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REVIEW

The impact of HIV-1 on neurogenesis: implications for HAND

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Abstract HIV-1 infection, in addition to its destructive effects on the immune system, plays a role in the development of neurocognitive deficits. Indeed up to 50 % of long-term HIV infected patients suffer from HIV-associated neurocognitive disorders (HAND). These deficits have been well characterized and defined clinically according to a number of cognitive parameters. HAND is often accompanied by atrophy of the brain including inhibition of neurogenesis, especially in the hippocampus. Many mechanisms have been proposed as contributing factors to HAND including induction of oxidative stress in the central nervous system (CNS), chronic microglial-mediated neuroinflammation, amyloid-beta (Aβ) deposition, hyperphosphorylated tau protein, and toxic effects of combination antiretroviral therapy (cART). In these review we focus solely on recent experimental evidence suggesting that disturbance by HIV-1 results in impairment of neurogenesis as one contributing factor to HAND. Impaired neurogenesis has been linked to cognitive deficits and other neurodegenerative disorders. This article will highlight recently identified pathological mechanisms which potentially contribute to the development of impaired neurogenesis by HIV-1 or HIV-1-associated proteins from both animal and human studies.

Keywords HIV · Neurogenesis · Cognitive · Tat · gp120 · Hippocampus

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Introduction

Since the introduction of combined antiretroviral therapy (cART) in 1996, mortality from human immunodeficiency virus 1 (HIV-1)-related complications has drastically diminished. It is now possible for patients infected with the virus to expect a dramatically increased lifespan compared to that of the pre-cART era [1]. cART regimens generally consist of combinations including two nucleoside reverse transcriptase inhibitors (NRTIs) and one protease inhibitor (PI) or two NRTIs and one non-nucleoside reverse transcriptase inhibitor (NNRTIs) [2]. Entry inhibitors, which interfere with the fusion of HIV-1 to host cells, can also be incorporated into HIV-1 treatment regimens. Entry inhibitors work by targeting CCR5, located on CD4 + lymphocytes, which is a common receptor utilized by HIV-1 for entry into the cell [3]. Reduced viral loads, opportunistic infections, and increased T cell counts have all contributed to the decreased mortality in HIV-1 patients [4].

Although cART has dramatically increased the lifespan of HIV patients, neurological problems still persist, the reasons for which are still not fully understood. The prevalence of the less severe HIV-associated neurocognitive dysfunction (HAND) continues to increase in spite of the success of cART in reducing viral load and decreasing opportunistic infections [5]. Possibilities contributing to the various forms of HAND include central nervous system

(CNS) entry by the virus itself, although neurons are generally not thought to be affected by the HIV-1 virus. It is supposed that activation of macrophages and microglia infected by HIV-1, which secrete neurotoxins induce neuronal apoptosis [6]. These infected macrophages and microglia produce chemokines and cytokines which affect not only neurons but astrocytes as well. Astrocytes, which normally serve as a protectant against neurons may now contribute to their damage [7]. A major culprit of neuronal apoptosis are thought to be viral proteins gp120 and Tat which induce the activation of caspases and promote the up regulation of the death receptor Fas leading to apoptosis [8, 9]. Other possibilities include persistent neuroinflammation within in the brain owing to the fact that the CNS can serve as a reservoir for the HIV-1 [10]. Also, some degree of neurotoxicity from the cART, including but not limited to, the induction of oxidative stress and neuronal damage in the CNS have been suggested in recent studies [11–20]. Other possible contributing factors to HAND include amyloid deposition, tau hyperphosphorylation, as well as comorbidities such as drug abuse, aging, psychiatric disorders, and other metabolic syndromes associated with the use of cART [21]. In this review we characterize the various forms of neurocognitive impairment associated with HIV-1 infection as currently categorized, as well as focus on HIV-1's effect on neurogenesis.

