

Review Article

HIV Neurotoxicity: Potential Therapeutic Interventions

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Individuals suffering from human immunodeficiency virus type 1 (HIV-1) infection suffer from a wide range of neurological deficits. The most pronounced are the motor and cognitive deficits observed in many patients in the latter stages of HIV infection. Gross postmortem inspection shows cortical atrophy and widespread neuronal loss. One of the more debilitating of the HIV-related syndromes is AIDS-related dementia, or HAD. Complete understanding of HIV neurotoxicity has been elusive. Both direct and indirect toxic mechanisms have been implicated in the neurotoxicity of the HIV proteins, Tat and gp120. The glutamatergic system, nitric oxide, calcium, oxidative stress, apoptosis, and microglia have all been implicated in the pathogenesis of HIV-related neuronal degeneration. The aim of this review is to summarize the most recent work and provide an overview to the current theories of HIV-related neurotoxicity and potential avenues of therapeutic interventions to prevent the neuronal loss and motor/cognitive deficits previously described.

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GENERAL MECHANISMS OF HIV NEUROTOXICITY

Just over a decade ago, the first reports of HIV-related neurotoxicity were published. Two proteins associated with the AIDS virus, gp120 (a coat glycoprotein) and Tat (transactivation) have been shown to be neurotoxic. The HIV-associated protein gp120 was shown to be neurotoxic to cultured dopamine neurons [1]. Exposure to gp120 for 3 days reduced the ability of neurons to transport dopamine and decreased the size of the dendritic tree. The neurotoxicity of Tat was first identified by Nath et al [2] when they described the reactive epitope of Tat as being Tat_{31–61}. Full-length Tat is 86–104 amino acids in length and the analysis of peptides of differing, overlapping, lengths did not yield toxic responses in primary neuronal culture. Shortly after this report, Cheng et al [3] reported that Tat was neurotoxic to fetal neurons through a calcium-dependent mechanism. One postulated mechanism for Tat toxicity is via increased oxidative stress. Direct intrastriatal injections of Tat results in a significant increase in carbonyl formation [4]. Increased gliosis has been observed, indicating neuronal death and infiltration by glia [4–6]. Cellular damage and death following Tat administration have also been linked to an increase in apoptosis [7, 8]. Other mechanisms for Tat neurotoxicity include altered calcium homeostasis [7, 9], stimulation of TNF- α and NF- κ B [10], stimulation of glutamate receptors [11], and activation of nitric oxide synthase and stimulation of nitric oxide pro-

duction [12]. Similar to Tat, gp120 has been shown to be neurotoxic via multiple pathways. Both in vivo and in vitro, gp120 administration has been shown to induce apoptosis [13, 14]. Antagonism of glutamate receptors, primarily the NMDA subtype, attenuates gp120-induced toxicity [11, 15]. Activation and stimulation of the nitric oxide synthesis pathways has also been reported following exposure to gp120 [15].

Biomarkers of oxidative stress have consistently been detected in brain tissues and cerebrospinal fluid of patients with HIV-associated dementia [16]. The role for HIV-1 proteins in the development of oxidative stress associated with HIV-1 infection was proposed [17]. It is still debated whether the oxidative stress in HIV is attributable to direct interactions of HIV-1 proteins with neural cells or whether it results from chronic inflammatory reaction induced by the exposure of the CNS tissue to virotoxins. However, it is evident that neurotoxic HIV-1 proteins released from cells harboring HIV-1 may directly trigger oxidative stress, both in cell culture [7, 18] and in animal models [4, 6]. Even a transient exposure to HIV-1 proteins may be sufficient to trigger a cascade of events that leads to neuronal degeneration [19]. Thus, Tat is an important mediator of neurotoxicity in the HIV-infected brain and investigation of its role in HIV-associated neurodegeneration is important for understanding of the pathogenesis of HIV cognitive and motor dysfunction.

