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Signaling pathways to neuronal damage and apoptosis in human immunodeficiency virus type 1–associated dementia: Chemokine receptors, excitotoxicity, and beyond

Marcus Kaul and Stuart A Lipton

The Burnham Institute, Center for Neuroscience and Aging Research, La Jolla, California, USA

Dementia can occur as a debilitating consequence of human immunodeficiency virus-1 (HIV-1) infection. The neuropathology incited by HIV infection involves activation of chemokine receptors, inflammatory factors, and *N*-methyl-D-aspartate (NMDA) receptor–mediated excitotoxicity, all of which can activate several downstream mechanisms. This article discusses recently identified pathways to neuronal damage triggered by HIV-1 and efforts aimed at development of applicable therapeutic intervention. *Journal of NeuroVirology* (2004) **10(suppl. 1),** 97–101.

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Introduction

Infection with human immunodeficiency virus-1 (HIV-1) can induce a syndrome of cognitive and motor dysfunction that has been designated HIV-associated dementia (HAD). Although in the era of highly active antiretroviral therapy (HAART), a milder form of neurologic dysfunction, termed minor cognitive/motor disorder (MCMD), may have become more prevalent than frank dementia, HAD and MCMD remain significant independent risk factors for acquired immunodeficiency syndrome (AIDS) mortality (Kaul *et al*, 2001; Power *et al*, 2002). This strongly suggests that despite improvements in control of peripheral viral replication and the treatment of opportunistic infections, HAART fails to provide complete protection from the development of HAD. This may, at least in part, be due to the fact that HIV protease inhibitors and several of the nucleoside analogues poorly penetrate into the central nervous system (CNS) (Kaul *et al*, 2001; Power *et al*, 2002). Altogether, evidence is accumulating that the neuropathology of HIV-1 infection involves the activation of chemokine receptors, inflammatory factors, and N-methyl-D-aspartate (NMDA) receptor–mediated excitotoxicity (Kaul *et al*, 2001; Power *et al*, 2002). This article will discuss recently characterized pathways to neuronal damage initiated by HIV-1 and efforts aimed at development of applicable clinical intervention concurrent with antiretroviral therapies.

Neuropathology of HIV infection

HAD is often accompanied by certain neuropathological findings, such as astrocytosis, infiltration of macrophages, increased number of microglia, multinucleated giant cells, myelin pallor, dendritic and synaptic damage, and apoptosis leading to the frank loss of neurons (Kaul *et al*, 2001; Power *et al*, 2002; Budka, 1991). The mechanisms that initiate HAD are only in part understood. However, the accumulation of macrophages/microglia has been reported to correlate with the severity

Address correspondence to Stuart A. Lipton, The Burnham Institute, Center for Neuroscience and Aging Research, 10901 North Torrey Pines Road, La Jolla, CA 92037, USA. E-mail: slipton@burnham.org

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of HAD (Glass *et al*, 1995), and we and our colleagues have shown that HIV-1–infected or immune-stimulated macrophages/microglia produce neurotoxins (Giulian *et al*, 1990; Gartner, 2000; Kaul *et al*, 2001). Importantly, neurons are not productively infected by HIV-1 and astrocytes only rarely, primarily in pediatric cases (Gartner, 2000; Kaul *et al*, 2001; Power *et al*, 2002).

Interestingly, even in the absence of intact virus, the HIV proteins gp120, gp41, gp160, Tat, Nef, Rev, and Vpr have been reported to initiate neuronal damage, at least *in vitro*, and in some cases *in vivo* in animal models (Brenneman *et al*, 1988; Dreyer *et al*, 1990; Toggas *et al*, 1994; Kaul *et al*, 2001). In this regard, the viral envelope protein gp120 has been of particular interest as it is essential for selective binding and signaling of HIV-1 to its target cell and for viral infection (Brenneman *et al*, 1988; Kaul and Lipton, 1999; Meucci *et al*, 1998; Chen *et al*, 2002; Kaul *et al*, 2001; Power *et al*, 2002). Moreover, intracerebroventricular injection of gp120 causes brain injury *in vivo* in rodents (Bezzi *et al*, 2001) and a transgenic mouse model expressing gp120 develops many neuropathological features observed in postmortem brain specimens from HAD patients (Toggas *et al*, 1994).

Chemokine receptors in HAD

Infection of macrophages and lymphocytes by HIV-1 can occur after binding of the viral envelope protein gp120 to one of several possible chemokine receptors in conjunction with CD4. Macrophages and microglia are primarily infected via the β-chemokine receptor CCR5 or CCR3, but the α-chemokine receptor CXCR4 may also be involved (Ohagen *et al*, 1999; Chen *et al*, 2002). The HIV coreceptors CCR5 and CXCR4, among other chemokine receptors, are also present on neurons and astrocytes (Meucci *et al*, 1998; Kaul *et al*, 2001). Several *in vitro* studies strongly suggest that CXCR4 is directly involved in HIV-associated neuronal damage, whereas CCR5 may additionally serve a protective role (Hesselgesser *et al*, 1998; Meucci *et al*, 1998; Kaul and Lipton, 1999).

