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Synaptic dysfunction in human immunodeficiency virus type-1-positive subjects: inflammation or impaired neuronal plasticity?

Valeriya Avdoshina, **Alessia Bachis**, and **Italo Mocchetti**
Laboratory of Preclinical Neurobiology, Department of Neuroscience, Georgetown University Medical Center, 3970 Reservoir Rd, NW, Washington, DC 20057 USA

Abstract

Many people infected with the human immunodeficiency virus type-1 (HIV) exhibit mild or severe neurological problems, termed HIV-associated neurocognitive disorder (HAND), even when receiving antiretroviral therapy. Thus, novel adjunctive therapies must be developed to overcome the neurotoxic effect of HIV. New therapies require a better understanding of the molecular and cellular mechanisms of HIV-induced neurotoxicity and the risk factors that, besides inflammation and T cell depletion and drugs of abuse, render the central nervous system (CNS) a target of HIV-induced neurotoxicity. HIV appears to impair neuronal plasticity, which refers to the innate ability of the CNS to respond to injury and promote recovery of function. The availability of brain-derived neurotrophic factor (BDNF), a potent neurotrophic factor that is present in abundance in the adult brain, is essential for neuronal plasticity. BDNF acts through a receptor system composed of Trk and p75NTR. Here we present experimental evidence that some of the clinical features of HIV-mediated neurological impairment could result from altered BDNF/TrkB/p75NTR regulation and function.

Keywords

apoptosis; drug abuse; gp120; neuroAIDS; p75NTR; proBDNF

Introduction

Human immunodeficiency virus type-1 (HIV) infection is a global health problem. HIV promotes a progressive depletion of T cells, causing acquired immunodeficiency syndrome (AIDS) and 2 million AIDS-related deaths per year [1]. The introduction of aggressive treatment with highly active antiretroviral therapy (HAART), consisting of a cocktail of drugs that inhibit viral replication, has been shown to improve immune recovery, delay progression to AIDS and reduce mortality among HIV-infected subjects [2]. However, HIV-infected individuals must continue treatment with antiretroviral therapy for their entire lives, as the virus almost invariably re-emerges when the drugs are withdrawn.

An individual's susceptibility to the viral infection and subsequent disease severity and clinical manifestations are influenced by a variety of factors. These include use of illicit drugs which decreases the immune response [3], as well as host genetic variability. For instance, Caucasian individuals deficient in CCR5, one of the main chemokine co-receptors for HIV entry into macrophages [4], are resistant to HIV infection [5–7]. Moreover, genetic

Correspondence: Italo Mocchetti, Georgetown University Medical Center, WP13 New Research Building, 3970 Reservoir Rd, NW, Washington DC 20057, Tel 202-687-1197, Fax 202-687-0617, moccheti@georgetown.edu.

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epidemiological cohort studies have shown polymorphisms in genes such as cytokines and their receptors and several human leukocyte antigen (*HLA*) alleles [8] which influence HIV progression to AIDS.

HIV infecs the brain despite antiretroviral therapy

HIV also infects the central nervous system (CNS) [9]. HIV infection of the CNS (often referred to as neuroAIDS) promotes neurological signs termed HIV-associated neurocognitive disorder (HAND) in more than 50% of patients not receiving any form of antiretroviral therapy [10]. HAND symptoms may include asymptomatic neurocognitive impairment, minor cognitive disorders or, in its more severe form of HIV-associated dementia (HAD), profound motor and behavioural/psychosocial abnormalities that disrupt work or other activities of daily living [11]. HAND pathology includes loss of both synaptic connections and neuronal differentiation [12]. In addition, HIV promotes neuronal apoptosis, especially in children [13, 14]. HAART has decreased the severity of neurological signs [12, 15]. Indeed, recent estimates since the advent of HAART indicate that HAD is present in 1% to 2% of subjects with AIDS. Yet, HAART has not eliminated mild neurocognitive deficits and asymptomatic neurocognitive impairments [16]. Moreover, by controlling the viral load, HAART allows an individual with HIV to typically live longer with milder medical symptoms. Age can then play a role in HAND because age-associated medical comorbidities, including cardiovascular disease, are significant risk modifiers for cognitive loss in HIV-positive subjects [17, 18].