Neurocognitive impairment in HIV-1 infection and AIDS

Not long after the first reports of AIDS patients in the early 1980s, clinicians began observing complications which affected the central and the peripheral nervous systems. It was noted that a number of AIDS patients developed a progressive encephalopathy resulting from HIV infection (apart from other pathogens, diseases, or opportunistic infections) which was termed "sub-acute encephalitis" [22, 23]. The term "AIDS dementia complex" was introduced by Navia and Price [24] in the late 1980s and elucidated the idea that AIDS dementia can be associated with motor deficits and neurological impairments may be the first evidence of HIV infection in a patient. In 1991, The American Academy of Neurology AIDS Task Force established criteria defining levels of HIV-associated dementia (HAD) [25]. In 2007, US National Institute of Mental Health suggested the term "HIV-associated neurocognitive disorder" (HAND), which would encompass the entire spectrum of neurological disorders associated with HIV-1 infection. This began with asymptomatic neurocognitive impairment (ANI), minor neurocognitive disorder (MND), and HAD [22, 26]. Patients classified as having ANI have impairment and cognitive functioning deficits in a minimum of two cognitive areas assessed by neuropsychological testing of at least five cognitive domains. With classification of ANI, the patient does not have any deficits in performing acts of daily living. The definition of MND requires, at a minimum, mild interference and functions of everyday living in addition to the ANI criteria. HAD, the most severe of the HAND, is marked by a severe acquired cognitive impairment with significant difficulty in everyday functioning. As in other stages, HAD is not explained by other disorders or forms of dementia [22, 26].

Adult neurogenesis

Although it was once thought to be a process which ceased prenatally, it is now well accepted that the birth of new neurons, or neurogenesis, occurs in the adult mammal in both sub-ventricular zone as well as the sub-granular zone of the dentate gyrus of the hippocampus [27]. Neurogenesis occurs in multiple steps and comprises the proliferation and division of multipotent non-differentiated neural progenitor cells (NPCs). These non-differentiated NPCs then give rise to the major cells of the brain including neurons, astroglia, and oligodendrocytes [28]. Microglia, the resident macrophages of the brain, are excluded from these lines as they are mesoderm derived and non-neural in lineage. The hippocampus plays a major role in memory, learning, and emotion. Further, it has been shown that changes to the hippocampus are associated with neurodegenerative and psychiatric disorders [29, 30]. Importantly, the hippocampus has been shown to be particularly susceptible to inflammatory insult owing to its density of receptors for inflammatory mediation [29]. Therefore, it could be suggested that inflammatory insult to the CNS affecting the hippocampus could have detrimental effects on its vital roles including declarative memory, spatial memory, learning, emotion, and synaptic plasticity [29]. Many technical advances in laboratory methods in the 1990s, including immunohistological techniques and confocal microscopy, led to further understanding of the process of adult neurogenesis [31].

As noted by Green et al., embryonic neurogenesis forms the structure of the hippocampus and establishes the foundation for its role in later life. The purpose of adult neurogenesis has yet not been fully understood but it is believed that new neurons in the hippocampus are involved in the storage and retrieval of new memories [29, 32]. Increasing research tends to show the new neurons functionally integrate into existing neural circuits [32]. A loss of new neurons in this scenario could underlie the symptoms of short-term memory recall seen in HAND.

Modulation of neurogenesis by HIV-1

Neurogenesis, the proliferation migration and differentiation of NPCs, is affected in neurodegenerative diseases, but the exact mechanism by which neurogenesis is hampered during HAND is yet to be fully understood [33]. C-X-C chemokine receptor 4 (CXCR4), also known as fusin or CD184, is an α-chemokine receptor which is specific for stromal-derived-factor-1 (SDF-1, also known as CXCL12), and is a potent chemokine for lymphocytes. This receptor is one of many chemokine receptors which HIV can utilize to infect CD4 + T cells [34]. CXCR4 is known to be present in newborn neurons during embryogenesis and throughout adulthood where it plays a significant role in neuronal guidance. As neurons mature, levels of this receptor decrease. Research has shown that CXCR4 mutant mice have aberrant neuronal distribution, and deleterious CXCR4 have been associated with neurological disorders such as epilepsy [35]. As Kaul [36] notes, this is indicative of a potential for HIV-1 and its envelope protein gp120 to directly inhibit or interfere with the functions of neural stem and progenitor cells.

Additionally, although it is known that HIV-1 does not infect primary neurons researchers have shown that NPCs can be infected by the HIV-1 virus [37]. In an in vitro study showed that immature NPCs were also subject to infection in addition to other previously known cells including astrocytes and microglia. This further bolstered the evidence that systemic HIV-1 infection can lead to infection in NPCs, hampering neurogenesis [37]. In addition, research by Schwartz et al. showed that in the pre-cART era, pediatric *post-mortem* brain tissue had HIV-1 infection of NPCs. This suggests that early infection may be a contributing factor to the reduction of neurogenesis which may lead to neurocognitive dysfunction later in life [38]. Furthermore, infection of NPCs by HIV-1 initiated quiescence via CXCR4 and CCR5 [39]. As Kaul further notes, post-mortem brain tissue from HAD patients had fewer adult NPCs in the dentate gyrus (DG) than did non-demented and non-infected control specimens [36, 39]. Also in his experiments, it was demonstrated that in vitro treatment with HIV-1/gp120 significantly reduced the proliferation of adult progenitor cells and also led to a reduction in the proliferation of neural progenitors in the hippocampus compared to control specimens [7]. This was found to be due to the activation of the p38 mitogen associated protein kinase (MAPK) pathway which activated protein kinase 2 causing arrest of the cell cycle in the G1 phase [36, 7].

