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The Endocannabinoid System as a Potential Therapeutic Target for HIV-1-Associated Neurocognitive Disorder

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Abstract

Background: Despite the successful introduction of combined antiretroviral therapy, the prevalence of mild to moderate forms of HIV-associated neurocognitive disorders (HAND) remains high. It has been demonstrated that neuronal injury caused by HIV is excitotoxic and inflammatory, and it correlates with neurocognitive decline in HAND. Endocannabinoid system (ECS) protects the body from excitotoxicity and neuroinflammation on demand and presents a promising therapeutic target for treating HAND. Here, we firstly discuss the potential pathogenesis of HAND. We secondly discuss the structural and functional changes in the ECS that are currently known among HAND patients. We thirdly discuss current clinical and preclinical findings concerning the neuroprotective and anti-inflammatory properties of the ECS among HAND patients. Fourth, we will discuss the interactions between the ECS and neuroendocrine systems, including the hypothalamic-pituitary-adrenocortical (HPA) and hypothalamic-pituitary-gonadal (HPG) axes under the HAND conditions.

Materials and Methods: We have carried out a review of the literature using PubMed to summarize the current state of knowledge on the association between ECS and HAND.

Results: The ECS may be ideally suited for modulation of HAND pathophysiology. Direct activation of presynaptic cannabinoid receptor 1 or reduction of cannabinoid metabolism attenuates HAND excitotoxicity. Chronic neuroinflammation associated with HAND can be reduced by activating cannabinoid receptor 2 on immune cells. The sensitivity of the ECS to HIV may be enhanced by increased cannabinoid receptor expression in HAND. In addition, indirect regulation of the ECS through modulation of hormone-related receptors may be a potential strategy to influence the ECS and also alleviate the progression of HAND due to the reciprocal inhibition of the ECS by the HPA and HPG axes.

Conclusions: Taken together, targeting the ECS may be a promising strategy to alleviate the inflammation and neurodegeneration caused by HIV-1 infection. Further studies are required to clarify the role of endocannabinoid signaling in HIV neurotoxicity. Strategies promoting endocannabinoid signaling may slow down cognitive decline of HAND are proposed.

Keywords: HIV-associated neurocognitive disorders; endocannabinoid system; cannabinoid receptors; N-arachidonylethanolamine; 2-arachidonoylglycerol

Introduction

Despite effective combination of antiretroviral therapies, up to half of HIV-infected persons continue to have HIV-associated neurocognitive disorders (HAND), as determined with neuropsychometric testing.[1–3] Compared with the precART era, the more severe form of neurocognitive disorder, HIV-associated dementia (HAD), has become less common (from 20% to 6%) in people living with HIV/AIDS (PLWH), but the milder form of HAND still persists.[4,5] For individuals with

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HAND, the neurocognitive impairments can cause serious impairments in daily living, driving, managing medications, and employment.[6–8] Therefore, therapeutic strategies are needed to develop adjunct therapies, along with combined antiretroviral therapy (cART), to further hinder HIV-1 replication and HIV-related neurocognitive impairments.

The endocannabinoid system (ECS) in the brain is a neuromodulatory system that comprises cannabinoid receptor type 1[9] and type 2[10] (CB1 and CB2), the two major endocannabinoids, N-arachidonylethanolamine (AEA)[11] and 2-arachidonoyl glycerol (2-AG),[12] and their metabolizing enzymes fatty acid amide hydrolase (FAAH),[13] diacylglycerol lipase, and monoacylglycerol lipase (MAGL).[14] Their interactions with neurons, astrocytes, and microglia are necessary for endocannabinoid signaling.[15] The ECS plays an important role in modulating neurotransmitter release and synaptic plasticity, which can provide protection against excitotoxicity and neuroinflammation that are two main trademarks of neurodegenerative disorders, such as HAND.[16] Drugs can boost the ECS activity by imitating or enhancing its neuroprotective function. Studies have shown that alterations in the ECS implicated in some neurocognitive disorders possibly weaken the neuroprotection of the ECS in normal state, aggravating excitotoxicity.

Therefore, strategies to preclude the loss of endocannabinoid signals possibly retain its neuroprotective function, while drugs that mimic or boost endocannabinoid signaling may rescue for its decreased ability under neurotoxic or inflammatory conditions, such as HAND. Cannabis is used more frequently among PLWH than the general population,[17,18] perhaps as a way to cope with HIV-induced symptoms, such as pain and appetite loss, although it has the negative effects.[19] More importantly, cannabis-derived cannabinoids show a promise as neuroprotective agents with good prospects for the treatment of several neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease, and HAND, owing to their anti-inflammatory and anti-excitotoxic properties.[16,20,21]

Neuroendocrine dysfunction is emerging as a potential contributor of HAND. It is possible that HIV infection of the central nervous system (CNS) possibly results in abnormal hypothalamic–pituitary–adrenocortical (HPA) and hypothalamic–pituitary–gonadal (HPG) axes. However, ECS component overlaps with the HPA and HPG axes, and the interactions of ECS with HPA and HPG axes may influence the ECS as a potential therapeutic target. For instance, endocannabinoids widely distributed throughout the hypothalamus and limbic system regulate the release of excitatory and inhibitory transmitters, finally resulting in being constrained of the HPA activity.[22]

Conversely, glucocorticoids also inhibit the release of endocannabinoids and inhibit the excitatory inputs to corticotropin-releasing factor (CRF) neurons within the paraventricular nucleus (PVN), which can be hindered by CB1 receptor antagonists.[23] In addition, a large overlap exists between the ECS and receptors for gonadal steroid hormones,[24] suggesting that it could be an important neuroregulatory system that regulates gonadal steroid hormones. In this regard, interactions of the ECS with the HPA and HPG axes may influence the ECS as a potential therapeutic target for HAND.

To deepen our understanding of the role of ECS in HAND, we focused on reviewing how neuroHIV alters ECS and how cannabinoids affect HIV-1 infection and HAND. In this review, we first discuss the potential pathogenesis of HAND, including HIV-1-induced neuroinflammation indirectly affecting neurons, and the sustained release of neurotoxic HIV proteins that directly target neurons. Second, we discuss the structural and functional changes in the ECS that are currently known. Third, we discuss current clinical and preclinical findings regarding the anti-inflammatory and neuroprotective properties of the ECS. Fourth, we will discuss the interactions between the ECS and the HPA and HPG axes under HAND conditions. Finally, we discuss the significance of further research to determine the role of the ECS in HIV-induced neurotoxicity and hypothesize that measures to increase endocannabinoid signaling may halt cognitive decline.