MICROGLIA/ASTROCYTES AND OPIOIDS

Involvement of microglia and astrocytes in HIV-related neurotoxicity has been established. Yet, whether the effects observed due to microglia involvement are a direct result of HIV-1 stimulation or a byproduct of infection remains to be elucidated. Parallels can be drawn between microglia involvement in neurological disorders such as HIV-related dementia, multiple sclerosis, and Alzheimer's disease [20]. In each disorder, microglia involvement includes the inflammatory process and the release of cytokines, chemokines, and nitric oxide. In addition to the release of damaging chemokines and cytokines, the tumor suppressor transcription factor, p53, has been shown to be necessary to induce apoptosis [21]. This could provide a novel pathway for HIV induction of neuronal apoptosis and cell death. A quite different profile is observed with astrocytes. When astrocytes express Tat, survival is promoted via increased antioxidant mechanisms, but Tat is released into the extracellular space where the adjacent neurons can take up Tat where axonal transport can take it to distal sites where it will elicit toxic effects [22, 23]. As neurons die, reactive gliosis takes place. This is characterized by an increase in glial fibrillary acidic protein (GFAP) staining. An increase in GFAP staining has been reported in cells exposed to Tat [24]. Astrocytosis could be particularly relevant in individuals abusing intravenous drugs. Astrocytes express opioid receptors and stimulation of the mu-subtype of the opioid receptor family potentiates Tat toxicity in neurons and astrocytes [25]. In addition to intravenous drug use, stimulation of mu-opioid receptors acting synergistically with HIV proteins to elicit neurodegeneration has greater impact regarding the use of opioid analgesics for the relief of pain. The use of morphine, codeine, fentanyl, and so forth, would be prohibitive in patients afflicted with HIV due to the increased risk for synergistic toxicity. Administration of morphine has been shown to upregulate the expression of the CCR3 coreceptor and CCR5 receptor in astrocytoma cells, which would increase viral binding and trafficking of the virus and promote viral infection [26]. Collectively, mu-stimulating opioid ligands would increase the receptors necessary for the transmission of the virus (CCR3 and CCR5), and potentiate the neurotoxicity observed in the presence of gp120. Recently, investigations into other opioid subtype-selective (kappa and delta) and their possible functionality as therapeutic interventions have begun (refer to "potential therapeutic interventions"). The role of astrocytes and microglia in the pathogenesis of HIV-related neurotoxicity is becoming increasingly apparent. From harboring the virus, to secreting proinflammatory chemokines and cytokines, to potentiating the spread of the virus and the viral particles, astrocytes and microglia play an integral role in HIV-related neurotoxicity.

CHEMOKINES

Proinflammatory chemokines function to exacerbate HIV neurotoxicity as an extension of astrocytes and microglia function. Chemokine involvement has long been suspected

due to the actions of microglia following exposure to HIV-related proteins. The two prominent chemokine receptors that are involved in HIV neurotoxicity are the CXCR4 and CCR5 receptors, both of which are expressed on microglia [27]. The CXCR4 receptor belongs to the family of G-protein-coupled receptors and is believed to signal through a Gi/Go mechanism. Stimulation of these receptors results in an elevation in intracellular calcium, an effect which is reduced when pretreated with pertussis toxin to inactivate the receptor [28]. Initial hypotheses included gp120 direct interactions with neurons resulting in apoptosis, stimulation of astrocytes/microglia resulting in indirect effects on neurons, or possibly both mechanisms. Apoptosis induced by gp120 can be completely attenuated in the presence of the tripeptide, TKP, which prevents activation of microglia via CXCR4 receptors [29]. Antibodies to CXCR4 also prevented neuronal apoptosis due to caspase-3 activation [30]. Interestingly, the density of the CXCR4 receptor is inversely related to the concentration of fibroblast growth factor (FGF). As concentrations of FGF are increased, the density of CXCR4 receptors is reduced [31]. These effects are not due to direct actions of FGF on CXCR4 receptors, but through the FGF receptor kinase signaling pathway. Inhibitors of FGF receptor kinase attenuate the effects of FGF on CXCR4 receptor density [31]. Collectively, the effects of FGF in HIV encephalitis may be mediated through the inverse regulation of CXCR4 receptor expression. Similarly, stimulation of CHP100 cells, which constitutively express CXCR4 and CCR5 receptors, with phorbol 12-myristate-13-acetate downregulates CXCR4 and CCR5 and decreases the extent of gp120-induced cell death [32]. Alpha and beta chemokine ligands which are naturally released from microglia and astrocytes such as SDF1alpha, MIP1alpha, MIP1beta, and "regulated on activation, normal T-cell expressed and secreted" (RANTES) all interfere with the action of gp120 at CXCR4 and CCR5 receptors, and thus reduce cellular apoptosis and death [29, 30, 32]. SDF-1 results in a rapid release of tumor necrosis factor-alpha (TNF-alpha), which in turn exerts autocrine and paracrine effects on nearby cells. The release of TNF-alpha increases the synthesis of prostaglandins by activating the arachidonic acid cascade resulting in derangement of astrocytes-glia-neuronal communications [33]. In addition to increased prostaglandin formation, TNF-alpha increases the expression of proteinase-activated receptor-2 (PAR-2) which is responsible for cell survival [34]. Mice lacking PAR-2 are more susceptible to Tat-induced toxicity than wild-type [34]. SDF-1 promotes cell survival, which is not what would be expected considering that SDF-1 and gp120 are both agonists at the CXCR4 receptor. This discrepancy could be explained by differential effects on the p53 system. Stimulation of CXCR4 by gp120 stimulates p53 and increases the phosphorylation of Apaf-1 (proapoptotic) in neurons [35]. In addition, gp120 regulates the phosphorylation of p53 and regulates the expression of MDM-2 and p21 [35]. These effects are reversed by the p53-inhibitor pifithrin-alpha. Contrary to these findings, SDF-1 stimulates the acetylation of p53 and promotes the production p21.

