Supplementary materials
HIV-induced neurodegeneration

Neurotoxicity from inflammation in the HIV-infected host comprises a highly complex series of molecular events; its severity and trajectory can be altered by pathologic conditions in a vulnerable host prior to infection. Despite highly active antiretroviral therapies (HAARTs), earlier intervention, and more effective disease control, neurocognitive impairment and dementia remain major causes of disability, increased morbidity, and mortality.1,2 Underlying chronic distress and neuroinflammation add to disease burden and susceptibility in those at risk. Psychiatric disorders, addiction (especially with stimulants and opiates), high-risk sexual behaviors, sickness syndrome, and other chronic medical conditions characterize patient populations infected with HIV or those at high risk of HIV infection. Progressive neuronal injury leads to clinical sequelae of neural degeneration and cognitive impairment.3

Loss of blood–brain barrier (BBB) integrity

Those with early HIV infection and those at risk suffering from medical and behavioral conditions, ie, chemical/pharmacologic (drug) insults, psychiatric disorders, and medical illness, show blood–brain barrier (BBB) compromise. Stress-associated mast cell activation with corticotropin-releasing hormone (CRH) release, “leaky” basement membranes, permeability of perivascular endothelial cells, and active transport of high concentrations of circulating cytokines/chemokines contribute to BBB failure.4 Infected macrophages and T-cells invade the central nervous system (CNS) extracellular space and brain parenchyma. The loss of BBB integrity is complex and incompletely understood. This cascade of inflammatory events results in early HIV colonization of the brain.

Multifaceted neurotoxicity

The trajectory of HIV neurotoxicity involves HIV transit into the CNS by T-cells and perivascular and mobile macrophages which infect resident monocytes, macrophages, and microglia; astrocytes, though not shown to harbor HIV, are target cells that promote neuronal injury. Infected monocytes and macrophages release cytokines/chemokines, intact virions, and component viral proteins, mainly gp120 and transactivator of transcription (TAT), which perpetuate infection and neurotoxicity. Noninfected monocytes/macrophages respond to immune insults releasing cytokines/chemokines and other agents, which disrupt astrocyte glutamate (GLU) regulation. GLU dysregulation with excess production in astrocytes is a critical component of neuronal degeneration.5,6

Astrocytes are critical in maintaining GLU homeostasis. GLU is a toxic excitatory neurotransmitter which becomes disrupted at multiple steps in its metabolic pathways. Increased production and reduced clearance and metabolism of GLU elicit toxic neuronal activation. Excitatory amino acid transporters (types 1 and 2) are downregulated, decreasing glial and astrocyte GLU uptake. The enzyme glutaminase is upregulated, which generates glutamine, a GLU precursor to GLU, increasing intracellular/extracellular and intrasynaptic GLU. GLU increases from downregulation of GLU degradation enzymes (GCP 1 and GCP II). GLU astrocyte exocytosis increases extracellular GLU. GLU is excitotoxic through N-methyl-D-aspartate (NMDA) receptors which, when activated, increase intracellular Ca\(^{2+}\) release. Excess Ca\(^{2+}\) activates second messenger pathways responsible for gene transcription and signaling, ie, nuclear factor kappa B (NF-κB), JNK/STAT-1, and ERK 1/2. These trigger genomic events that accelerate production of proinflammatory agents, apoptosis, and oxidative stress, as well as further increasing GLU production and release. Cumulatively, these events decrease synaptic integrity and plasticity and perpetuate neuron apoptosis.

Excess GLU also enhances glial inflammation (gliosis) in concert with neural dysfunction; mounting glial activation generates a cascading effect that perpetuates neuroinflammation, neuronal dysfunction, network integrity, and cognitive decline.

CNS HIV infection of neuronal support cells and tissues generates a proinflammatory microenvironment. Neuronal damage is multifactorial, with toxic insults from increased intracellular, extracellular, and intrasynaptic GLU; cytokines. Oxidative stress from reactive oxygen radicals/nitric oxides; and membrane destabilization from prostaglandins/ arachidonic acid promotes neuronal damage. This is magnified by depletion of intracellular antioxidant detoxification molecules, ie, glutathione. Active viral replication maintains and progressively compromises CNS immunity with deteriorating neuron viability and neuronal networks. Degeneration of neocortical and limbic structures and their connectivity are principal sites responsible for cognitive decline and increased susceptibility to neuropsychiatric conditions.