The Mechanisms Underlying HAND

In PLWH, HAND have been prevalent since the epidemic began.[25,26] The clinical features of HAND are predominantly neurocognitive dysfunction, including difficulties paying attention, concentrating, moving rapidly, learning, and executive function.[5] HAD is characterized by impairment in cognitive function, processing information, and focusing or attention. Even though combined antiretroviral therapy has decreased the incidence of HAD,[27,28] approximately half of the infected-HIV patients develop a milder form of HAND,[1–3] which can have substantial effects on daily activities.[6–8] Even with mild HAND, HIV-infected individuals still maintain low plasma viremia[29–31] and signs of innate immunity.[32–34] Therefore, developing

adjunct therapies, along with cART, will prevent HIV-1 replication, suppress immune activation, and reduce neuroinflammation.

The pathogenesis of HAND mainly involves two pathways, the first being HIV-1-caused neuroinflammation that indirectly results in neuronal loss, and the second being sustained release of HIV-related neurotoxic proteins that directly target neurons and damage the neurons. More specifically, continued neuroinflammation within the CNS seems to outweigh in HIV-1-related neuronal injury.[35] HIV-1 virus can enter the macrophages, monocytes, and T cells within the brain shortly after infection,[36,37] and the virus can also infect microglia, endothelial cells, or astrocytes to establish a central reservoir.[35,38,39] Indirectly, HIV-1 infection causes neurons to be impaired by the production of neurotoxic mediators, such as inflammatory factors.[40–42]

Indeed, HIV-1 has been shown to induce neurotoxicity via releasing proinflammatory cytokines and chemokines in the CNS, triggering the production of TNF-α, RANTES/CCL5, and MCP-1/CCL2 from infected microglia and macrophages[43,44] and IL-8, IL-1β, and TNF-α from infected astrocytes.[35,38,39] Furthermore, HIV-1 results in HAND via the continuous release of neurotoxic HIV-1 proteins within the CNS that can target neurons directly.[34,45–47] HIV-1-associated neurotoxic proteins, such as the transactivator of transcription (Tat) and the envelope glycoprotein 120 (gp120), may be responsible for neuronal health in PLWH.[48–50]

Tat and gp120 affect neurons directly by activating glutamate NMDA receptors, altering chemokine receptor signals, and interacting with lipoprotein receptor-associated proteins.[51,52] Previous research has demonstrated that the influences of Tat on NMDA receptors in neuron culture can enhance glutamate-induced excitatory toxicity, resulting in increased intracellular calcium (Ca^{2+}) levels, dendrite injury, and synaptic damage.[51,53,54] Similarly, blocking chemokine receptor signaling prevents gp120-induced neuronal apoptosis when nonneuronal cells are absent.[55,56] Thus, even if the production of HIV-1-associated neurotoxic proteins from infected cells can potentially interact with the cells, HIV-1 itself cannot directly damage neural cells.

Ultimately, if the viral load is not controlled, HIV-1 can lead to neuronal loss. Cognitive impairments in HAND have been demonstrated to be well associated with synaptic damage than neurodegenerative deficits, as axonal degeneration, astrocytosis, and synaptic loss are also accompanied by cell death.[35,57] In addition, other studies sought to determine whether neurocognitive impairments still persist in HIV-infected individuals whose viral load is well controlled. Although some cohort studies have shown that cognitive function has not been affected in individuals with the absence of viremia,[58] others have revealed that the prevalence of HAND is still high in patients with HIV viremia.[59]

This could be explained by several nonexclusive mechanisms as follows. First, due to irreversible neuronal damage before initiating cART, the HIV-1 virus was not completely inhibited in the CNS since several antiretroviral drugs do not penetrate into the CNS and/or viral strains are immune to them.[38,49] Second, viral replication at even very low levels in the CNS could cause neuronal damage or dysfunction due to prolonged exposure to neurotoxic viral proteins and extensively inflammatory responses.[32,33,60] Third, it could be the neurotoxicity of antiretroviral drugs,[61–65] as well as exposure to other conditions that could affect long-term survivors' cognitive abilities, such as an elevated incidence of metabolic abnormalities and related vascular pathology or increased deposits of β-amyloid protein in the brain.[66] HAND persists despite the cART era, and this raises questions concerning the etiology of HAND and HIV-associated neurocognitive diseases, and the degree to which HAND can be recovered.

The Effects of HIV Infection on the ECS

The ECS modulates cognitive and immune function and provides a potentially therapeutic target for treating the impact of HIV-1 infection on the brain (i.e., HAND) because of its potential anti-inflammatory and neuroprotective properties.

Uses of *Cannabis sativa* have been around for centuries. Today, it is becoming increasingly legal to use cannabis for therapeutic purposes. Despite its popularity, it was not until 1964 that the major psychoactive ingredient in *cannabis*, called $\triangle$-9-tetrahydrocannabinol ($\triangle^9$-THC), was isolated and characterized.[67] Later, its molecular target was discovered. CB1[9] was identified in 1990, followed by the cannabinoid receptor (CB2).[10] However, their crystallographic structure was only described in 2016.[68,69] They both are seven-transmembrane G protein-coupled receptor that are expressed throughout the CNS[70] and in peripheral systems.[71] As cannabinoid receptors have been discovered to mediate the effects of naturally occurring plant cannabinoids, endogenous cannabinoid ligands have been identified (summarized in Table 1).[72–74]

Table 1. Cannabinoid Receptor Agonists and Antagonists

Category	Ligand[a]	Selectivity of receptor binding[a]	If the molecule is agonist or antagonist[a]
Endocannabinoids	AEA	CB1 > CB2 > VR1	Agonist
	2-AG	CB1/CB2	Agonist
	2-AGE	CB1	Agonist
	NADA	CB1	Agonist
	AG	CB1 > CB2	Agonist
Phytocannabinoids			
	Palmitoylethanolamide	CB2?	Agonist
	Δ^9-THC	CB1 > CB2	Agonist
	Δ^8-THC	CB1 > CB2	Agonist
	Cannabinol	CB1 > CB2	Agonist
	Cannabidiol	Low binding affinity	Agonist
	Virodhamine	CB2	Agonist
Synthetic cannabinoids			
	HU-308	CB2	Agonist
	JWH-133	CB2	Agonist
	Dexanabinol (HU-211)	No binding to CB1/CB2	Agonist
	HU-210	CB1 > CB2	Agonist
	Nabilone	CB1 > CB2	Agonist
	Levonantradol	CB1 > CB2	Agonist
	CP-55940	CB1 > CB2	Agonist
	R(+)WIN55,212-2	CB1 > CB2	Agonist
	S(-)WIN-55213	Low binding affinity	Agonist
	JWH-015	CB2	Agonist
	ACEA	CB1	Agonist
	ACPA	CB1	Agonist
	R-(+)-methanandamide	CB1	Agonist
	Dronabinol (Marinol)	CB1	Agonist
	Rimonabant (SR-141716A)	CB1	Antagonist
	SR-144528	CB2	Antagonist
	AM251	CB1	Antagonist
	AM281	CB2	Antagonist
	AM630	CB1 > CB2	Antagonist
	Virodhamine	CB1	Antagonist
	LY320135	CB1	Antagonist

[a]Summarized from Patel and Hillard,[72] López,[73] and Croxford.[74]

2-AG, 2-arachidonoyl glycerol; 2-AGE, 2-arachidonoyl glyceryl ether; ACEA, arachidonyl-2′-chloroethylamide; ACPA, arachidonyl-cyclopropylamide; AEA, N-arachidonylethanolamine; AG, Noladin ether; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; NADA, N-arachidonoyl-dopamine.

