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Neurotoxicity of human immunodeficiency virus-1: viral proteins and axonal transport

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Abstract

Human Immunodeficiency Virus-1 (HIV) infection of the central nervous system may cause a neurological syndrome termed HIV-associated neurocognitive disorder (HAND) which includes minor neurocognitive disorders or a more severe form of motor and cognitive impairments. Although treatment with highly active antiretroviral agents decreases the load of HIV in the brain, the prevalence of mild forms of HAND is actually increased due to longer life. Therefore, adjunctive and combined therapies must be developed to prevent and perhaps reverse the neurologic deficits observed in individuals with HAND. Key to developing effective therapies is a better understanding of the molecular and cellular mechanisms by which the virus causes this disorder. A number of HIV proteins has been shown to be released from HIV-infected cells. Moreover, these proteins have been shown to possess neurotoxic properties. This review describes new evidence of a direct interaction of the HIV protein gp120 with neurons, which might play a role in the etiopathology of HAND.

Keywords

Autophagy; BDNF; chemokine receptors; gp120; HIV-1-associated dementia; Tat

Introduction

Human immunodeficiency virus-1 (HIV) enters the central nervous system (CNS) and causes neurological impairments. The most significant of the primary HIV-associated CNS disorders include HIV-associated dementia (HAD) and its often antecedent syndrome, minor neurocognitive disorder (MND), which have recently been collectively termed HIV-associated neurocognitive disorder (HAND) (McArthur et al., 2010). The course of HAND is highly variable from patient to patient, and can present as an abrupt onset in neurocognitive decline, behavioral abnormalities and motor dysfunction over a few weeks or a protracted course over several months (Vivithanaporn et al., 2010). HAD is the most severe neurological acquired immune deficiency syndrome (AIDS) illness. Approximately 20–40% of untreated AIDS patients acquire the diagnosis, while in populations receiving highly active antiretroviral treatment (HAART) the estimated prevalence of HAD is less (~10%). Nevertheless, recent studies suggest that despite HAART, neurocognitive

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impairments progress (Price and Spudich, 2008; Cysique and Brew, 2009) or are not fully eliminated (Joska et al., 2010). Moreover, as a larger proportion of AIDS patients treated with HAART survive longer, neurocognitive impairments increase when compared to younger controls (Valcour et al., 2004). In addition, the brain pathology of these subjects may be complicated by co-morbidities including chronic substance abuse, previous head injury, or prior opportunistic infection of the CNS (McArthur et al., 2010).

The brains of HAND-affected individuals exhibit axonal injury or aberrant sprouting of synaptodendritic connections (Ellis et al., 2007). Although there is no consensus on the relationship between cellular dysfunction and mild neurological effects, the degree of synaptic degeneration appears to correlate with the severity of cognitive neurological impairment seen in the late stage of the disease (Ellis et al., 2007). In HAD, prior to HAART, neurons showed apoptotic features in several brain areas (James et al., 1999; Petito et al., 1999; Garden et al., 2002), which may explain cerebral atrophy and white matter abnormalities, as well as cell loss in subcortical regions (Albright et al., 2003; McArthur, 2004; Everall et al., 2005). Moreover, a number of researchers have reported pathological alterations of the basal ganglia in HAD, including neuronal loss in the putamen (Everall et al., 1995) and the globus pallidus (Fox et al., 1997), loss of nigro-striatal dopamine (DA) neurons (Reyes et al., 1991; Itoh et al., 2000), and dysfunctional DAergic transport (Wang et al., 2004). Consequently, it is not surprising to find clinical features of HAD resembling Parkinson's disease, such as loss of postural stability, involuntary movements, bradykinesia, and impairment in fine motor skills (Berger and Arendt, 2000; Koutsilieri et al., 2002; McArthur, 2004; Nath and Berger, 2004). Thus, it appears that HIV could reduce the innate ability of the CNS to cope with a neurotoxic environment. The exact mechanisms by which HIV promotes neurotoxicity and causes the pathology of HAD are not completely understood. Here we will present and discuss new theories about an interaction of HIV proteins with membrane associated receptors that leads to synaptic simplification and neuronal loss.

