Review Article

A Comprehensive Review on Alzheimer's Disease; Pathophysiology and Treatment

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ABSTRACT

Neurodegenerative disorders (NDDs) arise from the gradual and occasionally inevitable decline in brain cell activity and mortality. Alzheimer's disease (AD), also known as dementia is a prevalent neurological condition linked to genetic abnormalities or advanced age. A lot of work is being done to figure out how Alzheimer's disease (AD) develops. The buildup of tangled tau protein and sticky Aβ-peptides are hallmarks of Alzheimer's disease development, in addition to other pathological characteristics such as metal homeostasis, impaired energy metabolism, loss of synapses, and protein imbalances. Treatments now on the market, including medications like memantine and rivastigmine can offer some help in managing Alzheimer's, although their effects are more noticeable in later stages of the disease. These medications relieve symptoms and slow the disease's course, but they don't offer a permanent cure. The goal of this review is to elucidate AD's general pathogenesis, and also give details on the scope of symptoms-based therapeutic methodologies, and highlight new developments in the field of AD management.

Keywords: Neurodegenerative disorders, Alzheimer's disease, amyloid precursor protein, Tau- protein.

INTRODUCTION

The broad spectrum of neurological conditions known as neurodegenerative diseases (NDDs) cause gradual death of brain cells in peripheral nerve system (PNS) or central nervous system (CNS), negatively impacts the lives of millions of individuals globally. The fundamental communication circuitry breaks down as a result of the disintegration of neural networks and the death of neurons, which are incapable of efficiently renewing themselves because they are terminally differentiated. This leads to a decline in cognitive, behavioral, sensory, or motor abilities [1].

A hallmark of neurodegenerative conditions such as Lou Gehrig's (ALS) or amyotrophic lateral sclerosis (AD), Parkinson's (PD), Alzheimer's (AD), Huntington's (HD), and others is irreversible degradation in specific neurons clusters[2]. As the disease worsens, neurodegeneration usually progresses from subcortical regions to cortical regions. With different diseases, major loss of neurons varies: in Parkinson's disease (PD), in Huntington's disease (HD), in Alzheimer's disease (AD), and in Lou Gehrig's disease (ALS), the predominant loss of neuronal cells occurs in striatal regions [3].

Globally Millions of people are getting0impacted by neurodegenerative diseases. While the primary risk variable for the generation of any NDDs is age, new research shows that both an individual's genetic composition and environmental circumstances might raise chance of developing NDDs. Furthermore, though certain genes expressed within an individual are believed to be involved in neurodegenerative diseases (NDDs) [4], the onset and degree of neurodegeneration are primarily determined by the individual's current surrounding environment [5-6]. Several molecular and cellular problems, including accumulation of proteins, malfunctioning mitochondria, glutamate toxicity, calcium stress, proteolytic stress, oxidative stress, neurological inflammation, and advancing age, are present in Degenerative disorders of the brain and ultimately causes the damage of neurons[7].

1. Alzheimer Disease (AD)

The signs and symptoms that identify AD include neurological symptoms, a substantial protein conformational disorder (PCD) i.e primarily caused due to inappropriate management of proteins and aggregation of normally soluble forms[8]. Misfolding or altered structural forms might result from the conformational changes in soluble neuronal proteins caused by advancing age, external factors, or mutations in genes. Such modifications may cause these proteins to gather within neural structures and trigger aberrant neuronal activity, which may ultimately result in loss. [9]. German neurologist Alois Alzheimer is credited for defining Alzheimer's as a neurodegenerative illness following his examination of patient of 52yrs , who suffers through dementia, difficulty speaking, miscommunication and illusions. The autopsy revealed telltale signs - plaques and tangles in the cortex - that this wasn't ordinary dementia.

AD is characterized by formation of neurofibrillary tangles and neuritic plaques (Figure 1). These hallmarks are attributed to the accumulation of amyloid-beta peptide (Aβ) and tau proteins, particularly within the brain's most vulnerable regions, the medial temporal lobe and neocortical structures. Alzheimer's disease is a progressive neurodegenerative disorder, leading to irreversible damage and loss of neurons, particularly in the cerebral cortex and hippocampus [10].