N-arachidonoylethanolamine is isolated as the first endocannabinoid.[11] Later, another derivative of arachidonic acid, 2-arachdonoylglycerol, was discovered.[12] AEA is generated from membrane phospholipids by *N*-acetyltransferase action followed by N-acylphosphatidylethanolamine-specific phospholipaseD,[75] whereas 2-AG is produced by the enzyme 1,2-diacylglycerol lipase α/β (DAGL).[14] However, alternative pathways of 2-AG may occur since a study showed that $DAGL^{-/-}$ mice revealed only an 80% decrease in 2-AG concentrations.[76] Early studies on endocannabinoids (i.e., AEA and 2-AG) have shown that they are on-demand synthesized.

Their synthesis takes place locally, rather than being stored.[77] Notably, the endocannabinoids stored in lipid droplets are a pool of metabolic intermediates rather than a pool of biologically active lipids that send signals.[78,79] This finding does not contradict to the on-demand synthesis theory that explains endocannabinoid regulation in neuronal synapsis. The actions of endocannabinoids on their receptors cease upon degradation by their hydrolyzing enzymes. AEA is inactivated by FAAH, mainly located in the cell membrane,[80] while the primary catabolic pathway of 2-AG is through MAGL linked to the inner leaf of the plasma membrane, and, to some extent, by α/β-hydrolase-6 and -12 (ABHD6 and ABHD12).[81]

2-AG is also hydrolyzed by FAAH despite this degradation seems to be minor *in vivo*.[82] In addition, both AEA and 2-AG can be metabolized into arachidonic acid under the catalysis cyclooxygenase2.[83] N-palmitoylethanolamine (PEA) and N-oleoylethanolamine (OEA) are part of N-acylethanolamines (NAEs) family besides AEA, which are structurally analogous lipids.[84] 2-AG and its structural analog 2-oleoylglycerol (2-OG) are part of the family of 2-acylglycerols.[85]

Interestingly, there are some metabolic similarities between PEA, OEA, and 2-OG, but none of them target the CB1 or CB2.[86]

Since CB1 receptors are largely placed at axon terminals, activation of the receptors leads to a strong inhibition of neurotransmitter release to the synapse.[77] CB1 receptors are primarily observed presynaptically on neurons, including on GABAergic, glutamatergic, serotonergic, noradrenergic, and dopaminergic terminals,[70,87–89] but they also exist in various peripheral tissues, and on cells of the immune system, vascular smooth muscle, and ileum (Table 2).[90] In addition to the classic CB1 and CB2, other receptors can also be triggered by cannabinoids, including G-protein-coupled receptor 55 (GPR55),[91] G-protein-coupled receptor 18 (GPR18), G-protein-coupled receptor 119 (GPR119),[92] transient receptor potential vanillic acid 1 (TRPV1),[93] and peroxisome proliferator-activated receptor (PPAR).[94] These orphan GPRs, especially GPR55 and GPR119, have become potential targets of cannabinoids.[92,95]

The present study focuses on the neuroprotective role of CB1 by preventing glutamate production at excitatory synapses when they are activated.[19] Endocannabinoids produce postsynaptic diffusion through the synaptic cleft to act on presynaptic CB1 in this retrograde signaling system.[19] Feedback inhibition is provided by the ECS at glutamatergic synapses. Once the postsynaptic cell is excited, it synthesizes 2-AG that activates presynaptic CB1, which inhibits or reduces glutamate release. Amusingly, in a recent study, astrocytes generate 2-AG when they activate metabotropic glutamate receptors, followed by activating presynaptic CB1 to produce a form of synaptic inhibition.[96]

Presynaptic inhibition mediated by CB1 provides the basis for the neuroprotective properties of the ECS, thereby inhibiting glutamate release and dampening excitotoxicity caused by overactivation of the glutamate pathway. Neurodegenerative diseases are often characterized by excitotoxicity,[97] such as HAND,[7,30] where overexpression of glutamate receptors results in the loss of characteristics of postsynaptic structures.[97] Therefore, preventing CB1 may slow down the development of disease and attenuate related symptoms. Convincing evidence that CB1 protects against excitotoxicity was provided by Marsicano et al who demonstrated in a model of kainic acid-induced excitotoxic seizures that mice experience more severe seizures when their CB1 in all forebrain primary neurons except astrocytes are knocked out.[98]

Moreover, a study by Monory et al showed that hippocampal glutamatergic neurons express CB1, which is critical for cannabinoid-mediated security against kainic acid-induced acute excitotoxic seizures.[99] Subsequent studies further elaborated these findings, suggesting that virus-

Table 2. Locations and Functions of Cannabinoid Receptors

Receptors	Cell types vs. tissues/organs	Function
CB1		
Mainly in CNS	Hippocampus	Memory storage
	Hypothalamus	Neuroendocrine release, thermal regulation, appetite
	Cerebellum	Coordination of motor function, posture, and balance
	Cortex	Emesis
	Basal ganglia	Movement control
	Spinal cord	Nociception
Periphery		
	Immune cells	Anti-inflammatory effects
	Cardiac cells	
	Testicular cells	
	Lung smooth muscle cells	Bronchodilation
	Eye ciliary body	Intraocular pressure
CB2		
Mainly in periphery	Lymphoid tissues	Cell-mediated and innate immunity
	Macrophages	Anti-inflammatory effects
	Splenocytes	
	Microglia	
	Monocytes	
	Thymus	
	Spleen	
	Bone marrow	
	Tonsils	
CNS	Microglia	Mediated anti-inflammatory activity
	Astrocytes	

CNS, central nervous system.

mediated CB1 overexpression on the major hippocampal neurons prevents seizure-induced excitotoxicity[100] and that 2-AG is a key activator of CB1, which eventually mediates seizure inhibition.[101] CB1 agonists have potential protection properties, such as constraining excitotoxic neurotransmission via reducing intracellular Ca^{2+} and decreasing presynaptic glutamate release.[90]

However, direct treatment with CB1 agonists is limited because of the psychoactive side effects implicated in CB1 activation, including sensorimotor, and neurocognitive imbalances.[85] The protective effect of CB1 agonists in the models of neurodegeneration suggests the possibility of a protective effect against HAND. As a result, CB1 activation regulates HIV Tat protein-induced changes in network excitability. In an *in vitro* study, HIV neurotoxicity model demonstrated that AEA and 2-AG reduce Tat-induced intracellular Ca^{2+} levels and augmented neuronal survival; the CB1 inverse agonist, rimonabant, prohibits the cannabinoid-mediated neuroprotection.[102] Although this CB1-mediated neuroprotective mechanism is unknown, this study suggests that augmenting cannabinoid signaling may be beneficial to HAND.

