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Implementing Neuronal plasticity in NeuroAIDS: The Experience of Brain-derived Neurotrophic Factor and Other Neurotrophic Factors

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Abstract

Human immunodeficiency virus type-1 (HIV) causes mild or severe neurological problems, termed HIV-associated neurocognitive disorder (HAND), even when HIV patients receive antiretroviral therapy. Thus, novel adjunctive therapies are necessary to reduce or abolish the neurotoxic effect of HIV. However, new therapies require a better understanding of the molecular and cellular mechanisms of HIV-induced neurotoxicity. HAND subjects are characterized by being profoundly depressed, and they experience deficits in memory, learning and movements. Experimental evidence has also shown that HIV reduces neurogenesis. These deficits resemble those occurring in premature brain aging or in a brain with impaired neural repair properties. Thus, it appears that HIV diminishes neuronal survival, along with reduced neuronal connections. These two phenomena should not occur in the adult and developing brain when synaptic plasticity is promoted by neurotrophic factors, polypeptides that are present in adult synapses. This review will outline experimental evidence as well as present emerging concepts for the use of neurotrophic factors and in particular brain-derived neurotrophic factor as an adjunct therapy to prevent HIV-mediated neuronal degeneration and restore the loss of synaptic connections.

Keywords

BDNF; FGFs; GDNF; gp120; HIV; PDGF; TrkB

Introduction

Human immunodeficiency virus type-1 (HIV) infects the central nervous system (CNS) and promotes neurological problems in more than 50% of patients who do not receive antiretroviral therapy (Gonzalez-Scarano and Martin-Garcia, 2005; Price and Spudich, 2008). Symptoms include profound motor and behavioral/psychosocial abnormalities that disrupt work or other activities of daily living. These deficits can be mild, which are referred to as HIV-associated neurocognitive disorders (HAND), or severe, which are referred to as HIV associated dementia (HAD). HIV does not spare children because they can develop abnormalities manifested as attention deficit disorders (Cohen et al., 1991) and neuronal loss (Gelbard and Epstein, 1995).

HIV does not infect neurons; nevertheless, postmortem brains of HAD subjects have shown neuronal loss accompanied by synaptic simplifications (Everall et al., 2005). In addition,

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HIV impairs adult neurogenesis (Tran and Miller, 2005; Okamoto et al., 2007), the process by which new neurons are created even in the adult CNS. Experimental and clinical research has revealed that the loss of adult neurogenesis in the hippocampus can lead to depression, one of the cardinal symptoms seen in HIV positive subjects (Eriksson et al., 1998). In addition, there is a strong correlation between the delay onset of antidepressant activity and the time required for neurogenesis (Malberg et al., 2000). Thus, alternative adjunct therapies against HAND must take into account the multiple neurotoxic effects of HIV in addition to restoring the innate ability of the CNS to promote neurogenesis, survival, and adaptation to injury. Ideally, this therapy should use physiological compounds utilized by the CNS to prevent neuronal injury and promote survival of cells (biological therapies). These include neurotrophic factors, naturally occurring diffusible polypeptides that stimulate survival of a variety of CNS cells after injury as well as to induce and maintain the differentiation of surviving neurons to their mature phenotype. Moreover, these peptides, and in particular brain-derived neurotrophic factor (BDNF), have been shown to promote neurogenesis, and are equally vital for neuronal plasticity. This article will introduce new emerging concepts and principles in the use of neurotrophic factors as an adjunct therapy to prevent HIV-mediated neuronal degeneration and restore the loss of synaptic connections.

HIV and synaptic plasticity

The search for drugs that reduce neuronal injury requires a better understanding of the pathogenic mechanisms and the numerous steps involved in the pathogenic cascade. HAND/HAD pathology includes loss of both synaptic connections and neuronal differentiation (Ellis et al., 2007). In addition, HAD subjects exhibit depression and mania (Grant, 1990; Pumpradit et al., 2010) combined with cognitive and motor impairments. In fact, the clinical manifestations of HAD include tremor, gait ataxia, loss of fine motor movement, mental slowing, forgetfulness, poor concentration and behavioral abnormalities (McArthur et al., 2010). Neuroimaging studies of HAD patients have revealed generalized white matter reduction, with additional grey matter loss particularly in the basal ganglia and posterior cortex (Dal Pan et al., 1992; Aylward et al., 1995). Neuronal loss has been confirmed in postmortem brains in the basal ganglia and other regions of the brain including the hippocampus and frontal cortex (Davies et al., 1998; Everall et al., 2005). Pathological alterations of the basal ganglia in HAD include neuronal loss in the putamen (Everall et al., 2005) and the globus pallidus (Fox et al., 1997), degeneration of nigro-striatal dopamine (DA) neurons (Reyes et al., 1991; Itoh et al., 2000) (Itoh et al., 2000) and dysfunctional DAergic transport (Wang et al., 2004).

