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Beta Amyloid Proteins and Alzheimer's Disease Treatments

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Abstract

Alzheimer's Disease is a degenerative disorder of the brain that results in the deterioration of memory, language, and behavior. The accumulation of a protein called amyloid beta is responsible for the development of Alzheimer's Disease. This protein forms plaques in the brain, obstructing communication between neurons and playing a crucial role in the progression of the disease. Potential treatments aiming to reduce the presence of beta amyloid plaques include immunotherapy (both active and passive), enzymes that degrade beta amyloid, and inhibitors of beta secretase. Unfortunately, effective treatments for Alzheimer's Disease are currently unavailable due to the severe side effects and limited effectiveness of existing options. As Alzheimer's Disease is influenced by various factors including but not limited to amyloid beta proteins, a comprehensive study that includes clinical trials becomes vital in finding an effective treatment. Clinical trial data suggests that beta amyloid degrading enzymes show the most promise as a future treatment, as they have successfully reduced amyloid beta plaque levels in the brain with minimal side effects compared to the other treatments. This review aims to provide a basic understanding of Alzheimer's Disease by exploring the interactions between neurons, amyloid beta proteins, and other internal factors that contribute to the disease's development. Additionally, it highlights three potential treatments and their approaches to preventing or reducing amyloid beta proteins, supported by relevant clinical trial data. Finally, the review discusses the side effects and limitations of current treatment options while considering the potential of becoming viable future treatments.

Keywords: Alzheimers, Beta Amyloid Protein, Beta Secretase

1. Introduction

The initial identification of Alzheimer's Disease (AD) dates back to 1906 when German Physicist Alois Alzheimer first reported a case. Alzheimer's is the most prevalent cause of dementia, a clinical syndrome characterized by memory loss, impaired judgment, and difficulties in daily activities (Lopez et al., 2019). The accumulation of amyloid beta and hyperphosphorylated tau protein are the two primary factors known to contribute to the development of Alzheimer's disease. While much attention has been focused on these proteins, their build-up leads to the deterioration of synapses and affects dendritic spines. This loss of signal transmission between neurons ultimately results in apoptosis or cell death, causing the brain to shrink in size. AD can be categorized into two types based on different age groups: Familial Alzheimer's (early-onset), affecting individuals between the ages of 30-65, often influenced by genetic and environmental factors, and Sporadic Alzheimer's (late-onset), diagnosed in individuals over the age of 65 (Athar et al., 2021). Familial Alzheimer's represents a smaller percentage, around 5-10%, of all Alzheimer's cases and is considered rarer compared to Sporadic Alzheimer's. When it comes to Familial Alzheimer’s the scientific community primarily focuses on identifying early signs of the disease to enable earlier diagnosis and better management of symptom severity. However, more emphasis is placed on Sporadic Alzheimer’s since it is more common and would effect a wider population of people with Alzheimer’s. The treatments discussed in this review

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primarily target Sporadic Alzheimer's and aim to reduce and prevent the accumulation of beta amyloid protein. Beta amyloid protein contributes to the development of Alzheimer's by disrupting the balance between protein clearance and production, leading to the build-up of Aβ between neurons and hindering neuronal signaling. Another contributor to Alzheimer's is the formation of Neurofibrillary Tangles, caused by the tau protein. Tau protein assists in maintaining microtubules, internal structures that facilitate the transportation of nutrients and molecules from the cell body to the axon and dendrites. In Alzheimer's, chemical changes cause tau to detach from microtubules and adhere to other tau molecules, resulting in the formation of tangles and disrupting synaptic transmission between neurons. These factors lead to neuronal damage or death and contribute to the shrinkage or atrophy of the brain, a prominent clinical feature of Alzheimer's cases. Although both beta amyloid protein and tau protein are of importance, this review primarily focuses on treatments that specifically target beta amyloid protein. A correlation has been discovered, where an increase in beta amyloid in the brain is associated with an increase in tau. However, further research is required to fully understand this relationship. Recent clinical findings suggest that beta amyloid leads to the aggregation of tau, making it more harmful (Rajmohan & Reddy, 2017). Hence, the focus of this review is on targeting beta amyloid plaques, which significantly contribute to the progression of the disease. Multiple potential treatments are currently under investigation and have shown promising results in certain clinical trials. These treatments encompass Immunotherapy, Beta Amyloid Degrading Enzymes, and Beta Secretase Inhibitors, all of which aim to reduce or prevent the formation of amyloid beta plaques (Weller & Budson, 2018).