Targeting CB1 for the treatment of HAND and other neurodegenerative disorders involves several critical considerations. A CB1 agonist's therapeutic potential is limited to its adverse effects, such as motor slowing,[16,19,103] due to CB1 activation mostly mediating the psychoactive properties of exogenous cannabinoids. Moreover, cannabinoids have been shown to dampen cognitive functions, particularly inhibiting short-term memory,[104] which is an imperative consideration when the therapeutic aims to avoid cognitive slow. In addition, chronically taking cannabis could also result in dependence.[105–107] Therefore, although CB1 agonists have neuroprotective effects and can decrease neuronal injury in neurodegenerative diseases related to animal model, their adverse effects have stimulated interest in other ECS components. Alternatively, regulating CB2 and slackening endocannabinoid metabolism may be promising treatments with decreased side effects.

CB2 receptors are mostly located in immune cells and, once activated, they can regulate the migration of immune cells and the release of cytokines inside and outside the brain (Table 2).[90] Evidence has shown that CB2 could be expressed by some neurons, but its physiological mechanism remains obscure.[83] It is commonly believed that CB2 activation affects the immune system, but CB2 activation does not produce strong psychoactivity because the expression of CB2 in neurons is limited.[89] CB2 agonists are preferentially effective in inflammatory states since receptor expression is immune cell-specific and state-dependent, CB2 can inhibit the deleterious effects of immune activation in the CNS.

Chronic inflammation is associated with increasing numerous neurodegenerative disorders. For instance, reactive oxygen species (ROS) produced by microglia can damage neurons in Alzheimer's disease and Parkinson's disease.[108] Proinflammatory cytokines can also directly damage neurons and synaptic dendrites through excitotoxicity[109] or indirectly activate immune cells.[110,111] In some disease models, CB2 activation can counteract neuroinflammation. CB2 activation represents an encouraging therapeutic target that is involved in neuroprotection mechanisms, such as reducing proinflammatory cytokines[112] and ROS,[113] increasing anti-inflammatory cytokines,[90] impeding chemotaxis to various chemokines, and transforming microglia from proinflammatory.[114]

This extensive effect of CB2 agonists can well counteract a major source of neuroinflammatory damage. Indeed, CB2 agonists can decrease neurotoxicity and cognitive impairment in Alzheimer's disease,[115,116] Parkinson's disease,[115,117] Huntington's disease,[115,118] and multiple sclerosis[115,119] *in vitro* and *in vivo* (Fig. 1). Thus, CB2 agonists could potentially treat a wide range of neurodegenerative diseases by targeting

FIG. 1. Alterations in the ECS elements in neurocognitive diseases. Main findings concerning in members of the ECS in HIV-associated neurocognitive disorders, Alzheimer's disease, Huntington's disease, and Parkinson's disease. ECS, endocannabinoid system.

neuroinflammation. When HIV or simian immunodeficiency virus (SIV) is infected, CB2 is upregulated, causing potentially harmful neuroinflammation,[120] which makes CB2 an attractive therapeutic target against HAND.

In fact, in two *in vitro* experiments, the activation of CB2 by reducing the proinflammatory cytokine IL-1β prevents the synaptic loss caused by HIV protein gp120 in primary cultures.[121,122] CB2 activation may not only prevent the production of neurotoxic cytokines and ROS but also possibly lessen HIV infection in the CNS. Δ^9-THC acts via CB2 to inhibit the expressions of CD4, CXCR4, and CCR5 receptors that are necessary for HIV infection in monocyte-derived macrophages.[123] In addition, the activation of CB2 precludes the production and infection of $CD4^+$ T cells by hindering the rearrangement of the cytoskeleton required for virus fusion.[124] Direct activation of CB2 also reduces the ability of monocytes to cross the blood–brain barrier triggered by HIV.[125]

By activating CB2, HIV infection can slowly spread into microglia, and immune cells that possibly result in neuroinflammation. Although *in vitro* study shows that the CB2 activation provides on-demand neuroprotection in the presence of HIV, no study has yet used CB2 selective agonists in the HAND model, which makes it challenging to explain the influence of CB2. Although these therapeutic strategies have not been applied to human beings, evidence has suggested that cannabinoid agonists are well tolerated. Many PLWH use cannabis either as an appetite stimulant or in entertainment or medicine, but it has no serious adverse effect on overall immune function.[126]

However, no studies have yet shown that cannabis users are less vulnerable to HAND than nonusers. Indeed, it is possible that Δ^9-THC itself can damage neurocognitive function in both healthy controls and PLWH, which may be a result of Δ^9-THC of psychoactive effects rather than CB2-mediated effect.[127] Despite the above limitations, selective activation of CB2 remains a potential therapeutic approach for two reasons. First, since CB2 agonist mainly targets immune cells instead of nerve cells, it has a lower abuse potential and fewer psychoactive effects compared with CB1 agonist or other mixed agonist. Second, CB2 agonist is also most effective when neuroprotection is mostly needed during HIV infection since CB2 expression is increased.

As previously described, several putative endocannabinoids have been discovered.[19,76–79,83] Here, we mainly focus on two of the most well-characterized ligands, AEA and 2-AG. AEA generates signaling both retrograde and nonretrograde, and its functions are relatively slow.[82] 2-AG is the most famous retrograde messenger in the CNS and plays a critical role in time-dependent plasticity and long-term inhibition.[85] The concentrations of AEA and 2-AG can be elevated by preventing their degradative enzymes. Numerous selective inhibitions on endocannabinoids metabolic activities have been developed and extensively investigated in models of neuropsychiatry and neurodegeneration.[128]

Unlike the extensive and sustained activation of CB1 or CB2 released by agonists, increasing the activity of endocannabinoids by preventing metabolic enzymes can enhance endocannabinoids' signaling and reduce side effects of CB1 and CB2 agonists.[70,102] Metabolic enzyme inhibitors also prevent the rapid degradation of 2-AG and AEA when administered directly.[19] Collectively, the targeting of the ECS may be a promising strategy for alleviating the inflammation and neurodegeneration caused by HIV-1 infection.

