

REVIEW

Evidence for impaired amyloid β clearance in Alzheimer's disease

Kristin R Wildsmith*¹, Monica Holley², Julie C Savage², Rebecca Skerrett² and Gary E Landreth²

Abstract

Alzheimer's disease (AD) is a common neurodegenerative disease characterized by the accumulation of extracellular plaques and intracellular tangles. Recent studies support the hypothesis that the accumulation of amyloid beta ($A\beta$) peptide within the brain arises from an imbalance of the production and clearance of $A\beta$. In rare genetic forms of AD, this imbalance is often caused by increased production of $A\beta$. However, recent evidence indicates that, in the majority of cases of AD, $A\beta$ clearance is impaired. Apolipoprotein E (ApoE), the dominant cholesterol and lipid carrier in the brain, is critical for $A\beta$ catabolism. The isoform of ApoE and its degree of lipidation critically regulate the efficiency of $A\beta$ clearance. Studies in preclinical models of AD have demonstrated that coordinately increasing levels of ApoE and its lipid transporter, ABCA1, increases the clearance of $A\beta$, suggesting that this pathway may be a potential therapeutic target for AD.

Introduction

Alzheimer's disease (AD) is the most common form of dementia. It affects nearly 27 million people worldwide, and an estimated 4.6 million new cases were diagnosed this year. Nearly 60% of those afflicted live in the Western world and the majority of these individuals are over 65 [1]. The memory loss and cognitive decline that accompany AD impart a heavy burden both emotionally and financially on patients and their families. Pathologically, AD is characterized by the presence of extracellular plaques composed of aggregated amyloid beta ($A\beta$) and intraneuronal tangles composed of hyperphosphorylated tau. $A\beta$ is a peptide formed by the sequential cleavage of amyloid precursor protein (APP) by β -secretase (BACE1)

and γ -secretase. Evidence from genetic, biochemical, and animal model studies strongly supports the hypothesis that $A\beta$ is a causative agent in the pathogenesis of AD [2]. There is growing evidence that impaired clearance of $A\beta$ (specifically of the hydrophobic form, $A\beta_{42}$) is responsible for the most common type of AD: sporadic or late-onset AD (LOAD). Age is the greatest overall risk factor for developing LOAD. However, the *APOE ϵ 4* allele is the strongest genetic risk factor for LOAD as the ApoE4 isoform is less efficient than ApoE2 or ApoE3 at promoting $A\beta$ clearance. In this review, *in vivo* evidence supporting the hypothesis that impaired clearance of $A\beta$ contributes to the development of AD will be covered, along with the current understanding of the influence of apolipoprotein E (ApoE) and cholesterol metabolism on $A\beta$ clearance in the central nervous system.

In vivo evidence for impaired clearance of amyloid beta in Alzheimer's disease

In vivo microdialysis is a method used to measure levels of small diffusible proteins such as soluble $A\beta$ in the extracellular interstitial fluid (ISF) of the brain. This technique allows direct monitoring of protein levels in ISF over time in an awake, behaving animal. Microdialysis probes are small enough to measure protein levels within specific cortical or subcortical brain regions such as the hippocampus, striatum, and amygdala. When coupled with a γ -secretase inhibitor to halt production of $A\beta$, microdialysis can determine the kinetics of $A\beta$ clearance [3]. Combining microdialysis in genetic models of disease with pharmacological interventions has allowed insight into mechanisms of $A\beta$ clearance. $A\beta$ can be transported across the blood-brain barrier (BBB) by low-density lipoprotein receptor (LDLR) family members [4] or undergo proteolytic degradation intracellularly in microglia and astrocytes via neprilysin and extracellularly via insulin-degrading enzyme (IDE) (for an in-depth review of $A\beta$ -degrading enzymes, see [5]).

