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Review Article

Alzheimer's Disease-models and Current Approaches: A Review

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ABSTRACT

Alzheimer's disease (AD) is a complicated CNS disorders that particularly affect the medial temporal lobe and neocortical area of the brain. AD is characterised by the progressive depletion of neurons in the cortical and hippocampal areas of the brain. The main symptoms are memory loss, amnesia, motor disturbance, mood change, and so on. Alzheimer's disease was 1.9% standard in the South Asian region in 2005; between 2020 and 2040, it's expected to reach an estimated 3.6M to 7.5M cases, respectively. Conversely, a pathological condition is characterized by alterations in microtubule stabilization and amyloid beta formation, resulting from increased oxidative stress and mitochondrial damage. Impairment of cerebral ROS formation is associated with brain mitochondrial dysfunction and deregulated signal transduction. The timely acquisition of relevant animal models for drug candidate screening represents a significant obstacle in neurological research and drug discovery. In this review, we have discussed various *in-vivo* animal models that are helpful for neurological studies. In the end, the treatment for Alzheimer's Disease, modifying treatment strategies, is still under extensive research. We discussed various therapeutic targets to modify the treatment strategies and current drug treatment for AD.

INTRODUCTION

Alzheimer's Disease (ALZ D)

Alzheimer's disease, a prominent form of dementia, is typically defined as a gradually advancing neurodegenerative disorder, named after German psychiatrist Alois Alzheimer. [1] The condition is marked by the formation of neurofibrillary tangles within the cell, primarily consisting of hyperphosphorylated tau, along with extracellular plaques predominantly composed of amyloid (Aβ), alongside progressive neuronal degeneration, particularly in the cerebral cortex and hippocampal region, that adversely affects cognitive function. The cause of this ailment is presently ambiguous. Despite substantial investigation, the mechanisms driving Aβ deposition, NFT production, and deposition remain ambiguous, and currently, there is no therapy for this illness. Consequently, several signaling pathways linked to particular pathological processes have been investigated and evaluated as prospective targets for innovative therapeutic strategies in the management of AD in recent years. In 2005, the prevalence of dementia in South Asia was 1.95%; it is projected to increase to 3.65 million by 2020 and approximate 8 million by 2040.[2] An increasing percentage of the population in India is aging due to extended life expectancy and declining fertility rates. Individuals aged 60 years or older are projected to constitute 19.1% of the population by 2050.[3] The information is presented in Fig. 1[4], categorized by mild, moderate, and severe indications and symptoms.

Using histological alterations and the degree of cognitive impairment as the primary criteria, AD is clinically classified. Typically, four steps are (Fig. 1).[5,6]

Preclinical

This stage is usually ignored because there are no noticeable symptoms. Typically, cognitive impairment is

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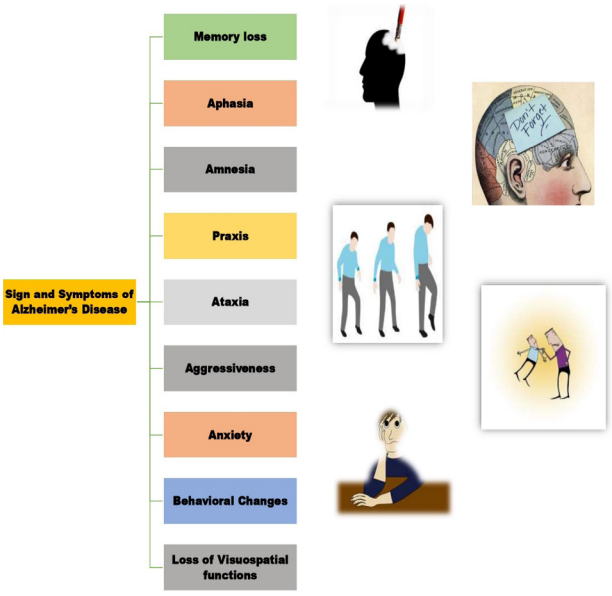

Fig. 1: Signs & symptoms of Alzheimer's disease[4]

classified as mild. The hippocampus & entorhinal cortex are among the earliest brain compartments to have prior engagement in pathological alterations during this phase (later). From a symptomatologic standpoint, individuals at this stage have rather scant long-term memories and mildly impaired memory. Their regular tasks are not clearly defined.

Mild Alzheimer's disease

Behavioral abnormalities commence during this stage of mild Alzheimer's disease. At this juncture, the cerebral cortex commences to undergo degenerative alterations. From a symptomological standpoint, there is amnesia, accompanied by an inability to remember newly acquired information and forgetfulness regarding events and appointments, subsequently leading to a deterioration in decision-making, solving of problems, and executive functioning. Moreover, patients frequently display modifications in personality, fluctuations in mood, and a diminished sense of spontaneity.

Moderate Alzheimer's disease

Symptoms exacerbate throughout this phase. Other regions involved in language, cognition, and sensory processing are impacted by the pathological lesion to the cerebral cortex. In addition to the exacerbation of earlier symptoms, behavioral problems and a tendency for social withdrawal begin to manifest. Language impairment and a deterioration in visual-spatial capabilities ensue. It is significant that individuals find it challenging to recognise their own dear ones at this moment.

Advanced Alzheimer's Disease

It is severe. At this level, patients completely forfeit their autonomy in daily activities. It is believed that all regions of the cortex are impacted by pathological degeneration at this stage. As the individual's cognitive faculties decline, additional systemic manifestations emerge, including olfactory and autonomic dysfunction, sleep disturbances, and extrapyramidal movement symptoms like to those observed in akathisia and Parkinson's.

