1. Introduction

The human brain has around 100 billion neurons in a healthy state, each of which has growing extensions and synapses that connect them.[1] A neurotransmitter is a microscopic chemical burst that transmits information between two synapses. Neuronal impulses that comprise the biological basis of memories, feelings, sensations, thoughts and the development of physical abilities can pass quickly across synapses.[2] The diseases, traumas, and ailments that accompany the brain's regular aging process destroy the synapses. This results in weakened nerve connections, which lowers the rate at which neurons communicate with one another. While it is common for people to lose some neurons as they age, this is not the usual maturing process. Rather, age-related changes in memory and thinking are not the usual cause of perplexity, confusion, and cognitive deficiencies that interfere with day-to-day functioning.[3]

Alzheimer's disease (AD) is a catastrophic age-related neurodegenerative illness for which there is no recognized cure at this time. It is distinguished by a sharply increasing loss of memory and cognitive function. The number of AD patients is increasing rapidly due to longer life expectancies.[4] Memory loss is one of the most prevalent symptoms, which is followed by language impairment, confusion, mood fluctuations, motivation loss, and, in later stages of the disease, behavioural issues. The body gradually loses its ability to operate, neurons become fewer in number, and finally death occurs[5]. Although the rate of disease progression varies, life expectancy is usually approximately 3 to 9 years.

According to a WHO report published in Global Health Estimates, non-communicable diseases now rank as seven of the top 10 causes of death worldwide, and AD and other dementias are now the world's leading cause of death.[6] Although this disease is not well understood, approximately 70% of the risk is thought to be genetic. Other risk factors include head trauma, depression, and high blood pressure. Examination of brain tissue is essential to confirm the disease[7]. Based on the illness, the patient's medical history, and cognitive testing with blood and medical imaging tests to rule out other potential reasons, a trustworthy diagnosis is formed. [8]. Mental and physical training is generally recommended to reduce the risk of AD, as there are no suitable drugs or nutritional supplements that can reduce the risk of developing AD[9]. Sixty percent of the world's 55 million dementia sufferers reside in low- and middle-income nations. Every year, there are around 10 million new infections recorded.[10]

There isn't a known treatment for AD which can actually halt disease progression. The current therapies are mostly analgesic, with only marginal benefits for symptoms. The three types of therapies that are now available are psychological, pharmacological, and caring. Currently, the USFDA has authorized four main pharmaceutical compounds to treat the cognitive issues associated with AD. The cholinergic inhibitor tacrine **(1)** was taken off the market in 2013 because of hepatotoxicity. Other drugs include three acetyl cholinesterase inhibitors, namely donepezil **(2),** rivastigmine **(3),** galantamine **(4)** and one N-methyl-D-aspartate (NMDA) receptor blocker, memantine **(5).** The chronology of discovery for the marketed anti-AD agents is given in **Fig 1.1.**

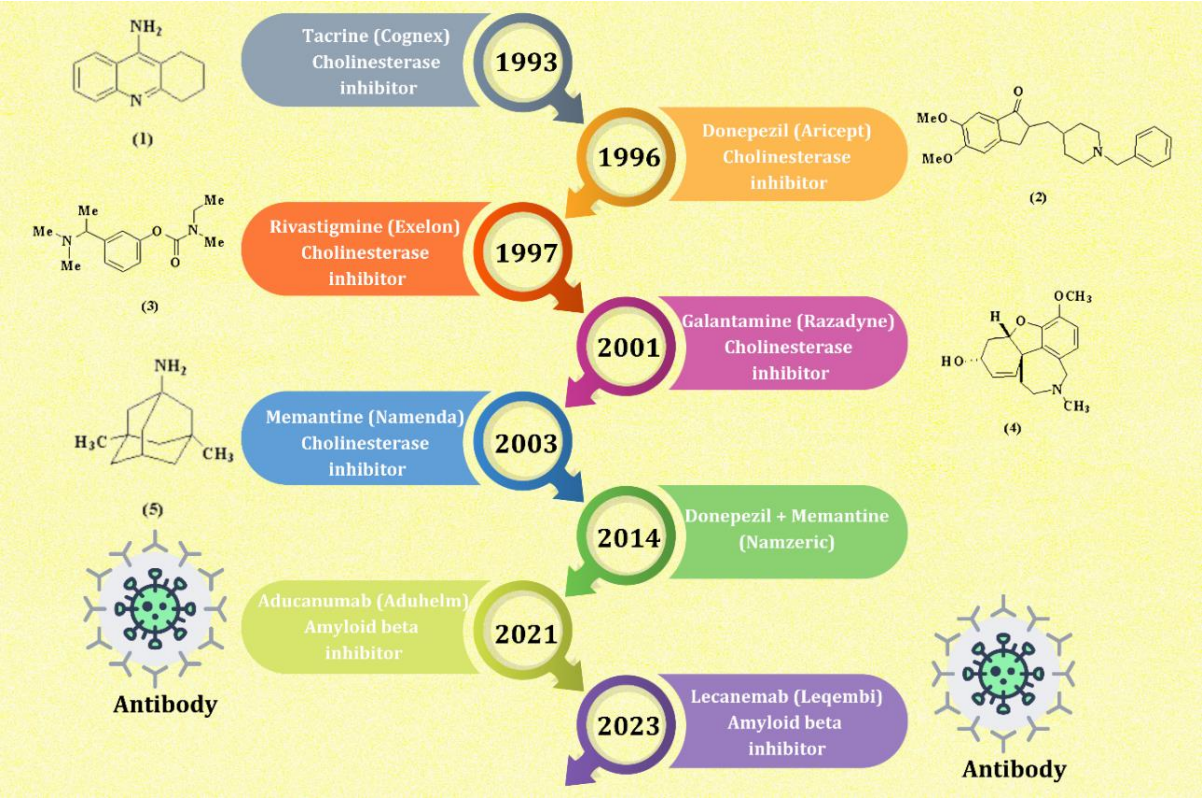


Fig 1.1: Chronology of approved drugs for the treatment of AD.

Owing to the complex nature of the illness, no drug has been proven to slow or stop the disease's progression[11]. These therapies are mostly successful in treating modest cognitive deficits and offer momentary symptom alleviation; nevertheless, they are unable to stop the course of AD or cure it. Consequently, rather than just providing symptomatic relief for patients, it is crucial to concentrate on creating molecules that truly address the condition, either by treating the disease itself or by delaying the onset of AD.

1.1. Risk Factors leading to AD

When it comes to AD, the main focus has traditionally been on treating the pathological changes and symptoms that patients experience in their brains; risk factors and how to control or avoid them have received less attention. The primary modifiable risk factors for AD include obesity and diet, smoking, alcohol, diabetes mellitus, hypertension, a lack of social activities, physical inactivity, and educational lag. The primary non-modifiable risk factors for AD are ageing and heredity **(Fig. 1.2).** [12]

1.1.1. Non-modifiable risk factors

The risk of AD rises with advancing age. AD is categorized as having an early onset (age 65) or a late onset (age >65) based on the patient's age. The bulk of documented AD cases frequently have a late beginning, while early onset cases are quite rare. The APP, PSEN1, and PSEN2 genes, which code for the amyloid precursor protein, are mutated in most instances of familial AD with early onset. The most of AD patients also include additional risk factors that are controllable and avoidable.[12,13]

