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INVITED REVIEW

Targeting the Glutamatergic System for the Treatment of HIV-Associated Neurocognitive Disorders

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Abstract The accumulation of excess glutamate in the extracellular space as a consequence of CNS trauma, neurodegenerative diseases, infection, or deregulation of glutamate clearance results in neuronal damage by excessive excitatory neurotransmission. Glutamate excitotoxicity is thought to be one of several mechanisms by which HIV exerts neurotoxicity that culminates in HIV-associated neurocognitive disorders (HAND). Excess glutamate is released upon HIV infection of macrophage/microglial cells and has been associated with neurotoxicity mediated by gp120, transactivator of transcription (Tat) and other HIV proteins. Several strategies have been used over the years to try to prevent glutamate excitotoxicity. Since the main toxic effects of excess glutamate are thought to be due to excitotoxicity from over activation of glutamate receptors, antagonists of these receptors have been popular therapeutic targets. Early work to ameliorate the effects of excess extracellular glutamate focused on NMDA receptor antagonism, but unfortunately, potent blockade of this receptor has been fraught with side effects. One alternative to direct receptor blockade has been the inhibition of enzymes responsible for the production of glutamate such as glutaminase and glutamate carboxypeptidase II. Another approach has been to regulate the transporters responsible for modulation of extracellular glutamate such as excitatory amino acid transporters and the glutamate-cystine antiporter. There is preliminary experimental evidence that these approaches have potential therapeutic utility for the treatment of HAND. These efforts however, are at an early stage where the next steps are dependent on the identification of drug-like inhibitors as well as the development of predictive neuroAIDS animal models.

Keywords Glutamate · HIV-associated neurocognitive disorder · Excitotoxicity · Glutaminase · Glutamate carboxypeptidase II

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Introduction

The introduction of combination antiretroviral therapy (cART) in 1996 brought a dramatic reduction in HIV RNA levels and thus morbidity and mortality rates in human immunodeficiency virus (HIV) infected individuals (Coiras et al. 2009). Although cART has been successful, it has not eradicated the disease as the virus can persist in resting memory $CD4^+$ T cells as well as macrophages and astrocytes (Coiras et al. 2009). These latent reservoirs of HIV are easily and quickly activated if cessation of cART treatment occurs (Lewin et al. 2008). Elimination of these reservoirs is a major goal of current research in the HIV field. Even with

continuous cART therapy, significant morbidity persists, in particular in the central nervous system (CNS) (Gorantla et al. 2012) where memory problems and dementia are common. It is thought that HIV-associated neurocognitive disorders (HAND) remain high due to both latent reservoir and reduced penetrance of cART to the brain.

HIV initially enters the brain by crossing the blood brain barrier via monocytes and lymphocytes very shortly after infection (Fig. 1). The virus then takes up permanent brain residence mainly in microglia, macrophages and astrocytes (Kaul et al. 2001; Tan and McArthur 2012). HIV does not infect neurons, though neural progenitor cells appear able to take up the virus (Kaul 2008). Neurotoxicity in patients with HIV-1 infection is thought to be mediated by HIV-1 proteins such as gp120 and transactivator of transcription (Tat), as well as other products released from infected cells. The mechanisms of neurotoxicity are thought to be both direct and indirect including glutamate excitotoxicity, oxidative stress, increase in apoptosis, altered calcium homeostasis, stimulation of tumor necrosis factor-alpha (TNF-α) and nuclear factor κB (NF-kB) and stimulation of nitric oxide production. These mechanisms are likely acting in concert.

Although multiple mechanisms are at play, the objective of this review is to present the evidence which indicates that glutamate excitotoxicity is a factor in HIV neurotoxicity and to focus on how this evidence suggests potential opportunities to ameliorate HAND through pharmacological manipulations of the glutamate system.

Mechanisms of glutamate excitotoxicity in HAND

The amino acid glutamate is the principal excitatory neurotransmitter in mammalian CNS where it is synthesized and stored in the neuronal cytosol in synaptic vesicles in millimolar concentrations (Nedergaard et al. 2002). Extracellular concentrations of glutamate in the synaptic cleft are kept low (nanomolar ranges) by excitatory amino acid transporters (EAATs). These are glutamate transporters which are located mainly on astrocytes and function in removing excess glutamate from the synaptic cleft after the completion of a signaling event, returning it to homeostatic levels.

The accumulation of excess glutamate in the extracellular space as a consequence of CNS trauma, neurodegenerative diseases, infection, or deregulation of glutamate clearance results in excitotoxicity. The presence of excess glutamate in the synaptic clefts activates glutamate gated ion channels and results in high levels of ion influx into neuronal cells allowing the over activation of downstream calcium ion-dependent effectors and signaling pathways, culminating in neuronal damage. Neuronal damage then causes further release of intracellular glutamate into the extracellular space affecting nearby neurons. Most acute and chronic neuronal diseases, including HAND, have implicated this type of bystander pathology of excitotoxicity.

HIV infection of macrophages and microglial cells causes excess glutamate release and impaired uptake

Macrophages and microglia, the resident macrophages in the CNS, are key cellular components of innate immunity. These cells can release a diversity of trophic factors and cytokines that control the behavior and/or destiny of other cells by promoting cell proliferation, migration, recruitment, and apoptosis. Additionally, macrophages and microglial cells play an important role in the phagocytosis of invading pathogens, tissue repair and the clearance of debris (Liu and Hong 2003). The activity of these cells is highly regulated both spatially and temporally due to the potential deleterious effects of their uncontrolled hyperactivation, which include increase in inflammation and cell death. Microglial cells are particularly susceptible to alterations in their surroundings, becoming easily activated, changing morphology and up-regulating the production of a number of membrane receptors and soluble factors (Kreutzberg 1996; Ransohoff and Perry 2009). Conditions that involve neuronal degeneration like HAND, Alzheimer's disease, cerebral ischemia and multiple sclerosis, have been associated with microglial cells pathological activity (Gao and Hong 2008; Zindler and Zipp 2010).