Higher cognitive functions depend on a highly complex synaptodendritic network in the frontal cortex. Damages to this network result in abnormal output, measured as deficiencies in cognitive skills and behavior. Cognitive impairments (moderate to severe) and frontocortical atrophy in HAD are similar to those observed in Alzheimer's disease (AD) (Thompson et al., 2007). This disease is categorized by a reduced number of neurons and connections in the cortex and hippocampus as well as impaired short-term memory (Scheff and Price, 2006). Granted that memory and attention alterations could be also due to the high prevalence of CNS comorbidities in HIV populations (e.g. drug abuse), it is important to keep in mind that these cognitive alterations correlate with the loss of synaptodendritic networks in the cortex and hippocampus. Moreover, neuroimaging studies have revealed microstructural abnormalities in the cerebral white matter (Lopez-Villegas et al., 1997), supporting the theory of synaptodendritic pathology as the main cause of neuronal loss.

Neurotrophic factors as biological therapies for HAND

Neurotrophic factors have been shown to reduce synaptic and axonal degeneration mediated by a number of neurotoxins and to interfere with the fundamental mechanism of apoptotic cell death in numerous neurodegenerative diseases. In addition, neurotrophic factors promote axonal growth when an appropriate growth-promoting substrate is present (Horner and Gage, 2000). Thus, HAND syndrome and pathology are excellent targets for a therapy based on neurotrophic factors. In addition, some neurotrophic factors are naturally implemented to promote neuronal differentiation and neurogenesis. The important question is which neurotrophic factors are more suitable to treat HAND pathology. The answer does not appear to be straightforward because there are many neurotrophic factors each exhibiting neurotrophic activity on either overlapping or distinct neuronal and glial populations. Indeed, “trophic ligands” influence neurons and glial cells by binding to specific membrane-associated receptors. These receptors are not necessarily equally distributed on all neuronal subtypes. Moreover, the levels of neurotrophic factors and/or their receptors could be decreased in the presence of axonal and synaptic pathology, which is a characteristic of many neurological disorders including HAND. Nevertheless, the remaining synapses may be influenced to release more neurotrophic factors. Alternatively, the delivery of recombinant neurotrophic factors may stimulate neuronal plasticity and promote neurogenesis which may help replace neurons and synapses that otherwise will be lost.

HIV neurotoxicity is promoted by HIV viral proteins, common agents released after HIV infection in the CNS. Thus, another intervention for HAND would be to block or eliminate the biological effects of these proteins. Viral proteins may interfere with neuronal survival by a number of mechanisms including production of free radicals, nitric oxide, and release of glutamate or other excitotoxins (i.e. quinolinic acid) or inflammatory cytokines (Kaul et al., 2001). The neurotoxic effects of these compounds can be blocked by several trophic factors delivered at pharmacological concentrations. Thus, there are several polypeptides that could exert trophic function on neurons and their synapses, yet only four have been experimentally tested as therapeutic compounds for neuroAIDS in animal models. These include fibroblast growth factor (FGF) (Sanders et al., 2000), brain-derived neurotrophic factor (BDNF) (Bachis et al., 2003), glial cell derived neurotrophic factor (GDNF) (Nosheny et al., 2006) and platelet-derived neurotrophic factor (PDGF) (Peng et al., 2008). To better comprehend the potential use of polypeptides as therapeutics, a brief description of their biological activity is necessary. BDNF will be reviewed as a separate neurotrophic factor because of its strong axonal growth properties.

FGFs

There are at least 10 members of the FGF family of growth factors that are expressed in the CNS (Turner et al., 2006). However, FGF2 (or basic FGF) and FGF1 (or acidic FGF) appear to be the most abundant in the adult CNS (Wilcox and Unnerstall, 1991; Gomez-Pinilla et al., 1992). There are several neurotrophic properties of FGFs that may be useful in a therapy for HAND. In fact, FGFs promote gliogenesis and neurogenesis when added to cultures of precursor cells from various brain areas (Vescovi et al., 1993; Qian et al., 1997) or *in vivo* in developing rats (Raballo et al., 2000) and adult rats (Shihabuddin et al., 1997; Yoshimura et al., 2001). In addition, FGFs enhance the survival of neurons following toxin-induced cell death (Frim et al., 1993; Zechel et al., 2010). FGF2 is also important because it is one of the most potent growth factor that is used to inhibit excitotoxicity (Fernandez-Sanchez and Novelli, 1993; Kirschner et al., 1995; Brandoli et al., 1998) as well as reduce inflammatory responses and improve recovery of function after mechanical injury or stroke (Peterson et al., 1996; Kawamata et al., 1997; Teng et al., 1999). Given the fact that glutamate and

inflammation play a key role in neuroAIDS, the FGFs approach will lead to amelioration of the pathology and symptoms that arise from excessive glutamate.

FGF2 also plays a key role in depression and in the mechanism of action of antidepressants. Indeed, alterations in FGF2 expression are seen in cortical brain regions in individuals with major depression compared to control subjects (Evans et al., 2004). Moreover, antidepressants such as desipramine (Mallei et al., 2002), electroshock (Follesa et al., 1994) or fluoxetine (Maragnoli et al., 2004) increase the synthesis of FGF2. This induction of FGF2 expression may explain the ability of antidepressants to increase neurogenesis. However, the neurogenic activity of antidepressant cannot rely solely on FGF2 because antidepressant agents have been shown to increase other trophic factors (Nibuya et al., 1996). Nevertheless, FGF2 may help blocking the outgoing pathology of depression in HAND subjects.

