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Immunomodulatory Properties of Kappa Opioids and Synthetic Cannabinoids in HIV-1 Neuropathogenesis

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Abstract

Anti-retroviral therapy (ART) has had a tremendous impact on the clinical outcomes of HIV-1 infected individuals. While ART has produced many tangible benefits, chronic, long-term consequences of HIV infection have grown in importance. HIV-1-associated neurocognitive disorder (HAND) represents a collection of neurological syndromes that have a wide range of functional cognitive impairments. HAND remains a serious threat to AIDS patients, and there currently remains no specific therapy for the neurological manifestations of HIV-1. Based upon work in other models of neuroinflammation, kappa opioid receptors (KOR) and synthetic cannabinoids have emerged as having neuroprotective properties and the ability to dampen pro-inflammatory responses of glial cells; properties that may have a positive influence in HIV-1 neuropathogenesis. The ability of KOR ligands to inhibit HIV-1 production in human microglial cells and CD4 T lymphocytes, demonstrate neuroprotection, and dampen chemokine production in astrocytes provides encouraging data to suggest that KOR ligands may emerge as potential therapeutic agents in HIV neuropathogenesis. Based upon findings that synthetic cannabinoids inhibit HIV-1 expression in human microglia and suppress production of inflammatory mediators such as nitric oxide (NO) in human astrocytes, as well as a substantial literature demonstrating neuroprotective properties of cannabinoids in other systems, synthetic cannabinoids have also emerged as potential therapeutic agents in HIV neuropathogenesis. This review focuses on these

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two classes of compounds and describes the immunomodulatory and neuroprotective properties attributed to each in the context of HIV neuropathogenesis.

Keywords

HIV-1; Neuropathogenesis; Cannabinoids; Kappa opioid receptors

Background

In 2009, there were an estimated 2.6 million individuals who became newly infected with HIV in the world; this represents a 21% decrease since the peak year of 1997. There were an estimated 1.8 million deaths in 2009, representing a 19% decrease from the peak year of 2004. The success made in reducing acquisition of HIV and improved mortality due to antiretroviral therapy (ART) has translated into an estimated 33.3 million individuals living with HIV (27% increase since 1999) (United Nations Program on HIV/AIDS (UNAIDS)/World Health Organization 2010). With the transformation of HIV from a death sentence to a chronic medical condition for many, long-term consequences of HIV infection have grown in importance. HIV-1-associated neurocognitive disorder (HAND) represents a collection of neurological syndromes that have a wide range of functional cognitive impairments. HAND includes asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and the more severe HIV-associated dementia (HAD). ANI is defined by neuropsychological test results at least one standard deviation below the mean in at least two specific cognitive areas; MND includes meeting criteria for ANI by neuropsychological testing, along with impairment of activities of daily living. The diagnosis of HAD requires neuropsychological test results at least two standard deviations below the mean in two or more cognitive areas and marked impairment of activities of daily living (Gannon et al. 2011).

Despite the therapeutic impact of ART, HAND still represents the most common form of dementia in adults under age 40 and remains an independent risk factor for mortality despite ART (Boisse et al. 2008). As such, it remains a serious threat to AIDS patients (Anthony et al. 2005; Clements et al. 2005; McArthur et al. 2005; Nath and Sacktor 2006; Heaton et al. 2011) and there currently is no specific therapy for the neurological manifestations of HIV-1. Several non-exclusive theories have been proposed as to why ART has not eliminated HAND. They include irreversible brain injury prior to initiating ART, incomplete viral suppression in the CNS due to poor CNS penetration of ART drugs and/or presence of drug-resistant viral strains, possible neurotoxicity of ART drugs, and increased rates of metabolic abnormalities and associated vascular pathology or increased β-amyloid deposition in the brain (Heaton et al. 2011). Another possibility is that even very low levels of viral replication in the CNS could result in neural injury or dysfunction due to prolonged exposure to inflammatory responses and neurotoxic viral proteins (Heaton et al. 2011).

Looking to other models of neuroinflammation for potential compounds that influence HIV-1 neuropathogenesis, synthetic cannabinoids have emerged as having neuroprotective properties and the ability to dampen pro-inflammatory responses of glial cells. Based upon

findings that synthetic cannabinoids inhibit HIV-1 expression in human microglia (Peterson et al. 2004; Rock et al. 2007) and suppress production of inflammatory mediators such as nitric oxide (NO) in human astrocytes (Sheng et al. 2005), as well as a substantial literature demonstrating neuroprotective properties of cannabinoids in other systems (Hampson et al. 1998; Shen and Thayer 1998; Nagayama et al. 1999; Chen and Buck 2000; Shohami and Mechoulam 2000; Marsicano et al. 2002, 2003), synthetic cannabinoids have emerged as potential therapeutic agents in HIV neuropathogenesis. Kappa opioid receptor (KOR) ligands have also demonstrated promising anti-inflammatory and neuroprotective properties in several in vitro models of HIV neuropathogenesis. The ability of KOR ligands to inhibit HIV-1 production in human microglial cells (Chao et al. 1996) and CD4 T lymphocytes (Peterson et al. 2001), demonstrate neuroprotection (Chao et al. 2000), and dampen chemokine production in astrocytes (Sheng et al. 2003) provides encouraging data to suggest that KOR ligands may also emerge as potential therapeutic agents in HIV neuropathogenesis.

