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Cannabinoids as Therapeutic Agents for Ablating Neuroinflammatory Disease

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Abstract

Cannabinoids have been reported to alter the activities of immune cells *in vitro* and *in vivo*. These compounds may serve as ideal agents for adjunct treatment of pathological processes that have a neuroinflammatory component. As highly lipophilic molecules, they readily access the brain. Furthermore, they have relatively low toxicity and can be engineered to selectively target cannabinoid receptors. To date, two cannabinoid receptors have been identified, characterized and designated CB_1 and CB_2. CB_1 appears to be constitutively expressed within the CNS while CB_2 apparently is induced during inflammation. The inducible nature of CB_2 extends to microglia, the resident macrophages of the brain that play a critical role during early stages of inflammation in that compartment. Thus, the cannabinoid-cannabinoid receptor system may prove therapeutically manageable in ablating neuropathogenic disorders such as Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, HIV encephalitis, closed head injury, and granulomatous amebic encephalitis.

Keywords

Alzheimer's; amyotrophic lateral sclerosis; cannabinoids; cannabinoid receptors; granulomatous amebic encephalitis; HIV encephalitis; multiple sclerosis; neuroinflammation

INTRODUCTION

The marijuana plant, *Cannabis sativa*, has been consumed therapeutically and recreationally for centuries because of its medicinal and psychotropic attributes. *Cannabis* contains a complex array of substances, including a group of terpenoid-like, highly lipophilic compounds referred to as cannabinoids. To date, over 60 cannabinoids have been identified from the marijuana plant. Cannabinoids account for the majority of the effects attributed to marijuana that users experience, including euphoria, impaired perception and memory, and mild sedation. While cannabinoids have been used to abolish loss of appetite and to ablate nausea and pain in patients suffering from severe medical disorders, these compounds also possess immune modulatory properties that may prove detrimental to human health. However, accumulating evidence suggests that cannabinoids also may serve as therapeutic agents in neuropathogenic diseases, pathologically hallmarked by elicitation of pro-inflammatory factors by cells of the central nervous system (CNS) and infiltrated peripheral immunocytes. Cannabinoids have the potential to be ideal therapeutic candidates in abolishing inflammatory neuropathies in that they can readily penetrate the blood brain barrier (BBB) to access the brain, have low levels

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of toxicity, and can specifically exert their effects through cannabinoid receptors. The major cannabinoid receptor type that appears to be targeted in neuroinflammation is cannabinoid receptor 2 (CB_2). This receptor has been identified in select cells of the CNS, can be induced on demand during early inflammatory events, and has been shown to attenuate pro-inflammatory cytokine production by microglia, the resident macrophages of the brain that play a central role in many neuropathological processes.

In the present review the immune modulatory properties of cannabinoids, including their relation to interaction with cannabinoid receptors as linked to inflammatory neuropathies will be discussed. Included in this review will be an overview of the signal transduction cascades associated with cannabinoid receptors, and the effects of cannabinoid receptor signaling on immune cell function and immunity, and more importantly in the CNS. These discussions will lay the groundwork for the critical element of this review, in which we explore the potential of cannabinoid receptors to serve as therapeutic targets to attenuate the elicitation of pro-inflammatory mediators during neuropathogenic diseases and disorders such as Alzheimer's disease (AD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS), HIV Encephalitis (HIVE), Closed Head Injury (CHI) and Granulomatous Amebic Encephalitis (GAE).

CANNABINOIDS AND CANNABINOID RECEPTORS

Exogenous Cannabinoids

The term "exogenous cannabinoid" has been applied to cannabinoids that are extracted from the cannabis plant or synthesized in the laboratory. Delta-9-tetrahydrocannabinol (THC), cannabinol (CBN), and cannabidiol (CBD) have been the most prevalent and studied cannabinoids found in *Cannabis sativa* (Fig. (1)). THC, the major psychoactive component of marijuana, also is its major immunomodulatory constituent and exerts primarily immunosuppressive effects. The purification and structural characterization of THC [1] led to the chemical synthesis of cannabinoid analogs that have been employed in structure-activity studies to characterize cannabinoid-mediated effects and define the mechanism by which these effects are elicited. Some of the synthetic cannabinoids that have been widely used include CP55940, HU-210, WIN55212, JWH-015, and ACEA (Fig. (1)). The use of naturally occurring exogenous cannabinoids such as THC, as well as synthetic compounds exemplified by CP55940, has been instrumental in identification of specific binding sites in mammalian brain and peripheral non-neuronal tissues [2,3]. These specific binding sites have been identified as representing cannabinoid receptors.

Endogenous Cannabinoids

"Endogenous cannabinoids" are constituent elements of an endocannabinoid system that encompasses cannabinoid receptors, their endogenous ligands or endocannabinoids, and the mediators responsible for their synthesis, metabolism and catabolism. Endocannabinoids (Fig. (2)) are hydrophobic lipid messengers that are derivative of integral components of the phospholipid bilayers of cellular membranes. The hydrophobicity of endocannabinoids prevents these compounds from translocating unassisted in aqueous cellular environments; therefore, these signaling molecules upon release activate cannabinoid receptors locally or on nearby cells. Endocannabinoids act as neurotransmitters, but unlike other neurotransmitters such as acetylcholine and dopamine, are not presynthesized and stored in vesicles, but are produced "on demand". The first endocannabinoid, arachidonoylethanolamide (AEA; anandamide) was isolated from porcine brain [4]. Chemically, anandamide is the amide constituent of arachidonic acid and ethanolamine and pharmacologically, binds receptors in the brain and at peripheral sites. A second endocannabinoid was isolated from canine gut and identified as 2-arachidonoylglycerol (2-AG) [5]. 2-AG has been found to be the most bioactive

and abundant endocannabinoid in the brain, with concentrations reported as considerably higher than those of anandamide [6,7]. The uptake and degradation of anandamide and 2-AG is rapid, a feature that is characteristic of neurotransmitters. One process by which anandamide is synthesized involves the hydrolytic cleavage of N-arachidonoylyl phosphatidylethanolamine (NAPE) by phospholipase-D (PLD) in a calcium-dependent manner [8–11] an enzyme that hydrolyzes the lipid oleamide in rat liver also has been shown to possess anandamide hydrolase activity in substrate selectivity experiments and has been designated fatty acid amide hydrolase (FAAH) because of its hydrolytic activity on the fatty acids anandamide and oleamide [12, 13]. Anandamide apparently is transported across the plasma membrane before it is degraded, and FAAH has been proposed as mediating its transport in addition to its degradation. FAAH also has been reported to catalyze the hydrolysis of 2-AG [14–16]. It has been proposed that 2-AG is synthesized by the hydrolysis of 1, 2-diacylglycerol (DAG) or 2-arachidonoyl-lysophospholipid by DAG lipase or lyso-phospholipase (PLC), respectively [6,17]. 2-AG also is apparently transported across the plasma membrane before it is degraded by FAAH, or the serine hydrolase, monoacylglycerol lipase (MGL).

Cannabinoid Receptors

The pharmacological evidence that a cannabinoid receptor existed in the brain was provided through studies that indicated that treatment of neuroblastoma cells with THC, or with levonantradol and desacetyllevonantradol, resulted in inhibition of the plasma membrane activity of adenylate cyclase, the enzyme that catalyzes the conversion of ATP to 3′,5′-cyclic AMP (cAMP) and pyrophosphate [18,19]. Specific antagonists to opiate, adrenergic and cholinergic receptors did not block the cannabinoid-mediated inhibition of adenylate cyclase activity. Furthermore, the inhibitory effect was stereoselective since dextronantradol did not produce a response, and was specific for psychoactive cannabinoids since CBN and CBD produced minimal or no response, features that could be attributed to the existence of a novel receptor. That this receptor required a guanine nucleotide binding complex, G_i, for its action was demonstrated through studies that revealed that the inhibitory effect on adenylate cyclase was sensitive to treatment with pertussis toxin (PTX) [20], a protein-based AB_5-type exotoxin produced by the bacterium *Bordetella pertussis* that catalyzes adenosine diphosphate (ADP)-ribosylation. Subsequent studies in which radiolabeled CP55940 was used allowed for the identification of specific ligand binding sites in rat brain [21].