Note

Numerous staging systems, such as the one started in 1996,[7] were developed for Alzheimer's disease (AD). This hypothesis categorizes the progression of Alzheimer's Disease into 6 stages built on the topographical staging of neurofibrillary tangles. The neuropathological benchmarks established by the "Reagan Institute" and the National Institute on Aging used for the clinical diagnosis of AD nclude Braak's stage. [6]

Risk Factors

The causes of AD are multifaceted. Due to their propensity to enhance tau protein phosphorylation and Aβ peptide levels, neurotoxic metal exposure from As to Al has been linked to AD. Other possible etiological causes include ageing, genetics, illness states, and environmental contaminants. Environmental toxins such as smoke, tobacco, and pesticides such as carbofuran and deltamethrin interfere with tau function by acting as etiological factors for AD (Fig. 2).[8] The diseases and conditions that can result in AD include head injuries, hypertension, and diabetes mellitus. [9, 10] Genes are a crucial factor in AD prevalence. Premature manifestation of AD, also known as familial AD, and the commencement of the disease developed before the age of 65 are connected with genetic alterations in the genes on chromosome 21q for APP, on chromosome 14 q for PSEN1, and on chromosome 1 q for PSEN2. The ε4 allele of the APOE polymorphism is what causes late-onset AD. [11] *APOE* is positioned on chromosome 19q. ApoE is connected to the transportation of cholesterol in the brain. Common allelic variants of *APOE* are ε2, ε3, & ε4. *LOAD* risk is caused by *APOE 4,* whereas *APOE 2* has a positive effect. Aging is the main factor of risk for sporadic AD. ROS produced during energy-generating metabolic reactions in aging

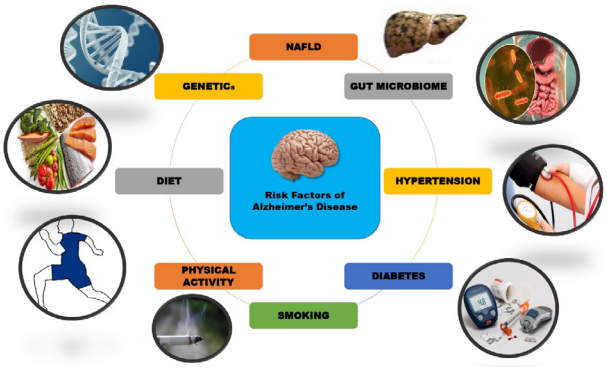

Fig. 2: Major risk factors that are associated with Alzheimer's disease (AD)[4]

contribute to AD, and messenger RNA mutations of the APP and ubiquitin B are another way in which aging affects AD. [12] The majority of cases of AD often begin after age 65. [13]

Pathophysiology of Alzheimer Disease

A substantial body of evidence from the past 30 years of research on AD suggests that the accumulation of incorrectly pleated amyloid and phosphorylated tau-proteins in affected patients' brains is causally related to the degeneration of neurons. [14] The two distinctive pathologies required for an AD diagnosis are NFT of the microtubule-binding phosphorylated tau-protein and extracellular Aβ plaque deposits. [15]

Amyloid Beta Formation

Amyloid plaques, also known as senile amyloid plaques or "military foci," are extracellular deposits of Aβ-40 and Aβ-42 peptides resulting from the aberrant processing of amyloid precursor proteins (APP) by β-secretases and γ-secretases, coupled with an imbalance in the production and clearance pathways, as indicated in Alzheimer's disease research. [16] In healthy neurons, α and β-secretases degrade APP, which comprises 3 domains: intracellular within the neuron, in the neurolemma, and extracellularly on the neuronal cell surface. During digestion, many soluble polypeptides are generated that can later be dismantled and repurposed within the cell. However, while β and γ-secretases collaborate, complications arise. During this digestive process, the insoluble amyloid-beta peptide, Aβ, is generated. [17] During this digestive process, the insoluble amyloid-***β*** peptide (A-beta) is generated. Amyloid-β plaques, potentially arising from the accumulation of amyloid-β peptides, are harmful to cellular health (Fig. 3). [18]

Neocortical early deposits are detectable (phase 1). A plaque subsequently forms in limbic regions, including the amygdala, cingulate gyrus, subiculum, and entorhinal cortex (phase 2). A deposit in subcortical regions, including the hypothalamus and basal neurons, signifies advanced growth (phase 3). Additionally, plaques are observable in the cerebellar cortex at the advanced stages of the disease, impacting the medulla oblongata, pons, and midbrain within the brainstem (phase 4). In advanced instances, the plaques additionally impact the cerebellar cortex (phase 5). Phases 1 and 2 were predominantly noted in asymptomatic patients, while phases 4 and 5 were associated with the manifestation of dementia. [19] The most definitive evidence of A beta accumulation is presented by research findings of instances of familial cases of Alzheimer's disease presence of APP, PSEN-1, or PSEN-2 alterations. As the predecessor of A2 peptides, APP modulates the degradation and buildup of A2 peptides. PSEN-1 and PSEN-2 are catalytic subunits of the secretase enzymes that cleave the APP. PSEN mutations lead to low-efficient APP processing and the production of longer and more hydrophobic A2 peptides, unlike what was thought to be.[14]

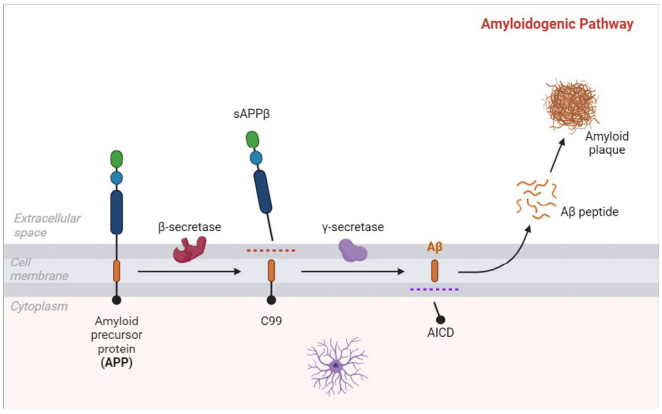

Fig. 3: Amyloidogenic Pathway- The pathway describes the graphical representation of insoluble Amyloid plaque formation in the neurons of the cerebral cortex area of the brain[17]

