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The comorbidity of HIV-associated neurocognitive disorders and Alzheimer's disease: a foreseeable medical challenge in post-HAART era

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Abstract

Although the introduction of highly active antiretroviral therapy (HAART) has led to a strong reduction of HIV-associated dementia (HAD) incidence, the prevalence of minor HIV-1 associated neurocognitive disorder (HAND) is rising among AIDS patients. HAART medication has shifted neuropathology from a subacute encephalitic condition to a subtle neurodegenerative process involving synaptic and dendritic degeneration, particularly of hippocampal neurons that are spared prior to HAART medication. Considerable neuroinflammation coupled with mononuclear phagocyte activation is present in HAART-medicated brains, particularly in the hippocampus. Accumulating evidence suggests that the resultant elevated secretion of pro-inflammatory cytokines such as interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α), and interleukin-1 β (IL-1 β) can increase amyloid- β peptide (A β) generation and reduce A β clearance. Recent advancements in Alzheimer's disease (AD) research identified A β biogenesis and clearance venues that are potentially influenced by HIV viral infection, providing new insights into beta-amyloidosis segregation in HIV patients. Our study suggests enhanced beta-amyloidosis in ART-treated HAD and HIVE brains, and suppression of A β clearance by viral infection of human primary macrophages. A growing awareness of potential convergent mechanisms leading to neurodegeneration shared by HIV and A β points to a significant chance of comorbidity of AD and HAND in senile HIV patients, which calls for a need of basic studies.

Keywords

Alzheimer's disease; amyloid- β peptide; cytokines; Human immunodeficiency virus (HIV); HIV-associated neurocognitive disorders (HAND); macrophage; microglia; microtubule-associated protein tau; neurodegeneration; neurofibrillary tangle; neurotoxicity

Introduction

Alzheimer's disease (AD), characterized by progressive cognitive decline and disability, is the most common form of senile dementia (Selkoe 2001b). To date there is still no curative treatment for AD. A similar troubling situation applies to HIV-1-associated neurocognitive disorders (HAND), the neurological complication of viral infection. With the widespread use of highly active antiretroviral therapy (HAART), HIV infected patients' life spans have been prolonged (Besson et al. 2001). This longer lifespan coupled with the adverse effects of

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HAART and HIV-1 viral neurovirulence will lead to an expanding population being ravaged by both HAND and AD. This review addresses how the reciprocal influence of HIV neuroinvasion and beta-amyloidosis might accelerate neurodegeneration.

HAART medication -associated complications

Since the implementation of HAART, the incidence of acquired immunodeficiency syndrome (AIDS)-defining illnesses like opportunistic infections and central nervous system (CNS) neoplasms has decreased, leading to a significant improvement in the survival of HIV-infected patients (Hogg et al. 1997; Besson et al. 2001). This means more HIV patients will live to an age where AD and cardiovascular system complications are common. Furthermore, patients are inflicted with several adverse effects associated with HAART medication, which predispose them to AD development. For instance, immune reconstitution syndrome, an autoimmune condition that occurs when reconstituted T cell populations attack opportunistic pathogens that have proliferated while the T cells were under siege from HIV, produces connective tissue disease symptoms or vasculitis (Stoll and Schmidt 2003; 2004; Gray et al. 2005; Kumarasamy et al. 2008), lypodystrophic and metabolic effects causing hyperlipidemia, alterations in body fat distribution to metabolically inactive areas, diabetes and coronary artery disease, which are all known AD risk factors (Heath et al. 2001; Heath et al. 2002; Newman et al. 2005; Guallar et al. 2008). Other complications reported in HAART-medicated patients include chemotherapy disability, osteopenia/osteoporosis (Lima et al. 2007), severe demyelination (Langford et al. 2002; Gray et al. 2005; Vendrely et al. 2005) non-AIDS – defining malignancies such as leukemia (Pantanowitz et al. 2006) and depression (Berger-Greenstein et al. 2007).