Research over the past two decades has revealed that a network of factors, including virotoxins gp120 and Tat and mediators released from activated glial cells, are involved in the neuropathogenesis of HIV-1 (D'Aversa et al. 2005; Gendelman 2005; Ghorpade et al. 2005; Gonzalez-Scarano and Martin-Garcia 2005; Kaul et al. 2005; Mattson et al. 2005; Kaul and Lipton 2006). More recent work has demonstrated that the nigrostriatal dopaminergic system is a critical brain region for the neuronal dysfunction and death seen in HAND (Ferris et al.; Aylward et al. 1993; Sardar et al. 1996; Itoh et al. 2000; Nath et al. 2000; Koutsilieri et al. 2002a, b; Wang et al. 2004; Paul et al. 2005; Gelman et al. 2006; Silvers et al. 2006). One interesting feature of the nigrostriatal dopaminergic system (midbrain and the substantia nigra specifically) that may help explain the susceptibility of this brain region to HIV-1-related damage is that this area contains a high concentration of microglial cells (Lawson et al. 1990), the resident macrophages of the brain, which are the only brain cell types that can support productive HIV-1 infection, express CXCR4 and CCR5 and are a rich source of inflammatory mediators (superoxide (O_2^-) and cytokines/chemokines) (Koenig et al. 1986; Wiley et al. 1986; Chao et al. 1995; Cosenza et al. 2002).

Among the cell types in the brain parenchyma, microglia are most capable of generating large quantities of the free radical O_2^- (Chao et al. 1995), which is rapidly metabolized to the highly cytotoxic reactive oxygen species (ROS) hydrogen peroxide and hydroxyl radical. Unlike microglia from certain rodent species, human microglia do not express inducible nitric oxide synthase (iNOS) (Lee et al. 1993; Peterson et al. 1994; Rock et al. 2005), but when activated, they release abundant amounts of interleukin (IL)-1β, which in turn induces iNOS and NO production by human astrocytes (Hu et al. 1999).

Although not a site of productive viral replication, astrocytes also play an important role in HIV-1 neuropathogenesis (Fine et al. 1996; Conant et al. 1998; Brack-Werner 1999; Persidsky et al. 1999; Lim and Garzino-Demo 2000; Boven et al. 2003; Khurdayan et al. 2004; Kim et al. 2004; Zhou et al. 2004). Astrocytes have been long recognized for their supportive functions in the CNS, including the metabolism of the excitotoxic neurotransmitter glutamate (Danbolt 2001), and we have found that IL-1β-stimulated astrocytes also produce NO (Sheng et al. 2005). Exposure of astrocytes to gp120 impairs

the ability of astrocytes to transport L-glutamate (Wang et al. 2003), and glutamate excitotoxicity is thought to be a central end-point pathway in HAD (Lipton and Gendelman 1995). HIV-1 gp120 also creates widespread dysregulation of many other important cellular genes in astrocytes (Su et al. 2002, 2003; Galey et al. 2003).

A growing body of evidence also supports the role of “oxidative stress” in HIV-1 neuropathogenesis (Sheng et al. 2000; Mollace et al. 2001; Aksenov et al. 2003, 2006; Minghetti et al. 2004; Pocernich et al. 2005; Turchan-Cholewo et al. 2006; Wallace et al. 2006). Brain sections obtained from patients with AIDS dementia show intense immunostaining for nitrotyrosine, indicating that reaction between NO and O_2^- has led to peroxynitrite formation resulting in oxidative damage (Boven et al. 1999). Furthermore, it has been reported that levels of the lipid peroxidation product HNE (4-hydroxy-2-nonenal) are increased in brain tissues of patients with HAD (Haughey et al. 2004).

Compounds that have anti-inflammatory effects on human microglia and astrocytes and demonstrate neuroprotection in the setting of HIV neuropathogenesis may have the potential to supplement ART and specifically address the long-term neurological consequences of HIV infection. In this review, we will address two such classes of compounds: synthetic kappa opioid receptor (KOR) agonists and cannabinoids.

Opioids

The effects of opioids are mediated mainly through opioid receptors classified as mu (μ), kappa (κ), and delta (δ) opioid receptors. A number of opioid agonists and antagonists have been evaluated in in vitro studies and for therapeutic potential in HIV-1 infection. Of these, KORs, which are widely expressed in the central nervous system, have emerged with the most promise (Table 1).

