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Neuronal injury in simian immunodeficiency virus and other animal models of neuroAIDS

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Abstract

The success of antiretroviral therapy has reduced the incidence of severe neurological complication resulting from human immunodeficiency virus (HIV) infection. However, increased patient survival has been associated with an increased prevalence of protracted forms of HIV encephalitis leading to moderate cognitive impairment. NeuroAIDS remains a great challenge to patients, their families, and our society. Thus development of preclinical models that will be suitable for testing promising new compounds with neurotrophic and neuroprotective capabilities is of critical importance. The simian immunodeficiency virus (SIV)-infected macaque is the premiere model to study HIV neuropathogenesis. This model was central to the seminal work of Dr. Opendra "Bill" Narayan. Similar to patients with HIV encephalitis, in the SIV model there is injury to the synaptodendritic structure of excitatory pyramidal neurons and inhibitory calbindin-immunoreactive interneurons. This article, which is part of a special issue of the *Journal of NeuroVirology* in honor of Dr. Bill Narayan, discusses the most important neurodegenerative features in preclinical models of neuroAIDS and their potential for treatment development.

Keywords

encephalitis; gp120; HIV; macaque; SIV; transgenic

Introduction

The control and eradication of the neurological complications associated with acquired immunodeficiency syndrome (AIDS) continues to be an important goal in efforts toward improving the well being of patients with human immunodeficiency virus (HIV). Bill Narayan dedicated his professional life with great determination and passion to better understand the pathogenesis of HIV infection in the simian immunodeficiency virus (SIV) model. His group (Narayan *et al*, 1995), as well as others (Lackner *et al*, 1991), elegantly demonstrated that in the simian model, SIV-infected perivascular macrophages enter the central nervous system

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Dedicated to the memory of Opendra "Bill" Narayan.

(CNS) early in the progression of the disease, leading to a spectrum of neuroinflammatory and neurodegenerative alterations characteristic of this condition (Bissel *et al*, 2002; Lackner *et al*, 1991; Orandle *et al*, 2002; Westmoreland *et al*, 1998). Similarly, mononuclear cells infected with HIV-1 traffic into the CNS shortly after acquisition (Gendelman *et al*, 1997; Gonzalez-Scarano and Martin-Garcia, 2005) and can cause a progressive neurologic disease that translates into HIV-associated cognitive impairment (HACI) (Heaton *et al*, 1995). The cognitive deficits in patients with HIV profoundly affect the quality of life of people living with this condition and have often been linked to HIV encephalitis (HIVE) (Cherner *et al*, 2002). This neuroinflammatory condition (Gendelman *et al*, 1997; Wiley and Achim, 1994) is characterized by the presence of HIV-infected microglial cells, formation of microglial nodules, multinucleated giant cells, astrogliosis, myelin loss, and neurodegeneration (Bell, 2004; Budka *et al*, 1987; Everall *et al*, 2005).

With the advent of highly active antiretroviral therapies (HAART), the abundance of HIV in the brain and overt dementia has declined; however, as the number of treated subjects with chronic HIV infection increases, the prevalence of HACI is actually rising despite HAART (Gray *et al*, 2003; Maschke *et al*, 2000; McArthur *et al*, 2003; Sacktor *et al*, 2002). It is now becoming apparent that these patients may be suffering from protracted forms of HIVE (Bell, 2004; Gray *et al*, 2003) that might lead to more subtle cognitive alterations rather than to overt dementia (Cherner *et al*, 2002; Diesing *et al*, 2002; Gonzalez-Scarano and Martin-Garcia, 2005; Lawrence and Major, 2002). Patients with protracted mild forms of HIVE sometimes display more severe neurodegenerative pathology characterized by the simplification of the synaptodendritic structure of pyramidal neuronal populations in the neocortex, indicating that HIVE has transitioned from a subacute to a chronic condition (Everall *et al*, 2005).

Thus, future therapeutic developments for neuroAIDS might require the implementation of neuroprotective approaches in addition to the antiretroviral regimes. Development of such therapies involves the availability of adequate preclinical models. Bill Narayan made important contributions in characterizing the SIV model of neuroAIDS (Narayan *et al*, 1995; Stephens *et al*, 1995). This model is considered the premiere model to study the pathogenesis of HIVE. Other models include the HIV transgenic (tg) rat (Reid *et al*, 2001) and the HIV-gp120 tg mice (Toggas *et al*, 1994). Similar to models where gp120 (Sundar *et al*, 1991) or tat (Bansal *et al*, 2000; Jones *et al*, 1998) proteins were injected into the brains of mice, the tg model is representative of the toxic effects of the HIV proteins. However, whereas the injection models mimic the acute toxic effects of the disease, the tg models illustrate the chronic effects. A more recent model includes the injection of HIV-infected macrophages into the striatum of nude mice (Anderson *et al*, 2003). These models are being utilized both to understand the pathogenesis of the disease and mechanisms of neurodegeneration and for the testing of potentially neuroprotective treatments.

