HIV-Associated Neurocognitive Disorder: Pathogenesis and Therapeutic Opportunities

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Abstract Human immunodeficiency virus type 1 (HIV) infection presently affects more than 40 million people worldwide, and is associated with central nervous system (CNS) disruption in at least 30% of infected individuals. The use of highly active antiretroviral therapy has lessened the incidence, but not the prevalence of mild impairment of higher cognitive and cortical functions (HIV-associated neurocognitive disorders) as well as substantially reduced a more severe form dementia (HIV-associated dementia). Furthermore, improving neurological outcomes will require novel, adjunctive therapies that are targeted towards mechanisms of HIV-induced neurodegeneration. Identifying such molecular and pharmacological targets requires an understanding of the events preceding irreversible neuronal damage in the CNS, such as actions of neurotoxins (HIV proteins and cellular factors), disruption of ion channel properties, synaptic damage, and loss of adult neurogenesis. By considering the specific mechanisms and consequences of HIV neuropathogenesis, unified approaches for neuroprotection will likely emerge using a tailored, combined, and non-invasive approach.

Keywords HIV · HIV-associated neurocognitive disorder · intranasal delivery · chemokines · oxidative stress · excitotoxicity · adult neurogenesis · synaptic signaling · cell cycle

Introduction

Over 40 million people worldwide are infected by human immunodeficiency virus-1 (HIV) (UNAIDS/WHO), and, while HIV is most well known for its devastating effects on the immune system and the resulting acquired immunodeficiency syndrome (AIDS), it can also cause several neurological disorders, collectively known as HIV-associated neurocognitive disorders (HAND). HAND syndromes (minor cognitive motor disorder, HIV-associated mild neurocognitive disorder, and asymptomatic neurocognitive impairment) are characterized by cognitive, motor, and behavioral abnormalities (Kaul et al. 2005) and are classified according to patient performance in areas of neurological and behavioral functioning and neuropsychological testing (Sacktor et al. 2001; Sacktor 2002; McArthur 2004; Antinori et al. 2007). Prior to the widespread use of highly active antiretroviral therapy (HAART), 20–30% of individuals with advanced HIV infection displayed symptoms of the most severe HAND disorder, HIV-associated dementia (HAD; Gonzalez-Scarano and Martin-Garcia 2005; Kaul et al. 2005). Since the widespread use of HAART, the incidence of HAD has dramatically decreased; however, as many as 40% of HIV-positive patients continue to suffer from HAND (Sacktor et al. 2001; Sacktor 2002; McArthur 2004; Antinori et al. 2007). Furthermore, although the incidence of HAD has decreased, its prevalence is actually increasing, due in part to the longer life expectancy for individuals with HIV and...
to patient resistance to HAART drugs (Gonzalez-Scarano and Martin-Garcia 2005). The persistently high prevalence of milder forms of HAND (Sacktor et al. 2004) suggests a shift in the relative distribution of HAND subtypes in the post-HAART era. In patients presenting with even the milder forms of HAND, quality of life is greatly affected, with these individuals suffering from disruptions in ability to perform activities of daily living, perhaps most importantly, that of adherence to the HAART regimen (MacArthur 2004).

HAD manifests as a subcortical dementia characterized by psychomotor slowing, changes in mood and anxiety levels and deficits in memory, abstraction, information processing, verbal fluency, decision-making, and attention (Niaia et al. 1986; Grant et al. 1987; Price et al. 1988; Portegies et al. 1993). Surprisingly, deficits in olfaction are established olfactory tests (Graham et al. 1995; Razani et al. 1996; Westervelt et al. 1997; Hornung et al. 1998; Mueller et al. 2002; Zucoco and Ingegneri 2004; Vance 2007). As this collection of symptoms would suggest, the brain regions most commonly damaged in HAD are the basal ganglia, deep white matter, hippocampus, and cerebral cortex (Gorry et al. 2003). Pathological features of HAD include pervasive reactive astrocytosis, myelin pallor, activated resident microglia, infiltration by circulating mononuclear cells, perivascular inflammation, microglial nodules, multinucleated giant cells, dendritic simplification, and cell death, both astrocytic and neuronal (Gorry et al. 2003; Kaul et al. 2005). Interestingly, rather than closely correlating with viral load in the central nervous system (CNS), clinical signs of HAD more closely associated with increased numbers of microglia, evidence of excitotoxins, and selective neuronal damage and loss (Kaul et al. 2005). These findings suggest that, although HIV invasion into the brain may be a necessary initial step in HAD progression, other mechanisms more directly lead to the functional losses associated with this disease.

