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Review Article

Amyloid Beta Accumulation in HIV-1 Infected Brain: The Role of Altered Cholesterol Homeostasis

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Abstract

The long-term survival of HIV-1 infected individuals credited to the availability and use of effective antiretroviral therapy (ART) is unfortunately now accompanied by an almost 50% prevalence of HIV-1 associated neurocognitive disorder (HAND). Increasingly, it has been realized that HIV-1 infected people on ART have clinical and pathological observations of Alzheimer's disease (AD)-like manifestations including neurocognitive problems, intraneuronal accumulation of amyloid beta (Aβ) protein, and disturbed synaptic integrity. Part of the current challenge facing the medical community and people living with HIV-1 infection is that the pathogenesis of HAND remains unclear, and little is known about how AD-like pathology is developed as a result of HIV-1 infection and/or long-term ART treatment. Here we discuss the potential role of altered plasma cholesterol homeostasis, a prominent feature of HIV-1 infection, on the development of intraneuronal Aβ accumulation in HIV-1 infected brain. We speculate that elevated plasma LDL cholesterol, once it enters brain parenchyma via an increasingly leaky BBB, can be internalized by neurons via receptor-mediated endocytosis, a process that could promote internalization of amyloid beta precursor protein (AβPP). Unlike brain *in situ* synthesized apoE-cholesterol, apoB-containing LDL-cholesterol could lead to cholesterol accumulation thus disturbing neuronal endolysosome function and ultimately the accumulation of intraneuronal Aβ in HIV-1 infected brain.

ABBREVIATIONS

AD: Alzheimer's Disease; Aβ: Amyloid Beta; AβPP: Amyloid Beta Precursor Protein; ART: Antiretroviral Therapy; BACE1: Beta-Site AβPP Cleavage Enzyme 1; BBB: Blood-Brain Barrier; HAND: HIV-1 Associated Neurocognitive Disorder; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein

INTRODUCTION

Greater than 40 million people are infected with the human immunodeficiency virus-1 (HIV-1). Encouragingly, pharmacotherapeutic treatment with antiretroviral therapeutics (ART) has effectively increased the life span of people living with HIV-1/AIDS. However, as people age with HIV-1 infection and the taking of ART, the prevalence of HIV-1 associated neurocognitive disorders (HAND) has increased [1,2]. Indeed, recent epidemiological studies indicate that the prevalence of HAND, a set of conditions ranging from subtle neuropsychological impairments to profoundly disabling HIV-1 associated dementia is greater than 50% of HIV-1 infected people in the USA [3,4]. As part of HAND in this ART era, there have been an ever-increasing number of clinical and pathological observations of Alzheimer's disease (AD)-like manifestations in people living with HIV-1 including neurocognitive problems, intraneuronal accumulation of amyloid beta (Aβ), and disturbed synaptic integrity [5-13]. Currently, the pathogenesis of HAND remains unclear, and little is known about how AD-like pathology is developed as a result of HIV-1 infection and/or long-term treatment with ART. Here, with a focus on brain deposition of Aβ we discuss the extent to which altered cholesterol homeostasis might play a role in the development of AD-like pathology in HIV-1 infected people.

Aβ DEPOSITION IN HIV INFECTED BRAIN

Brain deposition of Aβ, a proteolytic cleavage product of amyloid beta precursor protein (AβPP) catalyzed by beta-site AβPP cleavage enzyme 1 (BACE1) and γ-secretase, continues to be considered an important pathogenic factor of AD [14,15]. As such, gene mutations in AβPP and presenilin-1 (a γ-secretase) can lead to familial early onset AD, a relatively rare form of AD [14]. Endolysosomes are an important site for Aβ amyloidogenesis

and it is therefore obvious that trafficking of AβPP into endolysosomes would play a role in amyloidogenic processing of internalized AβPP [16-18]. Once AβPP is accumulated in the acidic environment of endolysosomes, amyloidogenic metabolism of AβPP is catalyzed by BACE-1 and γ-secretase [19-22]. Amyloidogenesis of endosome-derived Aβ is further influenced by the ability of Aβ degradation to be catalyzed by lysosome-resident cathepsins [23]. Remaining levels of Aβ can either accumulate in endolysosomes as intraneuronal Aβ or it can undergo exocytotic release into extracellular spaces, where diffuse Aβ plaque can form. Thus, amyloidogenic processing of AβPP can be enhanced by such factors as those that promote AβPP internalization [24], those that enhance protein levels and/or activities of BACE-1 and/or γ-secretase, those that prevent AβPP recycling back to the cell surface [25], and those that impair Aβ degradation in lysosomes [26].

