Review

The utilisation of genetics to advance the development of pharmaceutical treatments for late-onset Alzheimer's disease

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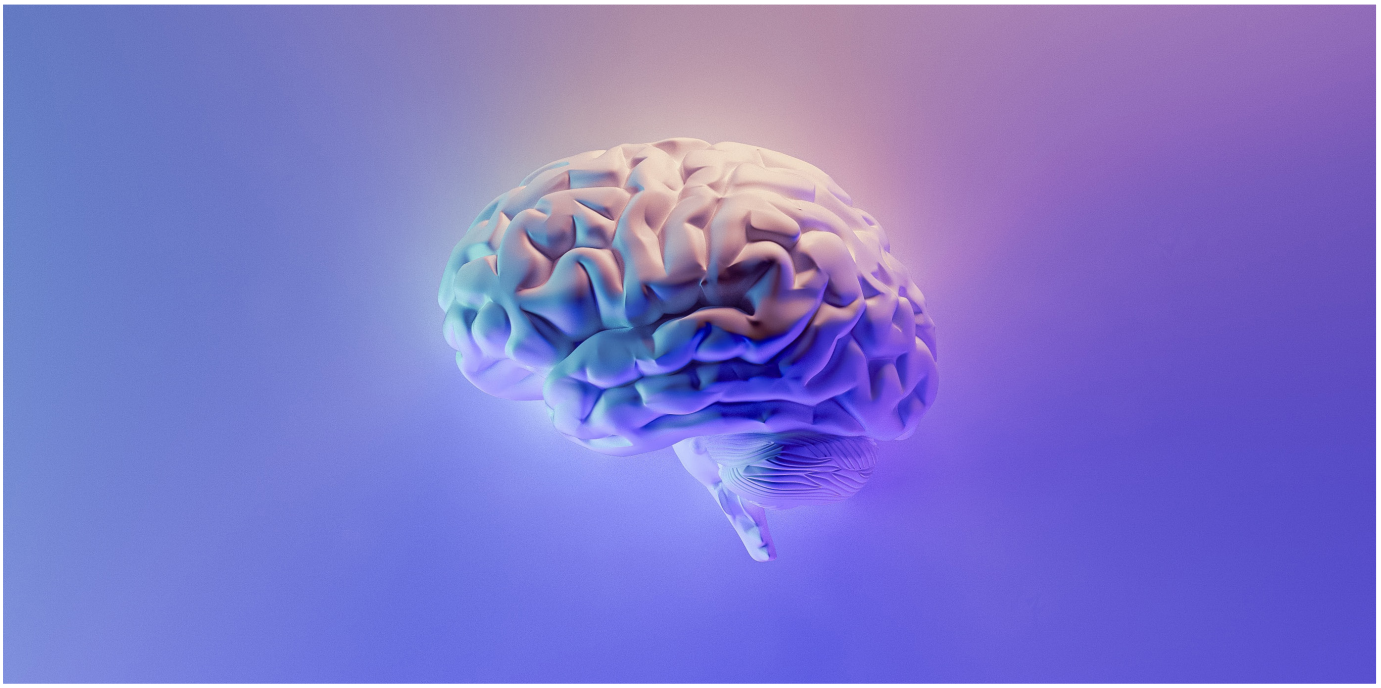

Abstract

Alzheimer's disease (AD), common in our elderly population, is set to almost double in prevalence within the next few decades. Current medications focus on symptom control and relief, but no treatments hinder disease progression. However, targeting genes associated with late-onset Alzheimer's disease (LOAD) to further the advancement and development of treatments for LOAD has been hypothesised. A literature search was completed on PubMed to investigate this. The search provided knowledge of the *APOE* gene and its contributions to the pathophysiology of LOAD, inciting key findings regarding AD treatments that can target apoE proteins, such as LDLRs, LXRs and recently, the development of mAbs. Several trials on mice, using fluvastatin to target apoE protein receptors, produced various benefits, such as decreased amyloid-beta plaques and increased Aβ clearance. Further mice trials to increase apoE quantity and lipidation using LXR and RXR's, provided similar benefits, and sometimes a reversal of all AD symptoms. Human drug trials did not reproduce similar therapeutic benefits and these drugs resulted in side effects such as liver toxicity. In addition, several mAbs such as donanemab, have been instrumental in AD research but they still produce severe side effects for patients, including micro haemorrhage and oedema. Genetic knowledge can help researchers develop appropriate drugs to target mechanisms associated with the *APOE* gene and LOAD pathology. However, more drug research is needed to investigate and mitigate dangerous side effects.