Pre-clinical and Clinical Evidences of Cannabinoids as Therapeutic Agents in HAND

Pre-clinical evidence accumulated over the last few years shows cannabinoids against HAND. A study on rat C6 glioma cells demonstrated that cannabinoids inhibit Tat-induced cytotoxicity.[128] It has been shown that treatment of C6 cells with Tat combined with IFN-1 inhibits iNOS expression and NO release in these cells. Stimulating CB1 also hindered Tat+ IFN-γ-caused and NO-mediated cell toxicity. Additionally, treating C6 cells with Tat+ IFN-γ generated a substantial inhibition of CB1 rather than CB2.[128] Eventually, treatment with Tat+ IFN-γ also resulted in a significant inhibition of AEA uptake of C6 cells, without influencing FAAH hydrolysis of AEA.

Overall, these data demonstrated that the ECS via regulation of NO synthesis decreased HIV-1 cytotoxicity caused by Tat.[128] Later, in an *in vivo* study, the gp120-induced neuronal apoptosis in the neocortex of rats resulted in a time-dependent elevation in the activity and immunoreactivity of FAAH (approximately threefold vs. the control), paralleled by increased activity of the AEA membrane transporter and decreased endogenous levels of AEA (approximately half).[129]

Additionally, the FAAH inhibitor methyl-arachidonyl fluorophosphate considerably decreased gp120-caused neocortex apoptosis in the brain of rat, while AEA

membrane transporters (i.e., VR1 receptors) or AEA binding receptor (i.e., CB1 and CB2) selective antagonists, such as SR141716, SR144528, and capsazepine, respectively, were ineffective.[129] Collectively, these findings suggest that gp120 reduces endogenous AEA levels by activating FAAH. Recently, human U87MG astrocytoma cells treated with gp120 showed a similar reduction in AEA tone caused by increased FAAH activity.[130] A recent study found that Tat expression in transgenic mice was sex-dependent on inhibitory neurotransmission and was inhibited by the FAAH inhibitor PF3845 through a CB1 mechanism.[131]

The therapeutic potential of cannabinoids for treating CNS disorders, including neurodegenerative conditions,[132] cognitive decline,[133] and appetite loss,[134] has been demonstrated. Despite extensive research on the cognitive effects of cannabis use in PLWH, the results are contrary, mainly owing to differences in disease progression and methodologies, such as cognitive functioning assessed and the amount of cannabis used. A well-documented and established effect of cannabis use on HIV-negative individuals is memory deficits, but its long-term effects are still unknown.[135,136] In a meta-analysis of cannabis's nonacute effects, learning and memory were found to be only mildly affected, and no other negative effects were noted.[137]

The authors pointed out, however, that numerous studies had methodological limitations and did not take into account confounding factors, such as other disorders and medications. It has been shown that cannabis use has varying effects on PLWH based on the stage of the disease.[138] Cannabis use led to neurocognitive dysfunction in PLWH who were symptomatic phase, while such symptoms were found in persons who were not infected or PLWH who were cannabis users or with no symptomatic stage.[139,140] Symptomatic PLWH with frequent cannabis use showed greater cognitive impairment, especially related to memory performance.

Considering that HIV-1 infection and cannabis use affect the immune system, the interaction between them are likely to be aggravated in patients who are more immunosuppressed.[141,142] Other studies have shown that cannabis has adverse effects on neurocognitive function in people who use it frequently. For instance, cannabis use has been found to have adverse effects on HIV-1 symptoms, whereas noncannabis use or nondependence had no effects on these symptoms.[135,137] Similarly, moderate-to-heavy users constantly behaved worse on cognitive tasks than mild users, regardless of HIV-1 status.[141] In a follow-up study, a significant effect of cannabis use on PLWH's global cognition had not been confirmed.[139]

Reciprocal Interactions of the ECS with the HPA and HPG Axes Influencing Therapeutic Targets

The viral reservoir resides in the CNS and serves as a source of HIV viral toxin, destroying mitochondria and promoting neurotoxicity. Evidence has demonstrated that HIV-1 virus or the HIV-1-related neurotoxic Tat can deregulate the production of neurosteroids, potentially resulting in dysfunction of neuroendocrine, such as HPA and HPG axes. However, HIV-endocrine interactions are becoming dynamic. Specifically, endogenous steroids or gonadal hormones affect HIV virus replication and, in turn, HIV-1-related neurotoxins can affect the release of these hormones. As a result, the relationship between the functions of the neuroendocrine systems and HAND is mutual. However, within the PVN, glucocorticoids cause the release of endocannabinoids and inhibit the excitatory inputs to CRF neurons as shown by being blocked by CB1 receptor antagonists.[23]

Because endocannabinoids are widely distributed throughout the hypothalamus and the limbic circuits, they occupy a unique niche to regulate the release of excitatory and inhibitory transmitters, and the final result is to constrain the HPA activity.[22] The ECS also overlaps considerably with receptors for gonadal steroids, suggesting that the ECS may be an important neuroregulatory system that can be used for regulating gonadal steroids. In this regard, interactions between the ECS and the HPA and HPG axes may influence the ECS as a potential therapeutic target for HAND. As such, we first review the clinical and pre-clinical findings for the HPA and HPG axes in HIV, and then, we review the interactions of ECS with the HPA and HPG axes in HIV.

The dysregulation of HPA axis in PLWH

In the precART era, HIV-related pathogenesis of the HPA axis was primary and related to opportunistic infection that promoted adrenal atrophy and the direct invasion of tumors or invasive disease.[143] In the post-cART era, a dysfunction of the HPA axis is believed to be secondary to hypothalamic or pituitary dysfunction. Estimates vary, but ~14–46% of PLWH exhibit abnormal of the HPA axis function, which is described by increased basal concentration of serum cortisol (i.e., hypercortisolmina) but abnormal adrenal insufficiency when exposed to stressors.[143,144] Many HIV-infected

PLWH develop hypercortisonemia early or late in the disease course.[145]

HIV can have a profound impact on the production of circulating steroids. These effects can reduce the levels of steroids in the circulation through the action of endocrine glands, including adrenal glands or gonads, or by targeting the source of adrenocorticotropic hormone (ACTH) and gonadotropin in the hypothalamus and pituitary.[144,146] As such, PLWH are usually influenced by dysfunction of the HPA axis. It is possible that this dysfunction contributes to the neuropsychiatric components of HAND, which are to a greater extent in PLWH. One possible mechanism could be an enzymatic conversion of adrenal androgen to cortisol or a compensatory increase in production of steroid, such as dehydroepiandrosterone (DHEA).[144,147]