A direct link between FGFs as a therapy in the pathology of HAND has been established in animal models. In fact, both FGF2 and FGF1 reduce the expression of CXCR4, a chemokine receptor that mediates the entry of T-tropic HIV (Dittmar et al., 1997) as well as the neurotoxic effect of its viral protein gp120 (Meucci et al., 1998; Zheng et al., 1999). Indeed, FGFs reduce the neurotoxic effect of gp120 (Sanders et al., 2000; Everall et al., 2001). Moreover, FGFs levels are inversely correlated with CXCR4 expression in postmortem AIDS brains (Sanders et al., 2000). Therefore, inhibitors of the expression/signaling of this receptor may have an important therapeutic property against HIV-mediated neurological impairment caused by CXCR4 activation. Nevertheless, the therapeutic potentials of FGFs in the treatment of HAND patients need scrutiny and caution because these growth factors have been shown to promote/support tumor growth and angiogenesis (Czubayko et al., 1994).

GDNF

The GDNF family of trophic factors consists of four members: GDNF, Neurturin, Artemin, and Persephin. This family has been shown to play a role in a number of biological processes including cell survival, neurite outgrowth, cell differentiation and cell migration. In particular, GDNF promotes the survival of rat dopaminergic neurons of the nigro-striatal system (Lin et al., 1993; Tomac et al., 1995), one of the major pathways involved in the control of motor activity. Moreover, Neurturin protects non-human primate DA neurons from MPTP, a toxin that has been known to cause Parkinson in humans. Therefore, GDNF and Neurturin have been suggested to be used in Parkinson's disease (PD). In addition, GDNF rescues motor neurons from axotomy-mediated cell death (Yan et al., 1995). This property is also shared by at least two more growth factors, ciliary neurotrophic factor (CNTF) and BDNF (Sendtner et al., 1990; Sendtner et al., 1992).

The trophic effect of GDNF and the related family members are mediated by a receptor complex formed by two subunits, RET, a transmembrane receptor tyrosine kinase, and glycosyl-phosphotidylinositol-anchored co-receptor GDNF receptor α (Paratcha and Ledda, 2008). Activation of this complex triggers different pathways, including the Ras-MAPK (mitogen-activated protein kinase), the phosphatidylinositol-3 kinase (PI3K)-Akt, the PLC-γ and the Src signaling pathway and consequently increases intracellular Ca^{2+}. These signaling pathways may not explain the trophic effect of GDNF. In fact, a new mechanism of GDNF signaling through RET has been proposed by showing that GDNF evokes phosphorylation of specific protocadherin proteins which, in turn, promote interaction with RET (Schalm et al., 2010). Protocadherins are found in synapses and have been implicated in neuronal survival, synaptic development (Katori et al., 2009), and learning and memory (Fukuda et al., 2008). The association of protocadherins with RET plays a key role in the receptor stability and ensures a delay in the degradation of RET. Any delay in the

degradation of this receptor allows neurons to survive longer in the presence of GDNF (Tsui and Pierchala, 2010).

The trophic property of GDNF could also be of a particular importance for HAND, especially in the late phase or HAD. During this stage, clinical features in HAD resemble those found in PD, such as the postural instability, involuntary movements, bradykinesia, and impairment in fine motor skills (Berger and Nath, 1997). In addition, the *substantia nigra* (SN) of HAD subjects exhibit lower expression of GDNF than HIV subjects without dementia (Fig. 1). Granted that results obtained from postmortem human brains may reflect secondary effects of the primary pathological events, both animals and human studies suggest that GDNF and Neurturin could play a role in protecting and/or enhancing the survival of SN neurons in HIV positive subjects.

The therapeutic application of GDNF in HAD requires more experimental studies. To the extent that we accept viral protein-mediated neuronal loss as a necessary animal model of HAD, studies have shown a profound degeneration of the SN of rats injected with gp120 in the striatum which inversely correlated with expression of GDNF. In fact, gp120 damages striatal neurons and initiates the degeneration of nigrostriatal DAergic fibers, thus causing a functional disconnect between the SN and the striatum (Nosheny et al., 2006). In these animals a decrease in GDNF expression in the SN precedes the degeneration of DA neurons and the increase in the number of apoptotic neurons. These results may invite some modifications of the classical views of HAD and support the neurotrophic factor hypothesis stating that lack or loss of trophic support could be one of the main causes of neuronal degeneration evoked by HIV. Most importantly these observations indicate the need for examining the trophic environment in HAD because lower trophic levels or activity could be a common risk factor for losing neurons and the development of neurological impairments. This issue rarely receives the attention it deserves, a problem that may have a negative impact on the success of future clinical trials.