The reason why HAND persists among HAART-treated individuals is still under debate. Some antiretroviral drugs are present at such low concentrations in lymph nodes that they may not stop HIV replication completely [19]. In addition, other components of HAART may not reduce HIV infection in the CNS because they poorly penetrate the blood–brain barrier (BBB) or because the virus develops drug resistance. It is noteworthy that neurologically impaired individuals have a higher viral load in the cerebrospinal fluid (CSF) than in plasma. Indeed, clinical evidence has shown that the CNS of these individuals acts as an HIV sanctuary site unless a highly CNS-penetrating antiretroviral regimen is initiated [20]. Thus, there is great need for a better understanding of how the virus causes neurological problems.

Neurobiology of HIV

HIV impairs synaptic plasticity

Infection of the CNS occurs very early after seroconversion [21]. HIV is carried through the BBB by infected monocytes and perivascular macrophages. Although HIV does not infect neurons, postmortem brains of subjects with HAND have shown a decrease in neuronal plasticity/function at several levels. In this review, the term plasticity refers to the ability of mature CNS to undergo changes in neuronal processes, including spine formation and reorganization of altered synaptic network, in response to an injurious stimulus. Impaired neuronal plasticity can be seen both at cellular and systemic levels. At the cellular level, subjects with HAND exhibit synaptodendritic damage and decreased synaptic and dendritic density [12] that can lead to interruption of the neural network and ultimately to caspase-3-dependent neuronal apoptosis [22]. This, in turn, manifests at the system level as grey and white matter atrophy [20, 23] in both cortical and subcortical regions as demonstrated at autopsy. The basal ganglia are particularly affected [24, 25]. The fact that HAART can reverse, although partially, HAND symptoms is consistent with the notion that synaptodendritic injury, and not neuronal loss, is the main cause of impaired neuronal function. Thus, the degree of neuronal pathology in HAND is more in line with lack or loss of synaptic plasticity than frank injury as it occurs in trauma, stroke or ischaemia. Synaptic

plasticity may vary considerably between individuals. Moreover, a complicating factor for neuroAIDS is the fact that a number of HIV-positive individuals also abuse various illicit drugs. Heroin abuse is a major transmission route for HIV, while abuse of stimulants, such as cocaine and methamphetamine, has become a primary risk factor for HIV infection. Other drugs of abuse such as alcohol, on the other hand, have been shown to increase oxidative stress and to cause brain tissue atrophy and poorer performance on a variety of neurocognitive assessments [26]. HIV may potentiate the effects of drugs of abuse in lowering neuronal plasticity at the cellular level. Thus, an ideal therapeutic compound for neuroAIDS should be able to promote neuronal plasticity even in the presence of illicit drugs and provide a gradual restoration of neuronal function by re-establishing the altered neural network.

CNS effects due to neuroinflammation

The search for pharmacological compounds that prevent HIV neuropathology requires a better understanding of the molecular and cellular mechanisms of HIV neurotoxicity. Why is plasticity impaired in HAND? Most subjects with HAND suffer from protracted forms of HIV encephalitis, a neuro-inflammatory condition characterized by the presence of HIV-infected microglial cells, formation of microglial nodules, multinucleated giant cells, astrogliosis and myelin loss [27–29]. Activated macrophages/microglia and distressed astrocytes may inhibit plasticity by reducing the uptake of excitotoxic neurotransmitters [30]. These, in turn, reduce the formation of dendritic spines and synapses. In addition, infected glial cells may release inflammatory cytokines such as interleukin-1β and tumour necrosis factor-α [31] and chemokines, including CXCL12 [32], which all impair neuronal survival [33–35]. Thus, glial cells, once compromised, have the ability to promote/exacerbate HIV-induced neurotoxicity by reducing homeostasis-mediated plasticity. Whether inflammatory cytokines reach levels that are harmful to neurons *in vivo* is uncertain, although *in vitro* data have shown that cytokines can promote neuronal loss. However, the role of microglia as the leading cause of the neuropathology of HIV remains speculative, as microglia can also be activated by distressed and dying neurons. Moreover, some regions of the forebrain such as the basal ganglia show selective vulnerability to synaptodendritic injury that cannot be explained solely by inflammatory cytokines. Furthermore, atrophy of axons and neuronal processes often precedes the death of the cell body and is seen in other neurodegenerative diseases that do not exhibit an immune response, such as Alzheimer's disease [36]. These considerations support the hypothesis that HIV promotes the release of a diversity of soluble host cell-derived factors and viral proteins that may cooperate in causing the pathology of synapses.

