Review

From human immunodeficiency virus (HIV) infection of the brain to dementia

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Human immunodeficiency virus (HIV) can cause both primary and secondary brain diseases. Numerous neuropathological studies have shown that up to 90% of patients with acquired immune deficiency syndrome (AIDS) have lesions in the nervous system. In this review, we discuss the entry of HIV into the brain, the general features of HIV associated neuropathology, the role of different brain cells in HIV mediated neuronal damage, and the putative molecular mechanisms involved. We conclude by correlating which factors might be important in the development of HIV associated dementia.

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HIV entry into the brain

It is unclear whether human immunodeficiency virus (HIV) enters the brain soon after the initial systemic infection or later during the course of the asymptomatic phase of disease.^{1–3} The brain is considered to be an “immune privileged site” as the blood-brain barrier (BBB) prevents free access to circulating cells and chemical substances. Free virus does not seem to have an important role in the entry of HIV into the brain. However, the contribution of the infection of endothelial cells by HIV needs to be addressed further, as it has been suggested that HIV may use these cells as a reservoir early in infection or as a site of acclimatisation to the brain microenvironment for subsequent entry.⁴ Nevertheless, the prevalent view is that HIV enters the brain inside infected cells of the monocytic lineage; this manner of entry is known as the “Trojan horse hypothesis” (reviewed in Nottet and Gendelman⁵). Moreover, circulating HIV infected monocytes are thought to release HIV viral proteins that cause the BBB to express cell adhesion molecules (CAMs), selectins, and cytokines.^{6–9} These selectins and CAMs can act as “hooks” that cells can latch onto to cross the BBB. Once inside the brain, HIV stimulates the release of chemoattractant cytokines called chemokines.¹⁰ These, in turn, increase the expression of CAMs on the BBB which can further increase the recruitment of more HIV infected monocytes into the brain. Overall, the tropism of HIV for entry into the brain and the neuronal damage it mediates seems to be correlated with inherent neurovirulent characteristics of HIV.¹¹

HIV associated neuropathology

Up to 90% of patients with AIDS have a variety of both primary and secondary HIV related brain diseases. Primary brain diseases are attributed directly to the effect of the virus on the brain, and include lymphocytic meningitis, HIV encephalitis (HIVE), HIV leucoencephalopathy (HIVL), vacuolar leucoencephalopathy, and vacuolar myelopathy.

Secondary diseases are a consequence of the immunodeficiency status of the patient and include opportunistic infections (for example, *Toxoplasma gondii*, cryptococcus, cytomegalovirus, JC virus) and primary non-Hodgkin's B cell lymphomas (reviewed in Budka *et al*,¹² Everall and Lantos,¹³ and McArthur¹⁴).

Some of the primary HIV associated brain diseases have similar histological features and are thought to demonstrate a pattern of damage along a pathological continuum. For example, multinucleated giant cells (MGCs) are considered to be a histological hallmark of HIVE but are also found in HIVL. Additionally, varying degrees of myelin pallor, activated macrophage/microglial populations, and neuronal loss can also be prominent. These mixed neuropathological characteristics usually blur our understanding of the course and progression of damage caused by HIV in the brain. However, the main conundrum is how these primary diseases relate to clinical the manifestation of dementia.

The detrimental effect of brain resident HIV seems to depend on increased viral load, neuronal damage, and significant levels of potential neurotoxins within the cerebrospinal fluid (CSF).^{15–16} Neuronal loss is generally thought to occur in the symptomatic phase of HIV disease and seems to be prevalent within specific regions and neuronal populations in the brain. Moreover, a consistent 38–50% neuronal loss in the cortex has been reported in AIDS independent of the clinical presence of dementia.^{17–19} Also, a 30–50% decrease of large, pyramidal neurons in the cortex and interneurons in the basal ganglia with accompanying simplification of neuritic arbor has been found.^{20–21}

Putative mechanisms of neuronal damage by HIV

Recent studies on postmortem brains from patients with AIDS have depicted the cellular distribution of HIV infection within the brain. They found that the brain's resident phagocytic immune cells, macrophages, and micro-

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glia were the major cellular reservoirs of HIV followed by astrocytes and in some cases a very small proportion of neurons.^{22,23} The favoured model of HIV mediated neuronal damage in the brain of patients with AIDS is one of "bystander effect", based on the cellular infectivity model summarised in the figure. Briefly, HIV infected macrophages and microglia are thought to release HIV proteins into the surrounding areas of the brain. These proteins can either promote further HIV replication in infected cells or activate neighbouring cells to produce aberrant levels of cytokines, growth factors, free radicals, and prime the release of neurotoxins (reviewed in Trillo-Pazos and Everall²⁴). These HIV driven effectors are thought to interact in a complex manner by interfering with intracellular signalling pathways necessary for neuronal viability (for example, decreased growth factor responsiveness, altered neurotransmitter action, aberrant cellular gene activation). These may, in turn, cause subtle changes in neuronal function such as cytoskeletal retraction, upregulation of Ca^{2+} binding proteins, and inhibition of apoptosis (fig).