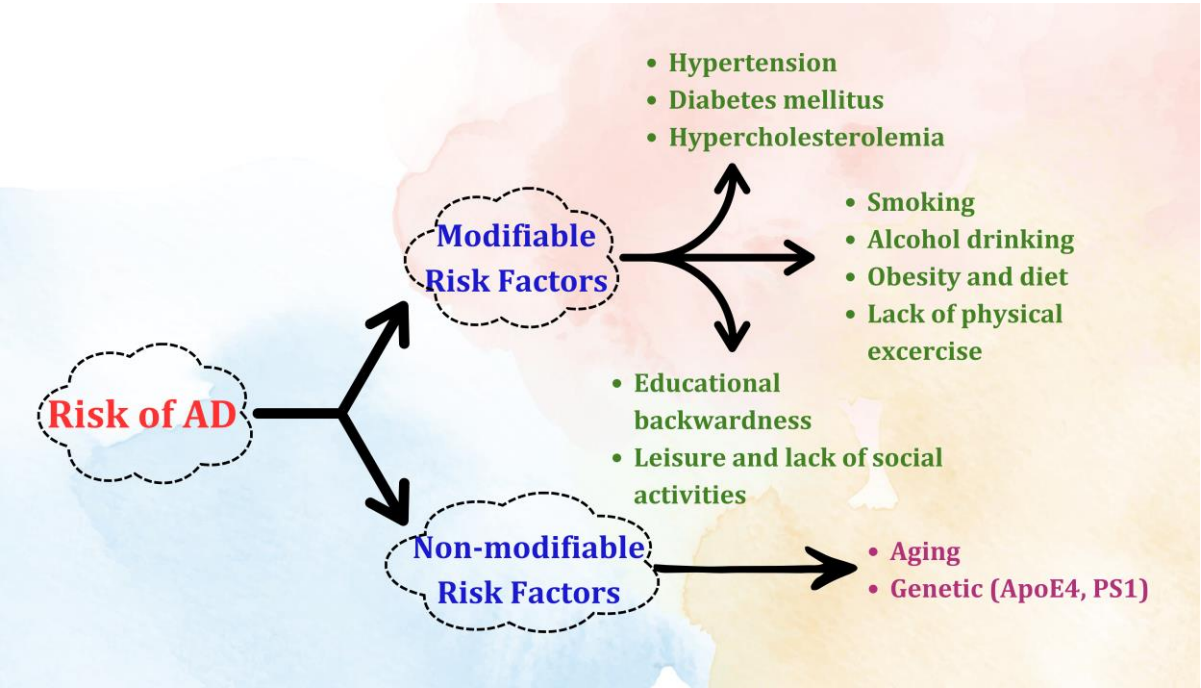


Fig 1.2: Risk factors leading to AD.

1.1.1.1. Genetic

Genetic risk factors are the second most important cause of AD, behind age. Genetic variation in the APOE gene, which codes for the 4 allele (APOE 4) of the cholesterol transporter apolipoprotein E, and mutations in the γ-secretase enzyme complex components,

such as presenilin 1 (PS1) and APP, are the main sources of genetic risk factors. [14–16] A study found that APOE 4 led to amyloid plaques and cerebral amyloid angiopathy via increasing Aβ aggregation and reducing Aβ clearance. It is thought to be one of the primary hereditary factors causing AD.[17,18]

1.1.2. Modifiable risk factors

A variety of pathophysiological factors have a major role in the development of AD. It has been shown that increased levels of neurofibrillary tangles and amyloid plaques are associated with **hypertension**.[19] There are certain findings which show relationship between **Diabetes mellitus (DM)** [20–22] and AD. However, there is inadequate information to establish the real significance of the relationship, leaving the subject of DM's involvement in AD up for debate. Transgenic AD mice with diet-induced **hypercholesterolemia** were used in a number of preclinical research to examine the relationship between hypercholesterolemia and increased Aβ deposition. [23,24] The use of statins, such as pitavastatin and atorvastatin, decreased microglia inflammation and the development of amyloid plaques. [25] Simvastatin, on the other hand, reduced cognitive deficits without affecting Aβ levels.[26,27]

Certain habitual behaviours, including consuming **alcohol and smoking**, can increase the risk of AD by two to four times. Furthermore, research has demonstrated an elevated incidence of dementia and AD among second-hand or passive smokers.[12] Middle-aged **obesity** increases the risk of AD and dementia. The two main early-onset AD symptoms linked to obesity are cortical atrophy and an increase in amyloid plaques. Cognitive deficits can be mitigated and the risk of dementia and AD reduced by eating a **healthy diet** rich in vegetables, whole grains, fruits, seafood, and olive oil. Conversely, a diet heavy in saturated fat and low in vitamin B6, B12, E, and D promotes the formation of Aβ plaques, which in turn raises the risk of AD and dementia in old age.[12] Finally, exercise lowers the risk of developing AD and dementia. Frequent **aerobic exercise** promotes brain plasticity and the non-amyloidogenic route of APP processing, hence reducing cognitive deficits.[28,29]

1.2. Pathophysiology of AD

A plethora of hypotheses have been suggested by to establish the pathogenesis and etiology of AD, unfortunately all of the theories **(Fig 1.3)** remain elusive because of the complex nature of disease. AD is broadly categorized into two main types; Familial Alzheimer's disease (FAD) accounting for 1-5% of AD cases and Sporadic Alzheimer's

disease (SAD) for over 95% of AD cases. FAD is predominantly characterized by autosomal dominant genetic mutations in amyloid precursor protein (APP), presenilin 1 (PS1) and presenilin 2 (PS2) genes, typically occurring between 30-65 years and progressing rapidly.

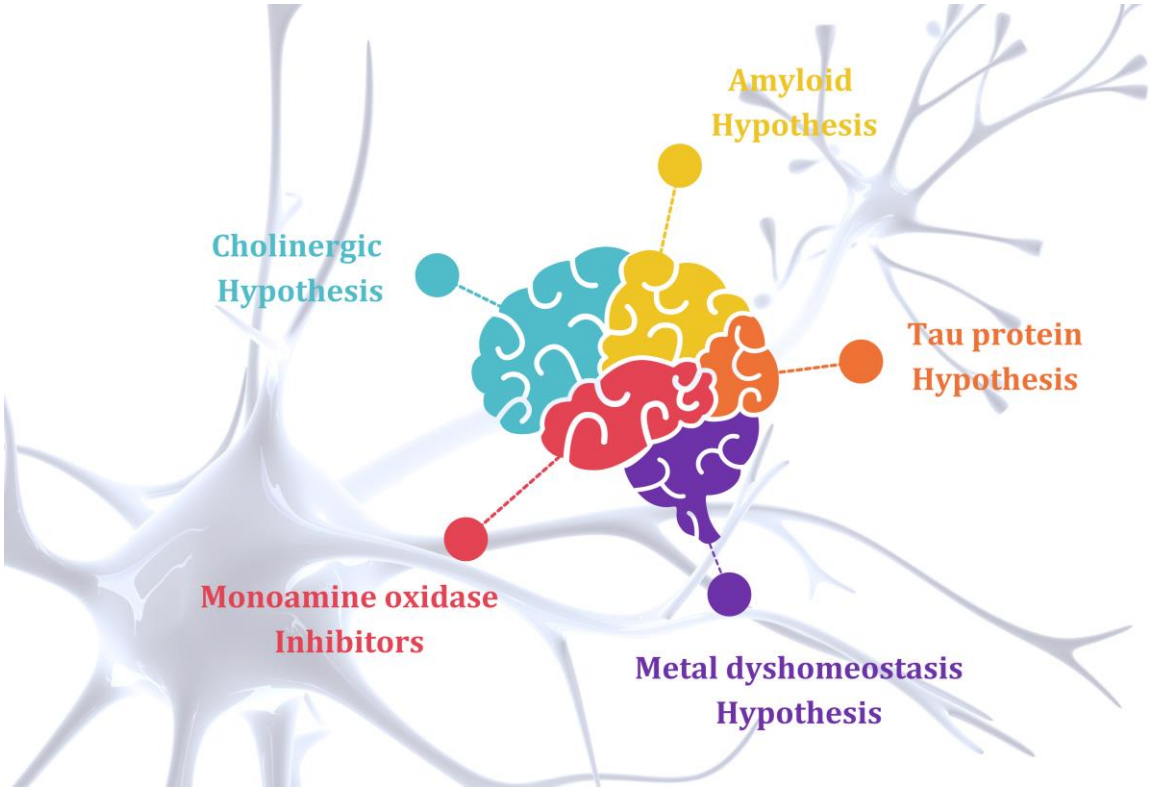


Fig 1.3: Pathophysiology of AD.

On the other hand, SAD, also known as late-onset AD, usually prevails after the age of 65 and is influenced by a combination of genetic risks, environmental factors, and various comorbidities.