Direct neurotoxic effect of HIV proteins

There are at least nine HIV proteins that are known to cause neuronal cell death (Fig. 1). Some of these proteins are shed from the virus or are released by infected cells. One viral protein that can cause neuronal injury is Tat, the transactivator of transcription. Tat is vital for HIV replication by influencing both transcription initiation and elongation [37] through chromatin remodelling at the HIV promoter. Moreover, Tat, which can be released from HIV-infected cells [38] at concentrations lower than those needed to support viral replication, reduces neuronal survival by several indirect and direct mechanisms, such as the production of inflammatory cytokines [39], impairment of mitochondrial function [40] and activation of ionotropic glutamate receptors [41]. The neurotoxic mechanisms of Tat have been reviewed in more detail elsewhere [42]. The accessory proteins Nef, Vif, Vpr and Vpu have also key roles in HIV pathogenesis. These proteins interfere with various host cell functions including cytoskeletal contraction [43] thereby optimizing viral replication or promoting (Vpu) the release of virions from infected cells [44]. These proteins once released from infected macrophages/microglia can cause neuronal apoptosis [45] by a number of

mechanisms including activation of caspase-8 (Vpr) and formation (Vpr and Vpu) or direct binding (Nef) to ion channels leading to lethal abnormal membrane depolarization [46].

Another viral gene product that causes neuronal apoptosis is the glycoprotein gp120. This protein exerts an important function in the cycle of viral infection. Indeed, gp120 is the envelope protein that binds to chemokine co-receptors CCR5 and CXCR4 and allows the virus to change conformation and enter cells [47]. Even a short exposure of neurons to gp120 can produce neuronal apoptosis by a variety of mechanisms [48, 49]. The viral protein has also been shown to promote axonal degeneration [50] and dendritic injury [51, 52], two key pathological events that may account for the synaptodendritic atrophy observed in HAD [53]. Moreover, *gp120* transgenic mice exhibit neuronal loss and dendritic simplification [54], a clear indication that gp120 alone decreases synaptic plasticity. Thus, a new mechanism of neurotoxicity could be proposed in which these proteins interact directly with membrane-associated receptors and activation of signalling pathways to reduce neuronal plasticity and promote cell death.

HIV and neurotrophin brain-derived neurotrophic factor (BDNF)

BDNF and neuronal plasticity

Neuronal plasticity is influenced either directly or indirectly by genetic factors as well as non-genetic factors such as age, experience, mood, exercise and drug abuse [55]. Most importantly, neuronal plasticity is brought about by neurotrophic factors, i.e. naturally occurring diffusible polypeptides that promote survival of a variety of CNS cells and are equally essential for inducing differentiation of surviving neurons into their mature phenotypes [56]. In some animal models, trophic effects on CNS neurons have been demonstrated on their processes rather than on their cell bodies. This is especially true for the neurotrophins, a neurotrophic family of trophic factors that includes nerve growth factor (NGF) [57], BDNF [58] and neurotrophin-3 and -4 [59]. BDNF is one of the most abundant neurotrophic factors in the adult CNS. Neurotrophic effects of the neurotrophins include synaptogenesis and sprouting of central cholinergic neurons [60], modulation of dendritic branching and spines in the cortex, and long-term potentiation in the hippocampus [61, 62]. Through these properties, the neurotrophins, and in particular BDNF, play a critical role in learning and memory and preservation of cortical circuits. Conversely, a reduction in BDNF secretion/activity has been associated with numerous functional deficits including loss of cortical and hippocampal synapses, impairment of spatial learning and memory and disruption of cortical organization in both rodents [63, 64] and humans [65–68].