HAND

HAND is a collective term used to denote the neurological complications of AIDS, which are typically subcortical, consisting of the triad of cognitive, behavior, and motor dysfunction (Ances and Ellis 2007). HAND manifests as HIV-associated minor cognitive/motor disorder (MCMD), a milder form, and HIV-associated dementia (HAD), the most devastating form (Letendre et al. 2008 380). HIV penetrates into the CNS early after peripheral infection of circulating T cells and monocytes (Koenig et al. 1986; Davis et al. 1992; An et al. 1999). The process for HIV entry into the CNS revolves around products secreted from immune-activated and virus-infected perivascular macrophage and microglia that affect blood-brain barrier (BBB) function, expression of cell adhesion molecules and chemokines, and lead to a disruption of brain microvessel integrity. To date, the four possible mechanisms that are supportive of viral entry into the CNS and are currently under investigation include: the surreptitious transmission of virus in infected macrophages (the Trojan horse model), direct infection of the BBB by HIV; transcytosis of HIV; and BBB disruption (Buescher et al. 2007). This neuroinvasion in turn elicits a series of neuroinflammatory responses, resulting in neurologic dysfunctions in a significant number of individuals with AIDS. The neuropathological correlates are collectively termed HIV associated encephalitis (HIVE), which are characterized by BBB disruption, leukocyte infiltration into the CNS, formation of microglia nodules and multinucleated giant cells, astrocyte activation and eventual damage and/or loss of neurons (Gendelman et al. 1997; Kramer-Hammerle et al. 2005; Buckner et al. 2006). To date the mechanisms leading to dementia in AIDS patients are not fully understood; however, it is thought that activated macrophage, microglia, and astrocytes produce chemokines and cytokines that in conjunction with secreted viral proteins damage the neuronal synaptodendritic arbor, resulting in loss of synaptic integrity and function, and eventual neuronal demise (Giulian et al. 1990; Gonzalez-Scarano and Martin-Garcia 2005; Bellizzi et al. 2006; Rumbaugh and Nath 2006).

In the era of HAART medication, HIVE may have shifted from a subcortical pathology towards a cortical pattern (Brew 2004), from a subacute rapidly progressive condition to a more subtle neurodegenerative process involving synapses, dendrites, and neuronal populations usually not affected by acute HIVE. Variants of HIV neuropathology in HAART-medicated patients that have been reported include severe white matter injury, extensive perivascular lymphocytic infiltration and A β accumulation of AD-like lesions (Gray et al. 2003; Green et al. 2005). Recent studies suggest that HIVE prevalence is actually rising as the number of treated subjects with chronic HIV infection increases, despite HAART medication (McArthur 2004; Everall et al. 2005). Consequently, considering the link between chronic neuroinflammation, neuronal/synaptodendritic degeneration and AD, the HAART-associated side effects and HAART-induced neuropathology are significant risks factors for AD development.

Enhanced amyloidosis in HAND brains

Amyloidosis composed of serum amyloid-A protein or lambda light chains has been reported in clinical HIV- seropositive patients in multiple sites of the body, including the kidney, and gastrointestinal tract (Chinnakotla et al. 2001; Chan-Tack et al. 2006; Miranda et al. 2007; Newey et al. 2007). HIV induces deposition of the same amyloid- β peptide (A β) found in AD (Finch and Morgan 2007), and A β immunoreactivity has been found predominantly in the neuronal soma, dystrophic axonal processes, and extracellular space (often as perivascular plaques) (Esiri et al. 1998; Izycka-Swieszevska et al. 2000; Green et al. 2005). In contrast, Gelman et al (Gelman and Schuenke 2004) reported that there was no statistically significant difference in A β plaques counts between AIDS patients and control subjects; instead, there were increased accumulations of ubiquitinated protein and decreased synaptic proteins in HIV-infected patients compared with HIV-seronegative subjects, suggesting HIV infection-mediated neuroinflammation might perturb synaptic protein turnover through the proteasome. The failure for them to see difference in A β plaques counts might be attributable to differences in experimental design. Firstly, all examined brain samples were restricted to patients who did not have a successful history of viral suppression by HAART, while Green et al have shown that HAART-medicated brains have significantly higher percentage of A β plaques as compared to pre-HAART patients (Green et al. 2005); secondarily, the majority (15 out of 25) of the patients was below 60 years of age from patients and sample size for each stratified group was small. Therefore, a more comprehensive study is needed to resolve this inconsistency.