PDGFs

PDGFs are a family of growth factors that have a broad spectrum of biological activity on cell growth and division (Farooqi et al., 2011). This family is composed of four different isoforms encoded by four different genes, PDGF-A, -B, -C and -D. PDGFs have a common structure (described mostly as dimeric glycoproteins) composed of two A (-AA), B (-BB), C (-CC) or D (-DD) chains or a combination of A and B (-AB). These distinct isoforms bind with different affinities to two structurally related receptor types, α and β. These receptors contain an intracellular tyrosine kinase domain that upon activation and dimerization of the receptor promotes tyrosine phosphorylation.

Members of the PDGF family are expressed in several tissues including the brain (Fredriksson et al., 2004). Nevertheless, while the mitogen activity of PDGFs for many cell types has been established (Li et al., 2003) their functional role in the brain is still under investigation. PDGF-A is a potent mitogen for glial cells, and in particular oligodendrocytes (Betsholtz, 2004); consequently, PDGF-A null mice display severe myelination deficiency in some brain areas (Fruttiger et al., 1999). Thus, PDGFs may have a therapeutic property for HAND because proliferation of cells and re-myelination could be a positive phenomenon in the neurodegenerative brain. Most importantly, experimental data have suggested that PDGFs have a role in neurogenesis, which, as mentioned above, is impaired in HAND. In particular, PDGF-BB has been shown to stimulate the growth of neuronal processes (Smits et al., 1991) as well as to promote the maturation of progenitor/stem cells *in vitro* (Pringle et al., 1992). Stem cells are capable of differentiation into neurons and glial cells. The neurotrophic activity of PDGF-BB is not limited to an *in vitro* model. In fact, this growth factor enhances neurogenesis *in vivo* after chemical lesion (Mohapel et al., 2005). Moreover,

a more recent study (Yao et al., 2012) has shown that PDGF-BB increases proliferation of neuronal stem cells in an animal model of HAND. Thus, PDGFs may have a therapeutic property for HIV subjects since enhancing neurogenesis can have a broad impact on improving neurological symptoms and mood-related behavior in these subjects.

Neurotrophins

Another family of neurotrophic factors with strong trophic activity is the neurotrophins. In mammals, this family includes nerve growth factor (NGF) (Levi-Montalcini, 1987), brain-derived neurotrophic factor (BDNF) (Barde et al., 1982), neurotrophin-3 (NT-3) and NT-4 (Maisonpierre et al., 1990). NGF was the first to be isolated, characterized and cloned. However, NGF has limited activity in the brain and only a few populations of cholinergic neurons of the basal forebrain appear to be sensitive to NGF. On the other hand, BDNF exerts multiple neurotrophic activities on a variety of neurons. Neurotrophic effects of BDNF include modulation of dendritic branching and spines in the cortex, and long-term potentiation in the hippocampus (Patterson et al., 1996; Zakharenko et al., 2003). Through these properties, BDNF plays a critical role in learning and memory and preservation of cortical circuits. Conversely, a reduction of BDNF secretion/activity is responsible for the loss of cortical and hippocampal synapses and fear learning. This has been demonstrated not only in animals but also in humans. In fact, impaired learning and memory have been observed in both human subjects (Egan et al., 2003) and mice (Soliman et al., 2010) in which the regulated BDNF secretion is reduced due to a single nucleotide polymorphism in the BDNF gene that encodes a valine (Val) to methionine (Met) substitution at codon 66 (Val66Met). In addition, correlative studies of human chronic neurodegenerative diseases characterized by reduced BDNF levels/activity have confirmed the role of BDNF in adult plasticity. For instance, a deficiency in BDNF synthesis has been described in postmortem brains (Phillips et al., 1991) or cerebrospinal fluid (Laske et al., 2007) of patients with AD.

BDNF treatment has the potential to reduce or abolish neuronal death in several brain areas. Moreover, BDNF and NT-3 prevent degeneration of motor descending pathways (Diener and Bregman, 1994; Schnell et al., 1994). Indeed, early experimental studies in animal models have shown a remarkable neuroprotective effect of BDNF against various neurotoxins that mimic human chronic neurodegenerative diseases such as PD and Huntington's disease (Hyman et al., 1991; Frim et al., 1994; Alberch et al., 2002). Similar neuroprotection has been observed in rodents and non-human primates after the lesion of the perforant path, an animal model of AD (Nagahara et al., 2009). BDNF can also prevent synaptic simplifications of neurons exposed to gp120 (Bachis et al., 2012). These and other experimental evidence have prompted the suggestion that BDNF could be a potential therapeutic agent for the treatment of these and other diseases characterized by loss of synaptic plasticity, including HAND. Overall, BDNF remains one of the best understood agents against neurodegeneration and thus it deserves a critical analysis of its biological effect. We will describe some experimental evidence that BDNF can be used as biological therapy against HAND.