In cerebrocortical neurons and neuronal cell lines, picomolar concentrations of HIV-1 gp120, as well as intact virus, can induce neuronal death via CXCR4 receptors (Hesselgesser *et al*, 1998; Ohagen *et al*, 1999; Kaul and Lipton, 1999; Zheng *et al*, 1999; Chen *et al*, 2002). In mixed neuronal/glial cerebrocortical cultures that mimic the cellular composition of the intact brain, this apoptotic death appears to be mediated predominantly via the release of microglial toxins, rather than by direct neuronal damage (Kaul and Lipton, 1999; Chen *et al*, 2002). However, nanomolar concentrations of (stromal cell derived factor) SDF-1α/β interacting with CXCR4 can induce apoptotic death of neurons in the absence of microglia, suggesting a possible direct interaction with neurons while interaction with astrocytes can also occur (Kaul and Lipton, 1999). In contrast to these findings, somewhat higher concentrations of SDF-1α have been reported to provide neuroprotection from X4-preferring gp120-induced damage of isolated hippocampal neurons (Meucci *et al*, 1998). However, the results obtained on isolated neurons may be different from those observed in mixed neuronal/glial cultures because the non-neuronal cells are known to modify the involved death pathways (Kaul and Lipton, 1999; Bezzi *et al*, 2001; Kaul *et al*, 2001; Power *et al*, 2002; Chen *et al*, 2002).

Recently, we have investigated the role of chemokine receptors in the neurotoxicity of gp120 using mixed neuronal/glial cerebrocortical cultures from rat and mouse. We found that gp120 from CXCR4 (X4)-preferring as well as CCR5 (R5)-preferring and dual-tropic HIV-1 strains all were able to trigger neuronal death. However, we also observed that the β-chemokines macrophage inhibitory protein (MIP)-1β and RANTES abrogate gp120 neurotoxicity (Kaul and Lipton, 1999). Interestingly, although HIV-1 gp120 of one X4-preferring strain lacked neurotoxicity in CXCR4-deficient cerebrocortical cultures, gp120 of another X4-classified strain retained some residual ability to induce neuronal death, as the dual-tropic $gp120_{SF2}$ did (Kaul, 2002). Surprisingly, $gp120_{SF2}$ showed even greater neurotoxicity in CCR5 knockout cultures, compared to wild-type or CXCR4-deficient cultures (Kaul, 2002). These findings are consistent with a primarily neurotoxic effect of CXCR4 activation by gp120. In contrast, activity of CCR5 is at least in part neuroprotective. Nonetheless, gp120 from R5-preferring HIV-1 can also induce neuronal death. However, it is important to bear in mind that the classification of HIV-1 as R5- or X4-preferring is largely based on the virus' ability to use certain receptors for infection of a target cell rather than activation or induction of a death signaling pathway. Consequently, this classification is only valid for an interaction of the HIV envelope that leads to infection. Therefore, in order to understand the mechanism(s) of HAD, gp120s from HIV-1s classified as preferring a certain chemokine receptor for infection may have to be reassessed for their ability to also interact with other receptors that trigger activation and downstream intracellular signaling. In particular, gp120s of R5-preferring macrophage-tropic strains may need to be tested for their ability to initiate cellular signaling via CXCR4.

Because inhibition of microglial activation is sufficient to prevent neuronal death after gp120 exposure, at least *in vitro*, it seems likely that stimulation of CXCR4 in macrophages/microglia is a prerequisite for the neurotoxicity of gp120 (Ohagen *et al*, 1999; Kaul and Lipton, 1999). In contrast, SDF-1 might directly activate CXCR4 in astrocytes and neurons to trigger neuronal death, for example, by reversing glutamate uptake in astrocytes (Hesselgesser *et al*, 1998; Kaul and Lipton, 1999; Bezzi *et al*, 2001; Kaul *et al*, 2001).

HIV-1 in the brain and NMDA receptor activation

Analysis of specimens from AIDS patients (Sardar *et al*, 1999) as well as *in vivo* and *in vitro* experiments indicate that HIV-1 infection creates excitotoxic conditions in the CNS (Kaul *et al*, 2001; Kaul and Lipton, 2002; Chen *et al*, 2002). Macrophages and microglia play a crucial role because they are the predominant cells productively infected with HIV-1 in the brain (Kaul *et al*, 2001; Power *et al*, 2002; Bezzi *et al*, 2001; Chen *et al*, 2002). Moreover, HIV-1–infected or gp120-stimulated mononuclear phagocytes have been shown to release neurotoxins that directly stimulate the NMDA receptor (Giulian *et al*, 1996; Kaul *et al*, 2001), including quinolinic acid, cysteine, platelet-activating factor (PAF), and a low-molecular-weight compound designated NTox (Giulian *et al*, 1996; Kaul *et al*, 2001).

