HHS Public Access

Author manuscript

Brain Res. Author manuscript; available in PMC 2020 December 01.

Published in final edited form as:

Brain Res. 2019 December 01; 1724: 146467. doi:10.1016/j.brainres.2019.146467.

Druggable Targets of the Endocannabinoid System: Implications for the Treatment of HIV-Associated Neurocognitive Disorder

Mariah M. Wu[a], **Xinwen Zhang**[b], **Melissa J. Asher**[a], **Stanley A. Thayer**[a,b]

[a]Graduate Program in Neuroscience, University of Minnesota Medical School, Minneapolis, MN 55455, USA

[b]Department of Pharmacology, University of Minnesota Medical School, Minneapolis, MN 55455, USA

Abstract

HIV-associated neurocognitive disorder (HAND) affects nearly half of all HIV-infected individuals. Synaptodendritic damage correlates with neurocognitive decline in HAND, and many studies have demonstrated that HIV-induced neuronal injury results from excitotoxic and inflammatory mechanisms. The endocannabinoid (eCB) system provides on-demand protection against excitotoxicity and neuroinflammation. Here, we discuss evidence of the neuroprotective and anti-inflammatory properties of the eCB system from *in vitro* and *in vivo* studies. We examine the pharmacology of the eCB system and evaluate the therapeutic potential of drugs that modulate eCB signaling to treat HAND. Finally, we provide perspective on the need for additional studies to clarify the role of the eCB system in HIV neurotoxicity and speculate that strategies that enhance eCB signaling might slow cognitive decline in HAND.

Keywords

HIV-1; cannabinoid receptor; anandamide; 2-arachidonoylglycerol; monoacylglycerol lipase; fatty acid amide hydrolase

1. Introduction

Nearly half of all HIV-infected individuals experience cognitive and motor impairments (Heaton et al., 1995; Tozzi et al., 2005); these symptoms are collectively termed HIV-associated neurocognitive disorder (HAND). Combined antiretroviral therapy (cART) has reduced the number of patients that progress to AIDS (Heaton et al., 2010; McArthur, 1993), and increased the lifespan of infected individuals (ATCC, 2008; Dore et al., 2003). However, while cART suppresses viral load, it does not eradicate HIV from the brain (Valcour et al.,

Correspondence: S. A. Thayer, sathayer@umn.edu.

2011). Thus, the prevalence of HAND remains high (Cysique et al., 2004; Sacktor et al., 2001; Saylor et al., 2016), with no effective treatment available.

One promising area of therapeutic development is the endocannabinoid (eCB) system. This biological system is composed of endogenous lipid-based signaling molecules that bind to cannabinoid receptors, and the machinery that synthesizes and metabolizes them (Fig. 1). eCB signaling is dependent on neurons interacting with other neurons, astrocytes, and microglia (Ashton and Glass, 2007; Navarrete et al., 2014). The eCB system plays a role in many physiological processes. Here, we review its ability to provide on-demand protection against excitotoxicity and neuroinflammation (Marsicano et al., 2003; Walter and Stella, 2004), two hallmarks of many neurodegenerative disorders including HAND (Amor et al., 2010; Dong et al., 2009; Green et al., 2018).

Drugs can enhance the eCB system by mimicking or potentiating its neuroprotective function. Changes in the eCB system associated with some neurological disorders might impair the neuroprotection that the system affords, exacerbating excitotoxicity. Thus, strategies to prevent loss of eCB signaling may preserve its neuroprotective function, and drugs that mimic or enhance eCB signaling may compensate for its diminished capacity in neurotoxic or inflammatory conditions, such as HAND. Cannabimimetic drugs are relevant to HIV because they are used to treat wasting and nausea in AIDS patients (Plasse et al., 1991), cannabis use among HIV-positive individuals is high (Okafor et al., 2017), and recent efforts to legalize medicinal and recreational marijuana are increasing access (Cerda et al., 2017). Here, we examine the components and pharmacology of the eCB system and discuss evidence of its neuroprotective and anti-inflammatory properties. We then evaluate the therapeutic potential of drugs that modulate the eCB system and speculate that strategies that enhance eCB signaling might slow cognitive decline in HAND.

2. Cannabinoid Receptors

CB_1 and CB_2 receptors have been studied extensively and are the best understood receptor components of the eCB system. However, eCBs also interact with ion channels and other G protein-coupled receptors (GPCRs). Anandamide activates the transient receptor potential vanilloid 1 (TRPV1) receptor, a calcium permeable, nonselective cation channel (Ross, 2003). Several orphan GPCRs, notably GPR55 and GPR18, have emerged as possible targets of eCBs (for review, see (Cuevas-Olguin et al., 2017)). While eCBs may act on these alternative targets in a manner relevant to pathophysiology, this review will focus on CB_1 and CB_2 receptors.

2.1. CB_1 receptor agonists

Cannabinoid type 1 receptors (CB_1Rs) are GPCRs abundantly expressed on neurons and astrocytes (Howlett et al., 2002; Matsuda et al., 1993; Navarrete and Araque, 2008) (Fig. 1). CB_1Rs on neurons localize to presynaptic elements, where they modulate neurotransmission. CB_1Rs on astrocytes modulate gliotransmission by regulating intracellular calcium, facilitating communication with neurons (Navarrete and Araque, 2008; Navarrete and Araque, 2010; Oliveira da Cruz et al., 2016). Histochemical studies have found CB_1R mRNA in the principal (excitatory) neurons of the cerebellum, hypothalamus,

thalamus, and lower brain stem (Howlett et al., 2002; Tsou et al., 1998a). CB_1Rs are also found in a subset of inhibitory neurons, particularly cholecystokinin (CCK)-positive interneurons of the hippocampus, amygdala, and cerebral cortex (Herkenham et al., 1991; Mackie, 2005), with no expression in parvalbumin-positive interneurons (Marsicano and Lutz, 1999; Matsuda et al., 1993). This distribution corresponds to the physiological role of eCBs in control of motor activity, nociception, learning and memory, food intake, and cognitive function (for review, see (Di Marzo et al., 1998)). Most CB_1Rs are coupled to $G_{i/o}$ (Pertwee et al., 2010), where activation of the $G_{\alpha i}/G_{\alpha o}$ subunit reduces cAMP production by inhibiting adenylyl cyclase, while the $G_{\beta\gamma}$ complex targets many physiological effectors, including inwardly rectifying K^+ channels, N- and P/Q-type Ca^{2+} channels, protein kinase signaling cascades, and others (Kano et al., 2009; Smrcka, 2008).

Here, we focus on the neuroprotective role of CB_1Rs that, upon activation, inhibit glutamate release at excitatory synapses (Gerdeman and Lovinger, 2001; Shen et al., 1996). These receptors are part of a retrograde signaling system in which eCBs produced postsynaptically diffuse across the synaptic cleft to act on presynaptic CB_1Rs. At glutamatergic synapses, this system provides a form of feedback inhibition. Upon excitation, the postsynaptic cell synthesizes the eCB 2-arachidonoylglycerol (2-AG) that then activates presynaptic CB_1Rs to inhibit and reduce glutamate release. Interestingly, a recent study showed that astrocytes produce 2-AG in response to activation of metabotropic glutamate receptors, with subsequent activation of presynaptic CB_1R to produce a form of synaptic depression (Smith et al., 2019).

CB_1R-mediated presynaptic inhibition provides a basis for the neuroprotective properties of the eCB system, whereby the ability to inhibit glutamate release dampens excitotoxicity caused by excessive activation of glutamatergic pathways. Excitotoxicity is a hallmark of many neurodegenerative disorders (Dong et al., 2009) including HAND (Green et al., 2018), where overstimulation of glutamate receptors leads to a characteristic loss of postsynaptic structures (Dong et al., 2009); thus, preventing it may slow disease progression and attenuate symptoms.

Compelling evidence that CB_1Rs protect against excitotoxicity comes from Marsicano *et al.* (2003), who demonstrated that mice lacking CB_1Rs in all principal neurons of the forebrain but not astrocytes experienced more severe seizures in a kainic acid model of excitotoxic epileptiform seizures (Marsicano et al., 2003). Furthermore, Monory *et al.* (2006) demonstrated that CB_1Rs on hippocampal glutamatergic neurons were central mediators of on-demand eCB-dependent protection against kainic acid-induced acute excitotoxic seizures (Monory et al., 2006). Subsequent reports expanded upon these results, demonstrating that viral-mediated overexpression of CB_1Rs in the principal neurons of the hippocampus protected against seizure-induced excitotoxicity (Guggenhuber et al., 2010), and that the eCB 2-AG is the key activator of the CB_1Rs that ultimately mediate seizure suppression (Sugaya et al., 2016).

In addition to preventing excitotoxicity by suppressing aberrant patterns of glutamatergic activity, CB_1R-mediated neuroprotection may also result from activation of cell survival signaling cascades, including the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and the

extracellular signal-regulated (ERK) pathway (Dalton and Howlett, 2012; Molina-Holgado et al., 2002). Thus, CB_1R agonists may be viable therapeutic options to attenuate changes in network function that contribute to neuronal damage. Indeed, CB_1R agonists attenuate excitotoxicity in several models of neurodegenerative disorders. The cannabinoid receptor agonist WIN55,212–2 reduced synaptically-mediated excitotoxicity evoked by reduction of ambient $[Mg^{2+}]$ in primary hippocampal cultures; this effect was blocked by the CB_1R inverse agonist rimonabant (SR141716A), indicating a role for CB_1Rs (Shen and Thayer, 1998). In rodent models of traumatic brain injury and stroke, pre-treatment with the cannabinoid agonists WIN55,212–2 and 2-AG reduced brain edema and infarct volumes (Nagayama et al., 1999; Panikashvili et al., 2001), and induced faster recovery of motor and behavioral function (Panikashvili et al., 2001). CB_1R activation slowed disease progression in a model of multiple sclerosis (de Lago et al., 2012) possibly via suppression of inflammation, although excitotoxic mechanisms also participate in this complex model. In both *in vitro* and *in vivo* models of Parkinson's and Huntington's diseases, administration of exogenous 2-AG attenuated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)- and mutant huntingtin-induced neurodegeneration, respectively (Mounsey et al., 2015; Scotter et al., 2010). Several studies have also demonstrated that cannabinoid agonists protect against amyloid β-induced alterations in neuronal function and cognitive impairment (for review, see (Aso and Ferrer, 2014)). Notably, Haghani *et al.* (2012) demonstrated that administration of 2-AG protected against amyloid β-induced changes in intrinsic excitability of CA1 pyramidal neurons and improved retention and recall in a passive avoidance test in mice that were bilaterally injected with the $A\beta_{(1–42)}$ peptide fragment. These effects were blocked by the CB_1R antagonist AM251, but not the CB_2R antagonist AM630 (Haghani et al., 2012). In the AβPP/PS1 mouse model of Alzheimer's disease, Aso *et al.* (2012) demonstrated that chronic administration of the synthetic CB_1R agonist arachidonoyl-2'-chloroethylamide (ACEA) protected neurons against Aβ toxicity and improved performance in the two-object recognition test (Aso et al., 2012). Despite these and other promising preclinical studies, results from several clinical trials on the effect of exogenous cannabinoids in relieving dementia and related symptoms were inconclusive (Krishnan et al., 2009).