Tau Pathology

Axons of brain neurons demonstrate the greatest expression levels of tau protein. Nonetheless, it is also found in oligodendrocytes, non-neural tissues, and the somatodendritic region of neurons. [20] The microtubule-attaching protein regulates axonal transit and development by facilitating the stability of microtubules (MTs) in the brain. Post-translational modifications (PTMs), chiefly phosphorylation, regulate tau's interaction with microtubules and various other, less recognized functions. [21] Phosphorylation is a post-translational change that may result in neurotoxicity and the development of aggregates. [22] The phosphorylated protein tau may have up to 85 sites for the phosphorylation of serine (S), threonine (T), and tyrosine (Y). The proline-rich region of tau, located adjacent to the domain responsible for microtubule interaction, encompasses many phosphorylated tau residues. [23] Neurons suffer from malnutrition due to the hyperphosphorylation of specific amino acids in tau proteins, resulting in cell death in Alzheimer's disease from cytoskeletal and transport system abnormalities. The progression of Alzheimer's disease and other tauopathies, along with intracellular neurofibrillary alterations, is significantly affected by hyperphosphorylated tau. [24] Tau undergoes multiple post-translational modifications prior to the development of tangles, which are distinct from the normal tau present in healthy brains. These alterations encompass hyperphosphorylation, acetylation, N-glycosylation, and truncation. Tau post-translational modifications facilitate tau misfolding and obstruct microtubule-bound tau interactions. [25] Microtubules operate like train tracks by facilitating the transport of nutrients and other substances. Tau proteins function as "links" that stabilize the microtubule architecture. Tau proteins are enhanced entangled in Alzheimer's disease, leading to instability in the microtubule structure. Cellular demise transpires when axonal transport is impeded.

Oxidative Stress

One of the major sources of adenosine triphosphate (ATP) production takes place in mitochondria through oxidative phosphorylation. The free radicals are commonly referred to as reactive nitrogen species (RNS), reactive oxygen species (ROS), and carbon and sulfur-centered radicals are produced (Fig. 4). [26] OS is significant in acute and chronic brain stroke, traumatic brain injury, and also neurodegenerative disorders. [27]

The formation of free radicals is inherently connected to metabolism and several enzymatic processes. Mitochondria (intracellular) and inflammation (extracellular) are the primary sources of free radicals. These reactive molecules can harm DNA, proteins, and lipids when antioxidant mechanisms are dysregulated, resulting in cellular cytotoxicity and tissue damage. These systems are rigorously regulated under physiological conditions. [28] Current ideas posit that oxidative stress (OS) is defined by an imbalance in reactive oxygen species (ROS) production, significantly influencing age-related neurodegeneration, cognitive decline, and antioxidant defense mechanisms. [29] Elevated concentrations of oxidized proteins, advanced glycation end products, and peroxidized lipids, alongside the presence of hazardous chemical compounds such as peroxides, alcohols, aldehydes, free carbonyls, ketones, and cholestenone, as well as oxidative alterations in nuclear and mitochondrial DNA within neurons, signify an increase in oxidative stress levels in Alzheimer's disease. The neuronal membrane of the central nervous system is predominantly composed of phospholipids containing polyunsaturated fatty acids, rendering it particularly susceptible to damage from free radicals. These various bindings facilitate increased lipid peroxidation and hydrogen ion removal, which is the most evident indicator of degenerative alterations in Alzheimer's disease.[31] Mitochondrial failure and oxidative stress are interconnected in Alzheimer's disease. Reactive oxygen species (ROS) will be produced due to mitochondrial metabolism, as neurons possess a substantial energy requirement for their extensive metabolic functions. Mitochondrial failure may consequently elevate ROS production, resulting in neuronal damage. [32] Free radicals that attack phospholipid polyunsaturated fatty acids inside the phospholipid bilayer can provoke oxidative stress, leading to lipid peroxidation and the formation of significant end products. [33] Mitochondrial respiratory chain is located inside the inner mitochondrial membrane. They consist of 5 complexes which are - I, II, III, IV, and V (Fig. 5) [34], that are components of an integrated system consisting of five protein complexes that catalyse the conversion of adenosine diphosphate to adenosine triphosphate. [35]

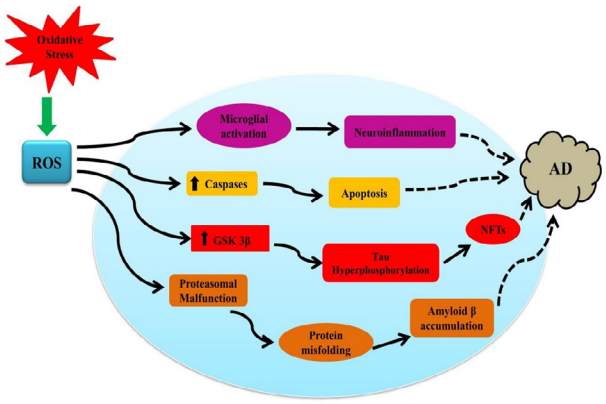

Fig. 4: The simplified diagram shows the relation between Oxidative stress (ROS) and different pathological hallmarks (Caspases, microglial cells, NFTs, and amyloid beta plaque) of Alzheimer's Disease[26,30]

