpression, by reducing the recruitment of astrocytes and microglia to the lesion, decreases motor impairment and dopaminergic neuronal loss (853). Instead, CB1 receptor activation does not seem to play a major beneficial role in PD models. As in the case of AD models, and again possibly due to maladaptive neuromodulatory actions, it seems to worsen some of the motor impairments, also following levodopa-induced dyskinesias. As a consequence, CB1 receptor inverse agonists/antagonists have proven beneficial in both rodent and non-human primate models of PD (256, 428, 868). In these models, the levels of endocannabinoids were shown to change following both damage of nigrostriatal neurons induced by various neurotoxins, and the establishment of dyskinesias due to prolonged L-DOPA treatment (868).

6. Huntington's disease

Striatal CB1 receptors disappear early in the course of HD, even before death of pallido-striatal neurons and the onset of choreic symptoms, both typical of this disease (292, 456). Indeed, it was clearly demonstrated in post mortem tissue from HD patients (293), as well as in a chemically induced model of HD (458), that a decrease in CB1 levels and signaling in the basal ganglia is one of the earliest changes in HD. Furthermore, decreased levels of endocannabinoids in the striatum were also documented in several HD models (36, 75, 458). In animal models of HD, such as R6/2 mice, which carry large CAG expansions leading to an early and severe HD phenotype, or quinolinate-lesioned mice and 3-nitropropionate- or malonate-lesioned rats, the concomitant suppression of the CB1 gene further accelerates the development of a severe clinical syndrome. "HD mice" treated with cannabinoids improve their clinical phenotype, brain lesions, synaptic density, and the levels of the neurotrophic factor BDNF, which enhances survival of striatal neurons (81, 260). Therefore, it seems that loss of CB1 is a key pathogenic factor in HD (82). Nevertheless, genetic rescue of CB1 receptors in medium spiny striatal neurons of R6/2 mice produced beneficial actions only on neuronal excitability and not on locomotion (622). In the same model, full knockout of CB1 or its deletion selectively in corticostriatal glutamatergic or striatal GABAergic neuron, evidenced that only a restricted population of CB1 receptors located on glutamatergic terminals projecting to the striatum is the target for the neuroprotective activity of endocannabinoids (141). These neurons are preserved during the progression of HD and might be potential targets for a neuroprotective therapy with cannabinoids. Also selective activation of CB2, as well as its overexpression, appear to be effective in HD models by counteracting inflammatory events and microglial activation (649, 766).

As mentioned above, endocannabinoid levels are usually decreased in the brain of HD models, and hence inhibitors of AEA and 2-AG metabolism should produce beneficial effects. However, MAGL and DAGL inhibitors produce paradoxical exacerbating and therapeutic effects in the malonate model of HD due to potentiation and inhibition, respectively, of neurotoxic prostaglandin-glycerol ester formation via the DAGLα-COX-2 pathway (864). The beneficial action of FAAH inhibitors, instead, is complicated by the concomitant elevation of TRPV1 tone, a phenomenon observed also in models of PD. Interestingly, AM404, an inhibitor of the endocannabinoid reuptake process, which also has affinity for TRPV1, reduces hyperkinesia, and causes recovery from neurochemical deficits, in a rat model of HD (457), suggesting that TRPV1, alone or together with CB1 receptors, might represent a novel therapeutic target in HD (257).

7. Amyotrophic lateral sclerosis

The role of the ECS in ALS has been so far investigated almost exclusively in the overexpressing mutated form (G93A) of superoxide dismutase (SOD)-1 transgenic mice, which models only a small percentage of cases of this incurable disease. In this model, both the cannabinoid WIN55,212–2 (69) and the selective CB2 agonist AM1541 (431, 792) delay disease progression. FAAH knockout in SOD1G93A mice results in raised levels of AEA and retarded appearance of disease signs, but so does genetic inactivation of CB1 (69). Thus the neuroprotective effects of endocannabinoids in ALS may be mediated by CB2, which counteracts the activation of microglial cells and neuroinflammation. However, the capability of CB1 receptors to control both glutamate and GABA transmission was potentiated in G93A-SOD1 mice, indicating that adaptations of the ECS might be involved in the pathophysiology of ALS (751). Endocannabinoid levels are elevated in the spinal cord of SOD1G93A mice (69, 921), and so is the expression of NAPE-PLD, whereas no change in DAGL and MAGL is found (591). In addition, elevated levels of CB2 are detected in the spinal cord both of SOD-1 mutants (591) and TDP-43 transgenic mice, another model of ALS (245), and, importantly, also in patients with the disease (932). No changes in CB1 expression in the spinal cord are instead found (245, 591).