Preclinical neuroscientists have also placed special emphasis on the functional (‘clinical’) properties of BDNF. Indeed, BDNF is important to many forms of plasticity in relation to chronic neurological conditions that are characterized by loss of specific BDNF-sensitive neuronal populations [69]. For instance, BDNF levels are decreased in nigrostriatal dopamine neurons in Parkinson’s disease [70, 71], and in cortical neurons in both Huntington’s disease [72] and schizophrenia [73]. In Alzheimer’s disease, which is categorized as a neurological disorder with reduced numbers of neurons and connections in the cortex and hippocampus, as well as impaired short-term memory [74], there is a deficiency of BDNF synthesis in the brain [75] or CSF [76]. Ageing, one of the major risk factors for neurodegeneration, is also associated with lower levels of BDNF [77]. Conversely, the delivery of BDNF into the CNS of animal models of ageing reverses neuronal atrophy and improves age-related cognitive impairment [78]. These findings suggest that the plasticity-promoting properties of BDNF could be extended to neuroprotection. Therefore, BDNF could be a potential therapeutic agent for the treatment of these neurological diseases. Most importantly, these observations suggest that an environment characterized by lower levels or activity of BDNF (or other neurotrophic

factors) could be a common risk factor for the loss of synapses (Fig. 2) and, consequently, the development of neurological diseases including HAND.

HIV reduces BDNF expression

New insights into the relationship between BDNF and HAND have been provided by the findings of a number of experimental studies. For example, HIV-positive subjects have lower concentrations of serum BDNF, but not of NGF, than HIV-negative individuals [79]. The decrease in BDNF is not linked to drug abuse or a particular allelic variant of *BDNF* (Val66Met) [79] which was previously shown to reduce the release of BDNF [65]. In addition, HIV decreases BDNF mRNA in T cells [79], suggesting a direct effect of HIV on BDNF expression. Given the well-known anti-apoptotic effect of the neurotrophins in T cells [80, 81], it is possible that a decrease in BDNF could be among the mechanisms employed by HIV to induce apoptosis of T cells. On the other hand, HIV also decreases BDNF in postmortem human brain, particularly in the cortex and striatum [82]. Moreover, the decrease in BDNF correlates with impaired cognitive and motor function, suggesting that loss of BDNF synthesis could be a risk factor for neurological complications associated with HIV infection. Overall, these results suggest that an altered expression of neurotrophins may contribute to the immune dysregulation of AIDS, and constitute one of the causes of the pre-HAND condition leading to synaptic simplification.

The effect of HIV on BDNF is most probably mediated by gp120 because exposure of rodent neurons to the envelope protein both *in vivo* [83] and *in vitro* [84] decreases BDNF. Moreover, $BDNF^{+/-}$ mice which undergo premature loss of cortical synapses [85] are also more sensitive to gp120-mediated neuronal apoptosis [83]. Conversely, the apoptotic effect of gp120 in neurons is inhibited by exposure to BDNF prior to gp120 [86] or by delivering BDNF into the brain [87]. Thus, in line with the hypothesis that neurotrophic factors are essential for synaptic plasticity and recovery of function [88], it is tempting to suggest that HIV, through gp120, reduces the trophic environment or minimizes the benefit of endogenous neurotrophic factors (Fig. 2).

