

Chronic HIV infection leads to an Alzheimer's disease like illness. Involvement of the kynurenine pathway

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Abstract. HIV disease is complicated by the development of a subcortical dementing illness known as AIDS dementia complex (ADC). Highly active antiretroviral therapy (HAART) has effectively lengthened HIV infected patients' life expectancy; indeed some are approaching an age where the risk of Alzheimer's disease (AD) is starting to become significant. Furthermore, many such patients have hyperlipidemia, which increases the risk of AD. Consequently, it is hypothesized that HIV infected patients are at an increased risk of AD or an illness that is very much like it. While this is a subcortical dementia and as such is quite different from AD, there are similarities especially in regard to the important role of neuroinflammation. Activation of the tryptophan metabolism via the kynurenine pathway (KP) and more particularly production of one of its end-products, excitotoxin quinolinic acid (QUIN), may play a central role in the amplification of the inflammatory mechanisms, amyloid plaque formation and even increase the rate of viral infection of brain cells. © 2007 Published by Elsevier B.V.

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1. Introduction

1.1. The kynurenine pathway (KP)

The KP is a major degradative pathway of tryptophan (TRP) that ultimately leads to the production of NAD (Fig. 1). Recent findings have shown that the KP is one of the major

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regulatory mechanisms of the immune response [1]. Two theories have been proposed: 1) that TRP degradation suppresses T cell proliferation by dramatically depleting the supply of this critical amino acid; 2) that some downstream KP metabolites act to suppress certain immune cells [1]. Induction of the KP regulatory enzyme indoleamine 2,3 dioxygenase (IDO) in dendritic cells completely blocks clonal expansion of T cells [2]. TRP depletion and IDO/KP activation have been implicated in the development of immuno-tolerance associated with pregnancy and persistence of tumors. The cellular location of the KP is only partly understood. It is complete in monocytic lineage cells [3], including macrophages and microglia. We showed that it is partly present in astrocytes [4]. The products of the KP have numerous neurotoxic and neuroprotective effects. Among them, QUIN is perhaps the most important. It leads acutely to human neuronal death and chronically to dysfunction by at least four mechanisms [5]. Another product of the KP, kynurenic acid (KYNA), is an antagonist of all ionotropic glutamate receptors and thus can antagonize some of the effects of QUIN and other excitotoxins. Several drugs that can block the KP are under investigation by our laboratory and others. For example, 4-chlorokynurenine crosses the blood brain barrier and blocks QUIN toxicity at the glycine site on NMDA receptors. KYNA analogs are in or about to enter clinical trials for treatment of epilepsy, stroke and possibly Parkinson's disease. These are fully discussed in the review by Stone [6].

1.2. The pathogenesis of Alzheimer's disease

Alzheimer's disease (AD) is the most common cause of dementia; however, the precise aetiology of AD is unknown. Most investigators now consider that AD should be viewed as a syndrome, rather than a single disease. Several mechanisms are thought to be involved in the development of the "Alzheimer's syndrome": an inflammatory response, several genetic and various environmental factors. While neuronal dysfunction and death are the likely substrates for dementia, it is clear that many complex mechanisms contribute to the final clinical picture of progressively declining cognition. Two significant abnormalities occur in the brain of AD patients: 1) intracellular twisted nerve cell fibers composed of hyper-phosphorylated Tau (HPT) protein [7], known as neurofibrillary tangles (NFT), and 2) the deposition of a sticky protein called β amyloid ($A\beta$) which forms extracellular amyloid plaques. $A\beta$ peptides occur in varying lengths, with $A\beta$ 1–42 apparently the most neurotoxic of the amyloid species, due in part to their tendency to form insoluble fibrils [8]. We and others have demonstrated that activated microglia and astrocytes encase the plaques [9] and others have shown the presence of infiltrating macrophages [10]. Clearly a complex and multifactorial inflammatory response occurs in vulnerable regions of the AD brain [11]. Compelling evidence suggests that the long-term use of anti-inflammatory drugs lowers the incidence of AD [12], but whether inflammatory mechanisms cause, or are caused by neuronal damage is still unclear. Damaged neurons, highly insoluble $A\beta$ deposits and NFT provide significant stimuli for inflammation.