Invasion of the brain seems to occur very early in the progression of the disease. However, there is no convincing evidence of HIV-1 neuronal infection despite the fact that HIV-1 associated neuronal dysfunction is accompanied by substantial neuronal loss in the neocortex, putamen, globus pallidus, substantia nigra and hippocampus (Everall et al. 1991; Masliah et al. 1992). Hence it is widely accepted that macrophages and microglial cells are responsible for producing and releasing the neurotoxic factors that cause neuronal death (Gendelman 2012). HIV-1 is capable of infecting $CD4^+$ macrophages and T-cells (Chen et al. 1983; Popovic et al. 1983; Klatzmann et al. 1984a, b). Infected macrophages are thought to cross the blood–brain barrier (BBB), turn into resident CNS macrophages and mediate the spread of the virus in the brain (Fig. 1). There is considerable evidence that supports this hypothesis ("Trojan horse" hypothesis) as the mechanism of brain infection by HIV-1 (Peluso et al. 1985; Budka 1986, 1991; Koenig et al. 1986; Kure et al. 1990; Dickson et al. 1993; Fischer-Smith et al. 2001). Upon activation, HIV-1 infected macrophages and microglial cells release chemokines, inflammatory cytokines (TNF-α, IL-1β, IL-

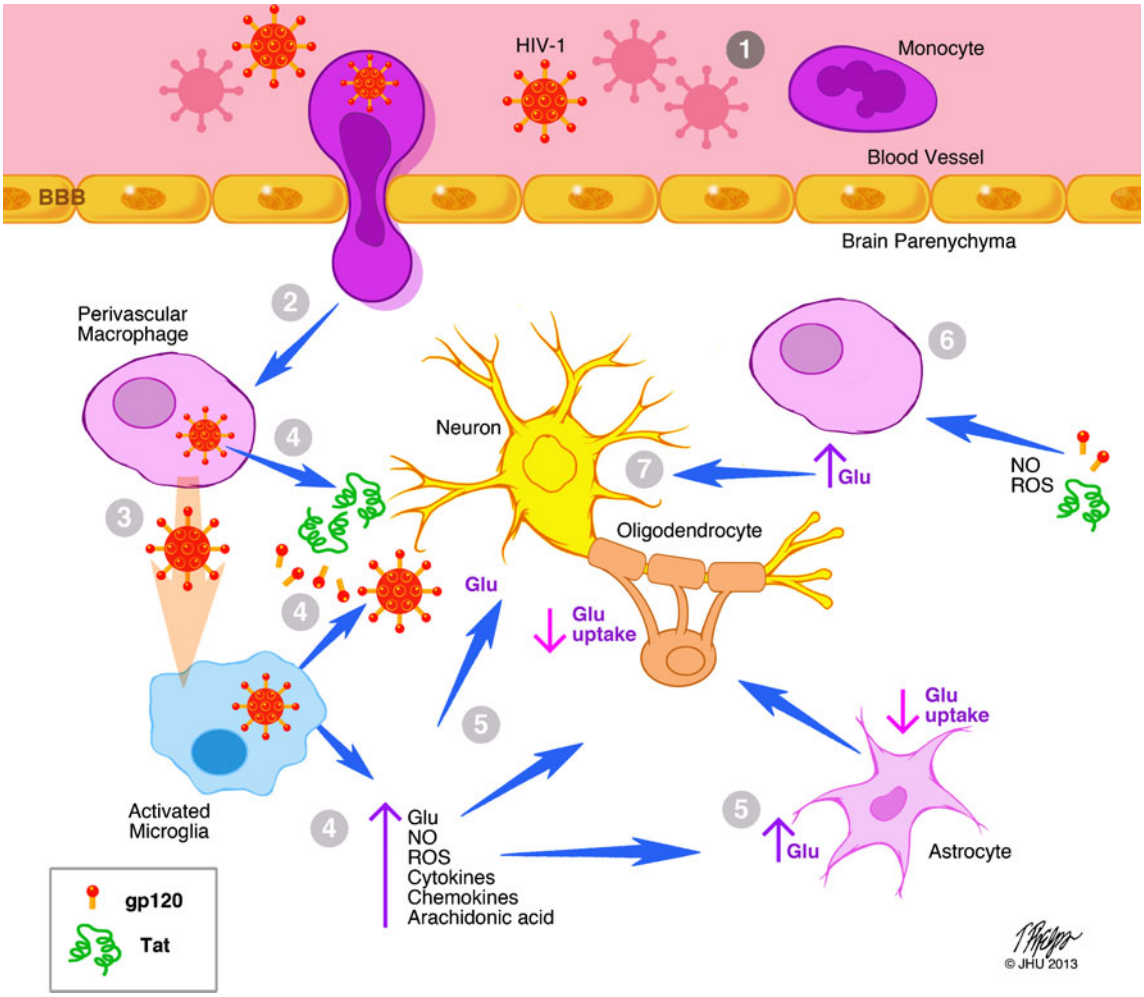

Fig. 1 Mechanisms of glutamate excitoxicity during HIV-1 infection (1) Infection of circulating monocytes with HIV-1. (2) HIV-1 infected macrophages cross the BBB and become perivascular macrophages. (3) HIV-1 infected perivascular macrophages in the brain parenchyma release viral particles that infect other brain macrophages and microglial cells. (4) Activated macrophages and microglial cells release viral proteins gp120 and Tat, glutamate and other factors such as NO, ROS, cytokines, chemokines and arachidonic acid that can either directly or indirectly affect glutamate metabolism and/or transport. (5) Decrease in glutamate uptake by oligodendrocytes and astrocytes due to increased levels of these toxins released by HIV-1 infected macrophages and microglial cells. These factors also cause an increase in vesicular glutamate release by astrocytes. (6) Viral proteins Tat and gp120 and oxidative stress induced by ROS and NO cause an increase in the activity of xCT in uninfected perivascular macrophages and microglia and as a consequence extracellular levels of glutamate increase. (7) Excessive extracellular glutamate triggers activation of glutamate receptors on neurons causing an increase in the intracellular calcium levels, cell death and neuronal degeneration

6), nitric oxide (NO) and glutamate. Excess glutamate can induce neuronal damage through N-methyl-D-aspartate (NMDA) receptor activation (Cutler and Dudzinski 1974; Fonnum 1984). Indeed, HIV-1 infected patients show elevated CSF glutamate levels that correlate with the severity of the dementia and the degree of brain atrophy (Ferrarese et al. 2001).