The drug discovery and development has become extremely difficult as investigation of the signalling pathways of each individual targets via *in vitro* and *in vivo* models have shown that validated target combination produce synergistic or additive effects because of their inter-relationship with another target. Therefore, these targets (**Fig 1.3**) and their effects should be thoroughly studied before design and development of anti-AD agents to avoid effects of antagonism or suppression and to improve potential synergy.[30,31] Some of the well-established therapeutic targets of AD are classified in (**Fig.1.4)**

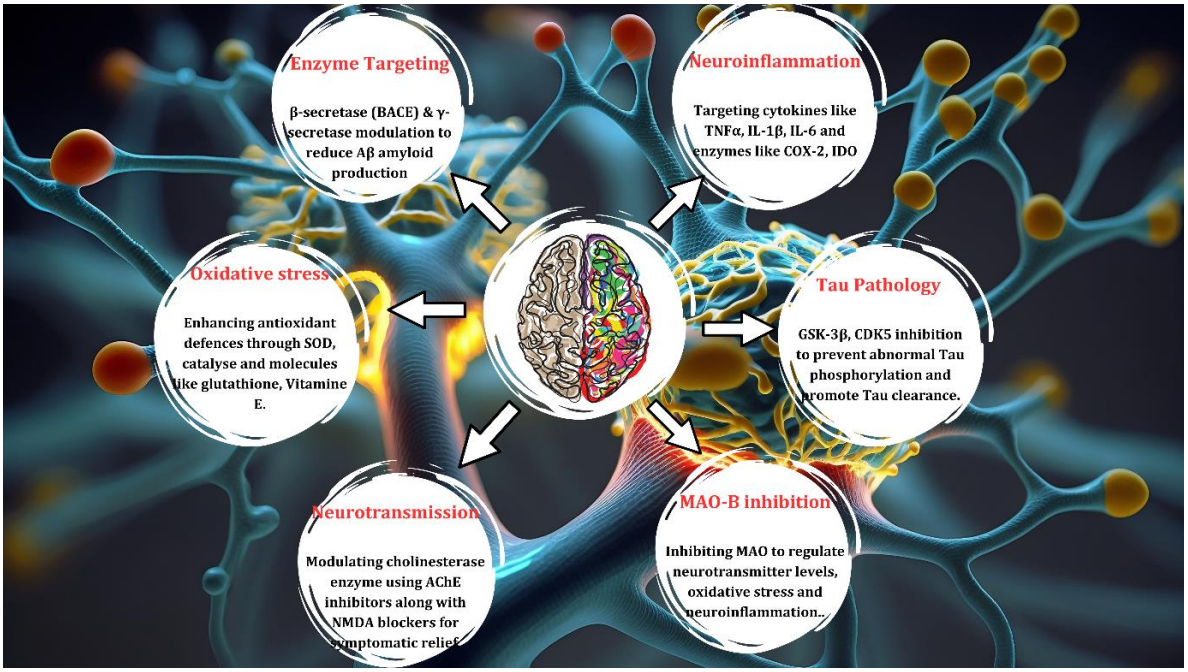


Fig. 1.4: Therapeutic targets of AD.

1.2.1. Cholinergic hypothesis

Acetylcholine (ACh) is an important excitatory neurotransmitter that regulates various activities like memory, learning, and other behavioural aspects of daily life. According to the cholinergic hypothesis, which was first applied to the pathophysiology of AD, the imbalance of ACh—whose levels decrease in the brains of elderly patients—is a major factor in the disease's progression.[32] More precisely, the cerebral neocortex, the hippocampus, the nucleus basalis of Meynert, and the fundamental forebrain cholinergic neurons (BFCNs) are in charge of cognitive function.[33] In essence, acetylcholine's synthesis, release, and particular affinity for cholinergic receptors, specifically nicotinic (Nn) and muscarinic (Nm) receptors, are what drive cholinergic neurons' signaling.[34] Acetylcholine is classified as a neuromodulator in the brain even though it is an excitatory neurotransmitter in the peripheral at the neuromuscular junction. This is because it is activated or inhibited by different types of environmental inputs.[35]

Choline and acetyl-coenzyme A (Acetyl-CoA) react in presence of choline acetyltransferase (ChAT) to produce ACh.[36] ChAT becomes an important target for the creation of anti-AD pharmacological molecules since it has been shown that the levels of catalyst ChAT change with age, which is directly connected with a reduction in the generation of ACh. Regrettably, there is a dearth of global research on ChAT targeting,

which makes it a promising field of study with potential applications in AD treatment.[37] Following production, vesicular acetylcholine transporter (VAChT) carries ACh to synaptic vesicles. Following depolarization, the neurotransmitter is released into the synaptic cleft where it binds to either the muscarinic or nicotinic receptor. Choline is then reabsorbed and transported back into the presynaptic neurons with the aid of choline transporters (mostly CHT1) after acetylcholine esterase (AChE) breaks down the excess ACh present in the synaptic cleft into acetate and choline. (**Fig 1.5)**

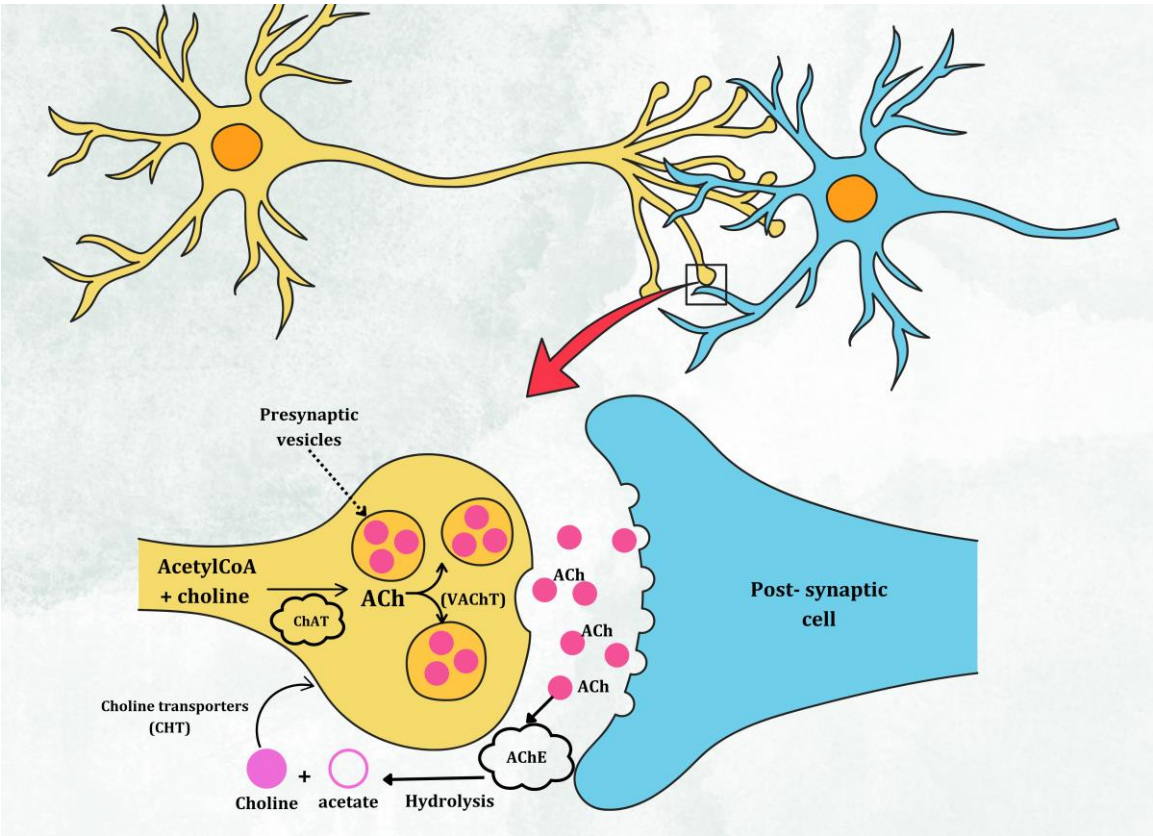


Fig 1.5: Schematic diagram showing cholinergic hypothesis.

The two types of ChEs are acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). AChE can be found in neuromuscular junctions and cholinergic neurons, whereas BuChE is linked to glial cells and is found in the hippocampus and temporal neocortex. Although AChE and BuChE serve different functions and are located in different areas, their structural make-up is fundamentally similar. When it comes to ACh, AChE has a greater affinity than BuChE. Rather than BuChE, AChE hydrolyzes ACh primarily.[38–40] **Fig 1.6** illustrates the two active sites of AChE, which are the catalytic active site (CAS) and the peripheral anionic site (PAS). Two binding sites in CAS interact with the substrate ACh in real life.

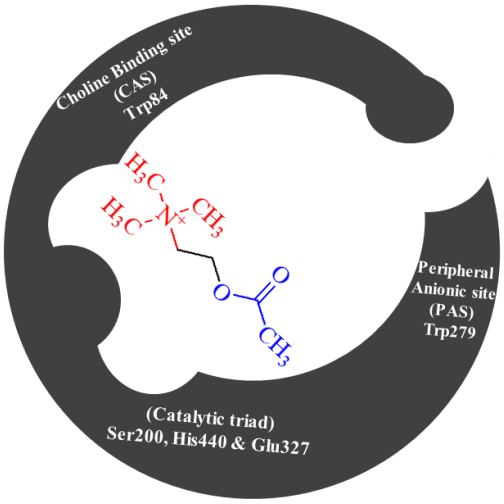


Fig 1.6: Schematic diagram of AChE binding pockets.

