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Review

HIV in the CNS: Pathogenic relationships to systemic HIV disease and other CNS diseases

Dianne M Rausch[1] and Miriam R Davis[2]

[1]*National Institute of Mental Health, Center for Mental Health Research on AIDS, Bethesda, Maryland, USA; and* [2]*Department of Epidemiology and Biostatistics, School of Public Health and Health Services, George Washington University, Washington, DC, USA*

Research on the pathogenesis of the human immunodeficiency virus (HIV) infection of the central nervous system (CNS) has reached a pivotal stage. While the incidence of HIV dementia appears to be declining, the prevalence of milder, yet debilitating, neuropsychological impairments may rise as individuals infected with HIV live longer. There are also concerns about CNS reservoirs of latently infected cells. Building upon progress in understanding HIV neuropathogenesis, the time is ideal to expand research on the interrelationships between the CNS and systemic HIV disease, and extend the boundaries of this research to the neuropathogenic similarities between HIV and other CNS inflammatory diseases. Neuropathogenic insights gained from these pursuits can spawn new treatment strategies for HIV/CNS disease as well as potentially other diseases of the nervous system. *Journal of NeuroVirology* (2001) **7,** 85–96.

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Introduction

HIV infection of the CNS produces a range of cognitive, motor, and behavioral abnormalities (Navia *et al*, 1986a; Price *et al*, 1988). HIV-associated dementia (HAD) is the most severe manifestation, typically found in late stages of AIDS. But during the course of HIV disease—even early after infection—more subtle neuropsychological (NP) impairments are detectable (Grant *et al*, 1995). NP impairments can be disabling (Heaton *et al*, 1994; Albert *et al*, 1995; Heaton *et al*, 1996), can interfere with patient adherence to complex medication regimens, and are an independent risk factor for mortality (Ellis *et al*, 1997).

The advent of highly active antiretroviral therapy (HAART) in 1995 has led to striking reductions in plasma viral load, opportunistic infections, and mortality from AIDS (Montaner *et al*, 1998; CDC, 1999; Powderly, 2000). During this era there also appears to be a reduction in the incidence of HAD (Dore *et al*, 1999; Sacktor *et al*, 1999b). However, as patients live longer, there is reason to predict growing prevalence of NP impairment and/or HAD. Further, because of poor drug penetration of the blood-brain barrier (BBB) or poor accumulation within the CNS, concerns persist about the possible evolution of drug-resistant virus in the CNS (Richman, 1996; Kepler and Perelson, 1998; Schrager and D'Souza, 1998). There are currently no FDA-approved treatments expressly designed for the CNS, although several nonantiretroviral drugs are in clinical trials.

The refinement of in vitro and animal models, the identification of rapidly increasing roles for chemokines and their receptors, and improvements in viral load monitoring have ushered in significant advances in our understanding of HIV neuropathogenesis. To build on that knowledge, researchers are poised to look beyond the confines of the CNS. New sets of questions can be posed about potential dynamic interrelationships between the CNS and the periphery. Researchers also can branch out to focus on common pathogenic threads uniting HIV neuropathogenesis with that of other neurological

Address correspondence to DM Rausch, National Institute of Mental Health, Center for Mental Health Research on AIDS, 6100 Executive Blvd, Room 6212, MSC 9623, Bethesda, MD 20892-9623, USA. E-mail: dr89b@nih.gov
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disorders, most notably multiple sclerosis and Alzheimer's disease. The pathogenic similarities between seemingly disparate disorders, with remarkably different etiologies, can inspire new hypotheses about HIV neuropathogenesis and its treatment.

HIV in the CNS

HIV commonly invades the CNS (Wiley *et al*, 1999; Masliah *et al*, 2000), and it does so early after peripheral infection (see reviews by Griffin, 1998; Kolson *et al*, 1998). HIV has been detected in the brain as early as 15 days after accidental intravenous inoculation (Davis *et al*, 1992). Early penetration into the CNS also holds true following peripheral inoculation of rhesus macaques with SIV (Hurtrel *et al*, 1991; Lackner *et al*, 1991; Sharer *et al*, 1991). The chief cellular targets of HIV infection within the CNS are microglia/macrophages (MG/MP) (Kolson *et al*, 1998). MG/MP is a generic term for monocyte-derived cells that, upon their migration into the CNS, differentiate into resident microglia, perivascular microglia and macrophages, meningeal macrophages, and choroid plexus macrophages, among others (Hickey, 1999a).