Growing evidence indicates that brain deposition of Aβ is increased in HIV-1 infected people [5,7,12,27-30]. Importantly, such increased brain deposition of Aβ correlates with HIV-associated cognitive impairment [31]. Although there exists some evidence of increased levels of extracellular deposition, Aβ is predominantly increased in the neuronal soma and dystrophic axons in brain of HIV-1 infected individuals [7,8,12]. In terms of possible underlying mechanisms, the HIV-1 proteins Tat and gp120 [32-35] as well as ART [29,36] have been implicated as possible causes of the neuronal deposition of Aβ. In addition to the above mechanisms, we posit and discuss here an alternative hypothesis that links altered cholesterol homeostasis to brain deposition of Aβ in HIV-infected brain.

ALTERED CHOLESTEROL HOMEOSTASIS BY HIV INFECTION AND ART

Dyslipidemia, characterized by elevated levels of triglycerides and low-density lipoprotein (LDL) cholesterol and decreased levels of high-density lipoprotein (HDL) cholesterol, is frequently observed in HIV-1 infected people and has become an ever-increasing problem in the ART era [37]. At this time, it is unclear the underlying mechanism by which the development of the dyslipidemia is caused by HIV-1 infection [38] and/or use of long term ART treatment [39]. Here, we will discuss whether altered cholesterol homeostasis could lead to intraneuronal accumulation of Aβ in HIV-1 infected brain.

ALTERED CHOLESTEROL HOMEOSTASIS CONTRIBUTES TO THE DEVELOPMENT OF AD

Altered cholesterol homeostasis in general and elevated LDL cholesterol more specifically represents a robust risk factor for AD pathogenesis. Evidence in support of this increased risk for AD onset and severity comes from various studies including findings that the presence of the APOE4 allele is the single strongest genetic risk factor for sporadic AD [40-43], and apoE, the product of the APOE gene, is a main carrier protein for the transport of cholesterol and lipids between astrocytes and neurons. Indeed, apoE4 may not only affect brain cholesterol homeostasis, it is also clearly associated with elevated levels of LDL cholesterol and decreased levels of HDL cholesterol [44,45]. In addition, elevated levels of plasma LDL cholesterol, independent of APOE genotypes, can increase brain deposition of Aβ as evidenced by epidemiological findings [46-48] and findings from animal studies conducted with AβPP transgenic mice [49,50], guinea pigs [51], rabbits [52,53], and rats [54]. Similarly, and again independent of the APOE genotype, low levels of HDL cholesterol are also associated with brain deposition of Aβ and an increased risk of developing AD, whereas high levels of HDL cholesterol appear to protect against the occurrence of AD [46,48,55,56]. Thus, altered levels of circulating cholesterol, independent of APOE genotype status, are associated with the pathogenesis of AD.

ELEVATED LDL CHOLESTEROL PROMOTES INTRANEURONAL ACCUMULATION OF Aβ

In brain under physiological conditions, the blood-brain barrier (BBB) restricts plasma lipoproteins, especially the larger LDL particles, from entering brain parenchyma and brain cholesterol is almost completely dependent on *in situ* synthesis of apoE cholesterol by astrocytes [57]. As such, apoB, the major LDL cholesterol carrier protein in circulating blood, is usually not present in normal brain [58]. However, under conditions when and where the BBB is disrupted, as occurs early in AD [59-64], LDL cholesterol can enter brain parenchyma, where it has the opportunity to contribute to AD pathogenesis. Indeed, apoB100 is present in AD brain and co-localizes with Aβ [53,58,65-67], and rabbits fed a diet enriched in cholesterol exhibit elevated levels of LDL cholesterol, disruptions in the integrity of the BBB [53,68] and increased brain levels of apoB-100, the exclusive apolipoprotein of LDL-cholesterol thus a marker of peripherally-derived cholesterol [53].

