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# Lipoproteins and Apolipoproteins in Alzheimer's Disease

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## 1. Introduction

Alzheimer's disease (AD) represents the so-called "storage disorder" of amyloid  $\beta$  ( $A\beta$ ). The AD brain contains soluble and insoluble  $A\beta$ , both of which have been hypothesized to underlie the development of cognitive deficits or dementia (1-3). The steady-state level of  $A\beta$  is controlled by the generation of  $A\beta$  from its precursor, the degradation of  $A\beta$  within the brain, and transport of  $A\beta$  out of the brain. The imbalance among three metabolic pathways results in excessive accumulation and deposition of  $A\beta$  in the brain, which may trigger a complex downstream cascade (e.g., primary amyloid plaque formation or secondary tauopathy and neurodegeneration) leading to memory loss or dementia in AD. Accumulated lines of evidence indicate that such a memory loss represents a synaptic failure caused directly by soluble  $A\beta$  oligomers ( $A\beta$ Os) (4-6), whereas amyloid fibrils may cause neuronal injury indirectly via microglial activation (7). Many attentions are paid to understand the mechanism underlying the neurotoxic action of  $A\beta$ Os so far. However, the exact metabolic conditions controlling the *in vivo* generation of soluble  $A\beta$ Os has been out of attention.

Several lines of evidence indicated that lipidic environments in the central nervous system (CNS) represent one of the prevailing metabolic conditions. We then hypothesized that an alteration of the lipoprotein-soluble  $A\beta$  interaction in the CNS is capable of initiating and/or accelerating the cascade favoring  $A\beta$  assembly (8). We found that dissociation of  $A\beta$ 42 from lipoprotein in the cerebrospinal fluid from AD accelerates  $A\beta$ 42 assembly (9). Thus, lipoprotein is a key molecule to maintain monomeric soluble  $A\beta$ 42 in CNS.

In this chapter, we review the issue regarding how lipoprotein and apolipoproteins contribute to physiological metabolic conditions. Then, we focus on how they constitute the

AD-related metabolic conditions in the CNS. We are certain that these points of view introduce a novel approach to find a therapeutic intervention for AD.

## 2. Lipoproteins, apolipoproteins, and A $\beta$ metabolism in the CNS

In the CNS, we need to be aware that cholesterol metabolism is quite different from that in systemic circulation. Lipidic environments in the CNS were regulated by HDL-like lipoproteins, mainly lipidated apolipoprotein E (apoE), which is in charge of cholesterol transport to and from neurons (10, 11). This is also the case in lipidated apolipoprotein J (apoJ) (12). In addition to lipid trafficking, apoE or apoJ as a form of HDL-like lipoprotein plays a major role in A $\beta$  metabolism in the CNS. Both apolipoproteins are well known as major carrier proteins for A $\beta$  (13-17). Interestingly, transgenic mouse models of AD (apoE<sup>-/-</sup>/apoJ<sup>-/-</sup>) revealed that both apolipoproteins regulate in a cooperative manner the clearance and the deposition of A $\beta$  in brain (18). The hypothetical pathways involved in the clearance of CNS A $\beta$  are efflux of A $\beta$  into the plasma via blood-brain barrier (BBB). Two lipoprotein-receptors, LRP-1 and LRP-2, seem to be responsible for efflux of lipoprotein-free or lipoprotein-associated (apoJ-associated) A $\beta$  from the brain to blood, respectively (19). *In vivo* relevance of LRP-1-mediated A $\beta$  transport has been confirmed in transgenic mice expressing low LRP-1-receptor and APP, which develops extensive A $\beta$  accumulation much faster than transgenic mice expressing high level of APP (20). Reduced expression of brain endothelial LRP-1 was also observed in AD patients, which was associated with impaired A $\beta$  clearance and cerebrovascular accumulation. LRP-2 appeared to function bi-directionally (influx vs efflux) at BBB. In contrast to LRP2-mediated influx (21), LRP2-mediated efflux of brain A $\beta$  was actively operated under physiological concentration of either A $\beta$  or apoJ (19). Interestingly, a recent study shows that apoE4 binding to A $\beta$  redirects its clearance from LRP-1 to VLDLR, which resulted in slower efflux of brain A $\beta$  than LRP-1 (22). In contrast, apoE2-A $\beta$  and apoE3-A $\beta$  complexes are cleared at BBB via both LRP-1 and VLDLR at a substantially faster rate than apoE4-A $\beta$  complexes (22). Impairment of the above-mentioned receptor-mediated clearance at BBB could contribute to the pathogenesis of AD. Alternatively, ApoE4-HDL shows less cholesterol exchange between lipid particles and the neuronal membrane as compared with apoE3-HDL (23), leading to altered membrane functions, e.g., signal transduction, enzyme activities, ion channel properties, and conformation of sA $\beta$  peptides, which contribute to the disease-related metabolic conditions. Furthermore, when the generation of HDL-like lipoproteins in the AD mouse model is suppressed or overexpressed via the specific regulation of ATP-binding cassette A1 (ABCA1), A $\beta$  deposition exhibits augmentation or reduction, respectively, which depends on the degree of ABCA1-mediated lipidation of apoE in the CNS (24, 25). From these points of view, lipidic environments in the CNS represent one of the prevailing metabolic conditions. We hypothesized that an alteration of the lipoprotein-sA $\beta$  interaction in the CNS is capable of initiating and/or accelerating the cascade favoring A $\beta$  assembly. Thus, we postulate that