Abbreviations

ABCA1 – ATP-binding cassette transporter A1
Aβ – Amyloid beta
AD – Alzheimer's disease
APOE – Apolipoprotein gene
apoE – Apolipoprotein E
ARIA – Amyloid-related imaging abnormality
CNS – Central nervous system
LDLR – Low-density lipoprotein receptors
LOAD – Late-onset Alzheimer's disease
LRP1 – Low-density lipoprotein receptor-related protein 1
LXR – Liver X receptors
mAb – Monoclonal antibody
PET – Positron Emission Scan
RXRs – Retinoid X receptor agonists

Introduction

What is Alzheimer's disease?

Alzheimer's disease (AD) is the most common type of dementia and is defined as a neurodegenerative disorder that progressively worsens over time, gradually affecting memory.[1] AD is extremely debilitating and is increasing in our elderly population. As of 2019, over 850,000

people in the UK over 65 were diagnosed with AD.[2] Statistics predict that with the current growing rates this will be over 1.5 million in 2040.[2] In 2012 an estimated 13% of people over 65 years old had AD.[3] AD is divided into two subsections, early-onset familial, or late-onset (>65 years old); they account for 5% and 95% of cases respectively.[4] Early symptoms of AD include loss of short-term memory, causing patients to show mild cognitive impairments. As AD advances, disorientation, language impairment, extreme behaviour changes, and difficulty with motor and sensory functions begin. Eventually, major organs and key bodily functions begin to deteriorate, and most cases of AD result in death. After diagnosis, the average life expectancy is between three and nine years.[5] The high occurrence and lack of suitable management make AD a crucial area for medical research. Currently, there is no treatment available that successfully reverses or permanently halts AD progression.[6] This paper examines the potential of genetics in targeted pharmaceuticals, signifying the utility of genetics in this area of medicine.

Genetics of Alzheimer's disease

Unfortunately, the pathogenesis of late-onset Alzheimer's disease (LOAD) is complex and multi-faceted, making it difficult to underpin the genetics. Lifestyle and environmental factors also impact an individual's lifetime risk of LOAD, further complicating the pathophysiology.[7] Consequently, no mutations are identified as being solely responsible for LOAD, but over 30 at-risk loci have been acknowledged through genome-wide association studies, and over half of these loci have some association with the *APOE* gene.[8]

The *APOE* gene is located on chromosome 19 and presents as three different polymorphic alleles: *ε2*, *ε3* and *ε4*, with *ε3* being the most common.[9] The *ε4* allele is associated with the biggest disease risk, with a single copy estimated to increase your risk of LOAD by three-fold, and two copies increase your risk by 9-to 15-fold.[9] The *ε4* allele is present in 13.7% of the general population but in approximately 40% of AD patients.[10] ApoE is the only cholesterol carrier in the brain and a major carrier in peripheral tissues. It plays a major role in lipid metabolism, homeostasis, and inflammatory response regulation. In the central nervous system (CNS), apoE is produced by astrocytes and will transport cholesterol to neurons in the brain via apoE receptors, such as low-density lipoprotein receptors (LDLRs).[11]

