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Review

Cell death in HIV dementia

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Abstract

Many patients infected with human immunodeficiency virus type-1 (HIV-1) suffer cognitive impairment ranging from mild to severe (HIV dementia), which may result from neuronal death in the basal ganglia, cerebral cortex and hippocampus. HIV-1 does not kill neurons by infecting them. Instead, viral proteins released from infected glial cells, macrophages and/or stem cells may directly kill neurons or may increase their vulnerability to other cell death stimuli. By binding to and/or indirectly activating cell surface receptors such as CXCR4 and the *N*-methyl-D-aspartate receptor, the HIV-1 proteins gp120 and Tat may trigger neuronal apoptosis and excitotoxicity as a result of oxidative stress, perturbed cellular calcium homeostasis and mitochondrial alterations. Membrane lipid metabolism and inflammation may also play important roles in determining whether neurons live or die in HIV-1-infected patients. Drugs and diets that target oxidative stress, excitotoxicity, inflammation and lipid metabolism are in development for the treatment of HIV-1 patients.

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Clinical Manifestations

Human immunodeficiency virus type-1 (HIV-1) infection is the commonest cause of dementia in adults less than 40 years of age. Prior to the availability of combination antiretroviral therapy, HIV dementia was noted in nearly 20% of patients with AIDS and often progressed rapidly over a period of 6 months.[1,2] These patients showed a subcortical dementia due to predominant involvement of the basal ganglia manifesting as psychomotor slowing.[3] Some patients also developed Parkinsonism, cognitive difficulties and behavioral abnormalites including psychosis and depression. Due to involvement of the dopaminergic system, these patients have extreme sensitivity to side effects from antipsychotic agents.[4,5] Since the availability of combination antiretroviral therapy, the incidence of HIV dementia has decreased and the clinical manifestations are less severe. However, due to improved survival rates, the prevalence rates of HIV dementia continue to rise.[6] In these milder forms of HIV dementia, cognitive dysfunction is more prevalent.

Our current understanding of the clinical features and pathophysiological mechanisms that underlie HIV dementia comes from the study of the clade B subtype of HIV-1, which is most prevalent in North America and Western Europe. However, there are nearly a dozen clades that have been identified and the most common HIV-1 clade worldwide is clade C. Epidemiological and pathological studies from these regions of the world, and experimental studies using these clades have not yet been performed. However, it is likely that important differences might exist among clades because viral sequences suggest that mutations may be present in regions of the virus implicated in the neuropathogenesis of HIV dementia.[7,8]

Pathology

The pathological hallmark of HIV-1 infection of the brain is the presence of multinucleated giant cells which are formed by syncytia of HIV-1-infected macrophages.[9] HIV-1 infects the perivascular macrophages, resident microglia[10] and some astrocytes.[11] Infection of other cell types may also occur but remains controversial. While the infection of macrophages and microglia is a productive infection with formation and release of viral particles,[12] infection of astrocytes may result in viral latency and small amounts of virus are only released upon stimulation by cytokines.[13] Prominent dendritic pruning[14], loss of synapses[15] and cell death[16,17] may occur in neurons. However, because neurons themselves are rarely infected, the damage to neurons is presumed to be indirect. Interestingly, while HIV-1 causes an immunodeficiency by loss of CD4 cells, the immune profiles within the brain suggest an immune activation involving mediators produced by microglia/macrophages and astrocytes.[18] Thus, there is an increased production of cytokines such as TNF-α, interleukin (IL)-6 and IL-1β, and chemokines such as MCP-1.[19,20] Of these mediators, MCP-1 levels in the cerebrospinal fluid (CSF) correlate positively with HIV dementia.[20]

The HIV-1 Virus: Structure and Replication

HIV-1 belongs to the retrovirus family because these viruses have a unique enzyme called reverse transcriptase that converts viral RNA to DNA upon viral entry into the cell. Viral replication occurs after proviral DNA is integrated into host cell

chromosomal DNA. The viral genome encodes two general classes of proteins, structural and regulatory.

The structural proteins form the envelope, the core and the matrix of the virus. Three regions within the HIV-1 genome, namely, *env*, *pol* and *gag*, encode all the structural proteins. The *env* gene codes for gp160 which is cleaved to form the two major envelope glycoproteins, gp120 and gp41. gp120 forms the surface spikes on the virion and gp41 is a transmembrane glycoprotein. The *pol* gene codes for reverse transcriptase, a protease that cleaves the polyproteins coded by the *pol* and *gag* genes into their active forms and an endonuclease that is responsible for viral integration into the host genome. The *gag* gene codes for all the core proteins. Regulatory proteins encoded by the viral genome control viral genome expression either at the level of proviral DNA or the viral mRNA. At least six genes (*tat*, *rev*, *nef*, *vif*, *vpu* and *vpr*) code for proteins that are involved in the regulation of viral replication. These regulatory proteins do not get incorporated into the viral particle, but regulate viral replication and release at multiple levels. For example, Tat, Rev and Nef are targeted to the nucleus of the cell. However, Nef can also be trapped within the cytoplasm of the cell (e.g. in astrocytes) and Tat may be actively released into the extracellular environment.[21] Some of the structural and regulatory proteins have been shown to cause neuronal dysfunction and/or death and thus may be referred to as virotoxins (Table 1).