The two cardinal features of AD, plaques and NFT, appear to be directly linked. There is evidence that $A\beta$ may lead to the formation of HP-tau, the essential forerunner of NFT [13,14]. $A\beta$ induces endothelial cells to produce IL-1 β and IFN- γ [15]. These cytokines may enhance $A\beta$ production – IL-1 β promotes the neuronal synthesis and processing of $A\beta$ [16] and activates astrocytes [17] – and leads to the formation of complement by

microglia which in turn forms the membrane attack complex that lyses cells [18]. Activated microglia are additionally important because they produce M-CSF which further stimulates microglia and up-regulates APP expression by monocytic cells [19]. Chemokines and chemokine receptors are probably important in this aspect of AD pathogenesis [20]. Up-regulated expression of CCR3 and CCR5 on microglia has been described [21]. The chemokines released during neuroinflammation in AD not only regulate the traffic of leukocytes and macrophages in brain tissue, but may also protect against neuronal degeneration in response to endogenous excitotoxins or to accumulation of A β .

In addition to local inflammation, oxidative stress is present in AD tissue. Markers of oxidative stress are elevated in AD; in particular, the end products of lipid peroxidation are increased in the CSF of AD patients and correlate with the degree of cognitive deficit [22]. Interestingly, QUIN leads to inducible nitric oxide synthase (iNOS) activation and to the formation of reactive oxygen species (ROS) [23]. These ROS induce the peroxidation of membrane lipids, a major outcome of QUIN toxicity [23,24]. In synaptosomes from rat brains, lipid peroxidation is increased by 256% after injection of QUIN 100 μ M [25]. Both QUIN-induced lipid peroxidation and neurotoxicity can be prevented by antioxidants [23].

Finally, Neprilysin (CD10), a membrane-bound zinc metalloproteinase able to degrade both A β 1–40 and A β 1–42 *in vitro* and *in vivo* [26,27], may be highlighted for its potential importance in AD neuropathogenesis. In the CNS of AD patients, neprilysin expression is decreased. Over time, this imbalance could result in a neuropathologic accumulation of A β and formation of senile plaques [28]. Thus, while it is not fully established what actually causes the formation of A β there is overwhelming evidence for amplification of A β formation and toxicity by neuroimmune interactions with astrocytes and microglia.

2. The continued importance of ADC and subclinical HIV brain disease

HIV disease in the era prior to the introduction of HAART was associated with the development of ADC in approximately 20% of patients with advanced HIV disease [29]. The incidence of ADC has decreased by 50% with the advent of HAART [30]. But HAART has not eradicated ADC. Indeed, the prevalence of patients with ADC has increased [31]. This is a consequence of the mean time to death increasing from six to 44 months [31]. Thus there are not only more patients with ADC, there are more disorders to which they are vulnerable, simply because they are living longer. HAART improves but does not uniformly normalize neuropsychological performance in patients with minor cognitive disturbance as well [32]. There are some emerging data for the possibility that ADC has changed in the era of HAART and HIV may lead to Alzheimer-like changes [33].

The data for the continued importance of subclinical HIV brain disease are emerging and are neuropsychological and derived from CSF. Neuroasymptomatic HIV infected patients who had been treated with HAART for 2 years still had mildly elevated CSF concentrations of neopterin with normal concentrations of β -2 microglobulin and HIV RNA in both compartments. This suggests that HAART cannot return all CSF parameters to normal. The elevated neopterin concentration implies that there is activation within the CNS of monocytes and/or microglia [34]. Such immune activation may be secondary to productive brain infection, which is below the detection limits in the CSF, or it may be related to local unchecked immune activation from past damage. In relation to neuropsychological

evidence, approximately 50% of HAART treated patients can change their neuropsychological performance even independent of alteration to the drugs in their HAART regimens and plasma viral load [35].