Neuronal loss and other Alzheimer's disease issues induce inflammation, which initially serves as an instant neuroprotective mechanism; however, if the immune response persists, it becomes detrimental and exacerbates the situation. The equilibrium between anti-inflammatory and pro-inflammatory signaling is disrupted by activated microglia, which subsequently produce several deleterious substances, including cytokines (interleukins) and TNF-α and reactive oxygen species (ROS).[36] Chronic neuroinflammation is believed to exacerbate amyloid and tau pathologies. Cytokines, particularly IL-6, are thought to facilitate tau hyperphosphorylation through the activation of protein kinases. Furthermore, IL-1 elevates acetylcholinesterase (AchE) expression as well as activity, leading to *in-vivo* investigations of cholinergic dysfunction and the demise of cholinergic neurons. [37]

Neurochemical Alteration

Acetylcholine

A significant symptom of AD is a decrease in neurons in the basal forebrain, which are big cholinergic neurons that supply the nucleus basalis of Meynert from the medial septum via the diagonal band of Broca.[38] During the development of a neuron, choline is used for two purposes: a) to make phosphocholine, which then becomes membrane phosphatidylcholine, and b) to produce acetylcholine, which is used as a transmitter.[39] The conversion of amyloid precursor protein (APP), a normal protein, to aberrant amyloid may be accelerated as a result of changes in membrane composition. APP must be cut at an aberrant location inside its transmembrane domain for amyloid to

S.No.	COMPLEX NAME
1.	**Complex I-** Nicotinamide Adenine dinucleotide Dehydrogenase- Ubiquinone Reductase (coenzyme Q)
2.	**Complex II-** Succinate Dehydrogenase (FADH2)-coenzyme Q
3.	**Complex III**- Ubiquinone-cytochrome C reductase
4.	**Complex IV-** Cytochrome C oxidase
5.	**Complex V**- Adenosine triphosphate synthase

Fig. 5: Mitochondrial Complexes[34]

develop. Acetylcholine is a neurotransmitter at the NMJ and autonomic ganglia, and central neurotransmission changes neuronal excitability, alters the release of presynaptic neurotransmission, and coordinates the firing between the neurons.

Ach has both excitatory (mediated by Glutamate receptors) and inhibitory transmitters (mediated by GABA receptors). The source of Ach in the brain is projection neurons, found in nuclei throughout the brain. [40] Choline acetyltransferase and Acetyl-CoA, two biosynthetic enzymes, catalyse a single-step synthesis to generate Ach, which is then produced in the cholinergic cell body and delivered to nerve ends by axons. The uptake of choline from the synaptic cleft into the nerve endings is also upregulated during increased neuronal activity. The choline used for the synthesis of each is derived from the recycling of choline from metabolised Ach, which is typically stored in the cytosol.[41] Calcium-stimulated docking and fusing of the vesicle with the nerve terminal membrane results in the release of ACh.[42] There are two classes of receptors of Ach: (1) Muscarinic receptors and (2) nicotinic receptors, depending on the chemical agents that mimic the Muscarinic and nicotinic at different sites. [43] Five polypeptide subunits make up the nicotinic receptor, an ion channel that has two subunits, one of each of the subunits, and two subunits. Action potentials are produced, and depolarisation of the target cell is caused by the opening of the channel created by the receptor when nicotinic receptors are activated. [44] Muscarinic receptors are GPCRs, composed of one polypeptide, and their activation of Post-synaptic cells is always slow to start and lengthy to last. They can be either excitatory or inhibitory. [45]

Glutamate

Glutamate is an excitatory transmitter in the CNS, and the transmission is mediated by glutamate and its receptors, including ionotropic glutamate receptors (iGluRs). Its subgroups are gated by N-methyl d-aspartate (NMDA), and its role in synaptic function and plasticity. [46] The long-term glutamate activation from presynaptic terminal AMPARs causes the blockade of NMDAR by the subsequent depolarization, which removes the Mg^{2+} at a resting potential of about -70mv. This high activation of NMDAR triggers the Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)-mediated signalling overflow that leads to increased synaptic power. [47]

GABA

The inhibitory neurotransmitter gamma-aminobutyric acid (GABA regulates synaptic plasticity, network plasticity, short and long-term neuronal activity, and membrane potentials via ionic action. [48] The high content of GABA has been reported in the astrocytes in a transgenic model of AD and in the brain of the human population, also. [46] Astrocytes are activated by injury and disease. The high content of GABA was released in astrocytes by astrocyte-GABA transporter GAT3/4 (human GAT 3/ mouse GAT4) to improve inhibition in dentate granule cells. [49] GAD65 and GAD67 are two isoforms that are activated by pyridoxal 5' phosphate, and GAD67 is located in GABAergic neurons. The biosynthesis of GABA requires the decarboxylation of glutamate, generating GABA and CO_2 by the enzyme glutamate decarboxylase. In the presence of its antagonists, glutamate activation has reportedly been shown to reverse the rise in calcium and NMDA. [49]

Dopamine

This receptor belongs to the GPCR family, which is primarily involved in neuronal signalling that facilitates behavioural processes. These act as major neurotransmitters that help in moment cognition and emotions. Levodopa (prodrug), which is turned into dopamine and has protective effects on learning and memory processes as well as aids in the elimination of amyloid beta plaques, is thought to have these effects. [50] Information transfer from the subiculum to the NAc is reportedly momentarily hampered in 6-year-old AD-like tg2576 mice due to the degradation of DAergic neurons, which is accompanied by decreased excitability of pre-subiculum pyramidal neurons. [51] Cholinergic projections depend on the D-adrenergic neurons' ability to act differently in the VTA. [52]

Glycogen synthase kinase 3 β

GSK-3 regulates microtubule dynamics in the brain by phosphorylating microtubule-associated proteins (MAPs), which have a role in neurogenesis, neuronal migration, neuronal polarisation, and axon development. [51] By enhancing tyrosine phosphorylation, which results in the phosphorylation of tau protein, GSK-3 is activated by amyloid peptides. The amyloidal and tau species that result in synaptic abnormalities and ultimately neurodegeneration are soluble oligomers rather than clumps. [53] When amyloid peptides and abnormally active GSK3 are combined, phosphorylated tau induces synaptic dysfunction, leading to a variety of synaptic abnormalities that begin in the MCI or pre-AD stages and progress to dementia. [54]

Inflammation

A persistent immunological response has been demonstrated to cause chronic inflammation in AD patients. Acute neuroprotective neuroinflammation is first brought on by neuronal loss and other AD diseases, but when the immune response continues, this is harmful and makes the illness worse. Activated microglia emit several harmful substances, including many cytokines (such as IL, TNF), ROS, and other inflammatory signalling disruptors. [36]. The escalation of amyloid and tau disorders is thought to be the cause of chronic neuroinflammation. According to reports, cytokines, particularly interleukin-6, activate protein kinases, leading to tau hyperphosphorylation.