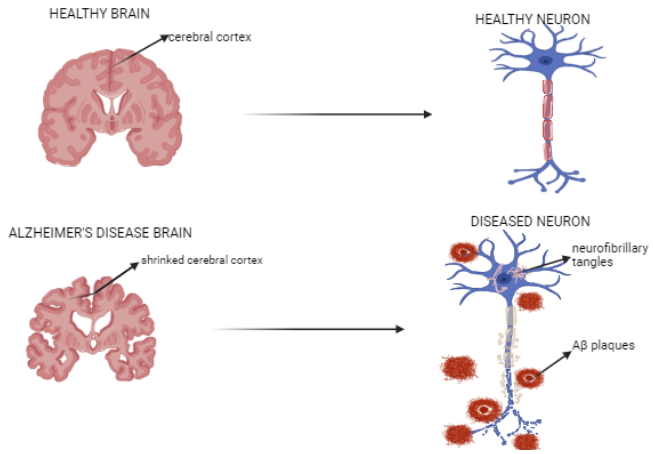

Figure 1: Normal brain and AD brain.

Deterioration of cognitive brain functions, including memory, speech, reasoning, and judgment, is a hallmark of dementia. This makes it much harder to carry out daily activities and maintain an independent lifestyle [11]. Although dementia is not a predictable side effect of aging, its risk rises dramatically with age [12]. The term "dementia" describes a wide spectrum of illness and conditions that result from the death or abnormal functioning of brain nerve cells. In Alzheimer's disease, progressive neuronal dysfunction and death lead to impairments in memory, cognition, and executive function. At advanced stages, the disease can even disrupt fundamental homeostatic processes, compromising activities like ambulation and swallowing [13]. A progressive decline in cognitive function can be attributed to various etiologies.AD is firmly grounded cause, but other factors like intoxications, infections, pulmonary and circulatory dysfunction leading to hypoxemia, nutritional deficiencies including vitamin B12 deficit, and neoplasms can also contribute [14]

2. Epidemiology of AD

In the aged population, Alzheimer's disorder is assumed that it was the main factor causing memory loss, and responsible for about two thirds of cases. [15, 16]. Thus, there is a severe health risk associated with AD incidence. Based on the most recent epidemiological evidence available at the time, specialists appointed by AD International in 2005 came to specific findings on the rates and estimated severity of dementia in 12 WHO zones [17, 18]. Their research indicated that 23.1 million people had dementia at the time, with an estimated 4.5 million additional cases occurring annually [17]. A survey released in 2015 stated that there were 49.5 million dementia patients worldwide at that time [19]. After the age 65, the number of cases seems to double for every five years. Conversely, a meta-analysis carried out in the past year indicated that the prevalence of AD, which rises rapidly in those over 65, either decreased or did not rise after the age of 90[20].

According to a nationwide research, between 2005 and 2010, the rate of Alzheimer's disease in people 50 years of age and elder increased approximately 5.59-7.10 cases /1000 people [21]. As per the findings of a 2017 meta-analysis, the predicted incidence of AD in Europe was 5.05%. According to reports, the average rate of AD in Europe is 11.08% per 100 person. It was reported that women had greater rates of both prevalence and incidence than males did, and that these rates generally increase with aging.[22] By the year 2050, the rate of dementia is expected to have quadrupled from the 24 million instances that are currently expected to exist globally. In the US alone, the projected annual cost of healthcare related to Alzheimer's disease is $162 billion. While Alzheimer's disease can occur at any age, it becomes more common with advancing age. Before 65, prevalence is very low, but it increases significantly after 85. Women are especially likely to develop Alzheimer's disease later in life [23].

3. Pathogenesis of AD.

A global effort is underway to elucidate the mechanisms behind AD and to generate effective therapeutic methods. Alzheimer's disease is defined by the progressive accumulation of abnormal protein aggregates in the brain. These hallmark features include extracellular deposits of Aβ plaques and neurofibrillary tangles (NFTs) that are formed intracellular. The initial pathology appears in the basal, temporal, and orbitofrontal neocortex, before spreading to encompass the wider cerebral cortex, hippocampus, amygdala, diencephalon, and basal ganglia. In severe situations, Aβ is present in cerebellar cortex, lower brain stem, and mesencephalon. Additionally, Aβ results in the generation of tau-tangles in brain's entorhinal and transentorhinal regions as well as the locus coeruleus. It moves to the hippocampus and neocortex at the crucial stage [24].