B. Peripheral Tissues

1. Cardiovascular system: blood pressure, cardiometabolic risk, and atherosclerosis

The ECS plays an important role in the development and/or progression of cardiovascular disorders (580, 818). AEA,

via a CB1-mediated mechanism, is responsible for cardioprotective anti-arrhythmic effects during anxiety-like behavior in a rat model (120), but also for maladaptive CB1-mediated hypotension associated with many pathological conditions, such as septic and hemorrhagic shock and myocardial infarction (296). During conditions when the ECS is dysregulated by excessive inflammation, CB1 activation by AEA may trigger ROS generation and promote ROS-dependent and -independent activation of MAPK, resulting in the death of endothelial cells in humans (711), and of cardiomyocytes in rodents (599), thus contributing to the pathophysiology of various cardiovascular diseases. These include diabetic cardiomyopathy, which is characterized by increased myocardial AEA levels, oxidative stress, activation of p38/Jun MAP kinases, TNF-α, IL-1β and COX-2, enhanced inflammation, and increased CB1 expression (707). In obese humans, high plasma levels of endocannabinoids correlate with impaired coronary endothelial function (646). The proinflammatory effects of CB1 in the cardiovascular system are also revealed using FAAH inhibitors or FAAH null mice in models of atherosclerosis and cardiomyopathy (802). Hence, CB1 inhibition may improve cardiac function and be cardioprotective not only indirectly, by counteracting the metabolic syndrome (see below), but also, in the above conditions as well as in a model of angiotensin II-dependent hypertension, via direct effects on the heart (777). However, in spontaneously hypertensive rats, AEA elevation through FAAH inhibition normalizes elevated blood pressure and cardiac contractility via CB1 receptor-mediated decrease in sympathetic tone, without affecting these parameters in normotensive rats. The supersensitivity of hypertensive rats to CB1 receptor-mediated cardiovascular depression was related to increased G protein coupling of CB1 (296). These studies were carried out with acute administration of a single dose of the FAAH inhibitor, whereas more recent studies highlighted how chronic CB1 inhibition in transgenic hypertensive rats with upregulated renin-angiotensin system activity improves blood pressure regulation and metabolic profile (777). The indirect and sustained activation of CB1 needs to be carefully addressed in the context of the cardiovascular system, since genetic deletion of FAAH in a doxorubicin-induced cardiomyopathy model promotes myocardial injury (600). Moreover, chronic pharmacological FAAH inhibition enhances intraplaque neutrophil recruitment in atherosclerotic mice (467).

Interestingly, CB2 exerts opposing, and hence protective, effects on cardiopathies compared with CB1 (818). Via CB2, 2-AG reduces myocardial infarct size, an effect not observed with AEA (468). As a consequence, a selective CB2 antagonist (but not rimonabant) abolishes cardioprotection against myocardial ischaemia (451). In vivo, the cardioprotective action of CB2 is mediated by activation of ERK (582).

In metabolic disorders accompanying obesity, the ECS is overactive in brain areas controlling appetite, but also in peripheral organs. Rimonabant improves both body weight and metabolic and inflammatory abnormalities in obese subjects (871), as well as in animals with obesity (216). There is a strong positive correlation in male obese patients between serum levels of 2-AG and high triglycerides and low HDL-cholesterol, two important biomarkers of cardiometabolic risk (212). Furthermore, elevated endocannabinoid plasma levels are associated with impaired coronary circulatory function in obese men (705). A stronger 2-AG/CB1 tone in the aorta and visceral adipose tissue occurs in high cholesterol-fed ApoE null mice, a model of atherosclerosis, concomitantly with the formation of atherosclerotic plaques and potentially increased recruitment of inflammatory cells (583). Furthermore, CB1 mRNA expression in coronary atheromas is significantly higher in patients with unstable angina compared with those with stable angina (828). As a consequence of the above and other studies in both animal models and humans, it can be suggested that blockade of CB1 receptors in peripheral tissues might counteract atherosclerosis. Indeed, oral treatment with rimonabant did reduce total atheroma volume in high cardiometabolic risk obese men (629). In a diabetes model of pro-atherosclerotic disease, CB1 antagonism attenuates inflammation and oxidant release (365).

Conversely, CB2 activation reduces atherosclerotic inflammation by reducing pro-atherosclerotic TNF-α-induced endothelial cell activation, and attenuating adhesion and migration of monocytes and consequently their infiltration in atherosclerotic plaques in vitro (708, 710), and in vivo, where deficiency of CB2 is associated with increased neointima formation and smooth muscle cell proliferation in response to carotid injury (575). The CB2 agonist JWH-015 reduces chemokine receptor expression in human monocytes (579). A protective role of CB2 in plaque vulnerability was also identified (581) and, accordingly, MAGL deficiency in ApoE-knockout mice improves plaque stability (890). Therefore, clinical trials should confirm that CB2 activation, possibly together with CB1 blockade, is a promising therapeutic strategy for atherosclerosis and ensuing cardiovascular risk (580).