BDNF and HIV Dementia, Basic Tenets

Very little is known about a possible role of BDNF in HAD, which as presented above exhibits certain clinical signs similar to AD and PD. Due to the similarity of AD, PD and HAD in terms of neuronal loss, one may suggest that BDNF treatment could be a beneficial therapeutic approach in these diseases. Moreover, it can be predicted that HIV may promote neuronal degeneration by lowering BDNF levels. This hypothesis has recently been tested in HIV positive subjects. It was found that BDNF levels are significantly lower in HIV positive individuals than in HIV negative subjects in both the serum (Avdoshina et al., 2011) and brain (Bachis et al., 2012). These data pose the question as to whether HIV promotes

synaptic simplification by reducing BDNF along with the other neurotrophic factors whose physiological role is to support and maintain synapses. This theory was first developed for sensory and sympathetic neurons the density of which is regulated by postsynaptic targets producing NGF (Johnson et al., 1980; Levi-Montalcini, 1987). Nevertheless, such a concept can also be applied to the CNS. Indeed, low levels of BDNF have been shown to impair the innervation of the cortex by serotonergic fibers (Lyons et al., 1999). Similarly, gp120-mediated reduction of BDNF levels appears to cause neuronal degeneration even in the absence of inflammation (Nosheny et al., 2004). These observations suggest that an environment characterized by low BDNF (or other trophic factors) levels or activity could be a common risk factor for the development of neurological diseases. This issue rarely receives the attention it deserves, a problem that may have a negative impact on the success of future clinical trials.

BDNF and Neuroprotection

The biological activity of the neurotrophins begins when they bind to a receptor complex composed of two different receptors. The first neurotrophin receptor that was characterized was a member of the tumor necrosis factor receptor family that was named p75 NGF (Johnson et al., 1986; Radeke et al., 1987). Since p75 binds to all neurotrophins with a similar affinity (Rodriguez-Tebar et al., 1990) it was subsequently renamed p75NTR. 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 (Kaplan et al., 1991). There are three structurally related Trks and each neurotrophin binds selectively to a respective Trk: BDNF binds to TrkB, NGF to TrkA and NT-3 to TrkC (Chao, 2003); however, at high concentrations BDNF can also bind to TrkC (Klein et al., 1991). Both Trk and p75NTR are necessary to confer high affinity binding to the neurotrophins and to influence their biological activities (Hempstead et al., 1991). When activation of p75NTR occurs without a concomitant activation of Trk, p75NTR promotes death of oligodendrocytes (Gu et al., 1999) as well as axonal degeneration in both peripheral nerves (Kenchappa et al., 2006) and CNS (Park et al., 2010). Thus, p75NTR exhibits an opposite action on oligodendrocyte survival than PDGF.

The brain expresses also a truncated isoform of TrkB or TrkB.T1. This receptor does not signal through a canonical tyrosine kinase domain. However, at physiological levels Trk.T1 negatively regulates full length TrkB (TrkB.FL) signaling so that it acts as a dominant/negative or BDNF-sequestering trophic activity (Carim-Todd et al., 2009). For instance, BDNF exerts strong pro-survival effects on injured motoneurons; however, in clinical trials BDNF has failed to benefit patients with amyotrophic lateral sclerosis (ALS). It was discovered that motoneurons express the TrkB.FL receptor but also high levels of TrkB.T1 receptor isoform, which, in turn, limited BDNF pro-survival effect. Indeed, deletion of TrkB.T1 in an ALS mouse model (Gurney et al., 1994), significantly slowed the onset of motor neuron degeneration (Yanpallewar et al., 2012). In addition, TrkB.T1 has been shown to promote the production of nitric oxide from astrocytes, which could cause neuronal degeneration (Colombo et al., 2012). Thus, expression of Trk.T1 on neuronal and glial populations must be considered when approaching the use of BDNF for human neurological diseases.

BDNF and gp120

TrkB mediates the neuroprotective effect of BDNF against gp120. In fact, TrkB-mediated activation of the extracellular-signal-regulated kinase (ERK) pathway blocks the pro-apoptotic effect of gp120 (Mocchetti and Bachis, 2004). Conversely, BDNF does not prevent gp120 toxicity in neurons that do not express TrkB (Ahmed et al., 2008). One of the

key mechanisms that may explain the neuroprotective effect of BDNF is its ability to down-regulate CXCR4. This receptor is abundant in neurons and areas of the CNS that also express TrkB, such as the cortex, hippocampus and striatum (Ahmed et al., 2008). CXCR4 is a G-protein coupled receptor that can be desensitized by tyrosine kinase intracellular signal crosstalk similar to that induced by TrkB (Daub et al., 1996). Evidence that neuronal CXCR4 is a BDNF target is overwhelming. Indeed, *in vitro* and *in vivo* data have shown that BDNF decreases the expression of CXCR4 (Bachis et al., 2003; Nosheny et al., 2007). Conversely, BDNF heterozygous animals exhibit increased levels of CXCR4 mRNA in the cortex, hippocampus and striatum when compared to wild type controls (Ahmed et al., 2008). Moreover, in BDNF heterozygous mice, increased CXCR4 correlates with a more robust neurotoxic effect of gp120 (Nosheny et al., 2004). Thus, from a pharmacological point of view, BDNF is particularly important as a neuroprotective compound against HIV or gp120 neurotoxicity that occurs through CXCR4 receptors.