Several glutamate targets (Fig. 2) have been shown to be affected by HIV infection. HIV-1 infected human macrophages and human primary fetal microglia cells have increased glutaminase mRNA and protein levels resulting in elevated extracellular glutamate levels that cause reduced viability of cortical neurons in co-culture or of neurons incubated with conditioned media from these infected cells (Tian et al. 2008; Erdmann et al. 2009; Huang et al. 2011; Zhao et al. 2012). MK-801 (dizocilpine) a non-competitive antagonist at the NMDA receptor abolished the effects on neuronal viability, suggesting this is an NMDA receptor-dependent process (Wong et al. 1986).

Treatment of macrophages and microglial cells with pro-inflammatory factors like lipopolysaccharides (LPS) or HIV-1 Tat protein generates reactive oxygen species (ROS), which seem to contribute to the accumulation of

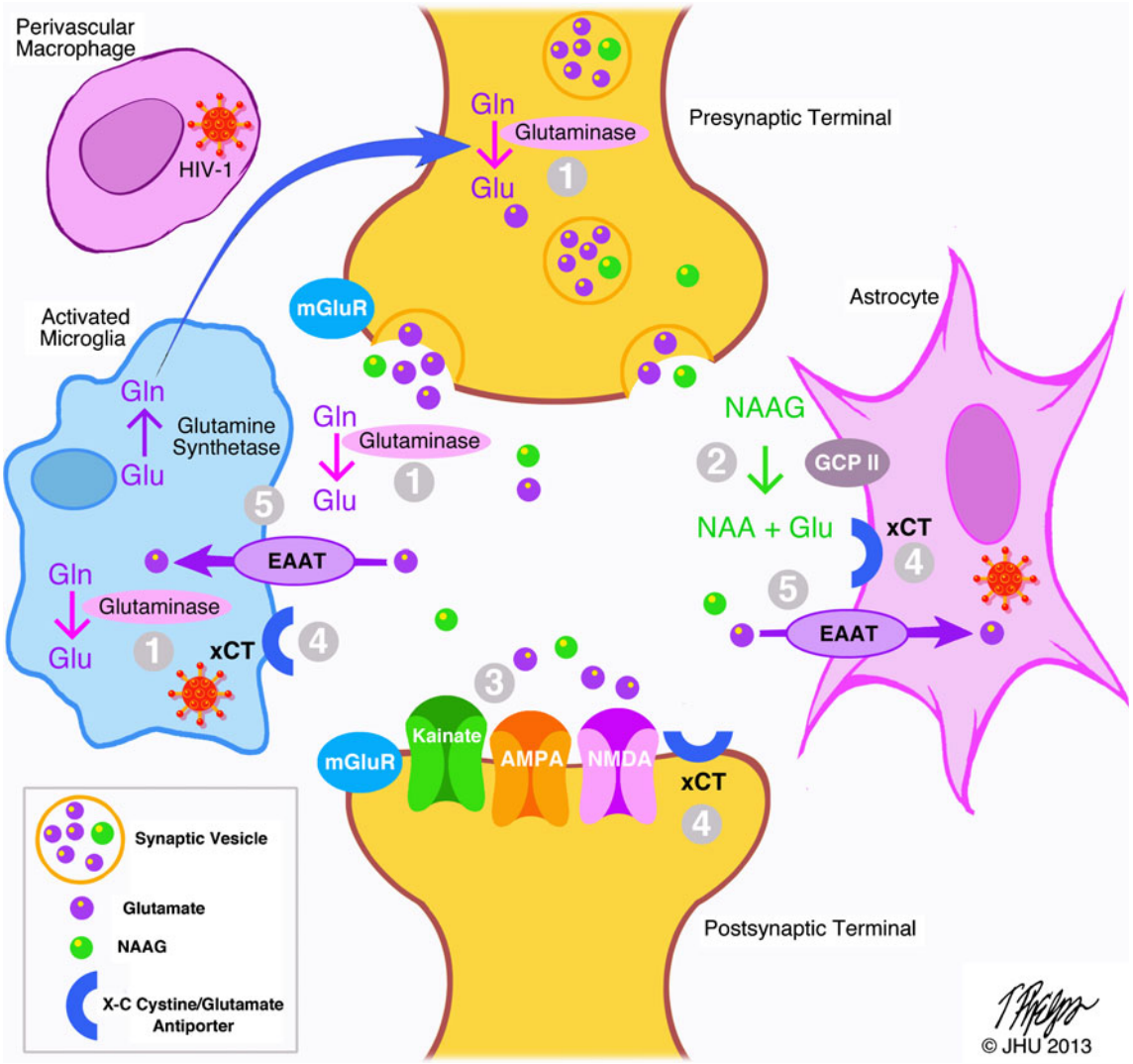

Fig. 2 Potential ways to regulate glutamate excitotoxicity for the treatment of HAND (1) Inhibition of glutaminase - glutaminase is a neuronal enzyme that produces glutamate by the deamination of glutamine. During HIV-1 infection, it is increased in glial cells and the synaptic cleft. (2) Inhibition of GCPII - GCPII is an astrocytic enzyme that catalyzes the hydrolysis of NAAG to N-acetyl aspartate (NAA) and glutamate. (3) Blockade of glutamate receptors- glutamate receptors such as NMDA, AMPA, kainate and mGluR are targets for inhibition of glutamate excitotoxicity in HAND. (4) Inhibition of xCT - xCT transports extracellular cys2 into cells and intracellular glutamate into the extracellular space. (5) Activation of glutamate transporters (e.g. EAAT1) – glutamate transporters mobilize glutamate away from the synaptic cleft. Glutamate and NAAG are released through intracellular vesicles at the presynaptic terminal during neurotransmission. The illustration shows NAAG and glutamate in the same vesicles but it is not known if they are in the same or different vesicles

