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Study on Chemical Insights into Alzheimer's Disease: Amyloid Beta and Tau Protein Interactions

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Abstract

Background: *Alzheimer's disease (AD) is the most prevalent form of dementia, affecting millions of individuals worldwide and posing significant challenges to healthcare systems. The disease is characterized by a gradual decline in cognitive functions, particularly memory, reasoning, and the ability to perform daily activities.* ***Aim & objective:*** *To study chemical insights in Alzheimer's disease, especially amyloid beta and tau protein interactions.* ***Results & Discussion:*** *The results of this review highlight several key findings regarding the molecular mechanisms involved in Alzheimer's disease (AD) and their implications for understanding the disease's progression and potential therapeutic targets. It discussed these Amyloid-Beta and Tau Protein Interactions, Role of Advanced Glycation End Products (AGEs), Neuroinflammation and Oxidative Stress, Genetic and Environmental Risk Factors, and Therapeutic Implications.* ***Conclusion:*** *The Biochemical mechanisms underlying Alzheimer's disease (AD), focusing on the interactions between amyloid-beta (Aβ) and tau proteins, which are central to the disease's pathogenesis. It highlights the complex interplay of genetic and environmental risk factors contributing to AD and also emphasizes the need for ongoing research to develop effective therapeutic strategies targeting these molecular pathways.*

Keywords: Alzheimer's disease, amyloid-beta, tau protein, neuroinflammation, advanced glycation end products, RAGE, neurodegeneration

INTRODUCTION

Alzheimer's disease (AD) is considered a neurodegenerative disease, meaning it causes decadence that affects or destroys memory and other important functions of memory, also called Senile dementia [1]. Strangely, cognitive impairment is divided into a pair of categories. Anterior onset/familial AD (fatty acids) and spastic AD (SAD) are the two varieties of AD [2]. Neurodegeneration refers to the loss of neurons in the brain particularly in the cortex, expected to occur or lead to symptomatic characteristics of dementia often cited in its progression are plaques and tangles [3]. Dementia, is a collection of symptoms that causes poor memory, difficulty learning, hard to functioning independently [4]. Moreover, signs and symptoms include unfounded emotion, confusion with time and location, difficulty completing adoring tasks, misplacing items, memory loss, poor judgment, and withdrawal from social activities [5]. The risk factors are genetics, Hypertension, low estrogen, insulin resistance, traumatic brain injury, rare vascular dementia, etc. [6]. Such targets of Alzheimer's were HMG-CoA reductase, Amyloid aggregation, tau, cholinesterase enzymes, oxidative stress, metal chelation, MAO-B, BACE-I, Sirtuin, caspase, GSK-3β, serotonin, NMDAR, mAChR, and nAChR, Nrf [7]. In particular for the class of pharmaceuticals known as the activity of HMG dehydrogenase inhibitors, which are that comprises cholesterol-lowering medications, it's among the most often prescribed and approved by the Food and therapies

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for decreasing cholesterol [8]. Therefore, the possible benefits of statins in preventing or abrupting the risk of AD and dementia were examined in research studies [9]. Those statins, such as Atorvastatin, Fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, etc. [10]. However, the role of statins in the improvement of cognitive function and the prevention of AD is controversial [11]. Many factors linked with increased frequency of AD include age, female sex, history of head trauma, genetics, and Down syndrome [12]. Patients of Down syndrome universally develop AD by the age of 40 characterized by extra chromosome 21 and increased expressions of the Amyloid β precursor protein gene [13]. Typically, persons above the age of 65 are prone to degeneration of cognition which has more degeneration that leads to Alzheimer's disease [14]. More studies and research are ongoing for the treatment, improvement, & development of Alzheimer's [15]. Current treatment focuses on maintaining mental functions and slowing the disease progression [16]. The following drugs are magisterial to treat Alzheimer are, Donepezil, Galantamine, Rivastigmine (AchE inhibitors), and Memantine (NMDA receptor antagonist) [17].

HMG CoA REDUCTASE

By decreasing total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) concentrations while increasing the level of high-density lipoprotein cholesterol (HDL-C) concentrations, HMG-CoA) reductase inhibitors are an effective diet and exercise therapy for hypercholesterolemia [18]. The acknowledged FDA indications for statins vary slightly from one another, although they are generally for the treatment and/or prevention of clinical atherosclerotic cardiomyopathy (ASCVD) (e.g., myocardial infarction or hemorrhage) in the context of both primary and secondary prevention [19].