Viral proteins and neurons

Despite the blood brain barrier, HIV invades the brain soon after systemic infection and infects primarily microglia and microphages (Stevenson and Gendelman, 1994; He et al., 1997; Ghorpade et al., 1998; Albright et al., 1999). Three major pathways have been proposed for HIV infection of brain cells: (1) transport of HIV into the brain by infected cells ("Trojan horse" hypothesis); (2) passage of cell-free virus into the brain; and (3) release of virus into the brain by infected endothelial cells (Albright et al., 2003). Moreover, it has been shown that few HIV-infected astrocytes can propagate infection and toxicity through a gap junction mechanism (Eugenin et al., 2011). HAART cannot totally eliminate HIV infection because the blood brain barrier limits the penetration of the therapeutics into the CNS. Moreover, despite the CNS surveillance by T cells, on a direct weight to weight comparison, the levels of immunological surveillance is far below that occurring in other tissues (Hickey, 2001). Thus, the CNS becomes a reservoir for HIV to hide and replicate (Kramer-Hammerle et al., 2005).

Macrophages and microglia cells express on their surface a major HIV receptor, CD4, an immunoglobulin receptor, and various HIV co-receptors (chemokine receptors). These receptors are known to promote attachment of the virus through gp160, a glycoprotein complex present on the HIV membrane which is comprised of two subunits, gp120 and gp41. Such binding allows fusion of viral and cellular membranes, leading to entry of the virus into the cell [reviewed in (Berger et al., 1999)]. Two chemokine receptors, CXCR4 and CCR5, appear to play a crucial role in HIV entry; CXCR4 receptor mediates the entry of the virus into lymphocytes, CCR5 into monocytes and macrophages (Deng et al., 1996; Dittmar et al., 1997) Nevertheless, CCR5 and CXCR4 using viral strains can co-exist in a single host (Koot et al., 1996).

How can HIV cause synaptic injury and neuronal loss? Neurons do not express CD4 and thus are not capable of productive infection; therefore, the effect of HIV must occur via an indirect mechanism. Many possibilities exist for indirect mechanisms. Infected non-neuronal cells may release host cell-derived factors, including cytokines and chemokines (Kaul et al., 2001). Such neurotoxic factors are likely to affect a diverse range of neuronal populations in different CNS structures, as well as in the white matter. Moreover, several HIV proteins could interact directly with neurons or glial cells and promote toxicity. These proteins include the envelope glycoprotein gp120 (Hesselgesser et al., 1998; Meucci et al., 1998), the transcription factor Tat (Nath, 2002; Maragos et al., 2003), Nef, the regulatory protein that promotes both viral replication and immune evasion of HIV (van Marle et al., 2004), the viral transcription protein Vpr (Patel et al., 2000; Jones et al., 2007), and others (Mattson et al., 2005). These proteins can be actively or passively released from infected non-neuronal cells such as microglia or macrophages. It is also possible that HIV may shed proteins after fusion with the host cell membrane or be released from cells. In either case, HIV would then shed gp120 which would interact with neurons. In addition, although astrocytes are only capable of restricted productive infection (Tornatore et al., 1994a), they can release viral proteins (Brack-Werner, 1999). HIV proteins that are not released from astrocytes, such as Nef (Tornatore et al., 1994b), could also alter astrocyte (Bezzi et al., 2001) or oligodendrocyte function (Radja et al., 2003) and disrupt their supportive and neurotrophic role. Free HIV proteins may also cross the blood brain barrier if that barrier's integrity is compromised in HIV positive subjects.

