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Neuroprotective Strategies for HIV-1 Associated Dementia

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OUTLINE

The human immunodeficiency virus-1 (HIV-1) commonly affects cognitive, behavioral and motor functions during the disease course. The neuropathogenesis of viral infection revolves around neurotoxins produced from infected and immune-activated mononuclear phagocytes (MP; perivascular macrophages and microglia). Direct infection of neurons occurs rarely, if at all. Neurologic disease arises in part as a consequence of MP metabolic dysfunction. Although the advent of highly active antiretroviral therapy (HAART) has attenuated the incidence and severity of neurologic disease, it, nonetheless, remains a common and disabling problem for those living with HIV-1 infection. Adjunctive therapies are currently designed to ameliorate clinical outcomes and are included in the therapeutic armamentarium. Anti-inflammatory drugs that inhibit cytokines, chemokines and interferons linked to neurodegenerative processes can significantly ameliorate neuronal function. HIV-1 neurotoxins have the unique ability to up-regulate glycogen synthase kinase-3β (GSK-3β) activity that in turn elicits neuronal apoptosis. GSK-3β inhibitors are neuroprotective in animal models of Neuro AIDS. They are also currently in Phase 1 clinical trials designed for safety and tolerability in patients with HIV-1 infection. Neurotrophins are only beginning to be realized for their therapeutic potential in HIV-1 associated neurologic disease. This review article provides a broad overview of neuroprotective strategies for HIV-1 infection and details how such strategies act and may be implemented for treatment of human disease.

Keywords: HIV-1-associated dementia; Neurotrophins; Neurodegenerative diseases; Neuroprotection; Neuronal injury; Monocyte-derived macrophages

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INTRODUCTION AND OVERVIEW

Human immunodeficiency virus-type 1 (HIV-1) associated dementia (HAD) is a late complication of progressive viral infection (Gendelman *et al.*, 2003). Twenty percent of those infected with HIV-1 will develop cognitive, motor or behavioral dysfunction with neurologic disability associated with advanced viral infection and acquired immunodeficiency syndrome (AIDS) (Navia *et al.*, 1986; Brew *et al.*, 1995; Kim *et al.*, 2003a). The behavioral symptoms appear as a direct consequence of neurodegeneration. The neuropathological features of central nervous system (CNS) disease include infected mononuclear phagocytes (MP; perivascular macrophages and microglia), astrogliosis, myelin sheath pallor, diminished dendritic arbor and synaptic density and neuron loss (Epstein and Gendelman, 1993; Masliah *et al.*, 1996; Krebs *et al.*, 2000). Although highly active antiretroviral therapy (HAART) has lowered the incidence of HAD, the prevalence of neurological impairments has remained high, as infected subjects live longer following viral infection (Sacktor *et al.*, 2000; Eggers *et al.*, 2003). The rapid evolution of research examining the process of neuronal dysfunction in neurodegenerative disorders has placed the studies of neuroprotection at center stage for both laboratory and clinical investigations. Apoptotic neurons in HIV-1-infected brain tissue demonstrate that although cell death is the endpoint of HIV-1 induced neurodegeneration (Gelbard *et al.*, 1995), it does not correlate with pre-mortem neurologic disease. Rather, diminution of synaptic and dendritic complexity appears to best influence neurologic disease (Everall *et al.*, 1999). Cortical synaptic density is reduced in mild to moderate HIV neurocognitive disorder. Hence, neuroprotective strategies initiated early in the disease course when neuronal loss is limited, rather than late when reversal of brain injury is more difficult to achieve, have a higher likelihood of success in improving neurologic function. Such intervention is promising, as neuroprotective strategies rescue neurons vulnerable to the ongoing neurodegenerative process (Moalem *et al.*, 2000; Lagreze *et al.*, 2001). Neuroprotective therapeutics may have several distinct targets including blockade of monocyte-derived macrophages (MDM) secretion of viral and cellular neurotoxins, strengthening of endogenous neuroprotective pathways, and anti-apoptotic effects for vulnerable neurons. Focusing on possible adjuvant treatments for cognitive and motor impairments in HIV-1-associated neurodegeneration may prove to be of greater clinical utility than manipulation of HAART in response to changes in viral burden. Treatment in earlier rather than the later stages of cognitive-motor disease (when damage to affected CNS pathways is already extensive) is essential for neuroprotection (Lange, 1995; Fiala *et al.*, 1998).

Our focus on pharmacologic maneuvers that activate innate neuroprotective mechanisms, such as anti-inflammatory, antiviral, glycogen synthase kinase-3β (GSK-3β) inhibitors, neurotrophins and growth factors is based on laboratory evidence that these agents attenuate HIV-1-associated neurodegeneration. Although neuroprotective studies are effective against toxic HIV-1 proteins in laboratory studies, there has been a paucity of investigations that has truly embraced translational research. Here, a logical progression from laboratory to animal studies, followed by clinical trials in patients with neurologic disease need be achieved (Bachis *et al.*, 2003; Dou *et al.*, 2003; Eugenin *et al.*, 2003). Thus, we hope that this review will serve as an important guide for future clinical trials and drug development for HAD patients.

HIV-1-ASSOCIATED DEMENTIA (HAD)

HAD is a subcortical dementia with associated cognitive impairment, mental and physical slowing, and variable degrees of behavioral changes. Memory loss, difficulties in reading and carrying out simple tasks that comprise the activities of daily living commonly occur. Motor symptoms typically manifest by a progressive gait disturbance with eventual profound weakness. The full-blown clinical syndrome of HAD is characterized by headache, hallucinations, seizures, florid dementia with incontinence, and penultimately, coma (Clifford, 2002).

Clinical Features

Up to 10% of HIV-1 infected patients present with a neurologic complaint, while 30-50% develop such impairments during disease. Nearly 90% show neuropathologic evidence of disease at autopsy (Kim *et al.*, 2003a). During the early phase of AIDS, profound neurological impairment can lead to HAD. A variety of names have been given to the disease complex that leads to memory, motor and behavioral impairments (Kernutt *et al.*, 1993) as a direct consequence of viral invasion and replication in the brain and includes subacute encephalitis, HIV encephalopathy (HIVE), HIV-1-associated cognitive/motor complex and the AIDS dementia complex (ADC). For the sake of simplicity we refer to the disease and its clinical manifestations as simply HAD. The primary cognitive symptom is for-

getfulness associated with slowness of thought, confusion, imbalance, and social withdrawal. The motor dysfunction is associated with rapid movements, clumsiness, tremor, gait slowing and unsteadiness. The most common behavioral symptom is loss of spontaneity and initiation. Sometimes organic psychosis, such as acute mania, may be a primary manifestation of disease (Simpson and Tagliati, 1994; Stankoff *et al.*, 1998). As dementia advances, cognitive impairment becomes more obvious, with psychomotor retardation and marked behavioral abnormalities. This may also be accompanied by disorientation, delirium, aphasia (impaired speech communication), apraxia (loss of voluntary movement ability), and dysphoric mood. Approximately 25% of immunocompromised HIV-positive individuals present as HAD in the later stages of disease (Kolson and Pomerantz, 1996; Bensalem and Berger, 2002; Smit *et al.*, 2004). The onset and progression of HAD varies. Dementia generally occurs late in HIV disease, following $CD4^+$ T lymphocyte counts of 200 cells/mm^3. The average survival following the onset of HAD is six months.

