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THE COMPREHENSIVE REVIEW OF AMLYIOD HYPOTHESIS IN ALZHEIMER'S (AD)

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ABSTRACT

Research on AD, or Alzheimer's disease, influenced via amyloid theory. But our knowledge of this framework has changed dramatically as a result of mounting clinical, genetic, and molecular evidence. It is now widely acknowledged that the most dangerous forms of Aβ are the smaller, soluble oligomers, early protofibrils, and quickly forming aggregates produced by processes like secondary nucleation and supersaturation, rather than the large, mature fibrils that were previously believed to be central to the disease. Amyloid toxicity is highly dependent on individual biological context, as seen by the significant influence of genetic variables, particularly APOE ε4 and TREM2 variations, on how the brain clears Aβ, how microglia react, and how well proteostasis is maintained. In this review, we give a summary of all available treatment approaches targeted at decreasing the generation of Aβ, preventing its aggregation, and improving its elimination. The clinical advantages, side-effect profiles, and practical issues, such as the requirement for close monitoring of ARIA, of the newly licensed anti-amyloid antibodies aducanumab, lecanemab, and donanemab are analyzed.

KEYWORDS: - Amyloid, Alzheimer's Disease, hypothesis.

INTRODUCTION

Studies have concentrated on understanding the biology as well as molecular mechanisms Alzheimer's disease's underlying (AD) in order to guide the development of therapeutics. This article reviews the primary therapeutic strategies that have been studied, all of which focus on the amyloid-β (Aβ) peptide. These therapeutic modalities often

fit into one of three primary categories: medications that inhibit β- or γ-secretase to lower Aβ synthesis, compounds that prevent Aβ from aggregating or forming dangerous aggregates, and active and passive immunotherapy methods meant to enhance the body's capacity to get rid of Aβ.

Since Aβ is the primary element of amyloid Plaques, researchers have a clear aim for treating Alzheimer's. Present Aβ-focused strategies aim to either reduce its synthesis, stop its aggregation, or enhance its elimination from the brain. The subsequent sections discuss progress in aggregation blockers and clearance therapies. This section specifically highlights advancements in reducing Aβ production.

(1). The Amyloid Hypothesis Development

Increased Aβ synthesis causes plaque development, which is followed by tau abnormalities, neuronal injury, and cognitive impairment, according to the classic amyloid cascade hypothesis of the 1990s. Familial AD cases, where APP and presenilin mutations increase Aβ42 levels and hasten plaque development, provided evidence in favor of this concept.

However, more recent studies paint a more nuanced picture. According to available data, neurons are mainly harmed by tiny, soluble Aβ oligomers and protofibrils rather than massive plaques. The mechanisms that propel rapid Aβ aggregation, such as secondary nucleation, supersaturation, metastability, and seeding, have been brought to light by developments in physical chemistry.

Additionally, genetic research has expanded our knowledge. Lipid is affected by variations in genes including APOE ε4 and TREM2.handling, microglial activity, and Aβ clearance. Altogether, these findings reframe Alzheimer’s disease as a disturbance of proteostasis and impaired clearance, rather than simply excessive Aβ production.

(2). Unmet Needs and the Therapeutic Environment

Anti-amyloid monoclonal antibodies like donanemab, lecanemab, and aducanumab have ushered in a new era in Alzheimer's treatment. For the first time, these medications have demonstrated the capacity to somewhat delay cognitive deterioration, especially when administered early in the illness.

However, a number of issues still exist. Patients experience a range of side effects from these treatments, including ARIA (amyloid-related imaging abnormalities) may restrict their application. People with advanced Alzheimer's disease also exhibit no progress.

These problems highlight the need for improved mechanistic models that can explain these different treatment responses and aid in the creation of more individualized and successful therapeutic strategies.

(3). The Proteostatic Reserve, or Amyloid Hypothesis

This notion offers a fresh perspective on Alzheimer's. According to this theory, the brain has an innate ability, or "reserve," that maintains the equilibrium of Aβ and stops it from becoming toxic. This reserve decreases with age or when factors like inflammation and heredity are involved. Even normal Aβ levels can become hazardous once they drop below a critical threshold, which can cause toxic oligomer production, seeding processes, and ultimately plaque accumulation.