Neuronal chemokine receptors and gp120

Gp120 is one of the most potent HIV viral neurotoxins with lethal activities in the picomolar range. Transgenic mice expressing gp120 exhibit neuronal loss and dendritic simplification (Toggas et al., 1994), pathological features seen in postmortem brains of HAD subjects. Debate exists on whether gp120 induces neuronal damage through inflammatory responses (indirect mechanism) or by directly interacting with neurons. Indirect mechanisms could occur through a variety of avenues. HIV infection causes HIV encephalitis which is characterized by neuroinflammation, astrogliosis and microgliosis, resulting in an overall production and release of pro-apoptotic chemokines, such as Interleukin-1β (IL-1β) and Tumor Necrosis Factor-α (TNFα). It was demonstrated that gp120 promotes the release of these cytokines, as well as other neurotoxic factors such as glutamate (Kaul and Lipton, 1999; Bezzi et al., 2001), which, in turn, evoke neuronal apoptosis. Therefore, gp120 may

potentially exacerbate the toxic action of neuroinflammation. On the other hand, independent experiments have shown that gp120 can be neurotoxic even in the absence of glutamate receptor activation (Bachis and Mocchetti, 2004) or pro-inflammatory cytokines (Bachis et al., 2006). Thus, it appears that the indirect mechanism alone cannot explain the neurotoxic effect of gp120.

Direct mechanisms may go farther to explain the neurotoxic effect of gp120. The envelope protein may promote neuronal loss via activation of chemokine receptors. *In vitro*, gp120 binds to CXCR4 or CCR5, even without CD4, in both neurons (Hesselgesser et al., 1998) and astrocytes (Liu et al., 2004). X4- and R5-gp120s bind to CXCR4 and CCR5, respectively. Intriguingly, these receptors are highly expressed *in vivo* throughout the brain (Klein et al., 1999; van der Meer et al., 2000; Tran et al., 2007; Trecki et al., 2010; Avdoshina et al., 2011). Several lines of independent investigations have shown that gp120 binding to these receptors promotes an apoptotic signal both *in vitro* (Hesselgesser et al., 1998; Meucci et al., 1998; Zheng et al., 1999; Biard-Piechaczyk et al., 2000) and *in vivo* (Bagetta et al., 1996; Bansal et al., 2000; Acquas et al., 2004). Apoptosis can be prevented by the CXCR4 antagonist AMD3100 (Donzella et al., 1998) both *in vitro* (Lazarini et al., 2000) and *in vivo* (Bachis et al., 2006). Conversely, DAPTA, a CCR5 antagonist (Polianova et al., 2005) prevents R5-gp120 neurotoxicity (Bachis and Mocchetti, 2005). Therefore, the cellular mechanism of how gp120 transmits a toxic signal through CXCR4 or CCR5 remains to be established.

CXCR4 and CCR5 are G protein coupled receptors. Several signaling molecules are associated with these receptors including inositol triphosphate and phospholipase C, and inhibition of adenylyl cyclase. CXCR4 activation by gp120 has been shown to increase cytosolic free Ca^{2+} (Holden et al., 1999; Zheng et al., 1999) and extracellular receptor kinase (ERK) (Lazarini et al., 2000). CXCR4-mediated increases in ERK and Ca^{2+} signal transduction have been shown to promote neuronal migration and differentiation (Lazarini et al., 2000). Further, ERK tyrosine phosphorylation has also been shown to promote neuronal survival (Volosin et al., 2006) and to be the main mediator of neurotrophic factor-induced neuritic morphogenesis (Naska et al., 2006). Therefore, it is unlikely that this pathway is the key in promoting the toxic effect of gp120, although the involvement of CXCR4-mediated activation of ERK and Ca^{2+} in gp120-mediated apoptosis may differ among cell types and context. Similarly, gp120 toxicity may depend upon activation of p38/mitogen-activated protein kinase (p38/MAPK) and c-Jun terminal kinase (JNK) in cerebrocortical cultures (Kaul and Lipton, 1999) or striatal neurons (Singh et al., 2005) but not in other cells (Meucci et al., 1998; Biard-Piechaczyk et al., 2000). Activation of JNK signaling cascade generally results in p53-mediated apoptosis, a key feature observed also in HIV subjects (Garden et al., 2002). Conversely, pharmacological inhibition of the JNK pathway prevents gp120-mediated apoptosis (Bodner et al., 2004). Overall these data suggest that gp120 exhibits a CXCR4-mediated intrinsic neurotoxic property that does not necessarily involve production of inflammatory cytokines. Nevertheless, M-tropic gp120 has been shown to induce the pro-inflammatory chemokine CXCL10 that promotes apoptosis through CXCR3 (Sui et al., 2004) or IL-1β (Bachis et al., 2010). Thus, gp120 may activate potential pathways for neurotoxicity based upon its affinity for different chemokine receptors.