Recent research has explored experimentally HIV-1's detrimental effects on neurogenesis by a myriad of experimental designs. Peng et al. [33] tested the hypothesis that HIV-1 infection or immune activated brain macrophages significantly affected NPC proliferation and differentiation by the regulation of cytokines. They found that media conditioned with lipopolysaccharide (LPS)-activated monocyte-derived macrophages (MDM) (LPS-MDM) or media containing HIV-infected MDM conditioned media (MCM) prompted modulated NPC proliferation. Specifically, LPS-MCM and HIV + LPS-MCM significantly decreased beta-III-tubulin and increased glial fibrillary acidic protein (GFAP) indicating and induction of gliogenesis and a decrease in neurogenesis [33].

An investigation by Mishra et al. examined human NPCs which were cultured both in the presence and absence of HIV-1 Tat. In their experiments, they utilized cellular proliferation assays including BrdU and Ki67 staining as well as well cDNA and protein arrays. Their data revealed that HIV-1 Tat protein severely reduced the proliferation of NPCs as evidenced by lower BrdU and Ki67 staining. Furthermore, they discovered that HIV-1 Tat hampered neurogenesis as evidenced by decreased numbers of Tuj-1 and double courtin-positive cells [40].

Lee et al. demonstrated a significant reduction in the proliferation of hippocampal NPCs in the DG in a transgenic mouse models of HAND with glial expression of the HIV envelope protein gp120. They identified gp120 first affected amplifying NPCs (ANPs) and also demonstrated that in the presence of gp120, newly generated neurons exhibited irregular dendritic development [41]. This group also found that exercise and treatment with selective serotonin reuptake inhibitors (SSRIs) increased ANP populations and rescued cognitive deficits in gp120 transgenic mice [41].

Das and Basu also noted that viral infections during pregnancy commonly cause malformations of brain development. These infections may affect CNS development and result in long-term cognitive deficits. As they show, both HIV and herpes virus infect NPCs, and over extended periods of time reactivation of virus may occur even later in life. In this case, the virus-infected NPC may undergo cell-cycle arrest, leading to impaired neurogenesis. These disturbances of neurogenesis post viral infection have direct and damaging implications in viral pathogenesis and long-term neurocognitive deficits in infected individuals [42].

During the course of HAND, immune-activated brain mononuclear phagocytes are the driving force of CNS inflammation which is alleged to inhibit neurogenesis [43]. As reported by Peng and colleagues, HIV-1 infected and LPS activated MDM inhibited NPC neurogenesis and enhanced astrogliogenesis via the secretion of pro-inflammatory cytokines including TNF-α [33]. In a more recent study, the same group showed that LPS-activated medium conditioned with MDM and HIV-infected/LPS activated MDM-conditioned media prompted janus-associated

kinase (JAK) 1/signal transducer and activator of transcription (STAT) 3 activation which was associated with an increase in GFAP, a marker of astrogliogenesis. In sum, these studies show a strong link between inflammation of the brain and impedance of neurogenesis which has far-reaching implications for the treatment of HAND [43].

It has been reported that growth factors such as platelet-derived growth factor-BB (PDGF-BB) supply the neurons in the CNS with trophic support. In a study by Yao and colleagues, they sought to determine whether PDGF-BB regulated neurogenesis within the context of HAND and drugs of abuse [44]. They demonstrated that pretreatment of rat hippocampal NPCs with PDGF-BB restored NPC proliferation which had been damaged by HIV-1 Tat and cocaine. In their model, they found that the transient receptor potential canonical (TRPC) channels in PDGF-BB mediated the proliferation of NPCs [44]. They further substantiated their findings in vivo utilizing Tat transgenic mice where it was found that hippocampal injection of recombinant adeno-associated virus (AAV) 2-PDGF-2 rescued impaired NPC proliferation that was induced by HIV-1 Tat and cocaine. These findings identified the TRPC1 channel as a novel target which regulates cell proliferation via PDGF-BB and implies there exists a therapeutic potential for impaired neurogenesis induced by Tat and cocaine [44].

Gorantla et al. also demonstrated that hippocampal damage by HIV-1 encephalitis in murine models could be partially restored by the administration of Copolymer-1 (COP-1). They showed that COP-1 exerts a strong neuroprotective effect by suppressing pro-inflammatory microglial responses, which occur during the course of HAND. In their study, they were able to partially restore hippocampal neurogenesis, in addition to mitigating TNF-α and IL-1β release. Their experiments showed a possible therapeutic value of COP-1 in HAND to oppose NPC ablation by HIV-1 and associated viral proteins [45].