BACE1

The aspartyl protease known as BACE1 (beta-site amyloid precursor protein [APP] cleaving enzyme 1) is related to pepsin20. Since BACE1 is a transmembrane protein, it differs from other peptidases in its family, such as D and E, which also contain a transmembrane domain (1–4). BACE1 is highly prevalent in different types of neurons and is broadly distributed in the brain, especially in oligodendrocytes, astrocytes, and neurons (1–4). the protein BACE1 localizes on the plasma membrane and in the endosomal compartments at the subcellular level. It was discovered found in amyloid-β (Aβ) plaque-surrounded intact synaptic terminals and dystrophic neurites. Two aspartic acid positions make up the active site on both secretases' extracellular domains, which also contain short cytoplasmic C-terminal domains and 21-residue helical transverse domains. In the brain, BACE1 and BACE2 are produced in the same cell types, but BACE2 is far less common.

MAO

The catecholamine oxygenase (MAO) gene, which codes for important amino acids A and B, is responsible for breaking down food and naturally occurring amino acids. Monoamine A predominantly deteriorates endorphins (NE) and Zoloft (5-hydroxytryptamine, 5-HT), whereas MAO B mostly deteriorates the amines (the PEA). Any of them can oxidize norepinephrine (DA). Substances usually referred to as "organic amines" include three types of synapses. Glucose. Serotonin oxidase B (the MAO-B) and monoamine oxidase A (MbAO-A), the two dimethyl oxidase enzymes, are blocked by a class of drugs known as agonists of dimethyl (MAOIs). Strong antidepressants are their most well-known application, especially for atypical and treatment-resistant depression. They are also used to treat several kinds of other illnesses, such as schizophrenia, social anxiety, and Parkinson's disease.

TAU

Neurodegenerative conditions, like Alzheimer's illness, gradual pronuclear paralysis, and frontotemporal dementia, are all influenced by the tau protein. Although there are no proven treatments for tauopathies at this time, there are several therapeutic candidates undergoing phase III trials and sixteen undergoing phase II trials. Several treatment modalities have the potential to ameliorate symptoms or reduce the onset of tauopathies. Targeting tau phosphorylation to tau the process of ace tau glycosylation, or tau deletion are some of these methods.

Tau has been researched for the possibility of acting potentially an inhibitor in cancers like cancer as well as for its significant function in neurological diseases. It has been discovered that Tau binds with protein mediators associated with carcinoma, highlighting a potential function for Beta for directing microtubule-independent biological processes.

AMYLOID

Alzheimer's illness (also known as AD is characterized by lesions containing amyloid beta (Aβ), a substance that accumulates in the brains of those who have the disease. Because of these outstanding experimental consequences, immunotherapeutic ways of attacking Aβ were once regarded as nearly likely effective in clinical usage (Figure 1). Nonetheless, uncertainties were raised about such a strategy because of the constant failure inside studies employing immunization additionally comprehensible anti-Aβ followed by anti-tau monoclonal antigens. The US Food and Drug Administration recently authorized Aducanumab, a novel anti-Aβ monoclonal antibody, which reminds us that Aβ-targeting immunotherapy approaches may still be promising.

Apart from amyloid beta (Aβ), tau protein is also essential for the emergence of neurodegenerative conditions like Alzheimer's disease [19].

HMG CoA

HMG-CoA reductase inhibitors, also known as statins, are a class of drugs that help lower cholesterol levels in the blood. They work by blocking an enzyme called HMG-CoA reductase, which is responsible for producing cholesterol in the liver (Figure 2). Statins help to reduce cardiovascular disease risk by reducing the amount of cholesterol produced in the liver [20].