HIV infection in the central nervous system

HIV primarily infects cells of the immune system, and untreated infection ultimately results in AIDS and eventually death in the vast majority of cases. Approximately 2–3 weeks after the primary infection, a patient with HIV infection enters the acute stage of infection, which presents most commonly as fever, skin rash, oral ulcers, and lymphadenopathy (Pope and Haase 2003). HIV specifically infects and kills CD4+ T cells, monocytes, and macrophages, and at this early stage of infection, the virus establishes a reservoir within the lymphoid tissue and enters into the CNS. In lymphoid tissue, productively infected, activated CD4+ T cells produce and release billions of virions daily, accounting for the systemic viral load (VL) detected by patient plasma sampling. Within the CNS the virus establishes its reservoir within the perivascular and perhaps the parenchymal macrophage populations (Morris et al. 1999). Virus detected through sampling cerebrospinal fluid (CSF) likely reflects contributions from both the systemic and CNS reservoirs, with the CNS reservoir contributing more to CSF VL in advanced infection (Ellis et al. 2000; Ritola et al. 2005).

Neuropathogenesis of HAND: overview

While neuronal cell damage and death are clearly associated with the development of HAD/HAND symptoms, HIV rarely, if ever, infects neurons themselves (McArthur et al. 2003; Gonzalez-Scarano and Martin-Garcia 2005; Kaul et al. 2005). Rather, productive HIV infection in the brain occurs in cells of the macrophage lineage, including monocyte-derived perivascular macrophages and microglia (Gorry et al. 2003; Kaul et al. 2005). According to the most widely accepted model, HIV invades the brain through a “Trojan Horse” method (Liu et al. 2002), crossing the blood–brain barrier (BBB) through infected monocytes that later differentiate into macrophages (Albright et al. 2003). This can occur within 1–2 weeks after virus enters into the systemic circulation (Davis et al. 1992; Gray et al. 1993). Subsequent infection and activation of neighboring cells occurs via direct contact with infected cells (Gonzalez-Scarano and Martin-Garcia 2005). Cells directly contacted by infected ‘Trojan horse’ cells include perivascular macrophages, astrocytes, and microglia (Williams and Hickey 2002; Gonzalez-Scarano and Martin-Garcia 2005). Importantly, while astrocytes do appear susceptible to HIV infection, they do not develop productive infection, and thus, perivascular macrophages and microglia are the only resident CNS cells capable of increasing HIV infection in the brain (Gorry et al. 2003; Gonzalez-Scarano and Martin-Garcia 2005).

Considering that HAND symptoms are closely associated with neuronal damage and loss, and the observation that HIV is unable to infect neurons, mechanisms other than direct infection must mediate the neuropathogenesis of HIV infection. Currently, two major models account for neurodegeneration and development of neurological symptoms in HAND: the direct model and the indirect model. Each of these models requires the initial productive infection of perivascular macrophages and microglia. The direct model proposes that viral proteins released from infected monocyte-derived cells cause neuronal death through direct interaction of viral proteins with neurons (Gonzalez-Scarano and Martin-Garcia 2005; Kaul et al. 2005). The
indirect, or ‘bystander,’ model proposes that neuronal death is mediated by the inflammatory response mounted by infected and uninfected non-neuronal cells against HIV infection and against HIV proteins released by directly infected cells (Gonzalez-Scarano and Martin-Garcia 2005; Kaul et al. 2005). Clearly, these two models are not mutually exclusive.

The indirect model of neurodegeneration in HAND centers upon soluble factors released by non-neuronal cells as part of an inflammatory response to viral particles. When activated through direct HIV infection or through exposure to viral particles, macrophages and microglia release numerous soluble molecules, including the viral proteins, gp120, Tat, and Vpr (only released from infected cells), quinolinic and arachidonic acids, nitric oxide (NO), platelet activating factor, superoxide anions, matrix metalloproteases, chemokines, growth factors, and proinflammatory cytokines, including tumor-necrosis factor (TNF; Albright et al. 2003; Gonzalez-Scarano and Martin-Garcia 2005). While some of these molecules, such as growth factors (i.e., brain-derived neurotrophic factor) and some β-chemokines (i.e. regulated upon activation-normal T-cell expressed and secreted (RANTES)), are believed to play a neuroprotective role, a number of the other non-viral factors have proven to be neurotoxic (Kaul and Lipton 1999; Klein et al. 1999; Gonzalez-Scarano and Martin-Garcia 2005; Kaul et al. 2005). Additionally, NO and TNF impair the neuroprotective functions of astrocytes, including maintenance of the BBB and glutamate reuptake, while also increasing rates of astrocytic apoptosis (Gorry et al. 2003; Gonzalez-Scarano and Martin-Garcia 2005). The concomitant release of excessive excitatory amino acids and other N-methyl-D-aspartate glutamate receptor (NMDAR) agonists, and a reduction in glutamate reuptake can create an excitotoxic environment that results in excessive activation of NMDAR. Consequently, intraneuronal Ca\(^{2+}\) concentrations reach toxic levels, which results in production of free radicals (including reactive oxygen species (ROS) and NO) and in neuronal death (Gonzalez-Scarano and Martin-Garcia 2005; Kaul et al. 2005). Oxidative processes and the resulting stresses are capable of inducing cell death, even in the absence of viral infection, as suggested by the role of oxidative stress in a number of other neurodegenerative diseases (Mariani et al. 2005).