There are several lines of evidence to suggest that KOR ligands may have therapeutic effects on HIV neuropathogenesis. Many years ago, our laboratory reported the presence of KORs in human fetal microglia and inhibition of HIV-1 expression in acutely infected microglial cell cultures treated with the KOR ligands U50,488 and U69,593. This antiviral effect of kappa ligands was blocked by the specific KOR antagonist, nor-binaltrophimine (nor-BNI) (Chao et al. 1996). We later investigated whether selective KOR ligands would exert antiviral effects in acutely infected mixed glial/neuronal cell cultures. The proinflammatory cytokines TNF-α and IL-1β have been found to profoundly suppress HIV-1 expression in this mixed glial/neuronal brain cell culture model (Lokensgard et al. 1997). While the KOR ligand U50,488 alone had little anti-HIV-1 activity, this opioid potentiated in a concentration-dependent manner the antiviral activity of tumor necrosis factor (TNF)-α, but not the antiviral activity of IL-1β. The KOR antagonist nor-BNI completely blocked the potentiating effect of U50,488 on TNF-α, suggesting the involvement of a KOR-mediated mechanism. Antibodies to TNF-α completely blocked the potentiating effect of U50,488, suggesting that the potentiating effect of U50,488 is dependent upon TNF-α. While U50,488 did not potentiate the antiviral activity of IL-1β, antibodies to IL-1β blocked the potentiating effect of U50,488 on the antiviral activity of TNF-α, suggesting that IL-1β also contributes to the potentiating effect of U50,488 on TNF-α (Chao et al. 1998). Again using primary

human brain cell cultures, we found that U50,488 also suppressed in a dose-dependent manner the neurotoxicity mediated by supernatants derived from HIV-1-infected microglia. This neuroprotective effect of U50,488 was blocked by the KOR antagonist nor-BNI. The neurotoxic activity of the supernatants from HIV-1-infected microglia was also blocked by the NMDA receptor antagonists 2-amino-5-phosphonovalerate (2-APV) and MK-801. HIV-1 infection of microglial cell cultures induced the release of quinolinate, and U50,488 dose-dependently suppressed quinolinate release by infected microglial cell cultures with a corresponding inhibition of HIV-1 p24 antigen levels (Chao et al. 2000). Treatment of astrocytes with U50,488 inhibited Tat-induced CCL-2 production in a concentration-dependent manner. The KOR antagonist nor-BNI completely blocked the inhibitory effect of U50,488, suggesting involvement of KOR. While U50,488 alone had a partial inhibitory effect on constituent NF-κB activation, it potently suppressed Tat-induced NF-κB activation (Sheng et al. 2003). Overall, these in vitro findings suggest that KOR agonists have immunomodulatory activity in the brain and may have therapeutic potential in HIV-1 neuropathogenesis by attenuating microglial cell production of the neurotoxin quinolinate and viral proteins and dampening chemokine production in astrocytes.

Because infiltrating monocytes and T-cells contribute to HIV neuropathogenesis, we and others also investigated the immunomodulatory effects of KOR ligands in these cell populations. In one study, peritoneal macrophages were treated simultaneously with U50,488 and lipopolysaccharide (LPS), and the levels of the cytokines IL-1, IL-6 and TNF-α were measured. The results showed that U50,488 had a suppressive effect on the production of TNF-α, IL-1, and IL-6. Naloxone was able to partially block U50,488 suppression, while nor-BNI was able to completely reverse the suppression of IL-6 production (Alicea et al. 1996). Our laboratory investigated whether U50,488 would exert such an anti-HIV-1 effect in acutely infected blood monocyte-derived macrophages (MDM). Treatment of HIV-1-infected MDM with U50,488 induced a concentration-dependent inhibition of HIV-1 expression. The dose—response relationship of U50,488 was U-shaped with a peak effect observed at 10^{-13} M. The KOR antagonist nor-BNI blocked this anti-HIV-1 effect, indicating involvement of KORs; further studies suggested that the anti-HIV-1 effect of U50,488 partially involved the production of CCL5 by MDM (Chao et al. 2001).

CD4 lymphocytes are a primary cell target for HIV-1, and these cells are known to express opioid receptors. In our laboratory, activated CD4 lymphocytes were infected with HIV-1, and p24 antigen levels were measured in supernatants of naltrexone-treated or untreated cultures. While naltrexone alone did not affect HIV-1 expression in activated CD4 lymphocytes, naltrexone increased the antiviral activity of AZT and indinavir by 2–3-fold. Similar findings with a KOR selective antagonist supported the possible involvement of KOR in naltrexone's potentiation of the antiretroviral drugs (Gekker et al. 2001). Beyond the effect on antiretroviral drugs, we also examined the effects of U50,488 on HIV-1 expression in acutely infected CD4 lymphocytes. When U50,488 was added to activated CD4+ lymphocytes, HIV-1 expression was inhibited in a concentration- and time-dependent manner. The KOR antagonist nor-BNI had no effect by itself on viral expression but blocked the antiviral property of U50,488, suggesting that U50,488 was acting via a KOR (Peterson et al. 2001).