More specifically, the compensatory increase in the increase of corticosteroid-binding globulin occurred during the transition to AIDS and/or decreased glucocorticoid receptor (GR) sensitivity to their homologous ligands.[144] An increase in proinflammatory cytokines elevates the ratio of GRα to GRβ (GRβ is the main negative inhibitor of bioactive GRα), thereby decreasing GR-mediated negative feedback loop inhibition.[148,149] HIV-infected cells may secrete several virotoxic proteins that may contribute to an imbalance in the HPA axis. For instance, HIV-1 Tat protein can also be used as a coactivator of GR to enhance the role of glucocorticoids, which may promote glucocorticoid resistance.[150]

Evidence has shown that Tat protein may also interact with these viral toxins, such as Nef and gp120, to affect the HPA function and has a significant effect on reproducing clinical phenotypes when expressed in mice.[145] Indeed, the HIV envelope protein gp120 increases ACTH and corticosterone levels in plasma and similarly increases pituitary ACTH levels in a transgenic mouse.[151] Gp120 increased corticotropin releasing hormone (CRH) messenger RNA (mRNA) expression and CRH levels in hypothalamus tissue of mouse or rat.[152] Taken together, HIV-related viral proteins, such as Tat and gp120, may promote glucocorticoid resistance alone or in combination. Since the HPA axis has a vital role in overcoming psychological and physiological challenges, its destruction may contribute to the observed neuro-HIV-like symptoms.

The dysregulation of HPG axis in PLWH

In line with the neuroendocrine dysfunction (i.e., HPA) in the postcART era, ~10–50% of PLWH suffer from hypogonadism, which is characterized by a reduction in testosterone levels in men and an imbalance between estradiol and progesterone levels in women.[153,154] Both men and women living with HIV who experience early menopausal attacks show hormonal deficiencies. More specifically, after the age of 50 for men, the levels of androgens, especially testosterone levels, gradually decrease while the physical and mental disorders caused by changes in hormone secretion in the body are reduced.[155] Menopause is a process in which women's hormone levels gradually decrease, or even disappear, which are due to the decline in ovarian function when they reach 45 years of age or older.[156]

Therefore, the benefits of gonadal hormonal therapy for the HIV population may be particularly significant if initiated early. Among men living with HIV, hypogonadism is primarily secondary, occurring in ~12–28% of young or middle-aged individuals.[157] Hypogonadism is associated with increasing age, prolonged HIV infection, and decreased $CD4^+$ T cell counts when hypogonadism occurs.[158,159] HIV-positive men experience an early transition to male menopause linked to low testosterone levels, normal or low luteinizing hormone (LH) levels, and a higher ratio of estradiol to testosterone,[160,161] which increases the risk of cardiovascular disease and frailty.[158,162] Similarly, HIV-positive women exhibit accelerated ovarian aging sooner than their control counterparts, with lower circulating levels of androgens and 17β-estradiol.[163,164]

Animal models are beginning to shed light on HIV-induced neuroendocrine dysfunction, despite the fact that the mechanism is still unclear. For instance, male mice with long-term HIV-1 Tat expression have short-term and long-term memory damage, while female mice have only short-term memory damage, and males and females are impaired in motor coordination and balance abilities.[5,30,32] Subtle sex differences were observed in neuropathology, with HIV-1 Tat inducing a higher density of presynaptic and postsynaptic markers in the female cortex and a decreased density of presynaptic markers in the male cerebellum.[153] In addition, the overall DNA methylation level is higher in Tat-exposed females.[165]

Interactions between the ECS and HPA and HPG axes

As described previously, HIV-1 virus first attacks the immune system, causing a severe depletion of $CD4^+$ T lymphocytes and an increase in viral load, which in turn causes significant physiological stress and thereby results in dysfunction of neuroendocrine

systems, including the HPA[143,145,154] and HPG axes[154] and ECS.[132] There is growing evidence that HIV envelope proteins gp120 and Tat might induce the hyperactivity of the HPA axis[21,145] and ECS.[128,166] The activation of the HPA axis and ECS in PLWH may play a key role in the process of infection progression to disease manifestation.[145,167] This is partly because glucocorticoids secreted by the HPA axis and endogenous cannabinoids released by ECS have the immunomodulatory effect of transferring Th1 to Th2 immunity, which is a hallmark of the progression of HIV infection.

In contrast, after using antiretroviral therapy, HIV viral load will decrease, which will influence the endocrine system. However, it is unclear whether endocrine indictors could be used to reflect the functional alteration of neuroendocrine systems affected by HIV. It is therefore of increasing interest to researchers to study the possible correlations between virological outcomes and endocrine systems among PLWH, particularly abnormalities in hormonal secretion of the HPA and HPG axes and ECS.

Glucocorticoids, gonadal hormones, and endocannabinoids secreted by the HPA and HPG axes and ECS regulate the body's adaptation to stress by altering the basal levels of these neuroendocrine biomarkers and maintaining stress-related homeostasis.[168,169] HIV-related infections result in dysfunction of the HPA and HPG axes and ECS and thus lead to a series of adverse effects of the physiological response.[145] In addition, HIV-infected individuals have also chronically suffered from great immune, physiological, and psychosocial stress. As a result of constant activation of the three endocrine systems, imbalances occur in the stress response pathway, resulting in abnormal glucocorticoids, gonadal hormones, and endocannabinoids being secreted.

Research has been conducted to investigate whether the three system functions are abnormal in PLWH by separately determining the levels of cortisol, testosterone, AEA, and 2-AG from the end-product of the HPA and HPG axes and ECS. There are conflicting findings concerning the HPA axis in studies, with some finding elevated cortisol levels[147,170,171] and others finding the opposite.[168,172,173] Given the limitations of using a single glucocorticoid concentration as a biomarker to assess the activity of the HPA axis, inconsistent findings should not be surprising. That is, a single glucocorticoid concentration does not accurately and fully reflect the activity of the HPA axis.