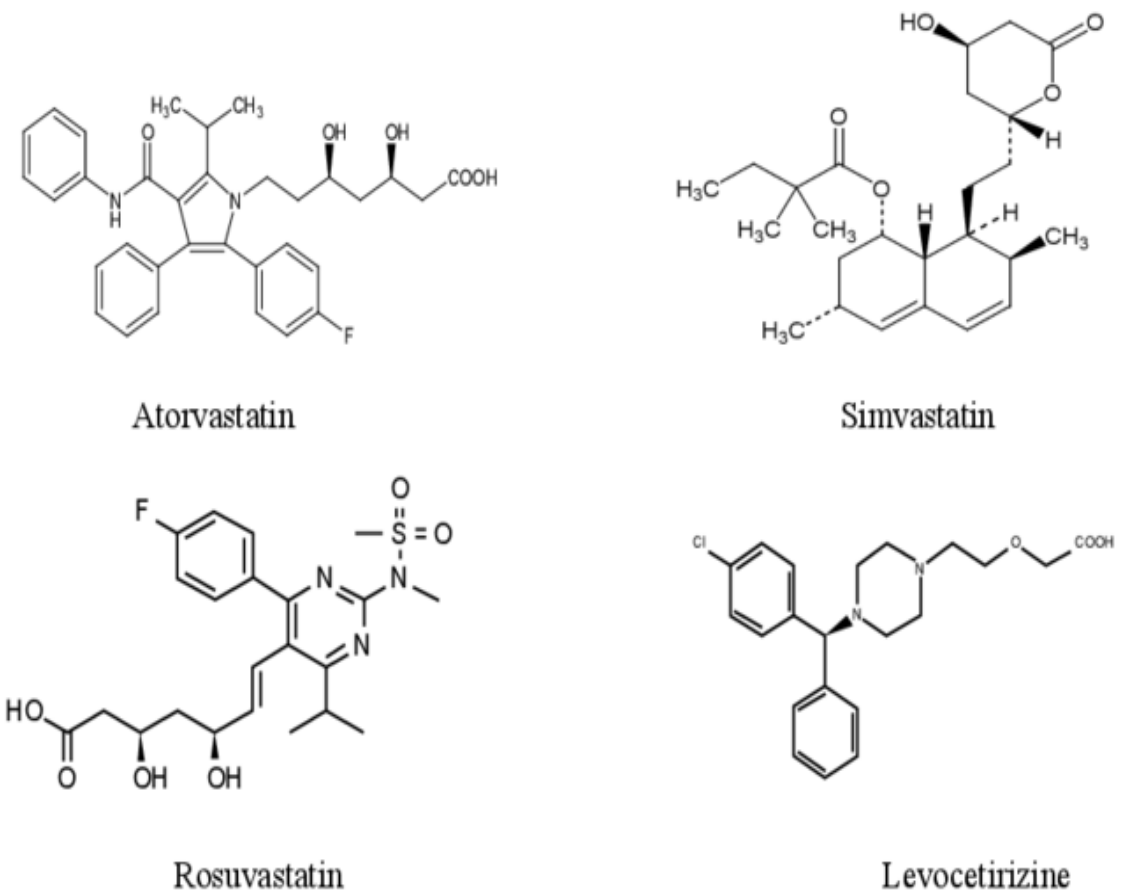

Figure 1. This figure represents the statin class of drugs chemistry followed by a) Atorvastatin, b) Simvastatin, c) Rosuvastatin, and d) Levocetirizine.

Mechanism

HMG-CoA reductase obstruction work by decreasing cholesterol synthesis by inhibiting the rate-limiting HMG CoA reductase [21]. In the presence of HMG CoA reductase Mevalonic, acid is converted, thereby reducing cholesterol synthesis and hence compensatory high in LDL receptor expression in live obtained.

