Neuropsychiatric Disease and Treatment

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REVIEW

The Role of Brain Derived Neurotrophic Factor in HIV-Associated Neurocognitive Disorder: From the Bench-Top to the Bedside

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment

Henry Michael[1]
Thabisile Mpofana[2]
Suvira Ramlall[3]
Frasia Oosthuizen[1]

[1]Discipline of Pharmaceutical Sciences, School of Health Science, University of KwaZulu-Natal, Durban, South Africa; [2]School of Laboratory Medicine and Medical Sciences, University of KwaZulu-Natal, Durban, South Africa; [3]Department of Psychiatry, University of KwaZulu-Natal, Durban, South Africa

Abstract: Human immunodeficiency virus (HIV)-associated neurocognitive disorder (HAND) remains prevalent in the anti-retroviral (ART) era. While there is a complex interplay of many factors in the neuropathogenesis of HAND, decreased neurotrophic synthesis has been shown to contribute to synaptic degeneration which is a hallmark of HAND neuropathology. Brain derived neurotrophic factor (BDNF) is the most abundant and synaptic-promoting neurotrophic factor in the brain and plays a critical role in both learning and memory. Reduced BDNF levels can worsen neurocognitive impairment in HIV-positive individuals across several domains. In this paper, we review the evidence from pre-clinical and clinical studies showing the neuroprotective roles of BDNF against viral proteins, effect on co-morbid mental health disorders, altered human microbiome and ART in HAND management. Potential applications of BDNF modulation in pharmacotherapeutic, cognitive and behavioral interventions in HAND are also discussed. Finally, research gaps and future research direction are identified with the aim of helping researchers to direct efforts to make these BDNF driven interventions improve the quality of life of patients living with HAND.
Keywords: neurotrophins, neuroplasticity, HIV/AIDS, cognition, BDNF

Introduction

About 36.9 million people live with HIV globally. The decline of AIDS related deaths, from a peak of 1.9 million in 2005 to 940,000 in 2018, has been attributed to the global scale up of ART with 21.9 million accessing treatment.[1] While medical morbidity has significantly improved in the ART era, HIV-Associated Neurocognitive Disorders (HAND) remain common with the prevalence of HAND globally estimated at 50%.[2] HAND can be categorized in increasing degree of severity into asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD).[3] The cognitive domains usually affected are psychomotor skills, speed of information processing, executive function, episodic memory, attention/working memory, language[3,4] and sensory perception.[5] These impairments disrupt work and daily activities of people living with HIV (PLWH), impact medication adherence negatively, lowers quality of life and can be linked to mortality independent of viral load.[6]

There is a complex interplay of biopsychosocial factors implicated in the pathogenesis of HAND as summarized in Table 1. These risk factors impact cognition in complex ways by altering mechanisms of neuroplasticity (Figure 1).[7]

Correspondence: Henry Michael
Discipline of Pharmaceutical Sciences, School of Health Science, University of KwaZulu-Natal, Westville Campus, Durban 4041, South Africa
Tel +27 732770601
Email doctorprince322@hotmail.com

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http://doi.org/10.2147/NDT.S232836

Table 1 Risk Factors of HIV-Associated Neurocognitive Disorders

Category	Sub-Category	Risk Factors
Biological	Viral-related	Low nadir CD4[115] Duration of infection[115] Detectable CNS viral load[116] Detectable plasma viral load[113] HIV-1 Subtype[111]
	ART-related factors	Late commencement of ART[117] ART side effects (metabolic, neurotoxicity)[118] Low CPE scores[94] Low ME scores[119] Sub-optimal ART adherence[110] ART resistance[110]
	Co-morbidities	CVD (hypertension, diabetes, obesity, hypercholesteremia, stroke)[116–118] Viral co-infection (HCV, HTLV, HIV-2)[110] Psychiatric disorders (anxiety disorders, depression, bipolar disorder)[114] Sleep disorders (Insomnia, obstructive sleep apnea)[103] Epilepsy and seizure disorders[120] Thrombocytopenia[121]
	Age	Age > 50 years[122]
	CNS Opportunistic infections	Toxoplasmosis, cryptococcal meningitis, CNS tuberculosis, CMV[123]
	Genetics	APOE ε4 gene[124] Genes relating to serotonin (SNPrs4570625, GALMrs6741892)[113] Genes relating to dopamine (DSD2, DRD4, DRD3)[113] Drug metabolism/transporter gene (CYP2B6)[113]
	Head trauma	Traumatic brain injury[110]
Psychological	Trauma	Chronic exposure to trauma and violence[114]
	Stress	Early life stress, perceived stress, PTSD[125,126]
	Stigma	Experienced, anticipated and internalized stigma[127]
Social/ Lifestyle	Employment	Low paying employment, Low skilled employment, Unemployment[128]
	Education	Low literacy levels[114]
	Isolation	Living alone[129]
	Poverty	Limited resources and impoverished communities[114]
	Healthcare access	Poor healthcare access[113]
	Exercise	Low physical activity and vigorous physical activity[130]
	Nutrition	Poor dietary diversity and vitamin deficiencies[131]
	Substance abuse	Methamphetamine, Alcohol abuse[114]

Abbreviations: ART, antiretroviral therapy; CPE, central penetrating effectiveness; ME, monocyte efficacy; CVD, cardiovascular disease; HCV, Hepatitis C virus; HTLV, Human T- lymphotropic virus; CMV, cytomegalovirus; PTSD, post-traumatic stress disorder.