In this context, this review in honor of Bill Narayan will be focused on describing the most important neurodegenerative features in preclinical models of neuroAIDS, with a special emphasis on the SIV model.

Mechanisms of neurodegeneration and cognitive impairment in patients with HIVE

The mechanisms leading to cognitive impairment and dementia in AIDS patients are not completely understood. However, studies suggest that when HIV-infected monocytes/macrophages activate neuroinflammatory cells such as microglia and astrocytes (Gendelman *et al*, 1994; Langford and Masliah, 2001; Minagar *et al*, 2002; Mirra and del Rio, 1989; Nath, 1999; Pulliam *et al*, 1991; Speth *et al*, 2005; Wiley, 2003), these cells produce chemokines, cytokines, and neurotoxins that, in conjunction with secreted HIV proteins, damage the synaptodendritic arbor of neurons (Bellizzi *et al*, 2005) (Figure 1). This in turn leads to neuronal dysfunction and cell death probably via apoptosis (Brandimarti *et al*, 2004; Giulian *et al*,

1990; Kaul and Lipton, 1999; Martin-Garcia *et al*, 2002; Meucci *et al*, 1998; Nath, 2002; Pulliam *et al*, 1994, 1998; Sanders *et al*, 1998; Wang *et al*, 2004). This model predicts that levels of HIV in the CNS might reflect the extent of the structural and functional pathology in the brain (Brew *et al*, 1995; Glass *et al*, 1995; McArthur *et al*, 1997).

The neurodegenerative process in patients with HIVE is characterized by synaptic and dendritic damage (Masliah *et al*, 1997) to pyramidal neurons (Ellis *et al*, 2007; Masliah *et al*, 1997), loss of calbindinimmunoreactive interneurons (Masliah *et al*, 1995), and myelin loss (Langford *et al*, 2002) (Figure 2). Although disruption of the corticocortical connections might result in learning and attention deficits, hippocampal pathology is linked to memory loss and corticostriatal damage, resulting in motor alterations (Moore *et al*, 2006). The neuronal populations most severely affected in these regions include large pyramidal neurons in the neocortex (Figure 2) (Budka *et al*, 1987; Everall *et al*, 1991; Fox *et al*, 1997; Masliah *et al*, 1992a; Weis *et al*, 1993; Wiley *et al*, 1991a), spiny neurons in the putamen (Masliah *et al*, 1992b, 1996), medium-sized neurons in the globus pallidus, and interneurons in the hippocampus (Fox *et al*, 1997; Masliah *et al*, 1992b, 1995).

The severity of the cognitive impairment in patients with HIVE is associated with the extent of the synaptodendritic damage to pyramidal neurons in the neocortex (Cherner *et al*, 2002). In HIV patients with a history of methamphetamine (METH) abuse, damage to calbindin-immunoreactive neurons correlates with the severity of the cognitive impairment (Chana *et al*, 2006; Langford *et al*, 2003). In both cases, macrophage infiltration in the CNS is also a good predictor of the cognitive impairment (Achim and Wiley, 1996; Glass *et al*, 1995; Wiley *et al*, 1991b); however, the levels of HIV burden in the CNS are less predictive of the cognitive and mood deficits in these patients (Glass *et al*, 1995; Wiley *et al*, 1994). Consistent with these neuropathological studies, analyses of the brains of AIDS patients and observations in animal models show similar alterations in neuronal markers such as *N*-acetylaspartate (NAA) by nuclear magnetic resonance (NMR) spectroscopy (Gonzalez *et al*, 2000; Marcus *et al*, 1998; Wilkinson *et al*, 1997).

In addition to the damage to *mature neuronal circuitries*, recent studies have shown that HIV proteins might contribute to the neurodegenerative process by *interfering with neurogenesis* in the hippocampus (Krathwohl and Kaiser, 2004; Lawrence *et al*, 2004; Tran and Miller, 2005; van Marle *et al*, 2005). Neurogenesis in the dentate gyrus is an active process in the mature CNS and plays a role in synaptic plasticity, memory, and learning (Gage *et al*, 1998). Environmental enrichment has been shown to stimulate neurogenesis and improve performance in memory tasks in mice (Brown *et al*, 2003; Bruel-Jungerman *et al*, 2005; Olson *et al*, 2006). The wnt (Lie *et al*, 2005) and probably the cyclin-dependent kinase (CDK) signaling pathways, as we have begun to explore, play an important role in this process. Therefore the neurodegenerative process leading to cognitive alterations in HIV patients includes both (1) damage to the mature synaptodendritic apparatus of developed neurons and (2) impaired ability of neuronal progenitor cells (NPCs) in the hippocampal dentate gyrus to generate new neurons (Figure 3).