Our neuropathological examination of autopsy brains of HIVE and HIV-seronegative cases revealed similar findings. Although intraneuronal A β immunoreactivity is also seen in aged control brains (Figure 1, A and B), it is significantly increased in ART-treated HIVE brains (Figure 1, C and D). Of note is that A β plaques are also observed in HIVE brains, in which perivascular diffuse A β immunoreactivity is also observed (Figure 1, E and F). Extracellular A β deposition was also found in ART-treated HAD brains but ART-untreated HAD show only intraneuronal A β accumulation (data not shown). The prevalence of this intraneuronal A β staining is about 30–40%, and extracellular A β is present in 4–13% of HIV-infected brains, with a significantly higher percentage of extracellular A β present in HAART-treated patients (Green et al. 2005). Accumulation of amyloid precursor protein (APP) with globular and/or bundled structures has been reported in HIVE brains, suggesting widespread axonal injury (Giometto et al. 1997). The observation of enhanced beta-amyloidosis in HAART-treated HAND brain is intriguing, but the underpinning molecular mechanisms are unclear. One potential mechanism is the effect of HIV protease inhibitor, which is a standard component of ART protocol, on A β degradation. Indeed, nelfinavir, a classic HIV protease, can inhibit activity of insulin degrading enzyme, a known A β degrading enzyme (Hamel et al. 2006). Thus, chronic treatment of HIV patients with HIV protease inhibitor in HAART or ART protocol may accelerate the onset of extracellular A β deposition, and other ART drug should also be tested for their effect on A β clearance and production. According to the prevalent A β theory this

might be multifactorial, involving a number of pathways whose consequences ultimately are centered on A β biogenesis and its clearance. Several significant potential contributors will be discussed below in light of recent findings from our group and others.

Tauopathy-related pathology in HAND brains

Microtubule-associated protein tau is one of major cytoskeletal molecules in neuronal axons, and hyperphosphorylated tau (pTau) is a major component of neurofibrillary tangles (NFT), the other pathological hallmark of AD. The amyloid cascade hypothesis proposes that A β pathology precedes and induces tau pathology (Selkoe 2001b). The accelerated A β amyloidosis in HIV-infected brains may explain the aberrations of tau or pTau levels in HIV-infected patients, since A β deposition precede and accelerate NFT formation in AD brains and animal models of AD, respectively. Cerebrospinal fluid (CSF) tau protein concentration was significantly higher in patients with HAD compared with neuro-asymptomatic HIV-1 cases and HIV-negative controls (Andersson et al. 1999). Compared with age-matched controls, pTau concentrations were also increased in HAD brains (Brew et al. 2005; Anthony et al. 2006). The highest levels of pTau are noted in HAART-treated subjects. However, there is also a conflicting report that CSF tau is not elevated in HAD subjects (Ellis et al. 1998; Green et al. 2005). This discrepancy might arise from differences in sampling size or severity of disease progression.

In accord, tau aggregation and NFT is neuropathologically more correlated with the progression of HAD, with the greatest levels of pTau being noticed in HAART-medicated patients (Anthony et al. 2006). However, within the age groups studied, these significant neuropathological changes remained subclinical and were not yet associated with cognitive impairment (Anthony et al. 2006). The molecular mechanism of tau phosphorylation and NFT formation in HIV-infected patients is poorly investigated. It might be secondary to altered amyloidosis process such as neuronal stimulation by viral proteins or pro-inflammatory cytokines both of which are produced by microglia. Indeed, microglial activation is correlated with pTau levels (Tan et al. 1999), and activated microglia induce pTau in neurons in IL-1 receptor antagonist (IL-1ra) and anti-IL-1 β antibody-sensitive manner (Sheng et al. 2000; Sheng et al. 2001; Li et al. 2003). Thus, activated microglia may contribute to neurofibrillary pathology through IL-1 production in HIV brain.