Tat promotes apoptosis

Tat is the protein that mediates HIV transcription and is important for viral replication. As mentioned above, Tat can be released from HIV-infected cells (Ensoli et al., 1993) and alter the blood brain barrier (Toborek et al., 2003). Virion-free Tat interacts with different membrane receptors, such as integrins (Albini et al., 1996) and low density lipoprotein receptor-related protein (LPR) (Liu et al., 2000). Integrins are a family of glycoproteins that are expressed on neuronal membranes and mediate the adhesion of neurons to the extracellular matrix (Cavallaro and Dejana, 2011). Thus, Tat can alter neuronal adhesion to extracellular matrix. Whether this effect is crucial for Tat neurotoxicity is still unclear because binding of Tat to integrins activates the protein kinase $p125^{FAK}$ (Milani et al., 1998) which is considered neuroprotective (Ivankovic-Dikic et al., 2000) and essential for dendritic morphology (Beggs et al., 2003).

Binding of Tat to LPR results in its internalization into neurons (Liu et al., 2000). Once inside, Tat is transported to the nucleus (Bruce-Keller et al., 2003). Whether nuclear Tat is neurotoxic is unclear; indeed, a nuclear effect of Tat is more consistent with its function as a transcriptional regulator (Zhou et al., 2004) rather than with its neurotoxic property (see later). There are also data showing that Tat binds to the *N*-methyl-D-aspartate (NMDA) receptor at the allosteric zinc site (Song et al., 2003) or its polyamine sensitive site (Prendergast et al., 2002). Tat may also potentiate glutamate overactivation of NMDA receptors (Haughey et al., 2001). Consistent with this hypothesis, blockade of NMDA receptor by MK801, a potent antagonist (Eugenin et al., 2003), or by memantine, an antagonist with moderate affinity for this receptor (Nath et al., 2000) reduces significantly Tat toxicity. However, additional experiments using different combinations of various NMDA receptor subunits are warranted to prove the relative affinity of Tat for this receptor.

It was recently demonstrated that after binding of Tat to LPR, a complex is formed between LRP and the NMDA receptor, mediated by an intracellular scaffolding protein, PSD-95 (Eugenin et al., 2007). PSD-95 contains many protein-binding domains, facilitating interaction with diverse synaptic and signaling proteins (Kim and Sheng, 2004). Thus, it is possible that Tat activates NMDA receptor through the cross-activation of several signaling pathways. Nevertheless, the effect of Tat on production of pro-inflammatory cytokines or other inflammatory response mediators cannot be overlooked (Nath et al., 1999; Pu et al., 2003). In fact, Tat promotes cellular events such as nitric oxide and reactive oxygen species production (Toborek et al., 2003), and mitochondrial membrane depolarization (Li et al., 2009) that are induced by cytokines and are known to be implicated in neuronal cell death. Thus, it can be concluded that the neurotoxic effect of Tat includes multiple mechanisms.

Diversity of mechanisms: microtubular transport and neurotrophic support

A number of cellular effects that are believed to participate in the neurotoxic effects of Tat and gp120 are similar. However, Tat and gp120 can promote neuronal loss through different mechanisms. Learning more about the differences of Tat and gp120 in their interaction with cellular signaling may shed light onto how HAND develops. For instance, in striatal neurons both Tat and gp120 activate caspase-3 (Singh et al., 2004). Depending upon experimental conditions and cell types used, both Tat and gp120 promote cytochrome C and endonuclease

G (Singh et al., 2004; Melli et al., 2006), which are components of the apoptotic cascades. Nevertheless, p38 MAPK activation alone mediates gp120-induced neurite dystrophy and cell death, while neither p38 MAPK nor JNK inhibition is sufficient to prevent Tat-induced neurite losses or neuronal death (Singh et al., 2005). Thus, while apoptotic neuronal loss is crucial for the neurotoxic effect of these two viral proteins, their mechanisms of action are different.