The last study above showed that the suppressive effect of KOR ligands on HIV-1 expression in acutely infected CD4 lymphocytes is concentration and time-dependent. This finding implies that the inhibition by U50,488 occurs at an early step in the viral replication cycle. In a follow up study, we hypothesized that U50,488 treatment of CD4 lymphocytes inhibited HIV-1 envelope (Env) glycoprotein-mediated membrane fusion. To address this we used a vaccinia virus-based assay to measure the effects of U50,488 treatment of CD4 lymphocytes on HIV-1_{IIIB} Env glycoprotein-mediated fusogenic activity, based on the cytoplasmic activation of a reporter gene. The results showed that U50,488 inhibited Env-mediated cell fusion in a bell-shaped concentration-response, which suggests that the effect operates in a very narrow therapeutic range and is likely quite complex. The KOR antagonist nor-BNI blocked of the inhibitory activity of U50,488, implying that U50,488 was acting via a KOR-related mechanism. Using flow cytometry, we demonstrated that the chemokine co-receptor CXCR4, but not CD4, was down-regulated as a consequence of KOR activation. These findings support the hypothesis that KOR activation on CD4 lymphocytes inhibits HIV-1 entry via down-regulation of CXCR4 (Lokensgard et al. 2002).

We also examined the effects of KOR ligands on the deleterious effects of other drugs of abuse on HIV neuropathogenesis. Treatment of microglia with cocaine promoted HIV-1 expression and pretreatment of microglia with KOR agonists as well as nor-BNI abrogated the cocaine-induced potentiation of viral expression. The mechanism whereby KOR ligands inhibit cocaine's stimulatory effect on viral expression involves the suppression of cocaine-induced activation of extracellular signal-regulated kinase1/2, thereby blunting cocaine-enhanced up-regulation of the HIV-1 entry chemokine co-receptor CCR5 (Gekker et al. 2004).

More recently, we looked at the effects of KOR ligands on neural precursor cells (NPCs). NPCs are self-renewing, multipotent cells capable of differentiating into neurons, astrocytes, and oligodendrocytes and have been shown to migrate toward sites of injury in the brain and to participate in the process of brain repair. We documented robust expression of KORs in highly enriched (>90% nestin-positive) human fetal brain-derived NPCs. We also found that U50,488, but not dynorphin$_{(2–17)}$, stimulated proliferation and migration of NPCs in a concentration-dependent manner. The KOR antagonist, nor-BNI, partially blocked the migratory and proliferative effects of KOR agonists supporting the involvement of a KOR-related mechanism (Sheng et al. 2007).

One of the proposed mechanisms by which KOR ligands may induce their immunomodulatory effects on HIV involves the ability of KOR to cross-desensitize the HIV-1 co-receptor CXCR4 in a bi-directional fashion (Finley et al. 2008). In a recent study using a combination of biochemical approaches, these investigators showed that both CXCR4 protein and mRNA levels are significantly reduced following KOR activation. They also determined that the IRFs (interferon regulated factors) and STATs (signal transducer and activator of transcription) were induced following KOR activation, that JAK2 (Janus Kinase), STAT3, and IRF2 were critical members of this signal transduction pathway and that these processes were important for the inhibition of CXCR4 expression (Finley et al. 2011).

Cannabinoids

Of the two classical cannabinoid receptors, cannabinoid receptor 1 (CB_1) receptors are expressed predominantly in the brain, and are abundantly expressed in the basal ganglia and hypothalamus. Activation of these receptors by natural cannabinoids, such as Δ^9-tetrahydrocannabinol (THC), as well as by synthetic cannabinoids has been extensively investigated (Howlett et al. 2004). Cannabinoid receptor 2 (CB_2) receptors are predominantly expressed in cells of the immune system, including microglia (Klein and Cabral 2006; Raborn and Cabral 2010) (Table 2).

The protective effects of cannabinoids on neuronal cell damage have been extensively studied in several rodent models (Facchinetti et al. 2003; Klegeris et al. 2003; Walter et al. 2003; Eljaschewitsch et al. 2006; Klein and Cabral 2006). These studies demonstrate that both CB_1 receptor-mediated (Shen and Thayer 1998; Nagayama et al. 1999; Marsicano et al. 2003) and non-receptor-mediated (antioxidant effects) (Chen and Buck 2000; Shohami and Mechoulam 2000; Marsicano et al. 2002) mechanisms are involved in the neuroprotective properties of cannabinoids. Cannabinoids alter immune cell functions (Klein et al. 2003), including certain functions of microglia, the resident macrophages of the brain parenchyma (Cabral and Griffin-Thomas 2008). These activities appear to be mediated through cannabinoid receptors (CB_1 or CB_2). Synthetic cannabinoid agonists have a beneficial effect in animal models of several neurodegenerative diseases, including multiple sclerosis (Croxford and Miller 2003), Parkinson's disease (Price et al. 2009), and Huntington's disease (Palazuelos et al. 2009).

Several studies have demonstrated the potential importance of cannabinoid receptors in HIV neuropathogenesis. A recent in vivo experiment linked the thermoregulatory effects of the synthetic cannabinoid, WIN55,212–2, which produced a dose-related hypothermia, and the HIV-1 co-receptor CXCR4 (Benamar et al. 2009). Using quantitative image analysis and immunohistochemistry in the cerebral cortex and white matter of patients with HIV encephalitis (HIVE), the authors observed that CB_1 was increased in HIVE brains, while CB_2 was significantly increased in the white matter of HIVE. At baseline, CB_1 was noted in neurons, and both CB_1 and CB_2 were noted in meningeal macrophages and subpial glia. In HIVE, CB_1 was found in white matter microglia and perivascular cells, while CB_2 was increased in perivascular macrophages, microglia, and astrocytes (Cosenza-Nashat et al. 2011).

