HIV Infection and Neurotoxicity Related to Drugs of Abuse

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Abstract

HIV, a neurotropic virus, immediately invades the brain following infection. HIV replicates in the brain in a modest number of astrocytes, microglia, and macrophages, inducing inflammatory and neurotoxic host responses. The term "Hiv-Associated Neurocognitive Diseases" refers to severe neurological illnesses brought on by HIV (HAND). The development of abnormally low levels of motor coordination, focus, and memory are hallmarks of HAND. From Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND), to the most severe HIV-Associated Dementia (HAD), HAND has a variety of clinical manifestations. The primary cause of HAND and the most prevalent neurologic condition affecting the brain in those infected with HIV-1 is HIV-Encephalitis (HIVE). There are nine main genetic subtypes of HIV-1, which are divided into three groups (M, O, and N) and demonstrate widespread genetic variation. More than 86% of the circulating HIV-1 variations belong to clades B and C. Clade C of the HIV-1 virus is more prevalent in Southern and East Africa, India, and Nepal than clade B, which predominates in North America, Western Europe, and Australia (responsible for around half of all HIV infections). According to reports, clade B of HIV-1 is more neuropathogenic than clade C. About 20%–30% of people with advanced HIV-1 clade B infection exhibited HAD symptoms before the widespread use of Highly Antiretroviral Treatment (HAART).

Keywords: Highly antiretroviral treatment • hiv-associated dementia

Introduction

About 30% of HIV-positive people in wealthy nations take intravenous drugs, which increases their risk of HAND. While opioids are only sometimes abused by HIV patients, cocaine and marijuana are the most often utilized substances among them. Tobacco, stimulants, cannabis, opioids, and alcohol are among the drugs of abuse that people with HIV are found to use, and they have an impact on the brain's synaptic plasticity and development. Depicts various substance abuse-related neurotoxic pathways in HIV infection that may affect neurocognitive abilities.

HIV and nicotine

HDAC2 has recently been found to be upregulated in cells that had been exposed to nicotine and HIV. Decreased dendritic spine density, synaptic plasticity, and memory formation have all been linked to HDAC2 overexpression. However, patients with HIV-1 infection who use nicotine may have improvements in their neurological impairments.

The down-regulation of Axin1, Wnt5a, Wnt7a, and the up-regulation of Gnao1 have been restored in nicotine-injected HIV-1 transgenic rats' prefrontal cortex, demonstrating improved Wnt/-catenin signaling. A neuroprotective effect in adults is established following the activation of this signaling pathway, which plays a significant role in the early development of the nervous system [1].

These findings are significant since central demyelination and neurodegeneration have been seen in people with HIV-1 infection. Calm3 and Cabp1's reduced expression was brought back to normal levels in the dorsal hippocampus thanks to the restoration of CREB signaling. Long-term synaptic plasticity and neuronal survival are important outcomes of this signaling system. The Tricarboxylic Acid (TCA) cycle and its associated mechanisms, such as the up-and down-regulation of Idh3B, have also been demonstrated to work normally in the dorsal striatum when nicotine is present.

HIV and psychedelics

The Human Leukocyte Antigen (HLA)-DR, a marker of macrophage activation, and HIV replication in monocytes and even astrocytes have been linked to stimulants like cocaine in vitro studies. A further HIV co-receptor that is upregulated by cocaine is Dendritic Cell-Specific Intercellular Adhesion Molecule-3-Grabbing Non-Integrin (DC-SIGN), which is another way that cocaine might cause HIV infection. In vitro studies have shown that cocaine can also cause monocyte transendothelial migration, endothelial adhesion molecule expression, and disruption of intercellular junctions in the Blood Brain Barrier (BBB) . HIV patients with cocaine use reportedly had worse HAART adherence and more neurocognitive impairment than non-users of drugs [2].

Contrarily, methamphetamine is a neurotoxic substance that damages dopaminergic neurons and lowers both norepinephrine and dopamine levels in the brain. Additionally, a smaller hippocampus volume in meth addicts with HIV was linked to a greater degree of cognitive impairment. Meth boosted HIV replication in astrocytes and elevated the expression of the HIV co-receptors CXCR4 and CCR5 .To prevent meth-neurotoxicity, BBB disruption and a rise in the expression of pro-inflammatory cytokinesis were seen.Interleukin-6 (IL-6) and cytochrome P450 2E1 (CYP2E1) were produced by astrocytes as a result of gp120 and meth working together.