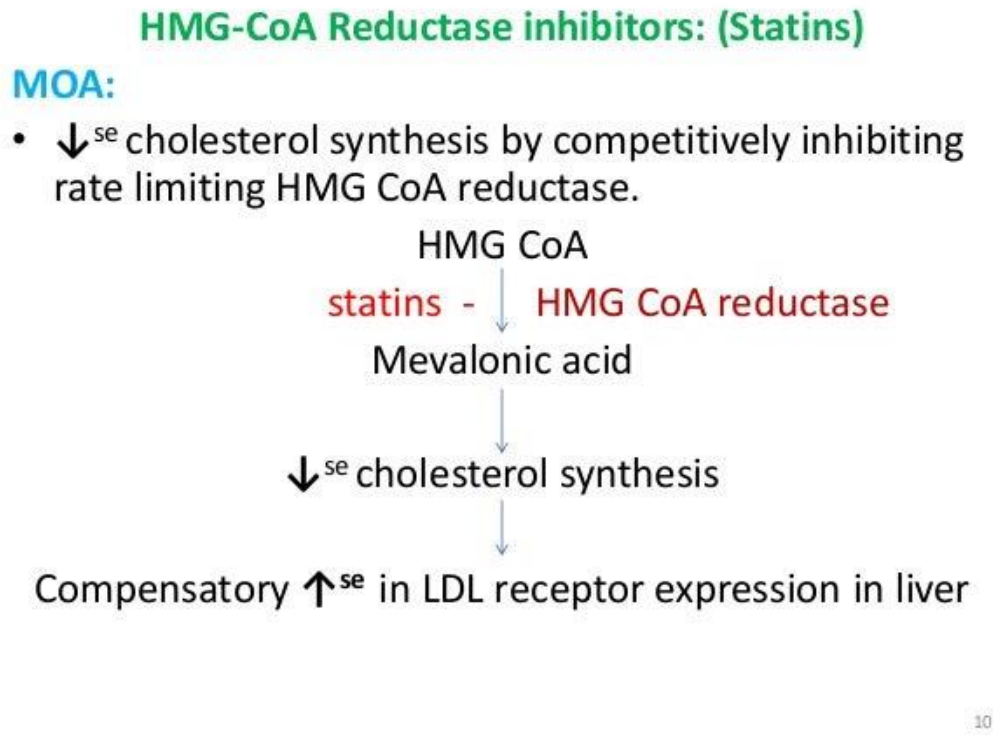

Figure 2. HMG-CoA Reductase Inhibitors (Statins) and their Mechanism of Action (MOA).

MOLECULAR MECHANISMS OF ITS EFFECT ON THE BRAIN

Significance of Cholesterol in the Aetiology of Alzheimer's Disease

Role of HMG CoA Reductase Inhibitors in Managing Alzheimer's Disease

Currently Available HMG CoA Reductase Inhibitors in the Market for Alzheimer's Disease Treatment

The medications in this class of drugs that are used as a continuous treatment for Alzheimer's disease include galantamine, rivastigmine, donepezil, amitriptyline (Elavil), aripiprazole (Ability), bnztropine (Cogentin), biperiden (Akineton), brompheniramine (Dimaphen DM), cabasepine (Tegretol), chlorpheniramine (ChlorTrimeton), chlorpromazine (Thorazine), atovastatin, rosuvastatin, simvastatin, pravastatin, fluvastatin, lovastatin, and pitavastatin [22].

The enzyme that breaks down acetylcholine after it is released from the presynapse, acetylcholinesterase (AchE), is reversibly inhibited by donepezil [23]. Aspects accessibility of glutamate in nicotinic neurons is increased by donepezil and kindred ACETYL CH inhibitors, improving the propagation. of cholinergic information [24]. It inhibits acetylcholinesterase, an enzyme that typically breaks down acetylcholine, in a selective and reversible manner. It is thought that this drug's fundamental pharmaceutical properties stem from the blocking of this digestive enzyme, which improves rgic communication and alleviates Alzheimer's disease symptoms. Donepezil is used to treat dementia (a brain disorder that affects the ability to remember, think, communicate, and perform daily activities and may cause changes in mood and personality) in people who have Alzheimer's disease (AD; a brain disease that slowly destroys the memory and the ability to think, learn, communicate and

handle daily activities) [25]. People with Alzheimer's disease (AD), a brain disease that gradually annihilates storage space along with their ability to think, learn, communicate, and handle ordinary tasks, undergo therapy with donepezil following for dementia, a neurological condition that affects memory, thinking, technically together with performing normal daily tasks and can bring about alterations in emotions and personality. Donepezil belongs to a group of drugs known as cholinesterase inhibitors. By boosting the quantity of a given naturally existing material in the nervous system, it stimulates cognitive capacity (memory, attention, social interaction, speaking, clear thinking, and doing daily activities). For Asd individuals, donepezil or might possibly slow down or avoid the impairment of cognitive and memory functions [26]. However, donepezil will not cure AD or prevent the loss of mental abilities at some time in the future.

Acetylcholinesterase inhibitors are a group of drugs that includes Galantamine. It functions by raising awareness of certain organic material in the mind that is essential for cognition and memory [27]. For those suffering from AD, Galantamine may either slow the decline of memory. And boost it. Galantamine comes in puff and solution form in different concentrations of 4mg, 8 mg, & 12 mg. The drug's solution form contains four mg of Galantamine per milliliter [28]. A controlled clinical research for Alzheimer's type dementia Showed the efficacy of an immediate-release tablet dose range of 16 with 32 pm a day of the week.