Synaptic dendritic networks in the brain undergo continuous remodeling, a process termed neuroplasticity. These changes include increased dendritic branching, augmentation of axonal collaterals, generation of new synaptic connections and activity dependent modification of existing synapses.[8] The early dementing process in HIV patients has been shown to be associated with synaptic degeneration rather than substantial neuronal apoptosis.[9] Inhibition of synaptic degeneration therefore provides an attractive therapeutic target to prevent HAND pathogenesis.[9] Mediators of this CNS plasticity include brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-1), acidic fibroblast growth factor (aFGF), macrophage inflammatory protein-2 (MIP2), stromal derived factor 1 alpha (SDF-1α) and leptin.[8,9] BDNF is the most potent member of the neurotrophin family.[10]

Role of BDNF in HAND Neuropathogenesis

BDNF is present in tissues both outside and inside the nervous system. It is found in platelets, plasma and serum. It is abundant in various brain regions including the hippocampus, prefrontal cortex and amygdala.[10] BDNF is synthesized as a larger precursor protein known as pre-proBDNF that is cleaved into proBDNF which can then be further cleaved by plasma or metalloproteases into mature BDNF. mBDNF and proBDNF elicit opposite effects through the activation of two distinct receptors, Trk and p75NTR, respectively.[11] Reduced BDNF levels have been associated with numerous structural and functional deficits including loss of cortical and hippocampal synapses, impairment of spatial learning and memory in both rodents and humans.[11]

BDNF plays a critical role in learning and memory. Increased BDNF levels have been shown to decrease the odds of developing HAND. Abassi et al in a Ugandan population, showed lower CSF BDNF levels in HIV patients with