Cortisol is converted to inactive cortisone with the aid of the 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD 2),[174] which is modulated by the negative feedback circuit of the HPA axis. The controversial caveat can be resolved by evaluating the HPA activity comprehensively with multiple biomarkers. A similar situation might be true for the HPG axis and ECS. Indeed, multiple steroid concentrations would provide a comprehensive analysis of the activity of the HPA axis and other neuroendocrine systems, including the HPG axis and the ECS.[175–177] In addition to the HPA axis, ECS and the HPG axis are also stress-sensitive neuroendocrine systems in human beings.[175,178,179] The steroids and endocannabinoids secreted by the three systems have traditionally been used as the corresponding biomarkers to assess the activities of the three neuroendocrine systems.[175,178]

More importantly, among these three systems, there are close interactions (Fig. 2). It has been demonstrated that endocannabinoid signaling modulates the HPA axis in response to stress,[180] and the CB1 receptor modulates the activity of the HPA axis.[181] Within the PVN, glucocorticoids cause the release of endocannabinoids and inhibit the excitatory inputs to CRF neurons, as shown by being blocked by CB1 receptor antagonists.[23] Because endocannabinoids are widely distributed throughout the hypothalamus and the limbic circuits, they occupy a unique niche to regulate the release of excitatory and inhibitory transmitters, and the final result is to constrain the HPA activity.[22]

A study found that administration of the CB1 receptor antagonist SR141716 to male mice increased serum corticosterone levels in a dose-dependent manner.[182] Glucocorticoid concentrations are increased when CB1 is directly activated, especially with high concentrations of direct agonists.[23,183] Haller et al demonstrated that inhibition of MAGL with JZL184 promotes the HPA activity in mice.[184] Conversely, ECS activation dampens the HPA activity in response to stress,[22,185] most likely by acting on the hypothalamus and amygdala.[22] The ECS is also implicated in the recovery of the HPA axis to baseline, which may be an effector in the long-term feedback circuit initiated by GR activation in the hippocampus[186] and prefrontal cortex.[187]

In particular, *in vivo* studies in Roberts' laboratory showed that CB1 blockade in the PFC of male rodents prolonged the recovery time of the HPA axis to baseline after stress response.[188] Cortisol and endocannabinoids are believed to be interconnected, and glucocorticoids inhibit the HPA axis by activating fast

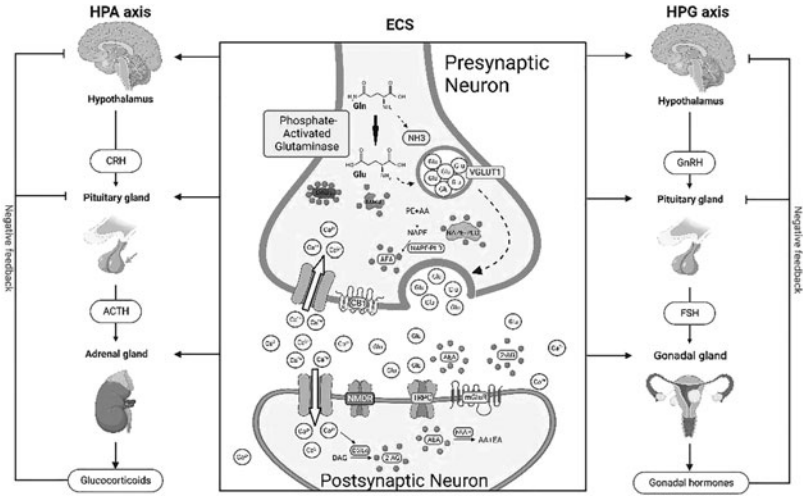

FIG. 2. Schematic presentation of the interactions among the ECS and HPA and HPG axes. AA, arachidonic acid; Ca^{2+}, calcium; DAG, diacylglycerol; DGL, diacylglycerol lipase; EA, ethanolamine; FAAH, fatty acid amide hydrolase; HPA, hypothalamic–pituitary–adrenocortical; HPG, hypothalamic–pituitary–gonadal; mGluR, metabotropic glutamate receptor; NAPE, N-arachidonoyl phosphatidylethanolamine; NAPE-PLD, N-arachidonoyl phosphatidylethanolamine phospholipase D; NMDR, N-methyl-D-aspartate receptor; PE, phosphatidylethanolamine; TRPC, transient receptor potential cation channel.

negative feedback.[23] Endocannabinoids derived from the ECS, such as AEA and 2-AG, and cannabinoid receptors (CB1 and CB2) also suppress the HPA activity.[189–191] In addition, direct stimulation of agonist on CB1 increases the levels of the circulating glucocorticoids, especially when the agonist concentration is high.[15,192]

Particularly important, the ECS overlaps considerably with receptors for gonadal steroid hormones,[180] suggesting that ECS may be an important neuroregulatory system that can be used for regulating gonadal steroid hormones. The ECS has considerable interaction with the HPG axis based on the following evidence, such as the regulation of ECS on gonadal steroids, the localization of receptors and metabolic enzymes of ECS in the HPG axis, and the alteration of the endocannabinoid signaling elicited by the changes in levels of gonadal hormones [180]. Indeed, ECS-deprived receptors and enzymes on structures in the HPG axis and the altered endocannabinoid signaling are induced by gonadal hormone fluctuation.[180]

It is typically thought that the HPG activity is constrained or restricted by cannabinoids and that its hormonal products are suppressed. Both males and females are inhibited by acute administration of THC in terms of LH and prolactin that are the HPG-related hormones.[24,193,194] In women, high doses of THC interfere with the timing of estrus and the menstrual cycle, thereby delaying and preventing them. There are also studies suggest that cannabis use may decrease serum LH and testosterone in men and shorten reproductive cycles in women.[195,196] The result on exogenous cannabinoid inhibits the HPG activity suggesting that endocannabinoids possibly modulate the HPG axis under normal conditions.

For instance, intracerebroventricular administration of AEA decreased both prolactin and gonadotropin-releasing hormone production by both males and ovariectomized (OVX) females, consistent with previous findings that THC has an inhibitory effect on HPG axis.[197,198] Nevertheless, AEA elevates plasma levels of LH and prolactin after the estradiol treatment.[199] Similar findings were observed in *in vitro* studies of medial hypothalamic basal neurons.[200–202] These findings suggest that the inhibitory effect of cannabinoids on the HPG can be reversed by estrogen.

The HPG axis also regulates the function and activity of ECS. More specifically, sex hormones possibly affect the functional activity of ECS in three ways, including influencing cannabinoid receptor expression, the synthesis or degradation of endocannabinoids, and degraded enzyme activity. First, gonadal hormones may

modulate expression of cannabinoid receptors and thus influence the ECS activity. Studies have found variations in endocannabinoid activity in female rodents across the estrous cycle, which suggests that gonadal hormones possible have an activating effect on ECS.[203,204] For example, a study has showed that CB1 receptor mRNA levels were lowest and AEA levels were highest in the pituitary gland during estrus in female rats.[203]

Estradiol administration was considerably associated with decreased CB1 mRNA expression in OVX females than in nontreated OVX females. Second, the most substantial alterations of endocannabinoids occur across the estrous cycle, suggesting that there are possible relationships between gonadal hormones and the ECS function. For example, Bradshaw et al investigated sex and cycle differences in endocannabinoid release in several brain areas of the rat, such as hypothalamus, pituitary, and midbrain.[205] Although there was no difference in AEA production in the hypothalamus or pituitary between males and females, female rats showed significantly higher 2-AG levels compared with males.