The ACETYL CH antagonist Rivastigmine functions by raising the level of acetylcholine, a neurotransmitter that fosters interaction among nerve Cells in the brain. Your symptoms of dementia can get better as a result [29]. Oral Administration of Rivastigmine is possible through an array or strips affixed to the pores as well as in transparent pills [30]. When dementia (memory loss or Cognitive abnormalities) linked to Parkinson's or schizophrenia is from Moderate to severe, Rivastigmine is utilized to treat the condition. While clients May see an improvement in their propensity for cognition, a drug called is not an effective panacea for dementia nor an intervention to halt schizophrenia from Growing worse. These drugs, such as Galantamine, gal, the synthetic compound Riv, and administered donepezil are utilized in treatment light to moderate Symptoms of Alzheimer's disease. Certain psychological along IQ issues might be alleviated or managed via the aforementioned drugs.

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Amitriptyline functions by boosting the brain's production of serotonin [31]. The brain releases serotonin, a substance known as a neurotransmitter, to the Body's nerves. It is speculated that Zoloft enhances mood, sleep quality, and the Body's pain threshold. The abundance of an M E IV (the APOE4)

consequences, Proteins, such as tau, fatty acids as well as lipoprotein cholesterol sensors, Receptors for the neurotransmitter (NR), the process of neurogenesis inflammation, and inflammatory processes are now just a few in a multitude target Categories to stay therapy for AD realized by the "a tendency Alzheimer's analysis this field (CADRO)" [32].

In areas of the brain that regulate muscular contraction, Benztropine helps to Rebalance the levels of catecholamine and acetylcholine [33]. PD alongside antipsychotic medication's negative consequences involving mobility are Lessened by the aforementioned.

Anticholinergic and antihistaminic properties are shared by Benztropine. Since Benztropine blocks acetylcholine, a neurotransmitter, it has anticholinergic effects [34]. In addition to its effects on bodily muscle contractions, acetylcholine Plays a role in brain augmentation and memory.

Even though Biperiden is a poor AchE enzyme antagonist and promises to Be potentially harmful at enormous concentrations, additional research based on Replicas of similar structures may lead to intriguing unfamiliar pathways for the Power source produced by the enzyme AchE inhibitors that inhibit AchE as well As thus, for the rehabilitation of Alzheimer's ailment along with additional neurodegenerative diseases. A drug called ha is a more senior citizen's Amphetamine that has a license to treat transpiring Alzheimer's disease and Other forms of dementia. Yet, the majority of medical professionals believe that the dangers and adverse consequences are too great for those who have Dementia [35].

One immigrant's (medication of the propyl amine genus is Brompheniramine, which is marketed under the trade names Dimetapp and others. Sneezing, dilated pupils' runny nose, and scratchy eyes are just a few of the manifestations of a sinusitis reaction and a typical cold which it is suggested to cure [36]. As an antihistamine from the alkyl amine class, the antidepressant maleate acts as an antihistamine antagonist by inhibiting the histamine 1 receptors [37]. It appears that histamine and antihistamines vie for receptor areas on effector cells. Additionally, sedative and anticholinergic (drying) effects of Brompheniramine.

Bipolar I have disorder's acute rather manic as well as blended instances, cranial migraines, (TN), and seizures are all managed and treated with carbamazepine [38]. Glaucoma should be avoided for partial seizures in intricate symptomatology. Grand amiss epileptic attacks, global tonic-clonal seizures (behavioral, chronological lobe), and Irregular seizure patterns [39]. The medication carbamazepine may be useful in managing agitation in people with severe dementia who are resistant to neuroleptic medicine on their own. The psychotropic drug ha and glucose together appear to be encouraging for the treatment of senior Alzheimer's patients [40]. However, some that can reduce agitation are as follows: medications for paranoia called anti-psychotic medications or neuroleptics, provoke bewilderment. Instances of this are quetiapine, Seroquel (Zyprexa), haloperidol (Haldol), and a medication known as (the drug Ability) Ziprasidone (Geodon), the painkiller (Risperdal), and Zoloft.

A healthy diet and vardenafil are administered to reduce the amount of lipids called triglycerides and cholesterol. When fats clog blood vessels, they can cause medical conditions like heart attacks, strokes, and chest pain. This medication could assist in preventing these issues. In summary, this study's findings imply that atorvastatin can have antioxidant benefits in the brain without also lowering cholesterol and by turning on the GSH system, which could facilitate cognitive advantages.