Neurons up-take cholesterol via receptor-mediated endocytosis, a process where lipoproteins bound to their receptors are internalized, transported to endolysosomes, hydrolyzed to free cholesterol, and from where free cholesterol is transported to various intracellular compartments via a mechanism involving the Niemann-Pick type C (NPC) type-1 (NPC1) and -2 (NPC2) proteins [69-71]. To accommodate the need for neuronal cholesterol, a large number of receptors for cholesterol uptake, including LDLR, very low-density lipoprotein receptor (VLDLR), LRP-1, apoE receptor, and sorLA-1, are highly expressed on neurons [72-75]. In addition, low levels of scavenger receptors B1 (SR-B1) and receptors for oxidized LDL are also expressed in neurons [76-78]. Thus, apoB containing LDL cholesterol, once it enters brain, can be internalized by neurons using receptors for cholesterol uptake. Because some of these receptors for cholesterol uptake, including LRP1 and LRP10, have been shown to interact with AβPP and affect AβPP trafficking [18,79,80], LDL cholesterol internalization could promote AβPP internalization into neuronal endolysosomes and enhance amyloidogenic processing of AβPP. In support, we have shown that LDL cholesterol treatment promotes AβPP internalization and increases amyloidogenic processing of AβPP in endolysosomes of primary cultured neurons [81].

Because apoB and apoE have different affinities for receptors for cholesterol uptake, neuronal uptake of apoB containing LDL cholesterol may result in drastic differences in intracellular cholesterol transport and distribution than that of apoE cholesterol. Additionally, while apoB leads to cholesterol being targeted by the lysosome degradation pathway [82,83], apoE mediates cholesterol recycling [84-86]. Thus, neuronal uptake

of apoB containing LDL cholesterol may lead to cholesterol accumulation in endolysosomes thereby disturbing endolysosome structure and function, a very early pathological feature of AD [19,87-90]. This concept is supported experimentally by findings by others and us that LDL cholesterol treatment increases cholesterol accumulation in neuronal endolysosomes and leads to endolysosome enlargement, elevation of endolysosome pH, and reduced endolysosome enzyme activities [81,91].

Because endolysosomes are the sites at which internalized AβPP cleavage to Aβ is catalyzed by BACE-1 and γ-secretase [19-22], and because lysosomes are the sites Aβ can be further degraded by cathepsins [23], disturbed endolysosome structure and function could lead to intraneuronal Aβ accumulation [92-94]. Indeed, we found that treatment of neurons with LDL cholesterol increased endolysosome accumulation of BACE-1, enhanced BACE-1 activity, decreased cathepsin activity, and increased endolysosome accumulation of Aβ [81].

In short, elevated plasma LDL cholesterol, once it enters brain parenchyma through a leaky BBB, can be internalized by neurons via receptor-mediated endocytosis thus leading to cholesterol accumulation in endolysosomes, disturbed structure and function of neuronal endolysosomes, enhanced amyloidogenic processing of AβPP, and increased intraneuronal Aβ accumulation. As such, elevated plasma LDL, as occurs in HIV infection, could contribute to intraneuronal Aβ accumulation in HIV-infected brain. Such a notion is supported by the following evidence.

BBB IS LEAKY IN HIV-INFECTED BRAIN

The BBB, an exclusive component of the endothelium of brain capillaries where tight junctions are formed, is an important physical and metabolic barrier that helps keep the central nervous system separate from the systemic circulation [95-97] thus regulating and protecting the microenvironment of the brain. The protection afforded by the BBB is essential for neuronal survival and proper CNS functioning [98] and once disrupted synaptic and neuronal functions can be compromised [99]. It is well documented that the BBB is leaky in HIV-1 infected brain, as evidenced by functional imaging (MRI or PET) and by the leakage of serum proteins in CSF or in postmortem brain [100,101]. Such BBB dysfunction is not only a feature of HIV-1 CNS infection but it has a crucial impact on the pathogenesis of HAND [100,101]. Breach of the BBB allows HIV-1 virus carried in monocytes to enter brain, where HIV-1 virus infects microglia cells and astrocytes. These infected cells further release inflammatory factors and neurotoxic viral factors that contribute to neuronal injury and the development of HAND [102,103]. Under conditions when the BBB is leaky, elevated plasma LDL cholesterol could also enter brain parenchyma and disturb neuronal cholesterol homeostasis such as cholesterol accumulation in endolysosomes. In support, dysregulation of lipids and cholesterol metabolism in brain can alter lipid storage in neurons and can contribute to in the pathogenesis of HAND [104,105]. Further studies are warranted to determine the extent to which altered brain cholesterol homeostasis is a result of altered levels of circulating cholesterol.