The mechanisms leading to neurodegeneration in HIVE might involve a variety of pathways, including excitotoxicity (Haughey *et al*, 2001; Kaul *et al*, 2001), oxidative stress (Nath, 2002), mitochondrial dysfunction (Maragos *et al*, 2002; Turchan *et al*, 2003), and calcium dysregulation (Haughey and Mattson, 2002; Mattson, 2002). In addition, several lines of investigation have found that interference with signaling pathways mediating neuroprotection might also play an important role. Among them, previous studies have shown that HIV proteins abnormally activate the glycogen synthase kinase-3β (GSK3β) (Maggirwar *et al*, 1999) and extracellular-regulated kinase (ERK) (Lannuzel *et al*, 1997; Rusnati *et al*, 2001) signaling pathways, which otherwise are regulated by fibroblast growth factors (FGFs) (Hashimoto *et*

al, 2002; Langford *et al*, 2005). Furthermore, HIV proteins trigger neurodegeneration by activating signaling pathways involved in apoptosis, such as Pyk2 (Del Corno *et al*, 2001), p38 and JNK (Kaul and Lipton, 1999; Lannuzel *et al*, 1997; Yi *et al*, 2004), and the RNA-activated protein kinase (Alirezaei *et al*, 2007).

More recently, and as part of a gene array study, we found that several components of the CDK5 signaling pathway are altered in patients with HIVE (Masliah *et al*, 2004). The CDK family is involved in regulating the cell cycle in dividing cells. To date, a total of nine CDKs and a number of cyclins (A to T) have been identified. Cyclin D activates CDK2, CDK4, and CDK6 during the G1 phase of cell division (Schwartz and Shah, 2005). The association between cyclin E and CDK2 is active at the G1/S transition and directs entry into S phase. The S phase is regulated by the cyclin A/CDK2 complex, and the G2 phase is modulated by the cyclin A/CDK1 (also known as cdc2) complex. Finally the cyclin B/CDK1 complex is necessary for mitosis to occur. Although in dividing peripheral tissues, CDKs play a role in modulating the progression of the cell cycle, in the mature CNS, CDKs are involved in synaptic plasticity and neuronal differentiation (Schwartz and Shah, 2005). Interestingly, in the nervous system, CDK5 is the predominant CDK, is highly expressed in neurons, and plays an important role in the mature and developing brain by regulating the phosphorylation of cytoskeletal and synaptic proteins (Fischer *et al*, 2005; Johansson *et al*, 2005).

Neuronal injury and NMR spectroscopy in SIVE models

Simian immunodeficiency virus is the closest known relative to HIV and like HIV, it infects CD4+ T lymphocytes, cells of monocyte/macrophage lineage, and brain macrophages (Lackner *et al*, 1991, 1994; Zink *et al*, 1998). SIV is a lentivirus with extensive sequence homology to HIV (Desrosiers, 1990a, 1990b; Gao *et al*, 1999); in rhesus macaques, SIV produces a clinical syndrome similar to that of human AIDS patients (Simon *et al*, 1992). The SIV-infected macaque is the premiere model of HIV neuropathogenesis; however, similar to HIV-infected humans, the low percentage (~25%) of animals developing SIVE and the prolonged progression (1 to 3 years) to AIDS somewhat limit the usefulness of this model (Westmoreland *et al*, 1998). However, this traditional model does permit close examination of the complex metabolic and histopathologic changes that occur in the days and weeks after SIV infection.

Recent advances in noninvasive neuroimaging using ^{1}H magnetic resonance spectroscopy (MRS) of HIV-infected individuals allow for the detection of brain abnormalities prior to the onset of neurological symptoms, and the reversal of abnormalities with antiretroviral therapy (Chang *et al*, 1999; Tracey *et al*, 1998). Metabolites most commonly studied in the CNS with HIV infection include the neuron-associated metabolite NAA, which decreases with neuron injury and death; choline (Cho), which is associated with cell membrane turnover and reactive gliosis; and *myo*-inositol (MI), a marker associated with inflammation and gliosis (Barker *et al*, 1995; Chang *et al*, 1999; Lee *et al*, 2003; Meyerhoff *et al*, 1993, 1999; Tracey *et al*, 1996). Changes in these metabolites have been studied in HIV infection, but a difficulty with such studies is lack of knowledge of the timing of infection and the nonuniform progression of CNS disease between patients. Thus, MRS studies in the SIV model present an excellent opportunity to probe the relationship between these resonances and the ongoing pathological changes during this time period.

In MRS studies of SIV-infected macaques, we observed decreases in the NAA/creatine (Cr) ratio (Greco *et al*, 2002), but these changes were subtle and rapidly resolved with control of viremia. However, we demonstrated that these transient changes in NAA/Cr best correlated with changes in synaptophysin during acute SIV infection in the macaque and reflect reversible neuronal injury during primary SIV infection (Lentz *et al*, 2005) (Figure 4). ^{1}H MRS has been widely used to study HIV-infected patients, and although early studies reported profound loss

in NAA/Cr (Barker *et al*, 1995; Chang *et al*, 1999; Chong *et al*, 1993; Jarvik *et al*, 1993; Menon *et al*, 1992; Tracey *et al*, 1996), such drops are less dramatic in the current HAART era. Improvement in the brain MR spectrum along with neurocognitive improvement has been reported following treatment with HAART (Chang *et al*, 1999; Stankoff *et al*, 2001), which parallels the effect of treatment in the model reported here. Still, a recent multicenter study reported an 8% decrease in NAA/Cr compared to controls in the centrum semiovale in patients undergoing HAART (Lee *et al*, 2003).