Figure S1 represents some of the multiple molecular mediators generated by HIV infection within the CNS and the multiple neurotoxic and inflammatory effects on both neuronal support cells/tissues and neurons.

Effects of chronic stress

During acute stress, glucocorticoids (GC) provide neuroprotection, blunting glial and other CNS inflammatory...
responses, indicative of their immunosuppressive effects. Induction of chronic stress in models of Parkinson’s disease results in long-term pathologically elevated concentrations of GC. Chronic exposure to GC during conditions of prolonged stress induces GC resistance (GCR) in immune/lymphoid tissues and organs. This progressively increases inflammation from HIV in the CNS. There is a limited understanding of GCR; excess GC has complex interactions with intracytoplasmic GC receptors. Activated GC receptors upregulate genes for proinflammatory cytokine production, viral replication in T-cells as well as in monocytes/macrophages, and glial and other support elements. GCR also enhances astrogial GLU neurotransmission. In Parkinson’s disease, this contributes to dopamine neuronal toxicity and cell death; this pattern is seen in other neuroinflammatory conditions.

Chronic neurodegeneration

Once infection is established, viral reservoirs remain within the brain despite low/absent cerebral spinal fluid viral load. Glial elements, monocytes, and perivascular/circulating macrophages are long-lived in the CNS, with glial cells lasting years to lifetime. With the advent of HAART, the prevalence and severity of neurocognitive disorders have decreased, with dementia dropping from >15% to less than 5%. “Asymptomatic” neurocognitive impairment, however, has increased to >30% over time. How pre- and post-infection comorbid conditions from disrupted stress homeostasis influence CNS HIV infection is largely unknown.

For progressive cognitive impairment, current recommendations include utilization of antiretrovirals with improved BBB penetration to decrease viral replication, free virion passage, and viral component (gp120/TAT) production. When effective, HAART blocks GLU production/action and the proinflammatory milieu. Reduced viral replication and medications purported to improve general cognition in practice have limited clinical utility.

Future directions

HIV neurotoxicity involves critical action points that determine the rate and severity of neurocognitive deterioration. When HIV enters the CNS, infection of monocytes, microglia, and macrophages; generation of intact virions and viral components (gp120/TAT); and cytokines/chemokines all contribute to activate astrocytes. GLU toxicity leads to neuronal damage, apoptosis, and overall loss of cognitive functions.

Notes: Macrophages, monocytes, and glial elements modulate actions of neurons through astrocytes. Virions and viral protein components (gp120, TAT), cytokines, membrane destabilization molecules, and glutamate (with other agents) stimulate remaining glial and other immune cells/tissues, generating a proinflammatory neurotoxic state. These adversely affect astrocytes, diminishing their support of neurons. This promotes neuronal dysfunction with loss of synaptic integrity and plasticity, morphologic and functional impairment, and apoptosis. Continued HIV invasion and replication perpetuate a cascading cycle of increasing inflammation and neurodegeneration. Macrosopic structural deficits develop with loss of cortical and subcortical functions and neuronal connectivity leading to clinical sequelae. Abbrivation: TAT, transactivator of transcription.
function. Once initiated, these processes feed forward, increasing involvement of more and more neuronal networks, with greater disability and functional impairment. To date, targeted therapies have been disappointing. Most antiretrovirals lack physicochemical properties to effectively cross the BBB and suppress the virus. GLU/NMDA receptor antagonists and synthesis inhibitors have not demonstrated therapeutic effects. Anticholinergics (used in Alzheimer’s disease), serotonin, and noradrenergic agonists have also failed to show significant benefits. These findings are not unexpected, given the inability to modify the course of other neurodegenerative disorders. Targeting chronic stress, GCR and CRH may offer limited potential as adjunctive therapies, but the overall complexities of these systems, the chronicity of ongoing infection, and the relative lack of sensitive surrogate markers for inflammation will limit treatment options in the near and mid-term future. Advances in basic neuroscience will be necessary to determine better therapeutic interventions for HIV-related and other neurodegenerative disorders.

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