BDNF and the immune system

There are other effects of BDNF that can be beneficial for HIV positive subjects. For instance, in the immune system BDNF decreases apoptosis of T cells (Maroder et al., 1996; De Santi et al., 2009). These cells are depleted in AIDS. Thus, one may envision the use of BDNF in conjunction with combination antiretroviral therapy (cART) to maintain the appropriate number of immune cells and to delay AIDS. However, this effect also has a broader implication for the CNS function. In fact, progressive neurological deficits occur after the onset of severe immunodeficiency. Thus, keeping healthy immune cells will reduce “inflammation” of the immune system that can amplify nervous system damage via inflammatory cytokines. These may enter the CNS by infected cells or be produced locally by microglia. For example, in a state of chronic inflammation induced in a non-human primate by infection with simian immunodeficiency virus, the brain was positive for peripheral circulating monocytes trafficking from bone marrow (Burdo et al., 2010). This event correlates with the severity of encephalitis. Unusual activation of cytokine and chemokine receptors in the context of HIV infection results in dendritic beading and loss of dendritic spines (Suzumura et al., 2006). These changes are accompanied by failure of long term potentiation (LTP), which might underlie impaired learning and memory. Given the well-known property of BDNF in promoting dendritic branching and spine morphology (Horch and Katz, 2002; Tanaka et al., 2008) which are key for the BDNF-mediated LTP (Figurov et al., 1996), BDNF could be used to prevent atrophy of dendrite branching and memory loss. Of course such treatment will require an early diagnosis of cognitive impairments.

p75NTR: the death receptor?

BDNF can avidly be transported in axons (Conner et al., 1998) and released upon activation of neuronal activity (Marini et al., 1998). When such transport is interrupted, the release diminishes and, consequently, neurons do degenerate as BDNF profoundly affects neuronal homeostasis and the ability of neurons to counteract naturally occurring neuro-inflammatory responses. This hypothesis has been supported in animal models of diseases. For instance, reduced BDNF release/levels have been associated with depression (Duman, 2004) and Huntington’s disease (Zuccato and Cattaneo, 2009). 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. A reduced availability of BDNF in the axonal terminal will culminate in a decreased release of BDNF which will profoundly affect 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). However, transport alone cannot dictate how much BDNF is released. In fact, one way of reducing BDNF release/levels is to affect the processing of BDNF from its precursor pro-BDNF (Fig. 2). Pro-BDNF, like other pro-neurotrophins, is cleaved into mature BDNF in the endoplasmic reticulum by the proconvertase furin (Seidah et al., 1996) or extracellularly by proteases such as plasmin and matrix metalloproteases (Pang et al., 2004). Pro-BDNF, which is found in human brains (Fahnestock et al., 2001) can be stored in synaptic vesicles and released from neurons (Yang et al., 2009). Conversion of pro-BDNF to mature BDNF is an important process for synaptic plasticity. In fact, pro-BDNF can bind with high affinity to p75NTR (Greenberg et al., 2009) and promote neuronal loss (Teng et al., 2005). This issue deserves more attention and further investigation because HAD brains exhibit higher levels of pro-BDNF and lower levels of BDNF than control and non-demented HIV subjects (Bachis et al., 2012). An altered mBDNF/proBDNF ratio in HAND could compromise synaptic connections and neuronal survival (Fig. 2). This scenario suggests that the neurotoxic effects of HIV may encompass a reduction of the neurotrophic factor environment. Understanding how HIV inhibits the availability of BDNF and other neurotrophic factors is crucial for the development of new therapies.

Therapeutic use of neurotrophic factors

Gene delivery

Neurotrophic factors are large hydrophilic molecules that do not cross the blood brain barrier. Therefore, these molecules need to be delivered to the CNS, which requires surgery and chronic instrumentations and therefore lowers the enthusiasm for clinical application. In addition, when infused into the ventricular system, growth factors have limited diffusion. In recent years new techniques to increase trophic factors into the human brain have been developed. One promising although still under experimentation is the delivery of viral vectors including adeno-associated viral vectors (AAV) (Nagahara and Tuszynski, 2011). Using appropriate promoters, these vectors permit stable, long term expression of transgene in brain neurons after a single injection with little or no discernible toxicity. One major advantage of this system is that it is reliant on neurotrophic factors that are endogenously synthesized, modified and released for a long period of time without causing any known neuropathology. For instance, the recombinant AAV serotype 2 vector expressing BDNF in the rat SN has been shown to reduce 6-hydroxydopamine induced degeneration of nigral DA neurons for up to nine months (Klein et al., 1999). The same vector injected into the striatum has been shown to reduce the neurotoxic effect of gp120 on DA neurons (Nosheny et al., 2007). Similarly, gene delivery of GDNF or Neurturin has been used successfully to reduce the degeneration of DA in rats (Gasmi et al., 2007) and non-human primates (Kordower et al., 2000).