The protection afforded by CB_1R agonists in neurodegeneration models suggests that they may also afford protection in HAND. Indeed, activation of CB_1Rs modulates changes in network excitability induced by the HIV protein Tat. Using an *in vitro* model of HIV neurotoxicity, Xu *et al.* (2017) demonstrated that the eCBs anandamide and 2-AG reduced Tat-induced increases in intracellular $[Ca^{2+}]$ and promoted neuronal survival; the CB_1R inverse agonist rimonabant prevented this eCB-mediated neuroprotection (Xu et al., 2017). While the mechanism of this CB_1R-mediated neuroprotection is unknown, this and other studies (discussed in subsequent sections) suggest that enhancing eCB signaling may be beneficial in HAND.

Several important considerations should be noted in regard to targeting CB_1Rs to combat HAND and other neurodegenerative disorders. Because CB_1R activation largely mediates the psychoactive properties of exogenous cannabinoids (for review, see (Howlett et al., 2002)), the therapeutic potential of CB_1R agonists is limited by adverse effects, including changes in feeding behavior (Haney et al., 2005; Wiley et al., 2005), motor slowing (More and Choi, 2015; Prashad and Filbey, 2017), and sedation (Zhornitsky and Potvin, 2012).

Cannabinoid-induced cognitive impairment, particularly inhibition of short-term memory (Ranganathan and D'Souza, 2006), has also been demonstrated; this is an important consideration when the therapeutic goal is to prevent cognitive decline. Furthermore, chronic cannabis use can also produce dependence (Lopez-Quintero et al., 2011; Volkow et al., 2014). Thus, while CB_1R agonists are neuroprotective *in vitro* and reduce neuronal damage in animal models of neurodegenerative disease, their shortcomings have spurred interest in other components of the eCB system. Selectively modulating CB_2R and slowing eCB metabolism are two promising approaches with reduced psychoactive side effects.

2.2. CB_2 receptor agonists

Cannabinoid type 2 receptors (CB_2Rs) are $G_{i/o}$ protein-coupled receptors found mainly in immune cells, including microglia, the resident macrophages of the CNS (Howlett et al., 2002; Nunez et al., 2004) (Fig. 1). Although some reports have described limited CB_2R expression in neurons (Gong et al., 2006), activation of CB_2Rs is generally thought to affect the immune system without the strong psychoactive effects of CB_1R activation. Similar to CB_1, CB_2Rs regulate signaling cascades that include adenylyl cyclase, MAP kinase, and Ca^{2+} signaling (Bayewitch et al., 1995; Slipetz et al., 1995). These pathways affect a variety of immune functions, including cytokine release (Cabral and Griffin-Thomas, 2009), cell proliferation (Carrier et al., 2004), migration (Walter et al., 2003), and gene expression (Mecha et al., 2015). CB_2Rs are undetectable in unstimulated microglia, and their expression increases in response to inflammatory stimuli (Cabral and Griffin-Thomas, 2009; Nunez et al., 2004); thus, CB_2R agonists are preferentially effective during inflammatory states. Because receptor expression is immune cell-specific and state-dependent, CB_2Rs can dampen the harmful effects of immune activation in the CNS with few adverse side effects.

Chronic inflammation is implicated in a growing number of neurodegenerative diseases. For example, reactive oxygen species produced by microglia damage neurons in Alzheimer's and Parkinson's disease (Javed et al., 2016; Shimohama et al., 2000). Pro-inflammatory cytokines can also damage neurons directly via excitotoxicity (Ye et al., 2013) and synaptodendritic damage (Festa et al., 2015), or indirectly through the recruitment and activation of immune cells (Kozela et al., 2011). In several disease models, CB_2R activation counteracts neuroinflammation. Neuroprotection occurs by reducing pro-inflammatory cytokines (Klegeris et al., 2003; Malek et al., 2015) and reactive oxygen species (Javed et al., 2016; Shimohama et al., 2000), increasing anti-inflammatory cytokines (Ehrhart et al., 2005; Malek et al., 2015; Molina-Holgado et al., 2003), inhibiting chemotaxis to a variety of chemokines (Romero-Sandoval et al., 2009), and shifting microglia from a pro-inflammatory M1 phenotype to an alternatively activated reparative M2a phenotype (Mecha et al., 2015). This broad range of effects is well-equipped to combat the main sources of damage during neuroinflammation. Indeed, CB_2R agonists reduce neurotoxicity and behavioral impairments in both *in vitro* and *in vivo* models of Alzheimer's disease (Jayant et al., 2016; Ramirez et al., 2005), Parkinson's disease (Ternianov et al., 2012), Huntington's disease (Palazuelos et al., 2009), multiple sclerosis (Shao et al., 2014), and amyotrophic lateral sclerosis (Shoemaker et al., 2007). Thus, CB_2R agonists hold the potential to treat many neurodegenerative diseases by targeting common neuroinflammatory mechanisms.

HIV causes potentially harmful neuroinflammation (Alonso et al., 1997; Everall et al., 2009; Ubaida-Mohien et al., 2017; Walsh et al., 2014), and CB_2Rs are upregulated during HIV and simian immunodeficiency virus (SIV) infection (Benito et al., 2005; Cosenza-Nashat et al., 2011). This makes CB_2Rs an attractive target for combating HAND. Indeed, activation of CB_2Rs protects against HIV-induced neuroinflammation *in vitro*, mainly by decreasing inflammatory signaling and suppressing the chemokine-like activity of viral proteins (Kim et al., 2011; Purohit et al., 2014). Kim *et al.* (2011) demonstrated that the HIV envelope glycoprotein gp120 induced synapse loss in primary hippocampal neuronal/glial cultures. Activating CB_2Rs prevented this synapse loss by decreasing production of the pro-inflammatory cytokine IL-1β (Kim et al., 2011; Zhang and Thayer, 2018). Similarly, a higher concentration of gp120 killed neurons in striatal neuronal/glial cultures, and the cannabinoid receptor agonist WIN55,212–2 blocked production of reactive oxygen species and pro-inflammatory cytokines, reduced microglial migration, and increased neuronal survival; these effects were largely CB_2R-dependent (Hu et al., 2013).

In addition to preventing the release of neurotoxic cytokines and reactive oxygen species, CB_2R activation may actually reduce HIV infection in the CNS. Δ^9-tetrahydrocannabinol (Δ^9-THC) acts through CB_2Rs to reduce expression of the CD4, CXCR4, and CCR5 receptors that are required for HIV infection in monocyte-derived macrophages (Williams et al., 2014). Additionally, CB_2R activation prevents productive infection of T-tropic HIV in human CD4+ T-cells by blocking the cytoskeletal rearrangements required for viral fusion (Costantino et al., 2012). CB_2R agonists also affect the migration of HIV-infected cells: the HIV protein Tat attracts immune cells by activating chemokine receptors, and cannabinoids prevent migration of microglia-like BV2 cells to Tat (Fraga et al., 2011). Direct activation of CB_2Rs also inhibits extracellular matrix adhesion, which monocytes use to cross the blood-brain barrier in response to HIV (Raborn et al., 2014). CB_2R activation could, therefore, slow the spread of HIV infection through microglial populations, and reduce recruitment of peripheral immune cells that may contribute to neuroinflammation.

Despite *in vitro* evidence that activation of CB_2Rs affords neuroprotection in the presence of HIV or its proteins, few *in vivo* studies have used drugs selective for CB_2Rs in models of HAND, making it difficult to interpret the contribution of CB_2 versus CB_1Rs. Nevertheless, the few *in vivo* studies that have specifically investigated CB_2Rs in HAND models suggest that their activation is beneficial. In a humanized mouse model infected with HIV, the CB_2R agonist Gp1a reduced levels of the pro-inflammatory cytokine TNFα and microglial activation, as measured by CD11b expression (Gorantla et al., 2010). In gp120 transgenic mice, the selective CB_2R agonist AM1241 rescued neurogenesis by increasing proliferation and decreasing apoptosis of neural precursor cells (Avraham et al., 2014). While intriguing, these studies did not investigate neuropathology in mature neurons, or assess functional/behavioral outcomes.

Although these treatment strategies have yet to be translated to humans, there is evidence that cannabinoid agonists are well-tolerated. Many HIV patients use cannabis, either recreationally or medically as an appetite stimulant, without severe adverse effects on overall immune function (Pacek et al., 2018). However, there is little evidence that cannabis users are any less susceptible to HAND than non-users. In fact, Δ^9-THC itself can impair

cognitive functioning in both controls and HIV-positive individuals (Thames et al., 2016), although this may occur via its psychoactive effects on CB_1 rather than a CB_2R-mediated effect (Terranova et al., 1995).

Several studies raise concerns about targeting CB_2Rs to treat neurodegenerative disorders such as HAND. While CB_2R activation is largely associated with anti-inflammatory effects, there is evidence suggesting a pro-inflammatory role. Specifically, CB_2R antagonism significantly reduced the release of prostaglandin E2 from primary microglial cells (Saliba et al., 2018), and topical application of 2-AG resulted in dermal inflammation that was blocked by a CB_2R antagonist (Oka et al., 2005; Oka et al., 2006). Furthermore, 2-AG enhances the motility of microglia in part via CB_2R activation, suggesting that these receptors play a role in the accumulation of microglia at sites of neuroimmune insult (Walter et al., 2003). Thus, further identification of the pro-inflammatory responses induced by CB_2R activation will help to define the potentially beneficial role of CB_2R agonists in neuroinflammatory disorders.

Because studies in humans focus on Δ^9-THC, dronabinol, cannabidiol, or some combination thereof, there is little data on whether a CB_2R-selective compound would fare better in humans. The currently available studies investigating medical marijuana in HIV have been limited by small sample size, short duration of study, and difficulty keeping participants blinded to Δ^9-THC-containing compounds (Lutge et al., 2013). One CB_2R-selective agonist, APD371, is currently in phase 2 clinical trials for the treatment of abdominal pain in Crohn's disease (ClinicalTrials.gov Identifier:); however, this compound has low brain penetrance (Han et al., 2017), which makes it better for treating peripheral diseases rather than HAND. To generate high-quality data on the efficacy of CB_2R agonists in HAND patients, well-controlled trials using selective CB_2R agonists that cross the blood brain barrier are needed.

Despite the aforementioned limitations, selective CB_2R activation remains a promising treatment avenue for two main reasons. First, because CB_2R agonists primarily target immune cells rather than neurons, they have a lower risk of abuse and fewer psychoactive effects than CB_1R agonists or mixed agonists. Second, because CB_2R expression is increased during HIV and SIV infection (Benito et al., 2005; Cosenza-Nashat et al., 2011), CB_2R agonists are most effective when neuroprotection is most needed.

3. Endogenous Ligands, Synthesis, and Metabolism

Several putative endogenous cannabinoids have been discovered (Hanus et al., 1993; Hanus et al., 2001); here, we focus on the two best-characterized ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG) (Fig. 1). AEA functions relatively slowly and generates both retrograde and non-retrograde signaling (Ohno-Shosaku and Kano, 2014). 2-AG is best known for its role as a retrograde messenger in the CNS, playing an important role in spike timing-dependent plasticity and long-term depression (Kano, 2014). AEA and 2-AG levels can be increased by inhibiting the metabolic enzymes that degrade them. Numerous selective eCB metabolic inhibitors have been developed and extensively characterized in neuropsychiatric and neurodegenerative models. Unlike broad and sustained CB_1 or CB_2R

activation produced by agonists, boosting eCB tone by inhibiting metabolic enzymes enhances eCB signaling on-demand and in a site-specific manner, resulting in fewer side effects (Farrell and Soltesz, 2018). Metabolic enzyme inhibitors also overcome the issue of rapid degradation of 2-AG or AEA following direct administration (Savinainen et al., 2001). In this section we will focus on the neuroprotective effects of these modulators, discussing common and unique aspects of their uses and mechanisms in neurological disorders, and their therapeutic potential in HAND.