extracellular glutamate and neuronal cell death in a process involving the glutamate-cystine antiporter (xCT) (Barger et al. 2007; Niki 2009).

It has been shown that up to 19 % of astrocytes in the brain of patients with HAND are infected with HIV-1 and that there is a direct correlation between the level of infected astrocytes and the degree of neuropathological changes (Churchill et al. 2009). Unlike macrophages and microglia, astrocytes are latently infected by HIV-1 making these cells incapable of releasing viral particles. Nonetheless, HIV-1 mRNAs (Tat, Rev and Ref) and proteins (Nef) accumulate inside astrocytes affecting their function (Sabri et al. 2003). Changes induced in astrocytes by HIV infection include activation, production and release of inflammatory cytokines and chemokines, and glutamate release (Fig. 1) (Benveniste 1998; Bajetto et al. 2002; John et al. 2003; Eugenin and Berman 2007; Farina et al. 2007).

Cytokines such as TNF-α and IL-1β released by activated microglia, macrophages or astrocytes treated with viral proteins like gp120 or Tat cause increased glutamate release and decreased extracellular glutamate uptake by astrocytes due to down regulation of EAAT1 and EAAT2 gene expression (Wang et al. 2004; Lee et al. 2005; Brabers and Nottet 2006; Cheung et al. 2008).

Moreover, excess extracellular glutamate can induce elevation of intracellular calcium levels in astrocytes which in turn increases even more the release of glutamate from those cells in an autocrine manner (Verderio et al. 2001; Verderio and Matteoli 2001). Calcium influx in astrocytes may decrease EAAT1 levels in these cells by a CD38-dependent mechanism contributing to the accumulation of extracellular glutamate (Bruzzone et al. 2004; Liu et al. 2010). In short, a major contributor to the neuronal toxicity due to glutamate in HAND seems to be the aberrant glutamate transport and/or metabolism in astrocytes caused by viral toxins, cytokines or glutamate.

Glutamate toxicity in HIV-1 infected patients could also depend on altered glutamate transport in oligodendrocytes (Domercq et al. 2007). Co-culture of LPS-activated microglia and oligodendrocytes or incubation of oligodendrocytes with conditioned media from LPS-activated microglia inhibited glutamate uptake by oligodendrocytes resulting in extracellular glutamate accumulation and cell death (Pang et al. 2010). Moreover, peroxynitrite, the product of the reaction between superoxide and NO, is a potent inhibitor of EAAT glutamate transporters GLAST, GLT-1 and EAAC1 (Trotti et al. 1996). Taken together, compromised clearance of extracellular glutamate from the synaptic cleft by oligondendrocytes, allows levels of glutamate to increase and cause toxicity in neurons.

GP120 neurotoxicity and glutamate

Gp120 is the main HIV envelope glycoprotein that, along with gp41, allows the entry of HIV-1 into cells via the CD4 receptor along with CCR5 and CXCR4 receptors. The amino acid sequence of this protein consists of five variable regions (V1-V5) and five constant domains (C1-C5) (Checkley et al. 2011). There is both in vitro and in vivo evidence indicating that gp120 triggers neurotoxicity (Doble 1999). Gp120 is toxic to cultured rat hippocampal neurons in vitro (Brenneman et al. 1988; Dreyer and Lipton 1995), produces cognitive deficits in rats (Glowa et al. 1992) and causes impaired neuronal development in rat neonates (Hill et al. 1993; Bagetta et al. 1994). Further, transgenic mice expressing gp120 in astrocytes develop neurodegeneration (Toggas et al. 1994). Gp120 neurotoxicity is thought to contribute to cortical atrophy (Lipton 1992a), a condition associated with cognitive impairment observed in some AIDS patients (Power and Johnson 1995).

NMDA receptor antagonists, but not CNQX, an AMPA receptor antagonist, prevent in vitro gp120 neurotoxicity in rodent cultures suggesting that gp120 neurotoxicity is mediated, at least in part, by the NMDA receptor (Lipton et al. 1991; Lipton 1992a, b; Muller et al. 1992; Savio and Levi 1993). Interestingly, if glutamate is removed enzymatically from the cell culture milieu, gp120 excitotoxicity is lost (Lipton et al. 1991). Furthermore, neurodegeneration in gp120-expressing transgenic mice can be ameliorated by the NMDA antagonist memantine (Toggas et al. 1996) and the glutamate release inhibitor riluzole (Sindou et al. 1994).

Gp120 is also known to trigger NMDA receptor-mediated cell death in human neurons (Corasaniti et al. 1995; Lannuzel et al. 1995; Wu et al. 1996). However, gp120 receptors (CD4 receptors) are not found in neurons so that gp120 neurotoxicity mediated by NMDA receptors is likely through an indirect mechanism (Lipton et al. 1991) involving glutamate release from infected macrophage and microglia. Macrophages are essential in order to see the neurotoxic effect of gp120 (Lipton 1992c). Unlike neurons, macrophages express CD4 receptors that recognize gp120. In addition, stimulation of macrophages with gp120 releases arachidonic acid which impairs glutamate uptake by astrocytes (Dreyer and Lipton 1995) thus providing an explanation for the build-up of glutamate in the synapse.