This model integrates data from clinical research, genetics, and biophysics. It sheds light on why APOE4 carriers are more likely to develop ARIA, why anti-amyloid medicines work best early in the disease, and why different people respond differently to Aβ-clearing treatments.

1. Pathophysiology

An accumulation of abnormal neuritis Alzheimer's disease is characterized by plaques and neurofibrillary tangles in the brain. Neurons are lost, particularly cholinergic neurons in the basal forebrain and neocortex along using these pathological Changes.

1. The Cholinergic Hypothesis: This idea suggests that a decrease in acetylcholine (ACh) levels brought on by neuronal death in the Nucleus Basalis of Meynert may worsen Alzheimer's disease. AD's early cholinergic neuron loss suggests that ACh plays a crucial function in memory and cognition. By destroying synapses and decreasing ACh release, beta-amyloid may exacerbate cholinergic function. Anticholinergic drugs have also been clinically shown to affect older persons' memory.
2. The most extensively accepted theory is the amyloid theory explanation for Alzheimer's, particularly in inherited forms. It states that APP, or amyloid precursor protein, is broken down by the enzymes β-secretase and γ-secretase to produce the Amyloid-beta (Aβ) peptide. A. Typically, α- or β-secretase breaks down APP into tiny, innocuous pieces. However, when γ-secretase cleaves APP after β-secretase., it generates a 42–amino acid peptide known as Aβ42. Increased levels of Aβ42 promote its accumulation into toxic amyloid aggregates, which damage neurons. Compared to other APP fragments, Aβ42 is especially prone to forming fibrillar deposits rather than undergoing normal degradation.

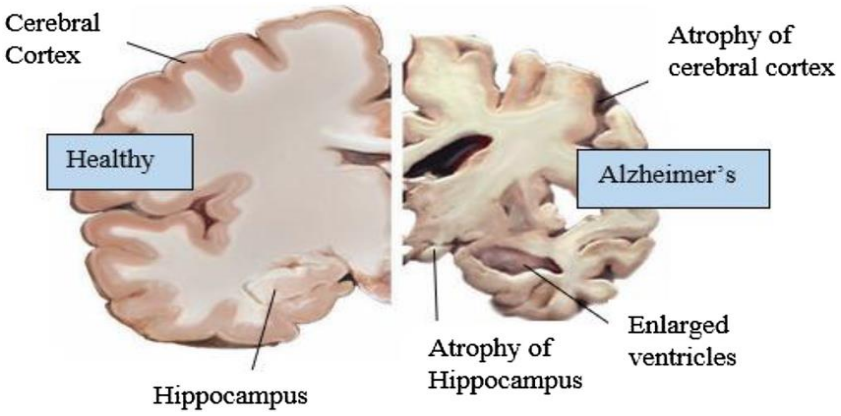

Figure no. 1: Healthy Brain vs Alzheimer's disease (Severe AD).

1.1 Histopathology

Neurotic plaques are microscopic formations composed of swollen nerve terminals encircling an extracellular amyloid-beta (Aβ) core. These Aβ deposits build up in the cortical gray matter, meninges, and brain around blood vessels in Alzheimer's disease. After appearing in several locations, the gray matter deposits eventually combine to form tiny clusters that resemble plaques. It is interesting to note that while some brain imaging studies have detected amyloid plaques in individuals without dementia, others with definite dementia show little to no plaque formation on their scans.

1.2 Cortical Neuronal Degeneration

Granulovacuolar degeneration, which affects hippocampal pyramidal neurons, is one of the prominent degenerative alterations connected to Alzheimer's. The loss of presynaptic boutons from pyramidal neurons is more closely associated with cognitive deterioration in AD. Neurons in certain cortical layers especially layers III and IV than to the number of plaques made of amyloid. This decrease in the synaptic connections appears to play a greater role in impairing cognition than plaque accumulation alone.

2. Etiology

A progressive loss of neurons that ultimately leads to widespread neurodegeneration is the hallmark of Alzheimer's disease. This process often starts in the hippocampal entorhinal cortex. AD with both early and late onset are influenced by Trisomy 21 and genetic factors, for instance, is associated with a higher risk of early-onset dementia.[11] AD is a complicated illness that is impacted by several risk factors. The best indicator is age; after age the risk of developing Alzheimer's disease nearly doubles after age 65 every five years. Another significant factor is cardiovascular diseases (CVD). They contribute to vascular-related cognitive decline, such as stroke induced dementia, in addition to increasing the risk of Alzheimer's. Managing cardiovascular health is a key tactic for lowering AD risk because CVD is modifiable.