Microdialysis studies comparing young (3 months old) and old (12 to 15 months old) PDAPP mice found that the half-life of $A\beta$ within the ISF is doubled in older animals, even when $A\beta$ production was stopped by a γ -secretase inhibitor [3]. These data imply that the brain's

*Correspondence: wildsmith.kristin@gene.com

¹Development Sciences, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA

Full list of author information is available at the end of the article

ability to clear A β diminishes with age. Hippocampal microdialysis revealed a strong correlation between the age-dependent decrease of A β_{42} in the ISF and increase of A β_{42} in the insoluble pool in APP transgenic mice [6]. Plaque growth is dependent upon high levels of A β in the ISF as APP/PS1 mice treated with a γ -secretase inhibitor demonstrated that even a modest decrease (~30%) of A β in ISF was enough to arrest plaque growth [7].

In vivo microdialysis studies determined that mice expressing the different human ApoE isoforms exhibit altered A β homeostasis in the ISF [8]. ApoE4 mice had higher ISF and hippocampal A β levels, beginning as early as 3 months of age. The half-life of A β was longest in ApoE4 mice (E4 > E3 > E2). Products of APP and rate of A β synthesis did not change between genotypes, strongly pointing to a difference in the clearance, rather than the production, of A β in the ApoE2, ApoE3, and ApoE4 mice.

One challenge of working with animal models based on the genetic forms of AD is determining how well pathologies correlate to the sporadic form of the human disease. An encouraging example supporting the translation of mouse models to humans is from *in vivo* stable isotope-labeling kinetic (SILK) experiments, which allow the determination of the rates of biosynthesis and subsequent clearance of A β peptides. These studies have demonstrated that the rates of synthesis and clearance are similar in normal subjects; thus, modest perturbations can result in accumulation of A β in the brain [9]. An important study, by Bateman and colleagues [10], demonstrated that clearance of A β is impaired by approximately 30% in patients with LOAD (5.6% per hour in AD versus 7.6% per hour in controls). Although the mechanism is still unknown, it is likely to reflect age-related impairment in A β clearance mechanisms which are influenced by *APOE* genotype.

Influence of apolipoprotein E genotype on amyloid clearance

Population studies have demonstrated that *APOE* genotype is the strongest risk factor for LOAD. Three common isoforms of ApoE, differing from each other at two amino acids, occur in humans: ApoE2 (cys112 and cys158), ApoE3 (cys112 and arg158), and ApoE4 (arg112 and arg158). Possession of one ϵ 4 allele imparts a threefold increase in risk for LOAD and two alleles impart a 12-fold increased risk [11], whereas the ϵ 2 allele decreases the likelihood of developing LOAD [12]. With a prevalence of about 15% in the population, the ϵ 4 allele has been estimated to account for 50% of all AD cases [13]. The ϵ 4 allele is also associated with an earlier age of onset [14,15] and increased A β deposition both in animal models of AD [8,16,17] and in human AD [18].

ApoE is the predominant apolipoprotein in the brain, where it is secreted primarily by astrocytes, but also by

microglia, in high-density lipoprotein (HDL)-like particles (reviewed by Bu [19]). Lipidation of ApoE is mediated primarily by ATP-binding cassette A1 (ABCA1) and secondarily by ABCG1 [20,21], and the lipidation status of ApoE has been shown to regulate its A β -binding properties [22]. Direct evidence that ABCA1-mediated lipidation influences amyloid degradation has been demonstrated in multiple transgenic models of AD. Deletion or overexpression of ABCA1 results in increased or decreased A β deposition, respectively [23-25]. Both intracellular and extracellular degradation of A β is also dramatically enhanced by lipidated ApoE [26]. ApoE4 is less stable [16,17] and a less effective lipid carrier under physiological conditions than ApoE3 or ApoE2 [27,28], and this probably contributes to its influence in AD pathogenesis. The effects of the various ApoE isoforms on A β clearance were further investigated in targeted-replacement mice expressing human ApoE isoforms at the murine locus. A β deposition and cognitive deficits are exacerbated in APP/ABCA^{+/-} targeted-replacement mice expressing ApoE4 but not ApoE3 [29].