Another feature that may be important for Tat and gp120 toxic effect is their ability to be endocytosed by neurons (Bruce-Keller et al., 2003; Bachis et al., 2006). Once inside, gp120 localizes in late endosomes (Bachis et al., 2006) and remains perinuclearly, Tat escapes from endosomes and migrates to the nucleus (Fig. 1). In the nucleus, Tat may alter transcription of survival factors such as p35 (Darbinian et al., 2008), a neuron-specific activator of cyclin-dependent kinase 5 (Cdk5), an enzyme with multiple neuronal effects implicated in synaptic plasticity. In fact, the induction of p35/Cdk5 kinase activity is critical for neurite outgrowth and survival (Song et al., 2005; Fu et al., 2007). These data suggest that Tat may be neurotoxic by altering both intranuclear and cytoplasmic (i.e. calcium dysregulation) events. As noted above, gp120 does not enter the neuronal nucleus but interacts directly with synaptic vesicles, microtubules and lysosomes (Bachis et al., 2006).

The entry of gp120 is a CXCR4-dependent mechanism (Bachis et al., 2003; Bachis et al., 2006). CXCR4 undergoes spontaneous and ligand-mediated endocytosis (Orsini et al., 1999; Signoret et al., 2000). Endocytosis is a fundamental cellular function involved in nutrient uptake, pathogen removal, and transport of signaling molecules from an extracellular environment to the cytoplasm (Ungewickell and Hinrichsen, 2007). The endocytosed material is first moved into an early endosome, from which it may either be returned to the plasma membrane via a recycling endosome, or transferred into a late endosome. The late endosome may move its contents into the trans-Golgi network, or into a lysosome, in which case the contents will be targeted for degradation (Maxfield and McGraw, 2004). However, there is evidence that abnormal ceramide metabolism in relation to aberrant lysosomal function can cause neurodegenerative diseases (Ditaranto-Desimone et al., 2003). Thus, once gp120 accumulates inside lysosomes, it may increase the production of toxic cytoplasmic inclusions such as ceramide (Haughey et al., 2004; Jana and Pahan, 2004). Data showing that HAD patients have high levels of brain ceramide (Haughey et al., 2004) support this neurotoxic mechanism of gp120.

Ceramide may not be the only cellular mechanism of neurotoxicity involving lysosomes. In fact, homeostasis in neurons involves clearance of proteins by autophagy, an evolutionary conserved pathway that involves sequestration of cytoplasmic material into the lysosomes (Kundu and Thompson, 2008). Autophagic vacuoles have been shown to accumulate in affected neurons in subjects with Alzheimer’s and Parkinson’s diseases (Wei et al., 2007; Pickford et al., 2008). The induction of autophagy is also associated with axonal degeneration in Purkinje cells (Wang et al., 2006) and it is also seen in HAD (Gelman et al., 2005). When lysosomes cannot recycle/degrade efficiently, an abnormal collection of undigested material within neurons occurs, leading to cell death (Zhang et al., 2001). Gp120 may alter the regulated retrograde flux that balances axonal transport and autophagy and cause apoptosis. Indeed, the death receptor signaling molecule TRAIL, which is up-

regulated by HIV (Ryan et al., 2004), regulates both apoptosis and autophagy. p53, which is also activated by gp120 (Garden et al., 2004), is another activator of autophagy (Wang et al., 2009). Finally the ubiquitin proteosome system, which is altered in HAD subjects (Nguyen et al., 2010) and is crucial for protein degradation is also implicated in autophagy (Kim et al., 2008). Thus, gp120 endocytosis may impair various cellular functions crucial for neuronal homeostasis. These considerations suggest that if gp120 accumulates inside lysosomes or other organelles it promotes neuronal apoptosis by preventing physiological autophagy.