The first cannabinoid receptor that was isolated was cloned from a rat brain complementary DNA (cDNA) library [2]. The cDNA encoded a 473 amino acid long, 7-transmembrane G-protein coupled receptor (Fig. (3)), which exhibited physiological properties consistent with those reported previously [19,20], such as its negative coupling to adenylate cyclase. Studies using radioligand binding assay and *in situ* mRNA hybridization demonstrated that the receptor was distributed throughout the brain and localized predominantly in the cerebellum, cerebral cortex, hippocampus, basal ganglia and spinal cord [2,22,23]. Immunocytochemistry using specific antibodies has revealed a similar pattern of distribution (Fig. (4)). Originally, referred to as the “neuronal” cannabinoid receptor, it has subsequently been designated CB_1. The cloning of rat CB_1, was followed by that of human CB_1 which yielded a sequence that encoded a protein of 472 amino acids in length which, while localized primarily to brain, was found also in testis [24]. Mouse CB_1 also has been cloned, sequenced and reported to share a 99% and 97% amino acid identity, respectively, to rat and human CB_1 [25,26].

A second, or “peripheral”, cannabinoid receptor was cloned from a human promyelocytic cell line (HL60) cDNA library [3]. The gene for this receptor, since designated CB_2, encoded for a 360 amino acid long, 7-transmembrane G-protein coupled receptor. This receptor, comparable to CB_1, was found to have an extracellular, glycosylated N-terminus and an intracellular C-terminus (Fig. (3)). Genes encoding CB_2 in mouse and rat also have been cloned,

and have been identified as coding for proteins of 347 and 410 amino acids, respectively [3, 27,28]. The amino acid sequence of CB_2 is not highly conserved among mammalian species as compared with that for CB_1 and shares only 44% amino acid identity with human CB_1. An additional distinctive feature of CB_2 is that its distribution is predominantly in cells and tissues of the immune system including thymus, tonsils and blood mononuclear cells. B lymphocytes, macrophages, monocytes, natural killer (NK) cells, and polymorphonuclear cells express CB_2, with B lymphocytes and T lymphocytes expressing the most and least amounts of CB_2, respectively [29,30]. Recent reports indicate that CB_2 is expressed also within the CNS and that this expression occurs during various states of inflammation [31–34].

There is increasing evidence that additional cannabinoid receptors exist. Much of this evidence has been obtained through *in vivo* studies in which CB_1 knockout or CB_1/CB_2 double-knockout mice have been used to investigate the pharmacology and pharmacokinetics of THC, anandamide, and cannabinoid analogs. However, a novel cannabinoid receptor that meets rigid criteria pharmacologically and functionally has yet to be cloned and characterized at the molecular level [35–38].

CANNABINOID RECEPTOR SIGNALING

CB_1 and CB_2, as G-protein coupled receptors, are involved in regulating signaling cascades which include adenylate cyclase and cAMP, mitogen-activated protein (MAP) kinase, and modulation of intracellular calcium levels. Upon binding of cannabinoids to CB_1, the receptor-coupled G protein exchanges the guanine nucleotide GDP for its active form GTP and the heterotrimeric G-protein dissociates into the α and βγ subunits. The βγ subunits are believed to take part in signaling pathways distinctive from those of the α subunit; for example, regulation of phospholipase C (PLC) isoforms and activation of the mitogen-activated protein kinase (MAPK) signaling network [39]. The α subunit binds to adenylate cyclase and renders this enzyme inactive thereby preventing synthesis of the second messenger cAMP and negatively affecting downstream signaling events that require cAMP. The activation of protein kinase A (PKA) requires that cAMP bind to the regulatory subunit of PKA, releasing its catalytic subunits, and allowing phosphorylation events to occur. One of these events is the phosphorylation of A-type potassium channels, which are down-regulated or inhibited upon phosphorylation. It has been reported that inhibition of neurotransmitter release by CB_1 may be caused by continuous potassium currents of unphosphorylated A-type potassium channels [39,40]. CB_1 also inhibits neurotransmitter release through inhibition of N-type calcium channels, in which calcium channel proteins are directly affected by the inhibitory G protein ($G_{i/o}$). The CB_1-mediated regulation of neurotransmitter release by way of potassium and calcium channels takes place within seconds of receptor activation, and this restriction of neurotransmission accounts for cognitive impairment and sedative-like effects experienced by marijuana users. However, longer activation of CB_1 induces immediate early gene expression of proteins that may be involved in neuroprotection, for example, the brain-derived neurotrophic factor (BDNF) that counteracts cell damage [40,41].

While the CB_1 is negatively linked to the cAMP network, its activation is positively linked to the MAPK network which plays a key role in cellular functions such as cell growth and apoptosis. For example, CB_1-expressing human astrocytoma cells treated with HU-210 and CP55940 exhibit activated p42/p44 MAP kinase [42]. This kinase complex, also referred to respectively as extracellular signal-regulated kinase (ERK) 1 and 2, is a key mediator of the MAPK signaling cascade from cell surface to nucleus. In rat and murine hippocampus, the exogenous cannabinoids CP55940 and WIN55212-2 and the endocannabinoids anandamide and 2-AG induced activity of another MAP kinase, p38, which is a stress-activated kinase responsible for the phosphorylation of other kinases in the MAPK cascade [40,42]. The activation of p42/p44 and p38 was reversed by PTX and the CB_1-specific antagonist

SR141716A, suggesting a functional linkage to CB_1. In addition, CB_1-mediated MAPK signaling has been reported to induce BDNF, a protein that promotes survival of neurons in the CNS and encourages the growth and differentiation of new neurons and synapses and other immediate-early genes that play a role in synapse plasticity [41].

CB_2 receptor signaling also regulates adenylate cyclase activity, cAMP synthesis, MAPK signaling and intracellular calcium levels [40,43–46]. As a decrease in cAMP production underlies a mechanism in which CB_1 prevents neurotransmitter release and maintains the homeostatic integrity of the CNS, decreased cAMP production also may represent a mode by which CB_2 signaling in response to endogenous cannabinoids maintains immunological homeostasis.

CANNABINOID EFFECTS ON IMMUNITY

Endogenous and exogenous cannabinoids may exert disparate effects on immune cells. Endocannabinoids as native compounds appear to elicit localized effects that are relatively short-lived and stimulatory in nature. For example, 2-AG has been reported to serve as a chemoattractant to myeloid leukemia cells, splenocytes, and microglia [47–49]. This endocannabinoid has been shown to induce directed migration (chemotaxis) as well as random cellular motion (chemokinesis) on the part of microglia [50]. On the other hand, there is some evidence that relatively stable analogs of endocannabinoids, such as 2-methylarachidonyl-(2′-fluoroethyl) amide (F-Me-AEA) can suppress immune responses as exemplified by the inhibition of T lymphocyte functions [51].

In contrast to endocannabinoids, exogenous cannabinoids exert effects on immune cells that appear to be more generalized in nature, to persist for a relatively longer period of time, and to be suppressive [52]. THC, CP55940 and HU-210 have been shown to abolish cell contact-dependent cytolysis of tumor cells by macrophages and macrophage-like cells, to inhibit the processing of antigens by macrophages, and to suppress proliferation of B lymphocytes and T lymphocytes [53–56]. THC also has been reported to inhibit the proliferation of cytotoxic T lymphocytes (CTLs) and their maturation into mature CTLs and to suppress the cytolytic activity of NK cells [53]. In addition, exogenous cannabinoids have been shown to affect the elicitation of cytokines and chemokines, promoting a switch in an expression profile from that of a pro-inflammatory Th_1 phenotype to that of an anti-inflammatory Th_2 phenotype [57–62]. And, in contrast to the endocannabinoid 2-AG, exogenous cannabinoids such as THC and CP55940 have been reported to inhibit immune cell recruitment and migration [63,64].