The amyloid cascade hypothesis suggests that AD degeneration is caused by amyloid beta (Aβ) accumulation in the brain.[12] This occurs through changes in Aβ metabolism, either through increased production or reduced clearance.[13] Increased Aβ in the brain will enhance oligomer formation, which eventually leads to severe damaging effects on synaptic function. In addition, inflammatory responses will occur and will lead to plaque formation. Over time, this leads to oxidative stress in the brain and causes various biochemical changes.[14] This cascade ends with increased Aβ and hyperphosphorylated neurofibrillary tau tangles, consequently leading to neuronal injury and cell death, producing the symptoms of AD.[14]

Pathological studies have investigated the implication the *APOE-ε4* gene has in AD pathogenesis. The pathogenesis can be categorised into a gain of toxic function, loss of physiological function, or both. A gain of toxic *APOE-ε4* gene function involves a decrease of Aβ clearance, increased Aβ aggregation in cells and increased neuronal toxicity. Post-mortem studies then confirmed that the *APOE-ε4* gene enhances inter-neuronal Aβ plaques accretion and neurotoxic Aβ oligomer formation.[15,16] A loss of physiological function in the brain encompasses decreased integrity of the blood-brain barrier, decreased synaptic function, and increased inflammatory function, which leads to neuronal injury, further increasing the vulnerability of the brain to the toxic *APOE-ε4* gene. This vulnerability leads to further damage, which produces the symptoms seen in AD patients. However, research found that *APOE-ε2* carriers have less chance of developing LOAD and, in a cross-sectional study, *APOE-ε2* was associated with decreased Aβ accumulation in participants with normal cognitive functions. In participants showing signs of cognitive deficit, *APOE-ε2* was slightly neuroprotective against Aβ depositions, concluding that *APOE ε2* does not have any part in the AD pathogenesis and aids in reducing the risk of LOAD.[9] But when both *APOE-ε2* and *APOE-ε4* alleles are present, the neuro-protectiveness of *APOE-ε2* will not outweigh the neuro-destructive nature of *APOE-ε4*.[9]

The latest AD research focuses particularly on gene-targeted therapies, involving the *APOE* gene. This review examines papers investigating this new research and the pharmacological approaches produced as a result.

Methodology

A literature search on PubMed was conducted to understand AD genetics. The search criteria excluded results from before 2003, ensuring up-to-date information and excluded papers not focused on LOAD, as the pathophysiology between early onset and LOAD is different. The filter "best match" was applied, to ensure the top papers answered the search title. Initially, the search term was 'Alzheimer's disease, "genetics"'. When selecting meta-analysis and systematic reviews, this search produced 6980 results, with the abstracts of top papers including the keywords LOAD, *APOE* and treatment. Next a more targeted search of 'LOAD, *APOE* gene' was completed to understand more about LOAD and the implications that *APOE* has to this subtype. Finally, a search of 'LOAD, *APOE* treatment, genetics' was completed. Relevant papers were identified through abstract keywords of monoclonal antibodies, aducanumab and donanemab. From papers found, citation chaining was used to ascertain more research papers and reviews, and from these papers, key information and findings were synthesised. In addition, a Google Scholar search provided recent figures on Alzheimer's prevalence.

Discussion

Modifying Aβ levels

In the brain, apoE mainly binds to LDLRs, such as low-density lipoprotein receptor-related protein 1 (LRP1), which are strongly linked to cholesterol homeostasis and clearing Aβ depositions.[11] In LOAD, LRP1 levels decrease, resulting in Aβ and cholesterol build-up, two hallmark signs of LOAD.[10] Consequently, researchers investigated whether overexpressing LDLRs could reduce Aβ build up, subsiding its destruction, and potentially being utilised as a therapeutic mechanism.[9] Research in mice that overexpress the amyloid precursor protein gene (APP transgenic mice), supports this theory, showing that LDLR deficiency increased Aβ deposition, whereas in LDLR overexpression it decreased Aβ depositions but also increased Aβ clearance.[17] One supporting study administered 5 mg/kg/day of Fluvastatin in 8-week-old mice. Studies have suggested that statins could help reduce AD risk. The exact mechanism is not understood; however, it is hypothesised that statins influence Aβ metabolism.[18] Their results showed that fluvastatin increased Aβ clearance and LRP1 expression at the blood-brain barrier, but no results showed decreased brain cholesterol levels. Although these studies' positive results provided a solid foundation, the research is new and further trials are needed.[18] Another study, also involving wild mice, tested caffeine and rifampicin, as these compounds have been reported as having a protective effect against AD, by potentially enhancing the clearance of Aβ from the brain. There were three groups: 40mg/kg caffeine daily, 20mg/kg rifampicin daily, and a control group, with approximately 4 mice per group. The study identified that these two structurally different compounds both contribute to LRP1 upregulation and increased Aβ clearance. However, researchers suggested other factors could explain these results, hypothesising the presence of an undiscovered receptor to regulate Aβ clearance.[19]