Neurotoxic Viral Proteins

There are several HIV-1 proteins that have been identified as neurotoxins. These include the structural proteins gp120 and gp41 and the nonstructural proteins Tat, Nef, Vpr and Rev. The HIV-1 coat protein gp120 is a potent neurotoxin with lethal effects on neurons (Figure 1) at concentrations in the picomolar range.[22] Transgenic mice expressing gp120 under the control of a glial fibrillary acidic protein (GFAP; astrocyte-specific protein) promoter exhibited dendritic abnormalities in neurons, gliosis and age-related changes in long-term potentiation (LTP; considered a cellular basis of learning and memory), open field activity and spatial reference memory.[23–25] The gp120 protein can directly modify neuronal function[26,27] and can indirectly damage neurons by disrupting glial functions. Gp120 can act on astrocytes to stimulate an inducible form of nitric oxide (NO) synthase,[28] inhibit β-adrenergic function,[29] induce tyrosine kinase activity,[30] modify the expression of adhesion molecules[31] and produce cytoskeletal changes.[32] Astrocytes normally protect neurons from excitotoxic damage by buffering the excitatory amino-acid glutamate. By actions that stimulate Na^+/H^+ exchange, gp120 induces alkalization, leading to the inhibition of Na^+-dependent glutamate influx in astrocytes.[33,34] The effects of gp120 on Na^+/H^+ exchangers, which can be blocked by amiloride, may lead to membrane depolarization.[35,36]

Cytokine levels and COX-2 activity are increased in HIV-encephalitis and have been implicated as mediators of neurotoxic processes.[37,38] The activation of monocyte/macrophages by gp120 can promote oxidative damage and increase the release of neurotoxic cytokines, including TNF-α, IL-1β and prostaglandin E2 (PGE2; an arachidonic acid metabolite from the cyclooxygenase and lipoxygenase pathway).[39–42]

The transmembrane protein gp41 that links gp120 to the envelope of the virion has been shown to be elevated in patients with severe HIV dementia. *In vitro*, gp41 is lethal to neurons in the low nanomolar range and requires the presence of glia, suggesting an indirect mechanism of cell death. Indeed, it has been demonstrated that astrocytes treated with the carboxy-terminus of gp41 have deficits in glutamate transport and release glutamate.[43] Neuronal death induced by gp41 occurs by mechanisms that involve activation of inducible nitric oxide synthase (iNOS), NO formation, depletion of glutathione and disruption of mitochondrial function.[44–46]

The HIV *trans*-acting protein Tat is essential for viral replication. Accumulating evidence suggests that Tat is also an important mediator of neurotoxicity with lethal effects in the low nanamolar range.[47–50] Brain regions that are particularly susceptible to the toxic effects of Tat include the striatum, hippocampal dentate gyrus and the CA3 region of the hippocampus.[16,50,51] Although neurons are rarely, if ever, infected with HIV, neurons can be exposed to Tat following active release from HIV-infected lymphoid cells and glial cells.[52–54]

In addition to the direct effect of Tat on neurons, Tat perturbs glial and monocyte/macrophage function, promoting the release of neurotoxic agents including matrix metalloproteinases (MMPs), IL-6, IL-8, RANTES, MCP-1 and TNF-α.[55–59] Although the exact role of these agents in Tat-mediated neurotoxicity remains to be determined, Tat-induced TNF-α release has been implicated in neurotoxicity and MCP-1 levels in CSF have been shown to correlate with the severity of dementia in patients with HIV encephalitis.[21,60–62] MCP-1 and MMPs released by Tat may also increase the permeability of the blood–brain barrier and promote the transmigration of monocytes across the blood–brain barrier.[63,64] Together, these findings suggest that Tat may be an important mediator of the inflammatory response in the brain.

The nonstructural protein Nef is required for the proper budding of virions from HIV-infected cells. Abundant Nef expression has been detected in astrocytes of HIV-infected patients with pathological indications of neuronal damage.[11,65,66] *In vitro*, Nef is lethal to neurons and glial cells in nanomolar concentrations and can increase the expression of MMPs, thus potentially modifying the permeability of the blood–brain barrier.[67,68] Nef has significant sequence homology with scorpion neurotoxins and like these venoms can cause the inactivation of a large-conductance potassium channels.[69–71] Based on these findings, it has been suggested that Nef contributes to the neuronal degeneration seen in HIV encephalitis.

An important HIV accessory protein, Vpr, is thought to be important for effective viral replication in the early stages of infection. Vpr is important for transport of the pre-integration complex, nuclear localization, induction of cell cycle arrest in G2, transactivation of the HIV-1 LTR and other cellular promoters.[72–76] Vpr is found in the serum and the CSF of HIV-1-infected patients.[77] In HIV-infected patients with neurological dysfunction, CSF levels of Vpr are elevated, suggesting an involvement of Vpr in AIDS-related neurological disorders.