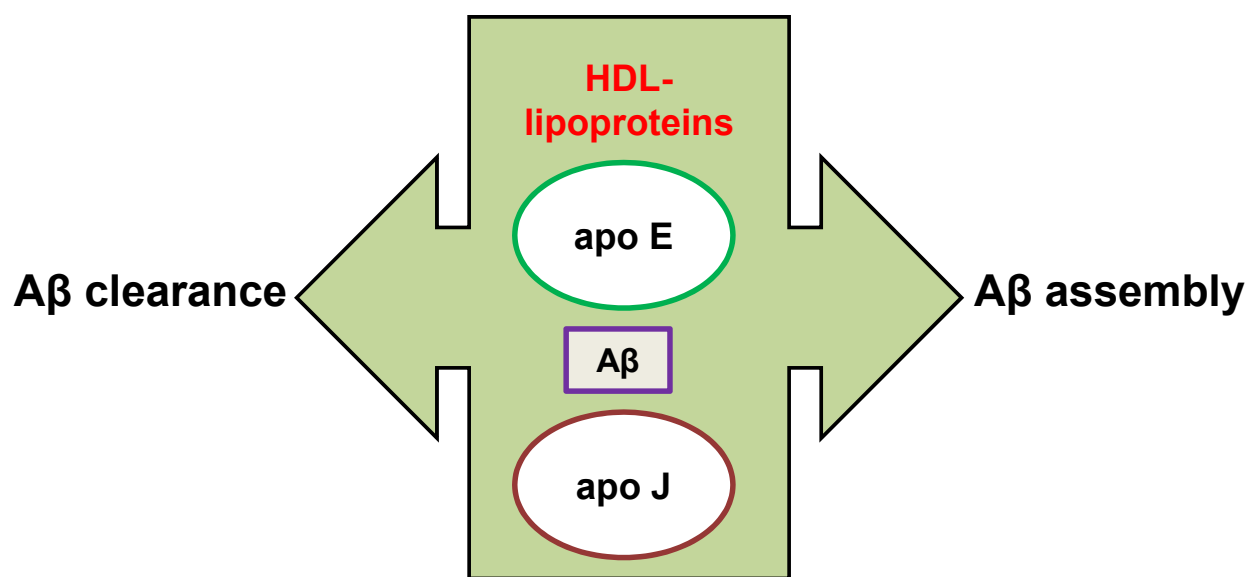
lipoproteins or apolipoproteins may regulate the metabolic conditions controlling the *in vivo* generation of soluble A $\beta$ Os.