It has been proposed that ApoE4 modulates amyloid pathology by enhancing A β deposition into plaques and reducing clearance of A β from the brain [17,30-33]. One of the first pieces of evidence linking ApoE to AD pathology was ApoE immunoreactivity in amyloid deposits and neurofibrillary tangles [34]. It has since been shown that ApoE forms complexes with A β , with ApoE2 and E3 binding A β more efficiently than E4 [35-37], and these complexes are thought to influence both seeding of fibrillar A β and transport of soluble A β . It has been shown that AD transgenic mice lacking *ApoE* have decreased plaque deposition and increased levels of soluble A β in the cerebrospinal fluid and ISF [32,38]. Crosses between AD transgenic mice and human ApoE targeted-replacement mice exhibit A β accumulation in an isoform-dependent manner, with greater A β deposition observed in ApoE4-expressing mice than those expressing E2 and E3 [8,16]. The cause of the accumulation is most likely due to the degree to which the isoforms impact A β clearance and deposition [8,39]. However, a recent study by Holtzman and colleagues [40] has provided new evidence that A β does not directly interact with ApoE to any significant extent. Instead, ApoE competes with A β in an isoform- and concentration-dependent manner for binding to lipoprotein receptor-related protein 1 (LRP1), and this could impact A β clearance by glia and across the BBB [40].

Apolipoprotein E facilitates amyloid beta clearance by proteolytic degradation

The expression of ApoE is transcriptionally regulated by ligand-activated nuclear receptors, which act broadly in

the brain to regulate lipid metabolism, inflammation, and neuroprotection. The principal type II nuclear receptors regulating ApoE expression are peroxisome proliferator-activated receptor gamma (PPAR γ) and liver X receptors (LXRs) [41], which form an active transcription factor through dimerization with the retinoid X receptors (RXRs). LXR:RXR, upon binding of endogenous oxysterol ligands, promotes the expression of reverse cholesterol transport genes (*ApoE* and *ABCA1*) [21,42]. Astrocytes upregulate ApoE mRNA and protein expression in response to RXR, PPAR γ , and LXR agonists, leading to the synthesis of ApoE-containing HDL particles [19,43]. There is strong evidence that the isoform of ApoE and its degree of lipidation influence the ability of ApoE to promote A β proteolysis both extracellularly and intracellularly and to modulate γ -secretase activity [26,44,45].

Microglia, which play a prominent role in A β degradation, are influenced by ApoE. Terwel and colleagues [46] demonstrated that ApoE secreted in media from primary astrocytes treated with LXR agonists stimulated phagocytosis of A β in primary microglia; however, the mechanistic basis of this finding is unknown. This corroborates earlier work from Giunta and colleagues [47], who described increased microglial phagocytosis of aggregated A β with the addition of recombinant ApoE3. The degree of lipidation and ApoE isoform impacts the efficiency of intracellular degradation of A β within microglia, and more highly lipidated ApoE isoforms (E2 > E3 > E4) are most effective [26]. Lee and colleagues [48] recently established that the cholesterol efflux function of ApoE is responsible for accelerating the transport of A β to lysosomes in microglia, where it can be degraded by lysosomal proteases.

Many studies in mouse models of AD have demonstrated that treatment with LXR agonists increases levels of ApoE and ABCA1, and this is correlated with cognitive improvements and decreased A β deposition [26,46, 49-53]. Similarly, PPAR γ activation can stimulate the degradation of A β [41,54]. In addition to its ability to increase ApoE and ABCA1 levels, PPAR γ activation has been shown to induce the expression of the scavenger receptor CD36 on microglia, which increased the uptake of A β [55]. LXR agonists and PPAR γ agonists have been valuable tools for elucidating the role of ApoE and mechanism of A β clearance in AD. Currently, therapeutic potential for LXR agonists has been limited by an unfavorable side-effect profile and inadequate BBB permeability. Therefore, bexarotene, a BBB-permeable US Food and Drug Administration-approved drug that stimulates both LXR and PPAR γ pathways, has been used in AD mouse models. The RXR agonist bexarotene facilitates degradation of soluble A β_{42} in a PPAR γ -, LXR-, and ApoE-dependent manner in both primary microglia and astrocytes [52]. Interestingly, the levels of IDE and

neprilysin were unchanged with bexarotene treatment, suggesting that type II nuclear receptor activation may facilitate soluble A β_{42} degradation through other mechanisms. *In vivo* microdialysis revealed that bexarotene reduced the half-life of A β in APP/PS1 and C57Bl/6 wild-type mice but had no effect on A β clearance in ApoE-null mice, and this clearly demonstrates that the bexarotene treatment increased A β clearance in an ApoE-dependent manner [52].