Indirect mechanisms of neuropathogenesis

More than a decade ago, it became clear that the neuron dysfunction or death that underlies clinical symptoms of HIV/CNS disease cannot result from direct infection of neurons. The reigning model of HIV neuropathogenesis attributes neuron dysfunction or death to the *indirect* consequences of infection of MG/MP (Giulian *et al*, 1990; Pulliam *et al*, 1991). Under this model, MG/MP release a barrage of cytokines and other soluble factors, including HIV proteins, that, in high concentrations and over extended periods, are toxic to nearby neurons. Cytokines and other inflammatory factors are also produced and released by *uninfected* MG/MP that are activated by cytokines or by soluble HIV proteins (Nuovo and Alfieri, 1996; Yeh *et al*, 2000).

The *combined* influence of both HIV infection and activation of immune-competent cells explains the important finding that HIV infection alone cannot fully account for the degree of dementia (Glass *et al*, 1995). In this autopsy study, the presence of activated MG/MP was better correlated with the degree of dementia than was viral load. HIV infection, in other words, sets the stage for secretion of inflammatory products, which in some cases leads to neuronal apoptosis, by either *infected* MG/MP (Pulliam *et al*, 1991), or by *uninfected*, yet immune-activated, MG/MP (Yeh *et al*, 2000). The number of activated cells is vastly increased by either astrocytosis or by influx of leukocytes (see next section).

The repertoire of candidate neurotoxins released by immunocompetent cells is large. Neurotoxic HIV proteins include gp120 envelope glycoprotein, Tat, and Nef (Kolson *et al*, 1998). The cytokines and other soluble factors that are significantly elevated in the brains or CSF of HIV-infected individuals include pro-inflammatory cytokines (TNF-α and IL1-β), chemokines (see next section), arachidonic acid, platelet activating factor, quinolinic acid, and nitric oxide (see reviews Kolson *et al*, 1998; Zheng and Gendelman, 1997). Quinolinic acid levels correlate with severity of impairments or dementia in humans (Sei *et al*, 1995) and motor impairment in animals (Heyes *et al*, 1992; Rausch *et al*, 1994). Release of TNF-α by MG/MP also may be critical, as levels of TNF-α mRNA at autopsy correlate with the severity of dementia (Wesselingh *et al*, 1993). Further, TNF-α may increase white matter pallor seen at autopsy because, on the basis of in vitro studies, its release from HIV-infected MG/MP kills oligodendrocytes (Wilt *et al*, 1995).

Chemokines

One of the prominent neuropathological findings with HIV infection is perivascular infiltration of monocytes across the BBB (Price *et al*, 1988). Recent research has highlighted the role of chemokines as key regulators of monocyte recruitment across the BBB into the CNS. This chemoattractant role for chemokines is distinct from their numerous other roles, most notably as coreceptors (with CD4) for entry of HIV into monocytes and lymphocytes. During infection of the CNS, release of specific chemokines induces selective migration across the BBB by those leukocytes with corresponding chemokine receptors. Chemokines and their receptors do not work alone, as the selectins and integrins (and their receptors) also participate in a multistep process of immune cell infiltration (Luster, 1998).

β-Chemokines figure prominently in HIV infection of the CNS (Meucci *et al*, 1998; Hesselgesser and Horuk, 1999). They are selective attractants for monocytes and lymphocytes. The CNS cells expressing β-chemokines (or their cognate receptors) are neurons, MG/MP, and the cells forming the BBB (endothelial cells and astrocytes) (Hesselgesser and Horuk, 1999).

The expression of several chemokines is upregulated during HIV infection, and this enhanced expression correlates with dementia. A groundbreaking autopsy study found the brains of HIV patients with dementia to have elevated levels of MIP-1α and MIP-1β, compared with patients without dementia (Schmidtmayerova *et al*, 1996). In the same study cultured monocytes infected with HIV produced elevated levels of the same β-chemokines. Similarly, studies in the SIV model found MIP-1α, MIP-1β, RANTES, MCP-3 and the α-chemokine IP-10 in brain (Sasseville *et al*, 1996; Westmoreland *et al*, 1998). IP-10 is one of the α-chemokines that selectively attracts activated T lymphocytes (Luster, 1998). IP-10 was found to be elevated in the CSF of HIV-infected patients with neurological deficits

(Kolb *et al*, 1999). Other CSF studies of HIV patients have found elevated concentrations of β-chemokines. Higher CSF levels of either MCP-1 or RANTES, or both, were found to be correlated with the degree of encephalitis (Cinque *et al*, 1998) and dementia (Conant *et al*, 1998; Kelder *et al*, 1998). MCP-1, MIP-1α, and RANTES were localized by immunocytochemistry to be most abundant in and around microglial nodules, a histopathological sign of HIV infection at autopsy (Sanders *et al*, 1998).