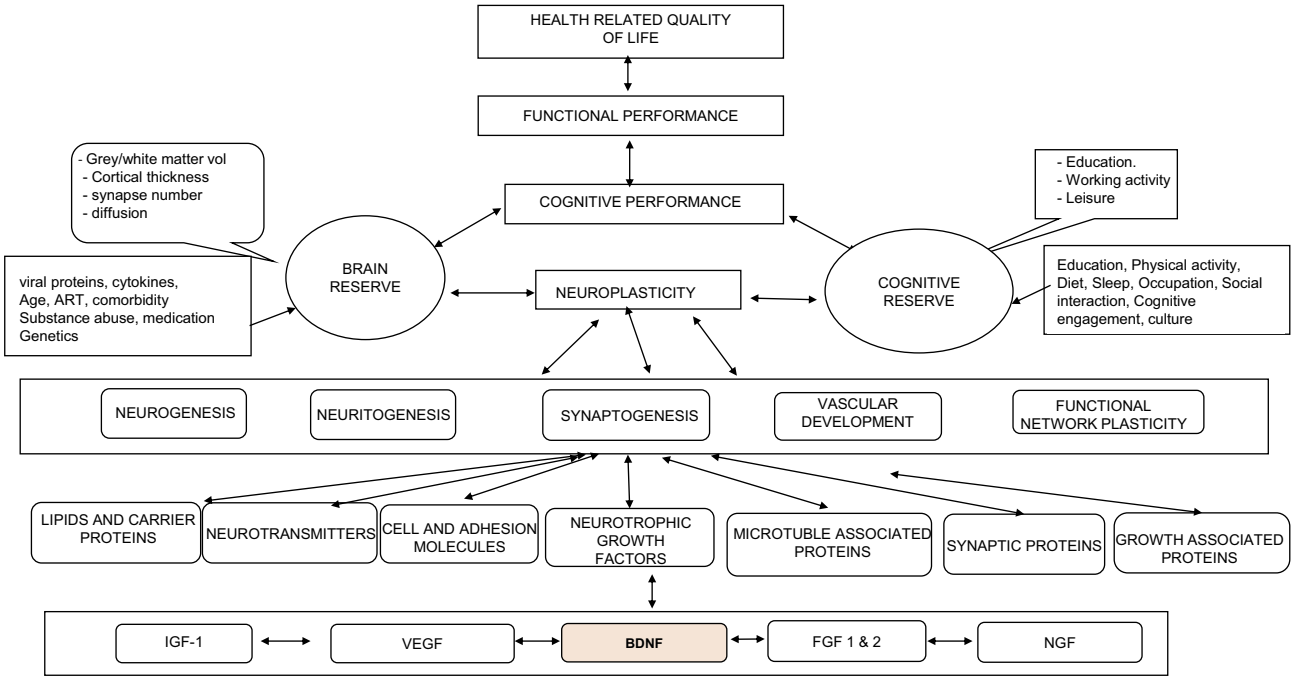

Figure 1 Biopsychosocial conceptual model of HIV-Associated neurocognitive impairment (neurotrophic pathway). This shows the multicausal factors (behavioral, psychological, sociological and biological) that impacts on cognition vis-à-vis functional impairment and overall health related quality of life. Bidirectional arrows re-enforce the complex interactions between factors.

Abbreviations: ART, antiretroviral therapy; BDNF, brain derived neurotrophic factor; VEGF, vascular endothelial growth factor; IGF, insulin-like growth factor; FGF 1 & 2, fibroblast growth factor 1 & 2; NGF, nerve growth factor.

dementia compared with HIV-positive individuals without dementia.[12] Falasca et al were able to correlate BDNF levels with different domains of neurocognition. They showed a significant correlation between reduced serum BDNF levels and poor performance on the Grooved Pegboard test for the dominant hand test but no association between BDNF serum levels and attention, executive function and working memory availability.[4]

Processing of proBDNF into mature BDNF has been shown to be reduced in HIV. This contributes to synapto-dendritic injury and synaptic dysfunction seen in HAND. Studies have shown that proBDNF levels in HAND subjects were higher than those in HIV-negative as well as HIV-positive subjects without dementia. The reduction in BDNF serum levels in HAND could also be attributed to thrombocytopenia which is quite common in people living with HIV.[13] Likewise, genetic factors such as rs6265 polymorphism in the BDNF gene could lower BDNF levels observed in HIV-1 positive individuals. This polymorphism results in a Val-Met amino substitution at codon 66 (Val66Met).[14]

Increased TNF-α expression reduces BDNF expression in HIV. TNF-α reduces the anterograde transport of BDNF while IL-1β released in response to gp120 or tat, decreases the retrograde transport of BDNF.[6] Preventing disruption in the bidirectional axonal and dendritic transport of BDNF by viral proteins has become a possible therapeutic approach to HAND.[15]

BDNF plays important roles in proliferation, apoptosis and T-cell survival.[16] BDNF can activate anti-apoptotic genes including Bcl-2 and reduce pro-apoptotic caspase-3.[17] Mature BDNF binds with high affinity to its receptor TrKB. This binding activates TrKB which in turn activates major signaling pathways, one of which is the PLC-ϒ1-PKC signaling pathway which promotes synaptic plasticity partly by inducing intracellular Ca^{2+} release.[18] Other pathways activated include the mutagen activated protein kinase (Ras-MAPK) signaling which promotes neuronal differentiation, the P13 kinase-AK+ signaling which promotes survival and growth of neurons[19] and the TrKB/ERK1/2/Ak+ pathway which significantly improves spatial memory.[20] BDNF has also been shown to activate NF-kβ which enhances both dendritic spine and excitatory synapse density.[18] Impairment in spatial learning have been seen in mice lacking in NF-kβ subunit. By contrast, proBDNF binds with high affinity to p75NTR/sortilin which in turn activates degeneration of p75NTR positive neurons through a c-Jun N-terminal kinase (JNK)-mediated mechanism.[21]

BDNF and Viral Proteins

BDNF reduces degeneration of synapses and axons triggered by viral proteins. These HIV proteins interact with surface receptors on the neurons or activate caspases to effect neuronal damage. The mechanisms by which these viral proteins induce neurotoxicity include production of free radicals, nitric oxide, release of excitotoxins such as glutamate, and through inflammatory cytokines.[22]

Glycoprotein protein 120 (gp120), a viral envelope glycoprotein, evokes neuronal toxicity and reduction of BDNF levels in the dorsal striatum in rodent models of HAND.[11] This reduction in BDNF levels causes synaptic injury and compromises neuronal function. Neurons exposed to gp120 exhibit lower concentrations of mBDNF and higher levels of proBDNF than controls.[3,11] In contrast, gp120-upregulated BDNF expression has been shown to contribute to the development of HIV-associated pain through wnt/β-catenin signaling in murine derived microglial cell lines.[22] This supports the evidence that BDNF from sensory neurons plays a critical role in mediating chronic pain. Distal sensory polyneuropathy has been associated with HIV-associated neurocognitive impairment especially with domains containing timed psychomotor tests.[23] While there has been no evidence correlating elevated neurotoxicity due to increased BDNF levels in the peripheral nervous system with neurotoxicity in the CNS, a few studies have suggested that increased BDNF signaling can be neurotoxic to the brain.[24] BDNF has been shown to exert dose-dependent opposite effects in the CNS.[25] In addition to an opposite dose-dependent effect of BDNF, there are also region-specific differences.[26] Evidence of these divergent effects of BDNF have been seen in the hypothalamus and nucleus accumbens compared to levels in the hippocampus.[27] It has also been suggested that increased BDNF levels in the CNS microenvironment could increase CCR5 expression which is capable of spreading viral infection.[28] This highlights the need for more studies to explain the mechanisms responsible for the opposite effects of BDNF expression in different brain regions.