2. Gastrointestinal tract

Although, under physiological conditions, CB2 receptors do not seem to play a major role in GI function, their activation in pathological states limits abnormal GI tract motility (232). FAAH inhibition also dampens intestinal contractility in pathophysiological states but not in normal animals (47). In contrast, the inhibition of DAGLα reverses slow motility, intestinal contractility, and constipation through the decrease of 2-AG signaling at CB1 (46), in agreement with previous findings showing that intestinal hypomotility in a mouse model of paralytic ileus is linked to the enhancement of endocannabinoid levels and CB1 ex-

pression in the gut, and is attenuated by a CB1 receptor antagonist (538).

As shown by using a selective inhibitor of MAGL, 2-AG protects against gastric damage induced by nonsteroidal anti-inflammatory drugs (434). When activated, the ECS reduces intestinal inflammation (264), and both central and peripheral cannabinoid receptors are responsible for the beneficial action of cannabinoid receptor agonists in mouse models of colitis (264). Indeed, the ECS is implicated in inflammatory bowel disease pathogenesis (9), and in several gut diseases the components of this system are upregulated, as in the case of AEA, but not 2-AG, levels in biopsies from the inflamed colon of patients with ulcerative colitis (172), or of AEA levels (171) and CB1 and CB2 expression (50) during active celiac disease.

3. Liver

Initial studies suggested that CB1 receptors are expressed at very low levels, and CB2 receptors are close to detection limit in the healthy human liver (412). Conversely, in the case of liver injury, CB1 receptors are upregulated in hepatocytes, hepatic myofibroblasts, and endothelial cells, whereas we now know that CB2 receptors are highly expressed in Kupffer cells of the healthy liver (526). CB1 stimulation of mouse and rat liver regeneration was reported (595, 686), although CB1 may also promote hepatocellular carcinoma initiation and progression (596). Indeed, the ECS has emerged as either one of the causes or a negative modulator of most pathological aspects associated with chronic liver disease progression (525). Liver injury is associated with increased endocannabinoid tone, with AEA being produced by hepatocytes, Kupffer cells, and endothelial cells and 2-AG by hepatic stellate cells and hepatocytes (49, 525). However, MAGL-mediated hydrolysis of 2-AG generates AA as a precursor for prostaglandin production, which exacerbates hepatic injury. Consequently, the genetic or pharmacological blockade of this pathway protects mice from liver injury also via non-cannabinoid receptor-mediated mechanisms (114). In liver injury, CB2 may become upregulated in Kupffer cells and hepatic myofibroblasts, and CB1 in hepatocytes, hepatic myofibroblasts, and endothelial cells (525).

CB1 is involved in the pathogenesis of liver fibrogenesis, alcoholic and metabolic steatosis, and circulatory failure associated with cirrhosis. Nonalcoholic fatty liver disease (NAFLD) evolves to liver inflammation, steatohepatitis, hepatocellular injury, and activation of fibrogenic pathways. The genetic or pharmacological ablation of CB1 protects the liver by decreasing fibrogenesis (851). Of note, a CB1-dependent increase in adipose tissue TNF-α expression is associated with reduced secretion of adiponectin, which has potent anti-inflammatory effects in the liver, and this could be a mechanism through which administration of rimonabant, by enhancing adiponectin production (62), reduces liver inflammation. Both AEA and CB1 levels become upregulated in mouse hepatocytes following high-fat diets leading to obesity and other metabolic disorders, and contribute to ectopic fat accumulation in the liver, which is the first step towards liver inflammation. Selective deletion of CB1 in hepatocytes is sufficient to prevent both high-fat diet- and alcohol-induced fatty liver. However, while lipid accumulation in hepatocytes following high-fat diet is due to an autocrine action of hepatocyte AEA, the ethanol-induced accumulation is due to a paracrine action on hepatocyte CB1 receptors by 2-AG derived from stellate cells (399, 643). Therefore, an efficient therapeutic strategy to counteract fatty liver might be the treatment with a CB1 antagonist with limited brain penetrance, thus minimizing the neuropsychiatric side effects of "global" CB1 inverse agonists such as rimonabant. Accordingly, a non-brain-penetrant CB1 inverse agonist was equieffective with rimonabant in reducing appetite, body weight, hepatic steatosis, and insulin resistance in diet-induced obesity mice (DIO), supporting the dominant role of peripheral hepatic rather than central CB1 in these effects (843).