Additionally, interleukin-1 increases the production and activity of acetylcholinesterase (AChE), which causes cholinergic dysfunction *in-vivo* studies and death of cholinergic neurons in the brain. [37]

Inflammatory response in the AD brain

The term "neuroinflammation" is used to describe an inflammatory response that involves the accumulation of glia and astrocytes originating in the central nervous system following an injury. Over time, a loss of neurons is brought on by the secondary reaction. According to specific theories, the inflammatory response is harmful and significantly contributes to neuronal degeneration. [55] Astrocytes and microglia are the prominent participants in the inflammatory processes in AD and are seen in large numbers throughout the brain. Near amyloid plaques and NFT in AD, a large quantity of inflammatory mediators is produced by brain tissues.[56] Producing pro-inflammatory cytokines and complement proteins, microglia play a crucial role in various inflammatory processes.[57] It has phagocytic and scavenger actions, as well as neurotoxic and neuroprotective effects on the brain. Some post-mortem studies have shown astroglioses, which are characterised by cell hypertrophy and an increased amount of glial fibrillary acidic protein (GFAP) in the brain tissue of AD patients. [58] The pro-inflammatory cytokines interleukins and tumour necrosis factor, as well as the chemokines macrophage inflammatory protein-1 (MIP-1) and monocyte chemoattractant protein-1, are all secreted more frequently when microglia are activated as a result of exposure to these factors. TNF-α and IL can impact the blood-brain barrier's capacity to function. Aβ elicits a phagocytic response in a time- and dose-dependent manner.[59]

Aside from microglia, astrocytes collect around amyloid plaques. They are located beside active astrocytes. [60] Interleukins, prostaglandins, leukotrienes, coagulation factors, thromboxane, complement proteins, proteases, and other substances have all been observed to be secreted by astrocytes.

Neurons have been linked to the creation of inflammatory byproducts and appear to play a part in the inflammation process of AD. Neurons in AD brains show increased quantities of complement protein mRNAs as compared to controls. AD neurons had higher amounts of pentraxins, C-reactive protein, and amyloid β Plague. [61] Numerous cytokines, including interleukins and tumour necrosis factor, can be produced by neurons. These pro-inflammatory byproducts of the neurons may, in reality, trigger further inflammatory processes that lead to neuronal impairment and death. [62]

Mitochondrial Dysfunction

Mitochondria are the key organelle where oxidative phosphorylation occurs to generate energy. The oxidative phosphorylation system (OX-PHOS) is attached to the inner mitochondrial membrane, where a series of complex proteins assemble. The electrons from NADH and FADH2 flow through this macromolecular machinery and are oxidised. ATP is synthesised by the energy released from the electron flow through Complex V, also known as F0-F1 ATP synthase. [63] Additionally, mitochondria play a crucial role in maintaining intracellular pH, regulating ROS metabolism, and ensuring Ca^{2+} homeostasis. The majority of the ROS burden produced in cells is primarily composed of ROS generated by mitochondria.[64]

According to several animal models and post-mortem AD brains, one of the fundamental mechanisms in the early stages of AD is mitochondrial failure. According to data from post-mortem brain research, cytochrome oxidase, α-keto glutarate dehydrogenase, pyruvate dehydrogenase, ATP synthesis, mitochondrial membrane potential, ROS generation, and mitochondrial biogenesis are all reduced. [65, 66] In post-mortem brain tissues of individuals affected by AD, decreased ATP-citrate lyase and acetoacetyl-CoA thiolase activity have been identified. Acetyl-CoA is therefore produced in less quantity as a result. The quantitative PCR method has been used to investigate the levels of mitochondrial gene expression. The study demonstrates downregulation of complex I, but upregulation of complex III and IV expression. [67] The DNA damage marker 8-hydroxy-2-deoxyguanosine, which is more susceptible to oxidative damage than nuclear DNA, accumulates in mitochondrial DNA at a considerably higher percentage than in age-matched control participants. [68] There have been reports of mitochondrial ultrastructural abnormalities in AD brains, including smaller mitochondria, aberrant or damaged cristae, impairment of dendritic cells, and arborizations of nerve cells. [69] Due to the imbalance between mitochondrial fusion and fission, which is tilted towards fusion, the structure and dynamics of mitochondria are altered. In post-mortem AD brain, it has been discovered that the amount of fusion-related proteins MFN 1, MFN 2, AND OPA 1 are lowered while the intensity of proteins linked to fission, such as Fis 1 and Drp 1, is raised[70,71] Through translocase of the outer membrane (TOM) and translocase of the inner membrane (TIM), Aβ and APP are localised in mitochondria. [72] The brains of AD patients have also been discovered to have altered amounts of Cu-Zn superoxide dismutase, catalase, and Mn-SOD.

