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Impact of Apolipoprotein E on Alzheimer's Disease

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Abstract

A key feature of Alzheimer's disease (AD) is deposition of extracellular amyloid plaque comprised chiefly of the amyloid β (Aβ) peptide. Studies of Aβ have shown that it may be catabolized by proteolysis or cleared from brain via members of the low-density lipoprotein receptor family. Alternatively, Aβ can undergo a conformational transition from α-helix to β-sheet, a conformer that displays a propensity to self-associate, oligomerize and form fibrils. Furthermore, β-sheet conformers catalyze conversion of other α-helical Aβ peptides to β-sheet, feeding the oligomer and fibril assembly process. A factor that influences the fate of Aβ in the extracellular space is apolipoprotein (apo) E. Polymorphism at position 112 or 158 in apoE give rise to three major isoforms. One isoform in particular, apoE4 (Arg at 112 and 158), has generated considerable interest since the discovery that it is the major genetic risk factor for development of late onset AD. Despite this striking correlation, the molecular mechanism underlying apoE4's association with AD remains unclear. A tertiary structural feature distinguishing apoE4 from apoE2 and apoE3, termed domain interaction, is postulated to affect the conformation and orientation of its' two independently folded domains. This feature has the potential to influence apoE4's interaction with Aβ, its sensitivity to proteolysis or its lipid accrual and receptor binding activities. Thus, domain interaction may constitute the principal molecular feature of apoE4 that predisposes carriers to late onset AD. By understanding the contribution of apoE4 to AD at the molecular level new therapeutic or prevention strategies will emerge.

Keywords

Alzheimer's disease; apolipoprotein E; isoform; domain interaction; amyloid beta peptide

I. ALZHEIMER's DISEASE: INTRODUCTION AND OVERVIEW

Alzheimer's disease (AD) is the most frequent cause of senile dementia, affecting 40% of Americans over age 85. Moreover, as the proportion of aged individuals increases, the burden of this disease is certain to worsen [1]. AD is characterized by progressive neurodegeneration associated with extracellular deposition of amyloid beta (Aβ) peptide as

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CONFLICT OF INTEREST
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plaque and accumulation of hyperphosphorylated Tau protein as intracellular neurofibrillary tangles. Aβ is a collection of peptides ranging in length from 12 to 42 amino acids derived from proteolytic processing of the transmembrane amyloid precursor protein by the consecutive action of β-and γ-secretases (Fig. 1). The major species, Aβ (1-40) and Aβ (1-42), are hydrophobic peptides that accumulate in amyloid plaque deposits that represent a clinical hallmark of AD. A central tenet of the "amyloid hypothesis" is that disease results from a persistent imbalance between Aβ production and clearance. Failure to efficiently degrade Aβ, or clear it from the extracellular space [2], appears to contribute to initiation and progression of disease. Under physiological conditions, Aβ-degrading proteases, including neprolysin and insulin degrading enzyme, function to digest Aβ directly; Fig. 1, path 1). Alternatively, Aβ may be subject to receptor-mediated clearance through interaction with members of the low density lipoprotein receptor (LDLR) family, including the LDLR, the low-density lipoprotein receptor related protein 1 (LRP1) or the very low density lipoprotein receptor (VLDLR) [3, 4]; (Fig. 1, path 2). Both proteolytic degradation and receptor mediated endocytosis represent physiological Aβ catabolic paths that counterbalance Aβ production. A third path (Fig. 1, path 3) involves the structural transition of Aβ peptides mentioned above. This process, considered to be a fundamental contributor to fibrillization and plaque formation, is initiated when Aβ transitions from α-helix to β-sheet secondary structure. This event precedes the pathological sequence of self-association, oligomerization and fibril formation, an end point that constitutes the structural basis of Aβ plaque deposits [5-7]. In addition, once produced, β-sheet conformers are capable of catalyzing the α-helix → β-sheet transition of other Aβ monomers [8, 9]. In this way, the pathological process is sustained by continuous production of β-sheet conformers that supply building blocks for fibril growth.