Pathogenic relationships between CNS and systemic HIV disease

For years, research on HIV-associated dementia (HAD) naturally focused on events within the CNS. It also focused primarily on pathogenic mechanisms occurring either early or late in HIV disease. But recent research on the existence of systemic HIV reservoirs (Chun *et al*, 1997; Finzi *et al*, 1997; Wong *et al*, 1997b) and leukocyte trafficking through the CNS has begun to spur interest in the possibility of dynamic interrelationships between the CNS and systemic disease. Such interrelationships, in fact, may be occurring throughout the course of HIV disease, not just early after infection or at end stages. Interrelationships—especially during asymptomatic phases of HIV disease—are vital to study because, with treatment advances, the burden of the epidemic in the US has shifted to a more chronic course (Rausch and Stover, 2000).

CNS trafficking refers to the movement of immune cells (or virus) from peripheral blood, across the BBB, through brain parenchyma, and then back into the periphery. Until the last decade, the dogma was that the normal CNS was immunologically privileged and that immune cells did not traffic into and out of the brain (Miller, 1999). Now there is greater recognition of immune cell trafficking as a dynamic process involving numerous cell types with divergent functions, cell surface markers, migratory capacity, CNS location, and turnover kinetics (Hickey, 1999a). Our understanding of the details of monocyte and other immune cell trafficking, under normal physiology and under the influence of HIV infection, is still rudimentary. It is not established, for instance, whether the virus remains in the CNS or is cleared from the brain (Zink *et al*, 1998). The most formidable problem for research is that access to human CNS tissue, except at autopsy, is severely limited. A further limitation is that CSF has uncertain value for studying events within the CNS, especially prior to advanced HIV disease (Price and Staprans, 1997; Ellis *et al*, 2000). Many of the questions that follow can be addressed in the SIV animal model.

Trafficking and autonomous versus transitory infection

HIV enters the CNS early (see prior description), before systemic infection typically is recognized and treatment initiated. Yet, HAD may not develop until years thereafter, when there is substantial viral replication in the CNS (Wiley *et al*, 1998; Wiley *et al*, 1999). After its early entry, what happens to the virus in the CNS, and what is its relationship to the periphery over the natural history of the disease? Does the virus entering early account for later CNS manifestations? This would be an *autonomous* infection, i.e., one that is persistent and self-sustaining, not dependent on subsequent trafficking of virus from the systemic circulation. Or is initial CNS viral infection short-lived, readily cleared from the CNS, and later dependent on continuous or repeated trafficking from the periphery to sustain CNS infection giving rise to HAD? This type of CNS infection would be *transitory* (see Figure 1).

The conceptual dichotomy between autonomous and transitory infection was first articulated by Price and Staprans (1997). As with any dichotomy, the answer may not exclusively be one or the other, but some combination of both. Understanding the extent of autonomous versus transitory infection in relation to disease stage has important implications for treatment and eradication of HIV. If autonomous infection in the CNS is the major culprit in HAD or milder forms of impairment, then treatment strategies should emphasize new medications directly for the CNS. If, on the other hand, virus is removed early and without clinical significance, but later trafficking of virus into the CNS is the culprit in HAD, then more effective control of HIV in the periphery is warranted. As long as peripheral control over viral replication is achieved, according to this line of reasoning, HAD would not develop (Gartner, 2000).