A long, thin pocket has two binding sites at its bottom. The other binding site, called the ester hydrolysis site, is catalysed by a trio of amino acid residues: Ser200, His440, and Glu327. One of these sites, called the α-anionic site, has an amino acid residue Trp84 that interacts with the quaternary ammonium moiety of the ACh. The PAS, also known as the β-anionic site, is situated around 14Å from the CAS, close to the pocket's entrance. There are several amino acid residues in PAS[41], but Trp279 is the most significant and is mostly engaged in the interaction with the substrate.[42] PAS plays a major role in the pathophysiology of AD because it interacts with the Aβ peptide, allowing it to build up in the brain as amyloid plaques, which in turn accelerate neuronal cell death.[43–45]

Though less so than AChE, BuChE hydrolyses Ach into acetate and choline in a manner akin to that of AChE.[46,47] It has been shown that as AD patients brains age, certain areas of their brains exhibit either increased or unchanged BuChE activity.[48] Furthermore, it has been shown that in late-onset AD, an elevated level of BuChE compensates for the reduced activity of AChE resulting from lower AChE levels in the AD brain[49].

As a result, both ChEs have become promising therapeutic targets for the creation of new cholinesterase inhibitors (ChEIs) that will be used to treat AD.

1.2.2. Amyloid hypothesis

Two notable clinical features observed in the brains of AD patients are extracellular Aβ plaques, often referred to as senile plaques, and neurofibrillary tangles, which are intraneuronal tangles of hyperphosphorylated tau protein.[50,51] Although these deposits were initially identified over a century ago, pathologist George Glenner of the University of

California isolated Aβ for the first time in 1984. Glenner further mentioned that the protein known as amyloid precursor protein (APP) is the source of Aβ. As an integral membrane glycoprotein, APP can be digested by proteases either the non-amyloidogenic α-pathway or the amyloidogenic β-pathway **Fig 1.7.**

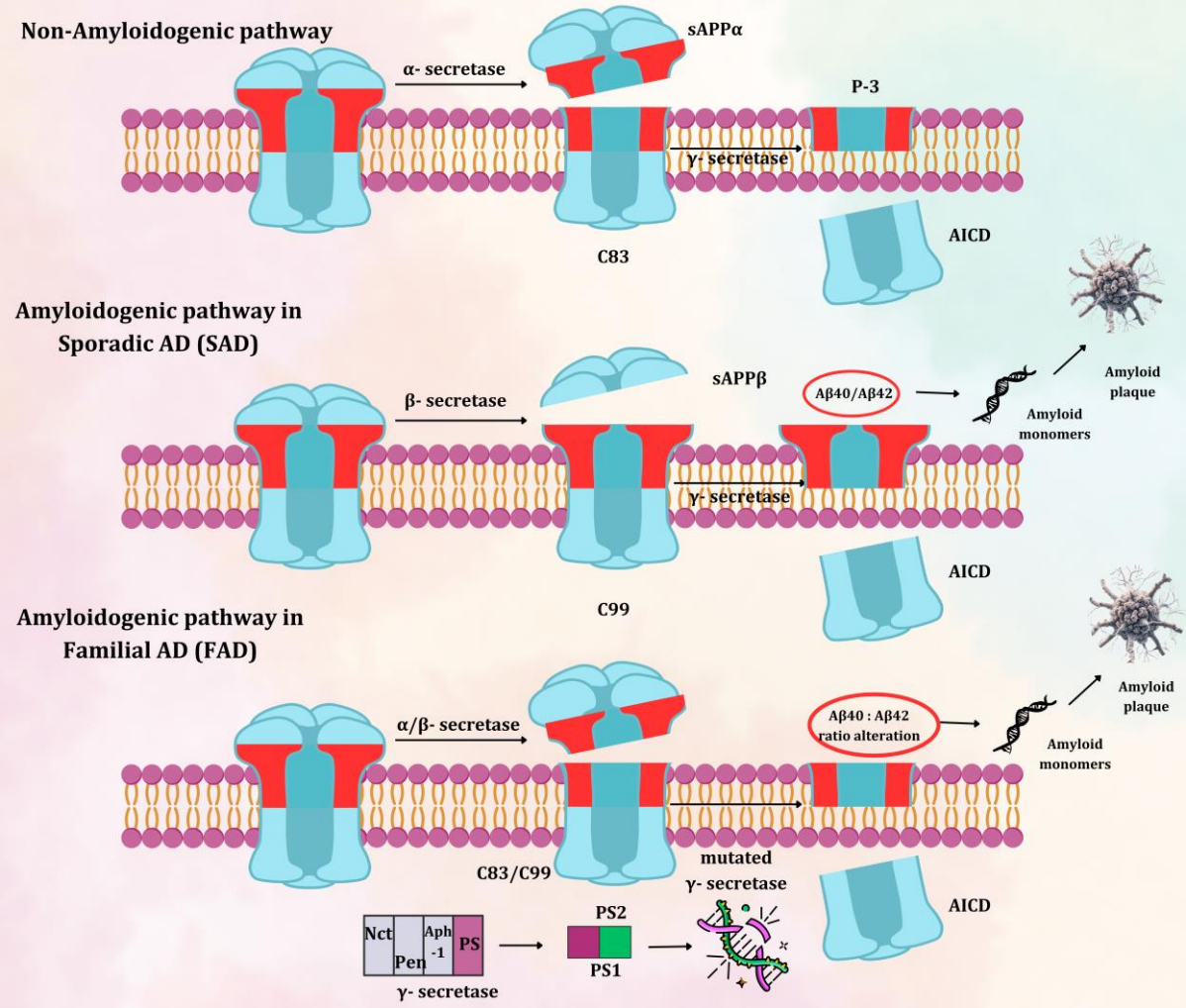


Fig 1.7: Amyloid cascade hypothesis of AD.

APP is typically cleaved simultaneously in the α-path (non-amyloidogenic) by α- and γ-secretases. α-Secretase cleaves the APP first to create the soluble extracellular APP fragment (sAPP-α) and C83 fragment. γ-secretase then cleaves the C83 fragment to create the p3 fragment. The p3 fragment's precise physiological function is still not fully understood. Because it is not involved in the synthesis of Aβ therefore the α-pathway is referred to as the non-amyloidogenic route. A soluble extracellular fragment (sAPP-β) and the C-terminal fragment (C99) of APP are initially produced by the β-secretase (BACE-1) in the β-pathway. The γ secretase further cleaves the C99 segment into 37–43 amino acids, which contain the

amyloid precursor protein intracellular C-terminal domain (AICD) and peptides known as Aβ. The two primary isoforms of Aβ peptides generated by this amyloidogenic pathway are $A\beta_{1-40}$ and $A\beta_{1-42}$. In the proteolytic cleavage, $A\beta_{1-42}$ is more fibrillogenic and hydrophobic in nature than $A\beta_{1-40}$, which is rather produced in abundance. These $A\beta_{1-42}$ monomers aggregate and misfold to produce extracellular plaques and amyloid fibrils. These clumps start the pathogenic cascade, which ultimately causes dementia and neuronal death. Additionally, $A\beta_{1-42}$ also produces neurotoxic Aβ plaques that persistently trigger inflammatory mediators including TNF-α and IL-6.

Moreover, $A\beta_{1-42}$ itself has the ability to operate as a donor of oxygen-free radicals, producing reactive oxygen species (ROS) that have an immediate impact on the normal physiological processes of neurons.[52] Accordingly, the theory postulates that AD develops as a result of a malfunction in either the process by which Aβ is produced, removed from the brain, or potentially both.[50]

1.2.3. Tau hypothesis

Tau protein, a highly soluble microtubule-associated protein (MAP), is essential for regulating the integrity and dynamics of microtubules (MTs), axonal transport, and neurite formation when it is in its normal phosphorylated state.[53] Tau protein is primarily regulated by post-translational modifications (PTMs), which include truncation, phosphorylation, acetylation, glycation, and methylation. Tau phosphorylation is the most common PTM. Overexpression of GSK-3β results in hyperphosphorylation, which modifies the functions and isoform expressions of tau.[54]

Tau is approximately three times more phosphorylated in the AD brain than it is in the normal brain, which causes MT disruption and filament formation**.** In addition to dissolving microtubules, hyperphosphorylated tau sequesters ubiquitin, normal tau, MAP-1, and MAP-2 into tangles of paired helical filaments (PHFs). These insoluble structures cause cell death by interfering with axonal transit, altering cytoplasmic activities.[55] Tau can lose its function in several ways, and it is likely that multiple mechanisms are involved in the development of neurodegeneration and diseases like Alzheimer's: **(Fig. 1.8)**

- **Hyperphosphorylation:** Excessive metabolism of Tau protein occurs due to increased activity of various kinases (GSK3, CDK-5, MARK, PP2A) leading to increased phosphorylation of MT. This causes disruption of MT as the Tau protein

breaks into multiple filaments which indeed lead to destabilization of MT and neuronal dysfunction[55].