The CB_2 appears to be the receptor that is linked functionally to the majority of cannabinoid-receptor mediated effects on immune cells, including those that are native to the CNS. This linkage is predicated not only on the basis that the CB_2 is localized predominantly to cells of the immune system [3,29], but also on the outcome of studies in which receptor-selective agonists [64], receptor-specific antagonists [64,65] and cannabinoid receptor knockout mice [64,66] have been used. In addition, treatment of macrophages from wild type mice with THC has been reported to prevent the activation of helper T cells, while THC treatment of macrophages from CB_2 knockout mice had little effect [66]. This functionally-relevant role for CB_2 appears to apply particularly to macrophages and macrophage-like cells in which this receptor is inducible and is present at high levels during the pro-inflammatory stage of responsiveness [67,68]. Studies using receptor type-specific antibodies have revealed CB_2 as localized to lamellipodia of activated microglia [50], suggesting that this receptor may play a critical role in directed cellular migration. These observations are consistent with those that indicated that 2-AG-induced migration of microglia was prevented by antagonizing CB_2 with the exogenous cannabinoid CBN [50].

CANNABINOIDS, NEUROPATHOGENESIS, AND INFLAMMATORY DISEASES OF THE CNS

Cannabinoids and Neuropathogenesis

The CB_1 and CB_2 have been implicated in a number of neuropathogenic processes in experimental animals and humans. However, the cannabinoid receptor type that is linked to an inflammatory response within the CNS appears to be CB_2. Microglia apparently act as the major expressers of this receptor during early stages of neuroinflammation. As resident macrophages in the CNS [69–74], they migrate and proliferate during and after injury and inflammation [75–78], phagocytose and process antigens, and once activated produce pro-inflammatory factors including the cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) α [78,79]. Pro-inflammatory mediators released from microglia not only are exocytotoxic, but also can secondarily activate astrocytes leading to a further induction of the expression of inflammatory factors. Paradoxically, microglia not only play a role in host defense and tissue repair in the CNS [69,80], but also have been implicated as contributing to nervous system disorders such as Mutiple Sclerosis (MS) [70,81–85]. This deleterious role of microglia is exacerbated as inflammatory factors that are elicited from microglia and astrocytes contribute to breakdown of the BBB and play a critical role in the influx into the CNS of immunocytes from peripheral non-neuronal sites that also express CB_2.

In vitro and *in vivo* studies have shown that cannabinoids can act on glia and neurons to inhibit the release of pro-inflammatory cytokines [60,61,86–92] and enhance the release of anti-inflammatory factors such as the cytokines IL-4 and IL-10 [93]. These observations suggest that these cannabinoids, as lipophilic molecules, can readily access the CNS and have the potential to ablate a variety of neuropathological processes that are associated with pro-inflammatory states. There also is accumulating evidence that expression of CB_2 is up-regulated *in vitro* by microglia and other immune cells in response to immune modulators [67] and *in vivo* during states of chronic neuroinflammation [68,94–97]. These results suggest that during inflammation a higher number of molecular targets may be available that may be amenable to manipulation for dampening an overexpressed immune response. Thus, through the use of CB_2-selective agonists it may be possible to target specific cell types such as microglia that are associated with inflammatory processes in the brain. Furthermore, such therapeutic manipulation may be applied under conditions of relatively low toxicity and devoid of psychotropic effects that could be engendered through activation of CB_1.

Amyotrophic Lateral Sclerosis (ALS)

ALS is a chronic neuromuscular disease that is characterized pathologically by progressive degeneration of cortical motor neurons (upper motor neurons) and clinically by muscle wasting, weakness, and spasticity that progresses to complete paralysis [98]. This adult-onset disease occurs in both sporadic and familial forms. The familial ALS (FALS) form is inherited as an autosomal dominant trait and accounts for 5% to 10% of cases of ALS. FALS has been linked to mutations in the superoxide dismutase 1 (SOD1) gene that codes for a zinc and copper binding enzyme which neutralizes supercharged oxygen molecule (superoxide radical) byproducts of normal cellular metabolism. One mode involved in ALS pathology is neuroinflammmation that is mediated by pro-inflammatory cytokines, prostaglandins, and nitric oxide (NO). A widely accepted animal model of FALS is the mutant SOD1 transgenic (i.e., $SOD1^{G93A}$) mouse that develops clinical symptoms similar to those observed for humans with ALS. It has been reported that CBN delays onset of symptoms in these mice without affecting survival [99]. More recently, The CB_2 agonist AM-1241 has been reported as contributing to prolonged survival of SOD1 mutant mice [100,101]. In addition, treatment with non-selective cannabinoid partial agonists prior to, or upon, the appearance of symptoms of ALS was shown to delay disease progression and promote prolonged survival of mice [101].

CB_2 was further implicated as linked to the prolonged survival in that levels of cognate mRNA and of receptor binding were up-regulated in a temporal pattern in spinal cords of the mutant mice in a mode that paralleled disease progression. In contrast, those for CB_1 were unaffected.

It has been demonstrated also that levels of endocannabinoids are affected in experimental ALS. The amount of anandamide and 2-AG, endocannabinoids that have been implicated in playing a neuroprotective role, increased in the spinal cord of SOD1 transgenic mice [102]. Anandamide and 2-AG not only are upregulated with disease progression, but also postsymptomatic treatment with WIN55212 resulted in a delay in disease progression [103].

Alzheimer's Disease (AD)

AD is the most common neurodegenerative disorder that causes senile dementia. The series of events that leads to AD is poorly understood and insights into its pathogenesis have been obtained primarily from assessment of human brain tissue at autopsy. Neurodegeneration in AD affects multiple neurotransmitter systems, including those of specific cholinergic, noradrenergic, serotonergeic, GABAergic, and glutamatergic neurons. The defining neuropathologic features of the disease are the presence of extracellular neuritic amyloid plaques and intracellular neurofibrillary tangles (NFTs) in the brain. The appearance of these stigmata is accompanied by synaptic and neuronal loss and gliosis in the cerebral cortex and the limbic system. The amyloid plaques consist of extracellular aggregates of amyloid β (Aβ) peptides [104–106] that often are surrounded by activated microglia and astrocytes. The NFTs consist of intraneuronal aggregates of paired-helical filaments that usually are composed of hyperphosphorylated microtubule-associated protein tau [107,108]. As neurodegeneration progresses there is accelerated neurofibrillary tangle formation, neuroinflammation, and neuronal loss. The three major animal models of AD that have been developed duplicate, at least in part, the neuropathology and cognitive and behavioral impairments associated with the disease. These consist of a cholinergic deficit model in which the nonselective antagonists of muscarinic receptors scopolamine and atropine are used to mimic a cholinergic deficit, a brain Aβ infusion model in which diverse Aβ fragments are introduced by intracranial injection, and an Aβ precursor protein (APP) transgenic mouse model in which APP is expressed in the brain [109].

Alterations in components of the cannabinoid system have been observed in brains of Alzheimer's patients, suggesting that this system contributes to, or is altered by, the disease. Assessment of normal aged and Alzheimer's human brains has revealed that, compared to normal brains, [^{3}H]CP-55940 binding was reduced in the hippocampal formation, caudate, substantia nigra, and globus pallidus [110]. However, in these studies levels of cannabinoid receptor mRNA did not differ for Alzheimer's versus those for control brains. Furthermore, the reductions in ligand binding did not correlate with, or localize to, areas of neuritic plaques and neurofibrillary tangles. It was suggested that the losses in cannabinoid receptors, while related to generalized aging and/or the disease process, were not selectively associated with the pathology characteristic of AD. On the other hand, CB_2 and FAAH have been reported to be selectively over-expressed in neuritic plaque-associated glia in AD brains [111].