3.1. Inhibition of AEA metabolism

AEA was first isolated in 1992 from porcine brain in a screen for endogenous ligands for the cannabinoid receptor (Devane et al., 1992). AEA behaves as a partial agonist at both CB_1 and CB_2Rs, and a full agonist at the TRPV1 receptor (Mackie et al., 1993; Sugiura et al., 1999; Sugiura et al., 2000). In the brain, AEA mediates long-term depression (LTD) via the CB_1 and TRPV1 receptors (Grueter et al., 2010; Ohno-Shosaku and Kano, 2014). AEA is an arachidonic acid (AA) derivative, generated from its membrane precursor *N*-arachidonoyl phosphatidyl ethanolamine (NAPE) through cleavage by a phospholipase D (NAPE-PLD) (Di Marzo, 2008; Liu et al., 2006). Hydrolytic metabolism of AEA occurs via fatty acid amide hydrolase (FAAH) (Cravatt et al., 1996), and oxidative metabolism through various lipoxygenases and cyclooxygenase-2 (COX-2) (Burstein et al., 2000). Pharmacological inhibition of FAAH is a promising approach to enhance AEA function.

Selective FAAH inhibitors have been developed and utilized for nearly 20 years. These drugs fall into several families: α-ketoheterocycles (e.g. OL-135), carbamates (e.g. URB597), alkylsufonylfluorides (e.g. AM3506), and aryl ureas (e.g. PF3845) (Blankman and Cravatt, 2013). Inhibition of FAAH activity blocks the degradation of AEA, and thus holds the potential to enhance AEA-mediated synapse-specific neuroprotection (Farrell and Soltesz, 2018).

FAAH inhibitors exhibit robust analgesic and anxiolytic properties. They show particular promise for alleviating neuropathic pain, including in a model of HIV sensory neuropathic pain in which both CB_1 and CB_2Rs were activated (Chang et al., 2006; Mitchell et al., 2007; Nasirinezhad et al., 2015; Russo et al., 2007). Several novel FAAH inhibitors have recently been developed; these inhibitors are as effective for pain as classical FAAH inhibitors, but with improved metabolic, pharmacokinetic, and brain penetrative properties (Bhuniya et al., 2019). Enhancing AEA levels using FAAH inhibitors also produced anxiolytic effects in a CB_1R-dependent manner in rodents, with few adverse effects (Busquets-Garcia et al., 2011; Gomes et al., 2011; Kinsey et al., 2011a; Kinsey et al., 2011b).

Inhibition of FAAH decreases the severity of seizures (Karanian et al., 2007): the FAAH inhibitor URB597 attenuated limbic seizures in a CB_1R-dependent manner without impairing short- and long-term plasticity (Colangeli et al., 2017). Activation of CB_1Rs is thought to be the primary mechanism of neuroprotection produced by FAAH inhibitors (Schlosburg et al., 2009), although recent studies suggest the TRPV1 receptor may contribute to this protection (Jee Kim et al., 2018; Naziroglu et al., 2018). Repeated seizures are commonly associated with neurodegenerative diseases such as Alzheimer's disease and traumatic brain injury (Vossel et al., 2017; Webster et al., 2017), and commonly occur in

HIV-infected individuals (Ssentongo, 2019). FAAH inhibition is protective in models of Alzheimer's disease, traumatic brain injury and amyotrophic lateral sclerosis (Bilsland et al., 2006; Tchantchou et al., 2014; Vazquez et al., 2015a). In these disease models, FAAH inhibitors reduce neuroinflammation via cannabinoid receptors, although additional mechanisms may be involved (Vazquez et al., 2015b). Notably, FAAH-mediated degradation of other fatty acid ethanolamide molecules, including palmitoylethanolamide and oleoylethanolamide, alongside AEA may play a role in the potent analgesic and anti-inflammatory effects of FAAH inhibitors (for review see (Alhouayek and Muccioli, 2014)).

Recent clinical evidence indicates several potential safety concerns with FAAH inhibitors. In a phase 1 study, the reversible FAAH inhibitor BIA 10–2474 was orally administered to healthy volunteers to assess safety. Three of four participants developed an acute and rapidly progressive neurologic syndrome, including headache, a cerebellar syndrome, memory impairment, and altered consciousness, and one participant became brain dead (Kerbrat et al., 2016). The underlying mechanism of this unanticipated neurologic disorder remains unknown; however, several off-target effects of BIA 10–2474 were subsequently identified *in silico* (Molinski et al., 2017) and *in vitro* (van Esbroeck et al., 2017). The selective FAAH inhibitor PF-04457845 was well-tolerated in humans with no evidence of cannabimimetic adverse events, but lacked efficacy in the primary end point (Huggins et al., 2012). However, this study holds promise that selective FAAH inhibition can be tolerated by humans. Despite the limitations from these and other clinical studies, preclinical data suggest that selective FAAH inhibition may be beneficial in HIV-associated neurodegeneration.

Several recent studies have evaluated inhibition of FAAH in HAND models. Genetic deletion of FAAH rescued neurogenesis in transgenic mice expressing the HIV envelope glycoprotein gp120 (Avraham et al., 2015). The FAAH inhibitor PF3845 also protected against neuronal damage induced by HIV viral proteins via a mechanism involving cannabinoid receptors (Hermes et al., 2018). Thus, FAAH inhibition has therapeutic potential in HAND, although more investigation is needed.

3.2. Inhibition of 2-AG metabolism

2-AG was first isolated as an agonist for cannabinoid receptors in 1995 (Mechoulam et al., 1995). Unlike AEA, 2-AG is present in the brain at high concentrations and is a full agonist for both CB_1 and CB_2Rs (Buczynski and Parsons, 2010; Gonsiorek et al., 2000; Sugiura et al., 1999; Sugiura et al., 2006). It is derived from AA-containing membrane phospholipids, particularly phosphatidylinositol bisphosphate (PIP_2). Phospholipase C (PLC) hydrolyzes the membrane phospholipid into diacylglycerol (DAG), which is cleaved into 2-AG by diacylglycerol lipase (DGL) (Kano et al., 2009; Sugiura et al., 2006). 2-AG production is Ca^{2+}-dependent, and it functions as a retrograde signaling molecule that is released postsynaptically after depolarization-induced Ca^{2+} influx or activation of $G_{\alpha q}$-coupled metabotropic receptors (Ohno-Shosaku et al., 2012). 2-AG diffuses across the synaptic cleft to stimulate presynaptic CB_1Rs, suppressing the release of neurotransmitters; 2-AG also mediates CB_1R-dependent LTD (Heifets and Castillo, 2009; Ohno-Shosaku and Kano, 2014). Hydrolytic metabolism of 2-AG occurs via monoacylglycerol lipase (MGL) and the serine hydrolases α/β hydrolase domain 6 and 12 (ABHD6 and 12) (Blankman et al., 2007;

Di Marzo, 2008). MGL is located in neighboring astrocytes and in the presynaptic terminal, where it hydrolyzes 2-AG into AA and glycerol, thus terminating retrograde signaling. In the brain, 2-AG hydrolysis is the main source of AA for COX-2-mediated production of prostaglandins (Di Marzo et al., 2015; Nomura et al., 2011). Thus, MGL and DGL inhibitors have been explored as an approach to treat neuroinflammation. DGL inhibitors show promise for treating metabolic disorders (Janssen and van der Stelt, 2016), although the psychiatric side effects associated with decreased eCB signaling limit the therapeutic potential of this approach. On the other hand, MGL inhibitors increase 2-AG levels and decrease AA production, thus simultaneously enhancing eCB signaling and decreasing prostaglandin production.

Selective MGL inhibitors were developed slightly later than FAAH inhibitors and include: first-generation MGL inhibitors (e.g. URB602, NAM, and OMDM169), o-aryl carbamates (e.g. JZL184), and o-hexafluorisopropyl carbamates (e.g. KML29) (Blankman and Cravatt, 2013; Granchi et al., 2017). Inhibition of MGL both increases 2-AG levels in the brain, which boosts cannabinoid receptor-mediated neuroprotection and decreases the production of prostaglandins, reducing neuroinflammation (Di Marzo et al., 2015).

Similar to FAAH inhibitors, MGL inhibitors attenuate neuropathic pain and anxiety mainly via CB_1R activation (Crowe et al., 2017; Kamimura et al., 2018; Kinsey et al., 2009; Kinsey et al., 2011a; Kinsey et al., 2011b; Sciolino et al., 2011). MGL inhibitors reduce seizures in several epileptic models, although the underlying mechanism remains contentious (Terrone et al., 2018; von Ruden et al., 2015b). Von Ruden *et al.* (2015) found that the MGL inhibitor JZL184 attenuated kindling progression in wild-type but not CB_1R knockout mice, suggesting that CB_1Rs suppress epileptogenesis (von Ruden et al., 2015a). However, in a recent study, Terrone *et al.* (2018) found that JZL184's therapeutic effect is predominantly anti-inflammatory and not CB_1R-dependent, caused by decreased availability of AA and reduced COX-2-mediated prostaglandin production (Terrone et al., 2018). One possible explanation for this difference is that the latter study used a chronic model of epilepsy, suggesting that the CB_1R-mediated pathway may play a role initially, but that chronic suppression of inflammation maintains the anti-seizure effect long-term. This transient role for CB_1Rs may result from 2-AG overload and desensitization of cannabinoid receptors following excessive inhibition of MGL (Chanda et al., 2010; Schlosburg et al., 2010). Overall, these studies indicate that MGL inhibition is neuroprotective via dual suppression of excitotoxicity and reduced neuroinflammation. A highly potent, orally available CNS-penetrant MGL inhibitor, ABX-1431, is currently in a phase 2 clinical trial for treatment of Tourette Syndrome and a phase 1 trial for neuropathic pain, suggesting therapeutic potential for this class of drugs (Cisar et al., 2018) (ClinicalTrials.gov Identifier: ,).

The effects of MGL inhibition in models of neurocognitive disorders has been extensively studied in recent years, with promising results. MGL inhibitors improved cognition and protected neuronal function in models of Alzheimer's disease and Down syndrome (Chen et al., 2012; Lysenko et al., 2014). The protection afforded by inhibition of MGL was independent of CB_1R activation, and instead involved neuroinflammatory pathways (Chen et al., 2012; Pihlaja et al., 2015; Piro et al., 2012; Yan et al., 2016) where activation of CB_2Rs on microglia reduced the production of inflammatory cytokines, and the decreased pool of

AA reduces prostaglandin production. These studies further suggest that inhibition of MGL might improve cognition in HAND patients.

Recently, we directly tested MGL inhibition in an *in vitro* model of HAND and demonstrated that the MGL inhibitor JZL184 protects against neuronal damage and excitatory synapse loss induced by HIV viral proteins (Zhang and Thayer, 2018). The protective mechanism involved activation of cannabinoid receptors, as well as decreased AA production. More studies in HAND models *in vivo* are needed to further evaluate MGL inhibitors in the treatment of HAND.

While MGL functions as the principle enzyme responsible 2-AG hydrolysis (Savinainen et al., 2012), ABHD6 and ABHD12, two other enzymes that hydrolyze 2-AG, play a smaller but still significant role. These enzymes have been evaluated for their role in eCB-mediated neuroprotection (Savinainen et al., 2012). Recent reports indicate that ABHD6 is the major 2-AG hydrolase in cell types not expressing MGL (Marrs et al.), while ABHD12 is more involved in phospholipid rather than 2-AG metabolism (Grabner et al., 2017). Only a limited number of ABHD6 inhibitors have been developed. These inhibitors include carbamate-based inhibitors WWL70, WWL123 and JZP430, and triazole urea-based inhibitors KT195 and KT20. Many of these drugs have significant off-target effects at high concentrations (Patel et al., 2015; Poursharifi et al., 2017); thus, there is a need for development of more potent and selective ABHD6 inhibitors.