The current use of cannabinoids in clinical medicine has focused on the treatment of neuropathic pain, nausea and anorexia. Dronabinol (Marinol), a synthetic THC, is used as an appetite stimulant, anti-emetic, and analgesic. It also has been used for HIV-wasting disease since the early years of the HIV epidemic (Timpone et al. 1997). Sativex, a cannabinoid extract oral spray containing THC, cannabidiol (CBD), and other cannabinoids is used for the treatment of neuropathic pain and spasticity in 22 countries including England, Canada and Spain. Nabilone (Cesamet), a synthetic cannabinoid is used as an antiemetic and for the treatment of neuropathic pain. Rimonabant (SR141716A), a selective CB_1 receptor antagonist, was used as an anti-obesity drug under the proprietary name Acomplia in the European Union until the use of this product was suspended in 2009.

One of the initial concerns regarding cannabinoid use among HIV-infected individuals, whether for recreational or therapeutic purposes, has centered on whether exogenous cannabinoids would worsen HIV-1 infection itself. One group investigated whether cannabinoids enhanced or suppressed HIV-1 infection in several cell lines (SupT, and H9, H9MN, and MT-2 cells). Of the cell lines tested, only the MT-2 cells were positive for both CB_1 and CB_2 mRNA. Using CP55,940, THC, WIN55,212–2, and WIN55,212–3 as their candidate cannabinoids, the authors attempted to determine whether different cannabinoid receptor agonists influenced infection of these cells by cell free HIV-1. Using syncytia formation as an indication of virus infection and cytopathicity, the authors concluded that cannabinoids may enhance HIV-1 infection of susceptible cells (Noe et al. 1998). In another study using a short-term exposure model of human endothelium, monocyte adherence was diminished with morphine and anandamide treatment, whereas monocyte adherence was enhanced with gp120. Short-term exposure to morphine or anandamide also resulted in nitric oxide (NO) release, whereas exposure to gp120 did not. Long-term exposure of endothelial cells to gp120, morphine or anandamide resulted in enhancement of monocyte adherence; these effects were further increased when exposed to gp120 in combination with either morphine or anandamide. The authors concluded that this was caused by a desensitization of the endothelium to further NO release after the initial exposure to either morphine or anandamide. From these results the authors concluded that exposure to morphine or cannabinoids may cause HIV to progress more rapidly because monocyte adherence and mobility is significantly increased, indicating a higher level of trans-membrane migration (Stefano et al. 1998a).

Based on further observations of macrophage behavior during chronic exposure to morphine and anandamide, these agents first induced a period of inactivity which was followed by a period of chemokinesis; NO was released by macrophages only when exposed to morphine and anandamide, but not gp120. Thus, the authors concluded that the chemokinetic inducing activities of morphine and anandamide may be the basis for excitotoxin liberation in neural tissues and/or a higher HIV-1 viral load (Stefano et al. 1998b). In an in vitro study investigating the effects of THC and CBD on cytokine production by human leukemic T, B, eosinophilic and $CD8^+$ NK cell lines as models they found that THC decreased constitutive production of CXCL8, CCL3, CCL4, and CCL5 and phorbol ester stimulated production of TNF-α, granulocyte macrophage colony stimulating factor (GM-CSF) and IFN-γ by NK cells. THC also inhibited CCL4 in human T-cell lymphotrophic virus type 1 (HTLV-1) positive B-cells but increased CXCL8, CCL3 and CCL4 in B-cells and CCL4 and CXCL8 in eosinophils. Both cannabinoids strongly inhibited IL-10 production by HUT-78 T-cells. The authors cautioned that because of the mixed and complex effects that these two cannabinoids have on cytokine production by various cell lines, cannabinoids may benefit some diseases while worsening others (Srivastava et al. 1998). Finally, in a study using a hu-PBL-SCID mouse model (human peripheral blood leukocytes [PBL] implanted into severe combined immunodeficient mice[SCID]) and infected with an HIV reporter construct in the presence or absence of THC exposure, it was suggested that exposure to THC in vivo can suppress immune function, increase HIV co-receptor expression, and act as a cofactor to significantly enhance HIV replication (Roth et al. 2005).

The concerns regarding whether exogenous cannabinoids would worsen HIV-1 infection have been tempered considerably with more recent data. Based on clinical data, there does not appear to be any significant effect of cannabinoid use among HIV-infected individuals regarding HIV RNA, CD4/CD8 levels and immune phenotypes, at least in the short term (Bredt et al. 2002; Abrams et al. 2003). In a randomized placebo-controlled study designed to evaluate the metabolic effects of smoked marijuana and dronabinol in HIV-infected patients receiving two early-era antiretroviral drugs, indinavir and nelfinavir, the authors concluded that despite a decrease in the maximum concentration of indinavir in those in the marijuana arm of the study, the magnitude of the observed pharmacokinetic changes was unlikely to impact antiretroviral efficacy of these two agents (Kosel et al. 2002).