Gp120 shed from HIV binds to chemokine receptors CCR5 and CXCR4. This leads to reduced intracellular processing of proBDNF which appears to occur through a decrease in furin and/or prohormone convertase synthesis/activity.[11] This increase in proBDNF/mBDNF ratio has been shown to correlate with HIV cognitive impairment in post-mortem samples of HIV-positive individuals.[11] The increase in CXCR4 expression due to decreased BDNF levels can facilitate entry of HIV into cells and spreading HIV infection.[4] BDNF, however, has been shown to down regulate the chemokine receptor CXCR4 to which gp120 binds and initiate apoptotic cascade.[29] This means that increased BDNF levels may reduce gp120 mediated direct neurotoxicity.[29]

Transactivator of transcription (tat) is the first protein to be produced by HIV-infected cell and is associated with BDNF in several ways. It continues to be transcribed in HIV-infected macrophages despite the use of ART and absence of viral replication.[30] This possibly adds to the reasons why there is still a high prevalence of HAND in the ART era. HIV1-tat coactivator interactions may reduce neurotrophic factor signaling. HIV Tat protein has been found to reduce the expression of BDNF by suppressing BDNF gene expression. Liu et al demonstrated a 50% decrease in BDNF mRNA levels when neurons were exposed to Tat for 24 hrs.[31] As a result, HIV tat decreases long-term potentiation (LTP), which is a long-lasting increase in synaptic strength that is critical for learning and memory. HIV Tat achieves this is by decreasing the phosphorylation of the transcription factor cAMP response element binding protein (CREB) thereby downregulating BDNF mRNA levels.[32]

Tat causes dendritic damage which is an important correlate of neurocognitive impairment in HIV and has been associated with specific neurocognitive domains such as learning and verbal fluency.[33] Conversely, BDNF has been found to support the stability of dendritic spines by increasing the density of dendritic spines possibly through the mechanism of increasing F-actin in spines.[31] Similar to gp120, tat also decreases the conversion of proBDNF to mBDNF.[30]

Tat increases the activity of NF-kβ which triggers the activation of immune cells. HIV uses the activation of immune cells as a signal for HIV transcription thereby reactivating the virus from latency, even in the presence of ART.[34] Altering this process could be beneficial in preventing stealth neurodegeneration. In addition to its functions in the immune system, NF-Kβ regulates neurogenesis and synaptic plasticity.[35] BDNF has been shown to activate NF-kβ which enhances both dendritic spine and excitatory synapse density.[18] Impairment in spatial learning has been seen in mice lacking in the NF-kβ p50 subunit.[36] The activation of NF-kβ by BDNF leads to neuroprotection but chronic activation reduces BDNF and ultimately causes cognitive impairment and neurodegeneration in the dentate gyrus. There is a positive feedback loop between NF-kβ and BDNF since NF-kβ also regulates BDNF expression.[35]

BDNF has been shown to be neuroprotective by enhancing mitochondrial biogenesis, transport and overall mitochondrial health.[24] HIV-1 tat and gp120 alter mitochondrial fission, mitochondrial transport and mitophagy in neurons and microglial cells.[24] Split mitochondria are distributed throughout the soma, dendrites and axons to provide usable energy to synapses for learning, memory and other cognitive functions. This has implicated mitochondrial dysfunction in HAND and illustrates yet another pathway in the role of BDNF in cognitive function.[24]

BDNF and Neurotransmitters in HAND

HIV impacts negatively on dopaminergic (DA) neurons within the fronto-striato-thalamic system. This causes specific cognitive, motor and behavioral deficits in PLWH.[37] A decrease in dopamine in the substantia nigra has been associated with poorer cognitive function across specific domains like speed of processing, memory, learning and verbal fluency.[38] In gp120-treated rats, DA levels were found to be lower than controls in the dorsal striatum and there was loss of nigrostriatal fibers due to intrastriatal gp120.[39] Recent studies seem to be contradictory showing an increase in DA levels in the CSF of therapy-naïve HIV patients. This increase in DA levels was in the asymptomatic stage of infection and could later exert toxic effects in DA neurons due to the oxidative properties of catecholamines.[40] Increased cytotoxicity of the DA neurons eventually leads to dopamine deficits that may exacerbate the progression of HAND.[41]