Also impacting the metabolic fate of Aβ are myriad extraneous factors that influence its propensity to form plaque deposits. One factor, in particular, that has a profound effect on Aβ metabolism is apolipoprotein (apo) E (Fig. 1, path 4) and the present review focuses on the unique and perplexing relationship between this protein, Aβ metabolism, lipid flux and AD.

II. THE apoE CONNECTION

Although it was originally discovered and characterized for its role in plasma lipoprotein metabolism, apoE is now recognized to have a major impact on neuronal function [10]. Human apoE is a 299 amino acid secreted protein that exists as one of three isoforms that differ by a single amino acid. The parent isoform, apoE3, possesses Cys at position 112 and Arg at position 158. ApoE2 has Cys at both these sites while apoE4 has Arg. Structural studies of apoE have shown it is comprised of two independently folded domains, a 22 kDa N-terminal (NT) four helix bundle domain and a 10 kDa C-terminal (CT) domain that are connected by an unstructured hinge segment (Fig. 2) [11, 12]. Cell types and tissues that express apoE include liver, macrophages and brain, predominantly astrocytes and microglia. In brain, apoE is secreted as a lipid-poor protein that accrues lipid to form brain specific lipoprotein particles [13]. ApoE has been shown to bind Aβ and studies comparing apoE3 and apoE4 have documented differences in their respective Aβ binding properties [14-18]. Such differences are entirely consistent with the revelation that apoE4 is the major genetic

risk factor for late-onset AD [19]. Indeed, individuals with a single copy of *APOE4* manifest a 5 fold increased chance of developing AD while those with two copies have an estimated 20 fold increased risk [20]. The positive predictive value for symptomatic AD in patients who carry at least one *APOE4* allele is >95%. Thus, early in the clinical course of dementia, when diagnosis may be ambiguous, the presence of *APOE4* raises the diagnostic accuracy of AD [21]. A fundamental question emerging from this striking genetic association relates to the molecular basis of this effect. A plausible explanation is that structural differences among apoE isoforms affect their respective interactions with Aβ. This may include isoform specific differences in Aβ binding or a differential ability to affect the conformational status of Aβ. Unfortunately, there is not enough information or experimental results available to answer these issues in a definitive manner. Indeed, it is not known whether Aβ binding to apoE is conformation specific or if it displays a differential binding affinity for Aβ monomers versus oligomers.

Regardless of the precise nature of its binding interaction with Aβ, it is generally recognized that structural differences among apoE isoforms underlie the pathology associated with apoE4 [22]. Moreover, if apoE3 is considered neutral, apoE2 is regarded as protective against AD [23, 24]. On the basis of *in vitro* binding assays, Strittmatter *et al*. [14] documented isoform specific differences between apoE3 and apoE4 in terms of Aβ binding. Noting that these isoforms differ from apoE4 by single amino acid substitutions within the NT helix bundle domain, it may be anticipated that the NT domain alone constitutes the critical part of the apoE molecule that is associated with AD pathology. This, however, appears not to be the case. The finding that Aβ interacts with the CT domain of apoE [17, 25-27] indicates isoform specific differences in Aβ-dependent AD pathology likely involves some form of communication between the NT and CT domains. Toward this end, a phenomenon known as “domain interaction” has emerged as a unique structural feature that distinguishes apoE4 from other isoforms.