HIV and marijuana

Cannabinoids have been shown to alter neurotoxic and inflammatory processes in HIV-positive persons who consume them. Deterioration in the hippocampus neurons' synaptic network was seen in studies on HIV gp120-treated cells. These happened as a result of CXCR4 activation, which opened up cell signaling pathways and caused IL-1 to be released. The N-Methyl-D-Aspartate (NMDA) receptor and a ubiquitin ligase are both activated by this -chemokine, which mediates synaptic loss. This receptor is in charge of regulating synaptic plasticity and memory performance.

The loss of synapses was thought to be a protective mechanism rather than an agonizing occurrence that keeps cells from becoming overstimulated Win 55212-2, a complete agonist for the cannabinoid receptor, served as a guardian for the hippocampus neurons against gp120-induced IL-1 production and synapse loss, though. It has been suggested that the CB2 cannabinoid receptor, not the CB1, is responsible for this defense. Win55212-2 did not, however, prevent synapse loss after exposure to the HIV-1 protein Tat. It was also shown that the GFAP/Gp120 transgenic mouse model's hippocampus saw reduced astrogenesis and gliogenesis in response to the cannabinoid CB2 receptor agonist (AM1241). For the treatment of neurodegenerative diseases and other ailments in the future, this research is crucial in the medical profession [3].

HIV and heroin

Because they work together to intensify immunosuppression, opioid medications and HIV viral proteins are referred to be cofactors for HIV infection. In addition to reducing overall spine density, HIV-1 Tat and morphine showed a synergistic effect in the up-regulation of inflammatory cytokines and chemokines. This was seen when the Mopioid receptor (MOPr) engaged with glutamatergic signals coming from the amino-3-hydroxy-5-methyl-4-isoxazole Propionic Acid (AMPA) receptors. Tat generated an excitotoxic manifestation that hindered ATP synthesis and disrupted cellular energetics by over-activating the NMDA receptor. Fitting et al. disclosed a novel HIV-1 discovery. Increased intracellular sodium (Na+) and calcium (Ca2+) in dendrites induces synaptodendritic damage in response to tat and morphine [4].

HIV infection and substance abuse

Lifelong alcohol dependence has been linked to memory, attention, and learning deficits. But not all cognitive impairments are temporary. Long-term memory injuries were shown to linger up to seven years, despite restraint showing the recovery of psychomotor skills and short-term memory. In a study that compared people who were HIV-positive and those who weren't who had a history of alcoholism, the HIV-positive group showed considerable cognitive impairment in the areas of verbal reasoning, auditory processing, and reaction time, whereas the other group showed no significant impairments. This demonstrated how HIV and alcohol affect the Central Nervous System (CNS) synergistically.

HIV-associated neurocognitive impairment: clinical studies on the effect of drug abuse

According to several studies, using cocaine, methamphetamine, and opioids increases the risk of neuronal damage and neurocognitive impairment in HIV-positive people. However, a recent large cohort study discovered that those who had previously used drugs (including alcohol, cocaine, cannabis, opioids and methamphetamine) did not have greater rates of neurocognitive or functional impairment in daily life. Less than a third of those polled said they had used drugs within the previous year, and the bulk of them weren't even regular users. The authors speculate that continuous drug abstinence phases could be sufficient for a full or partial recovery from neurocognitive impairment.These findings are in line with another longitudinal study in which meth users who abstained for a longer period (an average of 13 months) than those who did not were shown to have improved neurocognitive performance. These findings suggest that the neurocognitive damage caused by drugs of abuse in HIV-positive people may not be as severe as previously thought and that recent substance use may be more important in regulating HIV neuropathogenesis. The diagnosis of HIV-encephalitis is more common in people with HIV who abuse drugs compared to HIV-positive controls, providing additional evidence that drugs of abuse increase neuroinflammation and the accompanying neurodegeneration [5].

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