Therefore, stimulation of the CXCR4 receptor could result in activation of different p53 targets dependent on the stimulating ligand, which will determine whether activation of CXCR4 exerts a positive or negative influence on neurons. Collectively, these data demonstrate the importance of astrocytes/microglia in the pathogenesis of HIV-related neurotoxicity. Early hypotheses focused on the involvement of glutamate as an integral component of HIV neurotoxicity. Although glutamate is a major toxin involved in neuronal death, it is now apparent that the CXCR4 receptor mediates cell death via non-glutamate mechanisms [36]. Investigation into the development of CXCR4 antagonists, in conjunction with NMDA antagonists, would offer better protection against gp120-induced cellular death.

GLUTAMATE AND EXCITATORY AMINO ACIDS

As discussed in the previous section, CXCR4 receptors appear to have a major role in the development of HIV-related neurotoxicity. Another component of this toxicity is the role of glutamate in cellular death. The toxic component secreted from HIV-1-infected mononuclear phagocytes has been characterized as being a glutamate [37]. Some of the earliest studies demonstrated the addition of the N-methyl-D-aspartate (NMDA-) receptor antagonist memantine [38]. The addition of memantine not only increased the viability of neurons, but improved the dendritic arborization and synaptic density. The toxic effect is due to both the stimulation of NMDA receptors and the subsequent elevation in intracellular calcium. Coadministration of D-2-amino-5-phosphopentanoic acid (APV) or MK-801 (both NMDA receptor antagonists) or removal of calcium from the culture media all decrease cell death associated with gp120 exposure [39]. One hypothesis for gp120 effects on glutamate homeostasis involves the attenuation of glutamate uptake, and concomitant increase in glutamate release [40]. Both gp120 and Tat have been postulated to work through a glutamate-mediated mechanism. Nath et al [11] demonstrated that coadministration of both gp120 and Tat exerted a synergistic potentiation of toxicity in monkeys. The concentrations of both gp120 and Tat were at subtoxic concentrations, yet the addition of the two proteins together resulted in a significant amount of cell death. To determine if these effects could be mediated by glutamate, the addition of memantine completely blocked the toxicity exerted by the gp120/Tat combination [11]. The toxic effects of Tat alone have also been linked to glutamatergic effects. Exposure of rat cortical neuronal cultures to low (nanomolar) concentrations of Tat or gp120 (picomolar) increases the uptake of calcium into neurons and eventually leads to cell death [41, 42]. Coadministration with the glutamate antagonists completely blocked the observed increase in ^{45}Ca influx and cell death [41, 42]. Administration of non-glutamate drugs had no effect on calcium influx or cellular death. In addition to the reports of direct alterations in glutamate homeostasis leading to cellular dysfunction, other endogenous glutamate agonists have been shown to be elevated in HIV infected individuals. One compound that has been shown to be elevated in HIV-patients