Gp120 has also been shown to cause axonal degeneration (Melli et al., 2006) and dendritic injury (Everall et al., 2002; Iskander et al., 2004), two key pathological events that may account for the synaptodendritic atrophy observed in HAD (Masliah et al., 1997). Gp120-mediated neuronal degeneration can be prevented by nocodazole or colchicine (Bachis et al., 2006), two inhibitors of fast axonal transport (James et al., 1970; Samson et al., 1979), indicating that trafficking of gp120 along the axon is crucial for its neurotoxicity. The gp120-mediated axonal degeneration has four key features: 1: It takes place both in the CNS as well as in the peripheral nervous system (Bachis et al., 2006; Melli et al., 2006); 2: It occurs only when gp120 is applied directly to axons (Melli et al., 2006); 3: It is CXCR4 dependent (Bachis et al., 2006; Melli et al., 2006) and 4: It is caspase-3 dependent. Therefore, it is different from that observed during CNS development, which is caspase independent (Raff et al., 2002). In contrast, gp120-mediated degeneration of dendrites occurs without a significant change in apoptosis (Iskander et al., 2004). Interestingly, gp120 is seen around synaptic vesicles (Bachis et al., 2006) and associates with dendrites (Fig. 2A) and axonal microtubules (Fig. 2B). Such cellular mechanism may have a profound significance for gp120 neurotoxicity if we consider that microtubules are essential for intracellular transport of pro-survival proteins in both axons and dendrites. In addition, axonal transport in neurons necessitates the most rapid and lengthy mitochondrial movements and is required to maintain local ATP levels at the synapse. Microtubule/cytoskeleton-dependent movement of mitochondria has been shown to influence a variety of cellular behaviors including proliferation, differentiation and apoptotic events (Boldogh and Pon, 2007; Chen and Chan, 2009). Therefore, gp120 may be neurotoxic by reducing movements along microtubules or by impairing the function of motor proteins such as dyneins and kinesins, that, when impaired, promote a “dying-back” pattern of degeneration. This phenomenon may explain the synaptic simplification/atrophy seen in HAD subjects as well as the pathophysiology of degenerating sensory fibers and prominent loss of unmyelinated fibers that are seen in AIDS patients (Estanislao et al., 2004).

Gp120 reduces neurotrophic support

Axonal transport is absolutely necessary for delivering or transporting proteins, including neurotrophic factors, to and from the nerve terminals. Neurons rely on axonal transport of neurotrophic factors for their survival. For instance, the neurotrophin brain derived neurotrophic factor (BDNF), one of the most abundant neurotrophins in the adult brain, is produced in cortical neurons and anterogradely delivered to striatal neurons (Altar et al., 1997), where it is particularly important for their survival and for the activity of the cortico-striatal synapses (Zuccato and Cattaneo, 2007). Conversely, loss of BDNF has been

suggested to be a risk factor in chronic diseases of the basal ganglia such as Parkinson's (Nagatsu et al., 2000) and Huntington's diseases (Xie et al., 2010). BDNF is also abundant in the hippocampus where it is important for maintaining dendritic morphology and synaptic function (Horch and Katz, 2002), the survival of neurons and their connections (Mattson, 1997; Xu et al., 2000), and long-term potentiation (Figurov et al., 1996; Zakharenko et al., 2003). On the contrary, loss of BDNF has been associated with Alzheimer's disease and impaired cognition (Phillips et al., 1991). Indeed, there is evidence that reducing the production of BDNF in the hippocampus decreases hippocampal neuronal survival (Erickson et al., 2011).