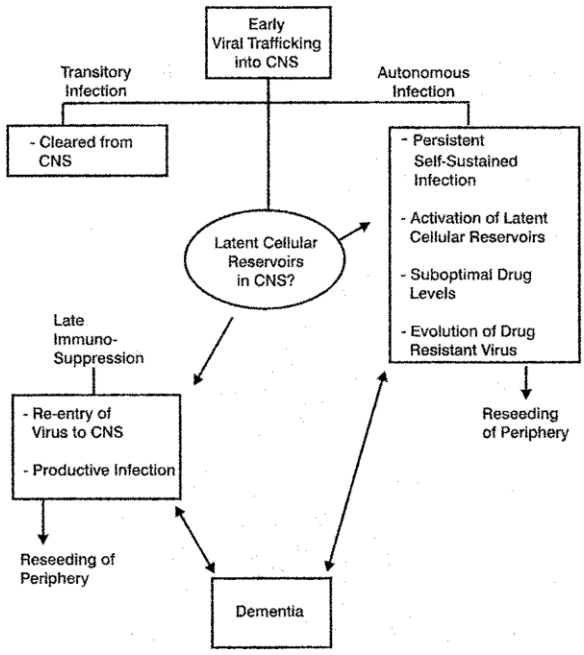

Figure 1 Transitory versus autonomous infection after HIV trafficking into the CNS.

To disentangle the relative roles of autonomous and transitory infection over the course of HIV disease would require repeated CNS and peripheral tissue sampling at different times during infection. CNS sampling can be accomplished in experimental animal models but it is not possible in humans. Thus evidence in humans favoring one or other type of infection at this point is largely indirect.

Autonomous infection of the CNS is thought to be plausible because of the cell types infected, their turnover characteristics, and because of the protected environment of the CNS. The most commonly infected cells (monocyte derivatives) are not lysed during production of viral progeny. They are long-lived, with some cell types (e.g., parenchymal microglia) persisting possibly for decades (Hickey *et al*, 1992; Lassman *et al*, 1993). Further, the CNS is to some extent both immunologically and pharmacologically protected from the systemic circulation by the BBB (Miller, 1999). These features generate concerns that, especially in a CNS environment of suboptimal drug levels, an autonomous infection could proceed unchecked, leading to evolution of drug-resistant viral mutations (Richman, 1996; Kepler and Perelson, 1998; Ellis *et al*, 2000). Such mutations would threaten *both* the CNS and the periphery should mutated virus traffic out of the CNS. Reseeding from the CNS to the periphery late in disease has been demonstrated with the SIV model (Zink *et al*, 1997).

Compartmentalization of HIV in the CNS has been found in numerous studies showing certain viral sequences, including drug resistance codons, to be different from those in other compartments (Pang *et al*, 1991; Korber *et al*, 1994; Wong *et al*, 1997a; Hughes *et al*, 1997; van't Wout *et al*, 1998; Liu *et al*, 2000). There are also reported genetic differences across distinct regions of the brain (Morris *et al*, 1999; Shapshak *et al*, 1999). The limitation of many of these studies to understanding the extent of transitory versus autonomous infection is that they were done on a small number of individuals, generally with advanced disease at autopsy. Further, most were cross-sectional, so it is difficult to address the timing of viral entry into the CNS. Longitudinal studies—with advanced imaging and repeated blood and CSF sampling—are clearly warranted to determine whether and to what extent productive replication is occurring throughout disease, and what is the source of virus—internal to the CNS or from blood trafficking? What sites, like the choroid plexus (Petito *et al*, 1999), might serve as a reservoir for CNS infection?

It is also vital to examine viral and host factors—throughout disease—that affect HIV and immune cell trafficking between the systemic circulation and the CNS. Viral strain (Zink *et al*, 1998), viral load, and integrity of the BBB (Petito and Cash, 1992; Dallasta *et al*, 1999) are likely important, as is the activation state of monocytes. Monocyte migration across an artificial BBB, for example, was shown to increase by 20-fold when monocytes were activated (Persidsky *et al*, 1997). Monocyte activation in this study was even more important than viral infection in enhancing monocyte trafficking. The activation state of monocytes affects the profile of cytokines that they produce and secrete (Frankenberger *et al*, 1996) and, as noted earlier, their neurotoxicity.

A related question is whether there is a reservoir of latently infected cells (monocytes, T cells, or astrocytes) within the CNS. If so, can latently infected cells be activated to sustain autonomous infection? Latent infection, a means for HIV to evade host defenses, refers to proviral DNA incorporated into the host cell's genome in a transcriptionally silent form until later activation and replication (Chun and Fauci, 1999). Peripheral tissues, such as lymph nodes, bone marrow and testis, hold latent viral reservoirs within resting CD4+ T cells. Because of T cells' slow turnover (months to years), latent infection may be responsible for lifelong persistence of HIV, despite HAART's suppression of virus in actively replicating cells (Finzi *et al*, 1999).