In addition to the alterations in NAA in the SIV-infected rhesus macaque model of neuroAIDS, significant changes in the levels of Cho/Cr and MI/Cr are detected by ^{1}H MRS during the first month of infection. For this study, animals were intravenously infected with SIVmac251 (Jarvik *et al*, 1993; Kodama *et al*, 1993) as previously described (Greco *et al*, 2002; Greco *et al*, 2004). *In vivo* ^{1}H MRS studies were performed in animals imaged before inoculation with SIVmac251, and at 11 and 25 days post inoculation (d.p.i.), and the second cohort was imaged before inoculation and at 13 and 27 d.p.i. A profound, yet transient, astrogliosis that correlated highly with viremia was observed in these animals. We also found that *in vivo* Cho/Cr levels tended to follow a similar temporal trend as plasma virus levels and cortical astrogliosis for the first 2 weeks after infection but diverged subsequently. The *in vivo* MI/Cr ratio increased with peak viremia, but remained elevated despite control of plasma virus. MRS studies performed at 1.5 T of the frontal lobes of HIV-infected patients have demonstrated increased Cho/Cr (Barker *et al*, 1995; Chang *et al*, 1999), increased MI/Cr (Chang *et al*, 1999; Lopez-Villegas *et al*, 1997), and decreased NAA/Cr (Barker *et al*, 1995; Chang *et al*, 1999; Lopez-Villegas *et al*, 1997). Additionally, several MRS studies of HIV-infected individuals have demonstrated early elevations of Cho/Cr and/or MI/Cr, with decreases in NAA/Cr more commonly observed later in the progression of the disease (Laubenberger *et al*, 1996; Lopez-Villegas *et al*, 1997; Tarasow *et al*, 2003; Tracey *et al*, 1996). Interestingly, the temporal courses of Cho/Cr and MI/Cr are distinct, and the former better follows the course of astrogliosis.

More recently, two novel, accelerated AIDS macaque models have been developed that demonstrate rapid disease progression and high rates of incidence of SIVE (Schmitz *et al*, 1999a, 1999b; Williams *et al*, 2001; Zink and Clements, 2002). One model uses a combination of viruses, one which results in $CD8^{+}$ T-lymphocyte depletion, and thus immune system suppression, in combination with a second virus that is macrophage-tropic that replicates efficiently within CNS macrophages (Clements *et al*, 2002; Zink and Clements, 2002). The other model uses monoclonal antibody (mAb) treatment to deplete systemic $CD8^{+}$ lymphocytes, which results in early and significant monocyte/macrophage accumulation in the CNS, rapid disease progression, and a high incidence of SIVE (Schmitz *et al*, 1999a, 1999b; Williams *et al*, 2001). Both models and studies by others using SIV-infected rhesus macaques support the role of the peripheral immune system in indirectly contributing to CNS disease progression and severity (Marcondes *et al*, 2001; Sopper *et al*, 1998).

We recently reported the effects of non-CNS penetrating, antiretroviral agents in controlling and reversing neuronal injury (Gonzalez *et al*, 2006; Williams *et al*, 2005) in an accelerated AIDS model. Utilizing the mAb-induced depletion of CD8+ cells in the SIV-macaque model, infected animals that did not receive therapy became moribund with AIDS within 8 to 12 weeks. Histopathological examination of brain tissues from these animals revealed severe inflammation, robust macrophage accumulation, multinucleated giant cell (MNGC) formation, productive viral replication, morphologic alterations of cortical neurons, and damage to the synaptodendritic neuronal arbor. However, animals that underwent daily therapy were found to have a reduction in peripheral activated/infected monocytes, a lack of active viral replication or MNGC formation in brain tissues, and a near complete reversal of neuronal injury, even though peripheral viral load levels remained high (10^{5} to 10^{6} copies/ml). MRS allowed for

noninvasive, *in vivo* monitoring of neuronal injury as measured by the ratio of NAA/Cr in both treated and untreated animals. All macaques were found to have large decreases in NAA/Cr levels during the first 4 weeks of infection; however, those receiving treatment thereafter underwent a nearly complete recovery to that of preinfection NAA/Cr levels. These results not only underscore the role of activated/infected peripheral blood monocytes in neuroAIDS, but also provide a plausible explanation for the clinical success of antiretroviral therapy in reducing the incidence of overt HIV-associated dementia since the 1990s despite the lack of CNS penetration by many of these drugs.