Neuropathology

HAD is often, but not always, manifested pathologically as macrophage-derived multinucleated giant cell (MGC) encephalitis, and is characterized by widespread activation of astrocytes and infiltration of monocyte-derived macrophages. An increase in both the number and size of astrocytes (referred to as astrocytosis and astrogliosis) usually precedes high levels of macrophage parenchymal infiltration. HIV-1 is selectively localized within brain MP; however, infected astrocytes may also be present in HAD with restricted virus replication (Canki *et al.*, 2001). Importantly, a high-level viral gene expression does not always correlate with the clinical manifestations of disease, including cognitive impairment (Kure *et al.*, 1990; Dickson *et al.*, 1991). Nonspecific white matter pallor and variable degrees of vacuolation of myelin can also be observed as neuropathological features of disease. Neuronal dropout is frequently seen in deep gray matter and cortex. Morphological studies revealed 18-50% of cortical neurons, 30-50% of large neurons of the frontal brain, and 20% of neocortical cells were decreased in numbers with associated loss in complexity of their dendritic arbor and synaptic connections (Everall *et al.*, 1993).

A critical question in the neuropathogenesis of HIV infection is how relatively few infected MPs can produce widespread neuronal dysfunction. Preclinical studies (Dickson *et al.*, 1993; Persidsky *et al.*, 1997; Xiong *et al.*, 1999; Persidsky and Gendelman, 2003) lend credence to the hypothesis that neurotoxins released by infected or activated MP induce a metabolic encephalopathy amplified by cytokines, acting in a paracrine manner, affecting normal neuronal signaling (Gendelman *et al.*, 1994b; 1998; Zheng and Gendelman, 1997; Yeh *et al.*, 2000; Zheng *et al.*, 2001a). HIV-1 appears necessary, but not sufficient alone, to induce neurological impairments (Kaul *et al.*, 2001; Langford and Masliah, 2001). Thus, the dysregulation of MP secretory products likely underlie the pathogenesis of HAD.

Viral Dissemination and Brain Entry

Virus enters the brain soon after infection and persists throughout the course of the disease, despite a vigorous innate and adaptive immune response (Gade, 1991; Tepper *et al.*, 1998). The blood-brain barrier (BBB) plays a critical role in regulating cell movements into the CNS due to several unique anatomical features (Ruffer *et al.*, 2004). One feature is that the presence of inter-endothelial tight junctions forms impermeable seals between cells. At the interface between the blood and brain, trafficking macrophages adhere to normal brain microvascular endothelium and undergo transmigration. Macrophages become infected during their later stages of cellular differentiation (Gendelman *et al.*, 1986; Gartner, 2000). During infection with HIV-1, the infected and infiltrating MP release cellular and viral toxins into the brain parenchyma (Gendelman *et al.*, 1994b; Cunningham *et al.*, 1997; Persidsky and Gendelman, 2002; 2003). Moreover, HIV-1 proteins affect expression of endothelial and astrocyte adhesion molecules including intracellular adhesion molecule-1 (ICAM-1), which serves to increase the trafficking of cells across the BBB (Woodman *et al.*, 1999). Pro-inflammatory cytokines that are relevant to tight junction disruption, such as tumor necrosis factor alpha (TNF-α), are involved with the complex interactions of cell adhesion molecules including ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) (Hurwitz *et al.*, 1994). Cytokines also regulate the migration of monocytes through the BBB (Fiala *et al.*, 1998; Toneatto *et al.*, 1999). Previous studies demonstrated that blocking antibodies to the adhesion molecule ICAM-1 significantly inhibited B cell migration. Chemokines such as stromal-derived factor-1 (SDF-1) and monocyte chemoattractant protein-1 (MCP-1) induce transmigration of leukocytes across the BBB as shown in a laboratory model system (Persidsky, 1999; Poluektova *et al.*, 2001; Alter *et al.*, 2003). HIV may enter the CNS through direct infection of cells that subsequently secrete HIV-1 proteins and cytokines linked

to BBB damage and monocyte infiltration. Infected monocytes enter the brain after the establishment of a chemokine gradient and disruption of the BBB. Interestingly, virus particles are present and bud into intracytoplasmic vesicles of macrophages providing a means for escape from immune surveillance. This "Trojan horse" mechanism can facilitate monocyte transmigration, increased secretion of inflammatory products, and a paracrine upregulation of adhesion molecules on brain microvascular endothelial cells (BMVEC) (Gendelman *et al.*, 2003). Such processes further enhance binding and continued infiltration of HIV-1 infected monocytes into the brain (Nottet *et al.*, 1996). Following BBB damage, increased neuronal injury or death may occur by permitting entry of more toxins or immune competent cells into the brain from the periphery.

Perivascular Macrophages and Microglia

Current studies have shown that the majority of HIV-1 infected cells are perivascular macrophages and brain-resident microglial cells, but not neurons (Gendelman *et al.*, 1994a; Persidsky and Gendelman, 2003). HIV-1 infection and brain MP activation are essential requirements to initiate neuronal damage. Production of neurotoxins from brain perivascular macrophages and microglia provides the major pathway for brain tissue injury during HAD (FIG. 1). These neurotoxins include, but are not limited to, viral proteins such as HIV-1 gp120, Tat, and Nef; eicosanoids (arachidonic acid and its metabolites), and platelet-activating factor (PAF); pro-inflammatory cytokines such as TNF-α and interleukin-1β (IL-1β); amines; free radicals such as nitric oxide (NO) and superoxide anion; and the glutamate-like agonist, and cysteine (Dreyer *et al.*, 1990; Yoshioka *et al.*, 1995; Westmoreland *et al.*, 1996; Krebs *et al.*, 2000; Jiang *et al.*, 2001; Smith *et al.*, 2001). These viral and cellular toxins are associated with clinical manifestations of disease (Persidsky *et al.*, 1996; Gendelman *et al.*, 1998; Yeh *et al.*, 2000; Anderson *et al.*, 2002; Persidsky and Gendelman, 2003). HIV-1 viral proteins can act on both neuronal and non-neuronal CNS cells, increasing the level of neurotoxins associated with neuronal injury. The neurotoxins produced by infected MP are probably regulated by a complex series of intracellular interactions between several different types of brain cells, including microglia, astrocytes, BMVEC and neurons (Epstein and Gendelman, 1993; Nottet *et al.*, 1996; Roberts *et al.*, 2003).

NEUROPROTECTIVE STRATEGIES

Neuroprotective strategies are based, in large measure, from studies of HIV-1 associated neuronal injury. Neuroprotection is considered as an adjunct to therapies designed to improve neuronal function and survival. The mechanisms of neuroprotection are aimed at minimizing the extent of cell damage in HIV-1 associated neurodegenerative disorder. Prior studies utilized agents that modulate neurotransmitter function, anti-inflammation or affect cell death pathways, providing new opportunities for pharmacological intervention during HIV-1 associated brain injury. However, previous studies that focused on anti-inflammatory mechanisms have not shown that strategies to reduce endogenous inflammation have conferred significant neuroprotection (Limoges *et al.*, 1997; Nottet, 1999). Thus, a number of studies have tried to attenuate neurotoxicity by blocking the actions of viral proteins (such as HIV-1gp120) (Meucci and Miller, 1996), enhancing the protective action of neurotrophins (Bachis *et al.*, 2003), or reducing CNS inflammation associated with secretory activities of HIV-1-infected microglia and macrophages (Chretien *et al.*, 2002). This part of the review focuses on the most relevant neuroprotective elements gathered from laboratory, animal, and human studies.