Table 1 Effects of HIV-1 proteins on signaling and enzymatic pathways in different types of brain cells

	Neurons		Astrocytes		Macrophages/microglia		Endothelial cells		
Structural proteins	**Upregulation/activation**	**Downregulation**	**Upregulation/activation**	**Downregulation**	**Upregulation/activation**		**Upregulation activation**	**Downregulation**	**Progenitors Downregulation**
Gp120	Ca uptake via L-type Ca channels	BDNF	iNOS	β-Adrenergic function	TNFα		Cytotoxicity/apoptosis		Proliferation
	CXCR4	Neuron-specific enolase	Tyrosine kinase		IL-1β		ICAM-1		ERK
	Apoptotic pathways	MAP kinase	Na/H exchange	Glutamate influx	PGE-2		Mu opioid receptor		
	Oxidative stress	Dopamine transport	Release of arachidonic acid	GFAP	Oxidative stress		PKC		
	Sphigomyelinase		ROS release	Glutamate transporter EAAT2	p53				
	p53		Cyclic GMP phosphodiesterase		Ntox				
	JNK and ERK		ICAM-1		Release of arachidonic acid				
	CXCL10		CXCL10		TGFβ-1				
	Mixed lineage kinase 3		Endothelin-1		Large-conductance apamin-sensitive potassium channels				
	PKC		CD23		Endothelin-1				
	Glutathione peroxidase				No effect on quinolinic acid production				
	Corticotropin-releasing hormone, vasopressin in hypothalamus								
	Glycine site of NMDA receptor								
	Nor-adrenaline release								
Gp41		Glutathione	Glutamate release	Amyloid precursor protein release	ILβ-1		No effect on T cell or monocyte adhesion		
			Complement factor C3		No effect on quinolinic acid production				
			iNOS						
			IL-10						
Tat	Polyamine-sensitive site and Zn allosteric site of NMDA receptor	Neprilysin	MCP-1, RANTES	Glutamate uptake	TNFα	cAMP	Oxidative stress	Claudin-1, claudin-5, and ZO-2	Proliferation of neuronal cells[a]
	Phophorylation of NMDA receptor	LRP ligands	iNOS		CCR5		MCP-1, IL-6, IL-8	No effect on occludin and ZO-1	Histone H3/H4-acetylation[a]
	Ca release from IP-3 pools	Dopamine release	IL-6, IL-8, IP-10		IL-1β, IL-6		E-selectin		Cytotoxicity of glial precursors
	Ca uptake via VOCC	Neuronal organization	MMP-1 and -2		Chemotaxis		T-cell adhesion		
	Oxidative stress		Id-1		Platelet activating factor		NF-κB, AP-1, PKC		
	Apoptotic cascade		GFAP		Quinolinic acid		FAK		
	Endonuclease G		Antiapoptotic pathways				iNOS and e-NOS		
	Par-4		XCL1						
	Acetyl choline release		VCAM-1, ICAM-1						
	Neurotoxicity in CA3 neurons of hippocampus		PKC, NF-κB						
	Long-term potentiation		PrP						
	GSK-3 β								
	MAP kinase		MAP kinase						
Nef	Neurotoxicity		Astrocytosis		MMP-9				
			IP-10		Quinolinic acid				
			MAP kinase, JNK, PKC						
Vpr	Apoptotic pathways		Necrosis						
	Forms ion channels								

VOCC = voltage-operated calcium channels; ICAM = intercellular adhesion molecule-1; JNK = c-Jun N-terminal kinase; ERK = p42 extracellular-regulated kinase; PKC = protein kinase C; LRP = low-density lipoprotein receptor-related protein receptor; PrP = Prion-related protein; focal adhesion kinase; ZO = zonula occludens. For the complete set of transcripts modulated by gp120 by microarray analysis and subtractive hybridization, see Galey *et al*. (2003) and Su *et al*. (2004). [a]Tat effects represent effects in neuroblastoma cells or PC12 cell line.

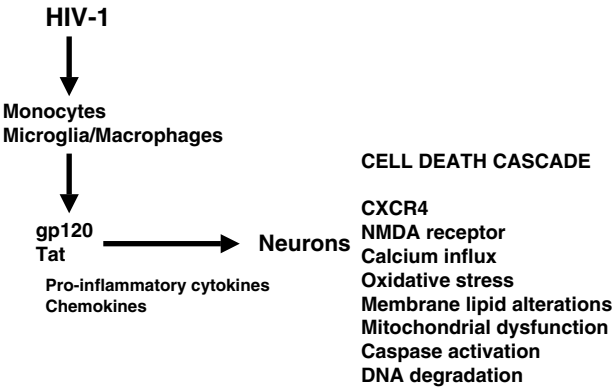

Figure 1 Mechanism by which HIV-1 may induce neuronal death in HIV-1 dementia. The virus infects monocytes and macrophages/microglia which enter the brain. The infected cells release cytotoxic HIV-1 proteins, most notably gp120 and Tat, which induce cell death cascades in neurons. The cell death cascade involves binding of gp120 and Tat to cell surface proteins such as CXCR4, overactivation of glutamate receptors (particularly the NMDA receptor), calcium influx, oxidative stress and release of cytotoxic membrane lipids such as 4-hydroxynonenal and ceramides. The latter events may trigger the intrinsic pathway of apoptosis, which involves mitochondrial membrane permeabilization, release of cytochrome *c* and activation of caspases and endonucleases, which finalize the cell death process. HIV-1 infection also induces monocytes and macrophages/microglia to produce proinflammatory cytokines which may potentiate neuronal cell death

In vitro, Vpr is lethal to neurons in micromolar concentrations when applied extracellularly by mechanisms that involve the formation of a large inward cation current and caspase-8 activation.[78,79] The N-terminal region of Vpr consisting of the first 40 amino acids has been found to be necessary and sufficient to form this sodium channel.[80] Similar effects were found when Vpr was expressed intracellularly in terminally differentiated neurons.[81] Thus, Vpr may be lethal to neurons by events triggered at the plasma membrane and intracellular associated processes.