Tat neurotoxicity and glutamate

HIV-1 Tat is a small basic protein (86–101 residues, depending on the viral isolate) encoded by the HIV-1 genome that plays an important role enhancing the efficiency of transcription from viral dsDNA (Debaisieux et al. 2012). Tat protein is encoded by two exons, the first one corresponds to the 72 N-terminal residues and the second one the remaining 14–32 residues (Cheng et al. 1998).

In addition to its role in viral replication, this protein is secreted from intact HIV-1 infected cells at nanomolar levels and is found in serum, CSF and brain of HIV-1 infected-patients (Xiao et al. 2000). Fragments of Tat have been shown to cause apoptosis in human peripheral blood mononuclear cells, T-cells, neuroblastoma, rat cortical neurons and human fetal primary neuronal cells (New et al. 1998). Moreover, injection of HIV-1 Tat in mice caused neurotoxicity, seizures, death, neuronal degeneration, astrocytosis and microglia activation (Sabatier et al. 1991; Philippon et al. 1994).

Tat peptides were shown to be neuroexcitatory and neurotoxic in cultured human fetal neurons triggering the release of calcium ion from intracellular stores (Haughey et al. 1999, 2001; Holden et al. 1999). This calcium release causes membrane depolarization, activation of metabolic pathways, ROS generation and apoptosis (Nath et al. 1996; Kaul et al. 2001). Release of Tat-mediated calcium ion seems dependent on NMDA receptor activation since NMDA receptor antagonists MK-801 and D-2-amino-5-phosphonovalerate (AP-5), significantly decrease cell death induced in neurons and astrocytes by Tat (Eugenin et al. 2007). It is thought that Tat causes the release of Zn^{2+} from its binding site on the NMDA receptor, causing activation

and increasing its capacity to allow calcium ion influx (Chandra et al. 2005). Tat can bind to lipoprotein related protein (LRP) receptor and form a complex with postsynaptic density protein-95 (PSD-95), NMDA receptor and neuronal nitric oxide synthase (nNOS) at the cell membrane in neurons (Eugenin et al. 2007). By a mechanism not fully understood this complex can cause apoptosis in both NMDA receptor positive and negative neurons.

Although most studies implicate NMDA receptors, some evidence suggests that the toxic effects of the Tat protein are mediated through non-NMDA receptors. In fetal neurons the non-NMDA receptor antagonists kynurenate, CNQX and NBQX significantly decreased Tat-induced cell death while there was no significant effect of MK-801 or AP5 (Nath et al. 1996; Cheng et al. 1998).

Tat has also been reported to cause an increase in expression levels and activity of xCT in rat primary microglia resulting in increased glutamate release (Gupta et al. 2010). Also, Tat decreases the expression of manganese superoxide dismutase, which could lead to lower capacity for anti-oxidant response in cells and ultimately induce oxidative stress (Flores et al. 1993).

Finally, Tat seems to have synergistic effects on other toxins like glutamate and HIV-1 gp120 causing a significant increase in their neurotoxic potency (Wang et al. 1999; Nath et al. 2000). Brief exposure of hippocampal neurons in neonatal rats to Tat and physiological levels of NMDA caused marked cell loss supporting the idea that locally released Tat could enhance NMDA receptor activation-dependent neurotoxic effects (Wang et al. 1999).

Accessory and regulatory HIV proteins neurotoxicity and glutamate

In addition to gp120 and Tat, other less well studied HIV proteins have been identified and have been shown to contribute to glutamate-related toxicity. These include gp160, gp41 and viral protein R (Vpr) (Hussain et al. 2008; Gorantla et al. 2012). Gp41 facilitates the release of glutamate from glial cells in vitro suggesting that this protein may contribute to the excitotoxic effects of HIV infection (Kort 1998). Gp41 was shown to be more effective than gp120 at releasing glutamate in rat parietal cortical slices (Wang and White 2000). Another study showed that both gp120 and its precursor gp160, can both alter NMDA-induced intracellular free calcium levels leading to neurotoxicity (Lannuzel et al. 1995). Vpr transgenic mice displayed higher levels of glutamate in the cortex and basal ganglia along with lower levels of glutamate transporters, EAAT1 and EAAT2 (Noorbakhsh et al. 2010; Power et al. 2012). These findings correlated to disturbances in both motor and cognitive behaviors (Noorbakhsh et al. 2010).

Regulation of glutamate excitotoxicity in HAND

Reduction of glutamate receptor signaling

Since the main toxic effects of excess glutamate are thought to be due to excitotoxicity from over activation of glutamate receptors, antagonists of these receptors have been popular therapeutic targets for treatment of HAND (Fig. 2). Early work to ameliorate the effects of excess extracellular glutamate focused on NMDA receptor antagonism, in particular with the use of 1-amino-3, 5-dimethyl-adamantane (memantine) (Lipton 2004). Memantine is an uncompetitive low affinity antagonist of the NMDA receptor that is approved to treat the symptoms of Alzheimer's disease. Memantine can block excessive glutamate activity without interfering with the normal functioning of the receptor (Lipton 2004). Preclinical research mainly focused on the effect of memantine on gp120 induced neuronal damage. Memantine can prevent gp120 toxicity (Lipton 1992b; Muller et al. 1992; Muller et al. 1996) as well as the combined toxicity of gp120 and Tat in neuronal cultures (Nath et al. 2000).