**Neuropathogenesis of HAND: mechanisms of inflammation-induced neuronal insults**

Both past and recent studies have provided a compelling argument for a role for inflammation in triggering events leading to neurodegeneration in HIV infection. Pulliam et al. (1997) first demonstrated that individuals with HAD express higher levels of circulating activated CD14+ monocytes that co-expressed CD69 than non-HAD individuals, and hypothesized that these activated monocytes enter the brain and subsequently initiate neurotoxin production. Ryan et al. (2001) subsequently confirmed an association between plasma soluble CD14 (sCD14) and cognitive dysfunction in HIV infection. More recently, Ancuta et al. (2008) showed that elevated sCD14 and lipopolysaccharide (LPS) levels are associated with HAD. These observations support an independent study which demonstrated that elevated systemic LPS levels and immune activation in chronic HIV infection resulting from microbial translocation are associated with HIV-induced depletion of gut-associated lymphoid tissue (Brenchley et al. 2006). These studies clearly support the hypothesis that systemic immune activation/inflammation triggered by HIV-induced transmicrobial translocation and monocyte activation increases the risk for development of HAND through trafficking of activated monocytes into the CNS.

The association between the abundance of activated macrophages/microglia in the CNS, neuronal damage, and cognitive dysfunction suggests that neuroinflammation resulting from systemic immune activation and/or inflammation triggers the neurodegeneration observed in HAND (Glass et al. 1995). Numerous in vitro and in vivo studies link HIV-induced inflammation-associated neurodegeneration with macrophage proinflammatory cytokine/chemokine production, excitotoxic neuronal injury, and oxidative stress (Kaul et al. 2001; Gonzalez-Scarano and Martin-Garcia). We will discuss each below.

a) **Chemokine/cytokine effects.** In response to HIV invasion of the CNS, microglia and macrophages within the brain mount an immune response that includes the release of both α- and β-chemokines. Since neurons express chemokine receptors (Horuk et al. 1997; Lavi et al. 1997; Rottman et al. 1997; Miller and Meucci 1999; Coughlan et al. 2000; Meucci et al. 2000), this HIV-induced inflammatory response may play a critical role in the effects of HIV infection on the CNS. Studies have found elevated levels of the α-chemokines, CXCL10/P-1o and CXCL12/SDF-1α, in the brains and CSF of HAD patients (Rostasy et al. 2003; Cinque et al. 2005). α-chemokines, which are expressed in many types of CNS cells even under normal conditions, bind CXCR chemokine receptors, thereby signaling a G\(_i\) protein-dependent increase in intracellular calcium. α-chemokines can have both neuroprotective and neurotoxic effects (Kaul and Lipton 1999; Zheng et al. 1999; Khan et al. 2008). Specifically, depending on conditions, CXCL12 can act to either enhance synaptic transmission or to activate caspase-3. When cleaved by matrix metalloproteinases, CXCL12 changes its
receptor specificity from CXCR4 to CXCR3, which enhances the neurotoxic functions of this chemokine (Kaul and Lipton 1999; Zheng et al. 1999; Zhang et al. 2003; Vergote et al. 2006). Similarly, CXCL10, which acts through CXCR3 without prior proteolytic cleavage, induces increase in intracellular calcium and activation of caspase-3 upon binding to its receptor (Sui et al. 2004, 2006).

In contrast to α-chemokines, β-chemokines are only expressed at relatively low levels in the brain under normal conditions. However, several β-chemokines are found at increased concentrations in the CNS following HIV infection: CCL2, MIP-1α, MIP-1β, and RANTES/CCL5 (Kelder et al. 1998). β-chemokines act through CCR receptors, and, as with α-chemokines, they are capable of both neuroprotective and neurotoxic functions in the brain (Schmidt Mayerova et al. 1996). CCL5, MIP-1α, and MIP-1β all provide protection against gp120-induced neurotoxicity in vitro (Meucci et al. 1998; Kaul and Lipton 1999). Contrarily, CCL2 is associated with an increased risk of HAND, which may be due to the role of this chemokine in the brain as a monocyte chemoattractant. Furthermore, microglia activated by interferons and astrocytes activated by IL-1β and TNF-α express CCL2, which could also contribute to the positive correlation between CCL2 levels and increased risk of HAND (Kelder et al. 1998; Sevigny et al. 2004, 2007; Ragin et al. 2006). Thus, β-chemokines may contribute to neuronal toxicity via existing pathways that are overstimulated by higher than normal concentrations of these factors.

In addition to α- and β-chemokines, elevated levels of the unique chemokine, fractalkine/CX3CL1, have also been observed in the CSF of HAND patients (Pereira et al. 2001). CX3CL1, a member of the CX3C family of chemokines, binds to endothelial cells and mediates monocyte attachment, potentially increasing monocyte migration across the blood–brain barrier and into the CNS, further increasing inflammation in the brains of patients with HIV infection (Ancuta et al. 2003; Geissmann et al. 2003; Maslin et al. 2005). However, as with α- and β-chemokines, CX3CL1 appears to have both positive and negative effects in the brain and, specifically, has been shown to provide a degree of protection against neurotoxicity (Mizuno et al. 2003; Deiva et al. 2004; Limatola et al. 2005). Thus, a delicate balance of neuroprotective and neurotoxic roles of the major players in this response likely determine the effect on neurons of an HIV-induced inflammatory response in the CNS. However, it seems that much of the protective function of chemokines is a counteraction to the negative effects of inflammation, such as toxicity induced by increased intracellular calcium, and that it may, therefore, be beneficial to treat HIV patients with drugs that protect the brain from HIV-induced inflammation.