Immunohistochemical staining of hippocampus and entorhinal cortex sections demonstrated that both FAAH and CB_2 were abundantly and selectively expressed in neuritic plaque-associated astrocytes and microglia. The expression of both CB_1 and CB_2 has been assessed in plaques in rat brain in the context of markers of microglial activation [112]. The number of CB_1-positive neurons was found to be greatly reduced in areas that contained activated microglia. Intracerebroventricular administration of WIN55212-2 prevented Aβ-induced activation of microglia, cognitive impairment, and loss of neuronal markers. In addition, treatment of microglia *in vitro* with HU-210, WIN55212-2, and JWH-133 resulted in blockage of their activation by Aβ peptide and abrogated neurotoxicity mediated by these cells. These

results are consistent with those that indicated that WIN-55212-2 exerted anti-inflammatory properties in a model of chronic brain inflammation produced by infusion of bacterial lipopolysaccharide (LPS) into the fourth ventricle of young rats [113]. In these studies, administration of 0.5 mg/kg and 1 mg/kg WIN-55212-2 reduced the number of LPS-activated microglia. WIN-55212-2 at 1 mg/kg also potentiated LPS-induced impairment of spatial memory as assessed using the water maze task. However, CB_1 was not identified on microglia and astrocytes. Thus, it was suggested that WIN-55212-2 exerted an indirect effect on activation of microglia and impairment of memory. On the other hand, it has been reported that stimulation of CB_2 results in suppression of inflammatory mediators such as NO, cytokines, and chemokines that play a role in microglial cell-associated neuronal damage [114]. Selective stimulation of CB_2 by JWH-015 resulted in suppression of IFNγ-induced expression of CD40, a co-stimulatory protein found on antigen-presenting cells (i.e., B lymphocytes, monocytes, and dendritic cells) that binds to CD154 (CD40L) on T lymphocytes resulting in their activation. In addition, this CB_2-selective agonist inhibited IFN-γ-induced phosphorylation of Janus kinase/Signal Transducers and Activators of Transcription (JAK/STAT1) and suppressed production of TNF-α and NO by microglia that was induced by IFN-γ or by Aβ peptide challenge in the presence of CD40 ligation. Furthermore, activation of CB_2 by JWH-015 attenuated CD40-mediated inhibition of phagocytosis of Aβ1-42 peptide by microglia.

Closed Head Injury (CHI)

Traumatic brain injury triggers a cascade of events that results in delayed edema, necrosis and impaired function. A plethora of mediators, including cytokines, accumulate in the brain after injury have been linked to the pathophysiology of brain injury. The synthetic, nonpsychotropic cannabinoid HU-211 (Dexanabinol), which acts as a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, was found to be effective in improving motor function recovery in a model of CHI in rats [115]. The drug also was found to be effective in reducing BBB breakdown and attenuating cerebral edema. It was suggested that the ability of HU-211 to exert its neuroprotective effect involved attenuation of Ca^{2+} fluxes through NMDA receptor-mediated calcium channels and reduction of depolarization evoked Ca^{2+} fluxes [116]. These neuroprotective effects of HU-211 have been confirmed not only for the animal model of CHI, but also for animal models of optic nerve crush, global ischemia and focal ischemia [117]. In addition, HU-211 has been shown to be a potent scavenger of peroxy and hydroxy radicals *in vitro* and to protect cultured neurons from toxicity of radical generators. It was indicated that HU-211 was unique among putative neuroprotective agents since it combined NMDA blocking activity and free radical scavenging properties [86]. HU-211 also has been reported to act as an inhibitor of TNF-α production at a post-transcriptional stage [86]. Because this cannabinoid, as well as pentoxyfilline and TNF-binding protein, improved the outcome of CHI, it was suggested that TNF-α acted as a primary mediator of neurotoxicity after traumatic brain injury. In a randomized, placebo-controlled, multicenter phase II clinical trial to establish the safety of intravenous dexanabinol in severe head injury, HU-211 was reported as safe and well tolerated in severe head injury [118]. Furthermore, treated patients achieved significantly better intracranial pressure/cerebral perfusion pressure control without jeopardizing blood pressure and exhibited a trend toward faster and better neurologic outcome.

Endocannabinoids also have been reported to have a potential for exerting neuroprotective effects in CHI. 2-AG has been shown to be released in mouse brain after CHI [119]. Furthermore, treatment of CHI with exogenous 2-AG exerted a neuroprotective effect that was mediated through CB_1 [119] in a mode that implicated inhibition of inflammatory signals that are mediated by activation of the transcription factor Nuclear Factor of Kappa Light chain gene enhancer in B-cells (NF-κB). Additional studies designed to examine the effect of 2-AG on the BBB and to assess for early expression of pro-inflammatory cytokines, implicated in BBB

disruption, demonstrated that 2-AG decreased BBB permeability, inhibited the acute expression of the pro-inflammatory cytokines TNF-α, IL-1β and IL-6, and augmented levels of endogenous antioxidants [120]. These collective results suggested that 2-AG exerted neuroprotection in part by inhibition of the early inflammatory response and augmentation of brain reducing power. These observations are consistent with those obtained from studies that demonstrated that the exogenous cannabinoid HU210 exerted *in vivo* modulation of LPS-induced alterations in brain and peripheral pro-inflammatory cytokines and HPA axis activity [121]. However, the CB_1 antagonist, SR141716A, attenuated the immunosuppressive effects of HU210 on IL-1β, but not TNF-α. Furthermore, SR141716A or the CB_2 antagonist, SR144528, alone attenuated LPS-induced increases.

Granulomatous Amebic Encephalitis (GAE)

GAE is a brain infection in humans that is caused by opportunistic amebae of the genus *Acanthamoeba* [122,123]. Opportunistic amebae are free-living protozoa that are cosmopolitan in the environment and have the potential to be pathogenic, especially for individuals whose immune systems are compromised. Ameba trophozoites are thought to enter the brain by the olfactory route following the nerve pathway from the nasal mucosa to the olfactory bulb or by hematogenous spread from a primary site of infection such as a cutaneous lesion. Once in the brain, trophozoites may be destroyed by microglia. Alternatively, *Acanthamoeba* may cause a subacute infection that is characterized by encystment and establishment of a chronic disease state that is associated with formation of granulomas and production of pro-inflammatory cytokines. Using a mouse model of GAE, THC has been shown to elicit dose-related higher mortalities as compared to vehicle controls [124]. The greater severity of disease for THC-treated mice was accompanied by decreased accumulation of macrophage-like cells at focal sites of infection in the brain. Furthermore, exposure of neonatal rat microglia to THC resulted in production of decreased levels of mRNA for the pro-inflammatory cytokines IL-1α, IL-1β, and TNF-α in response to *Acanthamoeba*.

HIV Encephalitis (HIVE)

HIVE, also known as Acquired Immune Deficiency Syndrome (AIDS)-dementia complex, results in progressive memory loss, intellectual deterioration, behavioral changes, and motor deficits. Neuropathology is characterized by neuronal loss, glial activation, presence of multinucleated giant cells, perivascular mononuclear infiltration, and in some cases, vacuolar myelopathy and myelin pallor [85]. Brain damage due to this disorder is due primarily to pro-inflammatory cytokines such as TNF, neurotoxins such as glutamate and NO that are elicited from activated monocytes and microglia, and HIV-specified gene products such as the transactivator *tat* and the envelope glycoprotein gp120 that are released from infected monocytes and microglia. Insights into the inflammatory processes associated with HIVE have been obtained using a number of *in vitro* and animal model systems [125]. However, mouse and non-human primate models have proven the most useful in replicating the multiple aspects of pathology that are associated with HIV infection of the human CNS. Two major severe combined immunodeficiency (SCID) mouse models have been exploited in studies of HIV-induced neuropathogenesis. In the first model, second-trimester human fetal brain is inoculated into the anterior eye chamber, or fetal brain cells are injected into the intrascapular fat pad of SCID mice [126,127]. In both systems, a BBB develops and neurons, astrocytes, and microglia can be identified. Upon infection of xenografts by HIV-positive human monocytes, features of HIV encephalitis such as the presence of multinucleated giant cells, an increase in number of astrocytes, and a decrease in the number of neurons are observed [126]. In the second model, human peripheral blood mononuclear cells, in concert with cell-free HIV introduced at the same time or one day later, are injected intracerebrally into SCID mice [128]. Transgenic mouse models that express the complete HIV genome in neurons [129] and the HIV envelope glycoprotein gp120 in astrocytes [130] also have been developed and have provided insights

regarding the role of HIV proteins in neurotoxicity. The simian immunodeficiency model comes closest to replicating events that are associated with HIV infection of the human CNS but has disadvantages related to ethical issues of working with non-human primates, the limited availability of such animals, and the high cost of their maintenance. The simian immunodeficiency virus (SIV), when introduced into rhesus monkeys and macaques which are non-natural hosts, elicits an AIDS-like disease [131]. SIV-infected animals experience a pattern of disease that, although accelerated, is similar to that experienced by humans infected with HIV. At the CNS level, animals display features typical of HIV-infected humans that include infiltrates consisting of macrophages/monocytes containing viral antigens, nucleic acid, and virus particles [132] as well as multinucleated giant cells, microglia nodules, and astrocytes [132,133]]. And, as in the case of HIV-infected humans, SIV-infected macaques develop cognitive and motor disorders [134,135].