The HIV phosphoprotein Rev is involved in the nuclear export of unspliced viral mRNAs. Rev contains a nuclear localization sequence and an RNA-binding domain in the N-terminal region that is critical for Rev function.[82,83] Extracellular Rev has neurotoxic properties. Intracerebroventricular injection of a synthetic peptide spanning the basic region of Rev was neurotoxic and lethal to rodents.[84] The neurotoxic effects of Rev may involve an interaction with acidic phospholipids and the formation of α-helical conformations. This interaction and conformational change of Rev may disrupt membrane topology and produce toxic or lethal effects.[84]

Host Genetics

Genetic factors that may increase or decrease the susceptibility of HIV-infected patients to neurological complications include CCR5, MCP-1 and ApoE polymorphisms. A variation in the chemokine receptor CCR5wt-Delta32 is associated with delayed disease progression, while the CCR5-59029-A/A variant is associated with a more rapid disease progression and greater neurological impairment.[85] Although rare in occurrence, the chemokine variant stromal cell-derived factor (SDF)1–3′-A/A has been associated with a more rapid disease progression and neurological deterioration in pediatric patients infected with HIV-1.[85] Homozygosity for the MCP-1-2578G allele has been associated with a 50% reduction in the risk for HIV-1 infection. However, once a patient is infected with HIV-1, homozygosity for the MCP-1-2578G allele is associated with accelerated disease progression and a 4.5-fold increased risk of dementia.[86]

Although initial studies found no correlation between the risk of HIV dementia and ApoE genotype,[87] later findings suggested that HIV-infected patients with the E4 isoform of ApoE are more likely to suffer neurological complications including dementia and peripheral neuropathy.[88] The biophysical determinants of the E4 genotype that predispose neural tissue to malfunction and injury have not been determined, although a role for the regulation of redox balance by ApoE has been suggested.[89,90] Although the pathological consequences of cholesterol accumulation in brains of HIV patients with dementia remain to be determined, modification of cholesterol levels has been associated with poor cognitive function and may impair learning and memory.[91,92] Emerging evidence suggests that dysfunctions of sphingolipid and sterol metabolism in the setting of HIV dementia may have important pathological consequences.[93]

Viral Genetics

HIV-1 may enter the brain soon after infection using blood-derived macrophages as carriers (Figure 1).[94] There is, in addition, evidence that HIV may also enter the brain by first infecting brain capillary endothelial cells.[95] These findings suggest that macrophage and endothelial-tropic strains of HIV have a neuropathic potential. Consistent with this hypothesis, most viruses isolated from the brain are macrophage trophic and use CCR5 as the principal co-receptor for binding and entry into cells.[96] Once in the brain, HIV-1 may infect resident microglia, and neural stem cells (Figure 2).

There is a broad range of viral diversity in the brain with replication-competent HIV-1 genomes, complex mixtures of defective viral forms and chromosomally integrated provirus present.[97] The hypervariable V3 domain of gp120 is an important determinant of neuropathogenesis, regardless of the HIV clade from which it was derived, and distinct HIV envelope sequences that are associated with the clinical expression of dementia have been isolated.[98] Cloning and sequencing of the entire V3 region has provided evidence that genetically unique sequences exist in different brain regions.[99] Viral variation in different brain compartments may be the product of selection pressures that result from variable access to antiretroviral drugs; or compartmentalized viral evolution. The influence of brain-specific actively replicating viral reservoirs may be important for the development of dementia. Indeed, it has been demonstrated that the CSF viral burden, but not the plasma viral burden, correlates with the presence and severity of dementia.[100,101] A positive correlation between CSF levels of β2-microglobulin and dementia has also been demonstrated, suggesting that immune activation is involved in neural dysfunction and degeneration in HIV dementia.[100] Compared to HIV patients with no