b) Excitotoxicity. Excitotoxicity is the process by which excess levels of an excitatory neurotransmitter or other agent evokes prolonged periods of neuronal membrane depolarization, thereby increasing calcium (Ca2+) levels, and consequently activating proteases, endonucleases, and other enzymes which damage cellular components. The most common form of excitotoxicity in the CNS is glutamate excitotoxicity, which is mediated by the NMDAR, a voltage and ligand-gated calcium ion channel that generates excitatory postsynaptic currents through calcium influx into the neuron. The subunit composition of NMDAR varies throughout neuronal development, and, to some degree, within different brain regions (Lynch and Guttmann 2001, 2002). Thus, different brain regions can respond differently to excess glutamate and other NMDAR agonists, possibly accounting for region specific damage in diseases in which excitotoxicity plays a role, such as HAND.

Glutamate, the major excitatory neurotransmitter in the CNS, must be maintained at physiological levels within the synapse to prevent sustained, toxic calcium influx (Rothman 1984; Hyre et al. 1997). In the HIV-infected brain, activated and infected macrophages release excitotoxic molecules that act upon the NMDAR, including released glutamate, QUIN, and the neurotoxic amine, N-Tox, and therefore, may evoke damaging periods of NMDAR activation (Giulian et al. 1990; Jiang et al. 2001; O’Donnell et al. 2006). Furthermore, activated macrophages release factors that act in a paracrine fashion to stimulate reactive CNS cells, most importantly the astrocytes and microglia. Astrocytes, in particular, play a critical role in the regulation of extracellular glutamate concentrations within the brain (Gegelashvili and Schousboe 1997; Kanai 1997; Vandenberg 1998), and when activated this normal maintenance function is altered. Therefore, altered glutamate release and uptake is thought to be a major pathway of neurodegeneration in inflammatory brain diseases such as HIV infection (Kaul et al. 2001). Notably, Ferrarese et al. (2001) reported that glutamate is elevated in the CSF of HIV-infected individuals, further supporting a role for glutamate-mediated excitotoxicity in the pathogenesis of HAND.

Although inward NMDAR-dependent currents evoked by glutamate derived from astrocytes and infected macrophages/microglia are the most commonly cited contributor to excitotoxic death in neurons of patients with HAND, other ionic currents may also play a role in excitotoxicity and neuronal dysfunction. Outwardly rectifying currents shape the action potential, interspike interval, and after
hyperpolarization, and act to determine overall membrane excitability. Prolonged exposure to glutamate evokes NMDAR-mediated excitotoxicity, but it is not fully understood how outwardly rectifying channels are modulated in response to such stimuli. Compensatory mechanisms are likely initiated in order to attempt to restore and maintain the resting membrane potential. These changes in ion channel biophysics are ultimately damaging to the neuron in the long-term because equilibrium likely favors a more depolarized voltage, thus depleting energy stores and maintaining continual activation of ion channels and calcium-dependent enzymes.

Any changes in ion channel properties, as well as membrane excitability, ultimately affect the manner in which a neuron operates and processes incoming synaptic signals. With respect to ion channels, there are several ways that HIV-related molecules can alter biophysical properties. Channel mean open probability, open duration, unitary conductance, or channel inactivation and deactivation all can be affected by various factors released by HIV-infected and/or HIV-activated immune cells in the CNS. TNF-α evokes an increase in A-type K⁺ currents in cultured embryonic rat cerebral cortex neurons (Houzen et al. 1997), and immune-activated macrophage-conditioned medium also increases transient A-type (Iₐ) as well as delayed rectifier (Iₖ) K⁺ current in cultured rat hippocampal neurons (Hu et al. 2009). Glutamate produces a Ca²⁺-dependent dephosphorylation of Kv2.1 channels, which disrupts channel clusters and increases mean open channel probability and conductance (Murakoshi et al. 1997; Misonou et al. 2004). Further support for Kv channelopathy in HAD is observed in gene expression profiling studies demonstrating a markedly decreased expression of two voltage-dependent K⁺ channels, which could likely cause substantially decreased Kv currents (Gelman et al. 2004). Kv channels can regulate back-propagating action potentials by influencing the postsynaptic NMDAR voltage-dependent Mg²⁺ blockade, thereby decreasing overall membrane excitability (Paulsen and Sejnowski 2000; Johnston et al. 2003; Birnbaum et al. 2004). Hence, modulation of Kv channels by some of these compounds could significantly affect NMDAR activation, membrane excitability, and action potential propagation. Given the numerous mechanisms by which HIV infection in the brain can induce excitotoxicity, from increases in extracellular glutamate to alterations of the channels that mediate the electrochemical functioning of neurons, therapeutics directed against this particular etiology of HAND are promising candidates for treatment.