A β biogenesis and clearance balance

A β production pathway

The prevalent A β theory hypothesizes that the primary influence driving AD pathogenesis is the accumulation of A β in the brain, which is proposed to result from an imbalance between A β production and A β clearance (Hardy and Higgins 1992; Hardy and Selkoe 2002). APP, which is a ubiquitously expressed type I integral membrane, can be successively cleaved by proteases known as β - and γ -secretases in the late endosomes to liberate heterogeneous A β species (39–43 amino acid, predominantly A β 40 and in a lesser amount A β 42) into the extracellular matrix in a function referred to as amyloidogenic processing. Alternatively, APP may be cleaved within the A β domain by β -secretases precluding the formation of A β (non-amyloidogenic processing) which leads to the shedding of a large soluble N-terminal fragment of APP (sAPP β) into the extracellular or intra-luminal space (Checler 1995; Carey et al. 2005; Newman et al. 2007). In addition, A β can be generated in the macroautophagy pathway, which is activated in early AD mouse models due to the impaired maturation of autophagic vacuoles (AVs) to lysosomes (Yu et al. 2005).

A β clearance pathway

Accumulating evidence underscores the notion that faulty clearance or enzyme-mediated A β degradation may account for A β accumulation as well, in particular for late-onset AD cases (Zlokovic et al. 2000; Selkoe 2001a; Tanzi 2005; Holtzman and Zlokovic 2007). It is known that intact soluble A β may be cleared from the brain via several routes: transport across vessel walls into the circulation mediated by blood vessel wall-expressed low-density lipoprotein receptor-related protein-1 (LRP-1) (Shibata et al. 2000; Lam et al. 2001), clearance from brain via binding of A β to soluble LRP-1 circulating in blood (acting as an endogenous peripheral 'sink') (Sagare et al. 2007), transport of A β across the blood-brain barrier from the abluminal to the luminal side via the P-glycoprotein (PgP/MDR1/ABCB1) efflux pump (Lam et al. 2001), and drainage along perivascular basement membranes, possibly into CSF (Weller 1998). It has been shown that the receptor for advanced glycation end products (RAGE) is a primary transporter of A β across the BBB into the brain from systemic circulation (Donahue et al. 2006). A β also undergoes enzymatic degradation. Multiple enzymes within the CNS are capable of degrading A β , most of which are produced by neurons or glia. Some of these enzymes are produced in the cerebral vasculature, where reduced A β -degrading activity may contribute to the development of cerebral amyloid angiopathy (CAA) (Miners et al. 2008). Two major peptidases that have been studied intensively and hold great therapeutic promise are neprilysin and insulin-degrading enzyme (IDE, also called insulysin) (Iwata et al. 2001; Farris et al. 2003). The levels of both of these enzymes are reduced in AD, although the correlation with enzyme activity is still not entirely clear, and over-expression of NEP and IDE has been shown to reduce A β levels in different systems ranging from cultured neurons, drosophila, and AD mouse models (Iwata et al. 2001; Farris et al. 2003; Leissring et al. 2003; Hemming et al. 2007; El-Amouri et al. 2008).

Overproduction of amyloidogenesis-promoting cytokines

Within the CNS, the major cell types infected by invading HIV are of macrophage/microglia lineage, and astrocytic infection, though to a much lesser extent. These cells can also be activated by released cytokines and shed viral proteins such as gp120, resulting in up-regulation of cytokines, chemokines, and endothelial adhesion molecules (Gartner 2000; Kaul et al. 2001; Kaul et al. 2005), among which the pro-inflammatory cytokines tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) play an important role in the induction of neuronal injury and death or neuroprotection (Brabers and Nottet 2006). In the brain, TNF- α is synthesized predominantly in microglia as a 26-KDa membrane-bound polypeptide precursor that is cleaved to be a bioactive 17-KDa subunit by TNF- α converting enzyme (TACE). The biological actions of released TNF- α are mediated through two distinct cell surface receptors, TNFR1 (p55) and TNFR2 (p75) which are constitutively expressed in neurons, glial cells and blood vessels, to which TNF- α exhibits fairly equal affinity, though each mediates distinct cellular responses (Hsu et al. 1996; Quintana et al. 2005). Through the action of these two receptors, TNF- α has a broad range of actions on neurons and glial cells, which may be either neuroprotective or neurotoxic, as reviewed elsewhere (Vitkovic et al. 2000; Pickering et al. 2005). Potently elevated levels of TNF- α have been associated with the pathological effects in a variety of conditions including AD and HIV, in addition, expression levels of both TNF- α receptors are increased in the brains of patients with AIDS compared with normal control brains (Sippy et al. 1995).