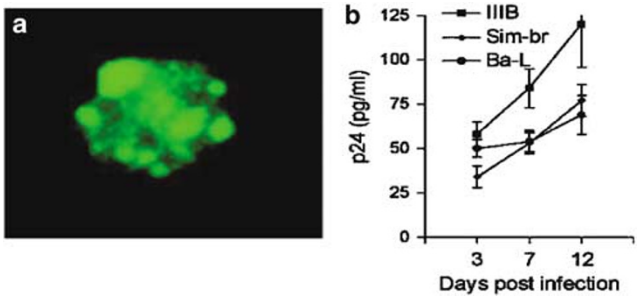

Figure 2 Infection of human neural progenitor cells by HIV-1. Using fluorescence-activated cell sorting, neural progenitor cells were isolated from dissociated fetal human cerebral cortical cells with a purity of 98%. In the presence of media containing epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF), these cells were cultured as floating neurospheres for more than 30 days. (**a**) Cells were infected for 3 h at 37°C with HIV-1_{NL4-3} containing a YFP insert in the *nef* coding region (HIV-YFP; MOI = 0.2). Cells were washed three times with PBS and lightly trypsinized (0.5 mg/ml trypsin for 10 min at 37°C). At 3 days after infection cells were fixed, and infection was visualized by immunofluorescent microscopy at $\times 100$ magnification. (**b**) Free-floating neurosphere cultures were exposed to the HIV-1 isolates IIIB, Ba-L or Sim-br (RT activity of $\sim 10^6$ cpm/ml) for 2 h at 37°C. To prevent carryover of contaminating viral DNA, viral inoculums were pretreated with RNAase-free DNAase (50 U/ml) for 30 m. HIV-1 Ba-L is a macrophage-tropic isolate that uses the CCR5 coreceptor and HIV-1 IIIB is a T-cell line-adapted isolate that uses the CXCR4 coreceptor; Sim-br is a primary brain isolate. After viral exposure, cells were washed, trypsin treated and the supernatant was sampled at 0, 3, 7 and 12 days, and p24 levels were measured by ELISA. In neurospheres, p24 levels increased in a linear manner over 12 days in cultures infected with HIV-1 IIIB and Sim-br, but only a small increase in viral production was detected in cultures infected with Ba-L. Data are mean $\pm$ S.D. (ANOVA with Tukey *post hoc* comparisons)

dementia, Tat sequences in the brains of HIV-1 patients with dementia showed greater nonsynonymous/synonymous substitution rates, with greatest sequence diversity in regions that influence viral replication and transport.[7,102] The functional significance of Tat molecular diversity in the brain remains to be determined.

Viral Effects on Neurogenesis

The brains of adult mammals contain small populations of cells that are capable of dividing and differentiating into neurons and glial cells.[103] In the dentate gyrus, new neurons are functionally incorporated into the hippocampus[104] and may participate in the formation of hippocampal-dependent memory.[105] Neurogenesis is decreased during aging[106] and by toxic stimuli, including stress, methamphetamine, opiates, alcohol and β-amyloid (a toxic form of amyloid found in the senile plaques of Alzheimer's patients).[107–109] Neural progenitors express a variety of chemokine receptors including CXCR4 and CCR5,[110] and thus have the potential to bind HIV-1. Based on the findings that HIV-1 infection in the brain is often associated with encephalitis and CNS inflammation, processes that have been shown to decrease neurogenesis,[111,112] it is possible that deficits of neurogenesis occur in HIV dementia. Consistent with this possibility, one study provided evidence for reduced numbers of proliferating cells in the hippocampus of HIV-1-infected patients,[113] and HIV-1 can successfully infect and replicate in neural progenitor cells (Figure 2).

Neurotoxic HIV-1 proteins may also contribute to deficits of neurogenesis in HIV dementia. The second exon of Tat contains a conserved Arg–Gly–Asp cell adhesion motif that binds to integrin receptors. Additionally, the basic region of Tat in the first exon also contributes to its cell adhesive properties.[114] It is thus possible that Tat may interfere with the normal development and migration of neurons, as well as remodeling after a traumatic insult to the accessory cells, by competing with extracellular matrix cellular proteins. Unpublished observations from our laboratory suggest that Tat interferes with the normal function of neural progenitor cells *in vitro* and *in vivo*. Although these initial findings are intriguing, further experiments are required to determine the pathogenic mechanisms of HIV-1 protein-induced neural progenitor cell dysfunction and the consequence of these interactions on cognitive function.

Cell Death Cascades

The biochemical and molecular cascades that result in the death of neurons in HIV dementia are complex, involving not only the virus and neurons, but also glial cells, macrophages and lymphocytes. In general, the mechanisms by which neurons become dysfunctional and die in HIV dementia are similar to those that occur in Alzheimer's disease.[115] In both cases, apoptosis, excitotoxicity and inflammation are involved. In Alzheimer's disease, the β-amyloid protein may initiate these cascades, whereas in HIV dementia HIV-1 proteins (particularly gp120 and Tat) are likely initiating factors.

Apoptosis

Analyses of the brains of patients who died with HIV-1 dementia, together with experiments in cultured cells, suggest that many neurons undergo a form of programmed cell death called apoptosis. DNA fragmentation, caspase activation and mitochondrial alterations consistent with apoptosis have been documented in affected brain regions of HIV dementia patients.[116] The tumor suppressor protein p53 may mediate apoptosis in HIV dementia because p53 levels are increased in affected brain regions of HIV dementia patients and cortical neurons lacking p53 are resistant to death induced by gp120 and Tat.[117] Neural cell death induced by isolates from macrophages infected with HIV-1 was prevented by overexpression of Bcl-2, suggesting that the neurotoxic macrophage-derived factors activate an intrinsic (mitochondrial) apoptotic cascade.[118] Prostate apoptosis response-4 (Par-4) is a leucine zipper protein that is thought to mediate apoptosis in several different cell types including neurons. Par-4 levels are increased in neurons in the hippocampus of patients with HIV encephalitis and in monkeys infected with a chimeric strain of HIV-1 and simian immunodeficiency virus. Par-4 production is rapidly increased in cultured hippocampal neurons after exposure to Tat, suppression of Par-4 production using antisense technology protects the neurons from being killed by Tat.[119] These findings suggest that Par-4 may be a mediator of neuronal apoptosis in HIV dementia.