HIV infected cells are known to express viral regulatory and structural genes on a temporal basis.^{25,26} Regulatory genes like negative effector (*nef*) and transactivator (*tat*) tend to be expressed earlier whereas structural genes like envelope (*env*) are expressed later in the life cycle of HIV. These genes code for the extracellularly released proteins *nef*, *tat*, and glycoprotein of 160 kD (gp160), respectively. Basic research since the late 1980s has uncovered a gamut of cytotoxic properties of these HIV proteins. These include:

- Nef protein which has been reported to down regulate viral transcription, increase viral latency and infectivity, and interfere with growth factor mediated signalling pathways involved in proliferation, differentiation, and apoptosis. It has also been shown to be homologous to scorpion toxin.²⁷ However, its importance in neuronal damage is only beginning to be addressed.
- Tat protein upregulates viral replication and increases the susceptibility of cells to HIV infection.^{28,29} In the brain, *tat* may both increase the recruitment of HIV infected cells into the CNS, by the upregulation of cytokines and chemokines,^{7,8} and be neurotoxic by increasing neuronal Ca^{2+} influx which has been linked to programmed cell death. Moreover, injection of *tat* into rodents has produced an inflammatory reaction within the brain, astrogliosis, neuronal loss in the grey matter, and increased production of cytokines and nitric oxide synthetase.³⁰
- The envelope gp120 glycoprotein is a spliced product of the *env* gene. Its main role is to bind the virion coat to appropriate cell surface receptors of the host cell, including the CD4, B7, and chemokine receptor complex in T cells. Gp120 was initially shown to be neurotoxic by increasing the influx of Ca^{2+} postsynapti-

cally through ionotropic membrane receptors, especially via the n-methyl-D-aspartate (NMDA) glutamate receptor. The NMDA receptor seems to have a central role in the formation of memory in the mammalian brain. However, over-activation of this receptor, as found in ischaemia and stroke, produces excitotoxic damage and neuronal death. Moreover, specific antagonists of the NMDA receptor blocks gp120 mediated neurotoxicity both in vitro and in animal models (reviewed in Lipton and Gendelman³¹). Other research has linked gp120 to the production of neurotoxins by macrophages and microglia,³²⁻³⁴ the upregulation of cytokines and disruption of neurotransmitter action (reviewed in Lipton and Gendelman³¹). In vivo research, has corroborated gp120 with neuronal damage, astrogliosis, microglial changes, and simplification of the dendritic-axonal network (reviewed in Trillo-Pazos and Everall²⁴).

Apart from putative toxic viral proteins increased levels of cytokines have been consistently reported in the brain and CSF of patients with AIDS. Cytokines are a large family of immunomodulatory proteins comprising interleukins (ILs), chemokines, tumour growth factors (TGFs), tumour necrosis factors (TNFs), and neurotrophic factors. In the brain, they have been found to be both neuroprotective at low levels and potentially neurotoxic at high levels (reviewed in Merrill and Benveniste³⁵ and Rothwell and Hopkins³⁶). Cytokines have pivotal roles in conditions of stress, growth, injury, and infection depending on their concentration, site, and duration of action as well as acting synergistically with other molecular effectors like free radicals and other cytokines. They are predominantly released by microglia, macrophages, and astrocytes within the brain constitutively and are upregulated in response to previously described stressors. There is accumulating evidence that there is increased production of potentially damaging cytokines in the brain during AIDS; these include:

- $\text{TNF}\alpha$ which is constitutively expressed throughout the brain and can be induced by gp120 and *tat*. It is involved in the activation of macrophages, general immune response, and in the programmed cell death of activated T cells.³⁵ In AIDS, $\text{TNF}\alpha$ has been correlated to astrogliosis, induction of ILs and colony stimulating factors, upregulation of potential neurotoxins like arachidonic acid, platelet activating factor, nitric oxide and the activation of HIV replication via the NF- κB transcription factor. $\text{TNF}\alpha$ is also thought to cause demyelination within the brain via the demise of oligodendrocytes. It also modulates Ca^{2+} currents, decreases glutamate uptake by astrocytes, and overstimulates glutamate receptors in neurons (reviewed in Merrill and Hopkins³⁵).

