Chapter 25

Lipoproteins and Apolipoproteins in Alzheimer's Disease

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http://dx.doi.org/10.5772/45977

1. Introduction

Alzheimer's disease (AD) represents the so-called "storage disorder" of amyloid β (Aβ). The AD brain contains soluble and insoluble Aβ, both of which have been hypothesized to underlie the development of cognitive deficits or dementia (1-3). The steady-state level of Aβ is controlled by the generation of Aβ from its precursor, the degradation of Aβ within the brain, and transport of Aβ out of the brain. The imbalance among three metabolic pathways results in excessive accumulation and deposition of Aβ 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 Aβ oligomers (AβOs) (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 AβOs so far. However, the exact metabolic conditions controlling the *in vivo* generation of soluble AβOs 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 Aβ interaction in the CNS is capable of initiating and/or accelerating the cascade favoring Aβ assembly (8). We found that dissociation of Aβ42 from lipoprotein in the cerebrospinal fluid from AD accelerates Aβ42 assembly (9). Thus, lipoprotein is a key molecule to maintain monomeric soluble Aβ42 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 Aβ 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 Aβ metabolism in the CNS. Both apolipoproteins are well known as major carrier proteins for Aβ (13-17). Interestingly, transgenic mouse models of AD (apoE$^{-/-}$/apoJ$^{-/-}$) revealed that both apolipoproteins regulate in a cooperative manner the clearance and the deposition of Aβ in brain (18). The hypothetical pathways involved in the clearance of CNS Aß are efflux of Aß 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) Aß from the brain to blood, respectively (19). *In vivo* relevance of LRP-1-mediated Aß transport has been confirmed in transgenic mice expressing low LRP-1-receptor and APP, which develops extensive Aß accumulation much faster than transgenic mice expressing high level of APP (20). Reduced expression of brain endotherial LRP-1 was also observed in AD patients, which was associated with impaired Aß clearance and cerebrovascular accumulation. LPR-2 appeared to function bi-directionally (influx vs efflux) at BBB. In contrast to LRP2-mediated influx (21), LPR2-mediated efflux of brain Aß was actively operated under physiological concentration of either Aß or apoJ (19). Interestingly, a recent study shows that apoE4 binding to Aß redirects its clearance from LRP-1 to VLDLR, which resulted in slower efflux of brain Aß than LRP-1 (22). In contrast, apoE2-Aß and apoE3-Aß complexes are cleared at BBB via both LPR-1 and VLDLR at a substantially faster rate than apoE4-Aß 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 sAß 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), Aβ 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-sAβ interaction in the CNS is capable of initiating and/or accelerating the cascade favoring Aß assembly. Thus, we postulate that

lipoproteins or apolipoproteins may regulate the metabolic conditions controlling the *in vivo* generation of soluble AβOs.

3. Aß 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 sAß 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 sAß from lipoprotein-particles occurs in brain parenchyma and the presence of soluble dimeric lipoprotein-free Aß 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 Aβ in AD brains (8, 26). At this moment, it remains undetermined whether dissociation of Aβ from lipoprotein or less association of Aβ 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 neurofibrially tangle (NFT) stages progress, indicating that the ECs of AD patients indeed bear metabolic conditions that accelerate Aβ assembly.

4. Aß is present in either lipoprotein-free or lipoprotein-associated form in cerebrospinal fluid (CSF)[9]

The presence of lipoprotein-free sAβOs 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 AβOs or AβMs. The SEC experiment using pooled CSF revealed that the dissociation of sAβMs 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 Aβ assembly, we compared the levels of lipoprotein-free sAβMs and sAβOs in LPD-CSF from the 12 sporadic AD patients and 13 NCs to evaluate the AβOs/AβMs ratio (the O/M index). The levels of 2C3 oligomeric conformers composed of Aβ42 are significantly higher in AD patients than in NCs. The O/M index for either Aβ42 or Aβ40 is also significantly higher in AD patients than in NCs. Of note, the relative amounts of total lipoprotein-associated sAβMs (~70%) versus lipoprotein-free sAβMs (~30%) remained