The neuroprotective effects of ABHD6 inhibition have been reported in several models of neurological disorders, including neuropathic pain, seizure, traumatic brain injury, and multiple sclerosis. The mechanisms underlying neuroprotection by inhibition of ABHD6 are varied. In a model of neuropathic pain, treatment with the selective ABHD6 inhibitor WWL70 attenuated thermal hyperalgesia and mechanical allodynia by reducing the production of prostaglandin E2 and expression of COX-2, indicating an anti-inflammatory effect (Wen et al., 2018). In a model of multiple sclerosis, ABHD6 inhibition reduced neuroinflammation by activating CB_2Rs (Manterola et al., 2018; Wen et al., 2015). A mouse model of traumatic brain injury reported that WWL70 protects through activation of CB_1Rs (Tchantchou and Zhang, 2013). In contrast to these studies, in a pentylenetetrazole-induced seizure model, ABHD6 inhibition alleviated epileptic symptoms through a cannabinoid receptor-independent pathway that involved $GABA_A$ receptors (Naydenov et al., 2014). Thus, the specific neuroprotective mechanisms of ABHD6 inhibition varies across different disease models and requires further investigation. Inhibition of ABHD6 provides a novel strategy to evaluate in HAND and avoids side effects associated with desensitization of cannabinoid receptors.

3.3. Dual inhibition of AEA and 2-AG metabolism

Dual FAAH and MGL inhibitors attenuate the neuroinflammation and excitotoxicity associated with neurological disorders, such as chronic pain and seizure (Naidoo et al., 2012; Sakin et al., 2015; Sakin et al., 2018; Woodhams et al., 2017). JZL195 is the most commonly used dual inhibitor; other dual inhibitors include organophosphates (e.g. isopropyldodecylfluorophosphonate), and o-hydroxyacetamide carbamates (e.g. SA-57) (Blankman and Cravatt, 2013). The ability of these dual inhibitors to enhance eCB-mediated

neuroprotection is unclear. In rodent models of pain, these dual inhibitors usually display higher efficacy than selective MGL or FAAH inhibitors alone, and a wider therapeutic window than cannabinoid receptor agonists (Adamson Barnes et al., 2016; Anderson et al., 2014). However, in an anxiety model, JZL195 did not reduce anxiety, in contrast to selective MGL or FAAH inhibitors (Bedse et al., 2018). Recent reports show that dual inhibitors produce more cannabinoid-related side effects compared to the selective MGL or FAAH inhibitors (Seillier et al., 2014; Wise et al., 2012). Thus, the relative risks and benefits of FAAH-MGL dual inhibitors must be evaluated further in neurological disease models, including HAND.

4. Pathological Impairment of the Endocannabinoid System

One important determinant of clinical outcome is the degree to which the target biological system is functional. Studies *in vitro* and *in vivo* have shown that exposure to excitotoxic stimuli alters the eCB system (Chen et al., 2003; Feng et al., 2016; Li et al., 2012) with increased CB_1R-mediated inhibition of GABA release changing the balance of network excitability. Currently, it is not known if eCB signaling is altered in the presence of HIV. In the context of another neurodegenerative disorder, Westlake *et al.* (1994) found reduced CB_1R agonist binding in the hippocampus and caudate of Alzheimer's patients using *in vitro* receptor autoradiography. Using *in situ* hybridization histochemistry, they also found regionally discrete losses of mRNA expression in Alzheimer's relative to normal brains (Westlake et al., 1994). Similarly, Ramirez *et al.* (2005) determined that cannabinoid receptors couple less efficiently to their G-proteins in Alzheimer's brains (Ramirez et al., 2005). These and other studies suggest that impaired CB_1R-mediated signaling might diminish the neuroprotective capacity of the eCB system, reducing the efficacy of exogenous CB_1R agonists.

Several reports indicate changes in CB_1 and CB_2Rs during SIV and HIV infection. Benito *et al.* (2005) identified increases in CB_2R immunoreactivity in cortical tissue from rhesus macaques with SIV-induced encephalitis (Benito 2005). In this same study, these SIV-infected macaques also showed increased FAAH immunoreactivity in brain cortical samples. These results agree with previous observations in Alzheimer's disease brains (Benito et al., 2003), indicating a common pattern of response despite different primary inflammatory insults. Indeed, Consenza-Nashat *et al.* (2011) found CB_1 and CB_2R upregulation in macrophages and microglia in tissue from patients with HIV encephalitis (HIVE). The functional consequences of these changes are unknown; thus, it is important to determine how eCB signaling changes during exposure to HIV to evaluate the feasibility of targeting components of the eCB system and, if necessary, devise strategies to protect or enhance signaling.

5. Conclusions and Perspectives

The unique pathophysiology of HAND may be particularly amenable to modulation by the eCB system. The excitotoxic component of HAND is attenuated by activating presynaptic CB_1Rs, either directly by agonists or indirectly through inhibition of eCB metabolism. The chronic neuroinflammation associated with HAND can be attenuated by activating CB_2Rs

on immune cells or inhibiting MGL-mediated AA production. Furthermore, expression of cannabinoid receptors is increased in HAND, potentially enhancing the sensitivity of the eCB system in the presence of HIV.

There are drawbacks to targeting certain elements of the eCB system. Of particular concern are the psychoactive effects resulting from CB_1R activation. Motor impairment and reduced short term memory limit the utility of CB_1R agonists. However, it may be possible to avoid the desensitization of cannabinoid receptors that accompanies chronic activation by enhancing endogenously produced agonists with MGL and FAAH inhibitors. Because HAND patients will likely not be treated prophylactically, it will be essential to understand the time course of the disease, particularly changes in neuroinflammation, to understand the relative importance of excitotoxic and neuroinflammatory targets.

In summary, we have discussed several promising targets in the eCB system for suppressing the neuronal damage that underlies HAND (Fig. 1). CB_2R agonists suppress neuroinflammation without the psychoactive side effects of non-selective drugs that also activate CB_1Rs. MGL inhibitors are promising because they potentiate endogenously produced 2-AG to inhibit glutamate release via CB_1Rs and suppress immune function via CB_2Rs, while also decreasing the pool of AA needed for the synthesis of prostaglandins in the CNS. Both CB_2R-selective agonists and MGL inhibitors are well-tolerated and are currently in clinical trials for indications other than HAND. The work reviewed here suggests that these agents may slow the progression of HAND in individuals living with HIV.

Acknowledgements

This work was supported by National Institutes of Health Grants DA007304 and DA044809 to ST. MW was supported by NIH training grant T32 DA007097.

Abbreviations

Δ^9-THC	Δ^9-tetrahydrocannabinol
2-AG	2-arachidonoylglycerol
AA	arachidonic acid
AEA	arachidonoyl ethanolamine (anandamide)
AIDS	acquired immunodeficiency syndrome
CB_1R	cannabinoid type 1 receptor
CB_2R	cannabinoid type 2 receptor
DAG	diacylglycerol
DGL	diacylglycerol lipase
FAAH	fatty acid amide hydrolase

GPCR	G protein-coupled receptor
HIV	human immunodeficiency virus
IP_3	inositol triphosphate
MGL	monoacylglycerol lipase
NAPE-PLD	*N*-arachidonoyl phosphatidylethanolamine phospholipase D
NAT	*N*-acyltransferase
NAPE	*N*-arachidonoyl phosphatidylethanolamine
PE	phosphatidylethanolamine
PIP_2	phosphatidylinositol 4,5-bisphosphate
PLC	phospholipase C
SIV	simian immunodeficiency virus
VGCC	voltage-gated Ca^{2+} channel

References

Adamson Barnes NS, et al., 2016 Actions of the dual FAAH/MAGL inhibitor JZL195 in a murine neuropathic pain model. Br J Pharmacol. 173, 77–87. [PubMed: 26398331]

Alhouayek M, Muccioli GG, 2014 Harnessing the anti-inflammatory potential of palmitoylethanolamide. Drug Discov Today. 19, 1632–9. [PubMed: 24952959]

Alonso K, et al., 1997 Cytokine patterns in adults with AIDS. Immunol Invest. 26, 341–50. [PubMed: 9129987]

Amor S, et al., 2010 Inflammation in neurodegenerative diseases. Immunology. 129, 154–69. [PubMed: 20561356]

Anderson WB, et al., 2014 Actions of the dual FAAH/MAGL inhibitor JZL195 in a murine inflammatory pain model. Neuropharmacology. 81, 224–30. [PubMed: 24384256]

Ashton JC, Glass M, 2007 The Cannabinoid CB2 Receptor as a Target for Inflammation-Dependent Neurodegeneration. Curr Neuropharmacol. 5, 73–80. [PubMed: 18615177]

Aso E, et al., 2012 CB1 agonist ACEA protects neurons and reduces the cognitive impairment of AbetaPP/PS1 mice. J Alzheimers Dis. 30, 439–59. [PubMed: 22451318]

Aso E, Ferrer I, 2014 Cannabinoids for treatment of Alzheimer's disease: moving toward the clinic. Front Pharmacol. 5, 37. [PubMed: 24634659]

ATCC, 2008 Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet. 372, 293–9. [PubMed: 18657708]

Avraham HK, et al., 2014 The cannabinoid CB(2) receptor agonist AM1241 enhances neurogenesis in GFAP/Gp120 transgenic mice displaying deficits in neurogenesis. Br J Pharmacol. 171, 468–79. [PubMed: 24148086]

Avraham HK, et al., 2015 Impaired neurogenesis by HIV-1-Gp120 is rescued by genetic deletion of fatty acid amide hydrolase enzyme. Br J Pharmacol. 172, 4603–14. [PubMed: 24571443]

Bayewitch M, et al., 1995 The peripheral cannabinoid receptor - adenylate cyclase inhibition and g protein coupling. Febs Letters. 375, 143–147. [PubMed: 7498464]

Bedse G, et al., 2018 Therapeutic endocannabinoid augmentation for mood and anxiety disorders: comparative profiling of FAAH, MAGL and dual inhibitors. Transl Psychiatry. 8, 92. [PubMed: 29695817]

Benito C, et al., 2003 Cannabinoid CB2 Receptors and Fatty Acid Amide Hydrolase Are Selectively Overexpressed in Neuritic Plaque-Associated Glia in Alzheimer's Disease Brains. J. Neurosci. 23, 11136–11141. [PubMed: 14657172]

Benito C, et al., 2005 A Glial Endogenous Cannabinoid System Is Upregulated in the Brains of Macaques with Simian Immunodeficiency Virus-Induced Encephalitis. J. Neurosci. 25, 2530–2536. [PubMed: 15758162]

Bhuniya D, et al., 2019 Discovery and evaluation of novel FAAH inhibitors in neuropathic pain model. Bioorg Med Chem Lett. 29, 238–243. [PubMed: 30503633]

Bilsland LG, et al., 2006 Increasing cannabinoid levels by pharmacological and genetic manipulation delay disease progression in SOD1 mice. Faseb J.