In cirrhosis, the advanced stage of liver fibrosis, both AEA and CB1 are increased in humans and rodents in the vascular endothelium with hepatic vasodilatation, ascites formation and variceal hemorrhage, and treatment of cirrhotic rodents with rimonabant increases blood pressure by decreasing peripheral vasodilation and reducing portal pressure (48, 229). It is possible that AEA also activates TRPV1, which might contribute to hyperdynamic circulation and mesenteric hyperemia in cirrhosis (574). Circulating AEA, but not 2-AG, levels are significantly higher in cirrhotic patients than in controls and correlate with parameters of liver function, such as serum bilirubin, but not with systemic hemodynamics (116). Finally, reduced CB1 signaling, using antagonists/inverse agonists or CB1 shRNA, also inhibits hepatitis C virus infection, possibly due to reduced lipogenesis (785).

Contrary to CB1, CB2 plays antisteatotic and antifibrinogic actions in the liver by switching Kupffer cells from a proinflammatory to an anti-inflammatory phenotype, thus reducing IL-1β release and by limiting steatosis (493). Kupffer cell treatment with a CB2 agonist also prevents the proinflammatory response to LPS, seemingly through inhibition of NF-kB. Accordingly, CB2 knockout mice receptors exhibit steatosis, and since CB2 receptors are not expressed in hepatocytes, their antisteatogenic action might indeed originate from Kupffer cells.

CB2 also plays an antifibrogenic role of in the liver, as established using a model consisting of treatment with carbon tetrachloride, which results in increased fibrosis in CB2 null mice (412). CB2 agonist treatment of rats with carbon tetrachloride-induced liver fibrosis improves this pathology and leads to reduced portal pressure (608). CB2 activation

decreases liver fibrosis by selectively reducing IL-17 production by T helper 17 lymphocytes via a STAT5-dependent pathway (314). CB2 decreases the extent of liver injury in models of acute liver damage (25, 49). Furthermore, while CB2 knockout mice exhibit accelerated liver hepatitis induced by carbon tetrachloride and delayed liver regeneration, a CB2 selective agonist reduces liver injury, accelerates liver regeneration, and protects from the apoptotic effects of carbon tetrachloride (850). The beneficial effects on liver regeneration are due to increased production of IL-6 from hepatic myofibroblasts. Therefore, CB2 agonists display potent hepatoprotective properties, in addition to their antifibrogenic effects.

4. Kidney

In various murine models of obesity and diabetes, endocannabinoids generated in renal cells activate CB1 and contribute to the development of oxidative stress, inflammation, and renal fibrosis. These effects are ameliorated by CB1 antagonists and CB2 agonists (41, 43, 410). The latter compounds are also useful in tubular nephropathy induced by cisplatin, a model of nephrotoxicity, with a mechanism involving the attenuation of TNF-α and IL-1β levels and of renal oxidative and nitrative stress leading to apoptotic and necrotic cell death (601). Accordingly, cisplatin-induced kidney inflammation is exacerbated in CB2$^{-/-}$ mice (598), and a novel selective CB2 agonist, LEI-101, prevents kidney dysfunction and damage induced by cisplatin in mice in vitro and in vivo (597). In nephropathy induced either by type 1-like diabetes (streptozotocin) or obesity-linked type 2 diabetes in mice, renal 2-AG levels are reduced (42, 944), thus impairing the endogenous CB2-mediated protection against albuminuria, podocyte protein downregulation, glomerular monocyte infiltration, and CCR2 upregulation (43).

Conversely, CB1 appears to contribute to nephropathy so that its chronic blockade improves renal function and survival in obese rats (390) and ameliorates albuminuria in streptozotocin- and obesity-induced diabetic nephropathy in rodents (41, 396). Indeed, renal CB1 expression is enhanced in both diabetic mice, where CB1 is overexpressed by glomerular podocytes (41), and rats (395). Genetic upregulation of CB1 and its pharmacological stimulation in rats increases proteinuria, a sign of kidney damage and of the progression of renal disease, associated in renal glomeruli with higher VEGF expression and reduced nephrin expression (370). In the *db/db* mouse model of type 2 diabetes, where CB1 is overexpressed in podocytes, rimonabant decreases urinary albumin excretion and mesangial expansion and inhibits proinflammatory cytokine synthesis (616). In a rat model of type 2 diabetes nephropathy, in vivo treatment for 3 months with a CB1 antagonist in the prediabetic stage prevents nephropathy, or reverses it when this is already developed (410). Palmitic acid, a player in renal tubular damage, upregulates CB1 mRNA and protein expression and promotes receptor internalization, and, by activating endoplasmic reticulum stress, induces intrinsic pathway apoptosis via CB1 (480). Higher CB1 expression and internalization are also reported in primary rat mesangial cells exposed to high glucose (481), and CB1 is among the most upregulated genes in mice subjected to unilateral ureteral obstruction, an experimental model of renal fibrosis. In the fibrotic kidney, 2-AG levels are significantly increased, and genetic or pharmacological blockade of CB1 reduces fibrosis. Of note, CB1 expression is very high in kidney biopsies of patients with IgA nephropathy, diabetes, and acute interstitial nephritis (462).