Neurotrophins

Neurotrophic factors, including brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and neurotrophin-3 (NT-3), are expressed in the CNS during health and disease (Connor and Dragunow, 1998; Moalem *et al.*, 2000; Du *et al.*, 2003; Paula-Barbosa *et al.*, 2003). Growth factors, such as nerve growth factor (NGF), fibroblast growth factor (FGF), and insulin-like growth factor I (IGF-I), are also referred to as neurotrophins (Hayashi *et al.*, 2000; Namiki *et al.*, 2000; Everall *et al.*, 2001). Expression of neurotrophins may also be associated with neurotoxicity during the early stages of neurodegenerative processes (Finklestein, 1996; Speliotes *et al.*, 1996; Fiedorowicz *et al.*, 2001; Ganat *et al.*, 2002). For example, dysregulation of neurotrophic factors are known to affect HAD pathogenesis, *i.e.*, down-regulation of neurotrophic factors contributes to neuronal injury and death (Chauhan *et al.*, 2001; Felderhoff-Mueser *et al.*, 2002; Johnson, and Sharma 2003). The neuroprotective effects of neurotrophins, through binding of their cognate receptors, act to limit neurotoxin- and lesion-induced neuropathologic damage and can

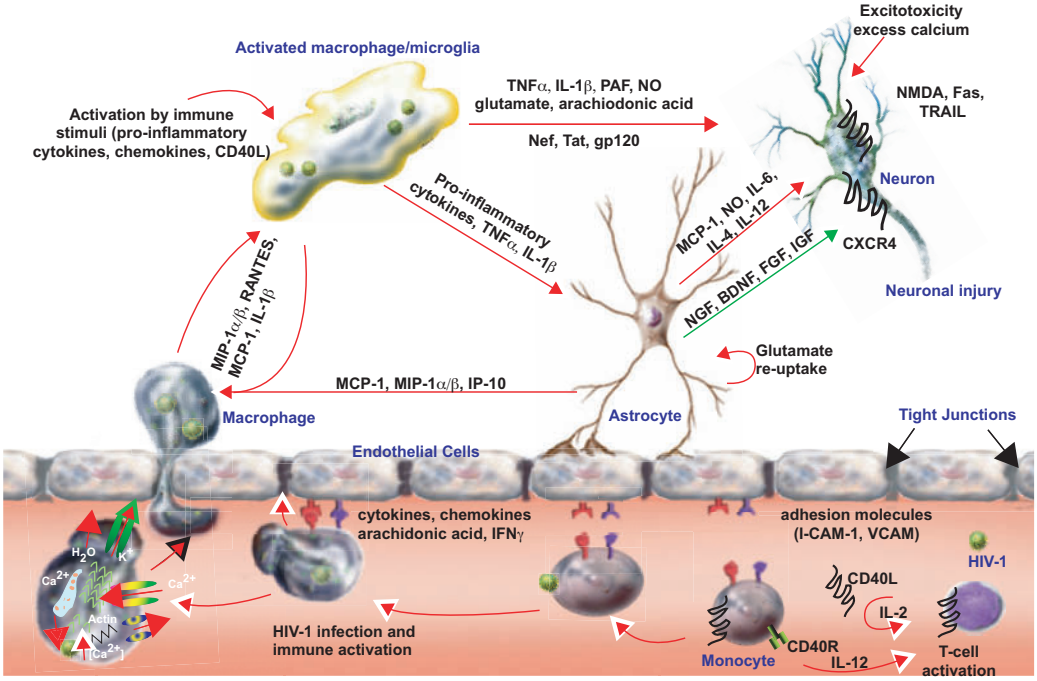

FIGURE 1 HIV-1 infection and MP activation induces widespread inflammatory responses in the brain. MP secretory activities result in a cascade of immunomodulatory activities that affect neuronal and blood-brain barrier functions. Activated perivascular macrophages and microglia secrete neurotoxins which include, but are not limited to, viral proteins (Nef, Tat and gp120) and proinflammatory cytokines (including TNF-α and IL-1β ; PAF; free radicals such as NO and superoxide anion; the glutamate-like agonist; and cellular factors (arachidonic acid and its metabolites); amines; resulting in neuronal injury. Astrocyte activation also plays a critical regulatory role in neuronal injury. Innate astrocyte immunity includes the secretion of cytokines and chemokines (such as MCP-1, NO, IL-6, IL-4, and IL-12) as well as a number of neurotrophic factors. HIV-1 infection of brain MP affects cell migration, adhesion molecule expression, blood-brain barrier compromise and neurodegenerative processes.

affect individual neuronal populations, dendritic length, spine density, synaptic transmission, anti-apoptotic signaling, or signaling to limit oxidative stress (Meucci and Miller, 1996; Connor and Dragunow, 1998; Ramirez *et al.*, 2001; Titanji *et al.*, 2003). The cellular localization of neurotrophic receptors changes after the excitotoxic insult, inducing increases in both neurotrophins and their receptors in the CNS (Alberch *et al.*, 2002). Neurotrophins can also confer protection by preventing apoptosis (Meucci and Miller, 1996; Macdonald *et al.*, 1999; Ramirez *et al.*, 2001).

A number of neurotrophic factors have a specific distribution in the brain, including promotion of survival and differentiation by multiple signaling pathways, including the activation of phosphotidylinositol-3-kinase (PI-3-K) and mitogen-activated protein kinase (MAPK) pathways by BDNF, NGF and IGF-I (Culmsee *et al.*, 2002; Jones *et al.*, 2003; Chang *et al.*, 2004). Activation of NF-κB and up-regulation of Bcl-2 expression by NGF and BDGF promote neuronal survival in HIV-1 associated neurodegeneration (Macdonald *et al.*, 1999; Ramirez *et al.*, 2001). The ability of neurotrophins to promote cell survival might offset the pro-apoptotic effects of HIV-1 associated neuronal injury (Zheng *et al.*, 2001b). The expression profile of neurotrophic factors, after brain injury, reflects an endogenous attempt at neuroprotection against biochemical and molecular changes after neuronal injury (Chiaretti *et al.*, 2003). Specifically, IGF-I inhibits GSK-3β activation and promotes axonal growth (Jones *et al.*, 2003; Lin *et al.*, 2004). GSK-3β is linked to apoptosis in the pathogenesis of many neurological disorders (Maggirwar *et al.*, 1999; Jope and Bijur, 2002; Wagman *et al.*, 2004).