To summarize, in the classic SIV macaque model of neuroAIDS, the brain undergoes a profound but transient astrogliosis as quantified by glial fibrillary acidic protein (GFAP) immunohistochemistry during the first month of infection. *In vivo* ^{1}H MRS during this period demonstrates that Cho/Cr more closely tracks changes in GFAP than MI/Cr, although both attain peak levels at the same time as GFAP peaks. Subtle changes in NAA closely reflect the synaptodendritic pathology observed in this model. Using the rapidly progressing SIV-infected macaque model, substantial neuronal injury along with profound SIVE is observed within weeks of infection. This new model coupled with MRS permits an efficient testing of hypotheses of the pathogenesis of neuroAIDS through studies of antiretroviral therapies, inflammation modulators, inhibitors of cell trafficking, and neuroprotective and neurotrophic agents.

Selective neuronal injury mediated by HIV proteins and comorbid factors in rodent models

In addition to the neurotoxic chemokines and cytokines produced by HIV-infected macrophages/microglia (Kaul and Lipton, 1999; Li *et al*, 2005; Ryan *et al*, 2002; Xiong *et al*, 2000), these cells have been also shown to release HIV proteins such as gp120 and Tat (Mattson *et al*, 2005; Xiong *et al*, 2000). The acute neurotoxic effects of HIV proteins have been modeled *in vivo* by injecting nanomolar amounts into the neocortex, limbic system, and striatum (Bansal *et al*, 2000; Lipton, 1992a, 1992b; Lipton *et al*, 1995). The chronic effects have been investigated in tg models overexpressing gp120 (Toggas *et al*, 1994) or Tat (Bansal *et al*, 2000) under constitutive astroglial promoters such as GFAP or under the control of viral vectors. Overall, these models have shown that gp120 is neurotoxic to excitatory pyramidal neurons, resulting in synaptodendritic injury in the neocortex and limbic system (Toggas *et al*, 1994, 1996). As a result of the synaptic damage, these mice develop alterations in long term potentiation (LTP) as well as behavioral deficits in the water maze (Anderson *et al*, 2003; D'Hooge *et al*, 1999).

Expression of Tat from astrocytes delivered into the brain has been shown to target synapses and to disrupt axonal functioning (Bruce-Keller *et al*, 2003). Tat also has been shown to cooperate with comorbid factors in HIVE patients such as METH (Langford *et al*, 2004; Maragos *et al*, 2002). Combined Tat and METH injected into the striatum is toxic to spiny neurons (Maragos *et al*, 2002). HIV proteins and METH in combination are also especially toxic to γ-aminobutyric acid (GABA)-ergic interneurons in the neocortex and striatum (Figure 5). METH is an important comorbid factor to consider because the drug abuser population is among the fastest growing HIV-infected group (Nath *et al*, 2001).

The selective neurotoxic effects of other HIV proteins are currently under investigation. Recent studies have suggested that HIV-gp120 might disrupt neurogenesis by promoting cell-cycle withdrawal of NPCs (Okamoto *et al*, 2007). In gp120 tg mice, neurogenesis is reduced by affecting the cyclin kinase pathway component cdc25c (Okamoto *et al*, 2007).

However, the mechanisms of toxicity of gp120 and Tat are complex and might involve cooperation with other molecules including excitotoxins such as glutamate (Kaul and Lipton, 2006), platelet-activating factor (PAF) (Gelbard *et al*, 1994; Westmoreland *et al*, 1996), and

tumor necrosis factor alpha (TNFα) (Buscemi *et al*, 2007). Although restricted in nature, these models offer an excellent opportunity for testing and development of neuroprotective agents for the treatment of patients with HIV cognitive impairment (Everall *et al*, 2002; Toggas *et al*, 1996).

Neuronal dysfunction in recent models of HIV-associated neuropathology

Two new models have been developed in recent years, the nude mice grafted with HIV-infected macrophages in the striatum (Anderson *et al*, 2003) and the HIV tg rat (Reid *et al*, 2001). A number of studies in the engrafted nude model have shown that the synaptodendritic structure in the striatum of the mice is damaged (Anderson *et al*, 2003). This was associated with alterations in LTP and behavioral performance (Persidsky and Gendelman, 2002; Zink *et al*, 2002) that can be partially reverted with neuroprotective agents such as lithium chloride and valproic acid (Dou *et al*, 2003, 2005). Similarly, we have shown that lithium is neuroprotective in the gp120 tg model (Everall *et al*, 2002) of neurodegeneration as well as in a model of Alzheimer's disease (Rockenstein *et al*, 2007) by reducing the activity of GSK3β, a kinase that regulates cell fate and synaptic plasticity (Hashimoto *et al*, 2002). Based on these preclinical studies, we conducted a pilot study with lithium in patients with HIV and cognitive alterations and showed that this neuroprotective agent is capable of reducing the deficits in this patients (Letendre *et al*, 2006). Therefore, the preclinical models simulate some important aspects of HIV-mediated neurotoxicity that might serve as targets for neuroprotective therapy development.