5. Bone

In a study with 64 rats with glucocorticoid-induced osteoporosis and divided for age, the decrease in bone mineral density and content of the tibia was reversed by rimonabant in young rats, and exacerbated in older rats, demonstrating that CB1 plays in bone turnover a role that is age dependent (769). Indeed, it was reported that CB1 protects against age-related osteoporosis by regulating osteoblast and adipocyte differentiation in marrow stromal cells (380).

Preclinical studies show that synthetic CB2 agonists rescue ovariectomy-induced bone loss, suggesting that these drugs may improve osteoporosis (805). In women, 17β-estradiol administration inhibits activity and formation of osteoclasts in vitro and increases CB2 expression, which may underlie the antiresorptive properties of estrogen and postmenopausal osteoporosis (745). Accordingly, CB2 activation plays a very important role in osteogenic differentiation of bone marrow-derived mesenchymal stem cells, by promoting expression of osteogenic genes, and enhancing deposition of calcium in extracellular matrix. CB2 knockdown by siRNA inhibits mineralization and alkaline phosphatase, and the expression of CB2 receptor is much lower in osteoporotic patients than in healthy donors (834). However, a recent study carried out with human osteoblasts evidenced a potential inhibitory effect of CB2 on 17β-estradiol-induced proliferation (362), thus suggesting once again that osteoblast/osteoclast balance regulation by the ECS may be more complex than initially suspected.

Iron overload has an important role in the dysregulation of bone metabolism in patients with thalassemia major, causing osteoporosis. Although a TRPV1 agonist does not affect two biomarkers of femoral and lumbar bone mineral density in osteoclasts from thalassemic patients in vitro, it dramatically reduces osteoclast number (749). As genetic ablation or pharmacological inhibition of TRPV1 is beneficial for the restoration of quiescent osteoclast activity in ovariectomized mice, TRPV1 activation by endocannabinoids/endovanilloids might be one of the cause of osteoporosis in these patients (747).

6. Reproductive system

Women with miscarriage (<8 wk of gestation) have higher FAAH activity in their peripheral lymphocytes, in agreement with the concept that dysregulated AEA signaling might prevent embryo implantation (507). Additionally, women with ectopic pregnancy express low levels of CB1 both in the Fallopian tubes and endometrium (364, 903). In vitro and in vivo studies showed that trophoblast stem cells missing CB1 receptors undergo defective proliferation and differentiation, required for normal placentation, thus leading to retarded fetal development and/or compromised pregnancy (832). Thus a dysfunctional ECS may partly underlie both miscarriage and extopic pregnancy.

Men with either asthenozoospermia or oligoasthenozoospermia, two major causes of infertility, exhibit very low levels of AEA, but also of PEA and OEA, which in vitro improve sperm motility without affecting mitochondrial activity (17). They may protect sperm from oxidative damage, a possible cause of male infertility (15). A marked reduction of endocannabinoid content due to increased degradation was observed in infertile seminal plasma (473). These findings are in agreement with the proposed role of CB2 and CB1 receptors in spermatogenesis and sperm cell motility, respectively.

7. Skin

The ECS is able to suppress cutaneous inflammation as well as human skin mast cell stimulation, which provides a promising strategy for the management of skin allergies. Endocannabinoids, by activating CB1 receptors, are able to limit the excessive number and the activation of mast cells in allergic diseases that in turn may be due to insufficient CB1 stimulation (829). In an animal models of allergic contact dermatitis, skin 2-AG levels are elevated and the treatment with a CB2 antagonist attenuates both the recruitment of eosinophils and the swelling in the challenged zone (639), whereas allergic inflammation is suppressed by ablation of CB2 (571). Conversely, in another study, mice lacking both cannabinoid receptors displayed aggravated allergic inflammation, whereas FAAH-deficient mice showed reduced responses in the skin (424). In agreement with this latter study, mice with keratinocyte-specific ablation of CB1 develop an increased contact hypersensitivity to 2,4-dinitrofluorobenzene and inflammatory keratinocytes hyperproliferation. The allergic tissue of these mice show enhanced expression of CXCL10 and CCL8, whereas primary $CB1^{-/-}$ keratinocyte cell cultures challenged with IFN-γ release these proinflammatory chemokines (276). In an experimental mouse model for Th2-type contact hypersensitivity, both mice lacking CB1 globally and only in keratinocytes show enhanced responses and a delayed epidermal barrier repair with increased production of CCL8 (277).

