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APOE-amyloid interaction: Therapeutic targets

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Abstract

Alzheimer's disease (AD) is a devastating neurodegenerative disorder that is growing in prevalence globally. It is the only major cause of death without any effective pharmacological means to treat or slow progression. Inheritance of the ε4 allele of the Apolipoprotein (APO) E gene is the strongest genetic risk factor for late-onset AD. The interaction between APOE and amyloid β (Aβ) plays a key role in AD pathogenesis. The APOE-Aβ interaction regulates Aβ aggregation and clearance and therefore directly influences the development of amyloid plaques, congophilic amyloid angiopathy and subsequent tau related pathology. Relatively few AD therapeutic approaches have directly targeted the APOE-Aβ interaction thus far. Here we review the critical role of APOE in the pathogenesis of AD and some of the most promising therapeutic approaches that focus on the APOE-Aβ interaction.

Keywords

Apolipoprotein E; Immunomodulation; Oligomers; Early onset AD; Therapy; Peptoids; Pathological chaperone; Beta amyloid; Interaction

1. The critical role of apolipoprotein E in the pathogenesis of Alzheimer's disease

Alzheimer's disease (AD) is a devastating age associated neurodegenerative disorder. It is the sixth leading cause of death in the USA, with its prevalence expected to grow rapidly as the average age of the world's population increases (Alzheimer's Association, 2019; Long and Holtzman, 2019). AD is the only cause of death among the top ten causes of death globally for which no effective pharmaceutical agents exist to halt or slow disease progression. AD is defined neuropathologically by the accumulation of amyloid β (Aβ) into extracellular plaques in the brain parenchyma and in the vasculature (known as congophilic [or cerebral] amyloid angiopathy [CAA]), and abnormally phosphorylated tau that accumulates intraneuronally to form neurofibrillary tangles (NFTs) (Long and

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Holtzman, 2019; Rabinovici, 2019; Wisniewski and Drummond, 2019). In our early studies, we discovered that apolipoprotein E (APOE) was a new amyloid-associated protein that was abundantly present in amyloid plaques. We hypothesized that APOE was a "pathological chaperone" that directly promoted aggregation/fibrillization of Aβ (Wisniewski and Frangione, 1992;Wisniewski et al., 1993). Subsequent work by Dr. Allen Roses and his group identified the ε4 allele of the APOE gene as a key genetic risk factor for AD (Strittmatter et al., 1993a; Corder et al., 1993; Schmechel et al., 1993). This seminal observation was confirmed in other populations in the US, Europe and Australia (Saunders et al., 1996; Laws et al., 2002; Martins et al., 1995). Many confirmatory studies have now shown that the APOE4 genotype is the most common and potent AD genetic risk factor identified thus far (Potter and Wisniewski, 2012; Martins et al., 2018; Belloy et al., 2019; Roda et al., 2019; Tzioras et al., 2019). Our work and that of others showed that APOE4 particularly promoted Aβ oligomerization/fibrillization in comparison to APOE2 or APOE3 (Wisniewski et al., 1993; Golabek et al., 1996; Wisniewski and Frangione, 1996; Wisniewski et al., 1995a; Castano et al., 1995; Wisniewski et al., 1994a; Wisniewski et al., 1994b; Sanan et al., 1994; Potter et al., 2001; Ma et al., 1994). This effect was associated with an earlier onset of disease and greater amyloid plaque and CAA burden, in both patients and AD model transgenic mice expressing different human APOE genotypes (APOE4 > APOE3 > APOE2) (Martins et al., 2018; Strittmatter et al., 1993b; Hyman et al., 1995; Fryer et al., 2003; Bales et al., 2009; Holtzman et al., 2000; Resnick et al., 2015; Lim et al., 2017; Morris et al., 2010).