The first in vivo evidence of memantine's neuroprotective effects was established in the gp120 transgenic mice with a significant enhancement of dendritic and presynaptic terminal densities after treatment (Toggas et al. 1996). Impaired synaptic transmission and long-term potentiation (LTP) have been reported in SCID mice injected with human macrophages infected with HIV-1 (Anderson et al. 2004). In this same study, memantine was shown to attenuate these deficits. Based on this preclinical evidence, a 20-week, randomized, double-blind, placebo-controlled trial involving HIV-infected participants with mild to severe cognitive impairment was carried out. Memantine showed good tolerability but no improvement in cognitive deficits; a longer follow-up is underway (Schifitto et al. 2007; Zhao et al. 2010).

Other NMDA receptor antagonists such as MK-801, AP-5 and 7-chloro kynurenic acid have also been shown to prevent gp120 induced neurotoxicity in vitro (Lipton et al. 1991; Lipton 1992a, b, c; Corasaniti et al. 1995). In contrast, the non-NMDA receptor antagonist, CNQX failed to show any protection (Lipton et al. 1991; Corasaniti et al. 1995). In a recent study in rat hippocampal neurons, several NMDA receptor antagonists were screened for their effectiveness to prevent Tat-induced cell death and synapse loss. MK-801, memantine and ifenprodil but not the GluN2A-selective NMDA receptor antagonist TCN201 were neuroprotective. Memantine and ifenprodil protected against Tat-induced cell death but had no effect on synapse loss. MK-801 and TCN201 had the opposite effects (Shin et al. 2012). In general, however, the use of glutamate receptor antagonists in patients has been fraught with side effects and few potent glutamate

receptor antagonists have made it through advanced clinical trials.

Inhibition of enzymes responsible for the formation of glutamate

Given the side effects observed in the clinic while trying to block postsynaptic glutamate receptors directly, one alternative is to try to reduce the presynaptic generation and release of glutamate. In this regard, two enzymes thought to contribute to increased levels of glutamate in the synapse are glutamate carboxypeptidase II (GCPII) and glutaminase. Inhibition of these two enzymes could help abrogate the effects of glutamate excitotoxicity (Fig. 2).

GCPII is a membrane-bound glial enzyme that catalyzes the hydrolysis of N-acetyl-aspartyl-glutamate (NAAG) to N-acetyl aspartate (NAA) and glutamate. NAAG is an abundant peptide neurotransmitter in mammalian brain that is thought to act as an agonist at group II metabotropic glutamate receptors and a mixed agonist at the NMDA receptor (Westbrook et al. 1986; Neale et al. 2000) , although some controversy exists regarding these activities (Fricker et al. 2009). GCPII-catalyzed hydrolysis of NAAG is believed to function both to terminate NAAG mediated neurotransmission and to liberate glutamate which then acts at various glutamate receptors. Consequently, GCPII inhibitors could help lower glutamate concentration at the synapse and alleviate glutamate excitotoxicity. This hypothesis has been substantiated by numerous reports where GCPII inhibitors have shown to increase extracellular NAAG and decrease glutamate in the brain measured by microdialysis (Slusher et al. 1999; Nagel et al. 2006) and provide neuroprotective activity in over twenty animal models of disease (Barinka et al. 2012) including inflammatory and neuropathic pain (Chen et al. 2002; Carpenter et al. 2003; Yamamoto et al. 2004), brain ischemia (Slusher et al. 1999), motor neuron disease (Ghadge et al. 2003), spinal cord and traumatic brain injury (Long et al. 2005; Zhong et al. 2005), peripheral neuropathy (Zhang et al. 2006; Carozzi et al. 2009), epilepsy (Witkin et al. 2002) and drug abuse (Peng et al. 2010; Xi et al. 2010). Further, a GCPII inhibitor, 2-MPPA (2-(3-mercaptopropyl) pentanedioic acid), was used in humans in an exploratory study to assess safety and tolerability of GCPII inhibition. 2-MPPA did not provoke any adverse CNS effects and was well tolerated (van der Post et al. 2005).

The potential therapeutic utility of GCPII inhibition in AIDS-related neurotoxicity was recently evaluated in an in vitro model using rat embryonic hippocampal cultures and gp120IIIB. Gp120IIIB exhibits specificity for CXCR4, the receptor known to induce neuronal apoptosis. 2-PMPA, a potent and selective GCPII inhibitor (Jackson et al. 1996) prevented gp120III-induced apoptosis in a dose-dependent manner. Apoptosis could be resumed in the presence of mGlu3 receptor antagonists or in the presence of antibodies to transforming growth factor (TGF)-β. The results suggest neuroprotection can be mediated through increases in NAAG and subsequent action at the mGlu3 receptors and TGF-β release. Consistent with the localization of GCPII in astrocytic cells, 2-PMPA failed to provide neuroprotection in the absence of glia (Thomas et al. 2009). Evaluation of GCPII inhibitors in animal models of HAND is underway.

Glutaminase catalyzes the hydrolysis of glutamine to glutamate and it is thought to be a major source of glutamate production in the CNS. HIV-1 infected human macrophages and human primary fetal microglia have increased glutaminase mRNA and protein levels (Tian et al. 2008; Erdmann et al. 2009; Huang et al. 2011; Zhao et al. 2012). Macrophages infected with various HIV-1 strains were reported to release high levels of glutamate in the presence of glutamine and this release was inhibited by glutaminase siRNA as well as several structurally diverse glutaminase inhibitors including 6-diazo-5-oxo-L-norleucine (DON), BPTES and its analogs (Zhao et al. 2004; Erdmann et al. 2007). Additional mechanistic studies of glutamate generation in HIV-1 infected macrophages revealed up-regulation of the glutaminase isoform GAC. Glutaminase is normally found in mitochondria but upon infection it is released into cytosol and extracellular space where high levels of glutamine could be rapidly converted to glutamate (Erdmann et al. 2009). Unfortunately, current prototype glutaminase inhibitors are non-specific and reactive (Zhao et al. 2004) or exhibit poor solubility (Wang et al. 2010; Hartwick and Curthoys 2011). Consequently, a meaningful evaluation of the potential of glutaminase inhibition to prevent glutamate excitotoxicity in animal models of neuroAIDS awaits the identification of better drug-like glutaminase inhibitors