Scientists are actively engaged in unravelling the fundamental mechanisms that drive Alzheimer's disease pathology, because its core pathological etiology is not yet fully known. Numerous theories about the etiology of AD have been proposed based on present understanding. The most commonly recognised mechanisms are, Amyloid Cascade Hypothesis, Tau Hypothesis, Mitochondrial Cascade Hypothesis.

4.1 Amyloid cascade hypothesis

Basic pathology involved in AD is build-up of Aβ-peptides in the brain that manifest as Aβ Plaques, where Aβ42 peptides is the most neurotoxic among them. Amyloid precursor protein (APP), a crucial protein present on cell membrane, undergoes abnormal cleavage during the beginning of amyloid pathogenesis [23].Instead of normal APP degradation ; Aβ42 prefers the generation of aggregated fibrillary amyloid protein. When an individual has AD, amyloid accumulates around meningeal, cerebral, and gray matter arteries [24].

The APP which is present in neuronal membrane undergo cleavage in the presence of enzyme proteases named α, β, and γ-secretase and results in the generation of Aβ-peptide. When alpha or beta secretase cleaves APP, it usually results in small fragments that do not cause neurotoxicity. However, the insoluble Aβ fibrils, known as

Aβ42, are generated when β, and γ-secretase sequentially cleave the APP protein. Subsequently, Aβ undergo oligomerization; penetrate into clefts in synapses, and tampers with synaptic transmission. Therefore, it forms insoluble Aβ fibrils through polymerization, later coalesces into plaques.

The Aβ aggregates attach themselves to the receptors of brain and glial cells, resulting in the impairment of axon functions, oxidative stress, cellular homeostasis, and subsequent toxicity of brain cells induced by synaptic dysfunction and neuroinflammation.. The presence of these aggregates disrupts normal cellular signaling pathway causing tau to be abnormally over-phosphorylated, a protein associated with microtubules 25. The gradual death of neurons and the weakening of connections between them disrupts memory, thinking abilities, and ultimately leads to death.

4.1.1 Amyloid precursor protein (APP): APP undergoes protein degradation to produce Aβ peptides. APP is a trans-membrane glycoprotein-1 which has a short intracellular tail, trans-membrane region, and big N-terminal extracellular domain. Although APP is expressed over all the body, it's most prominently expressed in brain's neural tissues. The exact role of APP remains a mystery. Introducing the APP gene into cells has shown it can control how nerve cell fibers grow, how these cells function, and even if they survive.These effects are linked to the release of soluble ectodomain that occur during normal APP cleavage [13,14].

One of the chromosomes linked with familial AD is chromosome 21, where single gene codes for APP [23]. Different APP isoforms are produced in a tissue-dependent manner via alternative splicing and differential processing [26]. Three major isoforms are produced by alternative splicing, which identified by their amino acid lengths: APP695, APP751, and APP770. All three of these isoforms are the major variants that has the ability to produce amyloid beta. While isoforms APP695 are primarily found in neurons and are thought to be the most hazardous, isoforms APP770 and APP751are primarily found in non-neuronal organs.

All isoforms have an extracellular portion that consists of E1 and E2, folded domains that are linked together through an adaptable acidic domain (AcD), and joined to transmembrane area utilizing a juxtamembrane linker that is primarily unstructured [27]. E1 has a copper/zinc binding domain (CuBD) and a heparin-binding domain (HBD) enclosed in a bigger growth factor-like domain (GFLD). CuBD and the second HBD are found in E2. While cytoplasmic adaptor proteins like Dab1and Mint, which regulate APP-dependent signaling, are bound by the YENPTY motif found in the short intracellular tail [28].