Both articles demonstrate major advances in LOAD therapy by lowering Aβ levels in the brain, eliminating plaque build-up, and focusing on one fundamental pathological aetiology of LOAD. However, further analysis reveals several flaws, including a lack of

understanding about the specific mechanism of action of these drugs, and that experts have suggested other possible receptors, indicating the need for more research. In addition, Quosa's 2012 study has higher validity compared to Shinohara's 2010 study, their use of genetically "normal" mice decreased the skewing of results, whereas genetically modified APP transgenic mice could increase drug effectiveness, making their results unreliable. Also, using mice creates a shared barrier for both papers, as it is untransferable for human application without further research.[18,19]

Targeting apoE quantity and lipidation

Due to implications in lipid homeostasis, LOAD-related pathways can be influenced by apoE lipidation. LXRs are regulators of lipid homeostasis. It is theorised that LXR's effect on LOAD is due to the regulation of ABCA1 expression, which affects apoE lipidation. Poor lipidation diminishes apoE's ability to break down Aβ.[20] LXRα/LXRβ deficient APP transgenic mice research showed this, as they had increased Aβ deposits and consequently AD signs in their brains.[21] LXRs T0901317 and GW3965 were developed to improve Aβ clearance and apoE production in neuronal cells. A study of Aβ plaque-free mice involved giving 50mg/kg a day of T0901317 for seven days. Results showed T0901317 increased expression of ABCA1 in their hippocampi, increased apoE, and improved contextual memory deficits[22] Similarly, a study involving GW3965 showed enhanced transcription of apoE and ABCA1, reducing Aβ levels in mice[23] Both LXRs improved Aβ clearance and altered apoE production in neuronal cells. Long-term administration showed 50% reductions in Aβ plaques.[24] However, first-generation LXRs were unsuitable for further development, due to high liver triglyceride levels. Newer LXRs had similar side effects in clinical trials, resulting in no drugs achieving FDA approval.[20]

The most popular RXR is bexarotene, an FDA-approved drug used to treat T-cell lymphoma.[25] A study of oral bexarotene in mice showed increased clearance of soluble Aβ. Within 72 hours of receiving bexarotene, 50% of Aβ was cleared.[26] However, clinical applications are limited due to reported liver toxicity. Additionally, in a double-blind placebo human clinical trial of 20 AD patients, bexarotene showed no impact in reducing Aβ or any AD symptoms, and it showed poor CNS penetration. The only effect was increased serum triglycerides, concluding that bexarotene cannot be administered outside clinical trials.[27] Analysis of the paper found their research weakness was the species barrier.[27] The effectiveness and penetration of drugs vary between mice and humans. The papers provide a basis for how we can utilise drugs but conclusively point towards the need for further research to investigate supplementary factors causing cholesterol levels to rise in the periphery.