Results of several in vivo models of HIV suggest cannabinoids may actually have beneficial effects. Chronic THC administration decreased early mortality from simian immunodeficiency virus (SIV) infection, and this was associated with attenuation of plasma and CSF viral load and retention of body mass (Molina et al. 2010). In vitro, THC decreased SIV viral replication in MT4-R5 cells (Molina et al. 2010). Chronic use of THC (12 months) did not alter lymphocyte subtypes, naive and memory subsets, proliferation, or apoptosis of T lymphocytes in male young adult rhesus macaques. However, chronic THC increased T lymphocyte CXCR4 expression on both $CD4^+$ and $CD8^+$ T lymphocytes compared to controls (Lecapitaine et al. 2011). In a feline immunodeficiency virus (FIV) model, macrophages were shown to express cannabinoid receptors, and recombinant feline interferon-γ and lipopolysaccharide (LPS)-induced NO production decreased after in vitro exposure to the synthetic cannabinoid CP55,940. This observation involved both CB_1 and CB_2 receptors (Ponti et al. 2001). In a model where hu-PBL were reconstituted into immunodeficient Balb/c-$Rag^{-/-}\gamma c^{-/-}$ mice and HIV-1-infected human MDMs were injected into the brain to induce viral encephalitis (hu-PBL/HIVE mice), the authors report that the hu-PBL/HIVE mice exhibit altered CB_2 receptor expression; no changes in CB_1 receptor and GPR55 expression were observed. Gp1a diminished microglial activation and decreased proinflammatory cytokine TNF-α expression in HIVE brains. The significant reduction in GVH-mediated deaths with Gp1a treatment suggested an immune-suppressive effect of Gp1a. There was a decrease in CCR5 expression on $CD4^+$ cells with HIV infection in hu-PBL/HIVE mice compared to hu-PBL mice, which was thought due to the progressive depletion of activated $CD4^+$ cells with infection. Overall the use of Gp1a did not reduce peripheral viral load in this model. Decreased expression of HIV-gag was observed in the brains of Gp1a-treated animals, but was not significant (Gorantla et al. 2010).

Using a model of the human blood brain barrier involving co-cultures of human brain microvascular endothelial cells (HBMEC) and human astrocytes, the authors showed that the cannabinoid agonists CP55,940 and ACEA: 1) inhibited HIV-1 gp120-induced calcium influx mediated by substance P, 2) decreased the permeability of HBMEC, 3) prevented tight junction protein down-regulation and 4) inhibited the transmigration of human monocytes across the BBB and blocked the BBB permeability in vivo. These results demonstrate that synthetic cannabinoids are capable of restoring the integrity of HBMEC following HIV-1 gp120-induced toxicity (Lu et al. 2008).

In our laboratory, we have found that suppression of HIV-1 expression in human microglial cells by the synthetic CB_1/CB_2 receptor agonists WIN55,212–2 and CP55,940 involves CB_2 receptors (Peterson et al. 2004; Rock et al. 2007). Evidence for this conclusion was provided by the findings that the CB_2 receptor selective agonist JWH-015 inhibited HIV-1 expression and that the CB_2 receptor selective antagonist SR144528 blocked WIN55,212–2's inhibitory effect. Surprisingly, the CB_1 receptor selective antagonist SR141716A behaved as an agonist in this culture system, suggesting human microglia possess functionally active non-CB_1/CB_2 receptors (Rock et al. 2007).

The inhibitory effect of WIN55,212-2 on IL-1β-stimulated expression of inducible nitric oxide synthase (iNOS) and cytokines/chemokines (TNF-α, CXCL10, CCL2, and CCL5) by human astrocytes, on the other hand was shown to be partially blocked by SR141716A and SR144528 suggesting that these glial cells possess functionally active CB_1 and CB_2 receptors (Sheng et al. 2005). In an additional study, we found that production of CX3CL1 by human astrocytes stimulated with IL-1β was inhibited in a concentration-dependent manner following pretreatment with the synthetic cannabinoid WIN55,212-2. The CB_2 receptor selective antagonist SR144528 significantly inhibited WIN55,212-2-mediated suppression of CX3CL1, suggesting a CB_2-receptor-related mechanism. IL-1β triggered the activation of p38 and ERK1/2 (p44/42) MAP kinase (MAPK) signaling pathways, but WIN55,212-2 mainly inhibited p38 MAPK phosphorylation. This finding was mirrored in experiments using known inhibitors of these MAPKs, suggesting that the suppression of CX3CL1 production by WIN55,212-2 involves inhibition of signaling via p38 MAPK (Sheng et al. 2009).