Regulation of glutamate transporters

Oxidative stress in macrophages and microglia is also thought to contribute to increased extracellular glutamate through xCT. Treatment of macrophages and microglial cells with pro-inflammatory factors like lipopolysaccharides (LPS) or HIV-1 Tat protein causes lipid peroxidation due to the ROS that are generated. Cells affected by oxidative stress show alterations in cell signaling, membrane organization, and protein and DNA modification (Niki 2009). In order to neutralize lipid peroxidation, glutathione-S-transferase (GST) catalyzes reactions between reduced glutathione (GSH) and oxidized lipids to form products like 4-hydroxynonenal (4-HNE) and acrolein. This detoxification process irreversibly consumes the GSH available in the cell decreasing the anti-oxidant protective power. Replenishment

of intracellular GSH is thought to occur through xCT which shuttles cystine (cys2) inside the cell in exchange for glutamate that is released from the cell. Cys2 is the main source of cysteine, required for GSH synthesis. This enhanced cys2 uptake to replenish GSH causes an increase in extracellular glutamate that in turn can contribute to neurotoxicity (Barger et al. 2007). The antiporter also supports a redox cycle over the plasma membrane where cys2 uptake is followed by intracellular reduction to cysteine and secretion of surplus cysteine into the extracellular space (Banjac et al. 2008; Conrad and Sato 2011). Overall, xCT appears to support an endogenous antioxidant response (through the uptake of cys2 as well as the release of cysteine) with the concomitant increase of extracellular glutamate. However, the antioxidant response can become neurotoxic when it is activated during inflammation associated with neurodegeneration. When macrophages are stimulated by LPS or TNFα, they import cys2 and release cysteine into the medium resulting in a reduced milieu conducive to T cell activation; the accumulation of extracellular thiols is inhibited by glutamate suggesting the involvement of xCT (Angelini et al. 2002). Exposure of cultured primary microglia to HIV Tat causes dose-dependent increases in extracellular glutamate; these increases become higher in the presence of morphine in accordance with the immunomodulatory properties of this opiate agonist. Tat-induced glutamate release was associated with increased expression of the xCT antiporter and was inhibited by the xCT prototype inhibitors DL-aminoadipic acid and 4-carboxyphenylglycine (Gupta et al. 2010). These findings suggest that Tat-mediated activation of xCT could be playing a role in HIV-related pathology and that xCT inhibitors have potential for the treatment of HAND.

HIV-mediated neurotoxicity can also result in inhibition of glutamate transporters GLT1, GLAST, and EAAC1 (Trotti et al. 1996) or in reduction of their expression (Noorbakhsh et al. 2010; Power et al. 2012). Since these transporters are involved in the reuptake of glutamate by the cell after glutamate neurotransmission, inhibition or reduction of expression of these transporters results in aberrant activation of glutamate receptors (Sheldon and Robinson 2007). Consequently, one potential approach is to search for transport activators that could increase either their activity or their expression. This approach has shown promise in other glutamate –related disorders such as ALS (Rothstein et al. 2005). Recent work reports on the identification of pyridazine derivatives that increase the protein levels of the glutamate transporter EAAT2 in astrocytes. (Xing et al. 2011). The effect of these activators in models of neurodegenerative disease including HAND awaits investigation.

Animal models to investigate effects of glutamate regulation in HAND

In order to investigate if glutamatergic-based therapeutics can be effective in eliminating the symptoms of HAND, one needs an appropriate preclinical animal model. The generation of animal models of HIV has proven to be very challenging owing to the fact that HIV itself is not infectious to rodents. In order to create an accurate animal model for HAND several criteria need to be met. The animal model needs to possess target CNS cells that are permissive to virus infection, have a chronic infection period, display altered blood–brain barrier function to permit transmigration of infected cells and have the ability to maintain viral reservoirs (Gorantla et al. 2012). It would also need to feature the generation of viral proteins such as Tat and gp120 as well as the release of neurotoxic products such as proinflammatory cytokines, chemokines, quinolinic acid, glutamate, arachidonic acid and nitric acid among others. Since the discovery of HIV, several animal models of HAND have been created (Table 1), but like many models of neurodegenerative diseases, no one current model recapitulates the exact characteristics of HAND or HIV-1 associated dementia (HAD) (Gorantla et al. 2012; Jaeger and Nath 2012).

Some of the first and most logical models to be generated were where the full-length HIV-1 DNA was inserted into the mouse genome under the control of various promoters (Santoro et al. 1994; Thomas et al. 1994; Gorantla et al. 2012). A HIV-1 transgenic rat was also developed and cognitive deficits such as impairments in spatial learning as well as evidence of other clinical manifestations of the disease have been reported making it a suitable model for testing therapeutics in rats (Reid et al. 2001; Vigorito et al. 2007; Lashomb et al. 2009). The most commonly used mouse models for HIV are those that express some of the viral proteins generated upon HIV infection such as Tat and gp120 (Toggas et al. 1994; Kim et al. 2003; Gorantla et al. 2012). *GFAP-Tat* Tg mice possess doxycycline-inducible expression of the Tat protein under control of GFAP promoter while *GFAP-HIVgp-120* Tg mice exhibit expression of gp120 protein driven by GFAP promoter that is not inducible (Toggas et al. 1994; Kim et al. 2003; Bruce-Keller et al. 2008). Spatial learning on the Morris water maze was shown to be impaired in the gp-120 mice (D'Hooge et al. 1999). This is thought to be due to excitotoxic mechanisms as a result of increased NMDA receptor signaling and impaired hippocampal long-term potentiation (LTP) which is believed to be the NMDA receptor-dependent biological correlate of learning and memory (Lipton 1994; Toggas et al. 1996). Indeed, as mentioned previously, the first in vivo evidence of the NMDA receptor antagonist, memantine's neuroprotective