❖ **Evaluation**

- Examine the medical and family history of the patient.
- Examine all of your current prescriptions to find any that could exacerbate or impair cognitive performance.
- To evaluate cognitive status, perform a bedside cognitive screening using a tool like the MMSE or MoCA.
- To rule out dementia's reversible causes, order blood tests.
- Tests including CBC, CMP, TSH, and vitamin B12 are frequently performed to rule out other illnesses that might be causing cognitive impairment, even though routine labs are usually normal in Alzheimer's disease.

2.1 Symptomatic Therapies for AD

- Given that Alzheimer's disease currently has no known treatment, regular clinical practice primarily focuses on the treatment of symptoms.
- Inhibitors of cholinesterase and partial Antagonists of NMDA receptors are the two primary drug classes licensed for AD.

2.2 Amyloid Hypothesis: (Therapeutic target)

These drugs function by raising the amounts of the neurotransmitter acetylcholine necessary for nerve cell transmission, learning, memory, general cognition.

3. Biochemical Markers of AD

Neuroimaging and biochemical indicators that support the preclinical and early detection of Alzheimer's have advanced significantly over the past ten years. These instruments are still primarily restricted to research settings and are not frequently utilized in routine clinical practice.

The demand for precise disease markers has increased with the development of new Alzheimer's medicines, particularly Aβ-targeting monoclonal antibodies. Before beginning this targeted therapy, the pathophysiology of AD must be properly identified.

One such functional imaging technique that aids in Fluorodeoxyglucose PET (FDG-PET) is an early and differential diagnostic. In people includes preclinical or early Alzheimer's disease, it can reveal decreased metabolic activity in important brain areas, especially the hippocampus.

One important imaging method for detecting Aβ accumulation is amyloid PET.in the brain. It enables direct visualization of amyloid deposits, a defining characteristic of Alzheimer's disease, and is more specific for diagnosing AD than many other neurodegenerative diseases. But its application is restricted due to amyloid deposits can also appear in some healthy older adults. Overall, amyloid PET is most useful for distinguishing disorders driven by Aβ accumulation from those caused by other abnormal proteins.

Cerebrospinal fluid (CSF) testing is a valuable tool for identifying Alzheimer's disease in its preclinical phase. It can detect biochemical signs of AD long before noticeable symptoms appear, making it useful for early diagnosis.

A nearly ten-year endeavor to locate the molecular relevant enzyme followed the identification of soluble Ab peptide in bodily fluids compatible with the APP's constitutive processing. The second target molecule for the development of medications to prevent the generation of amyloid was provided by the concurrent reports of the APP cleaving enzyme at the b-site BACE1 because it is closely associated with counterpart, BACE2, being cloned, using a range of techniques.

Due to the incompatibility of MW limitations (imposed by strength needs) Its size (for CNS permeability), beyond the p-glycoprotein mediated BACE1 inhibitor efflux from the central nervous system has proven to be a significant issue. This has slowed the advancement of numerous research efforts into the clinic to find to create BACE inhibitors to treat AD. However, the clinic has made headway; a number of pharmaceutical industry entrants are thought to be in or close to the clinic; such instances are included below. While the majority of researchers employed an iterative rational design approach that solved the molecular weight of a BACE1 inhibitor in relation to its potency and selectivity needs by combining medicinal chemistry with inhibitor structural elucidation, BACE1cocrystals exhibited in vivo activity with a strong peptide isostere inhibitor coupled to a carrier peptide that penetrates cells.

4. Therapies for Symptomatic Conditions

Since there is presently no treatment for Alzheimer's, clinical care mostly focuses on symptom management rather than curing the illness. The two main drug classes now Inhibitors of cholinesterase and partial NMDA (N-methyl Aspartate D) receptor antagonists have been licensed with the purpose of treating Alzheimer's disease.

4.1 Inhibitors of cholinesterase

These drugs function by increasing the brain's acetylcholine levels. Learning, memory, and general cognitive processing all depend on acetylcholine, a crucial neurotransmitter that facilitates communication between nerve cells.

The FDA has approved three Rivastigmine and other cholinesterase inhibitors donepezil, for Alzheimer's disease treatment.