is quinolinic acid. Activated macrophages produce quinolinic acid and this toxin has been implicated in a variety of neurological disorders. Macrophages exposed to Tat significantly increased their production of quinolinic acid, which correlated with an increase in indolamine 2,3-dioxygenase induction [43]. Interestingly, production of quinolinic acid occurs as part of the kynurenic acid pathway. Kynurenic acid is neuroprotective and functions as a glutamate antagonist [44]. A shift of the synthesis pathway favoring quinolinic acid results in neurotoxicity. Recent studies have added new insight into the mechanisms of HIV neurotoxicity involving the glutamate system [45, 46]. Not only does glutamate function through direct excitotoxic mechanisms by stimulating NMDA receptors, but also glutamate can induce the production of free radicals by inhibiting the uptake of cystine uptake and thus reducing the formation of glutathione [45]. Activated microglia express the glutamate transporter EAAT-1 and the density of this transporter increases with progression through the disease process. It would be suspected that this would provide protection against toxicity by increasing glutamate uptake and may in fact provide protection for a period of time. Later in the disease, when cognitive/motor deficits are more apparent and dementia begins, dysfunction of activated microglia could play a role in the neuronal apoptosis and death normally observed later in the disease [45]. Although it has been accepted that Tat toxicity involves a glutamate component, the exact mechanism by which this occurs has not been elucidated. Chandra et al [46] demonstrated that Tat releases Zn^{2+} from its binding site on the NMDA receptor. When Zn^{2+} is bound to the NMDA receptor, the receptor has reduced capacity to conduct Ca^{2+} through its channel. When Zn^{2+} is removed, even at neuroprotective concentrations, the NMDA receptor is activated; there is an increase in Ca^{2+} influx resulting in increased activity of an intracellular cascade leading to cellular death.

APOPTOSIS, CALCIUM, AND NITRIC OXIDE

As previously discussed, microglia involvement in HIV-related neurotoxicity involves oxidative stress, alterations in calcium homeostasis, activation of NMDA receptors, and apoptosis. Stimulation of NMDA receptors result in an influx of extracellular calcium. Elevations in intracellular calcium would activate nitric oxide synthase in neurons (nNOS, or NOS-1). Increases in nitric oxide can react with cellular superoxide forming the damaging peroxynitrite. This is further compounded by the contribution of nitric oxide from microglia which is inducible (iNOS or NOS-2). The involvement of nitric oxide in a variety of neurodegenerative diseases can be robust [47]. Polazzi et al [12] reported that Tat acts at the level of the iNOS gene to increase production of nitric oxide from activated microglia. Therefore, Tat does not act simply to increase the production of nitric oxide, but at the genomic level to induce the production of iNOS and interacts with NF- κ B and interferon-gamma to potentiate the damage resulting from the nitric oxide that is produced [12]. This cycle could potentially form a "feed-forward" cycle where overstimulation of NMDA receptors

leads to alterations in calcium homeostasis, increases in nitric oxide formation, neuronal death, microglia activation, and additional nitric oxide being induced from the activated microglia [48]. Inhibitors of the NMDA receptor (MK-801) or iNOS (1400 W) all reduced gp120-induced neurotoxicity [48]. These findings suggest an important role of iNOS in the development of HIV-related neurotoxicity. Changes in intracellular calcium regulation may involve Na^+/H^+ exchangers and L-type calcium channels [41]. Addition of amiloride attenuated the intracellular rise in intracellular calcium in both neurons and astrocytes. Blockade of L-type calcium channels with nimodipine, diltiazem, and $\text{CdCl}_2 + \text{NiCl}_2$ also significantly decreased the rise in intracellular calcium in neurons, with no effect in astrocytes. This differential effect on neurons and astrocytes could afford protection against calcium-related toxicity if appropriate drugs are used to distinguish between neuron and astrocytes actions. One possible mechanism for this increase in intracellular calcium involves Tat modulation of phosphoinositide (PI) turnover [9]. Exposure of cultured fetal neurons to Tat resulted in elevated intracellular calcium that is attenuated by antagonizing the effects of inositol 1,4,5-triphosphate on releasing calcium from intracellular stores. Specifically, Tat functions through a pertussis-toxin sensitive phospholipase C mechanism to increase intracellular calcium leading to glutamate receptor-mediated calcium influx and subsequent dysregulation of calcium homeostasis [9].

Multiple mechanisms can lead to cellular apoptosis. It is accepted that both Tat and gp120 exposures will elicit significant cellular damage and death, but the apoptotic mechanisms differ between the two proteins. Both gp120 and Tat have been shown to induce apoptosis in neuronal culture. TGF- β 1 reverses the alterations observed in calcium homeostasis and reduces the number of neuronal cells dying from apoptotic cell death following exposure to gp120 [49]. TNF- α augments the effects of Tat on apoptosis which seem to be mediated in part by oxidative stress [50]. Administration of antioxidants will partially reverse the effects of Tat, yet a component exists which is not due to oxidative stress. Using HIV-1 isolates, cell lines which overexpress Bcl-2 or Bcl-xL are protected from damage whereas the wild-type cells are significantly compromised [51]. Addition of a Bcl-2 antagonist to the overexpressing cells completely reversed the neuroprotection. Collectively, the Bcl-2 pathway is an important pathway for the pathogenesis of HIV-related neurodegeneration, and modulation of this pathway could afford protections against neuronal damage. Another pathway with importance for HIV neurodegeneration involves TNF- α and the TNF-related apoptosis-inducing ligand (TRAIL). In HIV infection, human monocyte-derived macrophages exhibit an increase in TRAIL levels and these cells are associated with neurons which are caspase-3 positive [52]. Analysis of specific protein actions has demonstrated that gp120 works in part through enhancement of COX-2 expression and activation of interleukin-1 converting enzyme (caspase-1). Antagonists of caspase-1 activity, acetyl-Tyr-Val-Ala-Asp-chloromethylketone (Ac-YVAD-CMK) and t-butooxycarbonyl-L-aspartic acid benzyl