Opposing roles of CB1 and CB2 are found in skin fibrosis models. FAAH was found to be downregulated in the dermal fibroblasts of systemic sclerosis patients, suggesting that the increased AEA levels due to defective FAAH may contribute to fibrosis in mice, possibly via CB1-coupled signaling (651). Accordingly, the skin from CB1 null mice was found to be resistant to fibrosis in the same model of inflammation-induced fibrosis (530). In the same animal model, the activation of CB2 expressed by leukocytes instead ameliorates fibrosis, and in systemic sclerosis fibroblast CB2 stimulation also results in a significant antifibrotic effect after blockade of adenosine A2A receptor stimulation, which promotes dermal fibrosis (70, 461).

Cannabinoid receptor agonists, like some phytocannabinoids, show antiproliferative, proapoptotic, and antiangiogenic effects in multiple models of melanoma and other skin tumors (70).

XI. SUMMARY: WHAT PATHOLOGICAL CONDITIONS MANIPULATION OF THE ECS IS MOST LIKELY TO BENEFIT?

After over 20 years from the development of pharmacological tools targeting the several proteins of the ECS, a plethora of options for their therapeutic use has been supported by preclinical studies (**TABLE 2**), but only one has made it so far through clinical development and to the market, and only for a couple of years. Yet, most of these options, especially if assisted by specific strategies aimed at augmenting their efficacy and safety (see below), are still open. In particular, inhibition of endocannabinoid inactivation, peripherally restricted targeting of CB1, and targeting of CB2 receptors for pathological conditions of peripheral organs still look like promising avenues for the development of new drugs.

XII. GENERAL CONCLUSIONS

In this article we have attempted to provide a wide and comprehensive, as well as balanced, view of the *1*) complex pharmacology of cannabis and phytocannabinoids and of their many physiological substrates and potential therapeutic actions; *2*) multifaceted aspects of the ECS, and the ever increasing complexity of its physiological functions and therapeutic exploitation. In doing so, we have respected the chronological order of the milestones of the millennial route from medicinal/recreational cannabis to the ECS, and beyond. In fact, we believe that some of the early steps in this path, which were originally neglected, should now be considered important again. As yet, the scenarios emerging from the experimental data described here, and the true possibilities of developing new therapies from this knowledge, are not easy to fully understandand. However, a few take home messages (see also **TABLES 1** and **2**) can still be taken from the reviewed data.

Table 2. *Some promising therapeutic effects of endocannabinoid system modulators and phytocannabinoids in animal models of pathological conditions*

Organ	Disorder	CB1 Activators (Either "Direct" or, When Indicated, "Indirect", e.g., Inhibitors of Endocannabinoid Inactivation)	CB1 Blockers (Neutral Antagonists or Inverse Agonists or, When Indicated, Inhibitors of Endocannabinoid Biosynthesis)	CB2 Activators (Either "Direct" or, When Indicated, "Indirect", e.g., Inhibitors of Endocannabinoid Inactivation)	CB2 Blockers (Neutral Antagonists or Inverse Agonists or, When Indicated, Inhibitors of Endocannabinoid Biosynthesis)	Phytocannabinoids (mechanisms and molecular targets possibly involved)	Reference Nos.
CNS	Epilepsy	FAAH or MAGL inhibitors				CBD, CBDV (TRPV1, ↓inflammation, GPR55?)	346, 353, 377, 407
	Schizophrenia	FAAH inhibitors	Antagonists or inverse agonists			CBD (FAAH, TRPV1), THCV (CB1, 5-HT_{1A})	5, 125, 243, 313, 423, 427, 472, 883, 945, 946
	Stroke/ischemia	Agonists; FAAH or MAGL inhibitors		Agonists; FAAH or MAGL inhibitors		CBD (CB2, 5-HT_{1A}, ENT, ↓inflammation)	13, 126, 233, 241, 255, 300, 325, 333, 402, 572, 658, 659, 663, 667, 815, 873, 896, 940
	MS	Agonists and FAAH or MAGL inhibitors (for spasticity)		Agonists; FAAH or MAGL inhibitors (neuroinflammatory component)	Inverse agonists (late)	Sativex (multi-target)	31, 32, 60, 131, 528, 693, 694, 909
	AD	FAAH inhibitors (early); MAGL inhibitors (because of ↓eicosanoids)	Antagonists or inverse agonists (late)	Agonists		CBD (PPARγ?)	23, 61, 138, 139, 248, 484, 534, 546, 685, 717, 783
	PD	FAAH inhibitors; MAGL inhibitors (because of ↓eicosanoids)	Antagonists or inverse agonists (also on levodopa-induced dyskinesia)	Agonists		CBD (antioxidant) Δ^9-THCV (CB1)	283, 284, 298, 630, 853, 868
	HD	Agonists				CBG (PPARγ?) Sativex (multi-target)	81, 82, 141, 292, 456, 622, 649, 766, 767, 863, 865
	ALS	FAAH inhibitors		Agonists			245, 431, 751, 792, 932
	Anxiety/fear	FAAH or MAGL inhibitors				CBD (5-HT_{1A})	11, 65, 79, 112, 180, 266, 295, 297, 350, 397, 426, 529, 724, 782, 793, 807, 885, 938, 941, 942
	Addiction (including hyperphagia)	FAAH or MAGL inhibitors (for some of the consequences of withdrawal)	Antagonists or inverse agonists; DAGLα inhibitors (for hyperphagia in obesity or binge eating)	Agonists (?)		Δ^9-THCV (CB1)	153, 154, 167, 219, 374, 388, 435, 441, 716, 811, 812, 858, 906, 934
	Neuropathic pain	Agonists; FAAH or MAGL inhibitors	Inverse agonists (for the inflammatory component)	Agonists; FAAH or MAGL inhibitors	Inverse agonists (for the inflammatory component)	CBD (TRPV1, 5-HT_{1A}, ↓inflammation, ENT, glycine receptors), CBC (through multi-target effects on descending antinociception) Sativex (multi-target)	86, 149, 162, 286, 349, 404, 433, 453, 519, 524, 690, 704, 739, 813, 817, 907, 925, 926