A novel, noninfectious HIV-1 tg rat expresses an HIV-1 provirus with a deletion of functional *gag* and *pol* genes (Reid *et al*, 2001). This tg rat model reportedly develops clinical manifestations of human HIV disease, and mimics the persistent infection that results from the presence of HIV viral proteins in the host. In the water maze behavioral test, HIV-1 tg rats showed a deficit in learning how to swim to the location of the hidden platform but did not show a deficit in their memory of the general location of the hidden platform (Vigorito *et al*, 2007). It is yet not clear which neuronal populations (if any) are affected in this model and what are the selective patterns of neurodegeneration. However, this model offers an interesting alternative for the study of HIV pathogenesis and the development of neuroprotective therapies.

In summary, damage to neuronal circuitries, similar to what it is observed in patients with HIVE, has been documented in animal models ranging from the SIV macaque models to the tg rat and mouse. Better understanding and characterizing the patterns of neuronal damage in these models is important in progressing towards the goal of developing neuroprotective therapies for HIVE.

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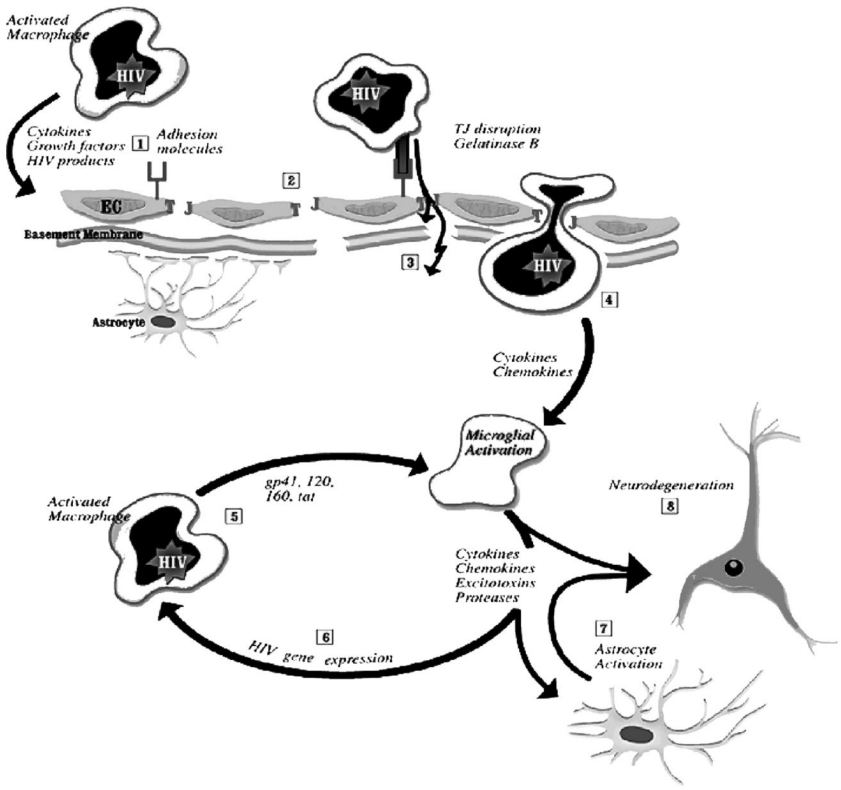

Figure 1.
Diagrammatic representation of the proposed mechanisms of HIV induced neuronal damage.