c) **Oxidative stress.** In addition to inflammation and excitotoxicity, much evidence supports a significant role for oxidative stress in the pathogenesis of HAND. In fact, oxidative stress is a well-characterized downstream effect of both inflammation and excitotoxicity. Changes in cellular lipid metabolism that occur as a result of oxidative stress, produce characteristic molecules, such as ceramide, sphingomyelin, and hydroxyoneal, all of which are found in individuals displaying HAND (Kaul et al. 2005; Sacktor et al. 2004). Additionally, oxidized proteins were detected in the CSF of patients with HAND, further supporting a role for oxidative stress in the development of this disease (Turshan et al. 2003). Treating rat cortical neuroglial cultures with gp120 results in glial production of ROS and neuronal death, both of which are blocked when the cultures are pre-treated with an antioxidant (Wakabayashi et al. 2003). HIV-proteins may directly increase oxidative stress to neurons by inducing mitochondrial dysfunction and through interactions with membrane or cytosolic bound proteins. This finding implicates oxidative stress as an important mode of neuronal death in the indirect model of HAND neurodegeneration. Additional studies have demonstrated neuroprotective capabilities of antioxidants in vitro (Turshan et al. 2003), and therapeutic properties of antioxidants in vivo in HIV patients, showing both inhibition of mental deterioration and improvement of general health (Shor-Posner et al. 2002). These findings demonstrate a significant pathogenic role for oxidative stress in HAND, and suggest that the endogenous cellular antioxidant response may serve as a potential therapeutic target in this disease.

**Neuropathogenesis of HAND: consequences of chronic neuroinflammation**

The pathways of neuronal damage described above are often considered the "classical" or "central" pathophysiology of HAD. However, new and often neglected studies have highlighted other consequences of neuroinflammation in HIV-infected and HAD individuals, that when observed in the light of physiological mechanism, become increasingly important in the study of disease progression.

a) **Synaptic disruption.** In addition to neuronal death, HAND is associated with neuronal damage, particularly synaptic disruption. The etiologies described in this review, specifically inflammation and excitotoxicity, provide mechanisms by which this HIV-associated synaptic damage may occur. Activation of calcium-dependent proteases that disrupt the postsynaptic density (PSD) is a likely mechanism by which synapses may be altered in the HIV-infected CNS. The smooth ER, which extends into the dendritic spine, contains IP₃ receptors that are tethered to mGluR and NMDARs by...
a complex of adaptor proteins, including Shank, GCAP, Homer, and PSD-95 (Tu et al. 1999; Sheng and Kim 2000; Sheng and Sala 2001; Sheng and Hoogenraad 2007). Secondary IP3-mediated calcium influxes are thought to play a role in LTP, however, prolonged synaptic depolarization and IP3-mediated signaling can also activate calpain proteases that can cleave PSD-95 which releases it from NMDAR (Lu et al. 2000). This could cause a large-scale decoupling of the postsynaptic complex from IP3 receptors. Interestingly, PSD-95 loss is also a hallmark sign of neurodegeneration (Gardoni 2008; Gardoni et al. 2009); hence, uncoupling or disruption of the PSD may be an important step in synaptic dysfunction and damage. Thus, inhibition of IP3-mediated calcium currents may prevent calpain or other protease activation, as well as block kinase enzymes from phosphorylating and modulating Kv channels. A summary of synaptic/cellular neurotoxic pathways and synaptic damage is presented in Figs. 1 and 2 to recapitulate the major findings discussed in this section and to illustrate the complexity of the pathological mechanisms evoked by CNS HIV infection.

b) Impairment of neurogenesis. The dogma of a fixed and static CNS has been replaced by an understanding of the brain as a plastic, complex, and highly dynamic environment where new neurons are continually generated in adult animals through the process of adult neurogenesis (ANG). ANG is not confined to rodents, as recent work has demonstrated the occurrence of ANG in humans and other primates (Eriksson et al. 1998; Gage 2000; Pencea et al. 2001; Kam et al. 2009). In fact, recent studies have demonstrated that disruption of ANG is significantly involved in HAND and other neurodegenerative diseases (ND; Haughey et al. 2002; Donovan et al. 2006; Kelleher-Andersson 2006; Chen et al. 2008; Galvan and Bredesen 2007; Zhang et al. 2007; Rodriguez et al. 2008; Taupin 2009). Furthermore, substantial evidence demonstrates that ANG is involved in learning and memory, olfaction, and anxiety-related behaviors (Revest et al. 2009), all of which are functions that are disrupted in HAD and ND.

The two regions of the brain that contain the highest amount of newborn neurons are the hippocampus and the OB (Altman and Das 1965; Altman 1969; Lois and Alvarez-Buylla 1993; Lois and Alvarez-Buylla 1994; Eriksson et al. 1998; Gage 2000). Neural progenitor cells (NPCs) arise in the subventricular zone (SVZ) or the dentate subgranular zone (SGZ). SVZ NPCs migrate laterally and superiorly eventually terminating in the subependymal zone of the OB and SGZ NPCs migrate superiorly into the dentate gyrus of the hippocampus. After reaching their target destination,
NPCs then begin to integrate into existing circuits, often forming inhibitory interneurons (Xiong et al. 2008). NPCs migrate from the SVZ to the olfactory bulb via the rostral migratory stream, which is lined with glial cells which provide trophic support to the migrating NPCs. As NPCs get closer to their destination, they begin to differentiate, and form immature neurons. Immature neurons then begin to synaptically integrate with already existing mature neurons.