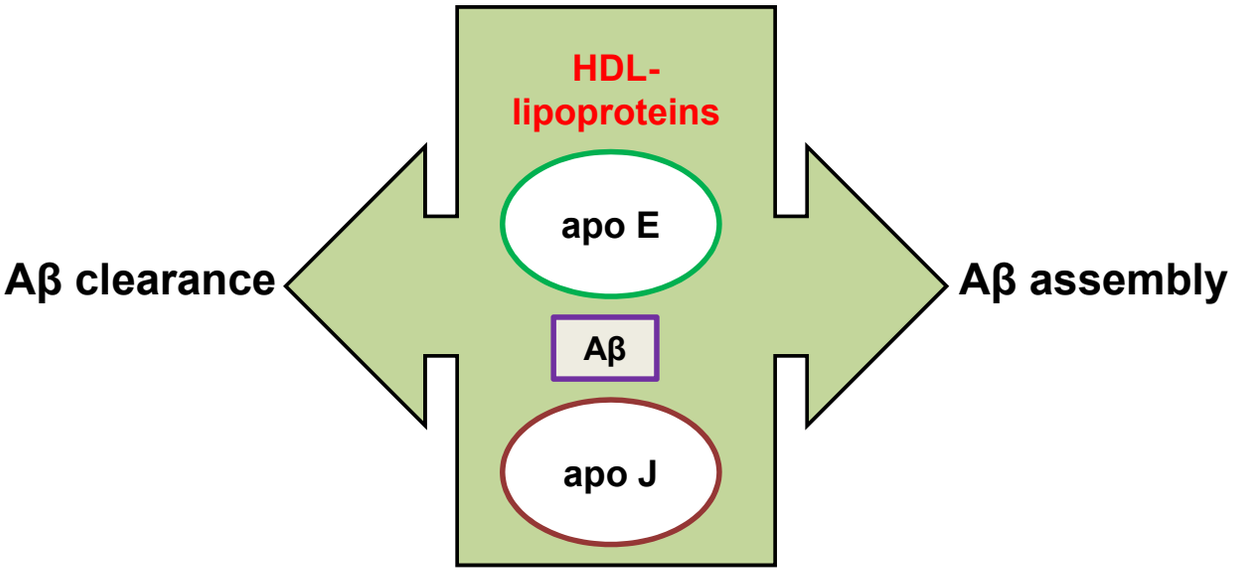

Figure 1. Hypothetical metabolic conditions favoring Aβ assembly. Functionally declined lipoproteins may accelerate the generation of metabolic conditions leading to higher levels of soluble Aβassembly in the CNS.

essentially unchanged in sporadic AD patients as compared with NCs. However, the relative amounts of lipoprotein-free Aβ42 was significantly lower in the sporadic AD patients (9.3 ± 3.9 %) than in NCs (13.2 ± 4.5 %), which is in accordance with our above-mentioned finding that the level of oligomeric 2C3 conformers composed of Aβ42 was significantly elevated in AD patients. Thus, it is likely that the conversion of lipoprotein-free monomeric soluble Aβ42 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 sAβMs 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 sAβMs is normally associated with lipoprotein particles, indicating that CNS constitutes a risky environment where the lipoproteins-sAβMs interaction is impaired, leading to Aβ assembly. From this point of view, a key molecule to maintain monomeric sAβ42 metabolism in CNS appears to be HDL-like lipoprotein particles. In this sense, the dissociation of sAβ42 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 Aβ42 assembly in the brain, but also results in a reduced clearance of physiological lipoprotein-associated sAβ42 peptides in the brain. Thus, above-mentioned CNS environments may strongly affect conformation of sAβ peptides, resulting in the conversion of sAβ42 monomers into sAβ42 assembly. The findings suggest that functionally declined lipoproteins may accelerate the generation of metabolic conditions leading to higher levels of sAβ42 assembly in the CNS.

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