Monoclonal antibody treatment

The newest treatment is monoclonal antibodies (mAbs). Aducanumab, a disease-modifying human mAb, became the first FDA-approved mAb in 2021.[28] Aducanumab selectively binds to Aβ, both oligomeric and fibrillar, meaning it directly targets the pathophysiology of LOAD.[29] In a double-blind, placebo-controlled randomised phase I trial PRIME, 165 participants with mild AD and positive Aβ positron emission scans (PET) were given a placebo or 1,3,6 or 10 mg/kg infusion of aducanumab for 12 months.[30] Results showed significant reductions in Aβ PET; for participants in the 3,6 and 10 mg/kg group there was a decline in Aβ, but in the 10mg/kg group, some participants now had negative Aβ PET.[31] The PRIME study showed concurrent results in *APOE ε4* carriers and non-carriers.[30] Nevertheless, the study had limitations, including a small sample size and reduced region sample, as they only included USA participants.[30] The next two phase III trials, EMERGE and ENGAGE were completed, with doses based on *APOE ε4* carrier status. Participants were given a low dose, high dose or placebo. In the low-dose group, carriers received 3 mg/kg and non-carriers received 6 mg/kg, in the high-dose group carriers received 6 mg/kg and non-carriers received 10 mg/kg. This was every four weeks for 72 weeks.[32] Post hoc analysis showed higher dose groups demonstrated greater reductions of Aβ plaques. However, futility analysis prompted the early termination of the trial, prompting questions about the validity of the trial's findings. The trial admits to lacking diversity in their population, further biasing their results.[32]

Both studies reported postponed clinical effects of aducanumab, estimating six-month delays in clinical improvement.[30,32] Throughout trials of aducanumab, there have been no reported deaths.[29] However, severe side effects include ARIA.[28] There are two types: ARIA-E (oedema) and ARIA-H (micro haemorrhage or hemosiderin deposition).[28] In the PRIME study, ARIA-E was the prevailing side effect, occurring in higher dose groups amongst *APOE ε4* carriers, with 41% suffering brain oedema.[30] Similar figures were reported in the phase III trials, where 35% of participants suffered ARIA-E.[31] Research on aducanumab has shown other side effects including headaches, nausea, and confusion. Due to disparities in research, further studies are needed to effectively judge the drug's efficacy against its risks.[28]

Donanemab, an immunoglobulin G1 mAb, was trialled after the initial results of aducanumab. Donanemab is designed to directly target insoluble Aβ and help remove Aβ plaques via phagocytosis.[33] TRAILBLAZER-ALZ 2 was a double-blind, placebo-controlled, phase III trial to assess the efficacy and adverse events caused by donanemab.[33] Participants aged 60–85 years were categorised into low/medium or high tau populations after receiving a mini-mental state exam and Aβ and Tau PET scans.[33] Donanemab showed 80% clearance in the low/medium group after 76 weeks and produced meaningful clinical benefits.[33] However, ARIA-E occurred in 24% of participants in the donanemab group, and three patients died after ARIA, two of these were *APOE ε4* carriers.[33] This trial had limitations, including population bias due to a majority white population.[33] Overall, this study concluded that donanemab slows AD clinical progression and has fewer ARIA incidents.[33]

Conclusion

Current research indicates that applying our knowledge of genes and targeting them, has had huge advancements in the treatment for LOAD. This highlights the importance of combining genetics and precision medicine, to aid researchers in developing even more effective LOAD treatments. Targeting LDLR receptors with different compounds has led to Aβ plaque decline, increased Aβ clearance, increased apoE expression and reversals of AD symptoms. LXR and RXRs help increase apoE quantity and lipidation, reproducing many of the same desirable effects as the LDLR targeting compounds. However, most research was done in mice and has not produced positive results in human trials. They have resulted in toxic side effects and no change in symptoms. Monoclonal antibody therapy has been the most promising development to come from genetics research into AD medication, the most successful of these being donanemab. However, severe side effects persist, regardless of the treatment of choice, making monoclonal antibody therapy less than ideal for some patients with AD, especially for *APOE ε4* carriers. In the future, further human clinical trials and randomised control trials are needed, hopefully, producing a more efficacious drug that can safely target the *APOE* gene, and the pathologies associated with it, to reduce LOAD in the general population.

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Hi! I'm a third-year medical student at the University of Exeter. My interests in medicine are currently surgery, neurology and oncology, particularly focussing on genetics and the potential they could have in helping develop safer and more successful treatments for patients in the future.