III. DOMAIN INTERACTION

The concept of domain interaction in apoE4 emerged from studies of plasma lipoprotein metabolism. Briefly, Gregg *et al*. [28] found that apoE4 distributes abnormally among lipoproteins in plasma. Whereas apoE3 localizes to high-density lipoproteins (HDL), apoE4 displays a preference for larger, VLDL particles. In pursuing this, Weisgraber found that apoE4’s preference for VLDL was directly related to the Arg for Cys substitution at position 112 in the NT domain of this isoform [29]. On the basis of an *in vitro* lipoprotein binding preference assay, X-ray crystallography and site directed mutagenesis, evidence was obtained that Arg112 affects the spatial orientation of Arg61, such that its positively charged side chain forms a salt bridge with the negatively charged side chain of Glu255 in the CT domain (Fig. 3) [30, 31]. Since Arg61 and Glu255 reside in different domains of apoE, the term “domain interaction” was coined to describe this phenomenon. A question emerging from these results is “how could domain interaction in apoE4 manifest pathophysiological consequences associated with AD”? One possibility is that it imposes a structural constraint [32] that affects how apoE4, or apoE4-Aβ complexes, are processed. For example, if domain interaction alters the lipid binding and accrual properties [27] or protease sensitivity of apoE4 [33], an impact on Aβ metabolic fate would be anticipated.

Evidence suggests domain interaction alters the orientation or alignment of CT domain α-helices such that the protein is attracted to more planar lipid surfaces [30]. Insofar as brain possesses only HDL particles with a high degree of surface curvature [34-36], it is conceivable that domain interaction alters the relative affinity of apoE4 for brain lipoproteins. If so, it may be that a higher proportion of apoE4 exists in a lipid-poor state. Considering that other apolipoproteins (e.g. apoA-I) are rapidly degraded if they are unable to accrue lipid [37], it follows that domain interaction-induced structural constraints that lead to defective lipid accrual would result in a lower concentration of apoE4 compared to other isoforms. In keeping with this postulate, Bales *et al*. [38] found that lower levels of apoE4 in brain are associated with increased Aβ accumulation, suggesting a domino effect on Aβ clearance capacity [39, 40]. If less apoE is available for interaction with Aβ, it follows that the probability A will enter the pathological path toward fibril formation will increase. The corollary to this, that increasing apoE expression facilitates Aβ clearance [39, 41, 42], is currently under intense investigation.

IV. THE EFFECT OF apoE LIPIDATION ON Aβ METABOLIC FATE

ApoE secreted from astrocytes and microglia gradually accrues lipid, ultimately forming a mature spherical lipoprotein particle. As shown in (Fig. 4), the process of apoE lipidation can be quantized into discrete stages. The first stage, lipid-poor apoE, is likely a transient species that rapidly associates with phospholipid and cholesterol through active transport (i.e. via ATP-binding cassette transporter A1 (ABCA1) [43, 44] or indirectly through passive accumulation. The latter mode is operative in *abca1* (-/-) mice where central nervous system lipoproteins exist as small, lipid-poor particles ~8 nm in diameter [45, 46]. These apoE-lipid complexes (Fig. 4, stage II) exist as discrete entities that manifest unique properties. A defining feature of these particles is the manner in which apoE physically contacts the lipid substrate. As mentioned above, apoE is comprised of two structural domains. Whereas the 10 kDa CT domain has a high affinity for lipid surfaces and initiates contact with lipid [47, 48], the 22 kDa NT domain four-helix bundle is exceptionally stable [49, 50] and displays a weak affinity for lipid surfaces [29]. Thus, when ABCA1 is absent or efflux accessible lipid is limiting, the CT domain sequesters available lipid, generating apoE lipid particles in which the NT domain maintains a four-helix bundle conformation. Insofar as the CT domain drives apoE interaction with ABCA1 [51], it may be envisioned that, when lipid availability is low, ABCA1-mediated cholesterol and phospholipid efflux generates stage II apoE lipid particles. Importantly, neither stage I nor stage II apoE particles are capable of functioning as ligands for members of the LDLR family [11, 52]. This is because critical positively charged amino acid residues in helix 4 of the NT domain (residues 136 – 150) do not adopt a receptor competent conformation at this stage of lipid particle maturation [53]. Interaction of lipid-poor or nascent apoE lipid particles (i.e. Fig. 4, stage I or II) with ABCA1 under conditions where lipid availability is not limiting will generate discoidal particles (Fig. 4, stage III) that serve as precursors of mature spheroidal lipoproteins present in brain. In stage III particles, the NT domain “opens” about a hinge region connecting helical segments essentially substituting helix-helix interactions that stabilize the four-helix bundle for helix-lipid interactions [54, 55]. On these particles, apoE adopts an extended conformation that circumscribes the perimeter of a disk-shaped lipid