Phosphorylated tau and Aβ pathologically aggregate in a sequential process. Monomers first aggregate into oligomers intraneuronally, which then further aggregate into the fibrils observed in amyloid plaques and NFTs. This pathology then spreads throughout the brain in a characteristic manner that is distinct for NFTs and plaques (Scheltens et al., 2016; Selkoe and Hardy, 2016; Braak and Braak, 1991; Thal et al., 2002). This process develops over two to three decades resulting in a long preclinical period when AD associated neuropathology is present in the brain without any associated cognitive impairment (Martins et al., 2018; Belloy et al., 2019; Dubois et al., 2016; Pletnikova et al., 2018). Significant evidence indicates that oligomers of Aβ and tau are the most neurotoxic species in AD as levels of oligomers correlate better with cognitive decline compared to the burden of plaques or NFTs (Selkoe and Hardy, 2016; Viola and Klein, 2015; Sengupta et al., 2016; Lane et al., 2018). APOE genotype determines the age of onset for Alzheimer's disease (APOE4 < APOE3 < APOE2) and directly influences the pathological aggregation of Aβ. Specifically, the Aβ-APOE interaction plays a key role in stabilizing toxic oligomers of Aβ, with APOE4 having a particularly pathological influence (Koffe et al., 2012; Hashimoto et al., 2012; Cerf et al., 2011).

In familial early onset AD (EOAD) there is either increased production of soluble Aβ (sAβ) or the production of more aggregation prone species, while in sporadic late onset AD (LOAD) there is impaired clearance of soluble Aβ (Selkoe and Hardy, 2016). EOAD pathology is also universal in Down syndrome (DS), which is attributed to the increased production of Aβ in DS due to the presence of three copies of the amyloid precursor protein (Head et al., 2016; Hartley et al., 2015).Autosomal dominant mutations in presenilin 1, presenilin 2 (PSEN1 and PSEN2) or the amyloid precursor protein (APP) account for only

~10% of all EOAD cases (~1% of all AD cases), leaving the cause of the majority of EOAD unexplained (Cacace et al., 2016; Guerreiro and Hardy, 2014; Wingo et al., 2012; Pimenova et al., 2017). LOAD afflicts > 95% of patients with AD and is related to both genetic and environmental factors (Guerreiro and Hardy, 2014; Karch et al., 2014; Bertram and Tanzi, 2012; Kim et al., 2014; Kim, 2018). A combination of genome-wide association studies (GWAS), linkage, and whole genome/exome sequencing have identified over 30 loci that confer increased risk for LOAD, including genes involved in innate immunity, cholesterol metabolism and synaptic/neuronal membrane function, suggesting that the pathogenesis of LOAD has considerable heterogeneity (Guerreiro and Hardy, 2014; Pimenova et al., 2017; Kim, 2018; Cuyvers and Sleegers, 2016; Karch and Goate, 2015; Jansen et al., 2019; Kunkle et al., 2019). Of these, APOE is the strongest identified genetic risk factor for LOAD (Potter and Wisniewski, 2012; Belloy et al., 2019; Huang and Mahley, 2014; Zhao et al., 2018). Variants of another gene that encodes the triggering receptor expressed on myeloid cells 2 (TREM2) have also been reported as a significant risk factor for LOAD, with an odds ratio approaching that of APOE4; however, these TREM2 variants are uncommon (Ulrich et al., 2017; Efthymiou and Goate, 2017; Shi and Holtzman, 2018).

This genetic diversity that drives AD pathogenesis suggests that AD is a syndrome associated with a neuropathological signature of Aβ and tau oligomer/fibril accumulation, where neither amyloid plaques or NFTs necessarily have a causative role. Our understanding of these complex pathways has greatly increased in recent years; however, despite this expanding knowledge base there has been a very high failure rate of ~99.6% of AD targeting clinical trials (Cummings et al., 2014; Banik et al., 2015; Schneider et al., 2014). There are many reasons for this high failure rate, which have been reviewed elsewhere (Long and Holtzman, 2019; Wisniewski and Drummond, 2019; Herline et al., 2018; Elmaleh et al., 2019); however, one factor associated with this lack of success is that relatively few therapeutic studies are targeting the critical role of APOE in AD. Even in EOAD and DS, where AD pathology is primarily driven by overproduction of Aβ, expression of the APOE4 genotype has an additive detrimental effect and lowers the age of onset, while APOE2 has a protective effect (van Duijn et al., 1994; Sorbi et al., 1995; Velez et al., 2016; Wijsman et al., 2005; Coppus et al., 2008; Wisniewski et al., 1995b; Royston et al., 1996). The paramount role APOE in AD pathogenesis is particularly highlighted in a recent report of a patient with the Colombia kindred PSEN1 E280A mutation, which typically causes the clinical onset of mild cognitive impairment (MCI) and dementia at the median ages of 44 and 49 years respectively (Arboleda-Velasquez et al., 2019; Zalocusky et al., 2019). This study found that the additional homozygous expression of the rare Christchurch APOE3 mutation of R154S (APOE3ch) resulted in resistance to the effects of the PS1 mutation; the patient did not develop MCI until her seventies, with very little tau pathology being detected by PET tracers (Arboleda-Velasquez et al., 2019). The APOE3ch variant protein has a significantly reduced ability to promote Aβ 1–42 peptide aggregation compared to wild-type APOE3, which was comparable to the effect of APOE2. The R154S mutation is in the region of APOE involved in lipoprotein receptor and heparin sulfate proteoglycan binding (Hashimoto et al., 2012). In addition, this region is involved in APOE binding to Aβ. Aβ binds to APOE both at the lipid binding region of residues 244–272 and at the N-terminal domain (Liu et al., 2011; Deroo et al., 2015; Luo et al., 2010). This case