The development of transgenic animal models has facilitated an understanding of how Aβ and soluble oligomers interact with mitochondria by different mechanisms. The transgenic animal models or cells that overexpress wild or mutant type amyloid precursor protein (APP) have shown mitochondrial dysfunction concerning the toxic actions of Aβ-42 or other amyloid beta peptides on mitochondria or to abnormal accumulations of tau protein. In triple transgenic AD mice, pyruvate dehydrogenase complex activity and respiration are inhibited with excess

ROS formation, which leads to oxidative damage.[73] Among other chaperone proteins in mitochondria, Hsp60, a marker of the mitochondrial matrix, when associated with Aβ, leads to mitochondrial peptidase (PreP) inhibition, which causes the removal of pre-sequences of N-terminal domains of mitochondrial tagged proteins. This misprocessing of these tagged proteins causes multiple functional defects of this organelle in AD. APP blocks protein import channels in mitochondria, preventing entry of nuclear-encoded mitochondrial proteins, including the subunits of respiratory complexes. Studies from isolated mitochondria show that soluble oligomers of Aβ can interact with mitochondrial proteins like adenine nucleotide translocase (ANT), components of TOM and TIM, cyclophilin D, uncoupler protein (UCP), and others. The soluble Aβ oligomers also interact with lipid bilayers, studied thoroughly by different groups, suggesting that such oligomers create membrane-spanning channels and this channel allows various ions to pass through. In astrocytes, Aβ has been reported to activate mitochondrial complexes to increase ROS production, which in turn causes mitochondrial dysfunction and glutathione deficit in both neuronal and astrocyte cells.

Apoptosis

A variety of mediators, including p21, p38, MAPK, p53, and caspases 2, 3, and 8, cause apoptosis, or preprogrammed cell death.[74] The lysosomal protease cathepsin D is highly sensitive in the brain and plays a critical role in regulating cellular death, which contributes to the pathophysiology of AD.[75] In response to agonist application, P2X7, a rare bifunctional purinoreceptor involved in the aetiology of AD, causes membrane blebbing and cellular death by necrosis or apoptosis by unlocking a non-selective cation channel or creating a sizable, cytolytic hole. Consistent activation of the P2X7 receptor by the agonist results in the development of a sizable aqueous hole that is permeable to molecules with a mass of up to 900 Da. In addition, rapid morphological alterations in the membrane and mitochondria, as well as cytoskeletal rearrangements, ultimately lead to cell death in brain tissues.[76]

Diabetes Mellitus

Some data suggest that AD may be caused by a problem with insulin and IGF-1 signalling. [77] The aetiology of DM-2 and AD is influenced by abnormal insulin signalling. This demonstrates its involvement in neurodegenerative processes and suggests the potential involvement of other pathophysiological pathways shared by metabolic diseases and neurodegeneration. Furthermore, it has been established that peripheral insulin can cross the barrier between blood and the brain and then enter the brain via a receptor-mediated transport mechanism. Following the interaction of insulin and IGF-1 with their receptors, two pathways are implicated in intracellular activities. Anomalies in the insulin molecular signalling system primarily cause Alzheimer's disease. Key tyrosine residues in the beta subunit are auto-phosphorylated as a result of insulin's interaction with its receptor; some of these are recognised by the PI3K regulatory subunit p85's Src homology two domains.[78,79]

In-vivo Animal Models

Spontaneous model

Elder animals can serve as a natural model of memory impairments and AD, since memory loss is a primary distinguishing trait of old age. Due to age-related cognitive loss and behavioural changes that replicate not just neurochemical and morphological changes, ageing animals are frequently employed in medication development [80], cholinergic hypofunction as well,[81] the pathogenesis of which resembles AD. Dopaminergic and glutamatergic impairment may also be involved in age-related cognitive disability, according to reports. This approach has the benefit of being non-invasive, all-natural, and devoid of any central neurochemical modifications.

The Colchicine model of memory impairment

Colchicine is an alkaloid derived from *Colchicum autumnale*, which also exhibits anti-inflammatory properties and has been shown to have anti-gout effects. It was used to stop amyloidosis decades later.[82] Colchicine inhibits axonal transport without impeding protein synthesis by depolymerising MT.[83,84] Colchicine, a cytotoxic substance, forms an irreversible bond with tubulin molecules, which prevents tubulin dimers from aggregating to the fastest-growing end and interrupts MT polymerisation. Colchicine severely damages hippocampus granule cells by obstructing axoplasmic transport. This results in neuronal death, which causes cognitive disability and spontaneous motor activity. Colchicine (15 mg- 5 mL/7.5 mg- 10 mL) intra-cerebroventricular (ICV) injection in rats might result in AD-like pathology and concomitant cognitive and behavioural changes.[84-86] The medication inhibits the ACh transferase in the memory-related forebrain and hippocampus.[83] Colchicine causes symptoms including irritable behaviour, aggressiveness, and weight loss when it enters the subarachnoid space. Colchicine treatment resulted in lipid peroxidation, lower levels of GSH, and decreased levels of acetylcholine in the rat brains, which in turn caused oxidative damage and cognitive impairment. After giving colchicine to rats, cognitive impairment and neurodegeneration were labelled as sporadic in the AD model.[84,85] Some of the side effects of the colchicine-induced model include decreased appetite, temporary diarrhoea, adipsia, and aphasia.[86]

Scopolamine-induced model of memory deficits

The fundamental importance of the cholinergic system in memory function is well-known. [87] AD-like memory loss and disorientation may be brought on by a decline in

the central cholinergic system.[88] It has been reported that neurons of cholinergic often die in brain regions connected to memory and cognition, such as the cortex, hippocampus, and nucleus basal of Meynert,[89] Therefore, measuring the quantity and health of cholinergic neurons using cresyl violet (Nissl) staining in several models of experimental animals' indicative of dementia type AD may be of all most significance to the continuing study in this subject. Thus, it is believed that cognitive deficiencies are related to a decrease in cholinergic activity. Cortical cholinergic neurons are significantly lost in AD patients, and the functions of central cholinergic neurons are compromised.[90] Memory loss can be caused by blocking central cholinergic activity.[91] An anticholinergic medication called scopolamine is commonly utilised in experimental settings to treat cognitive impairments. Scopolamine has been found to impair learning and memory in mice in a dose-dependent way by blocking the binding sites of ACh cholinergic receptors in the cerebral cortex, which harms the hippocampal neurons. [92]

Aβ-induced dementia model

Amyloid beta plaques characterise AD, and treatment of the Aβ peptide has been found to cause memory impairment.[93] It has been shown that an i.c.v. injection or infusion of amyloid beta into the brain results in brain malfunction, further neurodegeneration, and a very comparable disability of memory and learning as found in AD. [94] A protein buildup occurs as a result of the 14-day infusion of A into the rat brain's third ventricle, particularly in the hippocampus and cerebral cortex. This methodology is quite accurate for finding medications used in AD.