bilayer, contacting and stabilizing the edge of the disk [56]. This interaction is possible because of the amphipathic nature of apoE helix segments [57]. Such helices bind lipid surfaces via their hydrophobic face while their polar face is directed toward the aqueous milieu. Conversion of discoidal particles to spherical HDL requires the combined action of ABCA1 and ABCG1 [13], which funnel cholesterol and phospholipid into the particle as lipid modifying enzymes and transfer proteins remodel their composition. Lecithin:cholesterol acyltransferase (LCAT) catalyzes the transfer of an acyl moiety from the *sn*-2 position of phosphatidylcholine to the β-OH group of cholesterol, generating cholesteryl ester [58]. The cholesteryl ester product partitions between leaflets of the bilayer, creating a particle core that expands as a function of continued efflux and LCAT activity. Remodeling proteins, such as phospholipid transfer protein, redistribute lipid between lipoproteins and/or membranes as part of the maturation process [59]. Both stage III and stage IV apoE lipid particles manifest full LDLR family binding activity [47]. Thus, if Aβ associates with the CT domain of apoE, in order for these complexes to be cleared via LDLR family members, lipid particle maturation must be achieved.

In the absence of timely lipid particle maturation it is conceivable that apoE susceptibility to proteolysis increases. Toward this end, Huang *et al*. [60] showed that domain interaction enhances protease sensitivity in the CT domain of apoE4, generating truncated species that contribute to AD pathology. Harris *et al*. [61] went on to identify a chymotrypsin-like serine protease with a preference for apoE4 that generates “toxic” CT truncated fragments. More recently, Jones *et al*. [62] hypothesized that domain interaction in apoE4 alters protease sensitivity in the hinge segment connecting the NT and CT domains (see Fig. 2). If proteolysis of apoE occurs in this hinge segment, Aβ associated with the CT domain cannot be cleared via apoE-dependent LDLR family interactions. In this case, Aβ may have increased opportunity to interact with other Aβ molecules in the extracellular space and, as such, be subject to pathological folding events analogous to prion disease (see Fig. 1) [9, 63]. The extent to which Aβ interaction with different apoE isoforms affects its sensitivity to protease digestion has yet to be investigated in detail.

Insofar as apoE-Aβ metabolism is affected by multiple factors, scenarios may exist where apoE is either beneficial or detrimental. Because lipidation state is a major factor affecting apoE-Aβ metabolic fate, it is reasonable to consider that, when lipid is limiting, a greater proportion of apoE-Aβ will exist in a lipid-poor or nascent lipid particle state and, as a result, Aβ susceptibility to pathological folding will increase. On the other hand, if efflux accessible lipid is abundant, ABC transporter dependent lipidation of apoE-Aβ complexes will generate mature lipid particles that expedite Aβ clearance via LDLR family member interactions. This concept has gained support from studies in an Alzheimer’s susceptible mouse model over-expressing ABCA1, wherein Aβ deposition as plaque was dramatically decreased, presumably a result of increased apoE lipidation and enhanced Aβ metabolism [64]. More recently, Youmans *et al*. [65] employed a mouse model of AD to show that less apoE4 is lipoprotein associated (and possibly present in a less lipidated state) compared to apoE2 and apoE3. Importantly, these isoform specific differences correlate with differences in the relative abundance of soluble and oligomeric Aβ. In another study [66], *in vivo* and *in*

vitro evidence suggests apoE4 impacts the formation of Aβ oligomers through interaction with its C-terminal domain in a manner that is dependent upon its lipidation state.