Experimental evidence to support BDNF as a therapy for HAND

The potential use of BDNF or other trophic factors as therapeutic agents for neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases, is supported mainly by evidence from animal models [89] in which disease progress and delivery of BDNF can be better controlled than in clinical studies. However, as described above, clinical studies have shown that decreased BDNF levels in the brain correlate with functional neurological deficits, further supporting the notion that BDNF could be a useful therapeutic agent in various neurological diseases, including HAND. Support for BDNF as a potential therapeutic option for HAND comes from the important discovery of several cellular and molecular mechanisms of neuroprotection against the neurotoxic action of viral proteins. For example, BDNF blocks the neurotoxic effect of HIV proteins Tat and gp120 by the activation of anti-apoptotic genes including *Bcl-2* [90] or the reduction of pro-apoptotic caspase-3 [86]. This is not surprising as BDNF has been shown to reduce apoptosis [91, 92]. Nevertheless, BDNF can inhibit HIV-mediated neuronal loss by other mechanisms. Indeed, BDNF has been shown to downregulate the chemokine receptor CXCR4 [33, 86] to which gp120 binds and initiates the apoptotic cascade [93, 94]. Moreover, BDNF promotes adult neurogenesis [95] which is impaired in HAND [96]. There is concern about the efficiency of BDNF to cross the BBB; nevertheless, the interplay between BDNF and synaptic plasticity suggests that this neurotrophin could be used in combination with HAART to prevent HIV-mediated synaptic simplification and neuronal apoptosis.

Neurotrophin receptors

The cell death receptor p75NTR

Neurotrophins bind to two entirely distinct classes of receptors, p75NTR and Trks. p75NTR, a member of the tumour necrosis factor receptor family, was initially cloned and characterized as a low-affinity receptor for NGF with an apparent molecular weight of 75 kDa [97, 98]; however, this receptor binds to all neurotrophins with similar affinity [99] and therefore has been termed p75NTR (i.e. p75 neurotrophin receptor) [100, 101]. P75NTR does not contain a catalytic motif. Thus, upon activation, p75NTR recruits adaptor protein complexes that relay signals important for regulating neuronal cell survival, differentiation and synaptic plasticity. However, the structure of p75NTR also contains a death domain [102] which mediates cell death. Indeed, when activation of p75NTR occurs without a concomitant activation of Trk, p75NTR promotes death of oligodendrocytes [103] as well as axonal degeneration in the peripheral nervous system [104] and CNS [105]. P75NTR-mediated cell death appears to occur through activation of c-Jun N-terminal kinase (JNK) [106, 107], and inhibition of anti-apoptotic proteins Bcl-2 or Bcl-x_L [108]. It is intriguing that gp120 also activates JNK and other kinases upstream of JNK that play a role in apoptosis [109]. Therefore, these pro-apoptotic molecules may be augmented by p75NTR activation in HIV-positive individuals, thus lowering the threshold for HIV-induced neurotoxicity.

Trk receptors

The other component of the neurotrophin receptor complex is the proto-oncogene Trk. This is a receptor tyrosine kinase which, like other tyrosine kinase receptors, is activated by ligand-induced formation of non-covalently associated receptor dimers [110]. The neurotrophins cause dimerization of Trk, resulting in activation via transphosphorylation of the cytoplasmic domain kinases. This, in turn, activates major signalling pathways including the phosphoinositide 3-kinase-Akt, mitogen-activated protein kinase and phospholipase C-γ [111]. There are three structurally related Trks (TrkA, B and C) which show selective binding to the neurotrophins: BDNF binds to TrkB, NGF to TrkA and NT-3 to TrkC [112], although at high concentrations BDNF can also bind to TrkC [113]. *Trk* gene deletion in experimental animals produces loss of neurons and severe neurological impairment. However, Trk alone cannot discriminate between neurotrophins; both Trk and p75NTR are necessary to confer high-affinity binding and ligand specificity to the neurotrophins and to influence most actions of neurotrophins on neuronal differentiation and survival. Thus, p75NTR modulates Trk receptor function by promoting ligand binding as well as accessibility to neurotrophins through promotion of axon growth and target innervation. In addition, p75NTR can promote endocytosis and retrograde transport of Trk which facilitates neurotrophin signalling [114].

In addition to Trk, p75NTR can form a complex with the so-called truncated Trk (Trk.T1), an isoform of Trk generated from an alternative splicing which does not contain the tyrosine kinase domain. In certain neuronal populations, TrkB.T1 or TrkC.T1 can function as inhibitors of full-length Trk through a dominant-negative mechanism [91]. Nevertheless, Trk isoforms and p75NTR also exhibit some neurotrophic properties such as neuronal crest proliferation and differentiation and regulation of neuronal branching as well as BDNF signalling [115].