Brain Derived Neurotrophic Factor

BDNF is a 14 kDa protein that exists as a 28kDa dimer and is expressed in the hippocampus, amygdala, thalamus, projection areas of the olfactory system, inner and outer pyramidal layers of neocortex, claustrum, septum, cerebellum, and superior colliculus (Furukawa, 1992; Maness *et al.*, 1994). BDNF is the most studied neurotrophic agent for HIV-1 associated neuronal injury (Soontornniyomkij *et al.*, 1998; 1999; Boven *et al.*, 1999; Harrold *et al.*, 2001; Bachis *et al.*, 2003; Zheng *et al.*, 2004). Other neurologic disorders appear to be influenced by BDNF levels, which has been shown to benefit, at different levels, mood disorders,

stroke, and Parkinson's disease (Connor and Dragunow, 1998; Chauhan *et al.*, 2001; Alberch *et al.*, 2002; Felderhoff-Mueser *et al.*, 2002; Chiaretti *et al.*, 2003). For example, BDNF can affect neurotoxin- or lesion-induced damage in selected neuronal populations. BDNF enhances the survival of cholinergic neurons of the basal forebrain after a fimbria-fornix lesion and also protects dopaminergic neurons in the nigrostriatal pathway against neurotoxic damage.

Studies suggest important roles for BDNF in HIV-1 mediated neurotoxicity. BDNF inhibits caspase-3 activation, supporting neuronal survival and preventing HIV-1 gp120 mediated neuronal apoptosis (Bachis *et al.*, 2003). Activation of caspase-mediated apoptosis is an event that plays an important pathophysiological role in HIV-1 gp120-mediated cell death in macrophages, T-cells, and human embryonic kidney cells (Bachis *et al.*, 2003; Acquas *et al.*, 2004; Singh *et al.*, 2004). Apoptotic cell death is triggered by activation of the pro-apoptotic protease caspase-3. Inhibition of caspase-3 activity by BDNF can rescue neurons from undergoing apoptosis. BDNF agonism of tropomyosin-related kinase B (TrkB) receptors prevents glutamate-mediated neuronal apoptosis (Glazner and Mattson, 2000; Bachis *et al.*, 2003; Swanwick *et al.*, 2004). The excitatory amino acid neurotransmitter glutamate plays a major role in HIV-1 mediated neurodegenerative processes (Masliah *et al.*, 1996; Fox *et al.*, 1997; Ferrarese *et al.*, 2001; Belmadani *et al.*, 2003), in part by over-activation of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors. BDNF prevents glutamate-mediated excitotoxicity through modulation of NMDA receptors (Brandoli *et al.*, 1998). The neurologic deficits of HAD are thought to arise from glutamate excitotoxicity induced by secretory products from virally infected MDM. The ability of BDNF to prevent neurotoxin formation may occur by activation of transcription factor NF-κB, which in turn inhibits transcription of pro-apoptotic mediators (Glazner and Mattson, 2000). NF-κB is involved in immunologic responses, cell proliferation, growth factor regulation, and apoptosis. Thus, BDNF-mediated activation of NF-κB plays a critical role in neuroprotection (Lipsky *et al.*, 2001). Moreover, BDNF reduced the levels of CXC chemokine receptor-4 (CXCR4) and prevented neuronal cell death by blocking the neurotoxic effects of SDF-1α, a ligand for CXCR4. SDF-1-mediated cell death was quantitatively similar to that evoked by gp120 (Bachis *et al.*, 2003). Activation of CXCR4 can lead to the cell death of various neuronal populations. Thus, neuroprotective effects of BDNF may occur in part by decreasing CXCR4 abundance, thereby limiting activation of this receptor during HIV-1 neuropathogenesis. Lastly, BDNF activates several anti-apoptotic signaling pathways, including PI-3-K, MAPK, and up-regulates the expression of Bcl-2, further promoting neuronal survival. Taken together, strategies to enhance the biologic effects of BDNF or increase its expression may prove beneficial against this type of neurodegeneration.

Nerve Growth Factor

NGF was the first neurotrophic factor to be discovered and was one of the earliest to proceed to clinical trials. NGF, which is selectively trophic for small fiber sensory and sympathetic neurons, was selected as a potential therapy for diabetic polyneuropathy because of the debilitating neurologic consequences associated with degeneration of those neuronal populations. Recombinant human NGF (rhNGF) administration was effective at ameliorating the symptoms associated with both diabetic polyneuropathy and HIV-related neuropathy (Schifitto *et al.*, 2001; Apfel, 2002). An AIDS Alert report (see 'Aids Alert Report', 1998) from the Johns Hopkins University stated that using recombinant human NGF helped in the effective treatment of HIV-1 associated neuropathy. The researchers noted that the treated patients had decreased pain intensity and improved sensation. However, a more comprehensive study could not conclusively establish the efficacy of NGF therapy in distal sensory neuropathy (Simpson *et al.*, 2002). The reasons for this are likely to be complex and multifactorial, but one possibility for these results could be due to the increased presence of NGF autoantibodies in HIV-1-infected patients (Titanji *et al.*, 2003).

Substantial evidence suggests that NGF signaling prevents glutamate-mediated neurotoxicity generated during the response to tissue injury (Semkova *et al.*, 1996; Semkova and Krieglstein, 1999; Chiaretti *et al.*, 2003). Although the intracellular pathways through which NGF signaling protects TrkA- and p75 NTR-expressing neurons from glutamate receptor-mediated neurotoxicity are not yet defined, neuroprotection of NGF is mediated by TrkA and p75 NTR. NGF may have important therapeutic effects in HIV-1 associated neuronal injury, especially in the peripheral nervous system (PNS).

Fibroblast Growth Factor and Insulin-like Growth Factor I

In neurodegenerative disorders such as Alzheimer's disease (AD) and HIVE, FGF-I may provide protection against several neurotoxins by activating signaling

pathways of PI3K-Akt and GSK-3β (Everall *et al.*, 2001; Hashimoto *et al.*, 2002). PI3K-Akt signaling inactivates GSK-3β, leading to intracellular events crucial for cell survival. Both PI3K and Akt are activated by other growth factors, including platelet-derived growth factor, insulin, and BDNF. Growth factor-induced cell survival is dependent on the activation of PI3K. Studies show that inhibitors of the PI3K-Akt pathway block the effects of FGF-I on GSK-3β (Hashimoto *et al.*, 2002). Therefore, it is likely that the neuroprotective action of FGF-I results, at least in part, from inhibition of apoptosis. Interestingly, in individuals with HIVE, high levels of neuronal FGF-I expression correlate with improved cognitive performance and preservation of the dendritic integrity (Everall *et al.*, 2001). Alterations in FGF-I expression and GSK-3β activity in vulnerable neurons are now considered to be important during neuropathogenesis of HAD. Taken together, these data support the notion that up-regulation of FGF-I might protect the CNS from the neurotoxic effects of HIV.

IGF-I is a 70-amino acid peptide that has 50% sequence homology with insulin and 70% homology with IGF-II (Rinderknecht and Humbel, 1978). Like insulin, both IGF have A and B chains that are linked by disulfide bonds. Trophic effects of IGF-I process a wide range of actions in both central and peripheral nervous systems. As a cytokine, IGF-I has prominent neurotrophic effects, stimulating differentiation and promoting survival of specific neuronal populations (Torres-Aleman *et al.*, 1994; Nakao *et al.*, 1996; Camarero *et al.*, 2003). Accumulated evidence indicates that IGF-I decreases apoptosis of various cell types in response to a diverse array of stimuli (Hausenloy and Yellon, 2004). A previous study showed that IGF-I protects neurons from various neurodegenerative stimuli by preventing apoptotic and necrotic cell death, both dependent on the PI3K-Akt pathway (Heck *et al.*, 1999). In addition to protecting neurons from death, IGF-I is able to induce functional recovery of neurons following a variety of brain injuries.