Okadaic acid-induced Dementia Model

It is suggested that AD is critically dependent on a variance between tau phosphorylation and dephosphorylation. [95] GSK-3, PKC, MAPK, and cdk5 have all been shown to increase hyperphosphorylated tau at some, but not all, of the locations present in AD tau.[96] However, PP2A is primarily responsible for its dephosphorylation.[97] By raising phospho-tau, lowering phospho-GSK3, and forming *β*-amyloid in specific brain areas, okadaic acid impairs memory. Okadaic acid, a potent protein phosphatase inhibitor (PP1/2 inhibitor), is micro-infused unilaterally in the dorsal hippocampus region of a female rat that has had ovariectomy and is immobilised by stereotaxic equipment. After 14 days, the female rats exhibit cognitive deficits and pathological alterations resembling NFT, as demonstrated by a significant increase in hyperphosphorylation of tau (NFT) and ROS formation.[98] So many anti-dementia medications may be tested using the i.c.v. Injection of okadaic acid to produce memory deficits. Memory loss brought on by okadaic acid closely resembles many of the distinctive symptoms of AD.

ICV streptozotocin-induced animal model

A soil strain of the bacterium *Streptomyces achromogenes* was found to contain the glucosamine nitrosourea chemical streptozotocin (STZ) in 1956. Applied to pancreatic carcinoma, STZ is an agent that has specific characteristics within the class of anticancer drugs known as nitrosoureas. The potency of STZ to induce DM in animals has been well-studied. [99] Lannert and Hoyer created the i.c.v. The STZ dementia model in animals was developed in 1998. Rodents exposed to STZ intracerebroventricularly (i.c.v.) at a dosage of 3 mg/kg, spaced 48 hours apart in two split doses, exhibit a gradual memory loss that is strikingly comparable to AD i.c.v. Memory impairment caused by STZ exists independently of its hyperglycemic impact. It has been shown that i.c.v. STZ increases oxidative stress, leading to the generation of ROS and RNS, which in turn damage neurons. [100] Malondialdehyde levels are rising, tau protein is being hyperphosphorylated, there is a buildup of A in the brain, and genes involved in insulin signalling, including IGF-1 receptors, are being downregulated. [101] This model's key benefit is that it closely reflects parts of the pathophysiology of sporadic AD in humans. [102] Impaired brain energy metabolism has also been linked to decreased acetyl-CoA production, as well as problems with cholinergic transmission. Notably, following the injection of the drug, reduced ACh transferase activity in the hippocampal region of STZ-induced experimental animals was repeatedly found. [103] Additionally, increased AChE activity has been observed in the brain of STZ-induced rats, which could increase the metabolism of ACh, thereby enhancing the ACh deficits.

Heavy metal-induced AD

Numerous studies have demonstrated that heavy metals, including Fe, Cu, Cr, Co, Al, and Zn, can enhance the production of ROS, which can result in the progression of AD dementia and other kinds of dementia. [104] Metals, including Cd, As, and Pb, manifest toxicity by attaching to protein sulfhydryl groups and depleting GSH. Zn can increase the production of Aβ and also contribute to the evolution and continuation of AD-type dementia. It has been studied that Cu results in ROS formation, which is a primary factor in the progression of AD. An excess quantity of Al in water for drinking has been observed to cause AD by obstructing the clearance of the Aβ plaque, which interacts with insulin-degrading enzymes (IDE). Research has also suggested that administration of Al caused aggregation of tau, apoptosis, which increases neuron damage. When aluminum passes through the GIT and BBB, it can accumulate in large pyramidal neuronal cells of the brain, particularly in the hippocampal area, which is a primary target site for AD progression. [105]

Therapeutic Targets in Developing Disease and Modified Treatment for AD

As shown in Fig. 6, the various therapeutic targets that affect Alzheimer's. Some of them are given below:

Decrease in Aβ production: anti-secretases

Research has focused on modifying the enzyme pathways responsible for aberrant APP processing in an attempt to reduce the production of Aβ. To put it another way, they aim to block γ - and/or *β-secretase* and activate α-secretase.

The amyloidogenic route for processing APP is started by the enzyme β-secretase. [106] Because β-secretase has numerous other substrates in addition to APP, creating inhibitors for this enzyme is highly challenging. One of them, neuregulin-1, is essential for the peripheral nerves' myelination. [107] Because of this, unintended consequences from the enzyme's non-specific inhibition are possible. The inhibitor must be a big, hydrophilic molecule since aspartic protease belongs to that class; as a result, it won't be able to penetrate the BBB readily. To overcome these barriers and develop a medicine effective against AD, researchers are now exploring a variety of substances. Recent research has shown that the β-secretase inhibitors E2609 and MK-8931 are particularly effective in lowering Aβ levels in human cerebrospinal fluid (CSF) by 80%–90%. [108]

γ-secretase Inhibitors and modulators

The amyloidogenic pathway's last stage of APP processing is carried out by the enzyme β, γ-secretase, which also generates the peptides Aβ-40 and Aβ-42. Although the inhibition of this secretase in 2001 was hailed as a triumph with a positive impact on treating disease and the first time Aβ production had been reduced in an animal study, creating inhibitors of β-secretase and ***γ-secretase*** will present similar difficulties. [109]

Notch protein, which controls cell proliferation, growth, differentiation, and transmission as well as cell survival, is processed by the enzyme γ-secretase in addition to APP. [110] As a result, non-specific inhibition of this enzyme will have substantial negative consequences, severely hampering clinical studies.