Examination of brains of macaques with SIV-induced encephalitis has lead to the suggestion that the endocannabinoid system participates in the development of HIV-induced encephalitis [136]. Expression of CB_2 was found to be induced in perivascular macrophages, microglial nodules, and T-lymphocytes. In addition, the endogenous cannabinoid-degrading enzyme FAAH was overexpressed in perivascular astrocytes as well as in astrocytic processes reaching cellular infiltrates. It was proposed that activation of CB_2 that is expressed by such immune cells likely results in reduction of their antiviral response and favors the entry of infected monocytes into the CNS. It also has been reported that activation of CB_2 results in inhibition of the transendothelial migration of Jurkat T cells and primary human T-lymphocytes by interfering with the CXCL12/CXCR4 chemokine receptor system [137]. These observations lead to the suggestion that activation of CB_2 can alter the activation of other G protein-coupled receptors, such as CXCR4 that functions as a co-receptor for T lymphotropic HIV. A similar observation in terms of a linkage to the CB_2 has been made for the chemokine receptor CCR5 that acts as the co-receptor for monotropic HIV [64]. Activation of CB_2 with THC, CP55940, or with the receptor-selective compound O-2137 resulted in inhibition of the activation of CCR5 by its native chemokine ligand CCL5 (RANTES). Collectively, these results indicate that the $G_{i/o}$ protein-coupled CB_2 can “crosstalk” with a number of other G protein-coupled receptors, especially chemokine receptors, and thus can affect heterologous signal transduction pathways.

Multiple Sclerosis (MS)

MS is also known as “disseminated sclerosis” or “encephalomyelitis disseminate”. It is a chronic, inflammatory demyelinating disease of the human CNS that primarily affects adults. Symptoms include changes in sensation, muscle weakness, abnormal muscle spasms, difficulty with coordination and balance, cognitive impairment, and problems with speech, swallowing, and sight. The disease is characterized by degeneration of the myelin sheath that covers axons in which T cells play a prominent role. These cells attack myelin with the resulting inflammatory process stimulating other immune cells to produce soluble factors such as cytokines and antibodies. The inflammatory process results in breakdown of the BBB leading to swelling, activation of macrophages, and further production of cytokines and “cytotoxic” proteins such as metalloproteinases. Remyelination may occur in the early phase of the disease, but the oligodendrocytes that originally formed the myelin sheath cannot completely rebuild the destroyed myelin sheath around damaged axons and scar-like plaques develop.

Experimental Autoimmune Encephalomyelitis (EAE) in the mouse is a CD4+ T lymphocyte-mediated autoimmune disease that results from induction of primed myelin epitope-specific CD4+ T lymphocytes in mice that have been immunized with myelin proteins or peptides in complete Freund’s adjuvant (CFA) [138]. Demyelination in the CNS ensues due to migration of activated myelin-specific T lymphocytes across the tight endothelial junctions that comprise

the BBB and from the elaboration of chemokines and cytokines by these T lymphocytes. The resultant influx of peripheral mononuclear phagocytes into the CNS leads to progressive hind-limb paralysis. The EAE mouse model has been useful in studies related to pathogenesis and immune regulation of CD4+ T_H1/T_H17-mediated tissue damage. Theiler's murine encephalomyelitis virus-induced demyelinating disease (TMEV-IDD) is another model of chronic-progressive MS that is characterized by Th_1-mediated CNS demyelination and spastic hindlimb paralysis [125]. EAE also can be induced in inbred Lewis (LEW) and Dark Agouti (DA) rats since these animals are highly susceptible to encephalomyelitis induced with guinea pig myelin basic protein (MBP) emulsified in CFA [125]. DA strain rats also are highly susceptible to encephalomyelitis induced with proteolipid protein (PLP). A clinical picture similar to that observed for EAE in the mouse (i.e., loss of tail tonicity to hind limb paralysis) also can be obtained following adoptive transfer to mice of activated T lymphocytes from MBP/CFA-immunized mice [138].

Most studies aimed at assessment of effects of cannabinoids on MS have involved the use of the mouse EAE model. Mice deficient in CB_1 have been shown to tolerate inflammatory and excitotoxic insults poorly and to develop substantial neurodegeneration following immune attack [139]. Consistent with these observations, THC has been reported to markedly inhibit neurodegeneration in the EAE model and to reduce the associated induced elevated level of glutamate in cerebrospinal fluid [140]. Glutamate, the major excitatory neurotransmitter in the cerebral cortex, has been implicated in neurodegenerative disease when present at high levels. These therapeutic effects were reversed by the CB_1 antagonist SR141716A suggesting that inhibition of glutamate release occurred through activation of CB_1. Further support for a role of the CB_1 in moderating MS in experimental animals has been obtained from studies using CB_1 knockout mice [141]. These animals were susceptible to neurofilament damage and caspase 3 activation during chronic relapsing EAE (CREAE). Analysis of spinal cord from the knockout mice revealed that both neurofilament and MBP levels decreased over the course of disease, indicative of concomitant neuronal/axonal loss and demyelination. In addition, dephosphorylation of a neurofilament H epitope, assessed as a marker of axonal damage, was found to be increased significantly in knockout mice over their wild-type counterparts. In addition, active caspase 3 levels were increased in all animals during the disease process, with CB_1 knockout animals displaying highest levels. Collectively, the data suggested that signaling through CB_1 conferred neuroprotection during EAE. The density and expression levels of mRNA and the activation of GTP-binding proteins for CB_1 also have been assessed in mice with CREAE [142]. Changes in the status of CB_1, as affected by the development of CREAE, were region-specific. The CB_1 exhibited down-regulatory responses that were circumscribed to motor-related regions that, generally, were more marked during the acute and chronic phases of disease. It was suggested that these observations explained the efficacy of cannabinoid agonists in improving motor symptoms such as spasticity, tremor, and ataxia that are typical of MS in humans and in animal models. Control of spasticity in the MS model as mediated by CB_1 and not CB_2 also has been suggested through studies in which spasticity was induced in wild type and CB_1-deficient mice following the development of relapsing EAE [143]. CB_2-selective agonists such as RWJ400065 did not inhibit spasticity. The anti-spastic activity of RWJ400065 and the therapeutic effect of the non-selective CB_1/CB_2 agonists WIN55212-2 and CP55940 were lost in spastic, CB_1-deficient mice. In addition, Rolipram, an inhibitor of type IV phosphodiesterase that supresseses EAE in different species, has been found to attenuate clinical decline, reduce motor inhibition, and normalize CB_1 gene expression in the basal ganglia of EAE rats [144]. EAE rats also have been reported to exhibit changes in endocannabinoid levels [144]. Levels of anandamide and 2-AG were decreased in motor related regions such as the striatum and midbrain as well as in other brain regions. A role for CB_1 was proposed in cannabinoid-mediated delay in progression of EAE in the rat.

Studies employing a fetal mouse telencephalon aggregate cell culture model that allowed for comparison of tissue from CB_1 knockout mice with their wild type counterparts have lent additional support for a role of CB_1 in neuroprotection in EAE [145]. Treatment of CB_1 knockout cultures with IFNγ resulted in significant loss of the neuronal marker neurofilament-H as compared to wild type cultures, suggesting that the presence of the CB_1 gene was involved in neuroprotection. Activation of caspase 3, an indicator of an apoptotic mechanism of cell death, was found to be elevated in the knockout cultures. In addition, levels of dephosphorylated neurofilament were found to be higher in cultures from knockout animals, suggesting that dephosphorylation of neurofilament served as a marker for neuronal damage.

The role of cannabinoids in neuroprotection in mouse and rat EAE models has been confirmed using the TMEV-IDD model. Using this animal model, treatment with WIN 55212-2, ACEA, and JWH-015 during established disease resulted in ablation of neurological deficits [146]. These cannabinoids reduced microglial activation, abrogated Major Histocompatibility Complex (MHC) class II antigen expression, and decreased the number of CD4+ infiltrating T cells into the spinal cord. Recovery of motor function and decrease in inflammation was shown to parallel extensive remyelination. WIN55212 was reported to ameliorate progression of symptoms of clinical disease in mice with pre-existing TMEV-IDD [147]. This amelioration was associated with down-regulation of virus and myelin epitope-specific Th_1 effector functions (i.e., delayed-type hypersensitivity and IFNγ production) and inhibition of CNS mRNA expression coding for the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6. WIN 55212-2 also has been found to attenuate the increase in leukocyte rolling and endothelial adhesion in the brain that is associated with EAE, as visualized *in vivo* through the use of intravital microscopy and a cranial window implanted two days before in mice with EAE [148]. Furthermore, through the use of CB_1 (SR 141716A) and CB_2 (SR144528) antagonists it was demonstrated that the cannabinoid-mediated inhibitory effects on leukocyte/endothelial interactions were through CB_2.