Brain-derived neurotrophic factor (BDNF), nerve growth factor and activity-dependent neurotrophic factor protected cultured cerebellar granule neurons from being killed by Tat.[120] The neuroprotective effect of each trophic factor involved activation of the transcription factor NF-κB and upregulation of the expression of Bcl-2. The transcription factor CREB (cyclic AMP response element-binding protein) plays a key role in learning and memory, and mediates activity-dependent neuronal survival by upregulating the expression of BDNF.[121] Long-term exposure (hours to days) of cultured PC12 cells to Tat resulted in decreased levels of CREB expression and activity which preceded apoptosis.[122] Thus, in addition to activating proapoptotic cascades, neurotoxic HIV-1 proteins may inhibit pathways that promote cell survival.

Both infected and uninfected T cells undergo apoptosis during the course of HIV-1 infection. The mechanisms of apoptosis in T cells and neurons appear to be similar, involving death receptors (TNF receptors and Fas), some chemokines, calcium dysregulation, mitochondrial membrane permeabilization and caspase activation.[123] Both gp120 and Tat may be key triggers of apoptosis in different cell types that die in HIV-1 AIDS. HIV-1-infected monocytes produce a protein called FLJ21908 that is cytotoxic to CD4(+) and CD8(+) T and B cells, as well as in neuroblastoma cells.[124] FLJ21908 is present in the brain and lymph tissue of HIV dementia patients, suggesting a role for this protein in disease pathogenesis. Increased levels of the HIV-1 accessory protein Vpr have been detected in the CSF of AIDS dementia patients, and Vpr can kill cultured hippocampal neurons, apparently by forming ion-conducting pores in the plasma membrane.[79] Vpr has been shown to induce apoptosis of cultured neurons by a mechanism involving caspase-8.[78]

Culture medium collected from HIV-1-infected T cells induces neuronal apoptosis only when virions are present in the medium, whereas the medium from infected macrophages is toxic whether or not virions are present.[125] Several endogenous factors produced by macrophages may promote neuronal apoptosis, including excitatory amino acids, NO, MMPs and proinflammatory cytokines such as TNF-α and SDF-1.[126–128] Many HIV-1-infected patients also use drugs of abuse including heroin. μ-Opioid receptors are widely expressed by astrocytes and astrocyte precursors, where their activation by opioids such as morphine can induce apoptosis. Prolonged exposure of cultured striatal cells to Tat and morphine resulted in the preferential death of astrocyte precursor cells and astrocytes.[129] The available evidence suggests that interactive neurotoxic effects of viral infection and drugs of abuse accelerate the development and progression of HIV dementia.

Oxidative stress

Evidence for oxidative stress in HIV-1 dementia was obtained from analyses of brain tissue and CSF, including the presence of oxidized proteins.[130,131] Analyses of the brain tissue of HIV-1 dementia patients have revealed evidence for membrane-associated oxidative stress correlated with disease pathogenesis and cognitive impairment, including increased levels of the cytotoxic lipid peroxidation product 4-hydroxynonenal (HNE).[93,132] HNE is known to covalently modify numerous proteins on cysteine, lysine and histidine residues and, by this mechanism, can impair the function of membrane ion-motive ATPases and glucose and glutamate transporters.[133,134] Generation of HNE in response to gp120 and Tat may therefore play a major role in the neurotoxicity of these HIV-1 proteins. Indeed, HNE is known to mediate oxidative stress-induced apoptosis of cultured neurons[135] and can damage neurons and cause cognitive dysfunction *in vivo*.[136] Tat-induced apoptosis of cultured human cortical neurons was potentiated by TNF-α by a mechanism that involved increased oxidative stress.[61] Several antioxidants, including L-deprenyl and ebeselen blocked the toxicity of the CSF, suggesting a key role for oxidative stress in the neuronal death that occurs in HIV-1 dementia.[131]

Excitotoxicity and cellular calcium overload

The bulk of the evidence that neurons may die as a result of overactivation of glutamate receptors (excitotoxicity) in HIV-1 dementia comes from studies of the neurotoxic actions of gp120 and Tat. Gp120 can promote the release of arachidonic acid from glial cells, which can modify the kinetics of NMDA receptors on neurons to increase the mean open probability and channel open time.[137] The combined mechanisms of an increased pool of extracellular glutamate and deregulated NMDA receptor function can result in neuronal calcium overload and cellular dysfunction or death by mechanisms involving disruptions of redox balance and sphingolipid metabolism.[39,93,138] The glutamate receptor antagonist memantine has been shown to inhibit gp120-evoked calcium changes in neurons and astrocytes and protects neurons from gp120-induced cell death.[139–142] A clinical trial using this drug is currently under way in patients with HIV dementia.