3. Aspects of ADC and subclinical HIV brain disease common to AD

ADC is a predominantly subcortical dementia affecting cognition, motor function, and behavior chiefly involving the basal ganglia and deep white matter developing over weeks to months [34]. AD on the other hand is a cortical dementia chiefly involving cognition and behavior developing over years. Nonetheless, both disorders not infrequently involve the temporal lobe especially the hippocampus [36]. Commonality also extends to the general cellular level. Both disorders are characterized by inflammation, albeit of differing severities [37]. It is true that ADC is notable for inflammatory infiltrates of mononuclear cells. However, these are not the best correlate of ADC severity. Rather the degree of microglial activation is [34,38]. While AD is not characterized by inflammatory infiltrates, activated microglia and astrocytes are considered important in AD pathogenesis [37,39]. Some controversy remains, however, at an epidemiological level. Anti-inflammatory drugs including steroidal and non-steroidal medications are not effective treatment for AD [40]. These studies were relatively small and an effect may not have been seen because the majority of patients already had fixed damage through years of unchecked immune mediated damage. Indeed, recent evidence favors the efficacy of anti-inflammatory drugs in the prevention of AD as long as they have been given for several years [40].

As for specific cellular commonality, astrocytes and macrophages/microglia are important in both disorders. Activated astrocytes are invariant components of the senile plaques of AD. These cells predominantly over-express S100 β , which has dose-dependent cytotoxic and neurotrophic properties [41]. Even early, non-fibrillar amyloid deposits in AD contain such astrocytes, and the numbers and degree of activation of these wax and wane with the subsequent neuritic pathology of plaque evolution. Astrocytic over-expression of S100 β in the neuritic plaques of AD correlates with the degree of neuritic pathology in A β plaques, suggesting a pathogenic role for S100 β in the evolution of these lesions [42]. High levels of IL-1 β originating from activated microglia induce astrocytic over-expression of S100 β , which are also constant components of A β plaques in AD. Similar patterns of astrocyte activation, S100 β over-expression, microglial activation, and IL-1 β over-expression are seen in ADC [34,41]. Similarly, CSF levels of S100 β also correlate with the severity and rapidity of ADC progression [41]. CSF S100 β levels have also been found elevated in both conditions but the elevation in patients with ADC is almost 1000 fold higher than levels described for AD patients [41,43]. Moreover, a recent study has correlated CSF S100 β levels with brain atrophy in AD patients [43]. In both AD and ADC, macrophages/microglia are significant [37]. Macrophages/microglia infiltrate A β plaques, display intracellular A β and are surrounded by A β -free lacunae. Furthermore, macrophages/microglia partially encircle the walls of A β -containing vessels in amyloid angiopathy, and exhibit intracellular A β but not paracellular lacunae [44]. As mentioned above, ADC severity is best associated with the degree of microglial activation rather than productive HIV viral burden in the brain or the number of inflammatory infiltrates. Moreover, the monocyte subset CD14/69 is elevated in the blood of patients with ADC and

in those with AD [45]. Also, activated monocytes CD14+/CD16+ over-expressing APP on their membrane are found in cases with severe ADC [19]. This APP, at low level, may have some neuroprotective properties against gp120-induced neurotoxicity [46].

There is commonality too in the nature of the inflammatory products. IL-1 β and IL-6 are elevated in the brains and CSF of ADC patients [47] and both are considered to play pivotal roles in AD pathogenesis [48]. Furthermore, QUIN has been repeatedly shown to correlate with the severity of ADC [5] and recent evidence supports a role for it and the KP in AD [49–51] (see below).

4. Evidence that HIV may increase the risk of AD or an AD-like illness

4.1. Evidence from clinical data

HAART treated patients are now living longer. The mean age in a prevalence survey of neuropsychological abnormalities of an outpatient clinic at a tertiary referral hospital 10 years ago was 38.5 ± 7 years while the same referral population currently has a mean age of 49 ± 8.8 years [35].