Strong evidence for peripheral cellular reservoirs has clearly raised the specter of CNS cellular reservoirs (Schrager and D'Souza, 1998; Chun *et al*, 2000). Yet, the precise nature and extent of CNS reservoirs are elusive. There appears to be a small proviral load of HIV in the brain in *asymptomatic* HIV disease (Bell *et al*, 1993; Donaldson *et al*, 1994; Sinclair *et al*, 1994). The question is whether and under what circumstances it is sufficient to rekindle productive CNS infection and its clinical manifestations. In the absence of certainty, even the possibility of CNS reservoirs warrants the development of explicit CNS treatment strategies aimed at their reactivation and eradication, similar to those being tested for the periphery, e.g., IL-2 coupled with anti-retroviral therapy (Chun *et al*, 1999).

Impact of HAART

The introduction of HAART, as noted earlier, appears to have coincided with a reduction in the incidence of HAD. Clinical trials have found HAART to alleviate some NP impairments (Ferrando *et al*, 1998; Tozzi *et al*, 1999; Sacktor *et al*, 2000), although it is not clear if protease inhibitor in the combination confers any distinct advantages over combination therapy without protease inhibitor (Sacktor *et al*, 1999a). HAART's impact on the full array CNS impairments has not yet been studied.

HAART's apparent benefits are perplexing in light of poor CNS penetration of many of its constituent drugs (Enting *et al*, 1998; Flexner, 1998; Aweeka *et al*, 1999). Zidovudine (ZVD) and indinavir appear to have among the best CNS penetration, but both are substrates for active efflux (Banks, 1999; Martin *et al*, 1999). Their suppression of CNS viral replication cannot be studied in patients during asymptomatic stages. It is thus unclear whether HAART's seeming benefits may stem from partial, albeit sufficient,

control over viral replication in the CNS or from control of viral replication in peripheral compartments (thereby curtailing trafficking into the CNS). Another area to investigate is HAART's impact on peripheral monocyte activation and cytokine profiles. There is suggestive evidence that HAART shifts the cytokine profile of monocytes and T cells (Imami *et al*, 1999). Key areas of investigation are HAART's impact on monocytes, including their cytokine profiles, capacity to traffic into the CNS, and their neurotoxicity.

In summary, many questions for research surround trafficking of HIV into the CNS and the interrelationships with the periphery over the course of HIV disease. The impact of HAART on trafficking and on the nature and extent of CNS manifestations is also key. Better understanding of neuropathogenesis in the era of HAART is crucial as the nature of the HIV epidemic shifts to a more long-term course.

Pathogenic relationships between HIV and other CNS diseases

Until recently neuroscientists tended to emphasize the neuropathogenic differences across distinct CNS diseases. Attention was understandably drawn to the differences in an effort to characterize in detail neuropathogenic mechanisms unique to each. Now, a change in perception is emerging, building on momentum from advances in immunology, molecular biology, and neuroscience. Researchers have begun to recognize, and capitalize upon, some intriguing parallels in the neuropathogenesis of disparate CNS diseases (Dickson *et al*, 1993; Mrak and Griffin, 1997; Cotter *et al*, 1999; Gonzalez-Scarano and Baltuch, 1999; Hesselgesser and Horuk, 1999).

This section describes some of the key similarities in neuropathogenesis between HIV disease and two other neurodegenerative diseases, multiple sclerosis (MS) and Alzheimer's disease (AD). The section highlights the overlaps in three critical areas: chemokines and leukocyte chemotaxis; activation of inflammatory cells and release of soluble cytotoxins; and mechanisms of neuron dysfunction and death (Figure 2). The choice of MS and AD is for illustrative purposes, for these areas of overlap may well extend to other neurological disorders.