Additionally, HIV-infected or -activated macrophages/microglia and possibly astrocytes produce inflammatory mediators, including tumor necrosis factor (TNF)-α, arachidonic acid metabolites, free radicals (reactive oxygen species [ROS] and nitric oxide [NO]) and extracellular matrix-degrading enzymes, such as matrix metalloproteinases (MMPs), that may indirectly contribute to excitotoxic neuronal damage (Johnston *et al*, 2000; Kaul *et al*, 2001; Bezzi *et al*, 2001; Chen *et al*, 2002).

Along these lines, gp120 has been found to aggravate excitotoxic conditions by impairing astrocyte uptake of glutamate via arachidonic acid that is released from activated macrophages/microglia (Kaul *et al*, 2001). SDF-1, TNF-α, and prostaglandins also can stimulate a Ca^{2+}-dependent release of glutamate by astrocytes (Bezzi *et al*, 2001).

In our view, therefore, HIV-1 infection and its associated neurological dysfunction involve both chemokine receptor– and NMDA receptor–mediated excitotoxicity. Chemokine receptors are involved at different levels, first in HIV infection, and further, in the response to chemokines, which may be produced as a consequence of viral infection. For example, monocyte chemoattractant protein (MCP)-1, MIP-1α, MIP-1β, RANTES, and SDF-1 are all likely to interfere, directly and/or indirectly, with the physiological functions of neurons, astrocytes, and microglia (Kaul *et al*, 2001; Bezzi *et al*, 2001; Langford *et al*, 2002; Zheng *et al*, 1999; Letendre *et al*, 1999). However, the exact role(s) of these chemokines and their receptors in the brain under *in vivo* conditions, with and without HIV-1 infection, are not understood and the subject of ongoing research. For example, NMDA receptors respond to excitatory agents, such as neurotransmitters and neurotoxins, but G protein–coupled chemokine receptors might also influence their activity, and vice versa. Indeed, a β-chemokine, RANTES, can diminish neuronal damage induced by excessive NMDA receptor stimulation (Bruno *et al*, 2000). In turn, excitotoxic stimulation can enhance expression of CCR5 (Galasso *et al*, 1998). Whether these findings reflect feedback of chemokine signaling pathways that antagonize the stimulation of the NMDA receptor awaits to be elucidated.

Downstream pathways from NMDA receptors

If excessive stimulation of the NMDA receptor occurs and the initial excitotoxic insult is fulminant, the cells die early from loss of ionic homeostasis, leading to acute swelling and lysis (necrosis). If the insult is more mild, as it appears to be the case with HAD, neurons enter a programmed death pathway known as apoptosis (Garden *et al*, 2002; Kaul and Lipton, 2002). Neuronal apoptosis after excitotoxic insult involves Ca^{2+} overload, activation of p38 mitogen-activated protein kinase (MAPK), release of cytochrome *c* from mitochondria, caspase activation, free-radical formation, lipid peroxidation, and chromatin condensation (Garden *et al*, 2002; Kaul *et al*, 2001). The p38 MAPK phosphorylates and activates transcription factors, including myocyte enhancer factor 2 (MEF2). Interestingly, cleavage of MEF2 by caspases can also contribute to neuronal apoptosis (Okamoto *et al*, 2002). Caspase-3 and -7 generate truncated MEF2 molecules that lack transcriptional activity, but still bind to DNA. Thus, the MEF2 fragments apparently compete with uncleaved MEF2 and consequently interfere with survival-promoting gene transcription in neurons (Okamoto *et al*, 2002).

Antibody-mediated neutralization of TNF-α or inhibition of its downstream effector caspase-8 also prevents the neurotoxicity of HIVgp120 in cultured cerebrocortical neurons (Garden *et al*, 2002). Caspase-8 activation can trigger caspase-3 activity, leading to apoptosis. At least *in vitro*, proteins of the Bcl-2 family possess the potential to abrogate neuronal damage subsequent to HIV-1 infection (Chen *et al*, 2002). An apparent inability of neurons to upregulate Bcl-2 or Bcl-xL in response to the excitotoxicity generated by HIV infection might contribute to neuronal vulnerability (Chen *et al*, 2002).