Several mechanisms by which cannabinoids may exert a beneficial effect on HIV neuropathogenesis have been suggested. Using both pharmacological and biochemical knockdown methods, Raborn et al. demonstrated that the cannabinoids THC and CP55,940 inhibited migration of human U937 macrophage-like cells to the HIV-1 Tat protein, and that this modulation of macrophage migration was CB_2 mediated (Raborn and Cabral 2010). The CB_2 agonist JWH-015 suppressed IFN-γ-induced CD40 expression and phosphorylation of JAK/STAT1in microglial cells, inhibited microglial cell TNF-α and NO production induced either by IFN-γ or Aβ peptide, and attenuated CD40-mediated inhibition of microglial phagocytosis of $A\beta_{1–42}$ peptide (Ehrhart et al. 2005). WIN 55,212–2 stimulation of Tat + IFN-γ-induced expression of iNOS, NO release and NO-mediated cell toxicity in rat glioma C6 cells. HIV-1 Tat + IFN-γ also induced a significant inhibition of CB_1, but not CB_2, receptor expression and inhibited anandamide uptake by C6 cells with no effect on anandamide hydrolysis. The authors concluded that stimulation of the endocannabinoid system can reduce HIV-1 Tat-induced cytotoxicity, and is itself regulated by HIV-1 Tat (Esposito et al. 2002).

Final thoughts

HAND remains a significant threat to HIV-1-infected patients, and specific therapy of this crippling neurodegenerative disorder is lacking. This review focused on two potential classes of compounds, synthetic KOR ligands and synthetic cannabinoids, which may be exploited for their neuroprotective properties and abilities to dampen pro-inflammatory responses

of glial cells. While early work on these compounds is encouraging, there remain many gaps in knowledge that need to be filled. For KOR ligands, while the in vitro findings are promising, evidence for direct in vivo neuroprotective effects are still lacking, both in terms of confirmation of the in vitro effects, and demonstration of a meaningful, positive effect on disease progression. This lack of in vivo work limits our understanding of the clinical viability of this class of compounds. The work thus far on the neuroprotective role of synthetic cannabinoids has focused on mechanisms related to the CB1 and CB2 receptors, non-CB1/CB2-receptor mediated mechanisms must be considered as well, especially since candidate CB receptors are emerging (Cabral and Griffin-Thomas 2009). While short-term clinical studies have not demonstrated a deleterious effect of cannabinoids on HIV disease (Bredt et al. 2002; Kosel et al. 2002; Abrams et al. 2003), and much of the evidence supporting the neuroprotective effects of synthetic cannabinoids is also based on in vitro studies, encouraging evidence has emerged from studies using and SIV monkey models and hu-PBL/HIVE mouse models (Gorantla et al. 2010; Molina et al. 2010). Additional in vivo investigations would serve to flesh out the potential role of synthetic compounds in a treatment modality targeting HIV neuropathogenesis. While significant effort has been made to study and examine the role of these compounds in HIV neuropathogenesis, much work remains to fully elucidate their potential.

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Table 1

Selected KOR ligands

Class	Name
KOR Agonists	Butorphanol [17-cyclobutylmethyl-morphinan-3,14-diol]
	Spiradoline [2-(3,4-dichlorophenyl)- N-methyl- N-[(5R,7S,8S)- 7-pyrrolidin-1-yl- 1-oxaspiro[4.5]decan-8-yl] acetamide]
	Salvinorin A [methyl (2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-9-(acetyloxy)-2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxododecahydro-2*H*-benzo[f]isochromene-7-carboxylate]
	2-methoxymethyl Salvinorin B [(2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)- 9-(methoxymethoxy)- 2-(3-furanyl) dodecahydro-6a,10b-dimethyl-4,10-dioxo-2*H*-naphtho-[2,1-c]pyran-7-carboxylic acid methyl ester]
	Cyclazocine [2-cyclopropylmethyl- 2'-hydroxy- 5,9-dimethyl- 6,7-benzomorphan]
	Menthol [(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexanol]
	Dextromethorphan [(+)-3-methoxy-17-methyl-(9α,13α,14α)-morphinan]
	Pentazocine [2-dimethylallyl-5,9-dimethyl-2'-hydroxybenzomorphan]
	Norbuprenorphine [(5α,6β,14β,18*R*)-18-[(1*S*)-1-hydroxy-1,2,2-trimethylpropyl]-6-methoxy-18,19-dihydro-4,5-epoxy-6,14-ethenomorphinan-3-ol]
	Ketazocine [(2*S*,6*R*,11*R*)-3-(cyclopropylmethyl)-8-hydroxy-6,11-dimethyl-3,4,5,6-tetrahydro-2,6-methano-3-benzazocin-1(2*H*)-one]
	Enadoline [2-(benzofuran-4-yl)-N-methyl-N-((5R,7S,8S)-7-(pyrrolidin-1-yl)-1-oxaspiro[4.5] decan-8-yl)ethanamide]
	Dynorphin
	Asimadoline [N-[(1S)-2-[(3S)-3-hydroxypyrrolidin-1-yl]-1-phenylethyl]-N-methyl-2,2-diphenylacetamide]
	Tifluadom [*N*-[(5-(2-fluorophenyl)- 1-methyl- 2,3-dihydro- 1,4-benzodiazepin-2-yl) methyl] thiophene- 3-carboxamide]
	Nalfurafine [(2*E*)-*N*-[(5α,6β)-17-(cyclopropylmethyl)- 3,14-dihydroxy- 4,5-epoxymorphinan- 6-yl]- 3-(3-furyl)-*N*-methylacrylamide]
	HZ-2 [Dimethyl 3,7-dimethyl-9-oxo-2,4-dipyridin-2-yl-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate]
	Nalbuphine [(−)-17-(cyclobutylmethyl)- 4,5α-epoxymorphinan- 3,6α,14-triol hydrochloride]
	LPK-26 [2-(3,4-dichlorophenyl)-N-[(2S)-1-(2,5-dihydropyrrol-1-yl)-3-methylbutan-2-yl]-N-methylacetamide]
	BRL-52537 [2-(3,4-dichlorophenyl)-1-[(2S)-2-(pyrrolidin-1-ylmethyl)piperidin-1-yl]ethanone]
	ICI-204,448 [2-(3-[1-([2-(3,4-dichlorophenyl)acetyl]-methylamino)-2-pyrrolidin-1-ylethyl]phenoxy)acetic acid]
	ICI-199,441 [2-(3,4-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-pyrrolidin-1-ylethyl]acetamide]
	U50,488 [trans-3,4-dichloro-N-methyl-N[2-(1-pyrolidinyl)cyclohexyl]benze neaceamide methanesulfonate][a]
	U69,593 [*N*-methyl-2-phenyl-*N*-[(5*R*,7*S*,8*S*)-7-(pyrrolidin-1-yl)-1-oxaspiro[4.5]dec-8-yl]acetamide][a]
KOR Antagonists	5' Guanidinonaltrindole [5'-Guanidinyl-17-(cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7–2',3'-indolomorphinan]
	Buprenorphine [(2S)-2-[(−)-(5R,6R,7R,14S)-9α-cyclopropylmethyl-4,5-epoxy-6,14-ethano-3-hydroxy-6-methoxymorphinan-7-yl]-3,3-dimethylbutan-2-ol]
	nor-BNI [Norbinaltorphimine] [17,17'-(dicyclopropylmethyl)-6,6',7,7'−6,6'-imino- 7,7'-binorphinan-3,4',14,14'-tetrol]
	JDTic [(3R)-7-hydroxy-*N*-((1*S*)-1-{[(3*R*,4*R*)-4- (3-hydroxyphenyl)- 3,4-dimethylpiperidin- 1-yl]methyl}- 2-methylpropyl)- 1,2,3,4-tetrahydroisoquinoline- 3-carboxamide]