V. ApoE: IS MORE BETTER?

An obvious way to examine the effect of apoE on neurodegeneration is to assess the impact of its overexpression or gene disruption. Whereas the apoE null mouse appears normal [67], cognitive deficits and other phenotypic changes do occur with age [68]. It is noteworthy, however, that brain tissue possesses compensatory mechanisms, such as up-regulation of apoJ (also known as Clusterin), that are capable of fulfilling functions normally carried out by apoE including lipid association [69, 70], Aβ binding and receptor (e.g. LRP2/Megalin) mediated clearance [71-73]. Thus, the extent to which compensation by other proteins occurs must be kept in mind when interpreting experiments designed to manipulate apoE levels.

Studies by Holtzman *et al*. [74] found that expression of human apoE3 or apoE4 in a mouse model of AD reduced Aβ deposition. At the same time, Buttini *et al*. [75] reported differential effects on neuronal integrity in apoE null mice expressing human apoE3 versus apoE4. Another model has emerged from studies targeting nuclear hormone receptors that regulate apoE expression. Agonists of the liver X receptor [76, 77], the retinoid X receptor (RXR) or peroxisome proliferator-activated receptor gamma (PPAR-γ) lead to increased apoE production [78, 79]. Transactivation using the RXR agonist, bexarotene, LXR agonists (e.g. TO901317 or GW3965) or the PPAR-γ agonist, pioglitazone, results in coordinated up-regulation of apoE, ABCA1 and ABCG1 in brain [80-84]. In mouse models of AD, administration of such agonists leads to enhanced Aβ clearance and reversal of cognitive deficits associated with disease. The intriguing result that bexarotene had no effect when administered to apoE null mice [75] is consistent with the concept that increased expression of apoE promotes enhanced binding and clearance of soluble Aβ, effectively diverting it from path 3 to path 4 in (Fig. 1). While these results support a “chaperone” role for apoE in Aβ metabolism, they do not explain isoform-specific effects of human apoE on this process [85]. Moreover, it is reasonable to consider that, given apoE4’s strong connection to AD pathology, overexpression of this isoform may ultimately be detrimental, despite the fact that short-term up-regulation via nuclear hormone receptor activation improves Aβ clearance.

Contrary to data indicating up-regulation of apoE confers therapeutic benefit, others report that decreasing the level of apoE in brain improves Aβ clearance [86, 87]. If apoE levels are limiting while cells are replete with efflux accessible lipid, a greater proportion of the apoE protein pool will achieve a mature lipidation state, such that greater flux of apoE-Aβ through LDLR family member mediated endocytosis will occur. A deleterious scenario may exist, however, if there is an abundance of apoE but insufficient lipid availability. In this case a greater proportion of apoE will be unable to attain a mature lipidation state in a timely manner, resulting in longer residence time in the extracellular space, increased susceptibility to proteolysis and aberrant Aβ metabolism (i.e. pathological folding). An example of disrupted apoE lipidation is the ABCA1 null mouse, where the absence of this transporter led to an 80% decrease in apoE levels and a corresponding increase in amyloid load when

the mice were crossed into an Alzheimer's susceptible background [88-90]. The presence of apoE4 may exacerbate issues created by insufficient lipid availability due to its unique Aβ interaction properties, susceptibility to proteolysis and/or altered lipid accrual kinetics [85]. Thus, whereas pharmacological "tuning" of ABCA1 and apoE levels may provide therapeutic promise, knowing the exact contribution and role of the different apoE isoforms in lipidation and Aβ metabolizing pathways is required before proceeding with a unilateral approach. It is also worth noting that apoE expression levels are also affected by single nucleotide polymorphisms (SNPs) in the promoter region of *APOE* [91]. Furthermore, the finding that an "Aβ interacting domain" exists within the *APOE* promoter region [92] suggests Aβ itself may serve as a transcription factor capable of influencing apoE gene expression.

VI. FUTURE DIRECTIONS

AD is a complex, progressive disease with multiple contributing factors. The strong positive correlation between the ε4 allele of *APOE* and AD has driven a concerted research effort. This has led to the postulate that domain interaction in apoE4 is a cardinal feature that distinguishes this isoform from apoE3 and apoE2. Mechanism-based research, designed to explain how domain interaction in apoE4 increases the risk of late onset AD, presumably by influencing the metabolic fate of Aβ, has progressed steadily.