High levels of TNF- α expressed in microglia infiltrating with amyloid plaques is featured in AD brains and mouse models (Meda et al. 1995; Patel et al. 2005; Yamamoto et al. 2007a; Frank et al. 2008), and have pleiotrophic contributions to neuroinflammation-mediated cell death, synaptic transmission and synaptic plasticity (scaling) abnormalities implicated in AD (Albensi and Mattson 2000; Beattie et al. 2002; Volterra and Steinhauser 2004; Pickering et al. 2005; Stellwagen and Malenka 2006; Pickering and O'Connor 2007). TNF- α is not only

contributing to neurodegeneration, but it is also directly involved in A β generation and degradation. Work from our lab and other groups has demonstrated that TNF- α directly stimulates astrocytic BACE1 expression to enhance β -site processing of APP, and suppresses A β degradation in microglia (Blasko et al. 2000; Rossner et al. 2001; Hartlage-Rubsamen et al. 2003; Yamamoto et al. 2007a). This result is bolstered by a genetic manipulation study in which genetic deletion of TNFR1 gene in APP23 transgenic mice inhibits A β generation and plaque formation in the brain via reduction of BACE1 levels and activity (He et al. 2007). Apart from this, TNF- α can stimulate β -secretase activity to increase A β production (Liao et al. 2004). Interferon- γ and IL-1 β , whose expression levels are elevated in HIVE, act synergistically to increase astrocytic BACE1 levels and activity (Blasko et al. 2000; Hong et al. 2003; Liao et al. 2004; Cho et al. 2007; Yamamoto et al. 2007a). Glutamate neurotoxicity is implicated as a mediator of neuronal degeneration in HIVE, which is triggered primarily by massive Ca²⁺ influx arising from over-stimulation of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors (Erdmann et al. 2007; Tian et al. 2008). Interestingly, it is reported that sub-lethal NMDA receptor activation can inhibit the α -secretase candidate TACE to increase neuronal expression of Kunitz protease inhibitor domain - containing APP (KPI-APP) to promote neuronal A β production (Lesne et al. 2005). Consequently, the dramatic surge of above cytokines in HIVE, together with other factors like free radicals that also can up-regulate BACE1 expression (Tamagno et al. 2002; Tamagno et al. 2005; Sastre et al. 2006), have a significant chance to promote A β generation and subsequent accumulation in HIVE brains, as schematized in Figure 2.

The cytokine IL-1 β is a powerful driving force for leukocyte recruitment to the CNS (Gibson et al. 2004). It can override the intrinsic resistance of the CNS to leukocyte infiltration, resulting in acute cellular recruitment to the brain parenchyma (Depino et al. 2005; Shaftelet et al. 2007a). It is a key mediator of inflammation and neuronal death in acute CNS injuries, such as stroke and brain trauma (Allan et al. 2005), and has been implicated in chronic neurodegenerative diseases such as AD and HAD (Griffin et al. 1989; Royston et al. 1992; Corasaniti et al. 2001; Wyss-Coray 2006). An increase of IL-1 β concentration in the brain leads to deficits in cognitive and synaptic function typified by an attenuation in hippocampal-dependent learning and memory (Gibertini et al. 1995; Pugh et al. 2000; Shaw et al. 2001; Song et al. 2004), and in long-term potentiation (LTP) (Katsuki et al. 1990; Murray and Lynch 1998; Vereker et al. 2000; Kelly et al. 2003; Minogue et al. 2003; Maher et al. 2005; Griffin et al. 2006). Interestingly, mice deficient for IL-1R (the only known receptor for IL-1) exhibited deficits in a number of learning paradigms, as well as in LTP, suggesting a physiological role for IL-1 β (Avital et al. 2003).