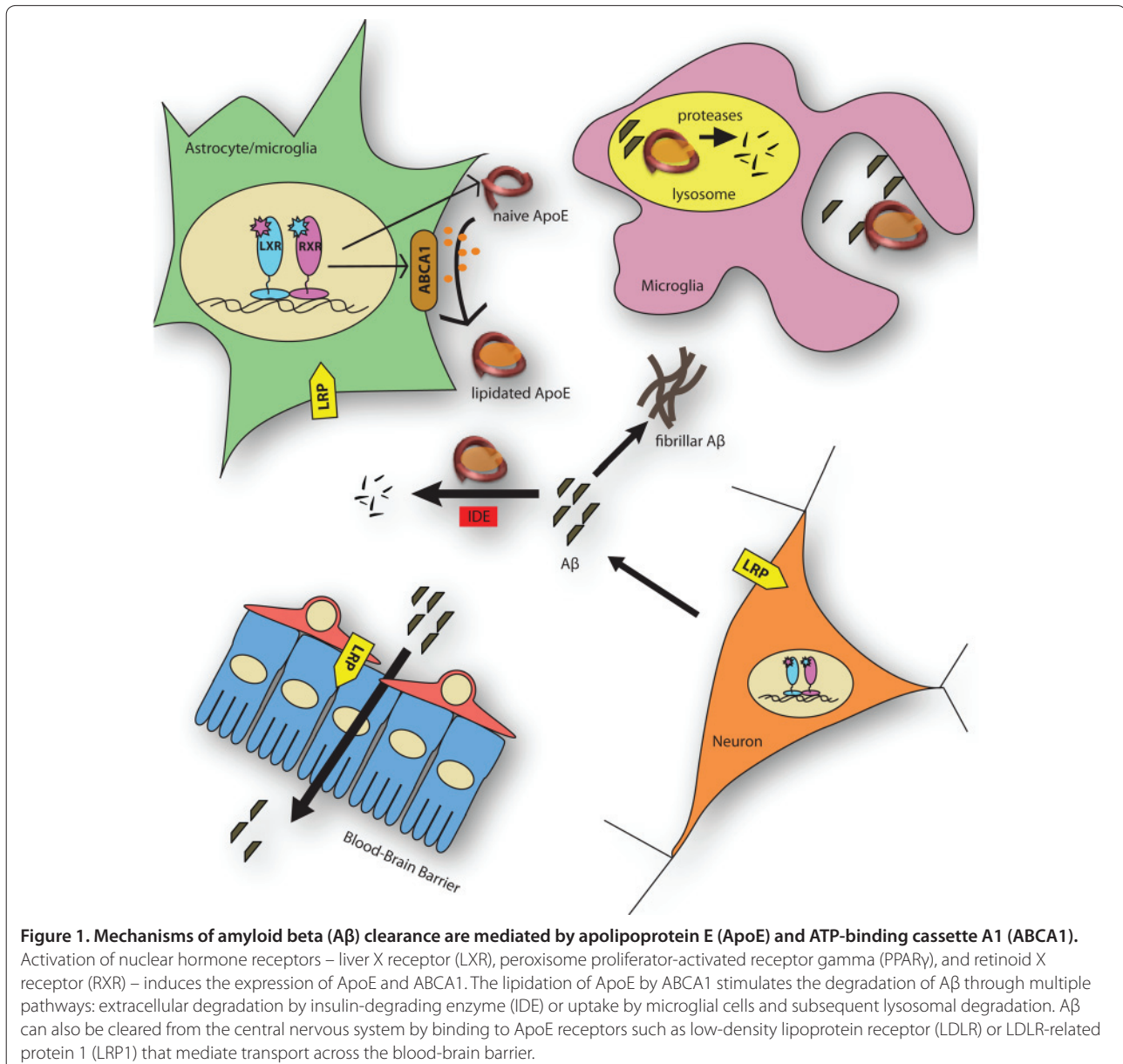
Brain to blood and peripheral clearance of amyloid beta