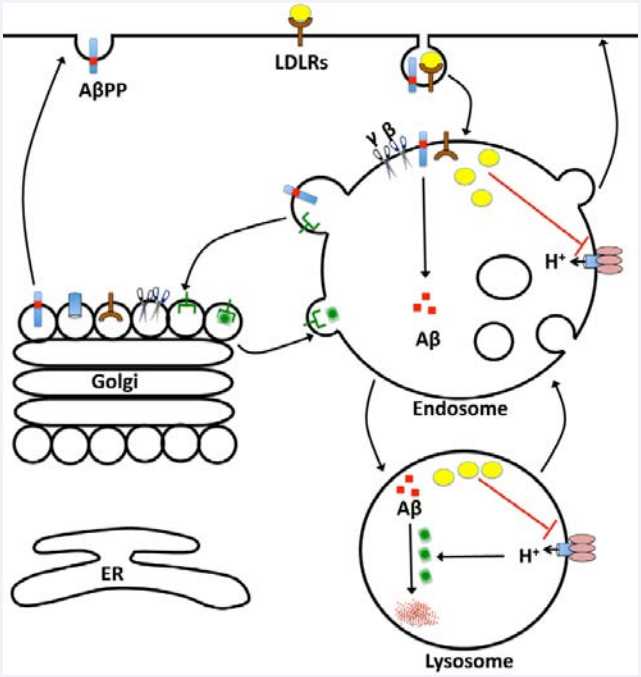

Figure 1 Proposed model of LDL cholesterol-induced intraneuronal Aβ accumulation in HIV-1 infected brain. Elevated plasma LDL cholesterol, once it enters brain, can be internalized by neurons via receptor-mediated endocytosis. The LDL cholesterol internalization process promotes AβPP internalization. Increased apoB containing LDL-cholesterol can lead to cholesterol accumulation in endolysosomes thus elevating endolysosome pH and impairing endolysosome function. Elevation of endolysosome pH can lead to increased BACE-1 protein levels and enhanced BACE-1 activity that leads to amyloidogenic processing of AβPP, and can reduce cathepsin activity thus impairing Aβ degradation in lysosomes.

ENDOLYSOSOME DYSFUNCTION IS A PATHOLOGICAL FEATURE OF HAND

Maintaining an optimum acidic environment is critical for physiologically important functions of endolysosomes, and neurons are especially vulnerable to perturbations of endolysosome pH, because neurons are long-lived post-mitotic cells that possess an elaborate endolysosome system for quality control and because they are extraordinarily polarized cells with extensive processes that require endolysosomes for membrane trafficking to maintain physiologically important neuronal functions including neurotransmitter release, neurite outgrowth, and synaptic plasticity. As such, endolysosome dysfunction could lead to neurodegeneration [106-108]. Recently, altered endolysosome structure and function has been reported in HIV-infected brain [109-112]. More importantly and relevant to our perspective, it has been shown that Aβ is accumulated in neuronal endolysosomes in HIV-infected brain [8]. As mentioned earlier, endolysosomes are major sites where Aβ is produced from internalized AβPP [16-18]. The fate of endosome-derived Aβ is further influenced by the ability of Aβ degradation to be catalyzed by lysosome-resident cathepsins [23]. Thus endolysosome dysfunction can impair Aβ degradation in lysosomes leading to intraneuronal accumulation of Aβ [26]. In support, we have

shown the elevation of endolysosome pH is accompanied by increased Aβ accumulation in neuronal endolysosomes [34,81].

CONCLUSION

We speculate that elevated plasma LDL cholesterol, once it enters brain parenchyma via a leaky BBB, can be internalized by neurons via receptor-mediated endocytosis. The LDL cholesterol internalization process promotes AβPP internalization, because of the physical interactions between LDLRs and AβPP. Unlike brain *in situ* synthesized apoE-cholesterol, increased apoB-containing LDL-cholesterol could lead to cholesterol accumulation in endolysosomes thus elevating endolysosome pH and impairing endolysosome function. Elevation of endolysosome pH on one hand could lead to increased BACE-1 protein levels and enhanced BACE-1 activity that leads to amyloidogenic processing of AβPP, and on the other hand could reduce cathepsin activity thus impairing Aβ degradation in lysosomes, thus leading to intraneuronal Aβ accumulation, as occur in HIV-infected brain (Figure 1).

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