ester-chloromethylketone (Boc-Asp-(OBzl)-CMK) block the release of interleukin-1 β and attenuate apoptosis [53]. Blockade of the inducible form of COX-2 with NS-398 also prevents the rise in cellular apoptosis [53]. Intraventricular administration of gp120 for up to 7 days resulted in an elevation in the expression of caspase-3 in rat brain [54]. Singh et al [55] expanded these findings to confirm those of Acquas et al [54] that demonstrated gp120 activation of caspase-3, but extended them to include the actions of Tat which appeared to promote apoptosis via an endonuclease G mechanism. The caspase inhibitor Z-DEVD-FMK significantly reduces gp120-induced elevations in caspase-3, but had no significant effect on Tat toxicity. These findings are the first to suggest that although both gp120 and Tat elicit robust neurotoxicity and cellular apoptosis, they can work through different apoptotic mechanisms.

STEROIDS

Sex steroids

Postmenopausal women who are infected with HIV are at risk for experiencing dementia and Parkinson's-like symptoms associated with low levels of estrogen [56] leading to speculation that estrogen may attenuate the development of these debilitating symptoms [57]. 17β -estradiol (E_2) has been generally observed to be neuroprotective in cell culture [58, 59]. A potential mechanism for E_2 protection may be the phenolic A ring, which would act as a direct free radical scavenger [60]. The concept of neuroprotection by E_2 has expanded beyond the realm of simple steroid-receptor interactions to include interactions with unidentified cell-surface receptors and direct modulation of neurotransmitter function [58, 59]. Potential exists for direct effects of E_2 as a free radical scavenger, interactions with cell-surface receptors, or with its nuclear binding site. From these studies, the latter appears to be unlikely since nuclear effect would commonly occur over hours or days. It is clear that E_2 affords some level of neuroprotection in all culture models, and this protection is dependent on a complex system of interactions from the extracellular to the nuclear space.

Collectively, previous reports have helped to partially elucidate the mechanisms of Tat and gp120 toxicity. Recent work has indicated that E_2 may slow the transmission of HIV [61], protect against the synergistic toxicity of Tat and gp120 [62], reduce Tat-induced inflammation in endothelial cells [63], and may prevent neuronal death in the presence of HIV-1 protease [64]. The synergistic toxicity following gp120 and Tat exposure can be extended to synergistic toxic effects of cocaine. Subtoxic concentrations of gp120 and Tat, plus physiologically relevant concentrations of cocaine, resulted in a significant increase in cell death [65]. This effect is blocked in the presence of E_2 , but not 17α - E_2 . Progesterone afforded minimal protection, yet surprisingly, testosterone exhibited protection on the level of E_2 [65]. The effects of both E_2 and testosterone were reversed by ICI-182,780, a selective estrogen antagonist, suggesting interactions with the cell-surface E_2 receptors. Not only does E_2 protect against oxidative cell

death, but also evidence suggests that it prevents apoptosis, through both a Bcl/Bax mechanism and interleukin-1 β [24, 66]. This inhibition is reversed by both ICI-182,780 and tamoxifen, E₂ antagonists. Further work is needed on this topic to determine the efficacy of E₂ neuroprotection with regard to HIV neurotoxicity [67].