HIV infection induces several processes by which ANG could be interrupted. HIV-induced alteration of general astrocyte function, including the trophic support these cells provide for both mature and immature neurons, may impair the proliferation and migration of NPCs and immature neurons along their migratory route (Fig. 3). Under this hypothesis, the OB, which is the most distant structure along the RMS, would be affected first in the earliest stages of the disease, which in fact is the case in most ND where olfaction is perturbed, such as HAND (Graham et al. 1995; Razani et al. 1996; Westervelt et al. 1997; Hornung et al. 1998; Mueller et al. 2002; Zucco and Ingegneri 2004; Vance 2007). Not surprisingly, cell cycle machinery play a role in regulating the fate of NPC (Herrup and Yang 2007). Interestingly, cell cycle proteins, such as the transcription factor, E2F1, and its regulator, the retinoblastoma gene product, exhibit increased levels and altered expression patterns in Alzheimer’s Disease (AD), PD, and HAND postmortem tissue (Jordan-Sciutto et al. 2002a, b; Hoglinger et al. 2007). Consistent with a role for these proteins in altered neurogenesis (Lee et al. 1992), mice carrying a gene-targeted deletion of E2F1 display substantially reduced ANG in the OB and hippocampus (Cooper-Kuhn et al. 2002). Furthermore, doublecortin (DCX), a microtubule protein expressed in immature neurons (Takacs et al. 2007), has several promoter sites that are regulated by cell cycle proteins, including the E2F consensus site (Karl et al. 2005). Thus, altered E2F1 function and a consequent disruption of DCX in HAND may cause an interruption in ANG, thereby contributing to the pathogenesis of these HIV-associated disorders. The CNS relies heavily on plasticity, hence, the disruption of ANG and its molecular regulation could yield devastating consequences for circuits and brain regions assaulted by HIV-induced toxicity.

Another mechanism by which HIV could impair ANG is the perturbation of metabolism and associated insulin signaling pathways. Insulin in the brain enhances working memory, promotes neuronal survival, and regulates reproduction via...
the hypothalamic–pituitary axis (Brüning et al. 2000). This hormone acts as a neuromodulator by affecting synaptic plasticity and neurotransmitter release (Plum et al. 2005). Importantly, several lines of evidence suggest that insulin and insulin-like growth factor (IGF) are very important in ANG. Hippocampal neural progenitor cells express the insulin receptor (IR) and IGF-1 receptors, and insulin and IGF-1 are known to stimulate ANG in the dentate gyrus. ANG, synaptic plasticity and learning potential are significantly compromised in the rodent model of type 1 diabetes (Stranahan et al. 2008; Zhang et al. 2008), suggesting that both endocrine and brain insulin play a substantial role in the generation of new neurons (Kamal et al. 2000). Lang et al. (2009) also show that ANG is severely impaired in the adult type-2 diabetic GK rats, demonstrating that aberrant insulin signaling or insulin resistance can disrupt ANG. IGF-1 also has received considerable attention in recent years as a potential modulator of ANG (Aberg et al. 2000, 2003; Lichtenwalner et al. 2001; Trejo et al. 2004; Anderson et al. 2002; Perez-Martin et al. 2003a, b). In adults, peripheral IGF-1 mediates an exercise-induced enhancement of neurogenesis in the hippocampus (Trejo et al. 2001) and also has a direct proliferative effect on adult hippocampal progenitor cells in culture (Aberg et al. 2003). Intracerebroventricular infusion of IGF-1 also eliminates the modest decrease in ANG that occurs in advanced geriatric animals (Lichtenwalner et al. 2001).

HIV infection alters insulin signaling, glucose homeostasis, lipid distribution, and metabolism in patients with or without HAART therapy (Grinspoon and Bilezikian 1992; Sellmeyer and Grunfeld 1996; Grinspoon et al. 1998; Kotler et al. 1999). Mechanisms of metabolic disruption in HIV-infected patients remain unclear, but it is hypothesized that peripheral chemokine signaling is at least partially involved in the alteration of insulin and glucose homeostasis (Hardy et al. 2001; Carper et al. 2008). In addition, patients on HAART therapy experience more pronounced metabolic disturbance, leading to aberrant lipid distribution (Safrin and Grunfeld 1999). HAART and some medications used to treat behavioral perturbations in HAD are known to cause a prolonged form of insulin resistance (Grinspoon and Bilezikian 1992; Hardy et al. 2001; Hughes et al. 2005; Carper et al. 2008). Some of these medications can bind the insulin receptor kinase domain and inhibit downstream phosphorylation of targets, or reduce voltage-gated K⁺ channels and other anion currents (Neye et al. 2006), which are known to affect glucose sensitivity and insulin response signaling (Xu et al. 2004; Desir 2005; Li et al. 2006; Tscherter et al. 2006). Thus, altered signaling from the IR
could potentially cause a form of insulin resistance, and may be one of the factors by which HAND continues to progress in patients on HAART.