Blankman JL, Simon GM, Cravatt BF, 2007 A comprehensive profile of brain enzymes that hydrolyze the endocannabinoid 2-arachidonoylglycerol. Chem Biol. 14, 1347–56. [PubMed: 18096503]

Blankman JL, Cravatt BF, 2013 Chemical probes of endocannabinoid metabolism. Pharmacol Rev. 65, 849–71. [PubMed: 23512546]

Buczynski MW, Parsons LH, 2010 Quantification of brain endocannabinoid levels: methods, interpretations and pitfalls. Br J Pharmacol. 160, 423–42. [PubMed: 20590555]

Burstein SH, et al., 2000 Oxidative metabolism of anandamide. Prostaglandins Other Lipid Mediat. 61, 29–41. [PubMed: 10785540]

Busquets-Garcia A, et al., 2011 Differential role of anandamide and 2-arachidonoylglycerol in memory and anxiety-like responses. Biol Psychiatry. 70, 479–86. [PubMed: 21684528]

Cabral GA, Griffin-Thomas L, 2009 Emerging role of the cannabinoid receptor CB2 in immune regulation: therapeutic prospects for neuroinflammation. Expert Rev Mol Med. 11, e3. [PubMed: 19152719]

Carrier EJ, et al., 2004 Cultured rat microglial cells synthesize the endocannabinoid 2-arachidonylglycerol, which increases proliferation via a CB2 receptor-dependent mechanism. Mol Pharmacol. 65, 999–1007. [PubMed: 15044630]

Cerda M, et al., 2017 Association of State Recreational Marijuana Laws With Adolescent Marijuana Use. JAMA Pediatr. 171, 142–149. [PubMed: 28027345]

Chanda PK, et al., 2010 Monoacylglycerol lipase activity is a critical modulator of the tone and integrity of the endocannabinoid system. Mol Pharmacol. 78, 996–1003. [PubMed: 20855465]

Chang L, et al., 2006 Inhibition of fatty acid amide hydrolase produces analgesia by multiple mechanisms. Br J Pharmacol. 148, 102–13. [PubMed: 16501580]

Chen F, et al., 2006 TMP21 is a presenilin complex component that modulates gamma-secretase but not epsilon-secretase activity. Nature. 440, 1208–12. [PubMed: 16641999]

Chen K, et al., 2003 Long-term plasticity of endocannabinoid signaling induced by developmental febrile seizures. Neuron. 39, 599–611. [PubMed: 12925275]

Chen R, et al., 2012 Monoacylglycerol lipase is a therapeutic target for Alzheimer's disease. Cell Rep. 2, 1329–39. [PubMed: 23122958]

Cisar JS, et al., 2018 Identification of ABX-1431, a Selective Inhibitor of Monoacylglycerol Lipase and Clinical Candidate for Treatment of Neurological Disorders. J Med Chem. 61, 9062–9084. [PubMed: 30067909]

Colangeli R, et al., 2017 The FAAH inhibitor URB597 suppresses hippocampal maximal dentate afterdischarges and restores seizure-induced impairment of short and long-term synaptic plasticity. Sci Rep. 7, 11152. [PubMed: 28894217]

Cosenza-Nashat MA, et al., 2011 Cannabinoid receptor expression in HIV encephalitis and HIV-associated neuropathologic comorbidities. Neuropathol Appl Neurobiol. 37, 464–83. [PubMed: 21450051]

Costantino CM, et al., 2012 Cannabinoid receptor 2-mediated attenuation of CXCR4-tropic HIV infection in primary CD4+ T cells. PLoS One. 7, e33961. [PubMed: 22448282]

Cravatt BF, et al., 1996 Molecular Characterization of an Enzyme That Degrades Neuromodulatory Fatty-Acid Amides. Nature. 384, 83–87. [PubMed: 8900284]

Crowe MS, et al., 2017 The monoacylglycerol lipase inhibitor KML29 with gabapentin synergistically produces analgesia in mice. Br J Pharmacol. 174, 4523–4539. [PubMed: 28963716]

Cuevas-Olguin R, et al., 2017 Interleukin 6 trans-signaling regulates basal synaptic transmission and sensitivity to pentylenetetrazole-induced seizures in mice. Synapse. 71.

Cysique LA, Maruff P, Brew BJ, 2004 Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus–infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: A combined study of two cohorts. J Neurovirol. 10, 350–357. [PubMed: 15765806]

Dalton GD, Howlett AC, 2012 Cannabinoid CB1 receptors transactivate multiple receptor tyrosine kinases and regulate serine/threonine kinases to activate ERK in neuronal cells. Br J Pharmacol. 165, 2497–511. [PubMed: 21518335]

de Lago E, et al., 2012 Cannabinoids ameliorate disease progression in a model of multiple sclerosis in mice, acting preferentially through CB1 receptor-mediated anti-inflammatory effects. Neuropharmacology. 62, 2299–308. [PubMed: 22342378]

Devane WA, et al., 1992 Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science. 258, 1946–1949. [PubMed: 1470919]

Di Marzo V, et al., 1998 Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action [Review]. Trends in Neurosciences. 21, 521–528. [PubMed: 9881850]

Di Marzo V, 2008 Endocannabinoids: synthesis and degradation. Rev Physiol Biochem Pharmacol. 160, 1–24. [PubMed: 18481028]

Di Marzo V, Stella N, Zimmer A, 2015 Endocannabinoid signalling and the deteriorating brain. Nat Rev Neurosci. 16, 30–42. [PubMed: 25524120]

Dong XX, Wang Y, Qin ZH, 2009 Molecular mechanisms of excitotoxicity and their relevance to pathogenesis of neurodegenerative diseases. Acta Pharmacol Sin. 30, 379–87. [PubMed: 19343058]

Dore GJ, et al., 2003 Marked improvement in survival following AIDS dementia complex in the era of highly active antiretroviral therapy. AIDS. 17, 1539–45. [PubMed: 12824792]

Egertova M, Cravatt BF, Elphick MR, 2003 Comparative analysis of fatty acid amide hydrolase and cb(1) cannabinoid receptor expression in the mouse brain: evidence of a widespread role for fatty acid amide hydrolase in regulation of endocannabinoid signaling. Neuroscience. 119, 481–96. [PubMed: 12770562]

Egertova M, et al., 2008 Localization of N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) expression in mouse brain: A new perspective on N-acylethanolamines as neural signaling molecules. J Comp Neurol. 506, 604–15. [PubMed: 18067139]

Ehrhart J, et al., 2005 Stimulation of cannabinoid receptor 2 (CB2) suppresses microglial activation. J Neuroinflammation. 2, 29. [PubMed: 16343349]

Everall I, et al., 2009 Cliniconeuropathologic correlates of human immunodeficiency virus in the era of antiretroviral therapy. J Neurovirol. 15, 360–70. [PubMed: 20175693]

Farrell JS, Soltesz I, 2018 Plants come to mind: phytocannabinoids, endocannabinoids and the control of seizures. Addiction.

Feng B, et al., 2016 Transient increase of interleukin-1beta after prolonged febrile seizures promotes adult epileptogenesis through long-lasting upregulating endocannabinoid signaling. Sci Rep. 6, 21931. [PubMed: 26902320]

Festa L, et al., 2015 Induction of Interleukin-1beta by Human Immunodeficiency Virus-1 Viral Proteins Leads to Increased Levels of Neuronal Ferritin Heavy Chain, Synaptic Injury, and Deficits in Flexible Attention. J Neurosci. 35, 10550–61. [PubMed: 26203149]

Fraga D, et al., 2011 Cannabinoids inhibit migration of microglial-like cells to the HIV protein Tat. J Neuroimmune Pharmacol. 6, 566–77. [PubMed: 21735070]

Gerdeman G, Lovinger DM, 2001 CB1 cannabinoid receptor inhibits synaptic release of glutamate in rat dorsolateral striatum. Journal of Neurophysiology. 85, 468–471. [PubMed: 11152748]

Gomes FV, et al., 2011 Facilitation of CB1 receptor-mediated neurotransmission decreases marble burying behavior in mice. Prog Neuropsychopharmacol Biol Psychiatry. 35, 434–8. [PubMed: 21111767]

Gong JP, et al., 2006 Cannabinoid CB2 receptors: immunohistochemical localization in rat brain. Brain Res. 1071, 10–23. [PubMed: 16472786]

Gonsiorek W, et al., 2000 Endocannabinoid 2-arachidonyl glycerol is a full agonist through human type 2 cannabinoid receptor: Antagonism by anandamide. Molecular Pharmacology. 57, 1045–1050. [PubMed: 10779390]

Gorantla S, et al., 2010 Immunoregulation of a CB2 Receptor Agonist in a Murine Model of NeuroAIDS. Journal of Neuroimmune Pharmacology. 5, 456–468. [PubMed: 20549374]

Grabner GF, et al., 2017 Monoglyceride lipase as a drug target: At the crossroads of arachidonic acid metabolism and endocannabinoid signaling. Pharmacol Ther. 175, 35–46. [PubMed: 28213089]

Granchi C, et al., 2017. A patent review of Monoacylglycerol Lipase (MAGL) inhibitors (2013–2017). Expert Opin Ther Pat. 27, 1341–1351. [PubMed: 29053063]

Green MV, et al., 2018 Scaling Synapses in the Presence of HIV. Neurochem Res.

Grueter BA, Brasnjo G, Malenka RC, 2010 Postsynaptic TRPV1 triggers cell type-specific long-term depression in the nucleus accumbens. Nat Neurosci. 13, 1519–25. [PubMed: 21076424]

Guggenhuber S, et al., 2010 AAV vector-mediated overexpression of CB1 cannabinoid receptor in pyramidal neurons of the hippocampus protects against seizure-induced excitoxicity. PLoS One. 5, e15707. [PubMed: 21203567]

Haghani M, et al., 2012 CB1 cannabinoid receptor activation rescues amyloid beta-induced alterations in behaviour and intrinsic electrophysiological properties of rat hippocampal CA1 pyramidal neurones. Cell Physiol Biochem. 29, 391–406. [PubMed: 22508047]

Han S, et al., 2017 Discovery of APD371: Identification of a Highly Potent and Selective CB2 Agonist for the Treatment of Chronic Pain. ACS Med Chem Lett. 8, 1309–1313. [PubMed: 29259753]

Haney M, et al., 2005 Dronabinol and marijuana in HIV(+) marijuana smokers: acute effects on caloric intake and mood. Psychopharmacology (Berl). 181, 170–8. [PubMed: 15778874]

Hanus L, et al., 1993 Two new unsaturated fatty acid ethanolamides in brain that bind to the cannabinoid receptor. J Med Chem. 36, 3032–4. [PubMed: 8411021]

Hanus L, et al., 2001 2-Arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB1 receptor. Proceedings of the National Academy of Sciences of the United States of America. 98, 3662–3665. [PubMed: 11259648]

Heaton RK, et al., 1995 The HNRC 500--neuropsychology of HIV infection at different disease stages. HIV Neurobehavioral Research Center. J Int Neuropsychol Soc. 1, 231–51. [PubMed: 9375218]

Heaton RK, et al., 2010 HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology. 75, 2087–96. [PubMed: 21135382]

Heifets BD, Castillo PE, 2009 Endocannabinoid signaling and long-term synaptic plasticity. Annu Rev Physiol. 71, 283–306. [PubMed: 19575681]

Herkenham M, et al., 1991 Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. Journal of Neuroscience. 11, 563–83. [PubMed: 1992016]

Hermes DJ, et al., 2018 Neuroprotective effects of fatty acid amide hydrolase catabolic enzyme inhibition in a HIV-1 Tat model of neuroAIDS. Neuropharmacology. 141, 55–65. [PubMed: 30114402]

Howlett AC, et al., 2002 International Union of Pharmacology. XXVII. Classification of cannabinoid receptors [Review]. Pharmacological Reviews. 54, 161–202. [PubMed: 12037135]

Hu S, Sheng WS, Rock RB, 2013 CB2 receptor agonists protect human dopaminergic neurons against damage from HIV-1 gp120. PLoS One. 8, e77577. [PubMed: 24147028]

Huggins JP, et al., 2012 An efficient randomised, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee. Pain. 153, 1837–46. [PubMed: 22727500]

Janssen FJ, van der Stelt M, 2016 Inhibitors of diacylglycerol lipases in neurodegenerative and metabolic disorders. Bioorg Med Chem Lett. 26, 3831–7. [PubMed: 27394666]

Javed H, et al., 2016 Cannabinoid Type 2 (CB2) Receptors Activation Protects against Oxidative Stress and Neuroinflammation Associated Dopaminergic Neurodegeneration in Rotenone Model of Parkinson's Disease. Front Neurosci. 10, 321. [PubMed: 27531971]

Jayant S, et al., 2016 Pharmacological benefits of selective modulation of cannabinoid receptor type 2 (CB2) in experimental Alzheimer's disease. Pharmacol Biochem Behav. 140, 39–50. [PubMed: 26577751]

Jee Kim M, et al., 2018 Analgesic effects of FAAH inhibitor in the insular cortex of nerve-injured rats. Mol Pain. 14, 1744806918814345.