Studies using the passive variety of EAE, induced in Lewis rats by adoptive transfer of myelin-reactive T lymphocytes, have indicated that WIN55212-2 ameliorates clinical signs of disease and diminishes T-lymphocyte infiltration of the spinal cord [149]. WIN55212-2 induced a profound increase of apoptosis in a dose- and time-dependent manner that was partially blocked by the CB_2 antagonist SR144528 and by PTX. Based on these results it was proposed that, while CB_2 played a role in this process, a receptor-independent mechanism, or a yet to be characterized novel cannabinoid receptor, also was involved. WIN 55212-2 also has been reported to increase cyclooxygenase-2 (COX-2) expression and prostaglandin-E_2 (PGE_2) release in endothelial cells following infection with Theiler's virus, one of the first events that occurs in the pathogenesis of TMEV-IDD [150]. Treatment with WIN 55212-2 resulted in up-regulation of COX-2 protein and PGE_2 release that was attributed to a mechanism independent of activation of CB_1 or CB_2.

More recent studies indicate that neuroprotective effects of cannabinoids can be exerted through activation of both CB_1 and CB_2. Using a chronic model of MS in mice it was reported that clinical signs and axonal damage in the spinal cord were reduced by the AMPA (α-amino-3-hydroxy-5-methylisoxazole-4- propionic acid) receptor antagonist, NBQX (2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione) [151], implicating AMPA as playing a direct role in excitotoxicity. HU210 reduction of the AMPA-induced excitotoxicity *in vivo* and *in vitro* was attributed to activation of both CB_1 and CB_2. Direct suppression of CNS autoimmune inflammation in the EAE mouse model has been demonstrated to be exerted through CB_1 on neurons and CB_2 on autoreactive T cells [152]. It was indicated that CB_1 expression by neurons, but not T lymphocytes, was required for cannabinoid-mediated suppression of EAE. On the other hand, expression of CB_2 by encephalitogenic T lymphocytes was indicated as critical for controlling inflammation associated with EAE. CB_2-deficient T

lymphocytes in the CNS during EAE exhibited reduced levels of apoptosis, a higher rate of proliferation, and increased production of inflammatory cytokines resulting in severe clinical disease. In addition, selective glial expression of CB_1, CB_2, and FAAH has been reported as associated with MS, supporting a role for the endocannabinoid system in the pathogenesis and/or evolution of this disease [153]. Brain tissue from MS patients was examined using double immunofluorescence cytochemistry. CB_1 was identified in cortical neurons, oligodendrocytes, oligodendrocyte precursor cells, macrophages and infiltrated T-lymphocytes. CB_2 was identified in T lymphocytes, astrocytes, and perivascular and reactive (i.e., MHC-II positive) microglia in MS plaques. The CB_2-positive microglia, while distributed evenly within active plaques, were located at the periphery of chronic active plaques. FAAH expression was restricted to neurons and hypertrophic astrocytes.

The role of 'indirect' agonists, compounds able to reinforce physiological endocannabinoid transmission and divorced of psychotropic effects has been examined in ameliorating neurological deficits due to MS [154]. Using the TMEV-IDD model, it was demonstrated that treatment with the selective anandamide uptake inhibitor UCM707 during established disease resulted in significant improvement in motor function. UCM707 was able to reduce microglial activation, diminish MHC class II antigen expression, decrease cellular infiltrates in the spinal cord, and decrease the production of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6. It has been reported also that the endocannabinoid system is highly activated during CNS inflammation and that anandamide protects neurons from inflammatory damage through a CB_1/CB_2-mediated rapid induction of microglial mitogen-activated protein kinase phosphatase-1 (mkp-1) that is associated with histone H3 phoshorylation of the mkp-1 gene sequence [155]. It was suggested that anandamide induced a rapid mkp-1 switching off of MAPK signal transduction that was activated by stimulation of pattern recognition receptors. It was proposed that the release of anandamide served as a mode of neuroimmune communication that could control and limit the immune response after primary CNS injury.

In addition, the cannabinoid system may share cellular mechanisms that affect brain disease progression [156]. For example, it has been demonstrated that COX-2, CB_2 and P2X7-immunoreactivities are increased in activated microglia/macrophages of MS and ALS post-mortem human spinal cord. It was hypothesized that the known increase of lesion-associated extracellular ATP contributed via P2X7 purinergic receptor activation to the release of IL-1β that, in turn, induced the production of COX-2 and downstream pathogenic mediators. Thus, while MS and ALS are inflammatory and degenerative disorders, respectively, shared cellular mechanisms may affect disease progression, particularly those that involve glial responses.

CONCLUSIONS

Cannabinoid receptors have been reported to play an important role in neuropathological diseases, and the involvement of CB_1 and CB_2 may be linked to different functional properties in the brain. The CB_1 appears to be critical for the overall homeostatic balance and regulation of the CNS, and data indicate that this receptor may have therapeutic potential in attenuating cognitive impairment and degeneration in CNS disorders such as AD, ALS, and MS. While many neuropathies are characterized by progressive decline in cognitive functions, a major pathological hallmark of CNS pathologies is inflammation. The CB_2 has been linked functionally to the modulation of inflammatory immune responses in both the periphery and the CNS. The CNS consists of a diverse array of cell types that includes neurons, oligodendrocytes and glial cells. While astrocytes are the predominant glial cell type of the CNS, microglia, as resident macrophages of the brain, function as immune effector and accessory cells. Paradoxically, they not only play a role in host defense and tissue repair but also have been implicated in a variety of inflammatory neuropathological processes. Microglia, in addition to exhibiting phenotypic markers for macrophages, express CB_1 and CB_2 [67,

157]. While CB_1 appears to be constitutively expressed in these cells at relatively low levels, CB_2 is expressed inducibly during the inflammatory process and at relatively high levels. Immune responses during the early phase of neuropathological processes appear to involve preponderantly the CB_2. The levels and functional relevance of this receptor may be amplified as disease progresses to later stages of inflammation. During this later phase, release of pro-inflammatory cytokines, chemokines, and other factors from microglia results in activation of astrocytes that contributes further to the cascade of pro-inflammatory events. The combined inflammatory response engendered by microglia and astrocytes leads to breakdown of the BBB and influx of inflammatory cells from peripheral non-neuronal sites. Thus, it is apparent that therapeutic intervention at an early stage of neuroinflammation is critical. The recognition that microglia express CB_2 and that its activation results in ablation of untoward immune responses indicates that this receptor may serve as an ideal therapeutic target. Cannabinoids, as highly lipophilic compounds, can readily penetrate the BBB and access the brain. Furthermore, these compounds can be designed to have low toxicity, minimal psychotropic properties, and to selectively target cells that express the CB_2, particularly microglia that serve as endogenous immune cells of the CNS and that play a prominent role in neuroinflammatory processes.