illustrates the dramatic effect that altering the APOE-Aβ interaction can have in vivo, indicating that abrogation of this interaction is highly protective against the subsequent development of dementia, even in settings with abundant Aβ deposition. Interestingly, another rare APOE variant p.V236E in the lipid-binding, C-terminal domain of APOE (also involved in Aβ binding) is associated with a markedly reduced risk of AD (Medway et al., n.d.). The key role of APOE in AD pathogenesis may also explain why AD is a uniquely human disease (Drummond and Wisniewski, 2017; Walker and Jucker, 2017). The most biologically proximate animals to humans are non-human primates (NHP). It is well established that many NHP species develop abundant age dependent amyloid plaques and/or vascular amyloid deposition, yet none of these species develop significant (or any) NFT pathology or AD like dementia (Walker and Jucker, 2017; Devinsky et al., 2018; Heuer et al., 2012). All NHP are homozygous for APOE4, in that NHP APOE has an arginine at positions 112 and 158 (Walker and Jucker, 2017; Morelli et al., 1996). However, NHP APOE has a threonine instead of an arginine at amino acid position 61, causing it to function biologically in a manner similar to APOE3 (Walker and Jucker, 2017; Morelli et al., 1996). Hence, NHP lack a biological APOE4 like protein to interact with Aβ and drive the subsequent steps needed for the emergence of the AD phenotype. These data suggests that the APOE-Aβ interaction could be a highly effective therapeutic target.

2. Targeting the major genetic risk factor for AD: Apolipoprotein E4

APOE has pleiotropic functions in the CNS that include being the major CNS cholesterol and other lipid carrier. In addition, it is involved in vascular integrity, synaptic plasticity, glucose metabolism and mitochondrial function (Belloy et al., 2019; Huang and Mahley, 2014; Zhao et al., 2018). Hence, one important consideration when targeting the role of APOE in AD is that these normal functions should not be compromised. In addition, APOE is highly expressed outside of the brain, therefore off target effects must be considered when developing a therapeutic approach. Furthermore, APOE concurrently influences both the clearance and aggregation of Aβ in an isotype specific manner (Potter and Wisniewski, 2012; Belloy et al., 2019; Zhao et al., 2018;Hudry et al., 2019; Huynh et al., 2017; Bell et al., 2007; Han et al., 2016); hence, therapeutic approaches need to carefully balance these potentially opposing roles. In AD, it is still unclear whether the pathogenic role of APOE4 results from a toxic gain of function or loss of protective function. Transgenic mouse studies suggest that APOE4 has a toxic gain of function specifically with regards to its interaction with Aβ, while other pathological efects of APOE4 (e.g. astrocyte activation and synaptic loss) may result from loss of protective function (Safieh et al., 2019).

APOE enhances aggregation of Aβ in the order of APOE4 > APOE3 > APOE2 (Wisniewski and Frangione, 1992;Castano et al., 1995; Wisniewski et al., 1994b; Ma et al., 1994; Hori et al., 2015). APOE isotype specific effects have also been observed with regards to the stabilization of Aβ oligomers, where APOE4 was again shown to have the greatest influence (Hashimoto et al., 2012; Garai et al., 2014). In physiological conditions, there is relatively minor interaction between APOE and soluble Aβ (Verghese et al., 2013).