Kamimura R, et al., 2018 Inhibition of 2-arachydonoylgycerol degradation attenuates orofacial neuropathic pain in trigeminal nerve-injured mice. J Oral Sci. 60, 37–44. [PubMed: 29503395]

Kano M, et al., 2009 Endocannabinoid-mediated control of synaptic transmission. Physiol Rev. 89, 309–80. [PubMed: 19126760]

Kano M, 2014 Control of synaptic function by endocannabinoid-mediated retrograde signaling. Proc Jpn Acad Ser B Phys Biol Sci. 90, 235–50.

Karanian DA, et al., 2007 Endocannabinoid enhancement protects against kainic acid-induced seizures and associated brain damage. J Pharmacol Exp Ther. 322, 1059–66. [PubMed: 17545313]

Kerbrat A, et al., 2016 Acute Neurologic Disorder from an Inhibitor of Fatty Acid Amide Hydrolase. N Engl J Med. 375, 1717–1725. [PubMed: 27806235]

Kim HJ, Shin AH, Thayer SA, 2011 Activation of cannabinoid type 2 receptors inhibits HIV-1 envelope glycoprotein gp120-induced synapse loss. Mol Pharmacol. 80, 357–66. [PubMed: 21670103]

Kinsey SG, et al., 2009 Blockade of endocannabinoid-degrading enzymes attenuates neuropathic pain. J Pharmacol Exp Ther. 330, 902–10. [PubMed: 19502530]

Kinsey SG, et al., 2011a Fatty acid amide hydrolase blockade attenuates the development of collagen-induced arthritis and related thermal hyperalgesia in mice. Pharmacol Biochem Behav. 99, 718–25. [PubMed: 21740924]

Kinsey SG, et al., 2011b Inhibition of endocannabinoid catabolic enzymes elicits anxiolytic-like effects in the marble burying assay. Pharmacol Biochem Behav. 98, 21–7. [PubMed: 21145341]

Klegeris A, Bissonnette CJ, McGeer PL, 2003 Reduction of human monocytic cell neurotoxicity and cytokine secretion by ligands of the cannabinoid-type CB2 receptor. British Journal of Pharmacology. 139, 775–786. [PubMed: 12813001]

Kozela E, et al., 2011 Cannabidiol inhibits pathogenic T cells, decreases spinal microglial activation and ameliorates multiple sclerosis-like disease in C57BL/6 mice. Br J Pharmacol. 163, 1507–19. [PubMed: 21449980]

Krishnan S, Cairns R, Howard R, 2009 Cannabinoids for the treatment of dementia. Cochrane Database Syst Rev. CD007204. [PubMed: 19370677]

Li Y, Krogh KA, Thayer SA, 2012 Epileptic stimulus increases Homer 1a expression to modulate endocannabinoid signaling in cultured hippocampal neurons. Neuropharmacol. 63, 1140–1149.

Liu J, et al., 2006 A biosynthetic pathway for anandamide. Proc Natl Acad Sci U S A. 103, 13345–50. [PubMed: 16938887]

Lopez-Quintero C, et al., 2011 Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). Drug Alcohol Depend. 115, 120–30. [PubMed: 21145178]

Ludanyi A, et al., 2011 Complementary synaptic distribution of enzymes responsible for synthesis and inactivation of the endocannabinoid 2-arachidonoylglycerol in the human hippocampus. Neuroscience. 174, 50–63. [PubMed: 21035522]

Lutge EE, Gray A, Siegfried N, 2013 The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. Cochrane Database Syst Rev. 4, CD005175.

Lysenko LV, et al., 2014 Monoacylglycerol lipase inhibitor JZL184 improves behavior and neural properties in Ts65Dn mice, a model of down syndrome. PLoS One. 9, e114521. [PubMed: 25474204]

Mackie K, Devane WA, Hille B, 1993 Anandamide, an endogenous cannabinoid, inhibits calcium currents as a partial agonist in N18 neuroblastoma cells. Molecular Pharmacology. 44, 498–503. [PubMed: 8371711]

Mackie K, 2005 Distribution of Cannabinoid Receptors in the Central and Peripheral Nervous System In: Cannabinoids. Vol., Pertwee RG, ed.êds. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 299–325.

Malek N, et al., 2015 Anandamide, Acting via CB2 Receptors, Alleviates LPS-Induced Neuroinflammation in Rat Primary Microglial Cultures. Neural Plast. 2015, 130639. [PubMed: 26090232]

Manterola A, et al., 2018 Re-examining the potential of targeting ABHD6 in multiple sclerosis: Efficacy of systemic and peripherally restricted inhibitors in experimental autoimmune encephalomyelitis. Neuropharmacology. 141, 181–191. [PubMed: 30171986]

Marrs WR, et al., The serine hydrolase ABHD6 controls the accumulation and efficacy of 2-AG at cannabinoid receptors. Nat Neurosci. 13, 951–7. [PubMed: 20657592]

Marsicano G, Lutz B, 1999 Expression of the cannabinoid receptor CB1 in distinct neuronal subpopulations in the adult mouse forebrain. European Journal of Neuroscience. 11, 4213–4225. [PubMed: 10594647]

Marsicano G, et al., 2003 CB1 Cannabinoid Receptors and On-Demand Defense Against Excitotoxicity. Science. 302, 84–88. [PubMed: 14526074]

Matsuda LA, Bonner TL, Lolait SJ, 1993 Localization of cannabinoid receptor mRNA in rat brain. J Comp Neurol. 327, 535–550. [PubMed: 8440779]

McArthur JC, 1993 Clinical-neuropathologic correlation in HIV-associated dementia. Neurology. 43, 2230–2237. [PubMed: 8232935]

Mecha M, et al., 2015 Endocannabinoids drive the acquisition of an alternative phenotype in microglia. Brain Behav Immun. 49, 233–45. [PubMed: 26086345]

Mechoulam R, et al., 1995 Identification of an Endogenous 2-Monoglyceride, Present in Canine Gut, That Binds to Cannabinoid Receptors. Biochemical Pharmacology. 50, 83–90. [PubMed: 7605349]

Mishra A, et al., 2016 Astrocytes mediate neurovascular signaling to capillary pericytes but not to arterioles. Nat Neurosci. 19, 1619–1627. [PubMed: 27775719]

Mitchell VA, et al., 2007 Actions of the endocannabinoid transport inhibitor AM404 in neuropathic and inflammatory pain models. Clin Exp Pharmacol Physiol. 34, 1186–90. [PubMed: 17880375]

Molina-Holgado E, et al., 2002 Cannabinoids Promote Oligodendrocyte Progenitor Survival: Involvement of Cannabinoid Receptors and Phosphatidylinositol-3 Kinase/Akt Signaling. J. Neurosci 22, 9742–9753. [PubMed: 12427829]

Molina-Holgado F, et al., 2003 Endogenous Interleukin-1 Receptor Antagonist Mediates Anti-Inflammatory and Neuroprotective Actions of Cannabinoids in Neurons and Glia. J. Neurosci 23, 6470–6474. [PubMed: 12878687]

Molinski SV, et al., 2017 Computational proteome-wide screening predicts neurotoxic drug-protein interactome for the investigational analgesic BIA 10–2474. Biochem Biophys Res Commun. 483, 502–508. [PubMed: 28007597]

Monory K, et al., 2006 The endocannabinoid system controls key epileptogenic circuits in the hippocampus. Neuron. 51, 455–66. [PubMed: 16908411]

More SV, Choi DK, 2015 Promising cannabinoid-based therapies for Parkinson's disease: motor symptoms to neuroprotection. Mol Neurodegener. 10, 17. [PubMed: 25888232]

Mounsey RB, et al., 2015 Increasing levels of the endocannabinoid 2-AG is neuroprotective in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease. Exp Neurol. 273, 36–44. [PubMed: 26244281]

Muccioli GG, et al., 2007 Identification of a Novel Endocannabinoid-Hydrolyzing Enzyme Expressed by Microglial Cells. J. Neurosci 27, 2883–2889. [PubMed: 17360910]

Nagayama T, et al., 1999 Cannabinoids and neuroprotection in global and focal cerebral ischemia and in neuronal cultures. J Neurosci 19, 2987–95. [PubMed: 10191316]

Naidoo V, et al., 2012 Equipotent inhibition of fatty acid amide hydrolase and monoacylglycerol lipase - dual targets of the endocannabinoid system to protect against seizure pathology. Neurotherapeutics. 9, 801–13. [PubMed: 22270809]

Nasirinezhad F, et al., 2015 Attenuation of persistent pain-related behavior by fatty acid amide hydrolase (FAAH) inhibitors in a rat model of HIV sensory neuropathy. Neuropharmacology. 95, 100–9. [PubMed: 25486617]

Navarrete M, Araque A, 2008 Endocannabinoids mediate neuron-astrocyte communication. Neuron. 57, 883–93. [PubMed: 18367089]

Navarrete M, Araque A, 2010 Endocannabinoids potentiate synaptic transmission through stimulation of astrocytes. Neuron. 68, 113–26. [PubMed: 20920795]

Navarrete M, Diez A, Araque A, 2014 Astrocytes in endocannabinoid signalling. Philos Trans R Soc Lond B Biol Sci. 369, 20130599. [PubMed: 25225093]

Naydenov AV, et al., 2014 ABHD6 blockade exerts antiepileptic activity in PTZ-induced seizures and in spontaneous seizures in R6/2 mice. Neuron. 83, 361–71. [PubMed: 25033180]

Naziroglu M, et al., 2018 Inhibitions of anandamide transport and FAAH synthesis decrease apoptosis and oxidative stress through inhibition of TRPV1 channel in an in vitro seizure model. Mol Cell Biochem.

Nomura DK, et al., 2011 Endocannabinoid hydrolysis generates brain prostaglandins that promote neuroinflammation. Science. 334, 809–13. [PubMed: 22021672]

Nunez E, et al., 2004 Cannabinoid CB2 receptors are expressed by perivascular microglial cells in the human brain: an immunohistochemical study. Synapse. 53, 208–13. [PubMed: 15266552]

Ohno-Shosaku T, et al., 2012 Endocannabinoids and retrograde modulation of synaptic transmission. Neuroscientist. 18, 119–32. [PubMed: 21531987]

Ohno-Shosaku T, Kano M, 2014 Endocannabinoid-mediated retrograde modulation of synaptic transmission. Curr Opin Neurobiol. 29C, 1–8.