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ABBREVIATIONS

2-AG
2-arachidonoylglycerol

ACEA
arachidonyl-2-chloroethylamide

AD
Alzheimer’s disease

ADP
adenosine diphosphate

AIDS
Acquired Immune Deficiency Syndrome

ALS
Amyotrophic Lateral Sclerosis

AMPA
α-amino-3-hydroxy-5-methylisoxazole-4- propionic acid receptor

anandamide
arachidonoyl ethanolamide

APP
Aβ precursor protein

ATP
adenosine triphosphate

BBB
blood brain barrier

BDNF

brain-derived neurotrophic factor

cAMP
3′,5′-cyclic-adenosine monophosphate

CB_1
cannabinoid receptor 1

CB_2
cannabinoid receptor 2

CBD
cannabidiol

CBN
cannabinol

cDNA
complementary DNA

CFA
complete Freund's adjuvant

CHI
Closed Head Injury

CNS
central nervous system

COX-2
cytochrome c oxidase subunit II

CREAE
chronic relapsing EAE

CTL
cytotoxic T lymphocyte

DA
Dark Agouti

DAG
1,2-diacylglycerol

EAE
Experimental Autoimmune Encephalomyelitis

ERK
extracellular signal-regulated kinase

FAAH
fatty acid amide hydrolase

FALS
Familial Amytrophic Lateral Sclerosis

F-Me-AEA
2-methylarachidonyl-(2′-fluoroethyl)amide

GAE
Granulomatous Amebic Encephalitis

HIV
Human Iimmunodeficiency Virus

HIVE
HIV Encephalitis

IFNγ
interferon-gamma

IL-1
interleukin-1

IL-4
interleukin-4

IL-6
interleukin-6

IL-10
interleukin-10

LEW
inbred Lewis

LPS
lipopolysaccharide

MAP
mitogen-activated protein

MAPK
mitogen-activated protein kinase

MBP
myelin basic protein

MGL
monoacylglycerol lipase

MHC
major histocompatibility complex

mkp-1
mitogen-activated protein kinase phosphatase-1

mRNA
messenger RNA

MS
Multiple Sclerosis

NAPE
N-arachidonoylyl phosphatidylethanolamine

NBQX
2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione

NFκB
nuclear factor of kappa light chain gene enhancer in B-cells

NFTs
neurofibrillary tangles

NK
natural killer

NMDA
N-methyl-D-aspartate

PGE_2
prostaglandin e synthase 2

PKA
protein kinase A

PLC
phospholipase C

PLD
phosholipase D

PLP
proteolipid protein

PTX
pertussis toxin

RANTES
Regulated upon Activation, Normal T-cell Expressed, and Secreted

SCID
severe combined immunodeficiency

SIV
simian immunodeficiency virus

SOD 1
superoxide dismutase 1

THC
Delta-9-tetrahydrocannabinol

TMEV-IDD
Theiler's murine encephalomyelitis virus-induced demyelinating

TNF-α
tumor necrosis factor-alpha

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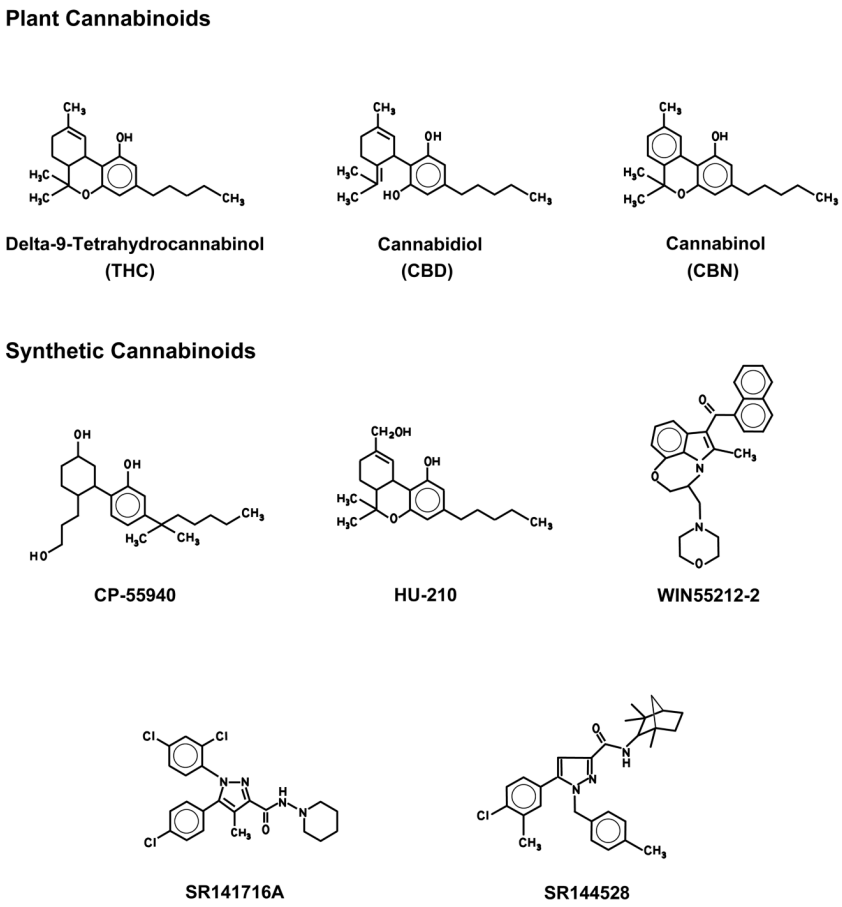

Figure 1.

Representative Exogenous Cannabinoids. Delta-9-tetrahydrocannabinol (THC) is a partial agonist for CB_1 and CB_2. Cannabidiol: 2-((1S,6S)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)-5-pentylbenzene-1,3-diol (CBD) and Cannabinol: 6,6,9-trimethyl-3-pentyl-6*H*-benzo[*c*]chromen-1-ol (CBN) exhibit minimal binding to CB_1 or CB_2. CP55940: (−)-cis-3-[2-Hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)cyclohexanol, HU-210: 1,1-Dimethylheptyl-11-hydroxytetrahydrocannabinol, and WIN55212-2: (R)-(+)-[2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de)-1,4-benzoxazin-6-yl]-1-napthalenylmethanone are full agonists for CB_1 and CB_2. SR141716A: 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(1-piperidyl)pyrazole-3-carboxamide hydrochloride is an antagonist for CB_1. SR144528: (1S-endo)-5-(4-Chloro-3-methylphenyl)-1-((4-methylphenyl) methyl)-N-(1,3,3-trimethylbicyclo(2.2.1)hept-2-yl)-1H-pyrazole-3-carboxamide is an antagonist for CB_2.

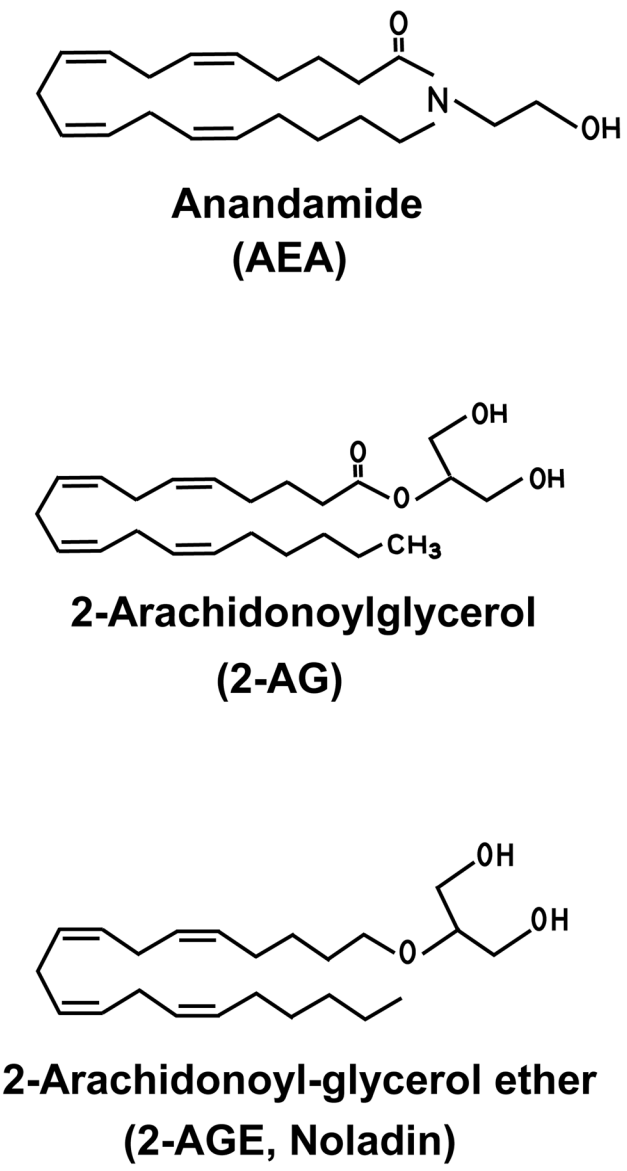

Figure 2.
Representative Endogenous Cannabinoids (Endocannabinoids). Arachidonoylethanolamide (Anandamide, AEA), 2-Arachidonoylglycerol (2-AG), and 2-Arachidonylglyceryl ether (2-AGE, Noladin ether, Noladin) show agonist behavior at CB_1 and CB_2.