Individuals with high dopamine availability have been found to show higher novelty seeking, impulsive, adventure-seeking behavior that can impact sexual behaviors.[42] This has implications in substance use disorders as exposure to most drugs of abuse raises dopamine levels above the norm associated with the natural reward system.[41] Early studies have shown association between BDNF and increased dopaminergic neuronal function and survival, as well as tendency to promote the action of drugs of abuse.[43] Based on BDNF's role in dopamine availability,[44] the question then arises "Can BDNF levels impact HIV transmission and prevention?". Miguez et al have shown more frequent high-risk sexual behaviors, substance use disorders and sexually transmitted diseases (STDs) in PLWH with low BDNF levels.[45] There is evidence that activation of D2 receptors also correlates with higher viral loads and production of neurotoxic factors thereby increasing the severity of HAND.[46]

HAND is associated with disrupted glutamate levels. BDNF prevents glutamate mediated neuronal apoptosis by inhibiting caspase 3 activation[47] and exerts its neuroprotective effect by activating synaptic NMDA receptors, effecting a nuclear calcium genomic response that activates the transcription of inhibin (Activin A). Activin A reduces the neurotoxic NMDA-receptor-mediated calcium influence which shields neurons from mitochondrial dysfunction.[48]

BDNF and Co-Morbid Mental Health Disorders in HAND

Depression is the most common neuropsychiatric condition in PLWH with a prevalence rate three times that of the general population.[49] The confounding effect of depression in HAND arises from similar neuropathology which involves the loss of adult neurogenesis in the hippocampus.[50] HIV-infected individuals however may experience depression despite elevated BDNF levels.[4] BDNF plays a regulatory role in serotonin systems and, like dopamine, serotonin is also involved in the reward system.[51]

Evidence supporting the BDNF hypothesis of depression in HIV-positive individuals have been lacking as there is little proof relating BDNF signaling to depressive symptoms in HIV.[52] BDNF is however decreased in the serum of antidepressant-naïve patients.[53] This shows that while BDNF expression and signaling may not lead to depressive symptoms, it may play a role in the therapeutic effects of antidepressants.[54] Selective serotonin reuptake inhibitors (SSRIs) increase BDNF levels thereby increasing adult hippocampal neurogenesis.[14]

Lithium and sodium valproate are two commonly used psychotropic drugs which are GSK3B inhibitors. One of the mechanisms by which HIV induces neurotoxicity is through abnormal activation of GSK3β.[55] GSK3β modulates cellular functions such as gene expression, neurogenesis and synaptic plasticity. It is also a regulator of neuronal and astrocyte cell death in response to neurotoxic stimuli.[56] This has made GSK 3B an important therapeutic target for HAND. BDNF inhibits GSK3B activity by binding to TrKB to activate PI3K and Akt.[57] BDNF modulation may therefore be a mechanism by which GSK3B inhibitors like Lithium and sodium valproate ameliorate HIV-1 mediated neurotoxicity.[55]

BDNF and Anti-Retrovirals in HAND

Neurocognitive functioning improves in patients who initiate ART. This shows that ongoing viral replication in the CNS is strongly associated with cognitive impairment. This improvement in neurocognition suggests that alteration of neuronal function prior to cell death may be a likely mechanism accounting for this.[58] However, some studies have shown dissenting results showing the potential neurotoxicity of ART and worse neuropsychological performance.[59] It should be noted that some of the reasons for worse neurocognitive outcomes in PLWH on ART could include inhibition of efflux proteins, drug uptake transporters, Aβ and pTau accumulation, impaired BBB and immune reconstitution inflammatory syndrome (IRIS).[60]

Long-term administration of nevirapine in mice models showed reduced hippocampal BDNF expression that led to cognitive and behavioral abnormalities while tenofovir had no impact on BDNF expression.[61] However, there have been conflicting results as regards BDNF levels in ART treated PLWH. Miguez-Burbano et al noticed high levels of circulating BDNF in PLWH in comparison with an HIV-negative control population which may have been the result of increased BDNF synthesis that accompanies the neuronal modelling activated by ART.[62] AZT-exposed mice showed increased BDNF expression in the hippocampus indicating the initiation of the neuronal survival processes.[63] More studies are however needed to delineate the mechanisms by which ART impacts on BDNF levels. CCR5 antagonists like Maraviroc have been found to improve the neurocognitive status of HIV+ patients and reduce the expression of several pro-inflammatory factors.[64] One of the possible mechanisms by which CCR5 antagonists affect neurocognitive benefit could be as a result of increased BDNF expression.[65]