Previous reports suggest that IGF-I responses are impaired during the course of HIV infection (Jain *et al.*, 1998; Rondanelli *et al.*, 2002; Ying Wang *et al.*, 2003). Reduced levels of serum IGF-I have been observed in HIV-infected patients, particularly those with wasting syndrome and in children with failure to thrive (Jain *et al.*, 1998). Decreased levels of IGF-I in the CNS may promote neuronal apoptosis in HIV infection, or alternatively, by mechanisms which contribute to IGF-I resistance (Ying Wang *et al.*, 2003). Activation of the IGF-I system confers protection against neurotoxins, indicating that an increased utilization of IGF-I-stimulated pathways may represent a potential therapeutic approach to rescue vulnerable neurons in patients with HAD.

Anti-Inflammatory Cytokines

Cytokines are extracellular proteins that are involved in many different processes, including cell growth and differentiation, development, and repair processes. A major function of cytokines consists of mediating interactions between immune and inflammatory systems. Most cytokines induce a specific immune response in the tissue compartment. Inflammatory cytokines, such as IL-1 or TNF, are produced by activation of macrophage/microglia and in turn may act in the CNS to mediate neuronal injury (Gendelman *et al.*, 1994a; Westmoreland *et al.*, 1996; Leskovar *et al.*, 2000; Yeh *et al.*, 2000; Hansen *et al.*, 2001; Castano *et al.*, 2002). Several pro-inflammatory cytokines have been implicated in promoting the activation of microglia/macrophages and act as a critical role in HIV-1-mediated neuronal cell damage (Yoshioka *et al.*, 1995; Minghetti and Levi, 1998). Activation of macrophage/microglia secreted inflammatory cytokines may create a pro-apoptotic environment in CNS parenchyma, thereby increasing vulnerability of neuronal or glial cells towards a variety of neurotoxic factors (Canetti *et al.*, 2001). Because of the efficacy of cytokine-mediated biologic effects, their activities have to be tightly controlled (Cheng *et al.*, 1994; Beech *et al.*, 2001). Cytokine inhibitors interfere with the binding of the cytokine to its specific receptor. The biological actions of cytokines include modulation of the synthesis of other cytokines and their inhibitors, and/or target cell activation by the latter productions. Moreover, the effects of anti-inflammatory cytokines, such as IL-4, IL-10, IFN-α, and IL-11, may confer protection against pro-inflammatory substances released from macrophage/microglia. These anti-inflammatory cytokines are produced by and act on both neurons and glia and are up-regulated in CNS degenerative disorders (Vitkovic *et al.*, 2001; Koeberle *et al.*, 2004). Their therapeutic potential will be realized by improving our understanding of their place in neural cytokine networks. Several lines of evidence have demonstrated that some cytokines (IL-4 and IL-10) may be neuroprotective by anti-inflammatory effects (Spera *et al.*, 1998; Dietrich *et al.*, 1999; Sholl-Franco *et al.*, 2002; Abraham *et al.*, 2004). Thus, anti-inflammatory cytokines may confer neuroprotection mainly by inhibiting production of the inflammatory cytokines and activation of macrophage/microglia.

Interleukin-10

IL-10 is synthesized in the CNS and acts to limit clinical symptoms of stroke, Alzheimer's disease, and other neurodegenerative disorders (Dietrich *et al.*, 1999). Expression of IL-10 is elevated during the course of most major diseases in the CNS and promotes survival of neurons and glial cells. IL-10 is considered to be an endogenous protective agent for neuronal cells and negative regulators for the CNS cytokine network by blocking the effects of pro-apoptotic cytokines and by promoting expression of cell survival signals (Molina-Holgado *et al.*, 2001). IL-10 has been shown to inhibit microglial/ macrophage cytotoxicity by down-regulating iNOS expression and free radical production (Dokka *et al.*, 2001; Parente and Solito, 2004). Stimulation of IL-10 receptors regulates numerous life- or death-signaling pathways, including PI 3-kinase, MAPK, and NF-κB, ultimately promoting cell survival by inhibiting both ligand- and mitochondrial-induced pro-apoptotic pathways. The CNS anti-inflammatory activities of IL-10 are mediated by three major pathways: reducing synthesis of pro-inflammatory cytokines, regulating cytokine receptor expression, and inhibiting receptor activation. The function of IL-10 in the brain could lead to development of innovative approaches for the use of anti-inflammatory cytokines in major debilitating diseases of the CNS, including HAD.

Erythropoietin

Epo was first identified as a hematopoietic cytokine that acts as a survival and differentiation factor (Genc *et al.*, 2004). It is a 34-kDa glycoprotein that functions as the main regulator of erythropoiesis. During development, the expression of Epo receptors (EpoR) in neurons and their biologic response to Epo provide evidence for a role for Epo-mediated signaling in the brain. Moreover, the absence of EpoR increased the number of apoptotic cells in the brain (Yu *et al.*, 2002). Epo is thought to be an inducer of neurogenesis during brain development (Yu *et al.*, 2002). The expression of Epo and its cognate receptor EpoR occurs in areas containing neurons especially vulnerable to ischemic insult, such as the hippocampus and the cerebral cortex. The regulation of both Epo and EpoR gene expression by hypoxia acts as a neurotrophic and neuroprotective mechanism, particularly during hypoxia, ischemia, and brain hemorrhage (Genc *et al.*, 2004). Recombinant human Epo has been shown to provide therapeutic benefit in a variety of nervous system diseases (Brines, 2002). It has been shown that Epo can influence the release of neurotransmitters and play an important role in synaptic plasticity in the adult brain. Epo protects neurons from excitotoxic- and NO-induced apoptosis by mechanisms that involve repression of programmed cell death (Gassmann *et al.*, 2003) and NF-κB (Digicaylioglu and Lipton, 2001). Moreover, the previous study has shown that Epo can also have a direct neuroprotective effect as a neurotrophin (Romsi *et al.*, 2002). In mother-to-infant transmission of HIV-1, increased neuroprotection can be accomplished by higher Epo dosing for longer durations (Gassmann *et al.*, 2003). Clinically, Epo can protect cortical neurons against apoptosis by HIV-1 gp120 (Digicaylioglu *et al.*, 2004). Hence, Epo may have potential therapeutic value for patients with HAD (Digicaylioglu and Lipton, 2001).