4.1.2 Processing of APP: Numerous research concentrate on the last phases of APP processing, which involve inserting the entire APP into internal membrane organelles like the plasma membrane and cleaving takes place. There are two possible pathways for the cleavage of membrane-inserted APP: the most prevalent pathway is non-amyloidogenic, but there is also an amyloidogenic one. The by-products produced by the two pathways differ in terms of their inherent functional characteristics, potential physiological functions, and pathogenesis [29,30]. α-, β-, and γ-secretases are the three primary secretases that are essential to the late processing of APP. ADAM9, 10, and 17 are possible examples of α-secretases. While γ-secretase in the brain consists of at least 4 main components, presenilins (PSEN1, PSEN2), niacstrin, PEN2, and APH1, BACE1 is the predominant β-secretase.

In addition to secretase activity, another crucial component of APP metabolism is APP trafficking via the secretory route. Figure 2 illustrates the different processes that comprise APP biogenesis.

APP trafficking inside cells

APP transcription occurs in the nucleus and produces mRNA, which is subsequently exported to the cytoplasm. Then, with the help of SRP or unknown targeting mechanisms, the APP mRNA translation occurs in the ribosome. Subsequently, the developing APP protein is transported to the ER for further biogenesis. Next, for maturation (post-translational changes), the APP protein reaches the Golgi apparatus. Following its transfer to the mitochondria, the entire APP is inserted into the membrane of the mitochondria. The entire APP is integrated into the plasma membrane (PM) from the mitochondrial membrane.

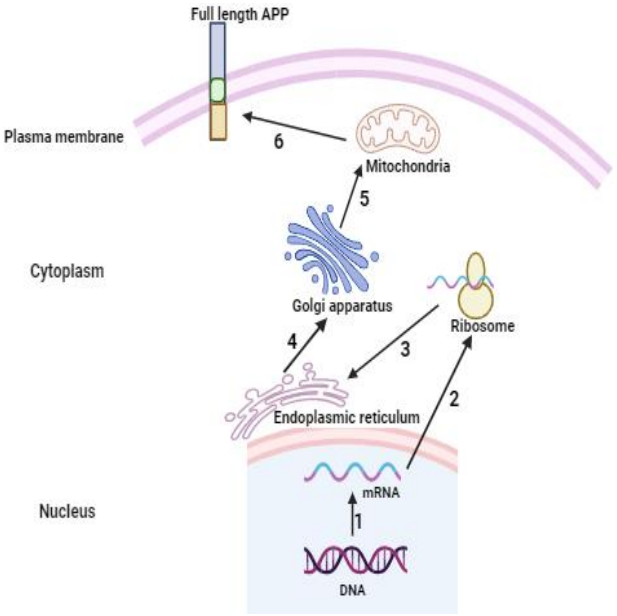

Figure 2: APP trafficking inside cells: 1. Transcription of DNA to mRNA, 2. mRNA gets transported to cytoplasm and undergo translation on ribosomes to produce nascent APP protein, 3. nascent APP get transported to endoplasmic reticulum for further biogenesis, 4. APP protein reaches Golgi apparatus for maturation, 5. the full-length APP gets transported to mitochondria, 6. the full-length APP will get incorporated into plasma membrane (PM)

Non-amyloidogenic Pathway: APP undergo cleavage in presence of α-secretase within the Aβ domain between Lys16 and Leu17 in the non-amyloidogenic route, leaving the C-terminal APP fragment, which contains 83 amino acids (C83), inside the cell membrane and generating a soluble N-terminal fragment (APPsα) outside of it. γ-secretases have the ability to further cleave the c-terminal APP fragment (C83), releasing a soluble p3 peptide fragment into the extracellular space and AICD (APP Intracellular Domain) into intracellular space of the cell. This process inhibits formation of peptides of Aβ. The sAPPα, when found extracellularly, it can lower the generation of amyloid beta by blocking the function of β-secretase (BACE1) an important enzyme which has a key function in one of stages of processing of amyloid precursor protein (APP). As a result of this inhibition, the synthesis of Amyloid beta peptide will be reduced and also disturbs the amyloidogenic pathway.