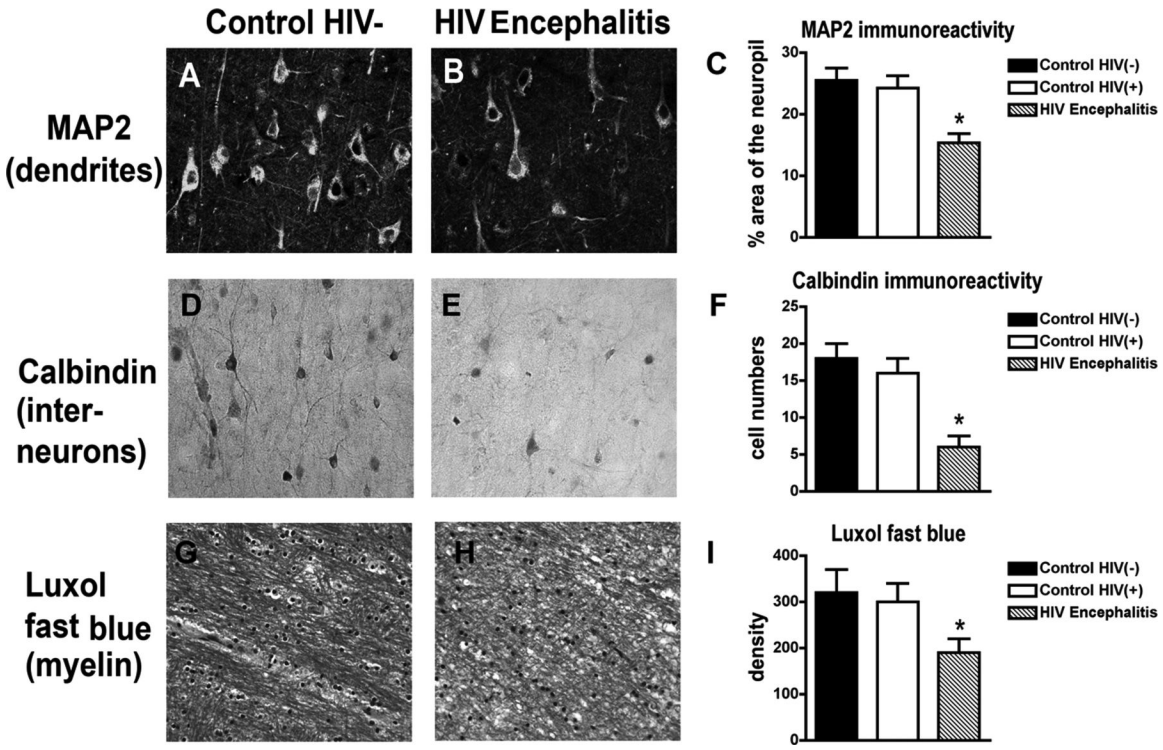

Figure 2.

Patterns of selective neuronal damage and myelin loss in the brains of patients with HIVE. **(A–C)** Decrease in the MAP2-immunoreactive dendritic arbor in HIVE. **(D–F)** Reduction in the numbers of calbindin-positive interneurons in HIVE. **(G–I)** White matter pallor and loss of myelin in the HIVE cases.

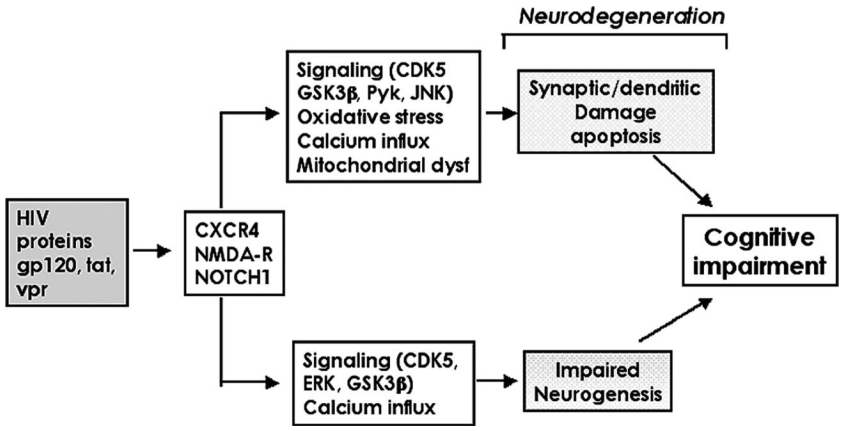

Figure 3.
Combined contribution of neuronal loss and defects of neurogenesis to the neurodegenerative process in HIVE.