- **Aggregation:** The filaments produced due to hyperphosphorylation of tau get aggregated leading to formation of clumps or oligomers in the cytoplasm of neurons. The process of aggregation can be triggered with oxidative stress, inflammation, or genetic mutations. This aggregated oligomers further interfere with cellular processes and form neurofibrillary tangles (NFT). The accumulation of abnormal tangles is thought to lead to the death of neurons, neurodegeneration and eventually diseases like Alzheimer's[55].

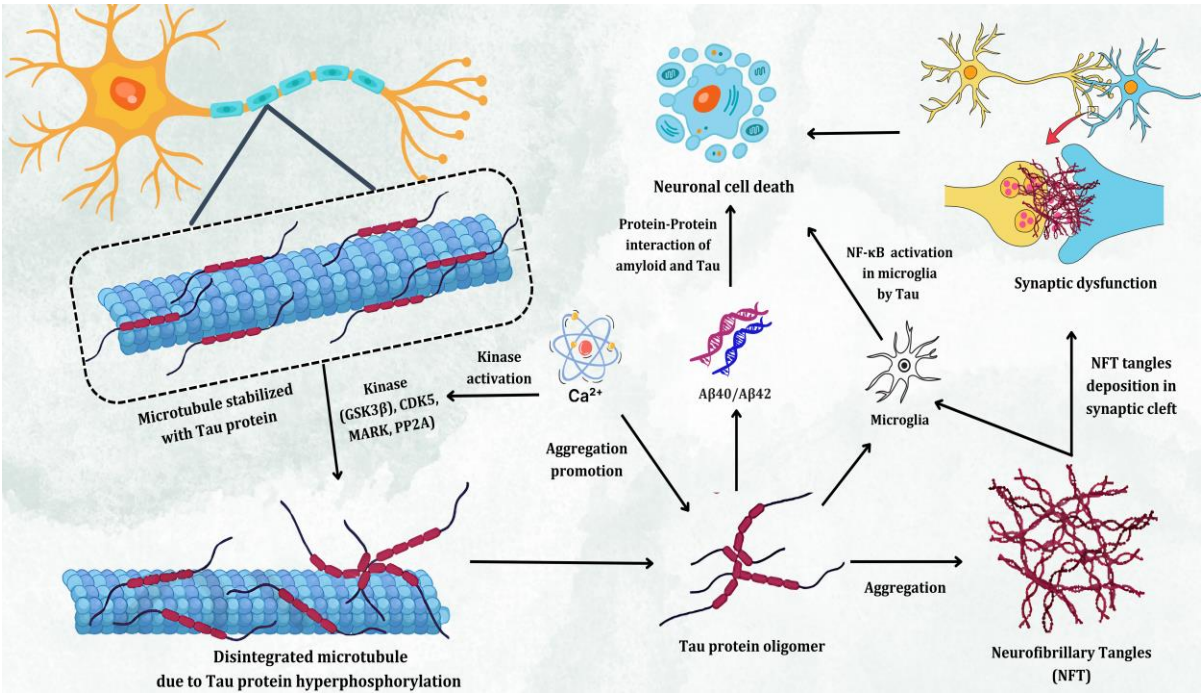


Fig 1.8: Formation of neurofibrillary tangles illustrating tau hypothesis of AD.

- **Protein-protein interactions:** Tau protein interacts with many other proteins in the cell. This interaction is hypothesized to be involved in dysfunction and neurodegeneration. For instance, pre-clinical evidence shows protein-protein interactions between tau and amyloid-beta protein led to the formation of abnormal toxic aggregates that contribute to AD[55].
- **Synaptic dysfunction:** The aggregated tau protein is assumed to be implicated in synaptic dysfunction, the communication or signaling process that occurs between neurons. Impaired axonal transport and the delivery of synaptic proteins and organelles to the synapse are some of the observed evidences of the NFTs found in

the patients of AD. In some cases, the tau protein may also modify synaptic proteins by affecting their expression or localization[55].

- **Calcium homeostasis:** Ca^{+2} is essential for healthy synaptic function. However, excessive influx of calcium into neurons can lead to the activation of enzymes such as kinases or proteases which can promote the aggregation or hyperphosphorylation of tau. This in turn may lead to synaptic dysfunction or loss of synapses[55].
- **Synaptic pruning: S**ynaptic pruning is a natural mechanism regulated by microglia—glial cells found throughout the brain and spinal cord. Comprising about 10-15% of all brain cells, microglia serve as the immune system's frontline defenders in the central nervous system[55]. Research utilizing *in vitro* mouse microglial cells and *in vivo* mouse models has demonstrated that the tau protein activates the NF-κB pathway in microglia, initiating an inflammatory response which could subsequently affect the synaptic pruning process.

1.2.4. Oxidative stress hypothesis

Naturally occurring in many biological processes, reactive oxygen species (ROS) are generated at the cellular level. More and more data point to the involvement of reactive nitrogen species (RNS) and ROS-induced oxidative stress in the neurodegenerative processes associated with AD **(Fig 1.9).**

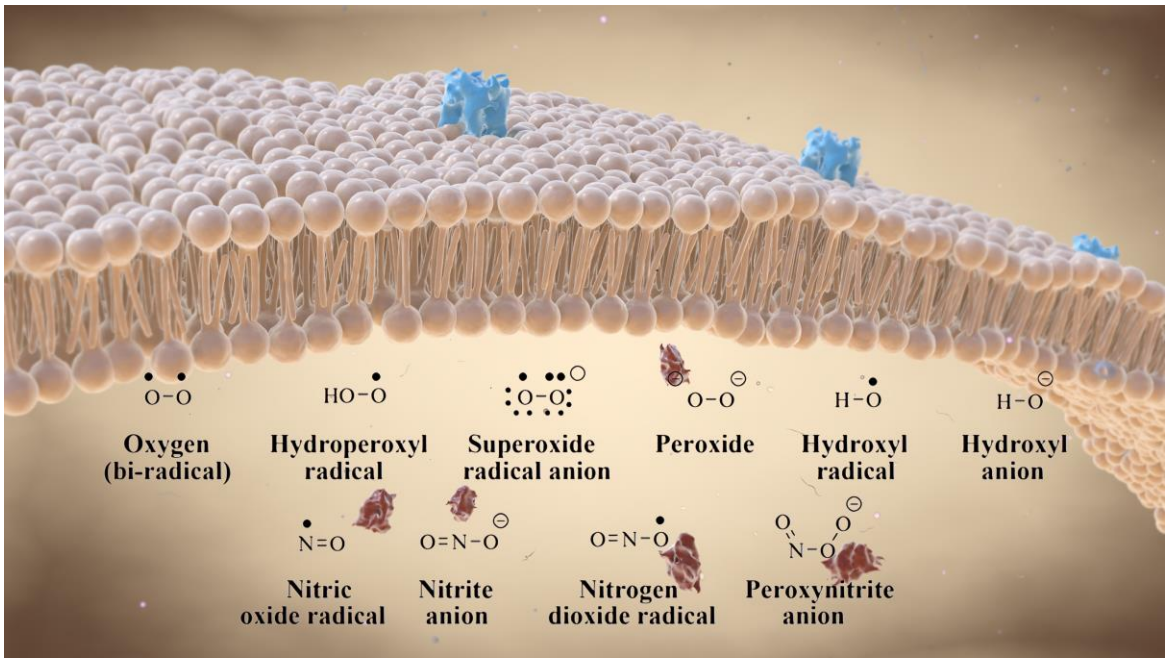


Fig 1.9: Reactive oxygen species (ROS, shown in the first row) and reactive nitrogen species (RNS, displayed in the second row) along with their chemical structures.