Enthusiasm surrounding pathogenic similarities should not lose sight of fundamental differences between HIV, MS, and AD. The foremost difference rests with etiology. The etiological agent in HIV disease is the virus; with MS, the etiology is not established, but evidence favors the early role of autoreactive T lymphocytes (CD4+) directed at myelin antigens (Williams *et al*, 1994; Brosnan and Raine, 1996; Conlon *et al*, 1999; Lassmann, 1999). With AD, the etiology is also not fully known, but most evidence points to genetic mutations which lead to the production of extracellular aggregates of β-amyloid protein (Selkoe,

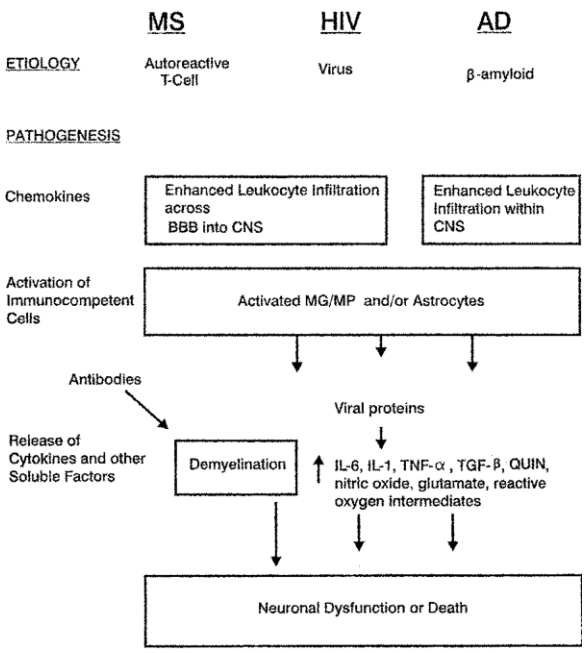

Figure 2 Etiology and neuropathogenesis of MS, HIV, and AD. Despite different etiologies, there are pathogenic similarities.

1999). The three diseases also exhibit differences in symptomatology, diagnosis, and clinical course, although there are some overlaps in the nature of cognitive impairments.

Finally, there are differences in CNS lesions and their regional distribution. Lesions in HIV disease are found mostly in subcortical structures, including the basal ganglia, and some cortical nuclei (Price *et al*, 1988; Budka, 1991; Masliah *et al*, 1997; Stout *et al*, 1998; Everall *et al*, 1999). With MS, the principal lesion is demyelination—the destruction of oligodendrocyte processes forming the myelin sheath—although there is recent evidence of axonal transsection too (Trapp *et al*, 1998). MS lesions are localized primarily in the optic nerve, spinal cord, brainstem, and cerebellum (McDonald and Ron, 1999). With AD, the pathological hallmarks are extracellular senile plaques and intraneuronal neurofibrillary tangles found in the cerebral cortex (temporal and parietal lobes), hippocampus and amygdala. Despite these differences, what becomes clear in subsequent sections are similarities in inflammatory processes and neuron dysfunction or death.

Chemokines and leukocyte chemotaxis

Chemokines are coming to prominence for their role as leukocyte chemoattractants in many CNS inflammatory diseases (Asensio and Campbell, 1999). Evidence of their role in regulating leukocyte infiltration across the BBB is being amassed for HIV (see prior discussion) and for MS (Ransohoff, 1999). Leukocyte infiltration across the BBB is not thought to be a major factor in AD because the inflammation is local, i.e.,

restricted within the brain (Xia and Hyman, 1999). Nevertheless, chemokines appear to play a more focal role in AD by attracting leukocytes residing *within* the CNS to senile plaques. In all three diseases, the accumulation of activated leukocytes within the CNS unleashes or contributes to inflammatory destruction of neurons or oligodendrocytes (see next section).

In MS, leukocyte infiltration is a major feature, apparently triggered by myelinreactive T cells which enter the CNS (Hickey *et al*, 1991; Brosnan and Raine, 1996; Ransohoff, 1999). The infiltrate consists mostly of macrophages and T cells (Cross *et al*, 1990, 1993), although B cells are increased later in disease (Ozawa *et al*, 1994). The chemokine profile in MS reveals upregulated expression of several β-chemokines (including RANTES and MCP-1) and IP-10, among others (Glabinski and Ransohoff, 1999). This chemokine profile resembles that with HIV, which, as noted before, consists of β-chemokines (MIP-1α, MIP-1β, RANTES, MCP-3) and the α-chemokine IP-10.