Instead, APOJ is the major CNS Aβ binding protein (Calero et al., 2000; Matsubara et al., 1995). However, a greater interaction between APOE and Aβ is observed in AD as the

aggregate state of Aβ shifts (Wisniewski et al., 1995a; Han et al., 2016; Golabek et al., 1995). The finding that APOE4 was less effective in clearing Aβ than APOE3 (Castellano et al., 2011) led to the initial hypothesis that blocking the interaction between Aβ and APOE could decrease the clearance of Aβ and therefore increase the formation of Aβ plaques. However, pivotal in vivo studies show that this does not occur. Blocking the Aβ/APOE interaction instead results in enhanced Aβ clearance from the brain and decreased plaque deposition (Sadowski et al., 2006; Sadowski et al., 2004; Yang et al., 2011; Liu et al., 2014; Pankiewicz et al., 2014). This is consistent with the finding that eliminating APOE greatly reduces the amount of amyloid plaque and vessel pathology in AD mouse models (Bales et al., 1997; Miao et al., 2005). Also supporting the hypothesis that APOE is an AD pathology promoter, rather than APOE4 having a loss of normal Aβ brain clearance function, is human data from a rare individual who lacks APOE due to an ablative APOE frameshift mutation. Despite complete absence of APOE this individual had no cognitive deficits, had normal brain MRI findings and normal CSF levels of Aβ and tau proteins (Mak et al., 2014). Multiple approaches for therapeutically targeting APOE in AD have been explored. Major examples of these are listed below.

2.1. Blocking the APOE/Aβ interaction

We have shown that treatment with a peptide that interferes with the Aβ/APOE interaction significantly decreased the amount of both parenchymal and vascular Aβ in three AD transgenic mouse models (Sadowski et al., 2006; Sadowski et al., 2004; Yang et al., 2011; Liu et al., 2014). This peptide (Aβ12–28P) is homologous to the APOE binding domain of Aβ, and therefore inhibits the Aβ-APOE interaction (Ma et al., 1996). The peptide was synthesized with D-amino acids and a proline substitution of valine at residue 18 of Aβ, which improved its resistance to proteolysis and ensures that it is non-toxic and non-fibrillogenic (Sadowski et al., 2006; Sadowski et al., 2004). Treatment of 3xTg mice with this peptide reduced both Aβ and tau pathology, while in TgSwDI mice with extensive CAA, it reduced vascular amyloid pathology (Yang et al., 2011; Liu et al., 2014). Hence, as illustrated in Fig. 1, altering the APOE-Aβ interaction can reduce all major AD related pathological lesions, in the absence of toxicity such as increased inflammation or microhemorrhages.

Corroborating results from another group have found that Aβ12–28P treatment caused a similar reduction of Aβ oligomer and plaque deposition in amyloid Tg mice with both an APOE2-targeted replacement (TR) or APOE4-TR mouse background, showing that the inhibition of the Aβ/APOE interaction is therapeutically beneficial regardless of the APOE isoform (Pankiewicz et al., 2014). More recently, we have enhanced our approach for potential future clinical application. We have designed and screened a large group of linear and cyclic peptoid compounds that block the Aβ/APOE interaction in a similar manner, to try to identify a compound that has higher effcacy and safety (Liu et al., 2017). The most promising candidate, CPO_Aβ17–21P, inhibited the APOE4/Aβ42 binding at a 2:1 M ratio and virtually blocked all binding at a 8:1 M ratio (peptoid:APOE4). This new candidate also had a significantly improved half-maximal inhibition (IC_{50}) in comparison to Aβ12–28P (Sadowski et al., 2004). The Aβ residues between 17 and 21 appear to be the critical region for Aβ binding to APOE, with the lysine at residue 16 being