One finding is that oxidative stress manifests itself before any other AD hallmark. Normal circumstances result in the generation of reactive oxygen species (ROS), and the delicate equilibrium between the rate at which they are produced and the rate at which they are removed by antioxidants, associated enzymes like catalase and superoxide dismutase along with some antioxidant substances like vitamin E, glutathione, and ascorbic acid. In this method, the cell redox equilibrium is shifted to oxidative unevenness and leads to ROS overproduction due to either increased ROS formation or impaired antioxidant system architecture.[56]

It is additionally known that redox-active metal ions, such as Fe(II/III) and Cu(I/II), may generate reactive oxygen species (ROS) via Fenton-like mechanisms. Oxidative stress results in increased activity of β- and γ-secretases and decreased activity of α-secretase, which in turn drives up the production of Aβ.[57,58] In addition to generating an increase in ROS concentration that reacts with biomolecules including lipids, proteins, nucleic acids, and carbohydrates, oxidative stress can also result in mitochondrial malfunction **(Fig 1.10)**.[59–61]

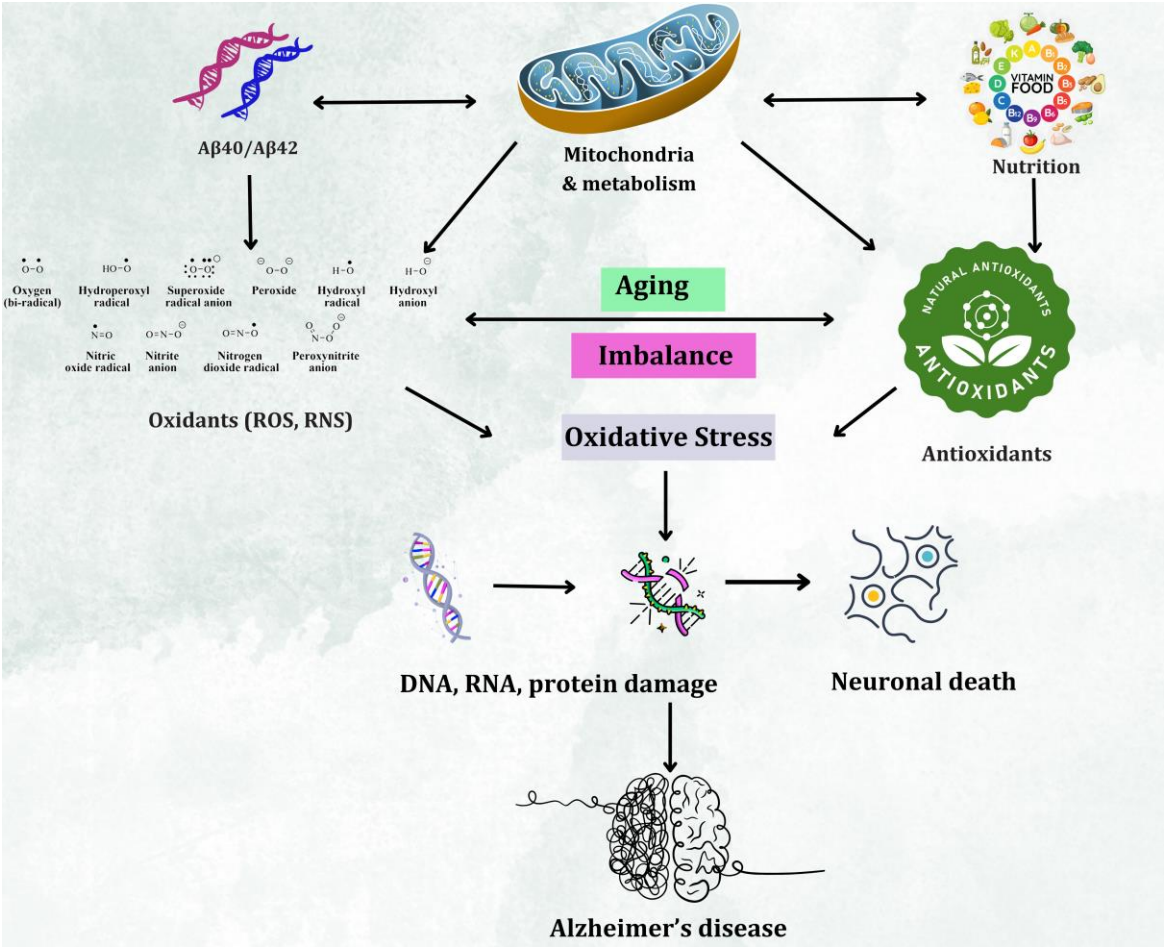


Fig 1.10: Oxidative stress hypothesis.

Therefore, in order to target or regulate oxidative stress in conjunction with other pathogenic variables, attempts have been made to produce more multifunctional antioxidants.

1.2.5. Metal ion dyshomeostasis

Many intracellular signalling proteins and enzymes depend on metals for proper operation. The amount of these metals is tightly controlled in a healthy person. Such homeostatic systems are disrupted in the context of normal aging or a neurodegenerative disease state. This results in deviations in the activities of metal-dependent enzymes, mitochondrial malfunction, and ROS production, all of which are well-known etiologies linked to Alzheimer's disease (AD).[62] The interaction of the Cu^{2+} ion to the Aβ precursor protein (AβPP) at its amino-terminus results in the export of neuronal Cu^{2+}, which in turn causes the metal-mediated Aβ aggregation. Reduced cellular Cu^{2+} levels cause AβPP mRNA expression, which in turn causes an excess of AβPP to be produced. $Aβ_{40–42}$ is produced by the successive cleavage of β and γ secretase.[63] Iron and other metal ions are not bound by the Aβ; instead, it immediately binds to both zinc and copper. Aβ peptides interact with Cu/Zn metals to produce complexes that cause toxicity to neural cells in various ways. The metal-Aβ combination enhances Aβ oligomerization, which damages synaptic functioning, Aβ fibrilization, which causes senile plaque development, and ROS, which causes oxidative stress **(Fig 1.11)**.[64]

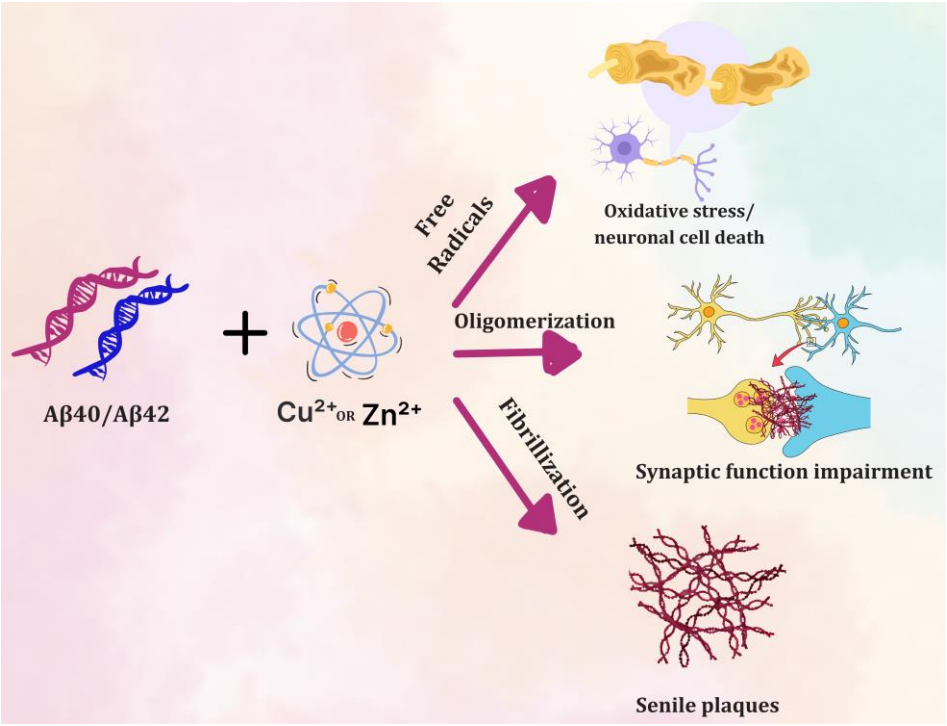


Fig 1.11: Metal mediated toxicity to neuronal cell.

1.2.6. Novel targets for treatment of AD

A complex pathology of AD is claimed to involve a number of variables, including excitotoxicity, apoptosis, neuroinflammation, and metals, in addition to the cholinergic, Aβ, tau, oxidative stress, and others theories. The aforementioned elements are intricately linked to build a complex cellular network. The relationship between these ideas about AD is depicted in **(Fig 1.12).** AD is classified as a multifactorial or multiple illness because of its intricate etiology.