Continued

Table 2.—*Continued*

Organ	Disorder	CB1 Activators (Either "Direct" or, When Indicated, "Indirect", e.g., Inhibitors of Endocannabinoid Inactivation)	CB1 Blockers (Neutral Antagonists or Inverse Agonists or, When Indicated, Inhibitors of Endocannabinoid Biosynthesis)	CB2 Activators (Either "Direct" or, When Indicated, "Indirect", e.g., Inhibitors of Endocannabinoid Inactivation)	CB2 Blockers (Neutral Antagonists or Inverse Agonists or, When Indicated, Inhibitors of Endocannabinoid Biosynthesis)	Phytocannabinoids (mechanisms and molecular targets possibly involved)	Reference Nos.
Liver	Alcoholic and/or nonalcholic steatosis, fibrosis, cirrhosis		Antagonists or inverse agonists, better if peripherally restricted	Agonists		Δ^9-THCV, CBD (multi-target)	48, 229, 314, 399, 412, 493, 525, 574, 608, 851
	Regeneration	Agonists					595, 686, 850
Cardiovascular system	Hypertension	Agonists; FAAH inhibitors	Antagonists or inverse agonists (when hypotension is due to septic and hemorrhagic shock)				212, 216, 296, 599, 705, 707, 711, 777, 802, 871
	Atherosclerotic inflammation and plaque vulnerability		Antagonists or inverse agonists	Agonists; MAGL inhibitors			365, 575, 579, 581, 583, 629, 708, 710, 828, 890
	Cardiopathies (e.g., diabetic)		Antagonists or inverse agonists, better if peripherally restricted	Agonists		CBD ($\downarrow$ ROS, $\downarrow$ NF-κB)	233, 255, 451, 468, 582, 815, 896
Kidney	Diabetic or cisplatin-induced nephropathy, fibrosis		Antagonists or inverse agonists, better if peripherally restricted	Agonists		CBD ($\downarrow$ inflammation)	41–43, 370, 390, 395, 410, 462, 480, 481, 597–599, 616, 944
Gut	Inflammatory bowel disease	Agonists; FAAH or MAGL inhibitors		Agonists		CBD (multiple targets), CBG (CB2, $\downarrow$ NO)	171, 172, 264, 433, 824
	Constipation (e.g., paralytic ileus)		Antagonists or inverse agonists; DAGLα inhibitors				538
	Diarrhea	Agonists; FAAH or MAGL inhibitors				Δ^9-THC (CB1)	46, 47, 135, 232, 387, 615
Skin	Fibrosis			Agonists			461, 530, 651
	Allergic dermatitis	Agonists; FAAH inhibitors			Inverse agonists		277, 424, 571, 639, 829
	Acne, seborrhea				Antagonists or inverse agonists	CBD (TRPV4, ENT)	70, 228, 640
Bone	Osteoporosis		Antagonists or inverse agonists	Agonists		CBD ($\downarrow$ GPR55)	27, 362, 379–381, 443, 617, 745, 748, 769, 780, 784, 804, 805, 810, 834, 844, 845, 914
Cancer	Glioma	Agonists		Agonists		Δ^9-THC (CB1, CB2), CBD (various)	83, 280, 768, 800, 857, 915
	Breast	Agonists		Agonists		Δ^9-THC (CB1, CB2), CBD (Ca^{2+}, ROS, etc.)	108, 238, 547, 610
	Prostate	Agonists				Δ^9-THC (CB1, CB2), CBD, CBG (Ca^{2+}, ROS, TRPM8, etc.)	91, 194