particularly important (Liu et al., 2011; Deroo et al., 2015), therefore it is consistent that a peptoid conforming to this sequence is an effective inhibitor of the Aβ/APOE interaction. Treatment of APP/PS1 Tg mice with CPO_Aβ17–21P resulted in significant reduction of soluble and insoluble Aβ peptide/oligomer levels in brain, lower numbers of amyloid plaques and significantly improved cognitive function (Liu et al., 2017). Importantly, all of these effects were observed after treatment with a 7.5 fold lower dose than required for the Aβ12–28P studies (Liu et al., 2014; Liu et al., 2017), indicating that CPO_Aβ17–21P has improved bioavailability/biostability over Aβ12–28P. Importantly, treatment of APP/PS1 AD transgenic mice with CPO_Aβ17–21P did not increase the soluble Aβ pool. Additionally, there was no evidence of increased brain inflammation after treatment (Liu et al., 2017), which has been another possible concern with therapeutic strategies that target Aβ. We are in the process of using an innovative “scaffold hopping” medicinal chemistry approach (Hu et al., 2017) from CPO_Aβ17–21P to drug-like small molecule candidates, along with a receptor-based scaffold-independent approach to further refine this therapeutic approach. Our preclinical studies in multiple AD models have demonstrated that blocking the APOE/Aβ interaction is a promising therapeutic approach that is capable of reducing AD associated neuropathology and improving cognitive performance, in the absence of toxicity.

2.2. APOE immunotherapy

Immunotherapy using anti-APOE antibodies is also a potential therapeutic strategy for AD. Initial studies showed that treatment with an antibody against endogenous mouse APOE (HJ6.3) significantly reduced Aβ pathology in an AD transgenic mouse model (Kim et al., 2012;Liao et al., 2014). Recently, this work has been extended to show that treatment with an antibody against human APOE (HAE-4) also significantly reduces Aβ plaque pathology in an AD transgenic mouse model expressing human APOE4 (APPPS1–21/APOE4 mice). This antibody recognizes both APOE3 and APOE4 and preferentially binds to non-lipidated, aggregated APOE (Liao et al., 2018). While the exact mechanism of action is still unclear, it was proposed that the binding of anti-APOE antibodies to APOE present in amyloid plaques stimulated microglial activation via their Fc domain, which therefore resulted in plaque clearance. Further testing of this approach is underway; however, one potential problem is that off-target antibody binding may detrimentally interfere with the physiological functions of APOE.

2.3. Altering APOE4 conformation

Another means of ameliorating the pathological interaction between APOE4 and Aβ is to make it behave more like APOE3. The point mutations present in APOE4 result in a unique conformation due to a specific interaction between its amino-terminal and carboxyl terminal domains. Small molecule inhibitors have been developed to interfere with this interaction and therefore alter the conformation of APOE4 so that it resembles that of APOE3 or APOE2 (Mahley and Huang, 2012; Chen et al., 2012; Brodbeck et al., 2011). One of these structure correctors has been shown to reduce the APOE4 effects on Aβ, tau phosphorylation and neurodegeneration in human iPSC derived neurons expressing APOE4 (Wang et al., 2018). This approach is being further developed and tested as it is still unclear whether it has therapeutic benefits in vivo.

2.4. Expression of APOE2

Another elegant method of targeting the AD pathology promoting effects of APOE4 expression is to genetically drive production of “protective” APOE2 expression. Early studies showed that viral vector mediated expression of APOE2 in AD transgenic mouse models expressing endogenous mouse APOE resulted in significantly reduced amyloid plaque burden, significantly reduced levels of insoluble Aβ42 and Aβ40, and significantly reduced synapse loss around plaques in comparison to viral vector mediated expression of APOE4 (Hudry et al., 2013; Dodart et al., 2005). Importantly, it was then shown that viral vector mediated expression of APOE2 partially countered the detrimental effects of human APOE4 expression in AD transgenic mouse models if given at early stages of pathology development: AAV-APOE2 treatment of APP.PS1/APOE-TR mice resulted in significantly decreased levels of insoluble Aβ42 and Aβ40 in the brain (Zhao et al., 2016).

A more recent study tested the delivery of AAVrh.10hAPOE2-HA, an AAVrh.10 serotype coding for an HA-tagged human APOE2 by intraparenchymal, intracisternal, and intraventricular routes of delivery to the CNS of African Green monkeys (Rosenberg et al., 2018). The data showed that while all three routes are capable of mediating APOE2 expression in AD relevant regions, intracisternal delivery of AAVrh.10hAPOE2-HA safely mediated wide distribution of APOE2 with the least invasive surgery, thus potentially providing the optimal strategy to deliver vector-mediated human APOE2 to the CNS. A phase I clinical trial is now on-going in AD APOE4 homozygous patients of AAVrh-10APOE2 delivered by intracisternal injection (Crystal et al., 2019).