2. Role of Amyloid Beta Protein in Alzheimer's Disease

Amyloid beta proteins play a significant role in the development of Alzheimer's disease (AD) by accumulating between neurons and forming amyloid beta plaques. These plaques disrupt neuronal signaling, leading to cell death, brain atrophy, and ultimately dementia (Chen et al., 2017). Amyloid Precursor Protein (APP) is a transmembrane protein that undergoes enzymatic breakdown, particularly by b-secretase, resulting in fragments with different functions. The cleavage between b-secretase and APP produces Aβ monomers. Aβ serves various roles in the brain, including neuroprotection, memory and synaptic plasticity regulation, cholesterol transport regulation, and acting as a transcription factor (Gouras et al., 2015). The Amyloid Hypothesis describes a cascade of events that explains the dynamic equilibrium of amyloid beta protein. This equilibrium relies on the balance between the clearance and production of Aβ. However, disturbances caused by oxidative stress or other factors can lead to an increased accumulation of Aβ and the formation of amyloid beta plaques. The increased Aβ levels trigger an inflammatory response by the immune system, resulting in cell death and the progression of AD (Folch et al., 2018).

3. Immunotherapy

Immunotherapy is a highly focused area of research in the treatment of Alzheimer's disease (AD). It involves activating the immune system by introducing specific antibodies to elicit an immune response. There are two types of immunotherapy: active and passive immunization. Active immunization involves administering synthetic Aβ fragments as a vaccine to activate the immune system's T-cells and B-cells, which can help reverse the deteriorating conditions caused by AD. On the other hand, passive immunization involves injecting externally produced monoclonal antibodies that target amyloid (Blasko & Loebenstein, 2003). While immunotherapy has shown promise in animal trials by reducing Aβ levels, there is limited human clinical trial data available. Some animals treated with active immunization experienced encephalitis (inflammation of the brain) and vasogenic edema (disruption of the blood-brain barrier causing fluid accumulation), while those treated with passive immunization showed amyloid-related imaging abnormalities (Wisniewski & Goni, 2014). These side effects raise concerns about the safety and effectiveness of immunotherapy in humans. Furthermore, passive immunization is considered short-term and costly compared to active immunization, which is more long-term and cost-effective. In a clinical trial involving mice, different vaccines were tested, and while they showed reduction in Aβ levels in the mice's brains, there were unwanted side effects due to immune responses. Researchers estimate that the vaccine may only be effective for a subset of patients (20-30%) due to genetic and immune response differences. Based on the available clinical data, it is evident that immunotherapy

Vol. 2024 (6) 212 – 216
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as a treatment for AD is complex and carries risks (Valiukas et al., 2022). Modifications are necessary to minimize side effects and ensure its effectiveness for the entire population. Ongoing research aims to address these challenges and improve the potential of immunotherapy in treating AD.

4. Beta Amyloid Degrading Enzymes

Extensive research has been conducted on Beta amyloid degrading enzymes (ADE) due to their highly effective role in degrading Aβ. These enzymes are naturally present in the brain and are responsible for breaking down small amounts of intracellular and extracellular Aβ. Neprilysin, Endothelin-Converting Enzyme, Insulin-Degrading Enzyme, and Plasmin are among the potential candidates for Aβ degradation, and their connection with Aβ deposition has been established. However, during the progression of AD, a decrease in protein expression and oxidative stress disrupts the function of ADE, leading to the formation of beta amyloid plaques (Schenk et al., 2012). In a clinical trial involving cultured cells of Chinese hamster ovaries and mice, Neprilysin was found to be a crucial enzyme correlated with amyloid beta deposition. Reduced levels of this enzyme were associated with higher percentage deposition. Endothelin-Converting Enzyme demonstrated a 90% reduction in extracellular Aβ concentration, although this varied depending on different controls and levels. Nevertheless, this enzyme plays a significant role in Aβ clearance, requiring further research. Insulin-Degrading Enzymes exhibited gene-dose dependent effects on Aβ deposition, showing different outcomes in transgenic mice compared to heterozygous mice. On the other hand, Plasmin, despite its involvement in various neuronal functions, did not show a direct impact on Aβ levels in plasminogen deficient mice (Wang et al., 2006). Gene therapy, a method of reconstructing genetic material for desired effects, has shown potential in increasing ADE expression. However, ethical concerns and limited knowledge hinder its application in humans. Gene delivery of certain degrading enzymes to APP has been experimented on transgenic mice, resulting in reduced amyloid beta levels. As an alternative, pharmacological agents have been explored to increase ADE expression in a more efficient and ethical manner compared to gene therapy (Sikanyika et al., 2019). Further research on enzyme activation holds promise for the development of new drugs to treat AD.