Given the tight relation between BDNF and neuronal survival, one may suggest that gp120 neurotoxicity includes a reduction of BDNF and other neurotrophic factors at the synapses. *In vivo* studies have shown that gp120 decreases the levels of BDNF in cortico-striatal terminals without affecting BDNF in the cell bodies (Nosheny et al., 2004), suggesting that gp120 modifies the anterograde transport of BDNF. Most likely this phenomenon is related to the ability of gp120 to alter microtubules/axonal transport. These data provide a scenario by which HIV shedding of gp120 promotes neuronal apoptosis by decreasing the microtubule-directed trafficking of vesicles containing BDNF (Fig. 3). A reduced availability of BDNF in the axonal terminal will culminate in a decreased release of BDNF which will affect profoundly neuronal homeostasis and the ability of neurons to counteract the inflammatory responses and production of cytokines that are caused by HIV infection (Kraft-Terry et al., 2010).

Conclusions

The studies described here and elsewhere show how HIV promotes neuronal cell death by indirect mechanisms involving viral proteins. Neurotoxic actions of viral proteins include an increase in the production of pro-inflammatory cytokines and a reduction of anti-apoptotic neurotrophic factors, such as BDNF and glial-cell derived neurotrophic factor (Nosheny et al., 2006) . Reduction of BDNF culminates in an up-regulation of CXCR4 and CCR5 (Nosheny et al., 2004; Ahmed et al., 2008; Avdoshina et al., 2011), two HIV co-receptors that also promote neuronal apoptosis. In addition, BDNF promotes adult neurogenesis (Li et al., 2008) that is believed to be essential for specific cognitive functions that decline in HIV positive subjects (Venkatesan et al., 2007). Moreover, BDNF exhibits protective activity against the neurotoxic effect of gp120 both *in vitro* (Bachis et al., 2003) and *in vivo* (Nosheny et al., 2007). Thus, BDNF could be a valid adjunctive therapy to reduce pathological signs of HAD that are due to loss of synapses. Most importantly, BDNF could be used in MND subjects who exhibit the clinical hallmarks of HAD (Pumpradit et al., 2010), albeit with less severe signs and symptoms (Cysique and Brew, 2009), to prevent the onset of frank dementia. An adjunct therapy is particularly important because of viral mutation and HAART resistance, failure of drugs to access viral sanctuaries in the brain, and toxicities of HAART.

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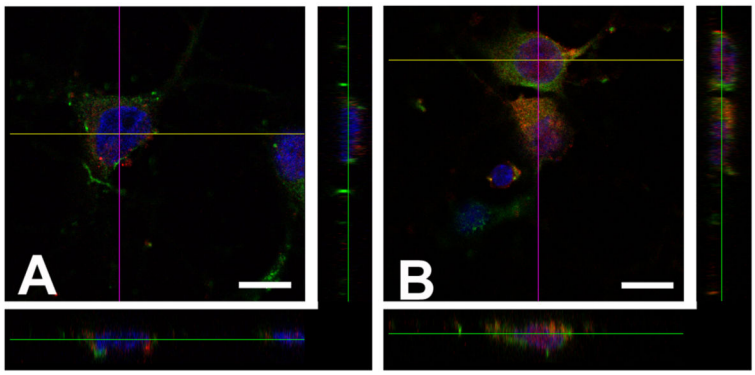

Figure 1. Differential intracellular localization of gp120 and Tat

Cortical neurons were prepared from E18 rat embryos as previously described (Avdoshina et al., 2010). Neurons were exposed to (**A)** gp120IIIB (5 nM) and (**B)** Tat (100 nM) for different time points. Neurons were then fixed and stained with anti-gp120 and anti-Tat antibodies (red), and co-stained with class III β-tubulin (green) and DAPI (blue). The figure shows representative images obtained 6 hr after gp120 or Tat exposure using a confocal microscope. Neurons were optically sliced and a Z-stack was created using the FluoView software. Orthogonal projections were created to show perinuclear and intranuclear localization of gp120 and Tat immunoreactivity, respectively. Bar = 10 μm.