Oka S, et al., 2005 Evidence for the involvement of the cannabinoid CB2 receptor and its endogenous ligand 2-arachidonoylglycerol in 12-O-tetradecanoylphorbol-13-acetate-induced acute inflammation in mouse ear. J Biol Chem. 280, 18488–97. [PubMed: 15749716]

Oka S, et al., 2006 Involvement of the cannabinoid CB2 receptor and its endogenous ligand 2-arachidonoylglycerol in oxazolone-induced contact dermatitis in mice. J Immunol. 177, 8796–805. [PubMed: 17142782]

Okafor CN, et al., 2017 Prevalence and correlates of marijuana use among HIV-seropositive and seronegative men in the Multicenter AIDS Cohort Study (MACS), 1984–2013. Am J Drug Alcohol Abuse. 43, 556–566. [PubMed: 27808576]

Oliveira da Cruz JF, et al., 2016 Astroglial type-1 cannabinoid receptor (CB1): A new player in the tripartite synapse. Neuroscience. 323, 35–42. [PubMed: 25967266]

Pacek LR, et al., 2018 Frequency of Cannabis Use and Medical Cannabis Use Among Persons Living With HIV in the United States: Findings From a Nationally Representative Sample. AIDS Educ Prev. 30, 169–181. [PubMed: 29688777]

Palazuelos J, et al., 2009 Microglial CB2 cannabinoid receptors are neuroprotective in Huntington's disease excitotoxicity. Brain.

Panikashvili D, et al., 2001 An endogenous cannabinoid (2-AG) is neuroprotective after brain injury. Nature. 413, 527–31. [PubMed: 11586361]

Patel JZ, et al., 2015 Optimization of 1,2,5-thiadiazole carbamates as potent and selective ABHD6 inhibitors. ChemMedChem. 10, 253–65. [PubMed: 25504894]

Pertwee RG, et al., 2010 International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB(1) and CB(2). Pharmacol Rev. 62, 588–631. [PubMed: 21079038]

Pihlaja R, et al., 2015 Monoacylglycerol lipase inhibitor JZL184 reduces neuroinflammatory response in APdE9 mice and in adult mouse glial cells. J Neuroinflammation. 12, 81. [PubMed: 25927213]

Piro JR, et al., 2012 A dysregulated endocannabinoid-eicosanoid network supports pathogenesis in a mouse model of Alzheimer's disease. Cell Rep. 1, 617–23. [PubMed: 22813736]

Plasse TF, et al., 1991 Recent clinical experience with dronabinol. Pharmacology, Biochemistry & Behavior. 40, 695–700.

Poursharifi P, Madiraju SRM, Prentki M, 2017 Monoacylglycerol signalling and ABHD6 in health and disease. Diabetes Obes Metab. 19 Suppl 1, 76–89. [PubMed: 28880480]

Prashad S, Filbey FM, 2017 Cognitive motor deficits in cannabis users. Curr Opin Behav Sci. 13, 1–7. [PubMed: 27482533]

Purohit V, Rapaka RS, Rutter J, 2014 Cannabinoid receptor-2 and HIV-associated neurocognitive disorders. J Neuroimmune Pharmacol. 9, 447–53. [PubMed: 25015040]

Raborn ES, et al., 2014 Cannabinoid inhibits HIV-1 Tat-stimulated adhesion of human monocyte-like cells to extracellular matrix proteins. Life Sci. 104, 15–23. [PubMed: 24742657]

Ramirez BG, et al., 2005 Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation. J Neurosci. 25, 1904–13. [PubMed: 15728830]

Ranganathan M, D'Souza DC, 2006 The acute effects of cannabinoids on memory in humans: a review. Psychopharmacology (Berl). 188, 425–44. [PubMed: 17019571]

Romero-Sandoval EA, et al., 2009 Cannabinoid receptor type 2 activation induces a microglial anti-inflammatory phenotype and reduces migration via MKP induction and ERK dephosphorylation. Mol Pain. 5, 25. [PubMed: 19476641]

Ross RA, 2003 Anandamide and vanilloid TRPV1 receptors. Br J Pharmacol. 140, 790–801. [PubMed: 14517174]

Russo R, et al., 2007 The fatty acid amide hydrolase inhibitor URB597 (cyclohexylcarbamic acid 3'-carbamoylbiphenyl-3-yl ester) reduces neuropathic pain after oral administration in mice. J Pharmacol Exp Ther. 322, 236–42. [PubMed: 17412883]

Sacktor N, et al., 2001 CSF antiretroviral drug penetrance and the treatment of HIV-associated psychomotor slowing. Neurology. 57, 542–4. [PubMed: 11502933]

Sakin YS, et al., 2015 The effect of FAAH, MAGL, and Dual FAAH/MAGL inhibition on inflammatory and colorectal distension-induced visceral pain models in Rodents. Neurogastroenterol Motil. 27, 936–44. [PubMed: 25869205]

Sakin YS, Tanoglu A, Gulsen M, 2018 Dual FAAH and MAGL inhibition might play a key role in visceral pain. Turk J Gastroenterol. 29, 625–626. [PubMed: 30260791]

Saliba SW, et al., 2018 Anti-neuroinflammatory effects of GPR55 antagonists in LPS-activated primary microglial cells. J Neuroinflammation. 15, 322. [PubMed: 30453998]

Savinainen JR, et al., 2001 Despite substantial degradation, 2-arachidonoylglycerol is a potent full efficacy agonist mediating CB1 receptor-dependent G-protein activation in rat cerebellar membranes. British Journal of Pharmacology. 134, 664–672. [PubMed: 11588122]

Savinainen JR, Saario SM, Laitinen JT, 2012 The serine hydrolases MAGL, ABHD6 and ABHD12 as guardians of 2-arachidonoylglycerol signalling through cannabinoid receptors. Acta Physiol (Oxf). 204, 267–76. [PubMed: 21418147]

Saylor D, et al., 2016 HIV-associated neurocognitive disorder - pathogenesis and prospects for treatment. Nat Rev Neurol. 12, 234–48. [PubMed: 26965674]

Schlosburg JE, Kinsey SG, Lichtman AH, 2009 Targeting fatty acid amide hydrolase (FAAH) to treat pain and inflammation. Aaps J. 11, 39–44. [PubMed: 19184452]

Schlosburg JE, et al., 2010 Chronic monoacylglycerol lipase blockade causes functional antagonism of the endocannabinoid system. Nat Neurosci. 13, 1113–9. [PubMed: 20729846]

Sciolino NR, Zhou W, Hohmann AG, 2011 Enhancement of endocannabinoid signaling with JZL184, an inhibitor of the 2-arachidonoylglycerol hydrolyzing enzyme monoacylglycerol lipase, produces anxiolytic effects under conditions of high environmental aversiveness in rats. Pharmacol Res. 64, 226–34. [PubMed: 21600985]

Scotter EL, et al., 2010 Neuroprotective potential of CB1 receptor agonists in an in vitro model of Huntington's disease. Br J Pharmacol. 160, 747–61. [PubMed: 20590577]

Seillier A, Dominguez Aguilar D, Giuffrida A, 2014 The dual FAAH/MAGL inhibitor JZL195 has enhanced effects on endocannabinoid transmission and motor behavior in rats as compared to those of the MAGL inhibitor JZL184. Pharmacol Biochem Behav. 124, 153–9. [PubMed: 24911644]

Shao BZ, et al., 2014 Activating cannabinoid receptor 2 alleviates pathogenesis of experimental autoimmune encephalomyelitis via activation of autophagy and inhibiting NLRP3 inflammasome. CNS Neurosci Ther. 20, 1021–8. [PubMed: 25417929]

Shen M, et al., 1996 Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. J Neurosci. 16, 4322–34. [PubMed: 8699243]

Shen M, Thayer SA, 1998 Cannabinoid receptor agonists protect cultured rat hippocampal neurons from excitotoxicity. Molec Pharmacol. 54, 459–462. [PubMed: 9730904]

Shimohama S, et al., 2000 Activation of NADPH oxidase in Alzheimer's disease brains. Biochem Biophys Res Commun. 273, 5–9. [PubMed: 10873554]

Shoemaker JL, et al., 2007 The CB2 cannabinoid agonist AM-1241 prolongs survival in a transgenic mouse model of amyotrophic lateral sclerosis when initiated at symptom onset. J Neurochem. 101, 87–98. [PubMed: 17241118]

Slipetz DM, et al., 1995 Activation of the human peripheral cannabinoid receptor results in inhibition of adenylyl cyclase. Molecular Pharmacology. 48, 352–361. [PubMed: 7651369]

Smith NA, Bekar LK, Nedergaard M, 2019 Astrocytic Endocannabinoids Mediate Hippocampal Transient Heterosynaptic Depression. Neurochem Res.

Smrcka AV, 2008 G protein betagamma subunits: central mediators of G protein-coupled receptor signaling. Cell Mol Life Sci. 65, 2191–214. [PubMed: 18488142]

Ssentongo P, 2019 Prevalence and incidence of new-onset seizures and epilepsy in patients with human immunodeficiency virus (HIV): Systematic review and meta-analysis. Epilepsy Behav. 93, 49–55. [PubMed: 30831402]

Sugaya Y, et al., 2016 Crucial Roles of the Endocannabinoid 2-Arachidonoylglycerol in the Suppression of Epileptic Seizures. Cell Rep.

Sugiura T, et al., 1999 Evidence that the cannabinoid CB1 receptor is a 2arachidonoylglycerol receptor. Structure-activity relationship of 2-arachidonoylglycerol, ether-linked analogues, and related compounds. J Biol Chem. 274, 2794–801. [PubMed: 9915812]

Sugiura T, et al., 2000 Evidence that 2-arachidonoylglycerol but not N-palmitoylethanolamine or anandamide is the physiological ligand for the cannabinoid CB2 receptor - Comparison of the agonistic activities of various cannabinoid receptor ligands in HL-60 cells. Journal of Biological Chemistry. 275, 605–612. [PubMed: 10617657]

Sugiura T, et al., 2006 Biochemistry, pharmacology and physiology of 2-arachidonoylglycerol, an endogenous cannabinoid receptor ligand. Prog Lipid Res.

Tchantchou F, Zhang Y, 2013 Selective inhibition of alpha/beta-hydrolase domain 6 attenuates neurodegeneration, alleviates blood brain barrier breakdown, and improves functional recovery in a mouse model of traumatic brain injury. J Neurotrauma. 30, 565–79. [PubMed: 23151067]

Tchantchou F, et al., 2014 The fatty acid amide hydrolase inhibitor PF-3845 promotes neuronal survival, attenuates inflammation and improves functional recovery in mice with traumatic brain injury. Neuropharmacology. 85, 427–39. [PubMed: 24937045]

Ternianov A, et al., 2012 Overexpression of CB2 cannabinoid receptors results in neuroprotection against behavioral and neurochemical alterations induced by intracaudate administration of 6-hydroxydopamine. Neurobiol Aging. 33, 421 e1–16.

