Journal of NeuroVirology (2000) 6, Suppl 1, S1–S4
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Symposium
HIV and the Nervous System: Emerging Issues

A recent symposium, 'HIV and the Nervous System: Emerging Issues,' focused on the complex effects of human immunodeficiency virus (HIV) infection on the nervous system. The symposium was held April 14–16, 1999 under the joint sponsorship of the National Institute of Mental Health (NIMH) and the National Institute of Neurological Disorders and Stroke (NINDS). The purpose of the symposium was to bring together diverse perspectives – immunological, virological, and neurological – in order to review current research findings and to identify pivotal questions for future research. The symposium emphasized research related to trafficking of virus through the nervous system, neuropathogenesis, and therapeutic approaches. This special issue is devoted to manuscripts reflecting topics from the symposium.

HIV's assault on the nervous system is one of the most serious clinical consequences of infection. Infection can lead to a spectrum of neuropsychological defects collectively referred to as HIV-associated dementia (HAD), which affects 15–30% of infected patients (MacArthur *et al*, 1993). While relatively mild in earlier stages of the infection, manifestations in advanced stages include global cognitive impairment, mutism, and paraplegia (Navia *et al*, 1986). Poor neuropsychological performance independently predicts poor survival (Price *et al*, 1999). Patients with severe symptoms are unable to be productive, to maintain their independence, and to adhere to complex medication regimens.

The advent of highly active antiretroviral therapy (HAART) has dramatically decreased the death rate from AIDS, but there are a number of significant limitations with current treatments. About 20–50% of treated individuals fail to have complete and durable responses to therapy (see review by Powderly, 2000, this issue). Further, the therapeutic efficacy of HAART on HAD is less clear. Most of the medications in this combination therapy do not readily penetrate the CNS (Price *et al*, 1999). While it appears that treatment with HAART or antiretroviral therapy results in cognitive or motor improvements (Price *et al*, 1999; Sacktor *et al*, 1999) with a decrease in plasma viral load (Tozzi *et al*, 1999), there is also evidence to suggest that HAART is less effective for HAD than for other AIDS-defining diseases (Dore *et al*, 1999). As more patients live longer, they may confront enhanced risk of neuropsychological dysfunction. Ongoing research strives to answer fundamental questions about HIV trafficking and neuropathogenesis, all in an effort to yield improved treatments and means to prevent HAD.

Trafficking into the CNS

Trafficking refers to the infiltration of HIV – within infected immune cells or as free virus – from peripheral blood, across the blood brain barrier (BBB), and then into, through, and out of the central nervous system (CNS). Trafficking of immune cells through the CNS is by nature a dynamic and complex process which potentially involves many cell types with divergent functions, cell surface markers, migratory capacity, location, and turnover kinetics (Hickey, 1999). Trafficking is poorly understood, not only under normal physiology but also under the influence of HIV infection. One principal reason is that experimental research provides only a snapshot of what occurs *in vivo* rather than a dynamic picture.

What is known is that the principal sites of productive HIV infection of the CNS are microglia/macrophages (MG/MP), immune cells of peripheral monocyte lineage (Kolson *et al*, 1998). MG/MP is a generic term for resident microglia, perivascular microglia and macrophages, meningeal macrophages, and choroid plexus macrophages, among others (Hickey, 1999). Astrocytes within the CNS and endothelial cells that form the BBB can be infected too, but the infection is less productive in terms of yielding fewer HIV structural proteins. Neurons are rarely, if ever, infected by HIV (Kolson *et al*, 1998). Much research has been devoted to uncovering how infection occurs and the functional impact on HIV trafficking. A major impetus has been the identification of chemokine receptors through which HIV gains entry into cells of the CNS, with or without the aid of the CD4 co-receptor. The latter is the primary HIV receptor found on lymphocytes and monocyte-derived cells, but not on astrocytes or endothelial cells (Gabuzda and Wang, 2000, this issue). Chemokine receptors or their natural ligands, the chemokines, play multifaceted roles in HIV infection beyond serving as entry points for HIV. They also appear to be upregulated during HIV infection to facilitate monocyte trafficking across the BBB (Wu *et al*, 2000; Xiong *et al*, 2000, this issue).

From knowledge of which cell types are infected, how they are infected, and the functional con-

sequences of infection, researchers seek to construct a more dynamic portrait of HIV trafficking and its relationship and timing to the onset of HAD. One interesting hypothesis, developed through sequencing of gp 160 genes from different peripheral and CNS tissues collected from a patient with HAD, is that infiltration of monocytes that trigger HAD occurs in late stages of disease, rather than in early stages (Liu *et al*, 2000, this issue). On the basis of research finding HIV in the CNS early after infection, researchers had assumed that reservoirs of HIV-infected cells persist from early stages of disease and, years later, give rise to HAD. Yet empirical verification of a CNS reservoir has proven elusive and rests primarily on inferences from viral gene sequence data from purported sanctuary sites (Wong *et al*, 1997).

The key questions propelling research on HIV trafficking are: What are the normal mechanisms and kinetics of immune cell trafficking into the CNS? How is normal trafficking altered by HIV infection and by what mechanisms? Which cells are responsible for HAD (MG/MP, astrocytes, and/or endothelial cells) and how does HIV gain entry into these cells? When during the course of HIV disease do infected cells responsible for HAD traffic into the CNS? What viral or host factors facilitate trafficking of HIV into the CNS? What role does free virus play in HAD and how does free virus passage into and through CNS parenchyma? Is HIV, either in infected cells or as free virus, cleared from the brain, and, if so, how and when in the course of HIV disease? Are there reservoirs of HIV-infected cells in the CNS that are impervious to HAART, and, if so, what cell types constitute the reservoir and what role does a reservoir play in HAD?