Another promising area of research, with the potential to give rise to therapeutic intervention strategies, is activation of nuclear hormone receptors that regulate production of apoE and ABC transporters [79]. By up-regulating these proteins, increased lipid flux drives apoE toward a mature lipidation state. In so doing, associated Aβ will be cleared via LDLR family members and degraded [64]. A factor that must be considered, however, is lipid availability/ supply for efflux dependent apoE particle maturation. Under physiological conditions, activation of nuclear hormone receptors serves as a mechanism to limit free cholesterol in tissues experiencing high cholesterol flux. As such, simply making more apoE and ABC transporters may have a negative impact if insufficient lipid is available to fuel the pathway. Indeed, it is likely that, in the absence of an efflux accessible lipid pool, increased production of apoE will result in a larger proportion of this protein present in a lipid-poor or nascent lipid particle state (stages I and II in Fig. 4). In this case, apoE association with Aβ may be pathological, driving Aβ toward fibril formation. Further confounding the balance between lipid availability, Aβ binding and apoE concentration, are isoform specific differences in apoE. While many interpretations are possible, the most prevalent is that apoE4, perhaps owing to domain interaction, is defective in one or more of lipid accrual, Aβ binding or protease sensitivity. Thus, the idea that more apoE4 is better is not necessarily true, especially long term.

Given the evidence that domain interaction may be directly related to pathological consequences associated with apoE4, pharmacological disruption of this structural feature has been pursued as an approach to abrogate the negative impact of this isoform. Using mitochondrial dysfunction as a model of AD pathology, Chen *et al*. [93] showed that treatment of apoE4 expressing neuro2a cells with a molecule capable of disrupting domain interaction effectively restores mitochondrial respiratory complex 4 levels. Subsequently,

Chen *et al*. [94] used a high throughput assay to identify a phthalazinone "structure corrector" that reversed impairments in mitochondrial motility and neurite outgrowth. Taken together, these data suggest that pharmacological disruption of domain interaction in apoE4 has the potential to ameliorate its pathological effects *in vivo*.

As the search for "magic bullet" small molecules capable of specifically disrupting domain interaction in apoE4 progresses, it is important to focus on the structural basis of this phenomenon as well as the precise nature of isoform-specific differences. At present, the sole defining feature of domain interaction is a salt bridge between Arg61 and Glu255 in apoE4 but not in apoE3 (see Fig. 3) [12]. However, despite the apparent lack of an Arg61 – Glu255 salt bridge in apoE3 [95], Narayanaswami *et al*. [96], Hatters *et al*. [97] and Chen *et al*. [64] have reported that the NT and CT domains in apoE3 are proximal to one another. Thus, it appears that subtle differences in the relative strength of domain interaction may distinguish these isoforms.

In summary, ongoing work on apoE-Aβ interactions has led to testable hypotheses that should yield definitive answers. We anticipate that a combination of structure-based studies, cell and model organism investigations as well as pharmacological intervention, will lead to new strategies for the diagnosis, prevention and treatment of this growing epidemic.

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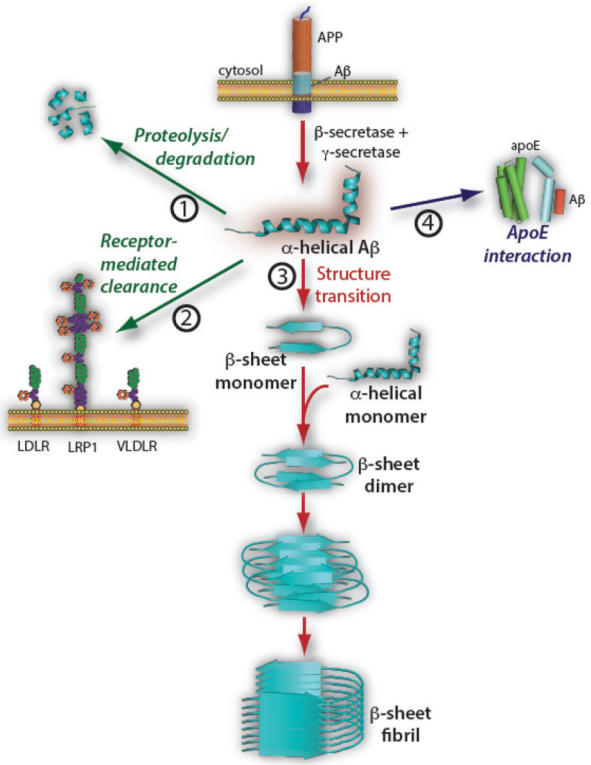