GSK-3β Inhibitors

GSK-3, the smaller of two protein-serine kinases (*i.e.*, GSK-3α and -3β), both coded by two different genes, consists of 482 amino acids with a molecular weight of 46,712 daltons, and contains a central protein kinase catalytic domain (Woodgett, 1991). It is a remarkable enzyme with an astoundingly diverse number of actions in intracellular signaling systems. Although GSK-3β originally was isolated from skeletal muscle, the enzyme is widely expressed in all tissues, particularly abundant in the brain (Yao *et al.*, 2002; Schaffer *et al.*, 2003). During brain development, GSK-3β is expressed in neurons and other brain cells. GSK-3β levels decrease significantly after postnatal day 20, which correlates temporally with the completion of dendrite extension and synapse formation. Moreover, expression of GSK-3β has been found in the adult brain, suggesting a fundamental role for GSK-3β in cellular signaling pathways (Nadri *et al.*, 2003). Activation of GSK-3β is regulated by: serine (inhibitory) and tyrosine (stimulatory) phosphorylation, protein complex formation, and its intracellular localization. Phosphorylation of GSK-3β signaling is mediated by growth factor receptors through the activation of protein kinase B (Akt), cyclic AMP signaling through activation of protein kinase A, and/or receptors that activate protein kinase C (Grimes and Jope, 2001a). However, the inhibitory control of GSK-3β by Ser^{9} phosphorylation is a critical factor in receptor-coupled signaling processes, in anti-apoptotic actions of the Akt signaling pathway, and in certain diseases (Yusta *et al.*, 2002). Originally identified as a regulator of glycogen synthesis, GSK-3β itself inhibits the activation of several transcription factors, which play an important role in affecting pro-apoptotic factors that contribute to neuronal loss and cell survival (Jope and Bijur, 2002; Stoica *et al.*, 2003). Among the intriguing links between GSK-3β and cell survival are the findings

that activation of GSK-3β is linked directly to increased neuronal apoptosis and is associated with the down-regulation of the activities of several transcription factors. These are critical promoters of cell survival (such as lithium) that protect neurons from the lethality of a wide variety of toxic insults. These actions of GSK-3β may be associated with neurodegenerative diseases such as HAD, and may be a key promoter of HIV-1-associated psychiatric disorders (Grimes and Jope, 2001a).

Overexpression of catalytically active GSK-3β at levels that induce apoptosis has been linked with HIV-1 protein-mediated neurotoxicity (Maggirwar *et al.*, 1999; Tong *et al.*, 2001). The importance of GSK-3β in many apoptotic conditions is further supported by evidence that selective small-molecule inhibitors of GSK-3β provide considerable protection from apoptotic cell death. Several inhibitors of enzymes have been found to be capable of mediating this modification following HIV-1 mediated neurotoxicity (Everall *et al.*, 2002; Dou *et al.*, 2003), such as lithium and sodium valproate (VPA) (Chen *et al.*, 1999; Linseman *et al.*, 2003). Lithium reduces GSK-3β-mediated *tau* phosphorylation (Lee CW *et al.*, 2003) and has been shown to promote neuronal survival in a number of other settings, including the inhibition of the canonical c-Jun apoptotic pathway (Hongisto *et al.*, 2003). Taken together with present data, the regulation of GSK-3β activity, by enzyme inhibitors within the brain, suggest that modulation of GSK-3β in neurons may be important for neuroprotective strategies. Thus, drugs that inhibit GSK-3β, such as lithium and valproate, could have therapeutic impact in patients with HAD. The following sections review these concepts.

Lithium

Lithium is most widely used for treatment of bipolar affective disorder. Several lines of clinical evidence suggest that lithium has neurotrophic actions. Chronic lithium treatment increases the volume of gray matter and the content of *N*-acetyl-aspartate (Manji *et al.*, 2000; Moore *et al.*, 2000; Silverstone *et al.*, 2003). Additionally, several reports support the concept that lithium can protect neurons from apoptosis by inhibiting the activity of GSK-3β (Grimes and Jope, 2001a; Bauer *et al.*, 2003; Hongisto *et al.*, 2003). This evidence provides an important clue towards solving one of the most intriguing properties of lithium, *i.e.*, its ability to afford neuroprotection against a wide variety of insults (Jope, 1999; Hongisto *et al.*, 2003; Rigoulot *et al.*, 2003). This lithium-mediated protection was correlated with its ability to inhibit increases in GSK-3β activity, up-regulation of Bcl-2, and down-regulation of apoptotic proteins p53 and caspase-3 activation.

Because lithium has been demonstrated to inhibit increases in GSK-3β activity (Bijur *et al.*, 2000), these findings have raised interesting questions regarding the therapeutic actions of lithium. There is substantial neuropathologic evidence of neuronal damage in HAD. The first critical question of whether or not lithium ameliorates this disease or reverses neuronal damage, mandates its use as adjuvant neuroprotective therapy in combination with HAART. Second, HIV-1 mediated neuronal injury is mediated in part by excessive GSK-3β activation (Maggirwar *et al.*, 1999). Third, recent observations demonstrate that lithium promotes neurogenesis in the dentate gyrus of rodent brain. We propose the biologic effect is likely due in part to inhibition of GSK-3β activity in vulnerable neurons that results in down-stream changes in neurotrophin (*i.e.*, brain derived neurotrophic growth factor) expression and the anti-apoptotic gene Bcl-2 (Chen *et al.*, 2000; Lee J *et al.*, 2002). Thus, lithium's dual effects of neurogenesis and decreased neuronal apoptosis might act at least additively on crucial GSK-3β-regulated functions (gene expression, cell structure and survival) (FIG. 2). However, other investigators have challenged this idea (Coyle and Duman, 2003), because lithium produces therapeutic effects only after its chronic administration, whereas the direct inhibition of GSK-3β by lithium is rapid. However, long-term treatment might be necessary for the therapeutic effects of lithium to be manifested as alterations in gene expression or cell structure and function.

Lithium has been found to increase the synthesis of neuroprotective proteins and to exert possible neurotrophic effects in the human brain (Jope, 1999; Bauer *et al.*, 2003; Rigoulot *et al.*, 2004). These properties suggest that lithium holds great promise in the treatment of AIDS-related neurological deficits such as dementia. Recently *in vitro* and *in vivo* studies showed that neuroprotective effects of lithium are mediated by inhibition of the phosphatidylinositol 3-kinase/Akt pathway against HIV-1 gp120 mediated neurotoxicity (Everall *et al.*, 2002; Dou *et al.*, 2003). Although few studies have directly linked the inhibitory effects of lithium on GSK-3β activity as neuroprotective, our group very recently demonstrated that lithium can provide therapeutic neuroprotection in a model of HIVE using severe combined immunodeficient (SCID) mice (data not published). Lithium may inhibit GSK-3β by either direct or indirect phosphorylation, leading to decreased neuronal apoptosis (Lesort *et al.*, 1999; Choi and Sung, 2000). Lithium inhibits Mg^{2+}-dependent GSK-3β activity by directly competing with Mg^{2+}