Neurological and psychiatric complications of ART are often difficult to distinguish from HIV-induced peripheral neuropathy. BDNF plays a role in the early stages of zalcitabine-induced mechanical allodynia.[25] The hypothesis is that BDNF-induced signaling pathway is activated by antiretroviral drug delivery, and this in turn may promote JNK activation and apoptosis, which ultimately leads to mechanical hyperalgesia. BDNF also induces caspase-3 activation which causes cell death. One major mechanism of NRTI-induced polyneuropathy is however mitochondrial toxicity.[66] There may be some differences in the nature of ART-induced mitochondrial toxicity in the PNS and the CNS but PNS mitochondrial toxicity can provide a possible explanation of how ART may alter mitochondrial function in the brain and cause neurocognitive impairment.[24] Mitochondrial dysfunction has been implicated in HAND by impairing synaptic plasticity through defective mitochondrial fusion and fission.[67] BDNF has been shown to support mitochondrial health by enhancing mitochondrial biogenesis, transport and metabolism.[24] Didanosine also has been shown to diminish expression of BDNF.[68]

Cognitive side effects with Efavirenz have been demonstrated in animal studies.[69] In a cross-sectional cohort study, HIV-positive subjects who discontinued EFV regimens had greater neurocognitive improvement than those on non-EFV regimens.[70] EFV users have been shown to have worse speed of information processing, verbal fluency and working memory when compared to Lopinavir/Ritonavir users in HCV seronegative individuals.[71] The possible mechanisms of Efavirenz-associated neurocognitive impairment include mitochondrial inhibition, reactive oxygen species generation, dendritic injury and release of cytokines.[24,72] There are no studies correlating Efavirenz neurotoxicity directly with BDNF levels but with increasing evidence showing BDNF mediation of neurotoxic mechanisms interfering with mitochondrial activity and bioenergetics, it is probable that alteration in BDNF may be implicated in Efavirenz associated HAND. Amprenavir and Lopinavir have been shown to disrupt astrocyte and glutamate functions but neither affected the expression of BDNF in astrocytes.[73]

Zidovudine was shown to decrease P3a latency in HIV patients. P3a latency has been shown to correlate with worsening CNS effect in HIV.[74] The P3a component of event related potential (ERP) is associated with stimulus novelty processing, allocation of attentional processing resources and cognitive processing speed. However, studies done investigating the role of BDNF in cognitive enhancement using this electrophysiological method showed no correlation with P3a latency.[75]

BDNF and the Human Microbiome in HAND

Impairment of the microbiota-gut-brain axis in HIV-positive patients may also be implicated in HAND. Some gut bacteria can interact with the CNS to modulate neuroplasticity, thereby affecting cognition and memory.[76] HIV disrupts the gut microbiota through depletion of the gut epithelial layer and CD4+ T cells in the gut-associated lymphoid tissue (GALT).[77] Mounting evidence reveals

that one of the mechanisms by which the gut microbiota effects neurocognitive changes is through the alteration of hippocampal BDNF expression.[78] For example, BDNF levels is impacted negatively by *Clostridium, Dorea* and *Blautia* but positively by *Prevotella* sp.[79]

Viruses also have potential functions in the human microbiome. Human endogenous retroviruses (HERV) are a family of viruses within our genome that have similar characteristics with exogenous retroviruses.[80] HERV expression has been proposed to play a role in CNS disorders like HAND, schizophrenia, bipolar disorder and multiple sclerosis. HIV infection activates HERVs such as HERV-K, HERV-H1F and HERV-W.[80] HERV -K is overexpressed in human neurons during HIV/AIDS and have been shown to exert neuroprotective effects in-vitro and in mice model by upregulating BDNF expression as one of its mechanism of action. This regulation of BNDF expression by HERV-K suggests a potential mechanism of reducing neuronal injury.[81]

Potential Role of BDNF in Therapeutic Management of HAND

BDNF has a potential of being more than just an endogenous neuroprotective agent but also a therapeutic immune agent. In addition, BDNF and its modifiers could be helpful in preventative interventions concerning PLWH given the association of neurocognitive impairment with risk-taking behavior.[82] An ideal drug used in HAND management should be able to penetrate the BBB, be efficacious, affordable, non-invasive and have minimal side effects.[83] Two options are possible: human BDNF or exogenous agents that can increase endogenous BDNF levels.