Fig. (1). Pathways of Aβ metabolism.

Soluble amyloid beta (Aβ) peptide is generated from proteolytic processing of amyloid precursor protein (APP) by the successive action of β- and γ-secretases in brain cells (top center). The level of Aβ production is counterbalanced by its degradation via protease digestion (Path 1) and receptor mediated endocytosis (Path 2). Alternatively, soluble α-helical Aβ may undergo a pathological transition to β-sheet conformer that promotes self-association and oligomerization (Path 3). How interaction between apolipoprotein (apoE) and Aβ (Path 4) influences Aβ metabolic fate is the subject of this review.

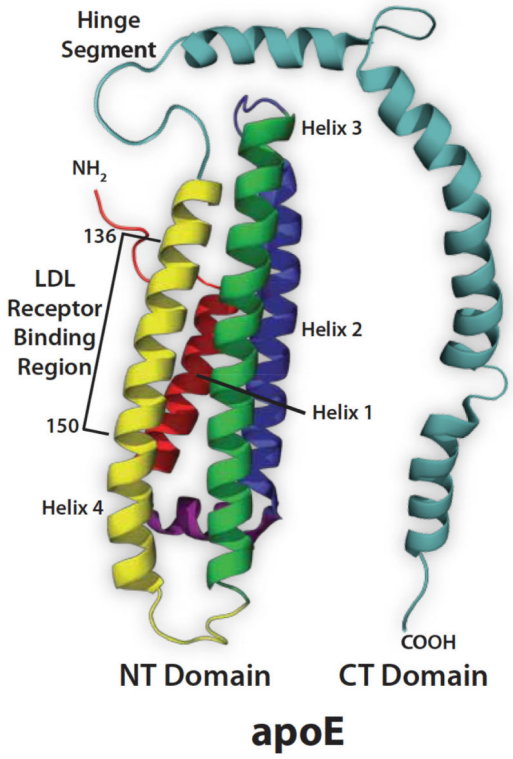

Fig. (2). Two-domain structural model of apoE.

Full-length apoE (299 amino acids) is composed of two independently folded structural domains. The 4-helix bundle structure of the N-terminal (NT) domain (X-ray crystal structure PDB ID:1LPE, Wilson *et al*., 1991) is connected to the modeled C-terminal (CT) domain by a flexible hinge segment that is sensitive to proteolysis. The NT domain contains the LDL receptor family binding recognition sequence (residues 136-150) while the CT domain is responsible for lipid binding and Aβ interaction.