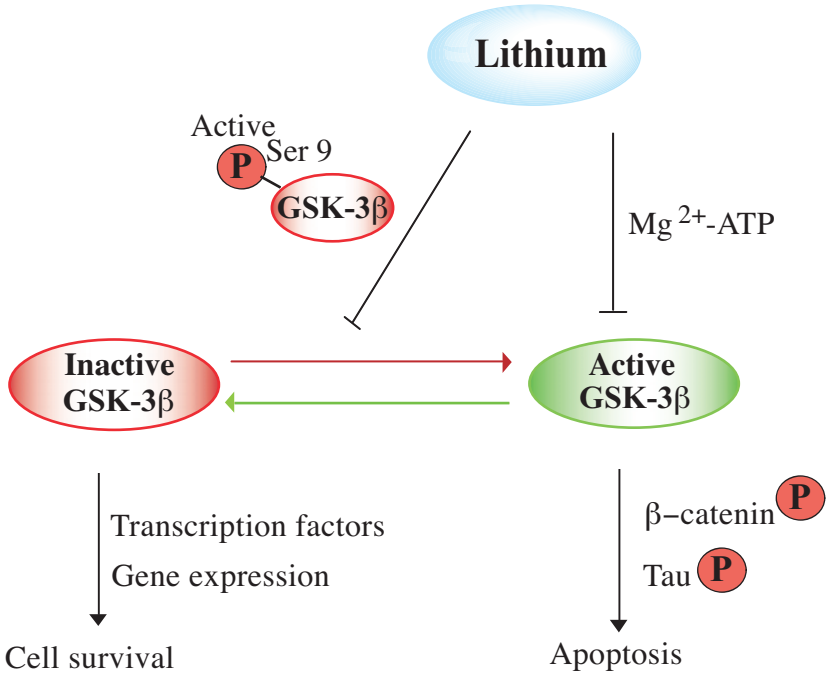

FIGURE 2 Lithium inhibits GSK-3β by competing with Mg^{2+} directed activity of GSK-3β. GSK-3β is inactivated by phosphorylation on a serine in the *N*-terminal domain: Ser^{9} in GSK-3β. The inactive phospho-serine-GSK-3 downregulates β-catenin and Tau phosphorylation affecting cell survival. Neuroprotection occurs through the action of GSK-3β phosphatase by leaving more of the GSK-3 in the phosphorylated inactive form (indicated as inhibition of GSK-3).

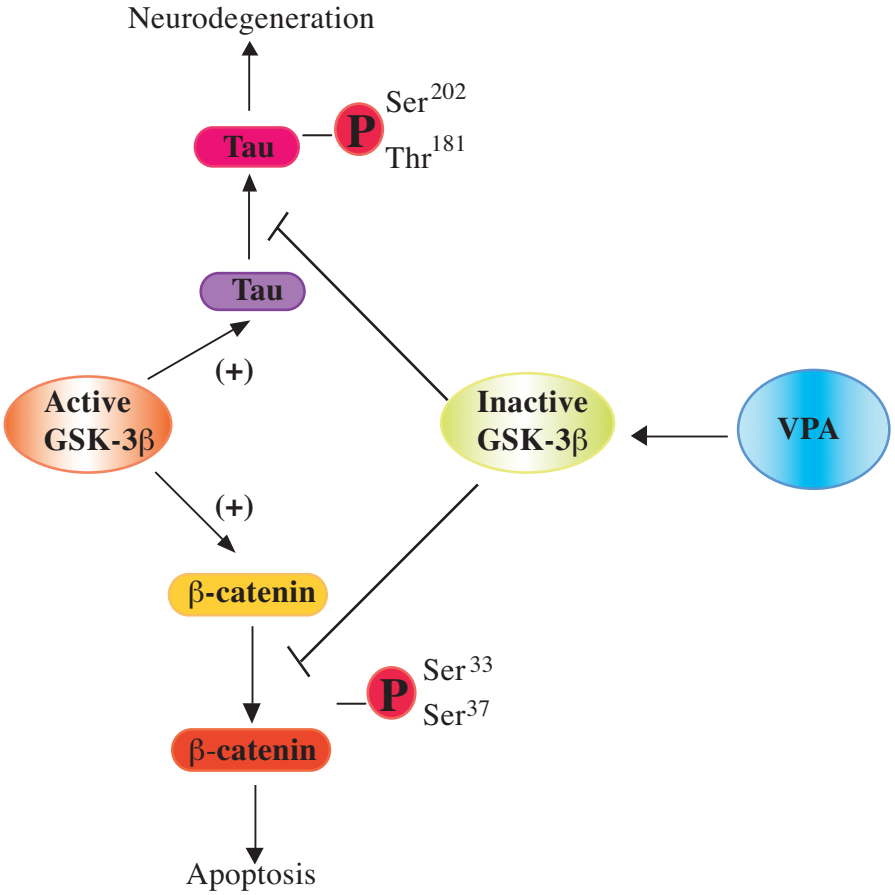

FIGURE 3 GSK-3β mediates phosphorylation of β-catenin, rendering the cell susceptible to apoptosis, or through Tau, leading to neuronal degeneration. The effect of VPA is in reduction of GSK-3β activity mediated phosphorylation.

(Klein and Melton, 1996), and thereby decreasing neurotoxicity (Everall *et al.*, 2002). The neuroprotective effect of lithium is not dependent on lithium's effects on cellular inositol metabolism, but rather on its ability to reduce GSK-3β-mediated *tau* phosphorylation (Hong *et al.*, 1997; Everall *et al.*, 2002). The indirect mechanism by which lithium inhibits the action of GSK-3β involves control of the post-translational modification of an enzyme that regulates its activity. Lithium can phosphorylate the serine (ser^{9}) in the *N*-terminal region of GSK-3β. The actual mechanism of enzyme inhibition has not been elucidated. It is thought that the increased phosphorylation of GSK-3β indirectly inhibits a protein phosphatase that normally activates GSK-3β (Yusta *et al.*, 2002). The anti-apoptotic mechanisms of lithium, derived from its inhibition of multiple transcription factors regulated by GSK-3β, may be another neuroprotective mechanism, based on the evidence that lithium enhanced mitogen-activated protein kinase (MEK) and extracellular signal-regulated kinase (ERK) phosphorylation in a concentration-dependent manner through an inositol and GSK-3β independent mechanism (Einat *et al.*, 2003; Jope, 2003; Pardo *et al.*, 2003). This degree of inhibition could shift the balance of signaling towards the enhanced production of anti-apoptotic agents that are associated with partial inhibition of GSK-3β, and thus facilitate activation of the associated transcription factors. Taken together, these findings provide considerable support for lithium and related compounds in the therapeutic arsenal for neuroprotection against HIV-1 neurotoxins.

Sodium Valproate

Sodium valproate (VPA) can also function as a mood stabilizer that modulates signal transduction at several targets similar to lithium. Therapeutic concentrations of VPA (0.6 mM) resulted in: (1) significant increases in both nuclear and cytoplasmic β-catenin protein levels; (2) decreases in the level of protein α-kinase C and epsilon isozymes (Chen *et al.*, 1994); and (3) down-regulation of myristoylated alanine-rich C-kinase substrate (MARCKS) (Manji *et al.*, 1999) through inositol-independent mechanisms (Lenox *et al.*, 1996). Although effects of lithium appear to be due to direct inhibition of GSK-3β, the precise mechanism for VPA-mediated inhibition of GSK-3β remains unclear. Others and our group recently reported that VPA inhibits GSK-3β mediated phosphorylation of *tau in vivo* (Grimes and Jope, 2001b; Dou *et al.*, 2003). Other studies also found that VPA inhibits the activation of GSK-3β *in vitro* (Chen *et al.*, 1999). VPA inhibition of GSK-3β may be substrate specific, or possibly due to differences in assay conditions. Regardless, VPA, at therapeutic concentrations (0.6 mM), significantly inhibited staurosporine-, heat shock-induced and GSK-3β-facilitated apoptosis.