Although promising, gene delivery in humans has been limited to few cases. There could be several reasons why the clinical application of gene delivery has not yet been widely used. For instance, some patients have suffered from intracranial hemorrhage (Christine et al., 2009). Another concern is that an abnormal overproduction of BDNF and other neurotrophic factors may cause side effects that may be intolerable over a long period of time. Such effects may be seen locally (fiber spouting around the site of BDNF production) or systemically such as weight loss (Cao et al., 2009). Clinical trials of gene delivery of AAV-neurturin to the SN of PD patients (Bartus et al., 2013) or to the striatum of non-human primates (Bartus et al., 2011) have shown no adverse effects of this growth factor even after several months. On the other hand, abnormal growing of cells has also observed in PD patients with AAV-neurturin (Marks et al., 2010). Thus, additional experimental “strategies” must be examined and tested.

Pharmacological regulation of neurotrophic factors

Ongoing research has demonstrated safer and more reliable methods to increase endogenous BDNF and other trophic factors to consequently influence neuronal survival. This could replace the need for delivering neurotrophic factors by invasive approaches. For instance, physical exercise has been reported to increase BDNF levels in the hippocampus (Cotman and Berchtold, 2002) which, in turn, promotes hippocampus-based learning, synaptic plasticity and neurogenesis (Vaynman et al., 2004). Antidepressant drugs, which are safely used in humans, also increase BDNF synthesis (Nibuya et al., 1996; Hashimoto et al., 2002).

There are also compounds that promote the endogenous release of the neurotrophins. Such compounds are gangliosides. Gangliosides are endogenous compounds that are classified as acidic glycosphingolipids because they contain sialic acid linked to an oligoglycosyl backbone attached to a ceramide base (Ledeen and Yu, 1982). Gangliosides are lypophilic and cross the blood brain barrier. Different laboratories have independently shown that GM1, the prototype of ganglioside, activates tyrosine phosphorylation of Trks (Ferrari et al., 1995; Mutoh et al., 1995; Rabin and Mocchetti, 1995) via the release of the neurotrophins (Rabin et al., 2002). Intriguingly, LIGA20, a semisynthetic derivative of GM1, has been shown to prevent gp210 neurotoxicity *in vitro* (Bachis and Mocchetti, 2006). These experimental data encourage further research into the use of small molecules to promote trophic activity. This is not important only for HAD but also for other neurological disorders. Thus, there are alternatives to minimize the use of chronic instrumentation.

Small molecules

Neurotrophic factors activate selectively different class of receptors. For instance, the site of BDNF binding has been located to the fifth extracellular domain of the Trk receptor, with this region regulating both the affinity and specificity of TrkB for BDNF (142, 143). Thus, it is possible to design a small peptide that crosses the blood brain barrier and binds specifically to the binding site and activate a given neurotrophic factor receptor. This strategy would mimic the activity of endogenous neurotrophic factors without the limitation of delivering them through invasive methods. In the last decade a number of attempts have been made to synthetize small ligands. A small peptide (16 aminoacids) identified form the TrkB crystal structure and containing the SRRGE motif crucial for binding to TrkB has been shown to mimic most of the neurotrophic activity of BDNF *in vitro* (Williams et al., 2005). More recently, a non-peptidergic compound derived from the loop II region of BDNF has shown to activate TrkB *in vitro* and *in vivo* (Massa et al., 2010). Thus, there are encouraging data that allow suggesting using small molecules to restore neurotrophic activity. It remains to be established whether small molecules could be administered chronically without side effects.

CONCLUSIONS

The dividing line between viral and host-mediated neurotoxicity in HIV infection is neither precise nor rigid. An effective therapy aimed at treating HIV-induced CNS diseases will require both cART and adjunctive therapies that include neuroprotective and neuro-regenerative agents. Besides their traditional role as molecules promoting survival and regeneration, neurotrophic factors are seen as potent mediators of synaptic plasticity and neurogenesis in the adult CNS. These effects could play a role in limiting AIDS-mediated neuronal degeneration and stimulating neuronal function. Although still tested only in animal models of HAD, the powerful properties of neurotrophic factors provide incentive for further research and raise hope for the therapeutic possibilities in the near future.

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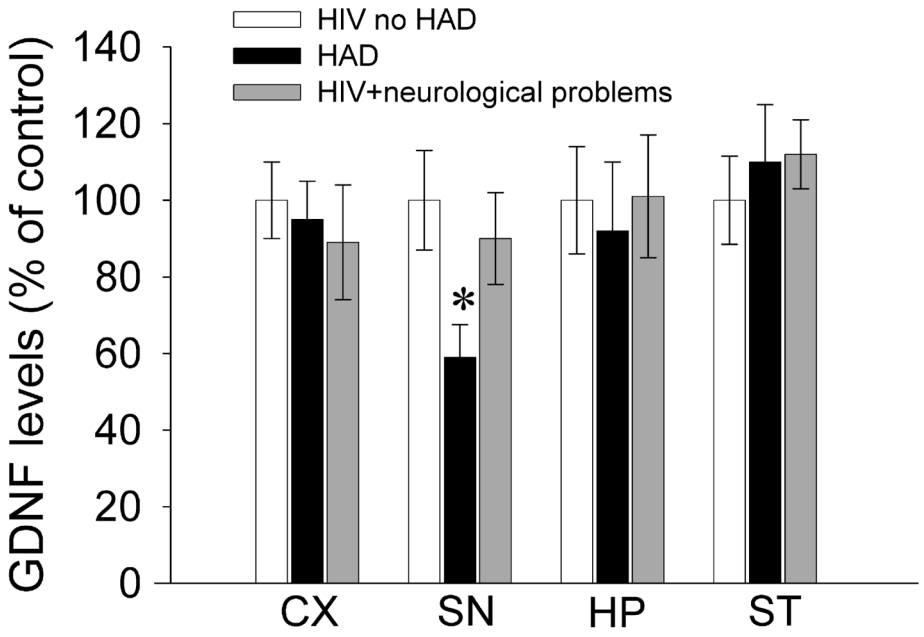