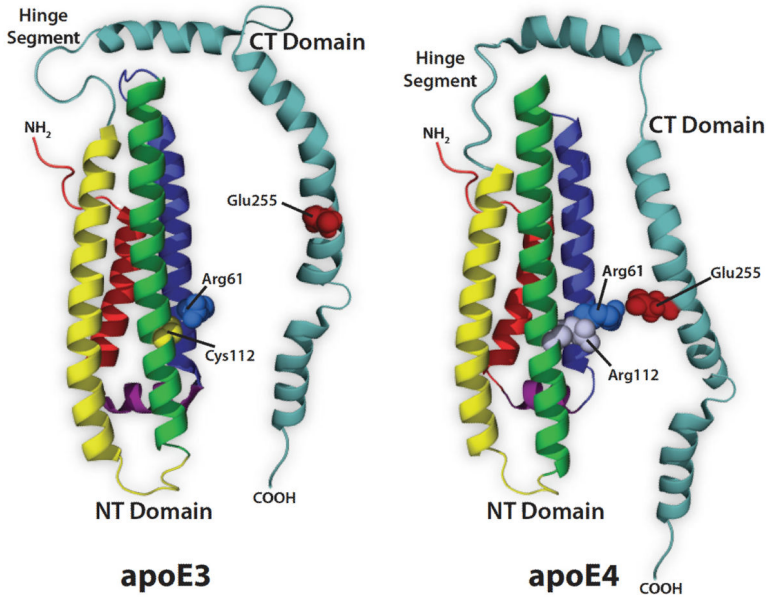

Fig. (3). Putative isoform specific differences in NT – CT domain interaction.

The NT domain 4-helix bundle is from the X-ray crystal structure of the isolated apoE3 and apoE4 domains (PDB ID:1NFN and PDB ID:1B68, respectively). The CT domain and hinge segment have been modeled for illustration (adapted from Zhong and Weisgraber (2009a)). Key residues, known to be involved in the isoform specific structural differences between apoE3 and apoE4 are indicated. In apoE4, the presence of Arg112 (compared with Cys112 in apoE3) on helix 3 changes the conformation of Arg61 on helix 2 to allow for greater NT and CT domain interaction via an Arg61-Glu255 salt bridge.

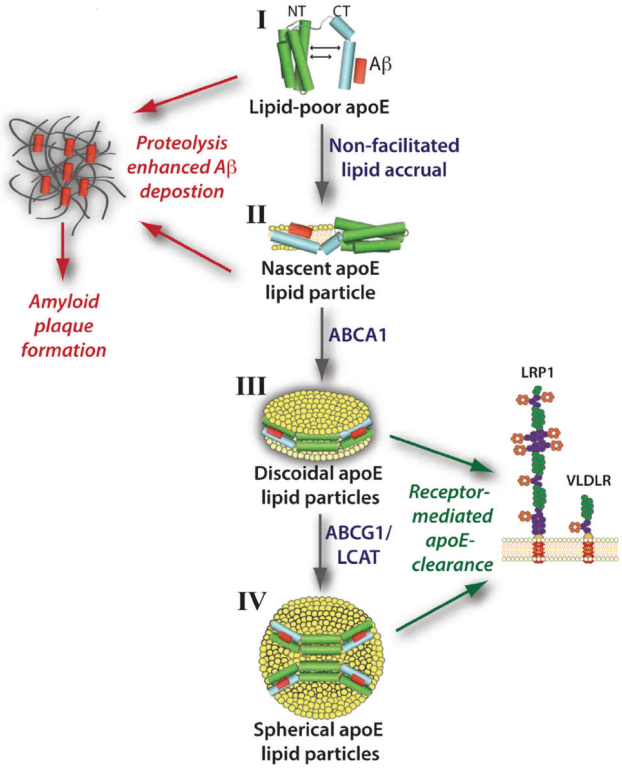

Fig. (4). Putative effects of apoE lipidation on Aβ metabolism.

Lipid-poor apolipoprotein (apo) E is secreted from astrocytes and glial cells in brain and is lipidated in discrete stages (I-IV) by the collective action of ATP-binding cassette (ABC) transporter proteins (ABCA1 and ABCG1), lipid modifying enzymes and transfer proteins (e.g. lecithin:cholesterol acyltransferase (LCAT)). Poorly lipidated apoE (stage I) and nascent apoE particles (stage II) are more susceptible to proteolysis which may lead to greater Aβ deposition and enhanced plaque formation due to impaired clearance, whereas lipidated discoidal (stage III) and spherical (stage IV) apoE-containing lipoproteins are ligands for LDL receptor family members, potentially leading to enhanced binding and clearance of apoE-Aβ complexes from brain.