Glucocorticoids

The ability of glucocorticoids to potentiate HIV neurotoxicity has long been known, but the mechanisms of this action are poorly understood. Synthetic glucocorticoids such as prednisone and dexamethasone potentiate the effects of gp120 on intracellular calcium concentration [68, 69]. This is particularly deleterious considering that these synthetic glucocorticoids are routinely used to treat *Pneumocystis carinii* pneumonia, which is commonly observed in AIDS patients. A possible mechanism for this action is via reduction in energy (ATP) levels which reduces mitochondrial membrane potential and promotion of extracellular calcium increases. Energy supplementation has been shown to ameliorate these effects of glucocorticoids [68]. These studies have been replicated in vivo using physiological concentrations of cortisol, resembling concentrations observed during stress with similar outcomes, increased mobilization of intracellular calcium, and increased depletion of ATP [70]. Concentrations of glucocorticoids and gp120, which are nontoxic independently, cause significant toxicity when coadministered in striatal cultures [69]. Administration of gp120 alone results in significant increases in reactive oxygen species, whereas coadministration with cortisol increases the amount of lipid peroxidation [71]. It is clear that glucocorticoids exacerbate HIV, and gp120, toxicity by potentiating increases in intracellular calcium and reducing cellular ATP levels. When combined, these effects predispose the cell to oxidative damage and death.

STRIATAL TOXICITY, DOPAMINE, AND DEMENTIA

HIV dementia is a subcortical dementia associated with dysfunction in the basal ganglia [72]. Currently, there are multiple HIV proteins that have been reported to exert neurotoxic effects. Several groups have demonstrated the presence of Tat protein in brains of patients with HIV encephalitis by immunostaining [73, 74]. Additionally, mRNA levels for Tat are also elevated in brain tissue of patients with HIV dementia [73]. Once released, Tat and gp120 have been shown to exert toxicity through an oxidative stress pathway [4–6, 75]. One neurological system that is involved in gp120- and Tat-induced neurotoxicity is the dopaminergic system. Patients develop symptoms of dopamine deficiency and exhibit heightened sensitivity to dopaminergic selective drugs as well as psychostimulants which act on dopaminergic neurons in the basal ganglia [76]. Other neurotransmitter systems that interact with the dopaminergic system, such as glutamatergic and opioid [77], also increase the sensitivity of the basal ganglia to the neurotoxic properties of gp120 and Tat. Therefore, the basal ganglia and the dopaminergic system

would be a likely target for the development of therapeutic agents to attenuate or prevent the development of HIV-associated dementia.

Administration of gp120 to striatal cell cultures elicits a toxicity that is reversed by coadministration of a glutamate antagonist [1]. Toxicity of Tat to striatal neurons is due, in part, to direct actions on the neuron which is not subject to desensitization [3]. The dementia that has been observed in HIV patients only occurs in about 20% of all infected people. Comparison of brain extracts from demented versus non-demented patients revealed that supernatants from demented patients showed significantly greater toxicity compared to supernatants obtained from nondemented patients [78]. One underlying mechanism for HIV-related dementia and Parkinson-like symptoms could be loss of dopamine transporters/function following gp120 and Tat exposure. Recently, Wang et al [79] reported that patients suffering from HIV-associated dementia exhibited a significant 13%–20% reduction in dopamine transporter density compared to seronegative controls. This study was the first to demonstrate HIV-induced damage to dopaminergic terminals in humans, which was inversely related to viral load (load increases, transporter density decreases). Additional studies are needed to further elucidate these mechanisms and offer insight into possible therapeutic interventions to prevent/attenuation HIV-associated neurotoxicity to dopamine neurons.

POTENTIAL THERAPEUTIC INTERVENTIONS

Currently, there are no therapeutic interventions which can be used to attenuate the development of HIV neurotoxicity and/or dementia. Based on the data that has been discussed, logical choices would be ligands which block some of the mechanisms associated with gp120 and Tat toxicity. This could include antagonizing NMDA glutamate receptors, blocking the intracellular rise in calcium, inhibition of NOS, or blocking the effects of microglia/chemokines. One of the first avenues pursued was antagonism of the NMDA receptor. A low concentration of NMDA, plus arachidonic acid enhances toxicity in neuronal culture. It is possible that gp120 activates phospholipase A2 to increase arachidonic acid release, which then sensitizes the NMDA receptor to the actions of glutamate. This effect is reversed by memantine, an NMDA receptor antagonist [80, 81]. Memantine is currently clinically used to treat spasticity and Parkinson's disease and may provide therapeutic relief of some of the symptoms of HIV neurotoxicity. Further work is warranted to more completely elucidate the function of memantine in the CNS and determine its usefulness in treating HIV neurotoxicity. A drawback to memantine use is that it will only be effective if used in a prophylactic manner. After neuronal death occurs, and the onset of dementia is apparent, memantine would have little therapeutic usefulness other than to slow the progression of dementia.