Figure 1. GDNF levels are decreased in the brain of HAD subjects

GDNF levels were measured by ELISA in human cerebral cortex (CX), substantia nigra (SN), hippocampus (HP), and striatum (ST). Brain tissues of either sex were obtained from the National NeuroAIDS Tissue Consortium (NNTC). Samples were from: HIV negative subjects (control, n=4), HIV^+ with normal neurocognitive diagnosis (HIV no HAD, n=7), HIV^+ subjects with HAD (n=8), and HIV^+ with neurological problems, caused by opportunistic infections, such as cytomegalovirus (HIV + neurological problems, n=7). Data are the mean ± SEM. More details about these subjects are given in Bachis et al., 2012. *$p<0.01$ vs HIV negative subjects (one-way ANOVA and Sheffe's test).

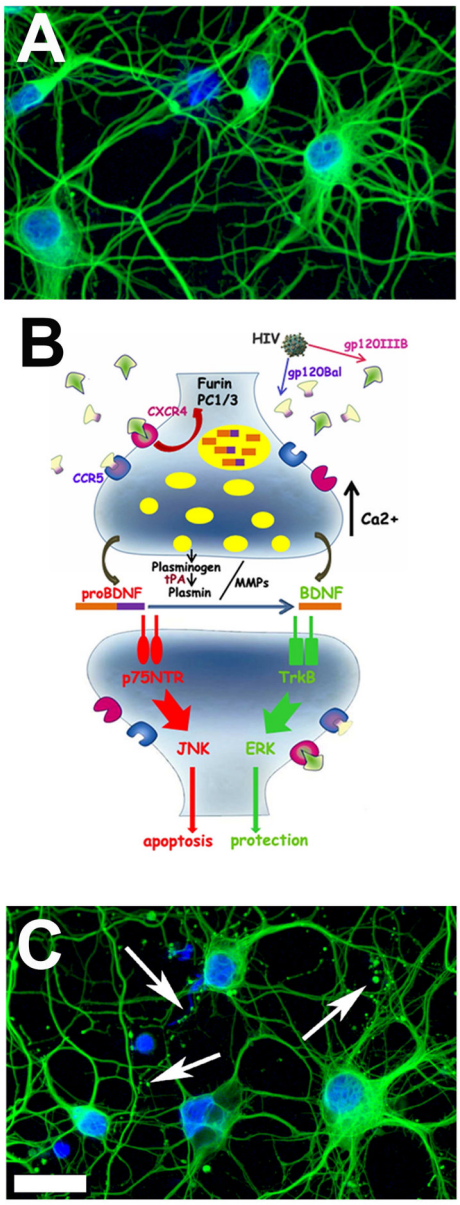

Figure 2. Neurotrophic factors hypothesis of HIV neurotoxicity

HIV, through gp120 binding to chemokine receptors, reduces neurotrophic factor levels. Many mechanisms can account for this effect. The example described in this figure pertains to BDNF. (**A**) Rat cortical neurons without HIV are healthy and exhibit numerous processes. (**B**) HIV, through gp120, decreases the processing of mature BDNF from pro-BDNF. This phenomenon would result in less BDNF and more pro-BDNF available to neurons whose axons degenerate through a p75NTR-mediated mechanism. (**C**) Examples of HIV-mediated degeneration showing synaptodendritic damage (arrows) of cortical neurons. Green=class III β– tubulin; Blue=DAPI. Bar = 20 μm.

Table 1

Neurotrophic activity of trophic factors in animal models of neurological diseases

Neurotrophic factors trials	Target neurons	Animal models	Clinical
BDNF, GDNF, CNTF	Motor neurons	ALS	BDNF
NGF, BDNF, FGF2	Basal forebrain Cholinergic, hippocampal and cortical neurons	AD	NGF, BDNF
BDNF, GDNF/Neurturin, FGF2	Dopaminergic neurons	PD	GDNF, BDNF
BDNF, NT-4, FGF2	Striatal neurons	Huntington's disease	
BDNF, NT-3, FGFs	Descending motor pathways	spinal cord injury	
BDNF, FGFs, PDGF	striatal, nigral, cortical,	HAND	

The activity of neurotrophic factors described here refers to prevention of cell death *in vivo*. Clinical trials of BDNF in ALS have shown modest or no effect. References are given in text.