ApoE and ApoE receptors have also been implicated in the clearance of A β across the BBB. Dysfunction of the BBB is seen in both human and animal studies of AD and is linked to poor cerebral blood flow, hypoxia, and accumulation of neurotoxic molecules in the parenchyma (reviewed in [56]). The transport of A β across the BBB is of considerable interest because only very small, nonpolar molecules are able to passively diffuse at the BBB. Unlike in peripheral blood-organ interfaces, peptides such as A β along with other nutrients and large molecules must be actively transported. Therefore, the equilibrium between A β in the plasma and parenchymal ISF can be influenced by the ability of receptors at the BBB to transport A β . The existence of such an equilibrium is the basis of the 'peripheral sink' hypothesis of AD treatment, which emphasizes clearance of peripheral A β species in order to provide a vacuum or 'sink' which favors transport of A β out of the brain and into the plasma [57].

Receptor-mediated transport of A β from brain to periphery is mediated principally by the ApoE receptor, LRP1, and impairing LRP1 function significantly decreases the clearance of A β from the brain [33,58]. Conversely, the receptor for advanced end glycation products (RAGE) transports A β in the reverse direction and contributes to A β accumulation at the BBB and in the parenchyma [59]. LRP1 and RAGE recognize and transport free A β , but the association of A β with ApoE influences receptor transport of A β . ApoE-bound A β is redirected from LRP1 to other LDLR family members, reducing the speed of A β clearance at the BBB [39,60]. The isoform of ApoE further influences this process, as discussed above.

Conclusions

Growing evidence from mouse models of AD and *in vivo* SILK studies in humans indicates that impaired clearance of A β leads to the development of AD pathology. ApoE plays an important role in mediating A β clearance through multiple mechanisms, as depicted in Figure 1. The expression of ApoE and ABCA1 is regulated by the activation of type II nuclear hormone receptors (LXR, PPAR γ , and RXR). ApoE is lipidated predominantly by ABCA1. Lipidated ApoE promotes the intracellular



degradation of Aβ by enzymes like neprilysin through its cholesterol efflux function. Extracellular degradation of Aβ by IDE is more efficient in the presence of highly lipidated ApoE. Aβ can also directly bind to ApoE receptors and cross the BBB. ApoE4 is less effective than ApoE3 and ApoE2 at stimulating Aβ clearance, and this may explain, at least in part, why it is such a strong risk factor for AD. Targeting the type II nuclear receptors, such as RXRs, has shown promising therapeutic benefit in mouse models of AD. Treatment with LXR, PPARγ, and RXR agonists decreased Aβ pathology and improved cognition in various studies, supporting the hypothesis that increasing the level of lipidated ApoE may be a strong therapeutic strategy for AD.

This article is part of a series on *Abeta Catabolism*, edited by Elizabeth Eckman. Other articles in this series can be found at http://alzres.com/series/Abeta_catabolism

Abbreviations

Aβ, amyloid beta; ABCA1, ATP-binding cassette A1; AD, Alzheimer's disease; ApoE, apolipoprotein E; APP, amyloid precursor protein; BBB, blood-brain barrier; HDL, high-density lipoprotein; IDE, insulin-degrading enzyme; ISF, interstitial fluid; LOAD, late-onset Alzheimer's disease; LRP1, lipoprotein receptor-related protein 1; LXR, liver X receptor; PPARγ, peroxisome proliferator-activated receptor gamma; RAGE, receptor for advanced end glycation products; RXR, retinoid X receptor; SILK, stable isotope-labeling kinetics.

Competing interests

KW is an employee of Genentech, Inc. (a member of the Roche group) and receives a fixed salary. GL is an officer of ReXceptor, Inc. (Cleveland, OH, USA). The other authors declare that they have no competing interests.

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Author details

¹Development Sciences, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, USA. ²Department of Neurosciences, Case Western Reserve University School of Medicine, 10900 Euclid Avenue, Cleveland, OH 44106, USA.

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