Opioid compounds have yielded the mixed results when attempting to determine their interaction with the gp120 or the Tat. Compounds which would normally be considered

mu-preferring have been shown to potentiate the toxicity of gp120 and Tat [25]. Conversely, other kappa- and delta-preferring opioid and nonopioid analgesic agents have been shown to be protective. The nonopioid compound, flupirtine, produces analgesia, but also possesses anticonvulsant and muscle-relaxant properties and has been shown to be cytoprotective against gp120-induced toxicity [80]. The kappa-preferring agonist, U50,488, suppresses microglia release of quinolinic acid [82]. Suppression of quinolinic acid release will decrease stimulation of NMDA receptors and consequently reduce excitotoxicity in neurons. We have shown that the peptidergic delta agonist, DPDPE, reduces oxidative stress in SK-N-SH cells exposed to Tat [83]. Our results also extend to the nonpeptidergic agonist, SNC-80, and the effects of both agonists are reversed by delta-preferring antagonists, suggesting a receptor-mediated mechanism for inhibition of oxidative stress [83]. Interestingly, opioids which are abused (morphine, heroin, and their derivatives) act primarily at the mu-subtype, which is the subtype primarily responsible for synergistic toxicity with gp120 and Tat. Agents which act at kappa- and delta-opioid receptors may provide viable analgesic options for individuals that are HIV infected.

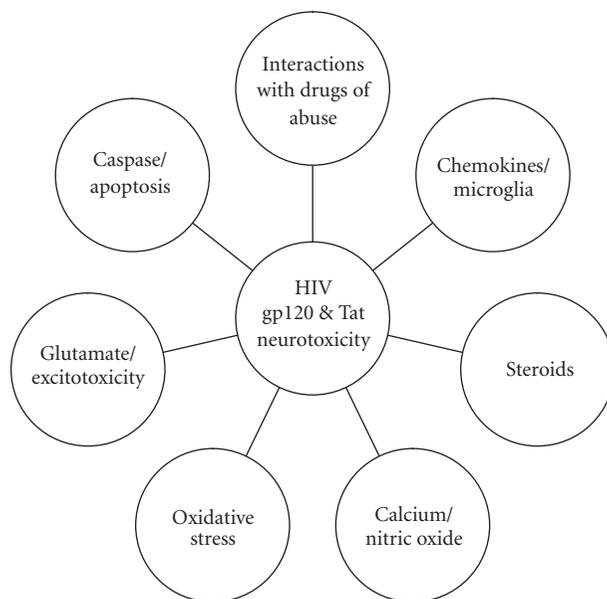
Another area that has garnered a great deal of interest in the last decade has been the effects of steroids on the neurotoxicity of HIV proteins. It has become clear that hormones released in response to stress, namely cortisol, potentiate the toxicity of gp120 and Tat [69, 70]. Intermediate (prednisone) and long-acting (dexamethasone) glucocorticoids are often prescribed for respiratory-symptoms-associated opportunistic diseases associated with HIV which could compound HIV-related neurodegeneration. More interest has been given to the protective effects of estrogen. We have shown that estradiol reduces the oxidative stress elicited by gp120 and Tat in SK-N-SH cells and this effect is reversed by the estrogen antagonist ICI-182,780 [84]. This work supported previous reports that estradiol attenuates the toxicity following HIV-1 protease administration [64], gp120 administration [85, 86], or coadministration of gp120 and Tat [62]. There have been mixed results concerning the effects of other sexsteroids such as progesterone, testosterone, and their derivatives. It appears that whether these hormones are protective or potentiating depends on the assay system that is being utilized and the manipulations that are used to optimize the assay. Further work on the effects is necessary to fully understand its protective potential in HIV model systems. Questions that must be asked are (1) are the effects of estradiol selective for estradiol, or can other "estrogens" elicit the same effect, and (2) are estradiol effects mediated by cell-surface receptors, intracellular receptors, or possible due to the structural nature of estradiol. Areas of current research that appear to be yielding exciting results are the use of selective-estrogen receptor modulators (SERMs) and the use of plant-derived estrogens. Early studies have shown that administration of some of these compounds can prevent, or attenuate, HIV protein-induced toxicity without the side effects associated with estrogen, such as promotion of estrogen-dependent tumors in females or feminization of males (unpublished observations).