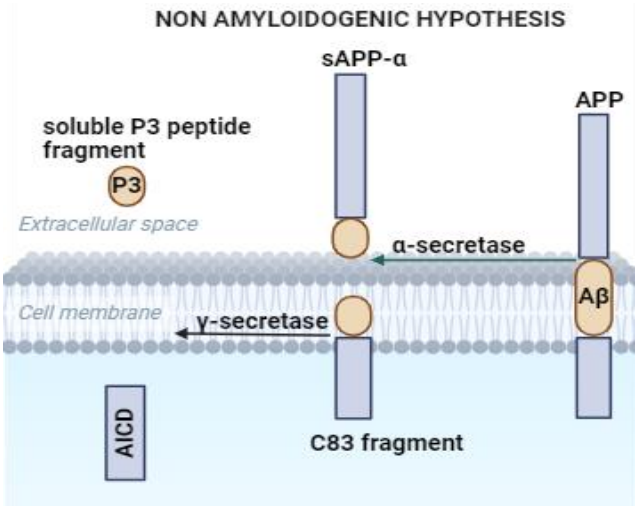

Figure 3: Non amyloidogenic pathway: Full length APP protein undergo cleavage by α-secretase and produces C83 fragment into intracellular region and sAPPα into extracellular region. Further the γ-secretase enzyme will cleave the C83 fragment into AICD (APP Intracellular Domain) into the intracellular region and soluble P3 peptide fragment into extracellular region, thus preventing the formation of Aβ.

Amyloidogenic Processing of APP: γ-secretase and β-secretase work together to cleave APP successively, which is a step in the amyloidogenic process. In this process, the APP undergo cleavage by the enzyme β-secretase, resulting in the production of sAPPβ ectodomain outside the cell and a 99 amino acid APP carboxy-terminal fragment (C99), which is present within the cell membrane. The C99 fragment further undergo cleavage by γ-secretase at various sites and results in the generation of Aβ-peptides of different chain length such as Aβ-37, Aβ-38, Aβ-39, Aβ-40, Aβ-42 and Aβ-43[31,32] and APP intracellular domain.

Aβ40 and Aβ42 are the 2 primary subtypes of Aβ polymers that directly contribute to the development of plaque and produce neurotoxicity. Compared to Aβ42, which functions as a toxic building block of Aβ assembly and is less abundant highly insoluble, severely toxic to neurons, and more aggregation-prone, Aβ40 is more plentiful and less toxic. The aggregation of Aβ40 or Aβ42 leads to several negative effects, including ion channel blockage, disrupted calcium homeostasis, increased oxidative stress in the mitochondria, and impaired glucose regulation and energy metabolism, all of which worsen neuronal health and ultimately cause death of neurons.

Despite the fact that Aβ40 is significantly more important when compared to Amyloid β-42. The tendency of Aβ42 to aggregate is increased by the hydrophobic nature of its two terminal amino acids. Aβ42 is therefore believed to be a crucial component in the start of the plaque-forming process and pathology of AD [33]. Furthermore, Evidence suggests that Aβ38, Aβ42, and the Aβ42/Aβ38 ratio in CSF can be utilized to distinguish Alzheimer's disease from other dementias[34-36]. Remarkably, studies have demonstrated the competition between amyloidogenic and non-amyloidogenic pathways, indicating that augmenting the former and diminishing the latter are feasible approaches to minimize Aβ production.

The membrane-associated enzyme beta-secretase is produced in the ER in pro-enzyme form. It requires multiple post-translational alterations in the Golgi to achieve its full activity, including phosphorylation, glycosylation, acetylation, and palmitoylation, all of which has been shown to be required for an enzyme to start amyloidogenic processes [37,38].

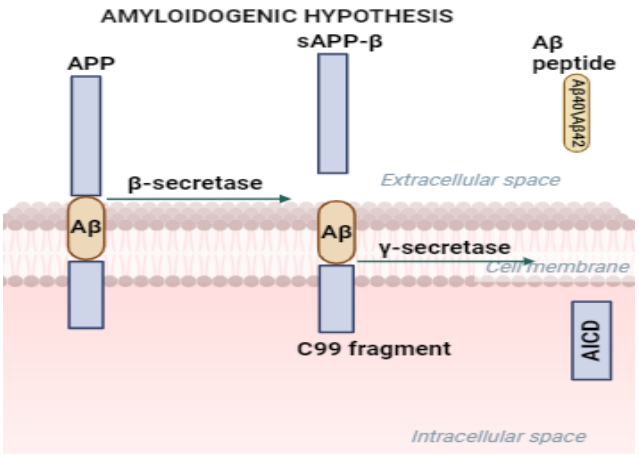

Figure 4: Amyloidogenic pathway: Entire APP protein will be cleaved by β-secretase into sAPPβ ectodomain in extracellular region, and C99 fragment will be retained in the cell membrane. Moreover, the γ-secretase enzyme will cleave the C99 fragment into Aβ-peptide and AICD, which causes plaque development.