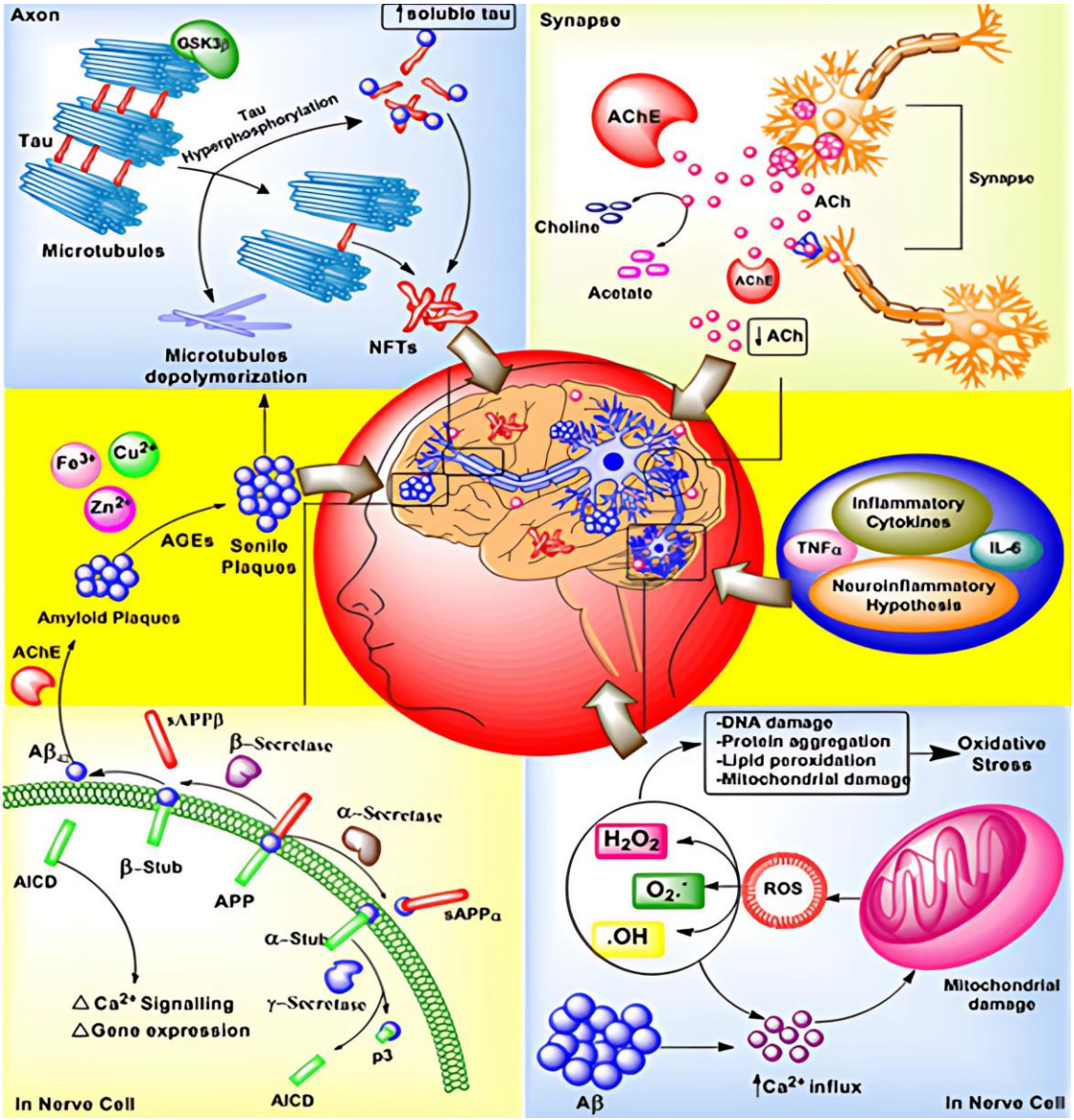


Fig 1.12: An overview of interconnection between various hypotheses of AD.[65]

Changes in the levels of monoamine neurotransmitters caused by monoamine oxidase (MAO) are closely linked to several neuropsychiatric disorders, including AD[66,67]. Preclinical

studies suggests that activation of MAO leads to the accumulation of amyloid-beta (Aβ) by disrupting the normal cleavage of the amyloid precursor protein (APP). Furthermore, the activation of MAO also plays a role in the formation of neurofibrillary tangles and cognitive decline resulting from the loss of neurons.

1.2.6.1. MAO inhibitors in AD

Both isoforms of MAOs (MAO-A and MAO-B), working with flavin adenine dinucleotide (FAD), are crucial for the oxidative deamination of various amines, including primary, secondary, and tertiary types. FAD plays a key role in this process. Neurotransmitters like dopamine, serotonin, and norepinephrine act as primary electron donors, producing imines that are converted into aldehydes and ammonia when hydrolyzed[68]. The enzyme aldehyde dehydrogenase (ALDH) helps convert aldehydes into acids, alcohols, or glycols, with aldehyde reductase (ALR) also involved in these transformations. These biochemical reactions generate several neurotoxic byproducts, including hydrogen peroxide (H_2O_2) and ammonia (NH_3). Overall, these reactions can be categorized into two types: one is oxidative, and the other is reductive **(Fig.1.13)**[69]

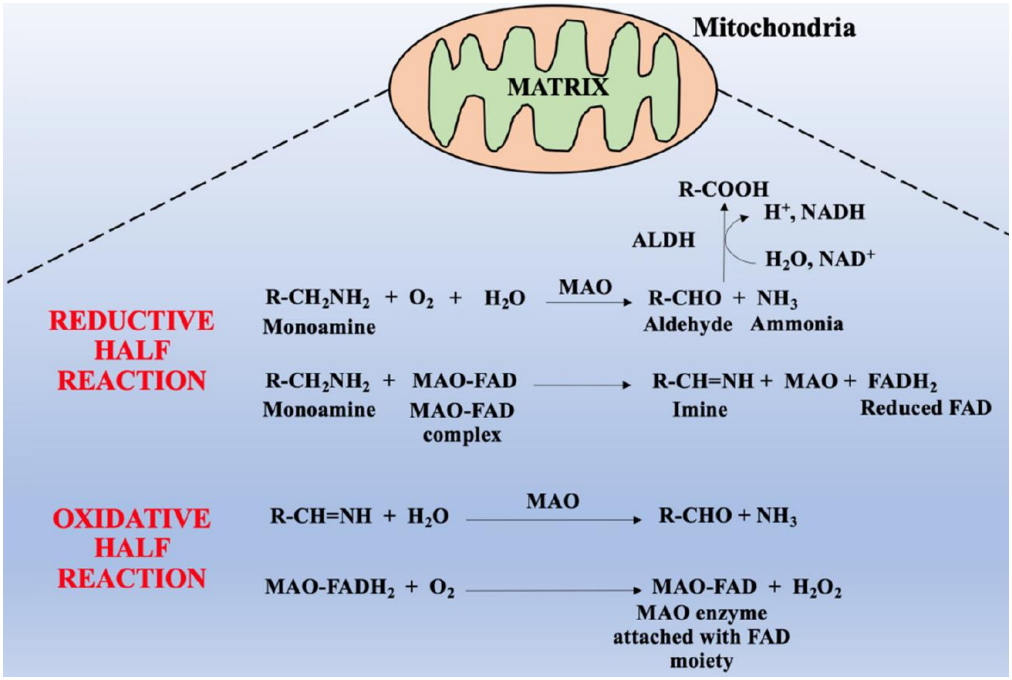


Fig 1.13: Reaction of MAO-catalyzed generation of ROS, leading to oxidative stress[69].

While MAO-A primarily metabolizes serotonin and norepinephrine, MAO-B preferentially degrades phenylethylamine and is involved in the catabolism of dopamine. MAO-B is located mainly in the outer mitochondrial membrane of neurons and glial cells.

The neuronal cell death by the MAO-B involves multiple mechanisms which are explained below:

- **Oxidative Stress:** The accumulation of H_2O_2 leads to increased oxidative stress, which has been implicated in the pathogenesis of Alzheimer's disease. Oxidative damage to lipids, proteins, and DNA by activating Nrf2, an inflammatory response in neurons that results in cellular dysfunction and contributes to the progression of neurodegeneration.[70]
- **Inflammatory Responses:** Reactive species, including H_2O_2, can activate microglia (the brain's immune cells), promoting a pro-inflammatory state. Chronic neuroinflammation is a recognized feature of Alzheimer's disease and might exacerbate neurodegeneration[71,72].
- **Aβ accumulation:** There is evidence suggesting that oxidative stress may promote the aggregation of amyloid-beta peptides, leading to plaque formation, a hallmark feature of Alzheimer's disease. The interaction between oxidative stress and amyloid pathology could create a vicious cycle that perpetuates neurodegeneration[73,74].
- **Tau protein hyperphosphorylation:** Oxidative stress can also play a role in the hyperphosphorylation of tau protein, leading to the formation of neurofibrillary tangles, another key pathological feature of Alzheimer's disease[75].

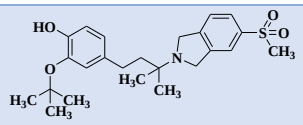
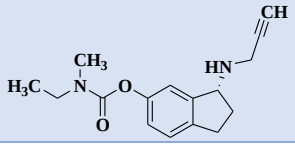
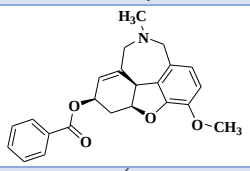
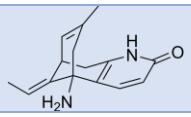
MAO-B plays a multifaceted role in the pathophysiology of Alzheimer's disease through its effects on neurotransmitter metabolism, production of oxidative stress, and subsequent contribution to inflammatory processes and amyloid pathology. Understanding these mechanisms can aid in the development of targeted therapies aimed at mitigating the progression of Alzheimer's disease. Ongoing research continues to elucidate the precise roles of MAO-B in neuronal health and disease, potentially paving the way for innovative treatments.