Continued

Table 2.—*Continued*

Organ	Disorder	CB1 Activators (Either "Direct" or, When Indicated, "Indirect", e.g., Inhibitors of Endocannabinoid Inactivation)	CB1 Blockers (Neutral Antagonists or Inverse Agonists or, When Indicated, Inhibitors of Endocannabinoid Biosynthesis)	CB2 Activators (Either "Direct" or, When Indicated, "Indirect", e.g., Inhibitors of Endocannabinoid Inactivation)	CB2 Blockers (Neutral Antagonists or Inverse Agonists or, When Indicated, Inhibitors of Endocannabinoid Biosynthesis)	Phytocannabinoids (mechanisms and molecular targets possibly involved)	Reference Nos.
	Colorectal	Agonists; FAAH or MAGL inhibitors				Δ^9-THC (CB1, CB2), CBD (various), CBG (various)	24, 306

See text for definitions.

Cannabis is not just Δ^9-THC, and hence "therapeutic cannabis" is a misleading concept, which should be developed through the understanding that several phytocannabinoids are likely to contribute to cannabis pharmacology and, hence, that completely different effects are likely to be produced depending on the plant variety and its preparation and administration route.

Because of the above, cannabis and phytocannabinoids do not only act on the ECS (in fact, only a minority of phytocannabinoids do) and, thus, it is possible to separate the unwanted effects of Δ^9-THC from the more manageable therapeutic options offered by other phytocannabinoids, also through the combination of the former with the latter compounds.

The physiological function of the ECS, and of endocannabinoids and CB1 and CB2 receptors in particular, is that of a pleiotropic prohomeostatic signaling system, which, in almost all mammalian tissues, acts to restore the physiological steady state after its acute or chronic perturbations. This role is also witnessed by the plethora of conventional and nonconventional therapies that have been reported to modify endocannabinoid tone (*557*). As a consequence, it should not be surprising to see that *1*) activation of CB1 or CB2 often produces biphasic or even opposing effects on a given physiological response depending on the "starting" state of the system; *2*) tissue endocannabinoid levels also often change in a biphasic manner during some prolonged pathological deviations from the physiological steady state; *3*) pharmacological manipulation of either CB1/CB2 activity or endocannabinoid levels through inhibition of biosynthetic or inactivating mechanisms might either help restore homeostasis or exacerbate the effects of the perturbation, depending on where (what cell) and when (what disease stage) it is effected; and *4*) even in those cases in which endocannabinoids always play a protective role throughout disease progression, the multiplicity of their molecular targets and metabolic pathways (the latter of which are often in common with other mediators acting at other targets), makes it difficult to globally acting CB1/CB2 agonists/antagonists, or selective inhibitors of endocannabinoid degradation or biosynthesis, to produce safe and efficacious therapeutic effects. In other words, if one looks at conventional strategies that the pharmaceutical industry has used to develop drugs in recent years, one immediately understands that these cannot be easily applied to the ECS.

However, the increasing understanding of ECS complexity provides us with the basis for the development of potentially even safer and more efficacious drugs. As an example, at least assuming that what we see in animal models also applies to the clinc, one should only remember how a dual CB1 antagonist/CB2 agonist might be efficacious for the late phase of some neurodegenerative disorders (AD, PD) or, especially if rendered non-brain-penetrant, for meta-

bolic, liver, and kidney disorders. Likewise, dual FAAH/TRPV1 or FAAH/COX-2 blockers should be safer and more efficacious than the corresponding single-target drugs against inflammatory and neuropathic pain, whereas dual CB1/CB2 agonists with antagonist activity at GPR55 could be useful for cancer, and so on and so forth.

Interestingly, we know that, although polypharmacology is already widely applied for the treatment of several multifactorial disorders, and efficacious synthetic multitarget compounds can be designed, some of these drugs are already found in nature, in both the cannabis plant (such as CBD, Δ^9-THCV, etc.) and mammalian tissues (for example, the several multitarget long-chain and endocannabinoid-related fatty amides mentioned in this article, but also glucocorticoids or shRNAs directed against cascades of several inflammatory signals).

In summary, phytocannabinoids and the ECS are very complex, but in view of the enormous opportunities that they have offered and still offer to understand human physiology, and hence to treat its pathological deviations, one should not give up trying to develop new therapies from them.

NOTE ADDED IN PROOF

The identification of the *N*-acyltransferase responsible for the calcium-dependent biosynthesis of NAPEs has been reported during the publication process of this article (Ogura Y, Parsons WH, Kamat SS, Cravatt BF. A calcium-dependent acyltransferase that produces *N*-acyl phosphatidylethanolamines. *Nat Chem Biol* 12: 669–671, 2016).

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DISCLOSURES

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