Similarly, the number of patients with raised cholesterol and triglycerides is increasing as a result of advancing age, HIV disease itself, and HAART, especially the use of the protease inhibitor drugs. The hyperlipidemia in HIV infected patients is often difficult if not impossible to control. Raised cholesterol concentrations have been repeatedly shown to be a risk factor for AD [52].

Another recently described potential risk factor for AD is testosterone deficiency [53] which itself can be associated with cognitive deficit [54]. HIV infected patients are frequently found to be testosterone deficient with prevalence rates as high as 30% in patients with advanced disease [55].

Also of importance is the finding in both ADC and neuro-asymptomatic patients of axonal injury, similar to that which occurs in patients with head injury [56,57]. The latter group is at an increased risk of AD making it likely therefore that HIV infected patients also have an increased risk.

4.2. Evidence from basic science data

A β fibrils stimulated, by 5 to 20-fold, infection of target cells expressing CD4 and an appropriate co-receptor by multiple HIV-1 isolates, but did not permit infection of cells lacking these receptors. A β enhanced infection at the stage of virus attachment or entry into the cell. This study suggests that A β deposition may increase the vulnerability of the CNS to HIV infection [58].

The binding of HIV-1 transactivator (Tat) protein to low-density lipoprotein receptor-related protein (LRP) has been found to promote efficient uptake of Tat into neurons leading to a substantial inhibition of neuronal binding, uptake and degradation of physiological ligands for LRP, including α 2-macroglobulin, ApoE4, APP and A β -protein. In a model of macaques infected with a chimeric strain of simian-human immunodeficiency virus (SHIV), increased staining of APP was associated with Tat expression in the brains of SHIV-infected macaques with encephalitis [59].

Rempel et al. demonstrated that Tat in nM concentration can strongly inhibit NEP [28]. Thus low-level productive HIV brain infection could inhibit NEP and lead to increased A β deposition and over time AD or an AD/ADC mixed clinicopathologic entity [60]. Furthermore we have shown that A β 1–42 induces QUIN production by human macrophages and microglia [50].

Additionally, there are several other interesting correlations between the AD neuropathology and the KP [49]. The KP is switched on when microglia and astrocytes are activated. Given that there are increased numbers of activated astrocytes and microglia in AD and ADC [61] it is biologically plausible that the KP is important in both diseases [5]. Elevated serum concentrations of KYN, an early product of the KP, have been found in AD and these correlate with the level of cognitive impairment [62,63]. TRP depletion is also associated with the profound impairment of the cholinergic system found in AD [64]. Levels of QUIN are elevated in ADC and correlate with brain volume loss and severity [65,66]. We have shown that astrocytes have a critical KP enzyme missing [4]: In physiological conditions, astrocytes and neurons do not produce QUIN [67] and in fact astrocytes degrade any that is present, but they do produce excess KYN, some of which is converted to KYNA, a neuroprotectant [4]. However, under pathological conditions where the astrocyte is stimulated, excess KYN is produced, which can be taken up by monocytic lineage cells and processed through the KP to yield neurotoxic concentrations of QUIN. It seems likely that this would also be true for microglia. Experimental injury of rat brains with QUIN induces an immediate increase in extracellular glutamate within rat brains [68]. Moreover, QUIN and A β are both able to inhibit glutamate uptake in astrocytes [69,70]. Together QUIN and A β may have a synergistic effect leading to neurotoxic concentrations of glutamate. Glutamate is known as one of the major neurotoxic mediators secreted by activated HIV-1-infected macrophages [71]. There is strong evidence that ADC is associated with NMDA receptor activation [72] and more particularly NR1 and NR2A subunits [73]. Interestingly, Priestley et al. showed that QUIN acts on receptors comprising NR1 and NR2A subunits [74]. Furthermore, as mentioned, markers of lipid peroxidation are found in AD [22] and a major aspect of QUIN toxicity is lipid peroxidation. There are also published data that support a novel role for QUIN as an amplifier of inflammation. We have shown that QUIN leads astrocytes to produce large quantities of MCP-1, RANTES and IL-8 [75]. These chemokines are also involved in neuroprotection [76,77]. Moreover, QUIN can lead to up-regulation of expression of CCR3, CCR5 and CXCR4 on astrocytes [75]. This may lead to an increase of the rate of viral infection of these cells [61,78].