Both 2-AG and AEA reached their maximal levels in the pituitary during early proestrus, whereas AEA production was highest in the hypothalamus during diestrus. It is interesting to note peak levels of AEA and 2-AG in the midbrain during late proestrus. Although the physiological implications of these cyclic fluctuations remain obscure, the most substantial alterations occur during the transition from anestrus to estrus, suggesting that the ECS may play a role in the regulation of gonadal hormones. Third, gonadal hormones may regulate the activity of endocannabinoid-related degraded enzymes and further influence the ECS activity. For instance, evidence shows that as FAAH activity increases around blastocyst implantation, AEA within women's uteruses decreases.[206] The FAAH gene sequence covers an estrogen response factor, and when activated, the FAAH gene is upregulated and thus affects estrogen production.[207]

As mentioned previously, ECS is regulated by the HPA and HPG axes, which may affect its receptors, cannabinoids, and related enzymes. Conversely, ECS can overwhelmingly influence endocrine activities, including hypothalamic releasing factors, pituitary steroids, and peripheral hormones.[73,208,209] The ultimate outcome is to affect the effectiveness of ECS as a potential drug target for HAND. However, in these studies, evaluating the interactions among ECS and the HPA and HPG axes may be limited in the clinical application because it is not possible to achieve rapid assays aimed at observing whether there are alterations in the expression of certain genes or relevant metabolic enzymes or receptors or the levels of endogenous molecules. It is more easily used in clinical applications with the development of molecular detection technology.

For example, liquid chromatography–tandem mass spectrometry (LC-MS/MS), the simultaneous quantitation of a variety of endogenous hormones and endocannabinoids that are used to evaluate the functions of the three systems and interaction among them has been achieved.[175,178] Although the concentrations of hormones and endocannabinoids have been suggested to evaluate the activities and the interactions of the HPA and HPG axes and ECS, these biomarkers based on the hormone concentrations have a deficiency that is susceptible to external interference.[144] A previous study suggested that the ratios between endogenous steroids are regarded as biomarkers to evaluate the interaction between the HPA and HPG axes.[210]

The ratio biomarkers are relatively stable since they can counteract external influences. Thus, the multicategory biomarkers (e.g., steroid concentrations in combination with ratio biomarkers) could provide clearer and more comprehensive details on the HPA and HPG axes, ECS, and their interactions than single biomarkers. Indeed, our research group has utilized the concentrations of glucocorticoids, gonadal steroids, endocannabinoids, and ratio biomarkers to evaluate the interactions within a neuroendocrine system and among the three systems in human and animal studies.[175,176,178,211] For example, the ratio of cortisol to AEA was used to assess the interaction between ECS and the HPA axis, and the ratio of testosterone to AEA was considered to evaluate the interaction between ECS and the HPG axis among patients.[175,178]

Conclusions and Perspectives

We review how ECS contributes to HIV-1 disease progression and how it can be used as a therapeutic target to reduce HAND pathophysiology. The ECS may be ideally suited to modulate the pathophysiology of HAND. Direct activation of presynaptic CB1 or a reduction in cannabinoid metabolism attenuates HAND excitotoxicity. The activation of CB2 on immune cells can reduce chronic neuroinflammation associated with HAND. Moreover, enhanced cannabinoid receptor expression in HAND may increase the ECS sensitivity to HIV. However, targeting certain elements of ECS has some drawbacks.

Particularly, the psychoactive effects caused by activating CB1 are of particular concern. There are several limitations to the use of CB1 agonists, including motor impairment and diminished the short-term memory. MAGL and FAAH inhibitors may be used to increase endogenous generation of agonists to prevent the desensitization of cannabinoid receptors that happens during persistent activation. Because patients with HAND may not be able to receive preventive treatment, understanding the disease duration, especially alterations in neuroinflammation, is crucial to understand the importance of excitotoxicity and neuroinflammatory targets.

In addition, due to the reciprocal inhibition of ECS by the HPA and HPG axes, indirect regulation of ECS by modulating hormone-related receptors may be a potential strategy affecting the ECS and may also alleviate the progression of HAND. Collectively, several promising targets in ECS to suppress the neuronal injuries that underlie HAND have been discussed. CB2 agonists inhibiting neuroinflammation were better than nonselective drugs that activate both CB1 and CB2, with psychoactive side effects. MAGL inhibitors have become promising reagents because of inhibiting glutamate release by enhancing endogenous production of 2-AG through CB1, and hindering immune function through CB2 in CNS. A CB2-selective agonist and MAGL inhibitor are well tolerated and are currently being studied for other indications than HAND, which may slow the progression of HAND.

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There have been no animal or human studies conducted by any of the authors for the purpose of this article.

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Authors' Contributions

L.C.: Conceptualization, writing—original draft preparation, and writing—review editing. Z.S., X.G., and Y.W.: Writing—review editing. J.Y.: Funding acquisition and reviewing. H.D.: Funding acquisition, and writing—reviewing and editing.

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Abbreviations Used

2-AG = 2-arachidonoyl glycerol
2-AGE = 2-arachidonoyl glyceryl ether
2-OG = 2-oleoylglycerol
AA = arachidonic acid
ACEA = arachidonyl-2′-chloroethylamide
ACPA = arachidonyl-cyclopropylamide
ACTH = adrenocorticotropic hormone
AEA = N-arachidonylethanolamine
AG = Noladin ether
Ca^{2+} = calcium
CB1 = cannabinoid receptor type 1
CB2 = cannabinoid receptor type 2
CNS = central nervous system
CRF = corticotropin releasing factor
DAG = diacylglycerol
DAGL = 1,2-diacylglycerol lipase α/β
DGL = diacylglycerol lipase
EA = ethanolamine
ECS = endocannabinoid system
FAAH = fatty acid amide hydrolase
gp120 = glycoprotein 120
GPR119 = G-protein-coupled receptor 119
GPR55 = G-protein-coupled receptor 55
GR = glucocorticoid receptor
HAD = HIV-associated dementia
HAND = HIV-associated neurocognitive disorders
HPA = hypothalamic–pituitary–adrenocortical
HPG = hypothalamic–pituitary–gonadal

Abbreviations Used (Cont.)

LH = luteinizing hormone
MAGL = monoacylglycerol lipase
mGluR = metabotropic glutamate receptor
mRNA = messenger RNA
NADA = N-arachidonoyl-dopamine
NAPE = N-arachidonoyl phosphatidylethanolamine
NAPE-PLD = N-arachidonoyl phosphatidylethanolamine phospholipase D
NMDR = N-methyl-D-aspartate receptor
OEA = N-oleoylethanolamine
OVX = ovariectomized
PE = phosphatidylethanolamine
PEA = N-palmitoylethanolamine
PLWH = people living with HIV/AIDS
PVN = paraventricular nucleus
ROS = reactive oxygen species
Tat = transactivator of transcription
THC = tetrahydrocannabinol
TRPC = transient receptor potential cation channel