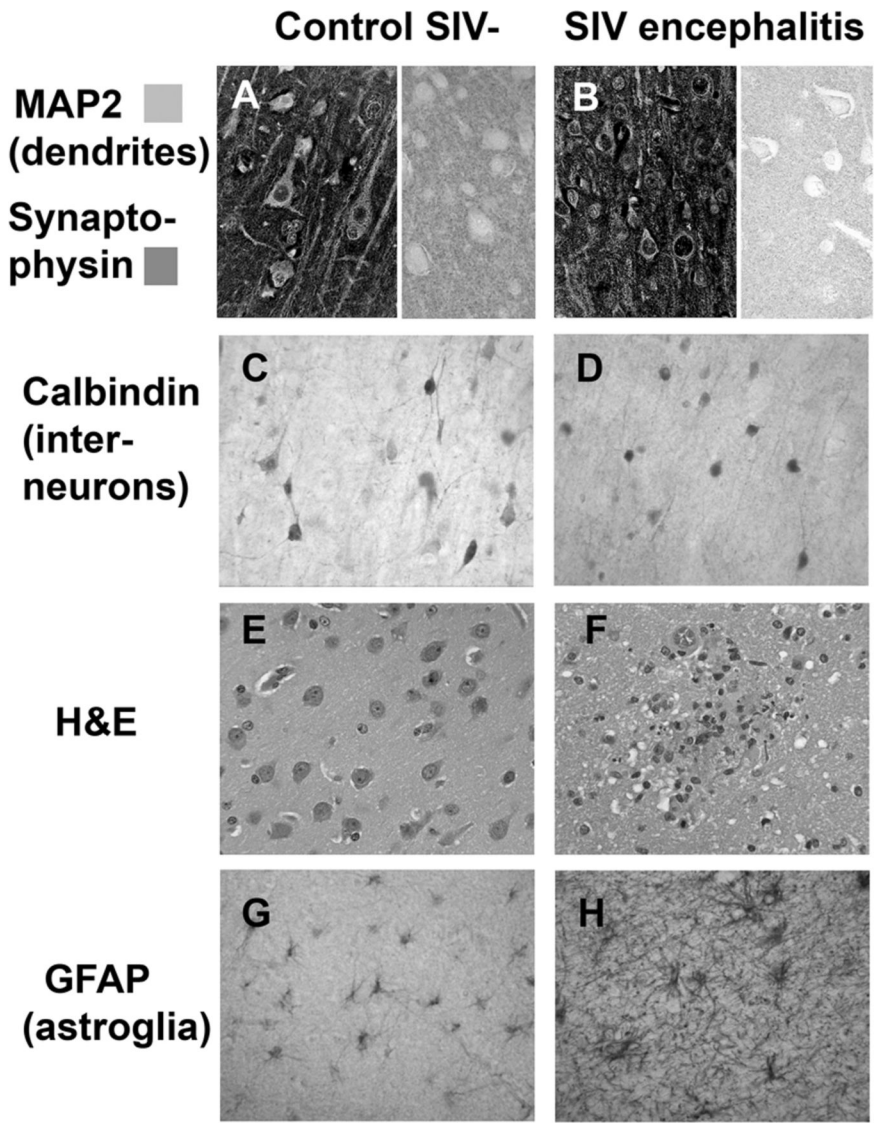

Figure 4.

MRS correlates of neuronal injury in the SIV model of HIV in the brain. **(A, B)** Comparison of the loss of MAP2-immunoreactive dendritic arbor and synaptophysin stained nerve terminals in SIVE. **(C, D)** Example of the alterations in calbindin interneurons in SIVE. **(E, F)** Comparison of the control neuronal distribution in SIV− and of microglial nodules with giant cells in SIVE. **(G, H)** Increased astrogliosis in SIVE.

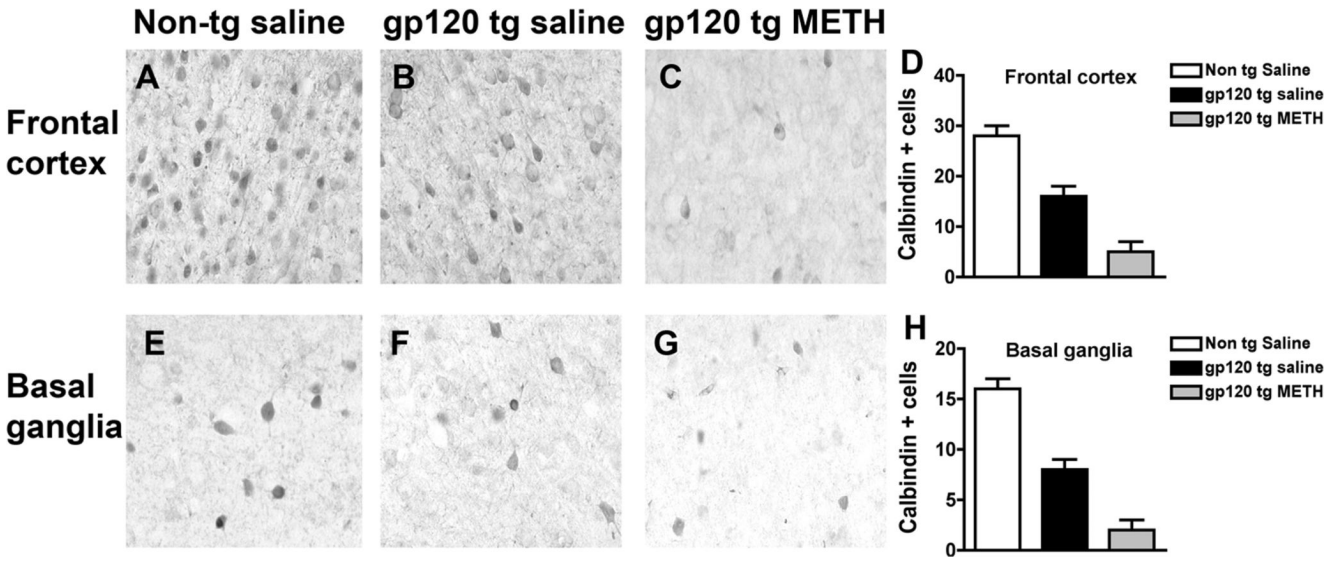

Figure 5.

Synergistic toxic effects of HIV proteins and METH in a mouse model. **(A–D)** Loss of calbindin interneurons in the neocortex of GFAP-gp120 tg mice challanged with methamphetamine. **(E–H)** Enhanced damage to calbindin neurons in the basal ganglia of GFAP-gp120 tg mice challanged with methamphetamine.