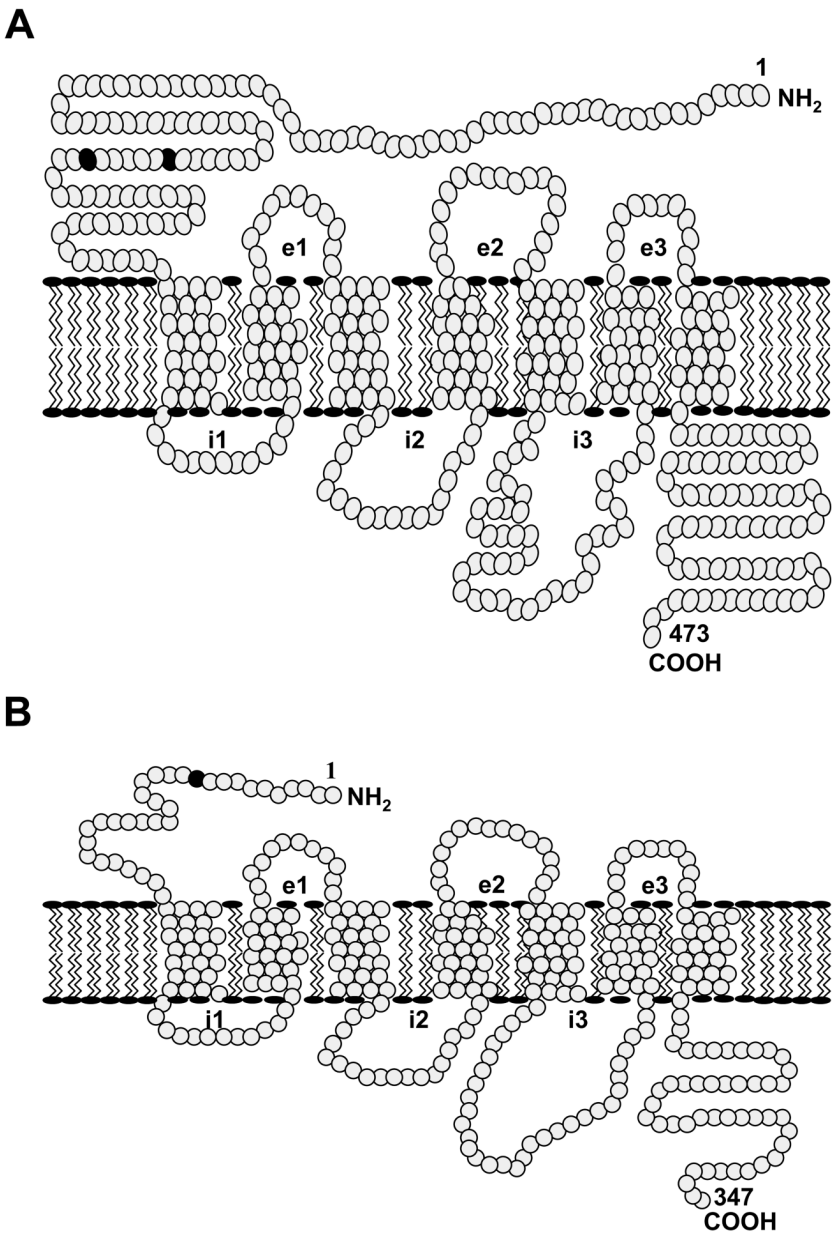

Figure 3.

Diagrammatic Representation of the Mouse CB_1 and CB_2. Receptor homology between the CB_1 and CB_2 is approximately 44% for the full-length protein and 68% within the seven transmembrane domains. (A) The solid circles denotes glycosylation sites at asparagine residues 78 and 84 of CB_1. (B) The solid circle denotes a glycosylation site at asparagine residue 11 of CB_2. The extracellular and intracellular loops are denoted as e1, e2, e3 and i1, i2, and i3, respectively.

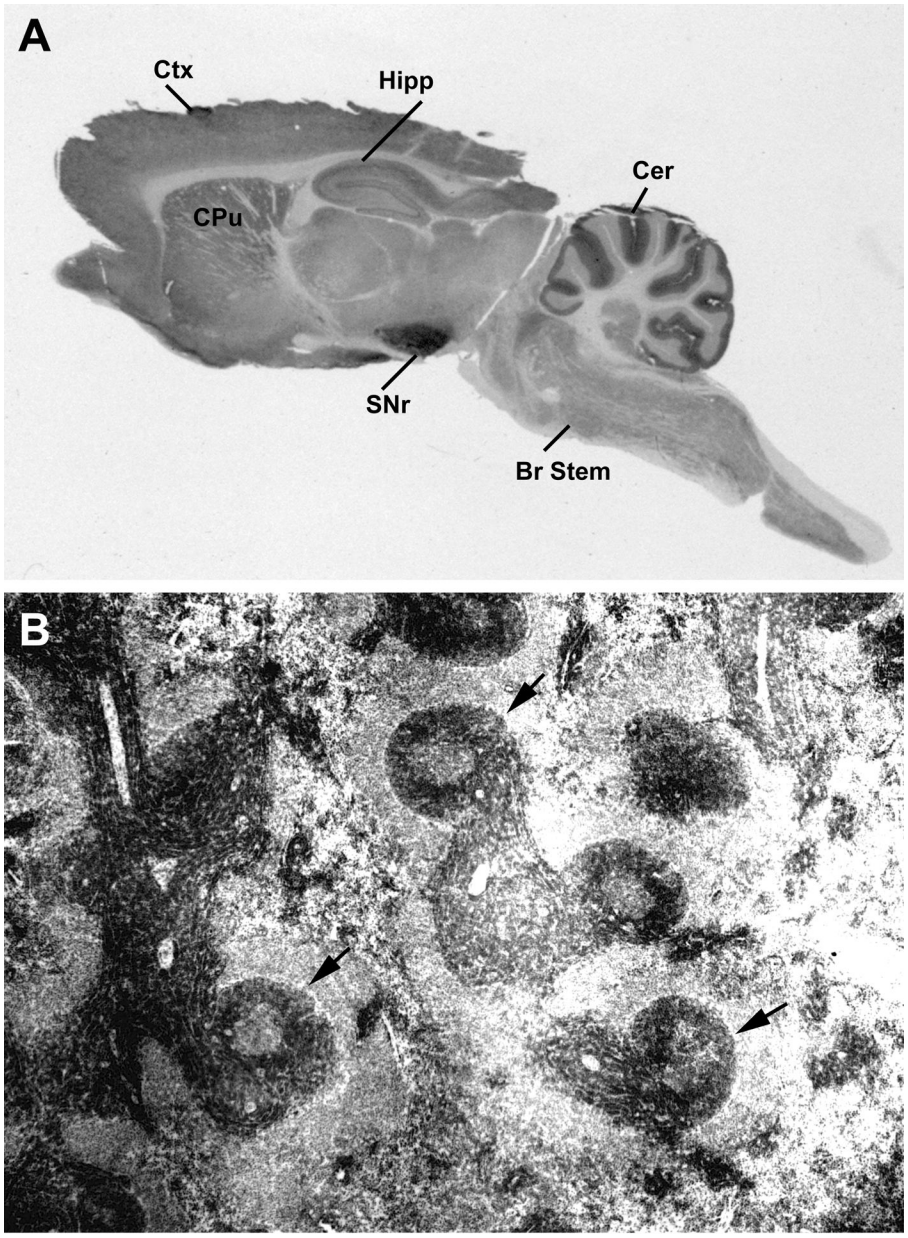

Figure 4.

Immunohistochemical Localization of the CB_1 and CB_2 in Rat Tissues. (A) Sagital section of rat brain. High levels of CB_1 protein are present in the caudate putamen (CPu), cerebral cortex (Ctx), granular layer of the cerebellum (Cer), hippocampus (Hipp), and the substantia nigra (SNr). (B) Rat spleen section. The arrows denote the B lymphocyte area of germinal follicles that have high levels of CB_2.