In addition to its detrimental role in neuronal injury (Allan et al. 2005), IL-1 β has been found to be involved in A β metabolism process, e.g., transcriptional upregulation of expression of APP gene by promoting binding of NF- κ B/Rel to 5'-regulatory region of the APP gene (Grilli et al. 1996; Yang et al. 1998), or supporting beta-secretase cleavage of the immature APP molecule (Blasko et al. 2000), and augmenting gamma-secretase activity (Liao et al. 2004). Nonetheless, a recent report demonstrated that IL-1 β up-regulated TACE to enhance alpha-cleavage of APP and reduced beta-cleavage in mouse neurons (Tachida et al. 2008). IL-1 β may also impair the microglia-mediated A β clearance (Hickman et al. 2008). More intriguingly, sustained hippocampal overexpression of IL-1 β in APP^{sw}/PS1 mice mediated chronic inflammation to ameliorate plaque pathology through enhancement of microglia-mediated plaque degradation (Shaftelet et al. 2007b), presumably through enhancing recruitment of bone-marrow-derived microglia into the CNS via increased leakage of BBB and robust upregulation of MCP-1 (Shaftelet et al. 2007a).

These provocative findings underscore the plastic roles that a particular cytokine can play. They act in highly context-dependent ways, not necessarily always being proinflammatory or

detrimental (Wyss-Coray 2006). Though the status of neuroinflammation as a “good guy” or a “bad guy” with respect to AD pathogenesis is still controversial (Rogers et al. 1996; Morgan et al. 2005; Wyss-Coray 2006; Lemere 2007), the observation of an ongoing robust activation of microglia and astrocytes, particularly in the hippocampus of HAART-treated patients despite HIV has become less common (Anthony et al. 2005; Bell et al. 2006) which means it poses a threat as a factor that is more conducive to development of AD.

Impaired enzymatic A β degradation

HIV encodes at least nine proteins that can be divided into three classes: structural - Gag, Pol, and Env; regulatory - Tat (transactivator of transcription) and Rev (Regulatory for expression of viral proteins); and accessory - Vpu, Vpr, Vif and Nef. These viral factors can damage neurons and interfere with the function of CNS through respective mechanisms (Ances and Ellis 2007); furthermore, some of these rogue molecules are implicated in A β pathology. For instance, Tat inhibited NEP activity by 80% in an *in vitro* assay, and recombinant Tat added directly to brain cultures resulted in a 125% increase in soluble A β (Rempel and Pulliam 2005; Daily et al. 2006). This indicates patients living with HIV may have faulty A β degradation. In addition, binding of Tat to LRP mediates neuronal uptake of Tat, and substantial inhibition of binding, uptake and subsequent degradation of several physiological ligands of LRP including A β (Liu et al. 2000). Gp41 peptides can impair protein kinase C response to down-regulate IL-1 β -induced elevation of secreted sAPP β (Chong and Lee 1999), which is a potent glial neurotrophic factor (Luo et al. 2001; Wang et al. 2004; Bell et al. 2008).

Our *in vitro* study showed a significant impairment of A β degradation by HIV-infected macrophage when compared to non-infected control cells (Figure 3).

The exosome connection

Exosome formation and function

Exosomes, small membrane vesicles secreted from cells into the extracellular space, were first observed in association with sheep reticulocytes (Johnstone et al. 1987), and have been observed in cells found in the CNS including macrophage, microglia, and neurons (Verani et al. 2005; Faure et al. 2006). Proteins sequestered into the limiting membrane of multi-vesicular bodies (MVBs) can be selectively incorporated into intraluminal vesicles (ILV) that are contained within the MVBs, and the internal vesicles can be targeted for lysosomal degradation. Alternatively, they can fuse with the plasma membrane releasing ILV into the extracellular space (Vella et al. 2008). Exosome secretion was previously considered a cellular mechanism to release unnecessary proteins, but recent studies have revealed additional roles such as proteolytic processing of certain target proteins like soluble TNFR (Hawari et al. 2004), intercellular trafficking of HIV (Loomis et al. 2006; Wiley and Gummuluru 2006; Vella et al. 2008), and as vehicles for stimulating anti-tumoral immune response, as reviewed elsewhere (Denzer et al. 2000; Fevrier and Raposo 2004).