Neuropathogenesis of HAD

The symposium also sought to highlight the latest findings about the neuropathogenesis of HAD. The findings presented confirmed the general outlines of the indirect model of neuropathogenesis of HAD. This model holds that HIV infection, or activation, of monocyte-derived cells in the CNS triggers the release of soluble factors, including cytokines, viral proteins, chemokines, and other factors that are toxic to nearby neurons (Epstein and Gendelman, 1993). This model accounts for neuron dysfunction and death in the absence of HIV infection of neurons. However, pinpointing the detailed mechanisms of neuropathogenesis *in vivo* has proved exceptionally difficult. Identifying the cellular and molecular culprits and determining how they induce neuron dysfunction and death are the driving forces underlying research. Detailed understanding of the process, from the earliest signs of neurotoxicity that precede neurobehavioral dysfunction, is critical (Rausch *et al*, 1999).

The identification of chemokines and their receptors has electrified research on neuropathogenesis. Chemokines are small molecular weight chemotactic peptides that act as inflammatory mediators in many nervous system diseases. They are divided among four different subfamilies according to structure, function, and gene localization (Glabinski and Ransohoff, 1999). Chemokines act on target cells through two main subgroups of receptors, CXCR and CCR, which can bind to chemokines belonging to the same subfamily. Apart from their normal functions, which are not fully understood, chemokine receptors are used as co-receptors for entry of HIV into numerous cell types, as noted above. Furthermore, the expression of CXCR4 and other chemokine receptors on neurons, while not sufficient for HIV infection, appears to provide a vehicle for neurotoxicity: chemokine receptors may render neurons vulnerable to apoptosis by the viral envelope protein gp 120 or excess levels of chemokines (Hesselgesser *et al*, 1998; Gabuzda and Wang, 2000, this issue). The mechanisms of neurotoxicity are not completely known, but may relate to the roles of chemokine receptors in neuronal signal transduction (Xiong *et al*., 2000, this issue). The pattern of chemokine receptor expression on neurons may ultimately explain why some individuals and/or some populations of neurons are more susceptible to HIV-induced neurotoxicity (Gabuzda *et al*, 1998). Similarly, research has been focused on the NMDA receptor on neurons whose natural ligand is the neurotransmitter glutamate. NMDA receptors may mediate neurotoxicity from viral proteins and other soluble substances released by HIV infection (Lipton, 1998).

The most fundamental questions guiding research on HIV neuropathogenesis are: What are the relative roles of viral proteins, cytokines, chemokines, and other soluble factors in HAD? What are the roles of chemokines and chemokine receptors in neurotoxicity? What is the normal function of chemokine receptors on neurons, and what is their regional pattern of distribution within the CNS? What is the role of NMDA receptors in neurotoxicity? What is the full sequence of molecular and cellular events leading up to HAD, including the earliest markers of neurotoxicity?

Implications for treatment

Dramatic new understanding of HIV trafficking and neuropathogenesis are expected to yield new treatment strategies for HAD. The most obvious new candidates for treatment are pharmacological agents that might block chemokine or NMDA receptors on neurons. Blockade of these receptors is seen as an ideal means to prevent a final common pathway used by many HIV-induced soluble neurotoxins. At present, there are no specific

treatments for HAD, and, as noted earlier, the clinical efficacy of HAART for HAD is unclear, although there appear to be short-term benefits. Many of the medications within this cocktail have poor penetration across the BBB, although detailed studies need to be performed (Price *et al*, 1999). Surveillance data on the incidence of HAD in HIV-infected persons in the current therapeutic environment in the U.S. must be updated.

There is mounting awareness of the need for better clinical monitoring of the onset and progression of HAD. Likewise, methods used to monitor the course of HAD may also have value in monitoring the patient's response to therapy for HAD. The measurement of HIV RNA levels in the cerebrospinal fluid (CSF) is considered one promising approach, yet the interrelationships between levels in CSF, CNS, and plasma are not clearly established (Cinque *et al*, 2000, this issue). There is some evidence that CSF HIV levels decline with antiretroviral therapy, but the response appears variable, in part reflecting the possible existence of stubborn CNS reservoirs (Cinque *et al*, 2000, this issue). Sequence data are beginning to be used to compare and contrast viral genotypes in paired samples of CSF and plasma in HIV-infected patients.

The key questions driving HAD treatment research are: What are the long-term effects of HAART on HAD and on CNS viral reservoirs? What is the regional CNS penetration of individual drugs contained in HAART? What methods can be used to monitor the course of HAD, the existence of viral reservoirs, and the response to therapy? What new treatments can penetrate the BBB and block chemokine and/or NMDA receptors on neurons, the receptors by which soluble factors appear to exert neurotoxicity? Can treatments be developed to block HIV-infected cells from crossing the BBB?

The manuscripts presented in this supplement of the *Journal of NeuroVirology* summarize many of the research findings which were presented at the symposium, 'HIV and the Nervous System: Emerging Issues'. These peer-reviewed manuscripts include reviews, research reports, and short communications. The depth and breadth of coverage should energize research and eventually generate new treatments to combat the effects of HIV in the nervous system.

Dianne Rausch
National Institute of Mental Health,
Center for Mental Health
Research on AIDS,
6001 Executive Blvd.,
Room 6212, MSC 9623
Bethesda, Maryland 20892-9623, USA

Al Kerza-Kwiatecki
National Institute of Neurological Disorders
and Stroke, 6001 Executive Blvd.,
Room 2110 Bethesda,
MD 20892, USA

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