The significance of chemokines in MS pathogenesis has come from two types of evidence. First, antibodies against the chemokine MCP-1 block the onset of acute symptoms in an animal model of MS (Karpus *et al*, 1995). Second, studies of human CSF reveal upregulation of certain chemokines (and their cognate receptors) at the time of initial MS attack or relapse (Sorenson *et al*, 1999). The latter study is reminiscent of findings with HIV disease, cited earlier, of chemokine upregulation in CSF being correlated with the degree of dementia.

The dense senile plaque of AD consists of the core deposit of the protein β-amyloid surrounded by microglia, astrocytes, and dystrophic neurites (Selkoe, 1999). Responding to chemotactic signals from β-amyloid (Maeda *et al*, 1997; Kopec and Carroll, 1998), microglia arrive to digest β-amyloid, only to be incapable of degrading large amounts (Paresce *et al*, 1997). What signals draw microglia to β-amyloid deposits? A working hypothesis is that enhanced chemokine expression by astrocytes or microglia controls chemotaxis of other microglia to β-amyloid deposits (Xia *et al*, 1997; Xia and Hyman, 1999). A role for chemokines and their receptors in the neuropathogenesis of AD has been supported by finding that β-amyloid induces secretion of the chemokine IL-8 by cultured astrocytes (Gitter *et al*, 1995) and that neuritic portions of plaques express high levels of CXCR2, the chemokine receptor for IL-8 (Xia *et al*, 1997; Horuk *et al*, 1997).

Activation of inflammatory cells and release of soluble cytotoxins

A unifying theme in the neuropathogenesis of HIV, MS, and AD is the sustained overproduction and release of pro-inflammatory cytokines and other soluble factors by activated immune cells, resulting in eventual injury or death to nearby neurons and/or oligodendrocytes (Benveniste, 1998; Cotter *et al*, 1999; Gonzalez-Scarano and Baltuch, 1999; McGeer and McGeer, 1999).

Overproduction of toxic inflammatory factors applies across these three diseases, despite dissimilarities in (1) the specific sequence of events (which also may be heterogeneous at different stages of each disease and across different subtypes of each); (2) the relative contributions of different cytokines and soluble cytotoxins; (3) the affected region of the CNS and its proximity to vasculature; (4) the contributions of distinct classes of activated immunocompetent cells (T cells, infiltrating monocytes, resident microglia, and/or astrocytes); and (5) the nature and degree of injury and death to neurons (or oligodendrocytes). The *indirect* mechanisms of cytotoxicity outlined here do not preclude the co-occurrence of *direct* cytotoxicity mediated by cytotoxic T cells (CD8+) in MS (Brosnan and Raine, 1996) and by β-amyloid in AD (Yankner *et al*, 1990). This also does not preclude a role for B cells in antibody-mediated damage to oligodendrocytes in MS. Demyelination in animal models requires *both* autoreactive T cells and antibodies to myelin (Lassmann *et al*, 1988).

There are some interesting overlaps in secretory products between HIV, MS, and AD (except for gp120 and other HIV proteins). Common to all three diseases are elevated levels of cytokines IL-1, IL-6, TNF-α, and certain isoforms of TGF-β (Benveniste, 1998). Similarly, all three have elevated levels of reactive oxygen intermediates, nitric oxide, and glutamate (released by inflammatory cells or neurons) (Piani *et al*, 1991, Bo *et al*, 1994; Stover *et al*, 1997; Lipton, 1998; Selkoe, 1999). Distinct immune cell types produce and secrete many of the same toxins. Low concentrations of these inflammatory products could be beneficial; however, high local concentrations of cytotoxins produced over a sustained period, regardless of cellular source, produce injury or death of neurons or oligodendrocytes. There is also recent evidence that dementia patients with HIV and AD both have greater percentages of monocytes in peripheral blood with the activation marker CD69 (Pulliam *et al*, 1997; Kusdra *et al*, 2000).

One of the best ways of assessing the significance of individual cytotoxins in disease is through correlation with disease progression. Levels of the cytokine TNF-α in human CSF are correlated with the degree of dementia with HIV (Wesselingh *et al*, 1993) and are correlated with relapse in MS (Sharief and Hentges, 1991). There has been no consistent evidence of cytokine levels in CSF increasing over the course of AD (Engelborghs *et al*, 1999; Lanzrein *et al*, 1998); however, there is new evidence of IL-1 overexpression correlating with dementia in AD (Nicoll *et al*, 2000). Establishing relationships between CSF levels and disease severity is complicated by the inherent limitations of using CSF levels to infer highly localized CNS inflammation. No single CSF marker for measuring progression has reached clinical use for the diseases discussed here.