4.2 Tau protein hypothesis

The discovery that NFTs are made of phosphorylated tau forms the basis of the tau hypothesis. Neurofibrillary tangles (NFTs), which are rigid fibres primarily composed of hyperphosphorylated tau protein that form in the cytoplasm of neurons, particularly in the axoplasm, are the

second common morphologic sign of AD[39,40]. Tau is a protein linked with microtubules that functions as a structural protein and is more frequently found in axons. The adult brain contains six different types of tau (3R1N, 4RON, 3R2N, 4R1N, 3RON and 4R2N). Under abnormal conditions, tau aggregation leads to neurofibrillary tangles (NFT), which damage the microtubules found in neuronal axons. Damaged microtubules will result in reduced microtubule activity and reduced neuroplasticity and neurodegeneration which also affect cellular functions, the polarity of cells, and intracellular communication.

As microtubule-associated tau protein strengthens neuronal microtubules, it facilitates the growth of axons and dendrites as well as axonal transport. As a result of tau hyperphosphorylation at several locations, microtubules become unstable and stops functioning, which causes them to dissociate from tau protein. when the tau fragments gets detached from microtubules, they will get aggregated and results in the formation of NFT'S intracellular.

According to the oligomeric tau theory, tau-oligomers are the main synaptotoxic type of tau; they arise before NFT's and trigger damage of brain cells and diminished memory even in initial phases of Alzheimer's illness[41]. Tau oligomers can change membrane permeability, this causes an ion imbalance and has the potential to leak into extracellular space. They also seem to function as precursors for the misfolding of tau [42].

The following protein kinases can phosphorylate tau: casein kinase 1, tau-protein kinases, microtubule affinity-regulating kinase 4, AMP dependent kinase 5, AMP activated protein kinase, GSK-3, and cyclin-dependent kinase 5. The GSK-3 theory of AD postulates that excessive phosphorylation of tau, increased Aβ output, microglia-mediated neuroinflammatory reactions, and memory impairment are all consequences of hyperactive GSK-3[43]. The activation of GSK-3 by excess enzymatic expression or alternatively, the association among the Tau and Amyloid ideas might take place through the effect of Aβ-oligomers. The observation that GSK-3 can be activated by both overexpression and Aβ oligomers suggests a potential unifying mechanism for AD. Aβ synthesis and Aβ-mediated neuronal death are influenced by GSK-3 activity, which phosphorylates tau [44].

The aggregation of Aβ protein may trigger changes in tau protein, leading to the development of tauopathies. Tau hyperphosphorylation, accumulation of tau and incorrect localization, are all aided by Aβ. Aβ pathology exacerbates tauopathy and drives neurodegeneration through diverse mechanisms, including**:** Neuroinflammation-mediated tau phosphorylation, Disruption of axonal transport, Suppression of proteasome-mediated tau degradation [45]. The synergistic relationship between Aβ and tau suggests that their combined pathological effects, rather than the independent actions of each protein, are responsible for dementia.

4.3 Mitochondrial cascade hypothesis

The link between amyloid precursor protein and Alzheimer's disease and mitochondria has long been recognized and studied. The leading theory on Alzheimer's suggests that tau and Aβ proteins harm brain cells by interfering with their ability to use antioxidants and energy sources. This disrupts how brain cells function and communicate, leading to decline. Since neurons rely heavily on energy, any change in mitochondrial function can have a particularly negative impact on their functioning [46]. Adenosine triphosphate, or ATP, is the energy source for mitochondria. Beyond energy production, mitochondria exert a critical influence on various cellular processes governing survival and death. These include the control of Ca2+ ions and free radical levels, acting as important second messengers.[47] Significantly, decreased ATP synthesis, ROS production and Ca2+ dyshomeostasis, are all impacted by mitochondrial dysfunction.