Implications of exosome in neurodegenerative disorders

It is intriguing that proteins associated with prion disease and AD can be selectively incorporated into ILV of MVBs and subsequently secreted into the extracellular space. It has been shown that the accumulation of the longer, more amyloidogenic A β 42 occurs predominantly in MVBs of neurons in normal mouse, rat and human brain, and that this accumulation increases with age in transgenic mice and human AD brains (Takahashi et al. 2002). Also of significance is the enrichment in the exosomes of GM1 gangliosides, which is an important component of cellular plasma membranes and especially enriched in lipid raft, and can bind to A β 42, A β 40 (Ariga et al. 2001) and APP (Zhang et al. 2007). There is mounting evidence in support of GM1-bound A β (GA β) found in human brain as a seed for A β

fibrillogenesis (Yanagisawa et al. 1995; McLaurin and Chakrabartty 1996; Yamamoto et al. 2005; Yamamoto et al. 2007b). Although it is still not clear what causes endocytic pathway abnormalities in AD brains, a recent *in vitro* study showed that it can result in accumulation of GM1 ganglioside in early endosome and accelerated release of exosome-associated GM1 ganglioside into the extracellular environment inducing A β fibril formation (Yuyama et al. 2008). It is of note that GM1-ganglioside level is elevated in the CSF of subjects seropositive for HIV. This elevation may be due to the fact that HIV budding occurs via exosomes that are enriched for GM1-ganglioside, or might be a result of endosomal pathway alterations owing to budding and accumulation of HIV virions within macrophage (Jouve et al. 2007). The enrichment of GM1 ganglioside in the extracellular space might promote the A β fibril formation process; this speculation is supported by results of our *in vitro* study in which HIV infection resulted in enhancement of A β aggregation by 3–4 folds. Therefore the commonality of utilizing exosomes as the same releasing mechanism for both HIV and A β is of immense interest and significance. Although a co-lease of both agents from neurons is an unlikely scenario considering no direct viral infection of neurons, it might be likely in infected macrophage. This might result in A β deposition within the macrophage, since our recent study demonstrated that fibrillar A β degradation in macrophage is dependent on lysosomes (Yamamoto et al. 2008), and may account for the A β immunoreactivity localized in perivascular macrophages in HIV-infected brain. However, the accumulation and enrichment of GM1 ganglioside-enriched exosomes from infected macrophages may act as a nexus promoting fibrillogenesis of A β secreted by neurons and activated astrocytes. This is summarized in a proposed mechanism shown in Figure 4.

Many amyloidosis facilitates HIV infection

It is very interesting that not only HIV viral infection can influence the amyloidosis process, but also that amyloidosis in turn can facilitate HIV viral infection. A β fibrils can stimulate viral infection of target cells expressing CD4 and an appropriate coreceptor by 5–20 folds by multiple HIV-1 isolates (Wojtowicz et al. 2002). In addition, another amyloid fibrils formed from naturally occurring fragments of the abundant semen marker prostatic acidic phosphatase (PAP) can drastically enhance viral infection by several orders of magnitude (Munch et al. 2007). These studies indicate that viral infection and A β production can mutually affect each other constituting a vicious cycle, and the complexity of their interaction is underappreciated. Intriguingly, apolipoprotein (apo) E isoform 4, the infamous risk factor for AD, is associated with an accelerated disease course and progression to death in HIV-infected patients, and apoE4 enhanced HIV fusion/cell entry of both R5 and X4 HIV strains *in vitro* (Burt et al. 2008). The sharing of the same disease risk factor not only suggests that current efforts to convert apoE4 to an "apoE3-like" molecule to treat AD might also have clinical applicability in HIV disease, but also underscores the speculation of a convergent pathogenic pathway for both AD and AIDS.