Human BDNF

Human BDNF (hBDNF)-based therapies pose several limitations. The evidence on their efficacy is weak, they are invasive injections, hence unsustainable for chronic administration, and are not readily accessible and affordable.[26] Tong et al shared their success in using lentivirus as a gene delivery vehicle to administer hBDNF into monocyte derived macrophages. Their in-vitro study showed the potential of hBDNF cells to protect neuronal cells from TNF-α and HIV-1 Tat mediated neurotoxicity.[26] There are however no clinical efficacy studies. While there is some enthusiasm with gene therapy, affordability of these therapies is a concern especially in the local resource-constrained neuroAIDS context where 70% of all people living with HIV are in Sub-Saharan Africa.[1]

Intranasal Insulin Therapy

Intranasal insulin therapy in preclinical studies using Eco HIV-infected mice have been shown to improve cognition through upregulation of BDNF levels.[84] A clinical trial is presently being done by Sacktor et al to assess safety and efficacy in HAND.[85]

Adjunctive Medication

Adjunctive medication that elevate BDNF levels may also find application in HAND management. Memantine is an uncompetitive antagonist of glutamate NMDA receptors used in the treatment of Alzheimer's disease. It upregulates BDNF expression and has been shown to prevent dopamine deficits in SIV-infected macaques.[86] Low dose memantine shows some potential in HAND management and treatment of substance use disorders in PLWH.[87] Antidepressants like the SSRIs (eg, paroxetine) increase BDNF synthesis which causes an increase in hippocampal neural precursor proliferation.[88] Letendre et al had earlier shown that SSRIs may reduce HIV replication in the CNS and improve neurocognitive performance. This has led to the term "antiviral SSRI".[89] However, there have been no double-blind randomized controlled clinical trials using SSRIs in HAND therapeutic management.

GSK3B inhibitors-lithium and sodium valproate have also shown some neuroprotective effect through increased synthesis of BDNF in the cerebral cortex.[90] Statins have immunomodulatory effects and can stimulate BDNF expression. They may be useful in the prevention and management of HAND especially in combating the metabolic effects of HIV and ART.[91] The increasing age of PLWH creates a higher risk of diabetes and heart disease which can compromise brain function.[38] Treatment of these co-morbid conditions can possibly increase BDNF levels and improve cognitive deficits.[92]

Anti-Retroviral Therapy (ART)

ART still remains the most effective HAND management strategy.[93] Research on the impact of ART on BDNF levels may help efforts to personalizing the ART regimen. Personalized ART regimen has been suggested since benefits of ART in HAND differ between individuals, type of ART, CPE of regimen, time of infection, co-morbidity and as well the neurocognitive domain most affected.[94]

Potential Role of BDNF in Non-Pharmacological Approach to HAND Management

The use of adjuvant medications has the downside of increasing the pill burden and dosing frequency of HIV therapy which can ultimately impact adherence in PLWH already experiencing neurocognitive deficits.[95] More convenient and safer methods of increasing BDNF have therefore been proffered as the present methods of direct delivery through recombinant protein or viral factors are also cumbersome and invasive.[50]

Transcranial Direct Current Stimulation

Transcranial Direct Current Stimulation (tDCS) has been proffered as one of the potential non-pharmacologic approaches to HAND. tDCS of motor cortex neurons in HIV patients have shown benefit in increasing BDNF levels and enhancing neurocognitive performance.[96] This technique holds some promise in HAND management as it is affordable and relatively safe. Ownby et al are presently conducting a clinical trial to investigate the effectiveness of computer-based cognitive training and tDCS in enhancing neurocognitive performance in older HIV-positive individuals.[97]

Diet

A few dietary phytochemicals have been proposed to induce hippocampal BDNF expression. Flavonoids like hesperetin, quercetin, naringenin and luteolin have been shown to improve cognition by promoting neurogenesis and synaptic plasticity through serum BDNF changes. Dietary flavonoids occur naturally in fruits, vegetables, chocolates and beverages like wine and tea,[98] which makes them easily accessible and cost-effective. There is however no clinical evidence showing their efficacy in HIV-associated neurocognitive disorders. Luteolin has however shown significant anti-HIV activity in reporter cells and primary lymphocytes at the Tat-long terminal repeat transactivation level.[99] Such flavonoids with BDNF expression activity as well as anti-HIV property hold some promise as adjunctive treatment with ART for the management of HAND. BDNF has also been found to mediate the neuroprotective actions of catechins (found in tea leaves, apple, grapes and red wine), rosmarinic acid (found in culinary herbs) and curcumin (found in turmeric).[21]

Probiotics, prebiotics (dietary fibers and oligosaccharides), omega-3-fatty acids and fermented foods (eg, yoghurt) have been shown to increase BDNF levels and improve cognition through their modulation of the gut microbiota. This have led to the term "psychobiotics".[100] Probiotics like *lactobacillus, Bifidobacterium, Prevotella, Faecalibacterium prausnitzii* have shown potential in preventing or slowing neurodegenerative processes.[76,79] However, there is little evidence for the efficacy of probiotics in HAND. Ceccarelli et al showed improvement of neuropsychological performance in an HIV positive 56-year-old Caucasian male after 6 months of probiotic supplementation.[76] The neurocognitive effect of probiotics in association with ART therapy needs to be explored with larger samples of patients to provide conclusive evidence of their role in HAND.