A wide array of other approaches has been used to try and prevent the pathogenesis of HIV-related neurodegeneration and dementia. One compound that has yielded interesting results is CPI-1189 in the treatment of HIV-related dementia. CPI-1189 works through an unknown mechanism, but appears to ameliorate TNF-alpha toxicity by increasing activation of ERK-MAP kinase [87]. CPI-1189 also attenuates culture toxicity in the presence of quinolinic acid and gp120 [87]. Excitement about CPI-1189 has waned after a more recent clinical trial has indicated that CPI-1189 is well tolerated, but did not demonstrate a significant improvement in neuropsychological measures [88]. Inhibition of matrix metalloproteinase with prinomastat reduced neuronal toxicity following exposure to supernatants from brain-derived Tat sequences obtained from demented patients [89]. The hypothesis put forth by Johnston et al [89] was that the particular Tat sequence from demented patients resulting in a higher level of toxicity due to induction of matrix metalloproteinases. Prophylactic treatment with lithium has also been postulated to be neuroprotective [90]. Pretreatment or coadministration of lithium to neuronal cultures exposed to gp120 was protected via a phosphatidylinositol 3-kinase/Akt pathway, but treatment following gp120 exposure was ineffective [90]. Targeting oxidative damage is another therapeutic avenue that has been explored. Compounds such as L-deprenyl, didox, imidate, diosgenin, and ebselen all prevented oxidative damage following exposure to CSF from HIV demented patients [91]. Human lipidated apoE3 has also been shown to protect neurons from Tat-induced toxicity via prevents of Tat-induced oxidative stress [92, 93]. Also Tat and apoE compete for the same binding site, resulting in increased extracellular Tat; the ability for apoE to prevent Tat-induced oxidative stress may outweigh the increase in extracellular Tat. More investigation into this effect would be warranted prior to making any definitive conclusions regarding the effectiveness of apoE. Involvement of chemokines, and in particular the CXCR4 and CCR5 receptors, in HIV-neurotoxicity and dementia has been demonstrated by many investigators. One hypothesis put forth involves the blockade of these receptors, leading to subsequent reductions in toxicity. Use of a novel CXCR4 antagonist, neomycin B hexa-arginine, has been shown to effectively cross the blood-brain barrier and reduce gp120-induced toxicity through a CXCR4-mediated mechanism [27].

Collectively, there appears to be no definitive therapeutic treatment for HIV-neurodegeneration and dementia. Some of the above compounds, such as the estrogenic compounds and the CXCR4 antagonist, neomycin B hexa-arginine, have shown some promise. Use of brain-derived neurotrophic factor (BDNF) has yielded favorable results, although delivery of a peptide into the brain offers some challenges [94]. A great deal of additional work is still necessary to determine the true effectiveness of any of these therapeutic approaches.

SUMMARY AND CONCLUSIONS

It is clear from the literature and ongoing studies that considerable work needs to be done to further elucidate the



SCHEME 1: Schematic of various into HIV neurotoxicity and the major factor involved. Although not an inclusive list, these are the major factors in the pathogenesis of HIV neurotoxicity and the development of dementia. The surrounding circles are not meant to imply that each factor is exclusive of other factors since considerable overlap exists between each of the components.

mechanisms of HIV neurotoxicity and the development of HIV-related dementia. It is also apparent that the development of therapeutically useful drugs will be delayed due to the complexity of the systems involved with HIV, and gp120/Tat in particular, toxicity. In Scheme 1, factors implicated in HIV neurotoxicity are depicted demonstrating the complexity of mechanisms underlying HIV neurotoxicity. Each of the surrounding circles also represent current avenues being pursued in the development of clinically relevant compounds to attenuate or prevent the progression of HIV neurotoxicity and dementia.

In sum, interest in elucidating the toxicity cascades for gp120 and Tat toxicity is great. Understanding these cascades is tantamount to developing therapeutic agents which could attenuate or prevent the neuronal degeneration associated with late-stage HIV infection. Agents with effects on multiple cascades are the most likely agents to provide relief from the progression of neuronal degeneration and may very likely come from sources not yet examined. An example could be the effects of lithium on gp120 toxicity as previously reported. Fully understanding the differences between individuals who are demented and those who are not will add significant amounts of information to our knowledge base. If the next decade has even greater productivity than the last, significant and robust advancements can be achieved.

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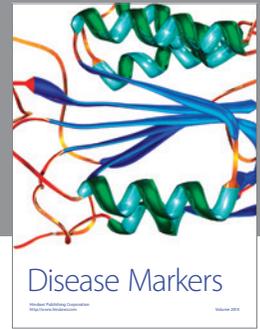
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