Summary

HIV neuroinvasion results in chronic inflammation in the brain, which is pathogenically implicated in AD. Recent findings presented above provide new insights as to how HIV infection can cause imbalance of A β biogenesis and clearance, accounting for accelerated beta-amyloidosis observed in HAND patients. The shifted neuropathology and adverse effects associated with HAART medication might cause these patients to be more susceptible to AD comorbidity. There is increasing awareness that HIV infection and A β may have shared pathogenic mechanisms responsible for neurodegeneration and dementia, hence a closer look into their interaction can provide not only more insights into their pathogenesis, but also helpful information to cope with this comorbidity for each of which there is no cure today.

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Figure 1. Enhanced β -amyloid depositions in HIVE brains

Anti-A β polyclonal antibody immunostaining of HIV-seronegative (A–B), HIVE (C–F) and AD (G–H) brains. A β -immunoreactive plaques were found in HIVE brains (asterisk, D), resembling those found in AD brain (asterisks, H). Intracellular A β immunoreactivity was observed in HIV-seronegative, HIVE and AD brains (arrows, B, D and H). Perivascular amyloid deposition was evident in HIVE brains (arrowhead, F). Original magnification, panels A, C, E, and G $\times 200$, B, D, F and H $\times 400$

Figure 2. Proposed mechanisms leading to enhanced intraneuronal and perivascular β -amyloid depositions in HIV brains

Activated microglia secreted elevated levels of proinflammatory cytokines ($IL1-\beta$, $TNF-\alpha$, $IFN-\gamma$) that can up-regulate BACE1 and APP expression in neurons, resulting in increased $A\beta$ generation. HIV viral protein Tat can be up-taken via LRP into neurons where it can inhibit Neprilysin activity, blocking $A\beta$ degradation. The reduced secretion of anti-inflammatory cytokines ($IL-4$ and $IL-10$) also contributes to impaired $A\beta$ degradation. Accelerated perivascular $A\beta$ deposition is a consequence of impaired efflux of $A\beta$ into plasma, and/or inhibition of perivascular $A\beta$ degrading enzymes by viral proteins.

Figure 3. Impaired fibrillar Aβ degradation in HIV-infected human macrophages

Human monocyte-derived macrophages (MDM) were infected with HIV-1 YU-2 (0.1pg p24/cell) or uninfected, and 3 day post infection subjected to pulse-labeling with 1.0 μM ¹²⁵I-labeled fibrillar Aβ42 for 1h at 37° C. The cells were washed out and chased for different time points as indicated in graph, when media were collected and fractionated with trichloroacetic acid (TCA) into TCA-soluble fraction containing degraded Aβ42 and TCA-insoluble fraction containing aggregated Aβ42 as described (Yuyama et al. 2008). HIV infection results in intracellular Aβ retention (A), significant reduction in Aβ degradation (B) and a concomitant increase of Aβ aggregation in extracellular space (C). *** denotes p<0.001 against control group at respective time points as determined by two-way repeated measurement ANOVA and Bonferroni post tests.

Figure 4. Proposed mechanisms leading to impaired intra-macrophage Aβ degradation and facilitated extracellular Aβ fibrillogenesis

Phagocytosed Aβ fibrils can be retrograde transported into aggresome and then refolding occurs with the help of chaperone molecules such as Hsp70; later they can be degraded by IDE or lysosomal enzymes, or exocytosed. Endocytosed Aβ fibrils can also be degraded via endosome-lysosome pathway. HIV might impair Aβ fibrils degradation in macrophage through elevating TNF-α and IFN-γ (inhibitory for Aβ fibrils degradation), decreasing IL-4 and IL-10 (stimulatory for Aβ fibrils degradation), and blocking endosome-lysosomal pathway, raising a possibility that Aβ may be co-released with virions into extracellular space where it can serve as a seed for fibrillogenesis.