2.5. Gene editing APOE4 to APOE3

Direct conversion of APOE4 to APOE2 or APOE3 using a gene editing strategy such as CRISPR could be a potentially straightforward therapeutic approach. Proof-of-concept studies in vitro using iPSCs and organoids has shown that this approach has potential; conversion of APOE4 to APOE3 in these models was shown to decrease Aβ, and to reduce tau phosphorylation and neurodegeneration (Wang et al., 2018;Lin et al., 2018). However, using gene editing as a therapeutic approach is still in its infancy and it is not yet known whether this would work in vivo.

3. Summary

There is extensive evidence that APOE alleles differentially modulate AD pathogenesis by varying effects on net Aβ oligomerization/aggregation versus clearance. The APOE4 isoform remains the most important genetic risk factor for AD. Recent studies have shown strikingly dramatic APOE mediated effects even in the setting of an EOAD PS1 mutation (Arboleda-Velasquez et al., 2019; Zalocusky et al., 2019). The road to the discovery of effective AD therapies has been marked by a long string of failures, at least in part, due to relatively few investigators directly targeting the critical role of APOE in AD. In this review, we summarize a few of what we feel are the most promising on-going approaches to overcome this shortcoming in the field. These approaches have great potential for both the prevention and/or treatment of AD in the absence of significant toxicity.

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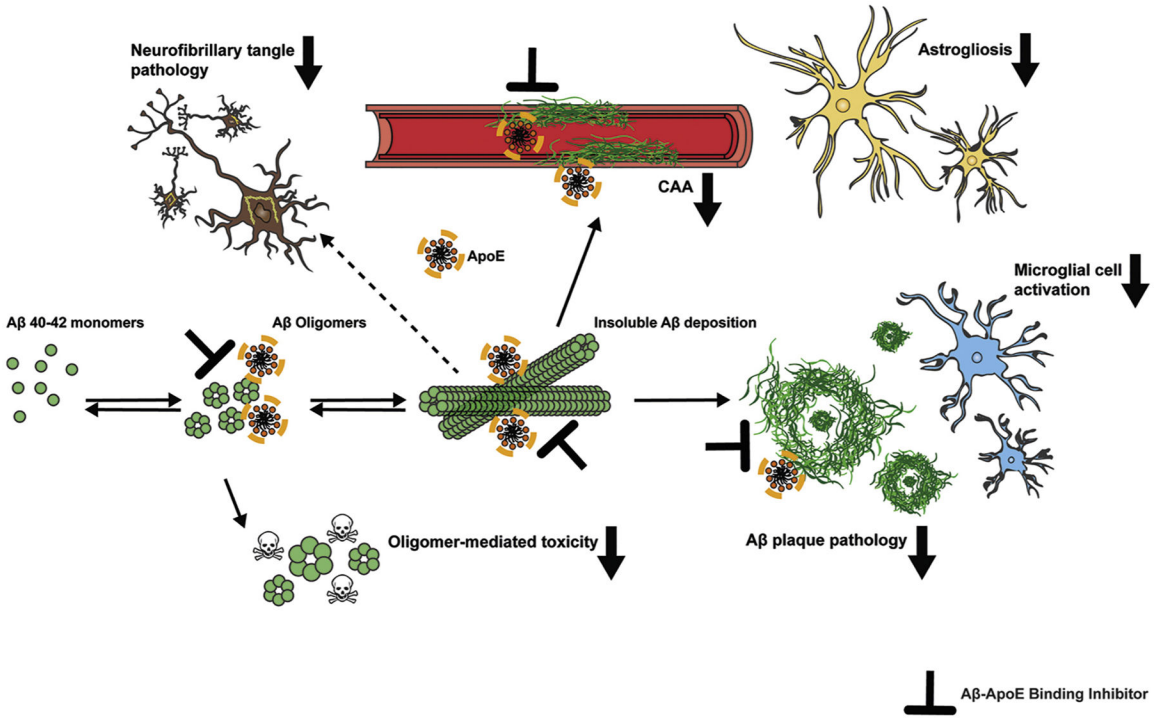

Fig. 1.

Illustration of the potential effects of blocking the APOE-Aβ interaction with resultant reduction of the major pathologies that characterize AD.