VPA-mediated neuroprotection involves diminished activity of GSK-3β (Tong *et al.*, 2001) via the inhibition of phosphorylation of β-catenin ($Ser^{33,37}$) and *tau* (Ser^{202} and Thr^{181}) (Dou *et al.*, 2003), as well as, the overall increase in total β-catenin protein levels (FIG. 3). Hyperphosphorylation of β-catenin and *tau* directly affects neuronal apoptosis and dysfunction (Ferrer *et al.*, 2002; Kim *et al.*, 2003b). β-catenin levels are markedly reduced in some neurodegenerative diseases, and decreased β-catenin signaling seems to increase neuronal vulnerability to apoptosis. Thus, inhibition of GSK-3β may serve to offset the β-catenin destabilization, thereby reducing the vulnerability of affected neurons to apoptosis. In our studies using a model of HIVE in SCID mice, we found that hyperphosphorylation of β-catenin occurs in the basal ganglia concurrently with gliosis and neuronal degeneration (Dou *et al.*, 2003). Similarly, specific phosphorylated isoforms of *tau* have been associated with other neurodegenerative disorders, including AD (Hong *et al.*, 1997). In our model, highly phosphorylated *tau* at Ser^{202} and Thr^{181} is consistently associated with neuronal injury in SCID mice with the neuropathologic features of HIVE. Both *tau* and β-catenin may represent important physiologic targets of GSK-3β contributing to neuronal loss and neuronal damage in the context of HAD. The results support the hypothesis that downstream targets for pathologically activated GSK-3β, including β-catenin and *tau*, might be a major event in the pathogenesis of HIVE or HAD. Furthermore, our data raises the possibility that VPA inhibits hyperphosphorylation of β-catenin and *tau* through the regulation of GSK-3β, thus promoting neuronal survival.

NMDA ANTAGONISTS

Previous studies have revealed that over-activation of NMDA receptors with resultant excitotoxicity, disruption of the cellular calcium homeostasis, and free radical formation are all key mechanisms involved in brain damage and neurodegenerative disease accompanied by deficits in cognition (Bi and Sze, 2002; Xiong *et al.*, 2003; Anderson *et al.*, 2004). Over-activation of NMDA receptors by glutamate or NMDA results in neuronal cell death (Lipsky *et al.*, 2001; Jiang *et al.*, 2003; Baptiste *et al.*, 2004). NMDA neuroprotection can occur through neurotrophins including BDNF, NGF, NT-3, and neurotrophin-4, the subsequent regula-

tion of glutamate positively affecting neuronal survival (Rocha *et al.*, 1999; Jiang *et al.*, 2003; Marmigere *et al.*, 2003).

The ability of HIV-1 proteins, released from HIV-1 infected and activated macrophages and HIV-1 infected astrocytes, to induce neuronal injury is related to excessive stimulation of NMDA receptors, with excessive influx of Ca^{2+} into neurons (Dreyer *et al.*, 1990; Giulian *et al.*, 1990; Lipton, 1992; Lo *et al.*, 1992; Diop *et al.*, 1994; Lannuzel *et al.*, 1995; Belmadani *et al.*, 2003; Eugenin *et al.*, 2003; Song *et al.*, 2003; Xiong *et al.*, 2003; Kaul and Lipton, 2004; Power *et al.*, 2004; Self *et al.*, 2004). Moreover, neurotoxic secretory factors from activated microglia and HIV-1 infected macrophages, ultimately induce activation of NMDA receptors, with associated neuronal injury (Yoshioka *et al.*, 1995; Lipton 1996; 1998; Jain, 2000; Eugenin *et al.*, 2003; Xiong *et al.*, 2003). Work from our group (Xiong *et al.*, 2004) showed that NMDA receptors are activated by amyloid precursor protein. It is well known that release of cytokines and other neurotoxic factors from MPs are involved in the pathogenesis of AD and HAD. Blocking neurotoxicity by NMDA receptor antagonists has therapeutic potential in several CNS disorders, including chronic neurodegenerative diseases, as well as, symptomatic treatment in other neurologic diseases (Molinuevo *et al.*, 2004).

Memantine, a non-competitive NMDA antagonist, has been clinically used in the treatment of dementia in Germany for over fifteen years (Bormann, 1989). The neurotoxicity caused by HIV-1 proteins Tat and gp120 can be completely blocked by memantine (Jain, 2000). Furthermore, memantine improved hippocampal synaptic transmission in the SCID mouse model of HIV-1 associated neurologic disease (Anderson *et al.*, 2004). In clinical applications, memantine treatment has been directed primarily toward HAD, AD and other senile dementias (Jain, 2000; Anderson et al 2004; Tariot *et al.*, 2004).

MONOCYTE CHEMOATTRACTANT PROTEIN-1

An inflammatory reaction, involving MCP-1 production and release, astroglia and microglia activation, and inflammatory cell infiltration, contribute to HIV-1-associated neurological disease (McManus *et al.*, 1998; Wang *et al.*, 2003). MCP-1 production from activated astrocytes positively affects neuroprotection through blockade of caspase-1.

MCP-1 protects mixed cultures of human neurons and astrocytes from Tat or NMDA-induced apoptosis. On balance, MCP-1 may have a dual protective and degenerative role in HAD as it is associated with inflammation and monocyte recruitment into the brain. Such recruitment positively affects the egress of additional monocytes into the brain and expands the viral reservoir and cellular sources of neurotoxic secretory activities (Kelder *et al.*, 1998). Nonetheless, MCP-1 can also inhibit Tat- and NMDA-induced apoptosis in mixed cultures of human neurons and astrocytes by reducing the extracellular levels of glutamate, and in neurons, by regulating Tat and NMDA receptor 1 (NMDAR1) expression (Eugenin *et al.*, 2003). The balance between inflammation and protection may play an important role in mediating the initial as well as the ongoing response of the CNS to injury.

CONCLUSIONS

Rational therapy for HIV-1 associated neurological disorders has been limited by the absence of large, adequate, and well-controlled clinical trials using HAART. This article reviews different options for the implementation of adjunctive therapies to HAART for HAD and peripheral neuropathy. In particular, GSK-3β inhibitors, neurotrophins, and some β-chemokines are agents that have afforded neuroprotection in preclinical *in vitro* and *in vivo* models. Most, if not all, of these agents are able to shift the balance toward anti-apoptotic survival pathways in neurons most vulnerable to HIV-1 neurotoxins. They provide the ability to augment HAART in the treatment of HIV-1 associated neurological disorders. Understanding the mechanisms of neuroprotection and immune function will help to design potential prophylactic treatment regimens for HAD. In order to provide this, research must proceed in parallel with clinical efforts to improve anti-retroviral regimens for HAD or HIVE, although the evolution of drug-resistant viral strains limits the sustained benefits of HAART. Neuroprotective therapies, which minimize CNS neurotoxicity associated with HAD and HIVE, will soon become primary treatment modalities augmenting the current HIV therapeutic modalities.

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