Therapeutics for HAND; current trials and considerations

Recent and past clinical therapeutic trials for the treatment of HAND have focused on drugs as adjucts to current HAART, and although only modest success with adjunctive therapies has been achieved the need for more effective protection against HAND has clearly been recognized (Clifford et al. 2009). In addition more effective utilization of HAART drugs, based upon individual drug CNS penetration and efficacy represents an immediate approach, and more effective delivery of HAART drugs through nanoparticle delivery offers exciting possibilities for future consideration (Dou et al. 2009). Some adjunctive therapies to HAART studied thus far include NMDAR antagonists, calcium channel blockers, antioxidants, and anti-inflammatory drugs that either specifically or non-specifically target suspected key pathways in HIV-induced neuronal injury. Several recent, large-scale trials conducted through the AIDS Clinical Trials Group (ACTG) focus on three of these drugs: minocycline, memantine, and selegiline.

Minocycline: anti-inflammatory

Minocycline is a second-generation tetracycline antibiotic derivative developed in the 1960s, and has become an attractive drug candidate to treat HAND and other neurodegenerative diseases. In addition to the antibiotic properties of this molecule, it also potentially has protective and anti-inflammatory effects in the CNS. Minocycline is able to cross the blood–brain barrier at a substantial rate (Colovic and Caccia 2003), thus allowing delivery at much lower concentrations than other medications. Minocycline has neuroprotective effects in quite a few models of neurodegenerative diseases, as well as in traumatic and ischemic brain injury (Chen et al. 2000; Du et al. 2001; Sanchez Mejia et al. 2001; Arvin et al. 2002; Van Den Bosch et al. 2002; Wu et al. 2002; Metz et al. 2004). Minocycline has the advantages of being inexpensive to produce, readily available in the pharmaceutical market, and safe to administer over a long treatment time course.

The mechanisms by which minocycline could potentially provide protection against HAND are numerous. Minocycline suppresses JNK activation and lowers nitric oxide levels in the brain in SIV models of infection (Follstaedt et al. 2008), and, in parallel with this finding, minocycline suppresses NO-induced activation of p38 and JNK in vitro. Moreover, minocycline can inhibit ASK1 activation and disrupts the cyclical inflammation/virus replication that is often the precursor to the encephalitic state (Zink et al. 2005). Neuroprotective properties of minocycline are also linked to suppressed activation of p38 mitogen-activated protein kinase, a key physiopathology of SIV encephalitis (Barber et al. 2004). In addition, minocycline can also protect the brain by inhibiting the immune cell infiltration and activation of microglia that lead to encephalitis (Tikka and Koistinaho 2001; Tikka et al. 2001; Zink et al. 2005). Finally, minocycline significantly inhibits HIV and SIV replication in vitro (Zink et al. 2005), making this drug an excellent candidate for limiting HIV replication within the brain, which has remained a difficult anatomical compartment for therapeutic interventions for HIV due to the lack of BBB permeability of many such drugs. A multicenter study of minocycline for the treatment of HAND (ACTG5235) is currently underway (http://clinicaltrials.gov/ct2/results?term=HIV+dementia).

Memantine: anti-excitotoxicity

Memantine is a voltage-dependent, open channel NMDAR blocker that decreases prolonged conductance of calcium via a simple uncompetitive bimolecular reaction with the receptor that does not appear to interfere with physiological function (Chen and Lipton 1997; Rammes et al. 2008). Memantine is effective in gp120 transgenic mice and HIV-SCID mice. Furthermore, it appears to have some efficacy in clinical trials in patients with Alzheimer’s Disease, another neurodegenerative disease associated with excitotoxicity (Raber et al. 1996; Anderson et al. 2004; Lipton and Chen 2003; Tariot et al. 2004), and is, in fact, currently FDA-approved for AD treatment.

The neuroprotective potential for NMDAR antagonists such as memantine, in cases of HAND has recently been investigated in a therapeutic multicenter trial of Namenda (memantine; Schifitto et al. 2007b). However, no clinically significant benefit in neuropsychological and behavioral testing performance was observed during the 16-week treatment phase of the trials, though there were potential neuroprotective effects demonstrated by magnetic resonance spectroscopy in the frontal white matter and parietal cortex in treated individuals. Further trials of pharmaceuticals that block excitotoxic pathways, in particular glutamate and QUIN production, and trial designs of longer duration are clearly needed and are likely to follow in the future (Bandaru et al. 2007; Brew et al. 2007; Clifford 2008; Evans et al. 2007).