### **3. A $\beta$ is present in either lipoprotein-free or lipoprotein-associated form in brain parenchyma**

To assess the above-mentioned issue, we examined whether the dissociation of sA $\beta$  from lipoprotein-particles occurs in the brain. The combination of size exclusion chromatography (SEC) and enzyme-linked immunosorbent assay (ELISA) revealed that the dissociation of sA $\beta$  from lipoprotein-particles occurs in brain parenchyma and the presence of soluble dimeric lipoprotein-free A $\beta$  in AD brains (8). These findings may support the hypothesis that functionally declined lipoproteins may be major determinants in the production of metabolic conditions leading to higher levels of soluble dimeric SDS-resistant form of A $\beta$  in AD brains (8, 26). At this moment, it remains undetermined whether dissociation of A $\beta$  from lipoprotein or less association of A $\beta$  to lipoproteins accounts for such a metabolic conditions. To further verify this hypothesis, we focused on the entorhinal cortex (EC), followed by biochemical analyses using an anti-oligomer specific antibody, namely 2C3 (9, 27). Fifty brains obtained from healthy elderly are composed of three Braak NFT stages; Braak NFT stages I-II (n=35, normal control); Braak NFT stages III-IV (n=13, MCI stage); Braak NFT stages IV-V (n=2, AD stages). Immunoblot analysis of the delipidated EC employing monoclonal 2C3 revealed that the accumulation of soluble 12-mers precedes the appearance of neuronal loss or cognitive impairment, and is enhanced as the Braak neurofibrillary tangle (NFT) stages progress, indicating that the ECs of AD patients indeed bear metabolic conditions that accelerate A $\beta$  assembly.

### **4. A $\beta$ is present in either lipoprotein-free or lipoprotein-associated form in cerebrospinal fluid (CSF)<sup>9</sup>**

The presence of lipoprotein-free sA $\beta$ Os in CSF was also assessed in age-matched normal controls (NCs) and patients with Alzheimer's disease (AD) by SEC and ELISA specific for either A $\beta$ Os or A $\beta$ Ms. The SEC experiment using pooled CSF revealed that the dissociation of sA $\beta$ Ms from lipoprotein particles indeed occurs in CSF, which was lower in AD than in NCs. Furthermore, the SEC experiment using lipoprotein-depleted pooled CSF (LPD-CSF) confirmed the presence of oligomeric 2C3 conformers (4- to 35-mers), which appeared to be higher in AD patients than in NCs. To address the issue on the presence of any metabolic conditions favoring A $\beta$  assembly, we compared the levels of lipoprotein-free sA $\beta$ Ms and sA $\beta$ Os in LPD-CSF from the 12 sporadic AD patients and 13 NCs to evaluate the A $\beta$ Os/A $\beta$ Ms ratio (the O/M index). The levels of 2C3 oligomeric conformers composed of A $\beta$ 42 are significantly higher in AD patients than in NCs. The O/M index for either A $\beta$ 42 or A $\beta$ 40 is also significantly higher in AD patients than in NCs. Of note, the relative amounts of total lipoprotein-associated sA $\beta$ Ms (~70%) versus lipoprotein-free sA $\beta$ Ms (~30%) remained



**Figure 1.** Hypothetical metabolic conditions favoring A $\beta$  assembly. Functionally declined lipoproteins may accelerate the generation of metabolic conditions leading to higher levels of soluble A $\beta$  assembly in the CNS.

essentially unchanged in sporadic AD patients as compared with NCs. However, the relative amounts of lipoprotein-free A $\beta$ 42 was significantly lower in the sporadic AD patients ( $9.3 \pm 3.9$  %) than in NCs ( $13.2 \pm 4.5$  %), which is in accordance with our above-mentioned finding that the level of oligomeric 2C3 conformers composed of A $\beta$ 42 was significantly elevated in AD patients. Thus, it is likely that the conversion of lipoprotein-free monomeric soluble A $\beta$ 42 into oligomeric assembly preferentially occurs in AD CSF, mirroring the disease-related metabolic conditions in the brain parenchyma.

## 5. Summary

We previously reported that ~90% of sA $\beta$ Ms that circulate in normal plasma is associated with lipoprotein particles (27). From the above data, it is plausible to assume that about 70% of CSF sA $\beta$ Ms is normally associated with lipoprotein particles, indicating that CNS constitutes a risky environment where the lipoproteins-sA $\beta$ Ms interaction is impaired, leading to A $\beta$  assembly. From this point of view, a key molecule to maintain monomeric sA $\beta$ 42 metabolism in CNS appears to be HDL-like lipoprotein particles. In this sense, the dissociation of sA $\beta$ 42 from or the lack of association with HDL-like lipoprotein particles not only constitutes a potential mechanism to initiate and/or accelerate the cascade favoring A $\beta$ 42 assembly in the brain, but also results in a reduced clearance of physiological lipoprotein-associated sA $\beta$ 42 peptides in the brain. Thus, above-mentioned CNS environments may strongly affect conformation of sA $\beta$  peptides, resulting in the conversion of sA $\beta$ 42 monomers into sA $\beta$ 42 assembly. The findings suggest that functionally declined lipoproteins may accelerate the generation of metabolic conditions leading to higher levels of sA $\beta$ 42 assembly in the CNS.

## Author details

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