Mechanisms of neuron dysfunction and death

Refined understanding of the mechanisms of neurotoxicity can inspire targeted therapeutic strategies to reverse injury at the earliest possible stage or to prevent cell death. If the mechanisms are similar across different diseases, the same targeted treatments may be effective. The *in vivo* mechanisms of neuron dysfunction and death in HIV, MS, and AD are poorly understood, but there are numerous similarities to pursue.

At first glance the inclusion of MS might seem questionable, for MS largely features injury and demise of oligodendrocytes. Axons were thought to be protected, and clinical manifestations were thought to reflect conductance block by demyelinated, yet intact, axons. New research, however, has revealed axonal transsection in MS (Trapp *et al*, 1998). Axonal loss is now postulated to be responsible for irreversible disability in MS (Trapp *et al*, 1998; Hickey, 1999b; Smith and McDonald, 1999). Axonal loss may be mediated by inflammatory factors in a manner similar to neurotoxicity with AD and HIV. After the death of oligodendrocytes, axons may become more vulnerable to the cytotoxic barrage from which they had previously been shielded by viable oligodendrocytes. High levels of some of the same cytokines are toxic to both neurons and oligodendrocytes (Selmaj and Raine, 1988; Benveniste, 1998). Although other neurotoxic mechanisms may be occurring (prolonged electrical silence, loss of trophic factors from oligodendrocytes, see review Scolding, 1999), neurotoxicity by inflammatory factors may be as salient a feature for MS as it appears to be for AD and HIV.

Much research has focused on neurotoxicity induced by excess levels of glutamate (Rothman and Olney, 1995; Choi, 1988). Excess levels of glutamate have been implicated, with varying levels of evidence, in all three diseases. In fact, excess glutamate has been implicated in so many neurological diseases that a landmark article referred to glutamate and other excitatory amino acids as a "final common pathway for neurologic disorders" (Lipton and Rosenberg, 1994). High extracellular levels of glutamate or glutamate agonists overstimulate *N*-methyl-D-aspartate (NMDA) receptors on neurons, resulting in the influx of calcium ions. High intracellular calcium levels, in turn, generate free radicals, activate proteases and phospholipase, and induce mitochondrial dysfunction, leading to necrosis or apoptosis (Lipton, 1998; Martin *et al*, 1998). There are numerous pathways in which the cascade of intracellular events can unfold, for no single pathway of excitotoxicity is uniquely associated with cell death (Rothman and Olney, 1995; Klegeris and McGeer, 2000). Excess levels of glutamate are also toxic to oligodendrocytes, which possess the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)/kainate type of glutamate receptor (McDonald *et al*, 1998). Even if the intracellular mechanisms of cell death are less clear, the initial step may be the overactivation of glutamate receptors.

Research is beginning to explore the mechanisms of cytokine-induced neurotoxicity and its application to disease states. TNF-α, a cytokine implicated in HIV, MS, and AD, has apoptotic effects on neurons, possibly by reducing gene expression of Bcl-2, a protein that normally inhibits apoptosis (Pulliam *et al*, 1998). Research also has focused on IL-1, which appears to alter neuronal signaling by inhibiting synaptic transmission (Xiong *et al*, 2000). Signaling abnormalities are also beginning to be demonstrated after neuronal exposure to chemokines upregulated in disease, with effects mediated by various chemokine receptors (e.g. CXCR4) on neurons (Hesselgesser and Horuk, 1999; Zheng *et al*, 1999). This is a new and intensive area of investigation because chemokine receptors are expressed on neurons throughout the brain yet their normal functions are poorly understood. Through their activation of G-protein-coupled receptors, chemokine receptors may play diverse roles in synaptic transmission, signal transduction, and neuronal survival (Meucci *et al*, 1998).

Conclusions and treatment implications

HIV neuropathogenesis research stands to benefit from better understanding of pathogenic relationships to systemic HIV disease and to other CNS diseases. These research directions will catalyze new avenues of treatment research. The classes of potential treatments include anti-inflammatories, NMDA blockers, chemokine receptor blockers, free radical scavengers, and antioxidants. The potential for cross-fertilization is driving a new era for HIV research.

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