Although the fundamental causes of the initial stages of AD are less known, changes in the dynamics of mitochondria and mitophagy are observed. Elucidating the mechanisms involved in damage of mitochondria in AD holds significant promise for advancing the learning of the pathology of this NDDs. Such insights could pave the way for the development of novel therapeutic strategies aimed at preserving synaptic activity and, consequently, cognitive function.

4. Therapeutic treatment of Alzheimer's disease

The etiology of AD is linked to multiple intricate mechanisms, such as insufficient parasympathetic neurotransmission, impaired metabolism of beta-amyloid (Aβ) proteins (Aβ aggregation), hyper phosphorylation of tau protein and its deposition (NFT), and the participation of oxidative and inflammatory networks. The licensed medications that are on the market now affect only one target (one drug, one target; ODOT); however, in recent times, research has focused on developing pharmaceuticals that can target numerous targets by using multiple treatment techniques.

Table 1 lists the single-target medications that the FDA has so far approved; these are the most successful in managing AD, and they include the glutamate antagonist memantine and the cholinesterase enzyme blockers, which are NMDA receptor blocker [48]. These medications are all intended to alleviate AD symptoms.

Table 1: FDA approved single-target medications which are most effective for AD management

DRUG	Mechanism of action	Drug targets	Managed symptoms
Memantine	NMDA receptor antagonist	NMDA receptor	Improves learning and memory
Donepezil	Cholinesterase inhibitor, the decrease in inflammatory cytokine expression in the initial phases, minimizing the consequences caused by oxidative damage, suppression of several features of excitability produced by glutamate.	Acetylcholine esterase	Improves cognition and behavior
Rivastigmine	Cholinesterase inhibitor; increases cholinergic function	Acetylcholine-esterase, butyrylcholinesterase	Enhances daily activities and cognitive abilities.
Galantamine	Blocker of cholinesterase.	AChE; nicotinic Ach receptor	Enhances cognitive abilities, everyday activities, and behavioral symptoms

While licensed medications offer some symptom relief, they fall short in effectively managing this complex illness. There's a critical need for more comprehensive treatment options. Research is being done to identify and create new medications for the treatment of AD. Researchers are developing a new generation of drugs that hold promise for Alzheimer's disease. These 'multi-target therapies' aim to tackle several key aspects of the disease simultaneously, including amyloid beta plaque build-up, tangles, oxidative damage, and damage of mitochondria. A lot of these medications are presently going through clinical studies.

Polypharmacophore design, or the construction of hybrid compounds that consist of conjugates, separated by spacers, comprising two or more different pharmacophores, is one of the contemporary strategies for developing multi-target medicines for the treatment of AD[49,50]. Ladostigil is an example for the drugs acting at multiple targets. Ladostigil is an innovative drug design. It's a hybrid medication, merging features of rivastigmine (a cholinesterase inhibitor) with N-propargyl to target both cholinesterase and monoamine oxidase enzymes in the brain. This medication wasn't effective in delaying the transition from mild cognitive impairment to Alzheimer's during phase 2 clinical studies [51].

5.1 Anti-Aβ drugs targeting Aβ: Anti-Aβ medications work by reducing the amount of Aβ in the brain. They achieve this by lowering its production, preventing its build up, and increasing its removal. There are two anti-Aβ drugs; beta-Secretase inhibitors and gamma-Secretase inhibitors.

β-Secretase inhibitors mainly decrease the synthesis of amyloid beta peptides. While BACE1 was once considered a promising target for Alzheimer's treatment, the majority of clinical trials designed to inhibit this enzyme have ultimately failed. Several compounds from the acyl guanidine class such as Verubecestat, Lanabecestat, and Atabecestat have been successfully entered into the final phases of clinical trials. However, due to cytotoxicity or a lack of clinical effectiveness, they were unable to get into market [52].

Verubecestat (MK-8931) is a BACE1 inhibitor which reached Phase III trials because it is capable of crossing the BBB effectively and its improved bioavailability. However, the medication failed to reverse participants' cognitive decline and increased adverse events (AE), leading to the early termination of two Phase III clinical trials [53].