Table 1 Rodent models of HAND

MODEL	COGNITIVE DEFICITS	REFERENCES
HIV-1 transgenic mouse full length HIV-1 DNA inserted into mouse genome	Not reported	(Santoro et al., 1994; Thomas et al., 1994; Gorantla et al., 2012)
HIV-1 transgenic rat insertion of HIV-1 genome	Spatial learning deficits in the Morris water maze	(Vigorito et al., 2007; Lashomb et al., 2009)
gp-120 transgenic mouse expression of gp-120 driven by GFAP promoter	Spatial learning deficits in the Morris water maze	(D'Hooge et al., 1999)
Tat transgenic mouse doxycycline-inducible expression of the Tat protein driven by GFAP promoter	Memory deficits in Barnes maze, Morris water maze, novel object recognition and fear conditioning	(Carey et al., 2012; Fitting et al., 2012)
Intracerebral injection of Tat or gp-120 proteins	Sensorimotor gating (pre-pulse inhibition) deficits. Morris water maze, Barnes maze, passive avoidance, fear conditioning and radial arm maze learning deficits	(Glowa et al., 1992; Pugh et al., 2000; Sanchez-Alavez et al., 2000; Li et al., 2004; Fitting et al., 2006; Fernandes et al., 2007)
HIV-1 infected HIS/SCID mouse	Not reported	(Jaeger and Nath, 2012)
HIVE mouse HIS/SCID mice infected with HIV-1 infected monocyte derived macrophages	Spatial learning deficits in the Morris water maze and the radial arm water maze	(Avgeropoulos et al., 1998; Zink et al., 2002; Sas et al., 2007)
HIV-1 mouse with virus modification coding region of HIV-1 gp-120 replaced with gp-80 from a rodent-infectious retrovirus	Not reported	(Potash et al., 2005)

effects was established in these gp120 transgenic mice (Toggas et al. 1996). Like the gp120 mice, the Tat transgenic mice also exhibit memory deficits as demonstrated by diminished performance in hippocampal-dependent memory tasks such as the Barnes maze, Morris water maze, fear conditioning and novel object recognition (Carey et al. 2012; Fitting et al. 2012). Interestingly, Tat transgenic mice display an increase in expression of the xCT antiporter which could be the response to increased oxidative stress and excitotoxicity (Bridges et al. 2004). Like gp-120, the Tat protein has been shown to interfere with LTP (Li et al. 2004; Fitting et al. 2012). Since the gp120 and Tat proteins both induce impairments to the glutamate system, these models can be appropriately used to test glutamatergic therapeutics. Direct injection of these proteins into brain areas has also been used to model HAND and have shown cognitive and sensorimotor gating impairments as well as interference in LTP (Glowa et al. 1992; Pugh et al. 2000; Sanchez-Alavez et al. 2000; Li et al. 2004; Fitting et al. 2006; Fernandes et al. 2007). As mentioned above, injection of HIV-1 Tat in mice caused neurotoxicity, seizures, death, neuronal degeneration, astrocytosis and microglia activation (Sabatier et al. 1991; Philippon et al. 1994). Future generation of double or triple transgenic lines combined with the introduction of some neurotoxic products or supernatants from HIV-infected macrophages might be needed to convey the collective effects of the various viral proteins and other HIV-generated toxins in the CNS.

To overcome the fact that HIV does not infect mice, two approaches were undertaken to circumvent the restriction of HIV-1 entry to rodent species. The first approach was on the host side with the generation of various types of humanized mouse models that incorporated a functional human immune system (HIS) into severe combined immunodeficient (SCID) mice and thus permitting HIV infection (Jaeger and Nath 2012). HIV-1 infected monocyte derived macrophages (MDM) were also injected into these SCID mice to create HIV encephalitic (HIVE) mice and many of the pathological features of HIVE as well as cognitive and plasticity deficits were reproduced in these mice which were attenuated with memantine (Tyor et al. 1993; Avgeropoulos et al. 1998; Zink et al. 2002; Anderson et al. 2004; Sas et al. 2007). These mice have been widely used for therapeutic testing but biosafety requirements make them difficult to work with (Gorantla et al. 2012). The other approach to overcome the issue of species recognition was on the side of the virus

itself. This was accomplished by replacing the coding region of HIV-1 gp120 with that of gp80 from a rodent-infectious retrovirus called ectotropic murine leukemia virus resulting in the EcoHIV construct (Potash et al. 2005). Cognitive testing has not been carried out in these mice nor have any defects in LTP or the glutamate system been reported to date. These mice have been successfully used for the preclinical evaluation of antiretroviral drugs and vaccines (Hadas et al. 2007; Saini et al. 2007).

All of these models have potential to be used to evaluate new therapeutics but each have their individual pros and cons and none of them encompass the entire HAND symptom repertoire. It is clear that the glutamate system is affected following HIV infection of the CNS and therapeutics aimed at ameliorating these deficits may be beneficial for the symptoms of HAND.

In summary, glutamate excitotoxicity is one of several mechanisms by which HIV exerts neurotoxicity that culminates in HAND. Glutamate is released upon HIV infection of macrophage/microglial cells and has been associated with neurotoxicity mediated by gp120, Tat and other HIV proteins. Several strategies have been used over the years to try to prevent glutamate excitotoxicity, including direct blockade of glutamate receptors. Unfortunately, this approach is fraught with side effects. Another approach has been to inhibit enzymes responsible for the production of glutamate such as glutaminase and GCPII or to regulate the transporters responsible for modulation of extracellular glutamate such as EAAT and xCT. These efforts however, are at an early stage where next steps are dependent on the identification of drug-like inhibitors as well as the development of predictive neuroAIDS animal models.

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