A cellular model of HIV infection in the brain to dementia: a hypothesis.
The stages following HIV entry into the brain can be split into four before the clinical outcome of dementia: (1) HIV entry into the brain is thought to be mediated by activated HIV infected monocyte cells with unregulated surface receptors that attach to the corresponding receptors on endothelial cells in the blood-brain barrier (BBB) (for example, selectins, CAMs),⁶⁻⁹ as described in the main text; (2) HIV colonisation of endogenous cells is thought to affect mainly macrophage and microglial cells, but some astrocyte infection by HIV has also been reported.^{22,23} It is at present unclear what the temporal sequence of cellular infection both within the brain and as a function of HIV disease progression is (refer to main text). This colonisation period probably determines what HIV associated primary diseases will be prevalent later on depending on viral and host genotype mediated factors;¹¹ (3) HIV mediated molecular dysfunction in the brain sometime after the virus has infected endogenous cells in the brain and has had an unknown period to adjust to its new environment or the actual lymphocyte trafficking of the brain has diminished sufficiently to allow partial or total HIV replication; a cascade of molecular factors are produced ranging from HIV proteins to potential neurotoxins (see main text) (reviewed in Trillo-Pazos and Everall¹⁴ and Lipton and Gendelman¹¹). This stage may represent a phase of damage consolidation in HIV associated primary diseases more generally; (4) HIV mediated neuronal damage is thought to occur when the aberrant molecular effectors, whether they be viral or cellular, act either synergistically or independently to undermine normal cellular function by hijacking intracellular signalling pathways (functional neuronal damage) or initiate the apoptotic pathway in neurons (neuronal loss) (reviewed in Everall et al,¹⁶ Masliah et al,²¹ and Trillo-Pazos and Everall¹⁴). Dementia may become clinically apparent when the accumulative damage reaches a “critical mass” that undermines the function of neurons in information processing, storage, and retrieval within the human brain.

- Interleukins are a large family of pro-inflammatory cytokines that have a multitude of pleiotropic roles including initiation of the immune response, activation of lymphocytes, and regulation of body temperature. They can be produced by glial cells, microglia, macrophages, and endothelial cells within the brain. In HIV infection of the brain, IL-1 and IL-6 have been found at elevated levels.³⁵ These ILs have been correlated with astrogliosis, the induction of other cytokines, enhanced HIV replication, and neuronal differentiation.
- TGF β is produced by cells of the glial and macrophage lineage within the brain. It curtails the immune response within the brain by inhibiting cytokine production and HIV replication.³⁵

So, in the HIV infected brain current evidence suggests a complicated model of neurotoxicity involving both viral and cellular factors culminating in functional neuronal damage and neuronal loss seen in AIDS (reviewed in Trillo-Pazos and Everall²⁴).

HIV associated dementia (HAD)

HAD is a progressive impairment of the cognitive, behavioural, and motor abilities of patients with AIDS, resulting in severe dementia and terminal illness within 6 months to a year of onset.³⁶ However, this prognosis may well change with the introduction of combination therapies. HAD is usually seen in the late stages of AIDS and does not seem to correspond to any one single HIV primary brain disease.¹² Moreover, specific neurovirulent HIV strains have been associated with the development of HAD¹¹ but other studies have found no such association.³⁷ Recent evidence from postmortem brains of patients with HAD suggests a tentative association between increased viral burden and neuronal damage^{15,22} but reports are conflicting. It seems that dendritic, synaptic, and cytoskeletal damage may occur first, followed by cortical pyramidal neuronal loss and then a more generalised loss during the evolution of dementing features.^{21,38} Moreover, increased levels of TNF α messenger RNA³⁹ and inducible nitric oxide synthetase⁴⁰ have been found to correlate with severity of HAD in postmortem brains. Furthermore, as described in this review functional neuronal damage is thought to be orchestrated by a poorly understood complex interaction between HIV viral proteins (for example, gp120, tat, and nef) and cellular products (for example, cytokines, growth factors) (fig). It is imperative to determine how these cited effectors, be they viral or cellular, affect the normal function of neurons to such an extent as to cause the cognitive impairment in patients with AIDS. Firstly, one needs to unravel the ordinary intracellular signalling pathways required for optimal neuronal survival and function within the human brain, and to determine how HIV affects them to such an extent as to undermine their ability to process, store, and retrieve information.

Basic research into the subtle mechanisms of neuronal damage in HIV infection has a crucial role to play if appropriate therapy is to be developed.

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