5.2 Drugs targeting $A\beta_{42}$: The production of Aβ42 occurs due to the proteolytic activity of γ-secretase and BACE-1 enzymes. Agents that target both of these enzymes would contribute to the decrease in the synthesis of Aβ42. Tarenflurbil is an anti-inflammatory medication that shares chemical similarities with ibuprofen. By allosterically altering γ-secretases catalysis of APP, it affects the enzyme and produces Aβ38 instead of Aβ42, which is less neurotoxic than Aβ4 [54]. Although the phase 2 study yielded positive findings, the agent's limited efficacy and poor brain penetrability caused it to be unsuccessful terribly in both the phase 3 trial and its follow-up phase 3 trials [55].

5.3 Drugs targeting tau protein: Studies have indicated that the tau protein is crucial for the formation and stability of cytoskeletal microtubules, albeit its exact function is yet unknown. Tau (p-tau) undergoes abnormal hyperphosphorylation, which decreases its affinity for attached microtubules. Aberrant phosphorylation of Tau causes formation of neurofibrillary tangles. Three primary criteria's that are involved in the therapy of anti-tau drugs: 1. Minimizing the aggregation and hyperphosphorylation of tau, 2. Strengthening microtubules and 3. Enhancing the elimination of tau.

GSK-3β inhibitor; Tideglusib is a thiadiazolone that decreases tau phosphorylation and irreversibly inhibits GSK-3β, Researchers evaluated the clinical efficacy of GSK-3 inhibitors for Alzheimer's disease in a Phase II, double-blind, placebo-controlled clinical trial, it did not demonstrate any clinical benefit and is still being investigated [56].

Tau aggregation inhibitor (LMTM); Compared to methylthioninium chloride, LMTM has a lower toxicity and

a higher bioavailability. A Phase III trial for LMTM failed to demonstrate any benefit in slowing cognitive or functional decline in people with mild to moderate AD, in older, healthy participants; however, a second Phase III experiment involving such participants is still ongoing[57].

5.4 Immunotherapy: Immunity can be broadly categorized into two types: active immunity, engendered by immunization, and passive defence, conferred by giving monoclonal antibodies to patients. These are the two primary categories of immunotherapeutic medications that can improve the immune system's ability to eliminate infections.

The ultimate objective of active immunization is to formulate a vaccine against Aβ42 that inhibits the formation of amyloid plaques. Aβ42 and tau levels have been reduced in phase 2 clinical trials of the vaccine, which showed improved cognitive outcomes. However, the experiment was stopped because several of the individuals developed meningo-encephalitis after receiving the shot [58]. To combat this issue, a novel vaccine. ACC-001 is designed to target disease by promoting clearance of Aβ plaques while minimizing unwanted immune system reactions. Phase II clinical trials involving patients with mild to moderate AD demonstrated adequate safety for ACC-001, even though it incorporated the QS-21 adjuvant [59].

A key objective of passive vaccination is the delivery of immunoglobulins (Ig) and monoclonal antibodies (mAB). Investigations are presently underway for biologics such as Apapeuzumab, solanezumab, and gantenerumab, which could yield encouraging outcomes. Solanezumab, a monoclonal antibody targeting soluble amyloid beta (Aβ) peptides, underwent Phase III trials for 80 weeks in patients with mild Alzheimer's disease. Significant improvements in cognition and functionality had been shown by this trial, and outcomes from CSF biomarker analysis suggested that solanezumab was linked with its target [60].

CONCLUSION

Alzheimer's disease is a complicated, long-term illness where age, other medical disorders, and external factors increases hereditary problems. The pathophysiology of AD eventually leads to cognitive decline and memory impairment and is strongly correlated with oxidative damage, inflammation of the brain, metabolic defects, and parasympathetic impairment in the central nervous system. In this review article the cause of Alzheimer disease is explained on the basis of Amyloid hypothesis, Tau protein hypothesis and mitochondrial cascade hypothesis. Investigation is being done to develop novel and effective technologies that will help to detect neurodegenerative illness early and treat it effectively. Some medications used to treat Alzheimer's disease include cholinesterase inhibitors and N-methyl-D-aspartate antagonists. Furthering our understanding of the intricate neurodegenerative pathways holds the key to unlocking effective disease-modifying therapies for these debilitating disorders. This necessitates continued research efforts focused on both elucidating these pathways and developing neuroprotective agents.

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