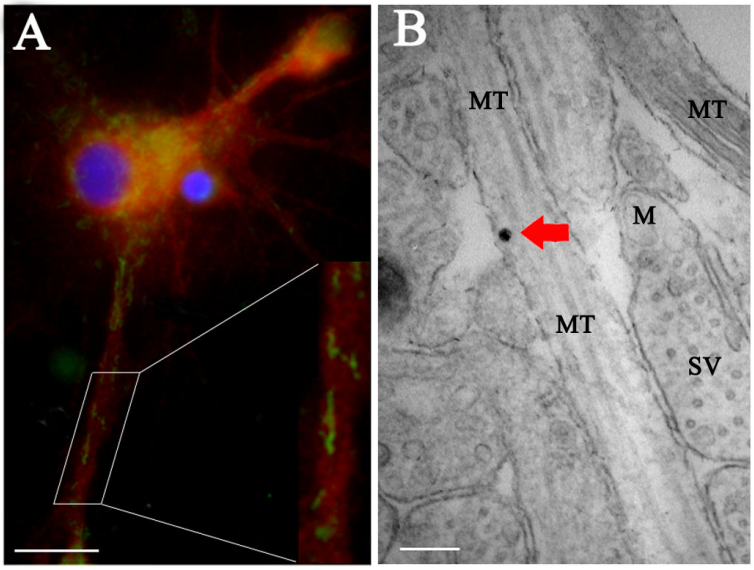

Figure 2. gp120 associates with microtubules

Cerebellar granule neurons were prepared from P8 rat pups as previously described (Bachis et al., 2003). Neurons were exposed to (**A)** gp120IIIB (5 nM) or (**B**) colloidal gold (25 nm mean particle size) gp120 for 30 min. In **A**, neurons were fixed and stained with a gp120 antibody (green) and microtubule associated protein-2 antibody (red) to label dendrites. Cells were then counterstained with DAPI (blue) and analyzed with a confocal microscope. Bar=10 μm. In **B,** neurons were processed for electron microscopy analysis of gold gp120 as previously described (Bachis et al., 2006). The picture shows several axons as determined by the presence of synaptic vesicle (SV) and the absence of polyribosomes. Red arrow indicates gp120 associated with microtubules (MT). M=mitochondria. Scale bar: 200 nm. (Modified from Bachis et al., 2006).

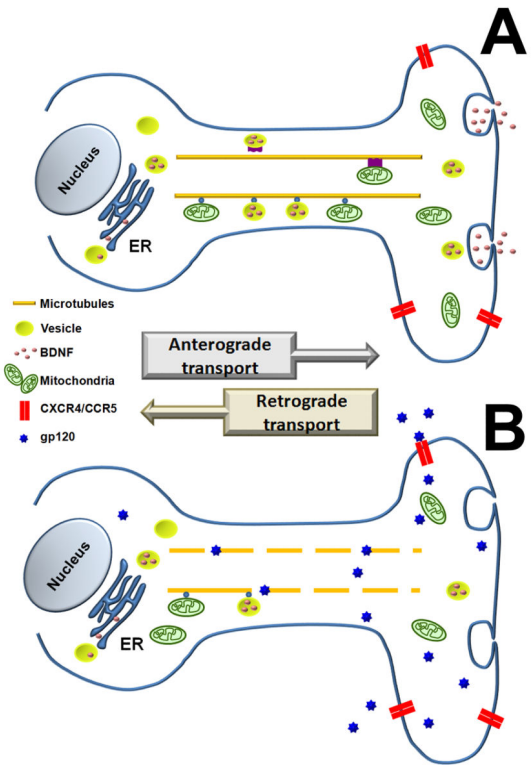

Figure 3. Hypothetical model of HIV neurotoxicity

(A) BDNF processed in the ER apparatus is packed and stored in vesicles. Vesicles are anterogradely transported via microtubules to the axonal terminal. From here, BDNF is released in an activity dependent manner. **(B**) Extracellular gp120 binds to CXCR4/CCR5 chemokine receptors and it is internalized. Endocytosed gp120 associates with microtubules and disrupts the microtubular transport of BDNF containing vesicles resulting in a decrease in BDNF content in the synapse.