Tat can directly interact with neurons and has been demonstrated to depolarize neuronal membranes independent of Na^+ flux.[49] Tat-evoked responses are similar to those induced by the non-NMDA agonist kainate, with the distinction that repetitive applications of Tat do not desensitize non-NMDA receptors.[49,143] Based on evidence suggesting that the desensitization of glutamate receptors inversely predicts agonist toxicity, this unusual action of Tat on membrane polarization has been suggested to be an important mechanism for the toxic effects of Tat.[144–146] As evidence, Tat-induced neuronal cell death can be significantly reduced by antagonists of excitatory amino-acid receptors.[49] Tat potentiates excitatory amino-acid (glutamate and NMDA) triggered calcium flux and neurotoxicity in cultured neurons.[147] Subtoxic concentrations of Tat combined with subtoxic concentrations of glutamate caused neuronal cell death. NMDA receptors play an important role in the neurotoxicities of both gp120 and Tat, which may explain the apparent efficacy of the noncompetitive NMDA receptor antagonist memantine in the treatment of HIV dementia patients.[148] Excitotoxicity is likely exacerbated by proinflammatory cytokines such as IL-1β and TNF.[149] While gp120 and Tat can render neurons vulnerable to excitotoxicity by enhancing activation of NMDA receptors, recent findings suggest an important role for the chemokine receptor CXCR4 in gp120-induced neuronal death.[150] The

latter study showed that a CXCR4 antagonist (AMD3100) can protect cultured neurons against gp120 toxicity.

Tat-triggered neuronal cell death is calcium dependent.[138] When applied onto neurons, Tat evokes an initial burst of intracellular calcium release through IP^3-sensitive pools, that is followed by glutamate receptor-mediated calcium influx.[151,152] The ensuing intracellular events of mitochondrial calcium uptake, disruption of redox balance and caspase activation result in neuronal death.[119,153] Consistent with these findings, inhibitors of IP_3 receptors, agents that stabilize mitochondrial membrane permeability, antioxidants, NO synthase and caspase inhibitors protect neurons from the toxic effects of Tat.[147,151,152] Calcium regulation in glial cells may also be perturbed during the course of HIV dementia. CSF from HIV dementia patients, but not CSF from HIV-1-infected but nondemented patients, disrupts cellular calcium homeostasis in cultured astrocytes.[154] An antagonist of L-type calcium channels, nimodipine, has been shown to protect neurons from the toxic effects of gp120 *in vitro*, but failed in a clinical trial, possibly because of the inability of this drug to inhibit gp120-triggered disruptions of calcium homeostasis in glia.[141,155]

Glial cell neurotoxins and inflammation

Infiltration of lymphocytes and macrophages, activation of microglia and astrocytes, and production of proinflammatory cytokines characterize the brains of HIV dementia patients. Examination of brain sections from HIV dementia and control brains with antibodies against iNOS, IL-1β and caspase-1 revealed that all the three markers of inflammation and oxidative stress are increased in areas of HIV-1 infection.[156] The latter markers were increased in microglia and astrocytes, suggesting that these cells may be sites of production of reactive oxygen species. Levels of macrophage inflammatory protein-1 alpha (MIP-1α), MIP-1β, and regulated upon activation normal T cell expressed and secreted (RANTES) were altered in the CSF of demented HIV-1 patients compared to nondemented patients, suggesting roles for these chemokines in disease pathogenesis.[157] Levels of the MMPs MMP-2, -7 and -9, and activities of MMP-2 and -9, are elevated in the CSF of HIV-1 dementia patients.[158] The latter study further showed that brain-derived cells release MMP-2, -7, and -9, suggesting a mechanism for disruption of the blood–brain barrier and increased immune activation in the CNS in HIV dementia. Hippocampal CA3 and CA4 neurons from patients with HIV encephalitis express higher levels of the chemokine receptor CXCR4 and lower levels of CCR5 than do neurons in control cases or AIDS cases without encephalitis.[159]

Monkeys infected with simian immunodeficiency virus exhibit increased levels of vascular cell adhesion molecule-1, suggesting a mechanism for recruitment of lymphocytes into the central nervous system.[160] Another possible mechanism for recruitment of monocytes into the brain involves HIV-1 protein-induced production of chemoattractant proteins by glial cells. For example, exposure of astrocytes to Tat induces them to produce MCP-1, and MCP-1 is elevated in the brain tissue and CSF of HIV-1 dementia patients.[21] Inoculation of HIV-infected monocytes into the basal ganglia and cortex of severe combined immunodeficiency disease (SCID) mice results in pathological features similar to those of human HIV-1 dementia. In such SCID/HIV-1 mice, the expression of TNF-α, IL-6 and vascular endothelial growth factor (VEGF) was increased.[161] The increased production of these proinflammatory proteins was associated with neuronal damage, as indicated by decreased levels of microtubule-associated protein-1 immunoreactivity. Pivotal roles for inflammatory processes in the neurodegenerative process in HIV-1 dementia are further suggested by studies showing that an inhibitor of TNF-α and MMPs, as well as a platelet-activating factor antagonist, reduce neuropathology in a mouse model of HIV-1 encephalitis.[162]