Toxic effects of HIV on CNS neurons

HIV and proBDNF

p75NTR can also bind the larger precursor (pro) neurotrophin proteins (proneurotrophins) including proBDNF [116]. Proneurotrophins are abundant in the mature brain [117] and can be released from neurons [118]. Proneurotrophins can be cleaved in the endoplasmic reticulum by the proconvertase furin [119] or extracellularly by proteases such as plasmin and matrix metalloproteinases [120], and thus converted to mature neurotrophins (Fig. 3A). Conversion of proneurotrophin to mature neurotrophin is an important process for synaptic plasticity. In fact, proNGF and proBDNF have the opposite effects to the mature neurotrophins, including neuronal apoptosis [121], axonal degeneration in the developing as well as mature nervous system [105, 122, 123], presynaptic terminal retraction [124] and long-term depression [125]. Furthermore, proneurotrophins have no affinity for Trk (Fig. 3B). Elegant studies have demonstrated that proneurotrophins bind to a dual receptor system formed by p75NTR and sortilin, a type I transmembrane protein [126–128] that is structurally unrelated to both Trk and p75NTR. Thus, neuronal survival/death depends on whether proBDNF rather than mature BDNF is released, and on the ability of extracellular proBDNF to bind to p75NTR. It is interesting that p75NTR generates ceramide through sphingomyelin hydrolysis [129, 130]. Ceramide, a sphingolipid that is significantly increased in HIV-infected cells [131] as well as in the brain and CSF of subjects with HAD [132], promotes apoptosis of various cells [133], including neurons [134].

Why is proBDNF important in HAND? The severity of cognitive impairment in HIV-positive subjects correlates with synaptodendritic degeneration [12], a phenomenon that can be evoked by lack of trophic support. However, as discussed above, proBDNF is a negative regulator through p75NTR of synaptic plasticity and axonal growth. Thus axonal degeneration can also be initiated by proBDNF. HIV has been shown to alter metalloproteinases within the CNS [135]; therefore, HIV might decrease the processing of proBDNF to mature BDNF (Fig. 3B) and, consequently, promote an environment that is conducive to the activation of p75NTR (Fig. 3C). This hypothesis is supported by recent data showing that the pro-apoptotic effect (including synaptic simplification) of HIV and gp120 in rodents is blocked by a p75NTR antagonist [82]. Moreover, lysates from the frontal cortex or striatum from subjects with HAND contain more proBDNF than those from HIV subjects without dementia [82]. Although conclusively demonstrating activation of p75NTR (or another receptor) *in vivo* in humans presents a technical challenge, a conclusion may be drawn about HIV toxicity and p75NTR activation from the fact that the levels of proBDNF were higher in HAND than HIV subjects without dementia. Because both the frontal cortex and striatum are part of the cognitive circuitry, it is possible that altered levels of proBDNF could be a risk factor for synaptic degeneration in subjects with HIV and therefore could be used as a biomarker for HAND.

Conclusions

The cellular mechanisms of HIV-mediated synaptic degeneration are currently incompletely understood. HIV may evoke neuronal injury through neurotoxins released by infected or immune-stimulated, inflammatory microglia and macrophages; it is also possible that microglia may monitor synaptic function and be involved in elimination of and scavenging synapses. On the other hand, loss of neurons and their branches underlies the pathophysiology of many neurodegenerative conditions that exhibit inflammation only at the end stage of disease. In these diseases there is evidence for ‘active’ mechanisms in which host signals trigger degeneration by means of pro-apoptotic receptors, including p75NTR. It has been suggested that this receptor causes loss of neurons in a number of neurological disorders including Alzheimer’s [136] and Huntington’s diseases [137], seizures [138, 139]

and retinal degeneration [140]. Moreover, p75NTR expression is upregulated in diseases that promote grey matter apoptosis [138, 141, 142]. p75NTR is activated by proBDNF whose levels are increased in subjects with HAD or in gp120-treated neurons. Extracellular proBDNF mediates biological effects that are opposite to those of mature BDNF, including neuronal apoptosis, long-term depression and presynaptic terminal retraction. These findings support a new model of HIV-induced neurotoxicity in which abnormal production of proBDNF by HIV activates p75NTR leading to the pathological changes of synapses and their connections in HAND (Fig. 3). Discovering how HIV evokes an accumulation/release of proBDNF should help clinicians identify new adjunctive therapies that may reverse HIV-mediated neuronal dysfunction.