Selegiline: antioxidant

Selegiline is a monoamine oxidase type B inhibitor (MAOIB) that has recently been used in clinical trials for the treatment of HAD (Sacktor et al. 2000; Schifitto et al.
There is evidence that Selegiline has a low-dose trophic effect on neurons, and also can reduce oxygenated free radicals. Transdermal administration of Selegiline results in less monoamine peripheral metabolites than the oral route, suggesting that certain toxicities may be avoided with higher transdermal doses of this pharmaceutical (Schifitto et al. 2007a, 2009). However, the most recent study with the transdermal application system did not yield expected results (Schifitto et al. 2009). This system demonstrated no effect on either magnetic resonance spectroscopy metabolites or protein carbonyl concentration from CSF, which can be a measure of oxidative stress. The authors hypothesize that changes in oxidative stress may occur before neural imaging performed in this study; hence, selegiline may yet prove to be an effective treatment as more advanced clinical analyses become available.

**Therapeutics for HAND; future considerations for adjunctive therapies**

In addition to current treatment approaches (HAART drug delivery, NMDAR antagonists, antioxidants, and anti-inflammatory drugs), novel agents and routes of delivery are also under consideration. Recent successes in the CNS delivery of trophic factors (insulin, IGF-1, and neurotrophin) have provoked interest in these agents as neuroprotectants against HIV. The development of intranasal delivery (IND) of neurotrophin, insulin, and IGF-1 has emerged as a potential therapeutic technique to reduce damage associated with stroke and memory degeneration associated with HAND, AD, or diabetes (Kern et al. 1999; Thorne and Frey 2001; Benedict et al. 2004; Thorne et al. 2004, 2008; Ross et al. 2004; Reger et al. 2008a; Reger et al. 2008b; Hanson and Frey 2007; Reagan 2007; Ross et al. 2008). IND allows rapid delivery from the nose to the CNS via an extracellular route, which does not require selective hormone binding or axonal transport mechanisms (Dhanda et al. 2005; Hanson and Frey 2007). One of the most interesting aspects of IND is that after molecule administration, there is virtually no rise in blood concentration of that particular molecule. Insulin, IGF-1, FGF-2, and HB-EGF have all been tested intranasally and were not elevated in the serum of the test subjects/animals nor were peripheral glucose levels affected (Jin et al. 2003; Thorne et al. 2004; Reger et al. 2006; Hanson and Frey 2007, 2008; Reger et al. 2008a, b; Marks et al. 2009). Delivery time and clearance rates are also quite remarkable for IND, where some studies show anywhere from 6 to 20 min of peak concentration (Thorne et al. 1995, 2004) and 4–9 h of clearance from the CSF (Thorne et al. 2004; Hanson and Frey 2007). Delivery systems for IND are fairly simple, mimicking commercially available nasal spray mechanical design, or for murine models, a standard P10-20 pipetman and associated sized plastic tip (Thorne et al. 2004; Benedict et al. 2007; Hanson and Frey 2007; Francis et al. 2008; Marks et al. 2009). There is also no associated damage to the olfactory epithelium, olfactory bulb, or disruption of olfactory receptor neuron axonal targeting (Marks et al. 2009). Thus, drug delivery to the CNS, IND appears to be a non-invasive, fast, safe, and cost-effective solution with little, if any, of the peripheral side effects that are often associated with oral and site-injection medications.

IND of insulin and other molecules has been demonstrated to mitigate many of the behavioral and pathological deficits associated with HAND and other ND. Specifically, Marks et al. (2009) demonstrated that chronic intranasal insulin delivery enhances odor discrimination and short- and long-term memory, as well as reduces anxiety. Reger et al. (2006, 2008a, b) also demonstrated that acute intranasal insulin delivery enhances memory in AD patients. IND also has rapid and continual effects where subjects receiving acute and/or chronic IND insulin have reported extended periods of enhanced mood, reduced anger, and enhanced self-confidence in clinical trials (Benedict et al. 2004). In a recent comprehensive review of HAND pathophysiology, the authors state "Now more than ever, patients are in need of therapy in combination with ART in order to alleviate the potentially greater neuropsychological decline over a longer lifespan" (Ferris et al. 2008). Thus, a combined HAART and intranasal therapy intended to address multiple etiologies of HIV-induced damage in the CNS could be a promising regimen for persons at high risk for HAND.

**Conclusion**

The therapeutic targets for HAND neuroprotection discussed in this review, as well as others, clearly need further consideration if effective treatment regimens for HAND are to be identified and developed. We believe that effective control of CNS viral replication through HAART is the essential primary approach, but that it should be complemented with adjunctive CNS-directed therapeutics. HIV-induced inflammation and its consequences, expressed both systemically and within the CNS, are attractive targets that could be approached through multiple pharmacologic agents. Minocycline is a promising candidate for treating the negative effects of this inflammatory response. Excitotoxicity is another mechanism of neural damage evoked by HIV and HIV-related molecules in the brain. The open-channel NMDAR blocker, memantine, has proven beneficial in animal models of HAND, but the recently published short-term clinical trial results are disappointing, and it is thus unclear how successful this agent will be in the long-term. The
possibilities for antioxidant therapies to reduce oxidative stress are quite numerous. Selegiline is one of many antioxidants, but it also yielded disappointing results in a recent short-term clinical trial. It is clear that the possibilities for future HAND treatments abound and that novel classes of potential neuroprotectant agents as well as increased duration of clinical trial testing and novel routes of administration should be strongly considered in future trials.

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