4.2 Donepezil

1. The recommended first-line drug.

2. Recommended for Alzheimer's disease in its mild stages.
3. Acts as an acetylcholinesterase inhibitor that is quick and reversible.
4. Given once every day, generally at night.

4.3 Clinical Trials

1. Donepezil improved global function and cognition in AD mild to moderate as compared to A placebo, according to a Placebo-controlled, double-blind, 15-week RCT (Donepezil Examine Group). One of the foundational RCTs mentioned in regulatory documents is this one.
2. Longer and larger multi centre trials: Regulatory approvals and labelling across illness severities resulted from numerous 24-week and longer RCTs and pooled analyses that confirmed efficacy.

4.4 Rivastigmine

1. Used in stages of moderate dementia and MCI.
2. Acetylcholinesterase and butyrylcholinesterase are inhibited slowly and reversibly.
3. Available in both transdermal and oral forms.

4.5 Clinical Research

1. The first RCTs, conducted in the late 1990s, showed the effectiveness oforal rivastigmine vs placebo in improving cognition and global function in probable AD (6 to 26-week studies; e.g., Agid et al. and others). These formed the evidence base for approval.
2. Patch vs oral trials / action study: larger randomized trials compared different transdermal doses (e.g., 13.3 mg/24h vs 4.6 mg/24h) and examined efficacy, tolerability, and GI adverse events supporting the Exelon Patch approval and dosing guidance.

RESULT AND DISCUSSION

This review consolidates clinical, genetic, molecular, and therapeutic evidence to re-evaluate the amyloid hypothesis in Alzheimer’s disease (AD). Accumulating data indicate that soluble amyloid-β (Aβ) oligomers and protofibrils, rather than mature amyloid plaques, are the principal neurotoxic species responsible for synaptic dysfunction and cognitive decline. Genetic studies strongly support amyloid involvement, as mutations in APP, PSEN1, and PSEN2 increase Aβ42 production, while APOE ε4 and TREM2 variants impair Aβ clearance and microglial function.

Histopathological and neuroimaging findings show a weak correlation between plaque burden and cognitive severity, whereas synaptic loss and neuronal degeneration, particularly in hippocampal and cortical regions, correlate more closely with clinical impairment. Biomarker studies using amyloid PET, FDG-PET, and CSF Aβ/tau ratios demonstrate that amyloid pathology begins years before symptom onset, emphasizing a prolonged preclinical phase of AD.

Clinical trials of anti-amyloid monoclonal antibodies (aducanumab, lecanemab, and donanemab) demonstrate significant amyloid reduction and modest slowing of cognitive decline when administered early in the disease. However, therapeutic benefits are limited in advanced stages and are associated with amyloid-related imaging abnormalities (ARIA), especially in APOE ε4 carriers. Symptomatic therapies such as donepezil and rivastigmine improve cognition and daily functioning but do not modify disease progression.

Overall, these findings support a revised amyloid hypothesis, emphasizing impaired proteostasis and reduced amyloid clearance rather than excessive production alone. The Proteostatic Reserve model explains individual variability in disease risk, progression, and treatment response, highlighting the need for early intervention and biomarker-guided, combination therapeutic strategies targeting amyloid, tau pathology, and neuroinflammation.

CONCLUSION

The conventional amyloid hypothesis, which first focused on a straightforward, linear accumulation of plaques, has undergone substantial change. Alzheimer's disease is a very complicated condition influenced by numerous molecular processes. Current research indicates that the most harmful Aβ forms are not the large, mature plaques but the small, soluble, and highly reactive oligomers and protofibrils formed through mechanisms like secondary nucleation, supersaturation, and seeding. These insights, combined with strong genetic contributions from APOE ε4, TREM2, and related variants, show that Aβ toxicity is strongly shaped by the brain's clearance capacity, microglial activity, lipid metabolism, and overall Proteostatic stability.

Therapeutic development has progressed from broad secretase inhibitors and aggregation blockers to more specific immunotherapies. When given in the early stages of the disease, recently approved monoclonal antibodies like donanemab, lecanemab, and aducanumab show a slight slowing of cognitive loss, which is a significant advancement. However, these treatments also reveal major challenges, including wide variability in patient response, the risk of ARIA, and limited benefit in advanced disease. These limitations highlight the importance of better patient selection, biomarker-based diagnosis, and individualized therapeutic strategies.

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