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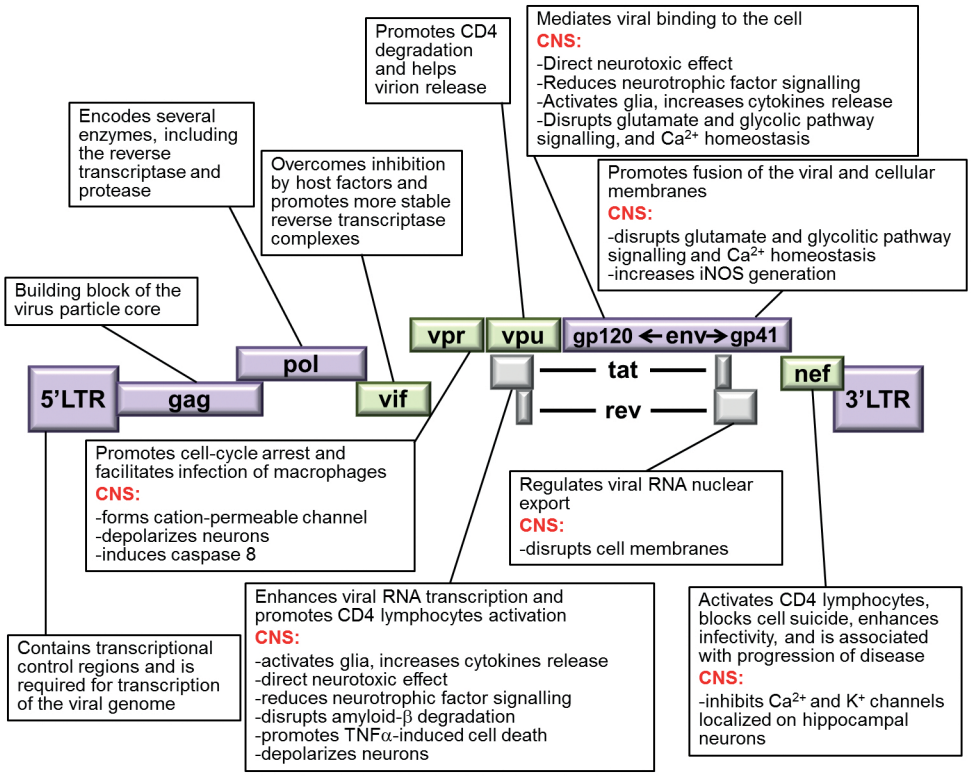

Fig. 1.
Schematic diagram of HIV proteins and their function. Adapted from [12].