The scaffolding protein PSD-95 (postsynaptic density-95) links the NMDA receptor–operated ion channel with neuronal nitric oxide synthase (nNOS), a Ca^{2+}-activated enzyme, and thus brings nNOS into close proximity to Ca^{2+} (Sattler *et al*, 1999). Excessive intracellular Ca^{2+} overstimulates nNOS and protein kinase cascades, causing the generation of cytotoxic free radicals, including ROS, NO, and peroxynitrite ($ONOO^-$). ROS and NO can form the highly cytotoxic $ONOO^-$ (Kaul and Lipton, 2002). Interestingly, a study in postmortem brain specimens from HIV patients indicated that the expression of immunologic NOS (iNOS) and gp41 correlate with the occurence and severity of HAD (Adamson *et al*, 1996). Furthermore, the neurotoxic effect of gp120 is, at least

in vitro, also dependent on NOS (possibly both nNOS and iNOS) (Dawson *et al*, 1993; Dreyer *et al*, 1999).

In addition to the intracellular effects of NO, we have recently identified a potential extracellular proteolytic pathway to neuronal injury that is mediated by nitrosylation and subsequent activation of MMP-9 (Gu *et al*, 2002). Proteolytically active MMP-9 incites neuronal death, presumably by disrupting the interaction of cellular adhesion factors and extracellular matrix. It is important to note that the expression and activation of MMPs, including MMP-2 and MMP-9, is increased in HIV-infected macrophages and also in postmortem brain specimens from AIDS patients when compared with uninfected controls (Johnston *et al*, 2000).

Taken together, activation of MMPs may go hand-in-hand with excitotoxic brain injury and NOS activity. Indeed, we found that nitrosylation of MMP-9 resulted in its activation (Gu *et al*, 2002). Subsequently, we investigated the *in vitro* effects of NO-activated MMP-9 on neurons in cerebrocortical cultures (Gu *et al*, 2002). For these experiments, recombinant (R)-proMMP-9 was preactivated with the endogenous NO donor *S*-nitrosocysteine (SNOC) before addition to the cultures. Neuronal apoptosis was assessed 18 h later. Because NO had already been released from SNOC by the time the cultures were incubated with the activated MMP, direct release of NO from SNOC or the formation of peroxynitrite due to the release of NO from SNOC and subsequent reaction with superoxide anion (O_2^-) could not trigger neuronal death (Gu *et al*, 2002). However, NO-activated MMP-9 significantly increased the apoptosis of neurons, whereas treatment with inactive proMMP-9 or the MMP inhibitor GM6001 blocked the neuronal cell death (Gu *et al*, 2002). In addition, many neurons came up off the dish after exposure to NO-activated MMP-9. These results strongly suggest that inactive (pro)MMP-9 protein does not have a deleterious effect on neurons. However, NO-triggered activation converts MMP-9 into a neurotoxin.

Therapeutic approaches for treatment of HAD

A truly effective pharmacotherapy for HAD has yet to be developed. Accumulating evidence regarding the pathogenesis of HAD suggests that several potential therapeutic strategies may be applicable in addition to antiretrovirals (ARVs). The clinically tolerated NMDA receptor antagonist memantine is among the agents under consideration (Kaul and Lipton, 2002). Others include β-chemokines; chemokine and cytokine receptor antagonists, e.g., against CXCR4 and CCR5 activation; inhibitors of MMPs, p38 MAPK, or caspases; and antioxidants (Kaul *et al*, 2001; Power *et al*, 2002; Kaul and Lipton, 2002).

Chemokine receptors mediate HIV-1 infection and specific chemokines may even block infection *in vivo*. Additionally, elevated concentrations of β-chemokines in the CSF of HIV patients correlate with relatively better neuropsychological performance (Letendre *et al*, 1999; Kaul *et al*, 2001). Thus, the β-chemokine–CCR5 interaction is of great potential therapeutic interest.

Concerning NMDA receptor antagonists, our group found that memantine is an uncompetitive, open-channel blocker of the NMDA receptor–associated ion channel. Memantine blocks the NMDA receptor–operated channel only when it is open for pathological periods of time. Conversely, memantine has little effect during normal neurotransmission, when there is less NMDA receptor–dependent channel activity (Chen *et al*, 1992; Kaul and Lipton, 2002). In fact, memantine was shown to hold promise for HAD in a recent phase II clinical trial (Le and Lipton, 2001), and demonstrated a clear positive effect in a phase III trial of Alzheimer's disease patients with moderate-to-severe dementia (Reisberg *et al*, 2003).

Our group has also shown that nitroglycerin, which produces a NO-related nitrosonium ion (NO^+), acts, at least in part, at redox modulatory sites on the NMDA receptor/channel complex to diminish receptor activity and consequent neuronal damage due to excessive Ca^{2+} influx (reviewed in Kaul and Lipton, 2002).

In order to take advantage of two well-established, clinically safe drugs that avoid the serious adverse side effects of many NMDA receptor antagonists and for the purpose of combining their therapeutic potential for neuroprotection, we are currently studying combinatorial nitromemantine compounds.

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