The role of apolipoprotein allelic variants in innate immune responses of maturing human neuroepithelial progenitor cells (NEP) exposed to HIV-1 was explored by Geffin and colleages. In their study, they utilized a model system consisting of NEP that differentiated into both neurons and astrocytes in vitro [46]. Gene expression microarrays were used to determine a group of genes that were specifically upregulated by exposure to HIV-1 and were strongly influencing interferon induced responses. Their findings showed that in the apolipoprotein E3/E3 genotype, the innate immune response was significantly stronger than in the E3/E4 variant suggesting that maturing NEP cells respond to HIV by initiating a varying innate immune response based upon the apolipoprotein genotype of the cells [46].

It has also been suggested that, along with diminished neuronal survival and genesis, abridged neuronal connections may play a role in the reduced neurogenesis associated with HAND. As Mocchetti and colleagues [47] note, this occurrence should not ensue in the adult brain inasmuch as synaptic plasticity is promoted by neurotrophic factors which may be diminished during HIV-1 infection. In a comprehensive review, these researchers outlined a number of neurotrophic factors and their role in the mediation of neurotoxins which promote cellular death pathways in a number of neurodegenerative diseases [47]. As they note, neurotrophic factors promote the growth of axons and infer that the pathologies of HAND serve as excellent candidates for therapies based on neurotrophic factors. Fibroblast growth factors (FGFs), brain-derived growth factors (BDNFs), glial cell-derived neurotrophic growth factor (GDNFs), platelet-derived growth factors (PDGFs), as well as neurotrophins, are all potential therapeutic targets for the mediation of HAND [47].

In an interesting study by Lee et al., it was revealed that HAND is frequently accompanied by atrophy of the brain including the inhibition of neurogenesis and the growth of neurites, especially in the hippocampus. This is suggested to contribute to cognitive dysfunction as noted earlier. Utilizing a gp120 mouse model, they showed that running exercise stimulated NPC proliferation in the DG. The exercise also promoted increased survival of existing cells as well as generation of new NPCs. They also showed that sustained exercise increased BDNF in the hippocampus and reduced the over activation of cyclin-dependent kinase 5 (Cdk5). It can be concluded from their work, therefore, that increasing BDNF and arresting the over activation of Cdk5 can rescue the impairment of adult neurogenesis caused by HIV-1 gp120 [48].

In a previous work, it was shown that platelet-derived growth factor-BB (PDGF-BB) upregulated the proliferation of rat NPCs [49]. More recently it was also found that if NPCs were pre-treated with PDGF-BB, Tat-mediated NPC proliferation impairment could be reversed via the modulation of p38 and the c-jun N-terminal kinase (JNK)/MAPK pathways. Interestingly, it was also shown that the same pre-treatment promoted inactivation of glycogen synthase kinase-β (GSK-3β) via phosphorylation at Ser9. Furthermore, this experiment evidenced that nuclear β-catenin, which is a primary substrate of GSK-3β, increased in the PDGF-BB group. This supports the hypothesis that GSK-3β/β-catenin represents potential targets of NPC regulation and proliferation and may offer possible rescue interventions of Tat-induced neurogenesis impairment [50].

In a recent study, it was examined whether the deletion of the fatty acid amide hydrolase enzyme (FAAH), which regulates the degeneration of the endocannabinoid lipid

ligands could affect gp120's inhibition of neurogenesis in gp120 transgenic mice. They found that, in fact, the genetic knockout of FAAH in the gp120 mice showed significant decreases in astrogliosis and gliogenesis, which was accompanied by increase in neurogenesis. It was suggested this was a result of the creation of new NPC niches in the transgenic mice, suggesting a possible future therapeutic pathway to treat the inhibition of neurogenesis in the HIV-1 infected brain [51].

Conclusion

Taken together, these studies show a strong link between HIV-1, and especially its secretion of proteins gp120 and Tat, with reduced neurogenesis. Since HAND is frequently accompanied by atrophy of the brain including the inhibition of neurogenesis and the growth of neurites, especially in the hippocampus, this disturbance in neurogenesis could be an underlying factor in its development. HIV-mediated reductions in neurogenesis are subserved by a variety of pathways including, but not limited to, p38, JNK, MAPK, and GSK-3β. Thus amelioration of HIV-induced disruption of neurogenesis could be an important therapeutic target for future pre-clinical and clinical studies.

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