Lipid metabolism

Levels of cholesterol, ceramide and sphingomyelin are significantly increased in the brain tissues and CSF of HIV dementia patients.[93] Membrane lipid peroxidation and increased ceramide production may be central to the death of neurons in HIV dementia because exposure of cultured neurons to gp120 and Tat resulted in increased cellular levels of HNE and ceramide. Moreover, the ceramide precursor palmitoyl-CoA sensitized neurons to Tat and gp120 toxicity, while an inhibitor of ceramide production reduced Tat and gp120-induced increases of ceramide and HNE and protected the neurons from Tat and gp120-induced death.[93] HIV-1 infection may promote a lipid imbalance in neural cells, resulting in an overproduction of ceramide and consequent cellular dysfunction and death. Individuals with an apolipoprotein E4 allele are at an increased risk for Alzheimer's disease, and recent evidence suggests that the E4 allele also increases the risk of dementia in HIV-1-infected people.[88] Cutler *et al*.[132] found evidence of dysregulated lipid and sterol metabolism in HIV dementia patients with an E4 genotype. Levels of sphingomyelin, ceramide and cholesterol were significantly increased in the medial frontal cortex, parietal cortex and cerebellum of HIV dementia patients with an E3/4 or E4/4 genotype compared to patients with an E3/3 genotype.

Consistent with an important role for sphingomyelin hydrolysis and ceramide production in the pathogenic actions of neurotoxic HIV proteins, Jana and Pahan[163] confirmed that gp120 and Tat induce ceramide production in cultured neurons. They further showed that gp120 and Tat induce sphingomyelinase activity by a mechanism involving induction of oxidative stress by CXCR4 activation. gp120 has a galactosylceramide-binding domain, and other proteins with such a domain regulate membrane trafficking from golgi to lipid rafts,[164] suggesting a potential role for perturbed membrane cycling in HIV-1 dementia pathogenesis. Emerging findings suggest that membrane microdomains called lipid rafts play important roles in the pathogenesis of HIV dementia. Lipid rafts are regions of the plasma membrane that have high levels of cholesterol and sphingomyelin. Receptors for many different cytokines and growth factors are concentrated in lipid rafts. Lipid rafts are believed to be portals through which many different types of viruses, including HIV-1, enter cells[165] and may also be regions where gp120 and Tat exert their neurotoxic actions.[93,132]

Treatment with Antiretroviral Agents is not Sufficient

Within recent years, several antiretroviral drugs have become available that target either the reverse transcriptase or the HIV protease.[166] Very recently, a drug that prevents HIV entry into cells has also been approved for use in HIV-1-infected patients.[167] No drugs have yet been available against any of the other viral gene products. Nevertheless, treatments for AIDS patients, including the widely used nucleoside analogs and protease inhibitors, may impact on the cell death process induced by HIV-1 proteins.[168] Nucleoside analogs have been shown to increase mitochondrial DNA damage and inhibit mitochondrial replication, which would be expected to exacerbate cell death. On the other hand, protease inhibitors can prevent apoptosis by protecting mitochondria.

It is clear that control of the virus in the peripheral blood can partially reverse HIV dementia, resulting in improvement in cognitive and psychomotor function.[169,170] Most antiretroviral drugs do not readily cross the blood–brain barrier. However, improvements in neurological function may be noticed within weeks to months, suggesting that viral products are an important driving force in this cascade. Indeed, viral proteins such as gp120[171] and Tat[172] can cross the blood–brain barrier. However, control of viral replication in the central nervous system is still important because in some patients cognitive decline continues despite excellent control of the virus in the periphery. These patients typically have elevated viral loads in the CSF, a phenomenon called CNS escape.[173] This may occur due to poor penetration of the drugs across the blood–brain barrier and because of viral evolution in the brain. Further, once the cells in the brain are infected and viral integration has occurred, currently available antiretroviral drugs would have no effect on the production of nonstructural proteins such as Tat, which may still be released unchecked from infected microglia/macrophages and astrocytes. At this point of time, antiretroviral drugs alone are insufficient in the treatment of HIV dementia, and neuroprotective and anti-inflammatory approaches will likely be necessary. Finally, the evidence that lipid abnormalities and oxidative stress play important roles in the pathogenesis of HIV-1 dementia suggests that dietary modifications, including reductions in calories and cholesterol-elevating fats, may prove beneficial in the treatment of HIV-1-infected patients.[163]

Summary

The cellular and molecular alterations that result in synaptic dysfunction and neuronal degeneration in HIV dementia are beginning to be understood. In general, it appears that HIV-1 infects macrophages/microglia and possibly neural stem cells. The infected cells release neuotoxic HIV-1 proteins, such as Tat and gp120, as well as proinflammatory cytokines and excitotoxins. Neurons are damaged by HIV-1 and endogenous neurotoxins by mechanisms involving excessive calcium influx and oxidative stress. In addition to drugs that reduce viral load, therapeutic approaches to HIV dementia may include excitatory amino-acid receptor antagonists, antioxidants and calcium-stabilizing agents.

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