Terranova JP, et al., 1995 Inhibition of long-term potentiation in rat hippocampal slices by anandamide and win55212–2 - reversal by sr141716 a, a selective antagonist of cb1 cannabinoid receptors. Naunyn Schmiedebergs Archives of Pharmacology. 352, 576–579. [PubMed: 8751088]

Terrone G, et al., 2018 Inhibition of monoacylglycerol lipase terminates diazepam-resistant status epilepticus in mice and its effects are potentiated by a ketogenic diet. Epilepsia. 59, 79–91. [PubMed: 29171003]

Thames AD, et al., 2016 Combined effects of HIV and marijuana use on neurocognitive functioning and immune status. AIDS Care. 28, 628–32. [PubMed: 26694807]

Tozzi V, et al., 2005 Neurocognitive impairment and survival in a cohort of HIV-infected patients treated with HAART. AIDS Res Hum Retroviruses. 21, 706–13. [PubMed: 16131310]

Tsou K, et al., 1998a Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. Neuroscience. 83, 393–411. [PubMed: 9460749]

Tsou K, et al., 1998b Fatty acid amide hydrolase is located preferentially in large neurons in the rat central nervous system as revealed by immunohistochemistry. Neurosci Lett. 254, 137–40. [PubMed: 10214976]

Ubaida-Mohien C, et al., 2017 Modifications in acute phase and complement systems predict shifts in cognitive status of HIV-infected patients. AIDS. 31, 1365–1378. [PubMed: 28574961]

Valcour V, et al., 2011 Pathogenesis of HIV in the central nervous system. Curr HIV/AIDS Rep. 8, 54–61. [PubMed: 21191673]

van Esbroeck ACM, et al., 2017 Activity-based protein profiling reveals off-target proteins of the FAAH inhibitor BIA 10–2474. Science. 356, 1084–1087. [PubMed: 28596366]

Vazquez C, et al., 2015a Endocannabinoid regulation of amyloid-induced neuroinflammation. Neurobiol Aging. 36, 3008–3019. [PubMed: 26362942]

Vazquez C, et al., 2015b Endocannabinoids regulate the activity of astrocytic hemichannels and the microglial response against an injury: In vivo studies. Neurobiol Dis. 79, 41–50. [PubMed: 25917763]

Viader A, et al., 2015 Metabolic Interplay between Astrocytes and Neurons Regulates Endocannabinoid Action. Cell Rep. 12, 798–808. [PubMed: 26212325]

Viader A, et al., 2016 A chemical proteomic atlas of brain serine hydrolases identifies cell type-specific pathways regulating neuroinflammation. Elife. 5, e12345. [PubMed: 26779719]

Volkow ND, et al., 2014 Adverse health effects of marijuana use. N Engl J Med. 370, 2219–27. [PubMed: 24897085]

von Ruden EL, et al., 2015a Inhibition of monoacylglycerol lipase mediates a cannabinoid 1-receptor dependent delay of kindling progression in mice. Neurobiol Dis. 77, 238–45. [PubMed: 25796567]

von Ruden EL, et al., 2015b Analysis in conditional cannabinoid 1 receptor-knockout mice reveals neuronal subpopulation-specific effects on epileptogenesis in the kindling paradigm. Neurobiol Dis. 73, 334–47. [PubMed: 25123336]

Vossel KA, et al., 2017 Epileptic activity in Alzheimer's disease: causes and clinical relevance. Lancet Neurol. 16, 311–322. [PubMed: 28327340]

Walsh JG, et al., 2014 Rapid inflammasome activation in microglia contributes to brain disease in HIV/AIDS. Retrovirology. 11, 35. [PubMed: 24886384]

Walter L, et al., 2003 Nonpsychotropic Cannabinoid Receptors Regulate Microglial Cell Migration. J. Neurosci. 23, 1398–1405. [PubMed: 12598628]

Walter L, Stella N, 2004 Cannabinoids and neuroinflammation [Review]. British Journal of Pharmacology. 141, 775–785. [PubMed: 14757702]

Webster KM, et al., 2017 Inflammation in epileptogenesis after traumatic brain injury. J Neuroinflammation. 14, 10. [PubMed: 28086980]

Wen J, et al., 2015 Activation of CB2 receptor is required for the therapeutic effect of ABHD6 inhibition in experimental autoimmune encephalomyelitis. Neuropharmacology. 99, 196–209. [PubMed: 26189763]

Wen J, et al., 2018 WWL70 protects against chronic constriction injury-induced neuropathic pain in mice by cannabinoid receptor-independent mechanisms. J Neuroinflammation. 15, 9. [PubMed: 29310667]

Westlake TM, et al., 1994 Cannabinoid receptor binding and messenger RNA expression in human brain: an in vitro receptor autoradiography and in situ hybridization histochemistry study of normal aged and Alzheimer's brains. Neuroscience. 63, 637–52. [PubMed: 7898667]

Wiley JL, et al., 2005 CB1 cannabinoid receptor-mediated modulation of food intake in mice. Br J Pharmacol. 145, 293–300. [PubMed: 15778743]

Williams JC, et al., 2014 Delta(9)-Tetrahydrocannabinol treatment during human monocyte differentiation reduces macrophage susceptibility to HIV-1 infection. J Neuroimmune Pharmacol. 9, 369–79. [PubMed: 24562630]

Wise LE, et al., 2012 Dual fatty acid amide hydrolase and monoacylglycerol lipase blockade produces THC-like Morris water maze deficits in mice. ACS Chem Neurosci. 3, 369–78. [PubMed: 22860205]

Woodhams SG, et al., 2017 The cannabinoid system and pain. Neuropharmacology. 124, 105–120. [PubMed: 28625720]

Xu C, et al., 2017 Endocannabinoids exert CB1 receptor-mediated neuroprotective effects in models of neuronal damage induced by HIV-1 Tat protein. Mol Cell Neurosci. 83, 92–102. [PubMed: 28733129]

Yan W, et al., 2016 NO2 inhalation promotes Alzheimer's disease-like progression: cyclooxygenase-2-derived prostaglandin E2 modulation and monoacylglycerol lipase inhibition-targeted medication. Sci Rep. 6, 22429. [PubMed: 26928013]

Ye L, et al., 2013 IL-1beta and TNF-alpha induce neurotoxicity through glutamate production: a potential role for neuronal glutaminase. J Neurochem. 125, 897–908. [PubMed: 23578284]

Zhang H, et al., 2011 Cannabinoid receptor and N-acyl phosphatidylethanolamine phospholipase D--evidence for altered expression in multiple sclerosis. Brain Pathol. 21, 544–57. [PubMed: 21251115]

Zhang X, Thayer SA, 2018 Monoacylglycerol lipase inhibitor JZL184 prevents HIV-1 gp120-induced synapse loss by altering endocannabinoid signaling. Neuropharmacology. 128, 269–281. [PubMed: 29061509]

Zhornitsky S, Potvin S, 2012 Cannabidiol in humans-the quest for therapeutic targets. Pharmaceuticals (Basel). 5, 529–52. [PubMed: 24281562]

Highlights

- Nearly half of all HIV-infected individuals experience cognitive and motor deficits.
- HIV-induced neuronal injury results from excitotoxic and inflammatory mechanisms.
- The endocannabinoid (eCB) system provides on-demand protection against excitotoxicity and neuroinflammation.
- We discuss the potential of drugs that modulate eCB signaling to treat HIV-associated neurocognitive disorder.

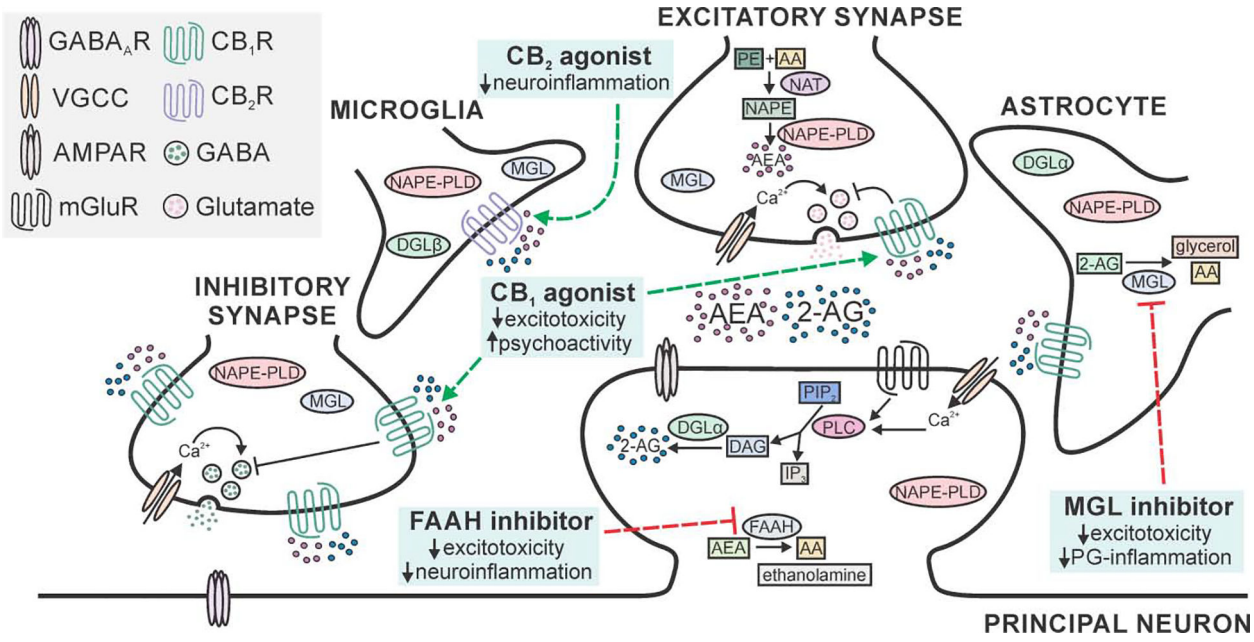

Fig. 1:

Neuroprotective targets in the eCB system. Schematic displays principal neuron receiving excitatory and inhibitory input with neighboring astrocyte and microglial cells. Cannabinoid type 1 receptors (CB_1Rs) are present on presynaptic terminals, with high expression on a subset of GABAergic terminals and widespread expression at lower levels on glutamatergic terminals (Marsicano and Lutz, 1999). Cannabinoid type 2 receptors (CB_2Rs) are found predominantly on cells of the immune system (microglia shown), with limited expression on neurons (not shown) (Nunez et al., 2004). All four cell types express diacylglycerol lipase (DGL) and *N*-arachidonoyl phosphatidylethanolamine phospholipase D (NAPE-PLD), the enzymes that synthesize the eCBs 2-arachdionoylglycerol (2-AG) and anandamide (AEA), respectively (Egertova et al., 2008; Ludanyi et al., 2011; Mishra et al., 2016; Viader et al., 2016; Zhang et al., 2011). For clarity, the pathways are described in detail in a single location with high expression. 2-AG is hydrolyzed by monoacylglycerol lipase (MGL) that is expressed in all four cell types, with the highest levels found in astrocytes (Muccioli et al., 2007; Viader et al., 2015). Fatty acid amide hydrolase (FAAH) is predominantly expressed in the somata and dendrites of principal neurons (Egertova et al., 2003; Tsou et al., 1998b). Important neuroprotective drug targets (blue boxes) include agonists for CB_1 and CB_2Rs (dashed green lines) and inhibitors of MGL and FAAH (dashed red lines). Abbreviations; 2-AG: 2-arachidonoylglycerol; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AA: arachidonic acid; AEA: arachidonoyl ethanolamine (anandamide); CB_1R: cannabinoid type 1 receptor; CB_2R: cannabinoid type 2 receptor; DAG: diacylglycerol; DGL: diacylglycerol lipase; FAAH: fatty acid amide hydrolase; GABA: γ-aminobutyric acid; $GABA_AR$: GABA type A receptor; IP_3: inositol triphosphate; mGluR: metabotropic glutamate receptor; MGL: monoacylglycerol lipase; NAPE-PLD: *N*-arachidonoyl phosphatidylethanolamine phospholipase D; NAT: *N*-acyltransferase; NAPE: *N*-arachidonoyl phosphatidylethanolamine; PE: phosphatidylethanolamine; PG: prostaglandin;

PIP_2: phosphatidylinositol 4,5-bisphosphate; PLC: phospholipase C; VGCC: voltage-gated Ca^{2+} channel.