There are several *in vivo* or *ex vivo* studies concerning astrocyte apoptosis and HIV brain infection [79]. Thompson et al. [80] have found that there is a correlation between an increased number of HIV DNA-positive astrocytes and an increased number of apoptotic astrocytes and rapid progression of patients to dementia. Furthermore, QUIN production is directly related to the viral load in patients with ADC [81]. We previously demonstrated that HIV-1 proteins Nef and Tat lead to production of high levels of QUIN by human macrophages [82]; that inhibition of QUIN production by HIV-1 infected macrophages strongly reduces neurotoxicity [83]; and finally that QUIN can amplify neuroinflammation and increase astroglial expression of HIV-1 co-receptors [78]. Interestingly, viral induction ofIDO in human macrophages differs according to particular HIV-1 isolates [84] and similarly, diverse HIV-1 primary isolates have different effects on astrocyte apoptosis [85].

Taken together these data provide a direct link between the astrocyte apoptosis and increased QUIN in ADC brains via a new mechanism by which HIV-1 may be involved in astrocyte apoptosis directly and indirectly via QUIN production.

Using immunohistochemistry, we provided the first evidence that IDO is over-expressed and QUIN over-produced within AD brains [51]. Both IDO and QUIN were detected in microglia, astrocytes and neurons within sections of the medial temporal lobe, frontal and cingulate cortex. Microglial and astrocytic expression of IDO and QUIN was highest throughout the perimeter of senile plaques, which were also diffusely labelled. Within the neuronal cell body in AD tissue, QUIN was present in granular deposits and was also seen in uniform labelling of NFT [51]. In ADC brains, co-expression of β -APP (β -APP globules indicating chronic cerebral damage) and HIV p24 has been found in areas with HIV-related lesions [56].

We observed an interesting association between cellular accumulation of QUIN in neurons and the presence of tangles. In contrast, murine microglia do not produce QUIN [86,87] and in murine models of AD no tangles are made [88]. This has allowed us to postulate a direct effect of QUIN on NFT formation in humans.

5. Hypothetical model

We hypothesize that there is a predisposition to amyloid plaque formation in the brain in ADC associated with neuroinflammation and the presence of HIV-1. In both AD and ADC, interaction of macrophages and astrocytes appear to play an important role [37]. We previously showed that A β 1–42 is able to induce QUIN production by macrophages/microglia [89]. Some HIV strains [84] and viral proteins, particularly Tat and Nef [82], are able to do the same. QUIN can induce astrocyte activation with the release of inflammatory chemokines such MCP-1 and expression of chemokine receptors CXCR4, CCR3 and CCR5. These latter effects may lead to an increase of the rate of viral infection of the glial cells [78]. Pulliam et al. [28] very recently demonstrated that Tat in nM concentration can strongly inhibit an important A β degrading enzyme called neprilysin (NEP) or CD10 [26].

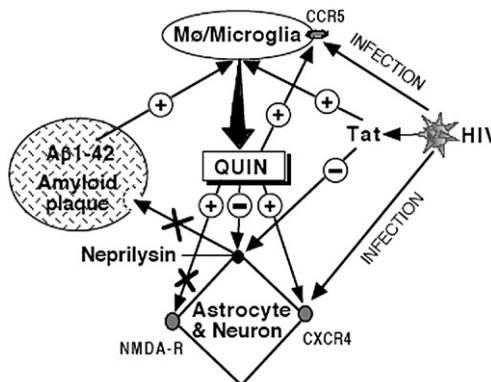


Fig. 1.

The NEP is a bound zinc metalloproteinase. NEP degrades both A β 1–40 and A β 1–42 *in vitro* and *in vivo* [27]. In the CNS of elder HIV patients, Tat released by infected cells can inhibit NEP and with normal A β catabolism. Over time, this imbalance could result in a neuropathologic accumulation of A β and the formation of senile plaques [28].

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