If you've received notification, you have high blood cholesterol, rosuvastatin is utilized to mitigate it. In addition, it is used to prevent coronary artery assaults as well as seizures due to heart disease [41]. Should you have diabetes, kidney illnesses, osteoarthritis, and inside problems with your relatives, a therapist might recommend the cholesterol-lowering medication. Mechanism of Action: The rate-limiting digestive MG-CoA aminotransferase is inhibited selectively and competitively by rosuvastatin

[42]. This allows mevalonate, an early form of cholesterol, to be naturally produced from 3-hydroxy-3-methylglutaryl coq A [43].

Schizophrenia syndrome β-amyloid polypeptide Aβ42 and Aβ40 have been significantly decreased in both in laboratory and adhering live conditions settings by simvastatin [44]. High bloodstream Triglyceride (fat) and cholesterol-containing foods levels are treated with simvastatin in conjunction with a healthy diet [45]. This medication may help avoid health issues (such as heart attacks, strokes, stream channel or heart disorders, etc.) brought on by congested blood vessels [46]. On opposing 3-hydroxy-3-methylglutaryl-coenzyme A reductase, statins are part educational institutions the class with pharmaceuticals that lower cholesterol [47]. Fifty Due to inconsistent findings, it is still unknown if statins can help patients with dementia. Sixty accomplish reduce lipids levels, healthcare professionals recommend statin medication; simvastatin inhibits the synthesis of cholesterol [48]. This chemical requires a multi-step mechanism for production. The enzymes 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase is involved in the pathway's rate-limiting phase [49]. Pravastatin lowers plasma concentrations of 24S-hydroxycholesterol as well as Lipoprotein cholesterol for people with Alzheimer's disease (AD), but it has no effect on ApoE level Vega et al. (2003) [50]. Furthermore, throughout significantly influencing the pathophysiology of cognitive impairment chronic illness, cholesterol-lowering medications might decrease increased risk of insanity [51]. A study conducted on recombinant mice models of Alzheimer's disease revealed that atorvastatin decreased acute generations afterwards associated with Aβ adding indicated it would somewhat mitigate the damage caused by neuroinflammation in Alzheimer's disease [52–55].

Triglycerides, or fats, and elevated arterial circulation may be diminished in the blood by using fluvastatin works in tandem with a nutritious diet [56]. This medication may help avoid health issues, like atherosclerosis, or the hardening of the arteries, which is brought on by fat build-up in the blood vessels. Arterial Amyloid-bet (Aβ) concentrations have been demonstrated to drop in a dose-dependent way in no demented patients receiving a controlled-release version of lovastatin [57, 58].

Pitavastatin belongs to a group of drugs known as HMGCoA, reductase inhibitors, or statins. It functions by reducing the variety of cholesterol particles the body produces, which lowers the risk of cholesterol accumulating on artery walls and obstructing blood flow to the heart, brain, and other organs [59]. Pitavastatin inhibits the rate-determining mechanism in the synthesis of cholesterol sterol throughout the human hepatocyte system, Ogg the Commission of Arbitration enzyme I dehydrogenase. As a result, the liver has more LDLC receptors, which increases the amount of LDLC, that is, from the circulation [60].

CONCLUSIONS

The Biochemical mechanisms underlying Alzheimer's disease (AD), focus on the interactions between amyloid-beta (Aβ) and tau proteins, which are central to the disease's pathogenesis. It highlights the complex interplay of genetic and environmental risk factors contributing to AD and also emphasizes the need for ongoing research to develop effective therapeutic strategies targeting these molecular pathways. Alzheimer's disease (AD) arises from intricate biochemical processes, primarily involving amyloid-beta (Aβ) and tau proteins. Aβ aggregation leads to extracellular plaque formation, triggering neuroinflammation, oxidative stress, and synaptic dysfunction. Simultaneously, tau undergoes hyperphosphorylation, forming neurofibrillary tangles that impair neuronal stability and accelerate neurodegeneration. The interaction between Aβ and tau exacerbates disease progression, making them key therapeutic targets. Genetic factors, such as *APOE* ε4 and mutations in *APP*, *PSEN1*, and *PSEN2*, contribute to AD susceptibility, while environmental influences, including diet, vascular health, and lifestyle, further modulate risk. Despite extensive research, no cure exists, underscoring the need for targeted treatments. Future strategies must focus on disrupting Aβ and tau pathology, mitigating neuroinflammation, and enhancing neuroprotection. Advancements in biomarker research, precision medicine, and novel therapeutic approaches, such as immunotherapy and gene editing, hold promise for improving patient outcomes and altering the course of AD.

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