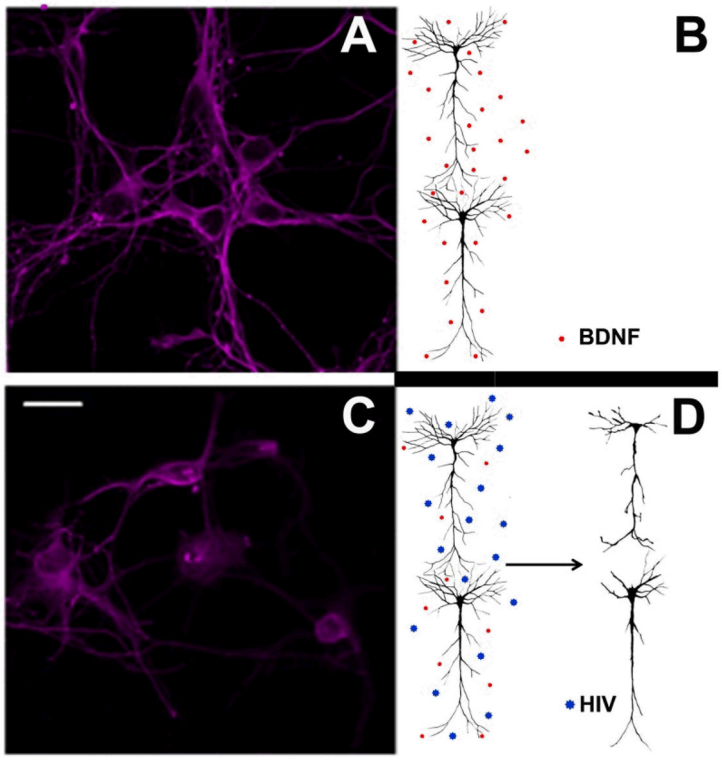

Fig. 2.

HIV induces synaptic simplification through gp120. A) Cortical neurons exposed to a physiological environment (B) in which BDNF and other neurotrophic factors, released in an activity-dependent manner, maintain an intact neuronal architecture. C) Image of neurons exposed to HIV or gp120 in which (D) the lack of trophic support evokes short processes and elimination or pruning of processes that eventually culminate in apoptosis. Scale bar, 10 μm.

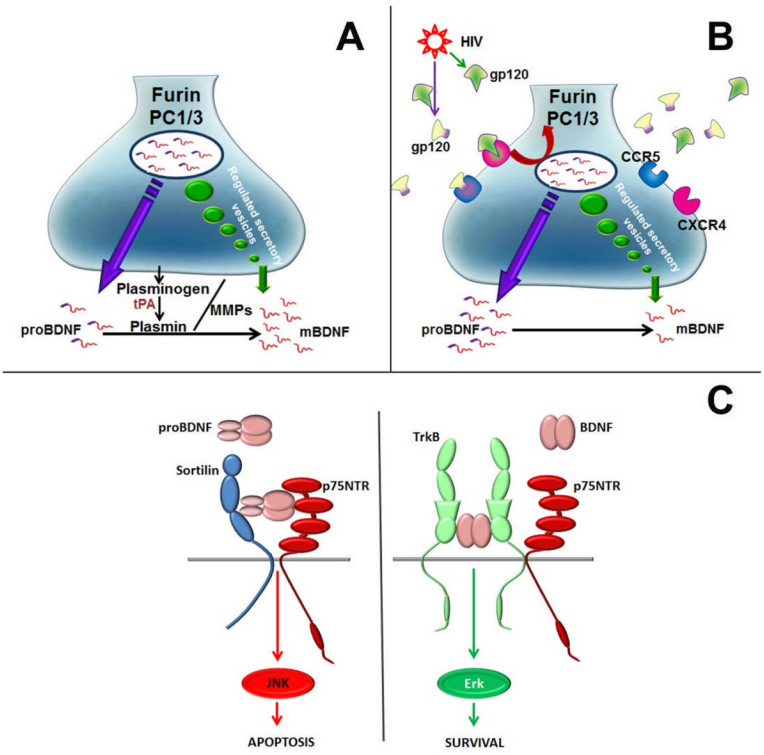

Fig. 3.

Proposed mechanisms of HIV-mediated synaptic simplification. (A) HIV-negative synapse. Under physiological conditions, proBDNF is released in an activity-dependent manner and is processed to mature BDNF either intracellularly by furin or extracellularly by plasmin and matrix metalloproteinases (MMPs). Plasmin is generated from plasminogen by released tissue plasminogen (tPA). (B) HIV-positive synapse. Gp120, shed from HIV, binds to chemokine receptors. This leads to reduced intracellular processing of proBDNF which appears to occur through a decrease in furin and/or prohormone convertase (PC1/3) synthesis/activity [82]. (C) Extracellular BDNF/proBDNF. Mature BDNF binds with high affinity to its cognate receptor TrkB and low affinity to p75NTR. This binding promotes synaptic plasticity through activation of ERK and/or PI kinase. By contrast, released 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.