1.3. Patented molecules and drugs in clinical trials

Extensive research is being carried out to bring out potential agents for the treatment of AD. Various research organization along with pharmaceutical companies have come together to produce newer drugs, as a result in the past, a number of compounds have been granted patented **(Table 1.2)** and entered clinical trials (**Table 1.2)**. Dementia, especially AD has become prevalent and will be one of the leading disease-causing deaths in the future.

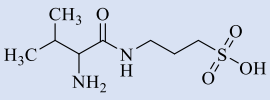
Therefore, there is an urgent need in the innovation of novel drugs along with other biomedical therapies not just to treat the disease but also for diagnosis at early stages and therapies for preventing the disease.

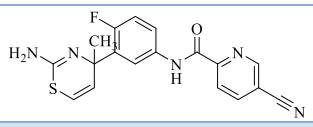
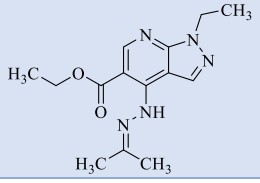
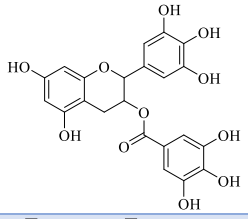
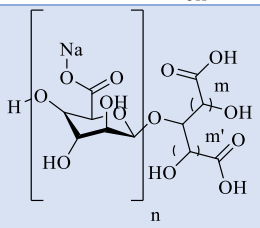
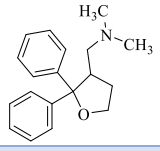
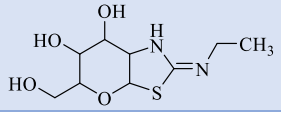
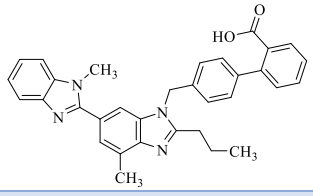
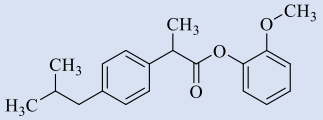
Table 1.1: Recent patented drugs for AD

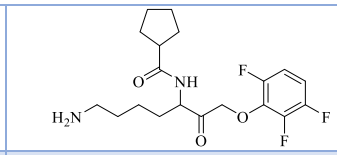
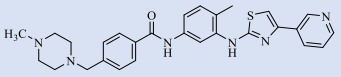
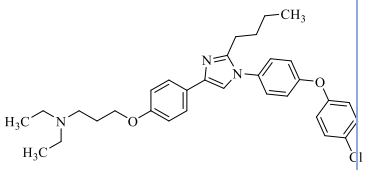
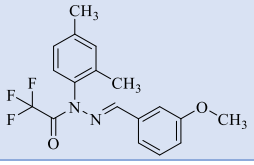
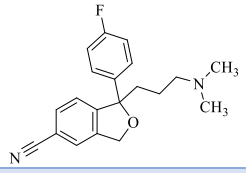
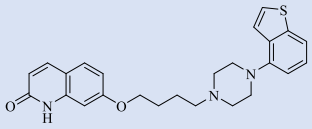
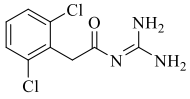
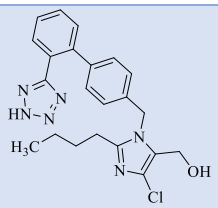
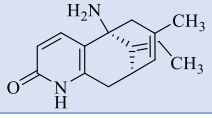
Drug/Molecule	Structure	Target	Mechanism of Action	Note
Lecanemab	NA	Amyloid-beta	Monoclonal antibody reducing plaques	FDA-approved, slows cognitive decline in early AD
Donanemab	NA	Amyloid plaques	Antibody targeting plaque reduction	Approved for early AD, reduces need for continuous dosing
CT1812		Synaptic protection	Clears amyloid from synaptic clefts	Protects neuronal connections
PU-AD	NA	Chaperone modulation	Reduces misfolding and oxidative stress	Neuroprotective by targeting cellular stress
Ladostigil		Monoamine oxidase and ChEIs	Dual inhibition of MAO and cholinesterase	Reduces oxidative stress and enhances cholinergic function
Memogain		Pro-drug of galantamine	Enhances cholinergic activity, cognitive effects	Nasal form, high brain bioavailability, fewer side effects
Huperzine A		Acetylcholinesterase	Inhibits AChE, increases acetylcholine	Natural product, enhances cognitive function
Mitochondrial-ER Agents	NA	Cellular energy and stress	Enhances mitochondrial and ER interactions	Reduces neuroinflammation and metabolic dysfunction

*Drugs with complex structures like protein, peptide, enzymes, antibody etc are represented as NA (not applicable).

Table 1.2: Current status of drug molecules in clinical trials for AD.

Drug Name	Structure	Mechanism of Action	Sponsor	Current Clinical Status	Ref
ALZ-801 (valiltramiprosate)		Aβ aggregation inhibition	ALZHEON (Alzheon Inc)	Phase 3 (ongoing)	76

Atabecestat		BACE1 reversible inhibition	Janssen Research and Development, LLC	Phase 2/3 (Terminated)	[77]
Etazolate		α-Secretase stimulator	Exonhit	Phase 2 (Completed)	NCT00880412
Epigallocatechin-gallate		α-Secretase stimulator	Taiyo International	Phase 2/3 (completed)	NCT00951834 [78]
GV 971		Aβ aggregation inhibitor	Shanghai Green Valley Pharmaceuticals	Phase 3 (terminated in 2022)	NCT04520412
Solanezumab	NA	Anti-amyloid mAB	Eli Lilly and Co.	Phase 3 (Failed in 2023)	NCT01900665
Gantenerumab	NA	Anti-amyloid mAB	Chugai Pharmaceutical Co., Ltd., Hoffmann-La Roche	Phase 3 (failed in 2022)	NCT04374253
Aducanumab	NA	Anti-amyloid mAB	Biogen, Neurimmune	Approved (7th June 2021)	[79]
Lecanemab	NA	Anti-amyloid mAB	BioArctic AB, Biogen, Eisai Co., Ltd.	Approved (6th january, 2023)	[80]
Blarcamesine		Sigma-1 receptor activator	Anavex Life Science Corp.	Phase 2b/3 (completed)	NCT04575259
Thiamet G		O-GlcNAcase enzyme inhibitor	Eli Lilly and Co.	Phase 2 (ongoing)	NCT05063539
Telmisartan		Angiotensin II receptor blocker	Boehringer Ingelheim, Sunnybrook Health Sciences Centre	Phase 2 (ongoing)	NCT02085265
ALZT-OP1		Aβ clearance promotor	AZTherapies, Inc.	Phase 3 (completed)	NCT02547818

Atuzaginstat		Irreversible inhibitor of gingipain	Cortexyme, Inc., Quince Therapeutics	Phase 2/3 (discontinued in 2022)	NCT03823404
Masitinib		Tyrosine kinase inhibitor	AB Science	Phase 3 (ongoing)	NCT05564169
Azeliragon		Receptor for advanced glycation end products (RAGE) inhibitor	Pfizer, TransTech Pharma, Inc., vTv Therapeutics LLC	Phase 3 (failed in 2020)	NCT03980730
J-147		MAO-B inhibitor	Abrexa Pharmaceuticals	Phase 1 (completed)	NCT03838185
Escitalopram		Selective serotonin reuptake inhibitor	JHSPH Center for Clinical Trials	Phase 3 (ongoing)	NCT03108846
Brexpiperazole		Partial agonist of 5-HT1A and dopamine D2 and D3 receptors	Lundbeck, Otsuka Pharmaceutical Co., Ltd.	Approved (in 10th may 2023)	NCT03724942, [81]
Guanfacine		α2A adrenergic receptor agonist	Imperial College London	Phase 3 (ongoing)	NCT03116126
Losartan		Angiotensin II receptor blocker	Merck, University of Texas Southwestern Medical Center	Phase 2/3 (completed)	NCT02913664, [82]
Liraglutide	NA	Glucagon-like peptide 1 agonist	Novo Nordisk A/S, University of Aarhus, Imperial College London	Phase 2b (Completed)	NCT01469351, NCT01843075
Huperzine A		Selective AChE Inhibitor	Debiopharm Group™, Neuro-Hitech, Inc.	Phase 3 (ongoing)	

*Drugs with complex structures like protein, peptide, enzymes, antibody etc are represented as NA (not applicable).

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