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A list of KOR agonists and antagonists

[a] Activity demonstrated in HIV neuropathogenesis as described in the text

Table 2

Selected cannabinoid ligands

Class	Name	CB_1 activity	CB_2 activity
Phytocannabinoids	THC [Δ^9-tetrahydrocannabinol] [(−)-(6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7, 8,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol][a]	Agonist	Agonist
	CBD [Cannabidiol] [2-[(1*R*,6*R*)-6-isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol]	Indirect Antagonist	Indirect Antagonist
Endogenous Cannabinoids	2-AG [2-Arachidonoylglycerol] [1,3-Dihydroxy-2-propanyl (5Z,8Z,11Z,14Z)-5,8,11,14-eicosatetraenoate]	Agonist	Agonist
	Anandamide [*N*-arachidonoylethanolamine or AEA] [(5*Z*,8*Z*,11*Z*,14*Z*)-*N*-(2-hydroxyethyl)icosa-5,8,11,14-tetraenamide][a]	Agonist	Agonist
Synthetic Cannabinoids	(+)-WIN 55,212-2 [(4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenyl-carbonyl)- 6H-pyrrolo[3,2,1ij]quinolin-6-one][a]	Agonist	Agonist
	CP55,940 [(−)-cis-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropy l) cyclohexanol][a]	Agonist	Agonist
	HU-210 [(6a*R*,10a*R*)- 9-(Hydroxymethyl)- 6,6-dimethyl- 3-(2-methyloctan-2-yl)-6a, 7,10,10a-tetrahydrobenzo [c]chromen-1-ol]	Agonist	Agonist
	JWH-018 [(1-pentyl-3-(1-naphthoyl)indole) or AM-67]	Agonist	Agonist
	ACEA [N-(2-chloroethyl)-5Z,8Z,11Z,14Z-eicosatetraenamide][a]	Agonist	
	O-2137 [(1R,3R)-1-[4-(1,1-dimethylheptyl)-2,6-dimethoxyphenyl]-3 methylcyclohexanol]		Agonist
	JW-133 [(6aR,10aR)-3-(1,1-Dimethylbutyl)-6a,7,10,10a-tetrahydro −6,6,9-trimethyl-6H-dibenzo[b,d]pyran]		Agonist
	JWH-015 [(2-Methyl-1-propyl-1H-indol-3-yl)-1-naphthalenylmethanone][a]		Agonist
	SR141716A [5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(1-piperidyl)pyrazole −3-carboxamide hydrochloride]	Antagonist	
	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]		Antagonist

A list of phytocannabinoids, endogenous cannabinoids, and synthetic cannabinoids with references to the dominant receptor binding activity

[a]Activity demonstrated in HIV neuropathogenesis as described in the text

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