5. Beta Secretase Inhibitors

Beta Secretase is an enzyme responsible for cleaving the transmembrane protein APP, which triggers the production of Aβ. Enzyme inhibitors are molecules that bind to this enzyme, reducing its activity and preventing it from catalyzing the reaction. BACE inhibitors have shown promise as a valid treatment for AD by blocking beta-secretase and halting the production of Aβ (Kumar et al., 2018). However, the development of these inhibitors faced a challenge with the Blood Brain Barrier (BBB), which restricts the passage of large or hydrophilic molecules into the brain's extracellular fluid. Scientists have since discovered methods to overcome this barrier. Some BACE inhibitors have reached phase I trials, but they were terminated due to liver abnormalities or issues with blood plasma (Lukiw, 2013). Gamma secretase is another enzyme involved in amyloid cleavage, and combining gamma secretase modulators with BACE inhibitors has shown effectiveness in reducing Aβ with minimal side effects (Madav et al., 2019). Clinical trials involving the beta secretase inhibitor MK-8931 demonstrated significant reductions in Aβ levels in the Cerebrospinal Fluid (CSF). In a separate one-week trial with 32 patients having mild to moderate AD, 84% of Aβ levels were decreased in the CSF. However, it is important to note that BACE inhibitors may not have a significant impact on patients with moderate AD, as the amyloid beta plaques would have already formed (Menting & Claassen, 2014). Further research is necessary to determine the potential of BACE inhibitors as a future treatment option. Additionally, managing side effects and addressing the limitations of this treatment approach are crucial areas for improvement.

6. Conclusion

The key findings of this literature review indicate that three treatments, namely immunotherapy, beta amyloid degrading enzymes, and beta secretase inhibitors, all aim to target and reduce the formation of beta amyloid plaques,

Vol. 2024 (6) 212 – 216
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which are known to be one of the main causes of AD. Immunotherapy involves the use of antibodies that target different forms of amyloid, and can be administered through passive or active immunization. While immunotherapy seems to be successful in targeting amyloid, further investigation is necessary due to the severe side effects, such as encephalitis and vasogenic edema. Passive immunization is unlikely to be a viable treatment option due to numerous disadvantages such as increased cost, severe side effects, and being a short term treatment. Moreover, data from active immunization clinical trials suggest that this treatment can only benefit a limited percentage of the population (20-30%) due to specific genetic factors, making future modifications complex and time-consuming (Valiukas et al., 2022).

Beta amyloid degrading enzymes directly act upon the beta amyloid plaques in the brain. Many scientists believe this approach has the potential to become the leading treatment for Alzheimer's in the future. However, this treatment faces a major roadblock, as it requires gene therapy to increase enzyme expression. Scientists are cautious about gene therapy as in the past there were problems such as targeting the wrong cells, creating an unwanted immune response, and other infections, so they are moving in a slow pace to understand more about gene therapy and apply that to beta amyloid degrading enzymes as a possible treatment for AD. Beta amyloid degrading enzymes have shown promising results in clinical trials with Endothelin-Converting Enzymes degrading 90% of extracellular Aβ. Proper management of side effects and successful results in clinical trials will pave the way for advancement in this treatment modality.

Lastly, Beta secretase inhibitors have demonstrated good results in clinical trials by directly blocking the enzyme beta-secretase from initiating the production of Aβ. In clinical trials, beta-secretase inhibitors have successfully lowered Aβ levels in cerebrospinal fluid (Menting & Claassen, 2014). However, the main drawback of this treatment is its inefficiency in patients already presenting with amyloid beta plaques, as it primarily stops the production of Aβ. Additionally, it can have some side effects such as liver abnormalities or problems with blood plasma. Therefore, scientists are hesitant on exploring more on this treatment option as it will not have a major effect on people already present with mild to severe AD.

It should be kept in mind that AD is caused by numerous additional factors, but after considering the advantages and disadvantages of all treatment options and the data analyzed in this literature review, beta amyloid degrading enzymes show the most promise for being a future treatment option. This is based on the positive outcomes that showcase significant reduction in Aβ levels. Gene therapy appears to be a roadblock for this treatment as it is still evolving, but scientists are gaining better control over it and are moving closer to conducting clinical trials. Moreover, making the treatment more affordable and accessible to a broader population is equally important. It is crucial to acknowledge that Alzheimer's disease (AD) is caused by various factors, beyond just beta amyloid plaques. Therefore, the treatment strategy should encompass comprehensive research into all these contributing factors to achieve the most effective results.

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Vol. 2024 (6) 212 – 216
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