Physical Exercise

Incorporating physical exercise to drug therapy may be another approach to increasing BDNF levels and neurocognition in HIV patients.[50] Exercise has been found in a HIV-gp120 transgenic mouse model to restore BDNF levels through cdk5 regulation which consequently normalizes dendritic branching.[88] Aerobic exercise such as walking and stretching enhance neural plasticity by upregulation of BDNF.[101] However, no studies have explored the effect of exercise and BDNF levels in HIV-positive individuals.

Sleep

The prevalence of sleep disturbances in PLWH is estimated at 58%.[102] The quality and duration of sleep can affect cognition in HIV-positive patients. This has been confirmed through objective and subjective measures of sleep.[103] Sleep improves synaptic plasticity, memory and learning hence reduced cognition has been correlated with decreased peripheral BDNF levels.[104] Non-pharmacologic interventions like cognitive behavioral therapy to help with sleep have been suggested but to date, the evidence for improving cognitive functioning in PLWH is not strong.[105]

Building Cognitive Reserve

In the presence of brain pathology, some individuals function better than others, showing better adaptation of cognitive networks; this phenomenon has been termed cognitive reserve (CR).[106] The concept of "reserve" has been richly explored in Alzheimer's disease. In AD pathology, high BDNF expression has shown to enhance CR.[107] There is need to translate this concept into HAND research and explore the impact of social interactions, environmental enrichment through education and physical activity on BDNF and cognition in PLWH. Knowing that learning and novelty stimulate neural plasticity,[108] there is an opportunity

to also explore interventional cognitive neurorehabilitation tools such as complex gameplay in PLWH and how they modulate BDNF levels.

Research Gaps and Future Direction

There is a need to further investigate the dual nature of BDNF effects so as to be able to modulate its levels for neuroprotection without detrimental effects as seen in nociceptive processes. The methodology of BDNF assessment will need to be strengthened such that the proBDNF and mBDNF isoforms are analysed and reported separately. This is necessary since the proBDNF isoform is associated with neurotoxicity and the mBDNF form with neuroprotection.[109]

There is a gap in literature on the potential impact of BDNF on risk-taking behavior and decision making. Future research will need to examine the impact on BDNF levels on cognitive domains of executive function which is critical for adherence to ART, safe sex and impulse control as regards substance use.[110]

Most studies on the effect of BDNF on neurocognition in HIV-positive individuals have been conducted in high-income countries with a prevalence of HIV-1 Subtype B. It is therefore important to study the role of BDNF within regions like sub-Saharan Africa which is the epicenter of the HIV epidemic. This recommendation draws from the knowledge that the HIV-1 sub-type C virus predominates in this region and variation in the neurovirulence and synaptodendritic alteration effect of HIV-1 subtypes have been established.[111,112] In addition, the association of low cognitive reserve with neurocognitive impairment in HIV,[113] makes it imperative to study the impact of confounding risk factors which are abundant in sub-Saharan Africa and their impact on BDNF and neurocognition. These factors include low literacy levels, limited access to healthcare, chronic exposure to trauma, poor dietary diversity, higher rates of treatment failure and late-onset of treatment.[114]

There is also low clinical knowledge of the acute and chronic impact of antiretroviral therapy on BDNF expression. Results of such studies coupled with BDNF-modulatory adjunctive medication for co-morbid disorders and as well BDNF-inspired non-pharmacological interventions can feed into designing personalized treatment for people living with HIV with neurocognitive impairment.

Conclusion

HAND impacts on the everyday functionality of PLWH despite treatment with ART. There is a critical need to develop treatment strategies to tackle the neurotoxic mechanisms in HAND and the resulting clinical deficits, especially in light of the high prevalence of HIV and increased survival rates accorded by ART. The human brain is complex. As shown in Figure 1, it will be simplistic to assume a "one-neuromarker-fits-all" approach to HAND management. A holistic approach of using neuromarkers, ART, adjunctive therapy for co-morbid disorders tailored to optimize neurocognitive outcomes, supportive cognitive and behavioral therapies and genomics will be required to effectively target neurocognition and reduce the prevalence of HAND in the ART era. However, integrating antiretroviral therapy, adjunctive therapy and non-pharmacological approaches to enhance BDNF expression vis-à-vis neurocognition may be a possible beneficial strategy in tacking HAND.

There is a need to identify biomarkers for HAND. BDNF could be one such biomarker that has a modest yet growing body of evidence in in-vitro, animal and human studies. Moreover, there is the exciting potential to access the BDNF system through non-invasive, non-pharmacological and possibly cost-effective ways that are necessary in local contexts of high disease burden and resource constraints.

Disclosure

The authors report no conflicts of interest in this work.

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