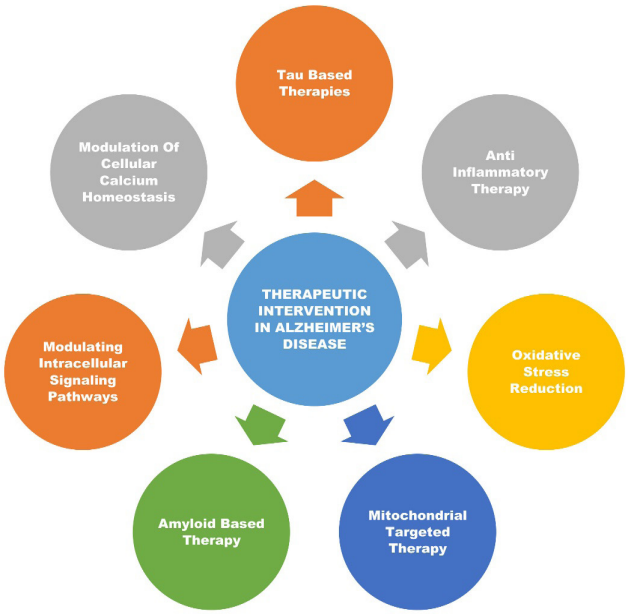

Fig. 6: Multitudinous Therapeutic targets engaged with the treatment of AD, Inhibitors of *β-secretase*[112]

Activation of α-secretase

The non-amyloidogenic route processes APP when the α-secretase enzyme is active, thereby reducing the quantity of APP that is accessible to amyloidogenic processing. The outcome is a soluble Aβ that has been demonstrated to function as a neuroprotector and synaptogenesis activator. As a result, α-secretase activation presents a promising approach for developing medications to treat diseases. The non-amyloidogenic pathway has been stimulated by a variety of substances that have been studied. These include protein kinase C activators, glutamatergic and serotonergic agonists, and acetylcholine muscarinic receptor agonists. However, very few of these drugs have progressed to clinical trials, as researchers have yet to discover any large molecules that can successfully control this system in animal models.

PKC modulator bryostatin-1 also seems to have immunomodulatory properties. It has been demonstrated to improve cognitive function in lab animals. [111]

In addition to inhibiting neuronal death caused by Aβ, etazolate enhances the neurotrophic activity of β-secretase, thereby reducing symptoms and altering the course of the illness. Etazolate was recently shown to be generally safe and well-tolerated in 159 people with mild to moderate AD. These positive preliminary findings suggest further development of EHT 0202 to assess its therapeutic effectiveness and validate its tolerability in a sizable cohort of AD patients over a long period. [112]

The primary use of the retinoid acitretin (a retinoic acid receptor agonist) is to treat severe psoriasis. It stimulates the expression of ADAM-10, the human APP's α-secretase, in preclinical models. Acitretin has been found to decrease the accumulation of Aβ in transgenic APP/PSI mice and to stimulate the non-amyloidogenic route of APP metabolism in neuroblastoma cells. [113]

Current Drug Therapy for AD

Donepezil (ACh inhibitor)

In 1996, the United States FDA authorised the use of donepezil for treating all types of (mild, moderate, severe) AD. Acetylcholinesterase is inhibited reversibly by the piperidine derivative donepezil hydrochloride. When acetylcholine is released from the presynapse, an enzyme called acetylcholinesterase breaks it down. Donepezil inhibits ACh hydrolysis by binding reversibly to AChE. Donepezil increases the quantity of ACh available at synapses, improving cholinergic neurotransmission. Galantamine and rivastigmine are other cholinesterase inhibitors that are used in clinics. Functional ability, behaviour, and cognition —the three main categories of AD symptoms —are all effectively treated by them.

The nicotinic receptors found in cortical neurons are upregulated by donepezil. With larger dosages, adverse symptoms such as insomnia, cramping in the muscles, exhaustion, and anorexia are frequent. Other side effects due to the drug's vagotonic qualities include bradycardia, rhabdomyolysis, and nightmares. [114]

Memantine (NMDA antagonist)

In 2003, the US FDA authorised memantine as a treatment for moderate to severe AD. Eli Lilly discovered memantine in 1968 and patented it. It is an antagonist of low to moderate affinity for NMDARs. It has a somewhat beneficial clinical impact on cognition, general functioning, daily living activities, and neuropsychiatric symptoms. Headache, nausea, dizziness, diarrhoea, hypertension, anxiety, and influenza are the most typical side effects. [115]

Epothilone D (microtubule stabiliser)

Tauopathies may benefit from the use of MT-stabilising medications that are already utilised to treat cancer. Treatment with Epothilone D significantly improved microtubule density, axonal integrity, rapid axonal transitions, and cognitive function *in-vivo* without inducing any adverse effects. [116] The trial ended in 2013 with BMS-241027's investigation for AD being suspended due to side effects that ultimately led to clinical failure after Phase I. [117]

Minocycline (anti-inflammatory, anti-apoptotic)

The tetracycline derivative minocycline is a potent neuroprotective compound with anti-inflammatory and anti-apoptotic activity. In mouse models of illness, minocycline readily crosses the BBB, potentially slows disease development, and lowers neuron dysfunction. Minocycline therapy reduced the amount of insoluble tau aggregates produced and the level of hyperphosphorylated tau. [118] The production of the caspase-3-cleaved form tau structure can be successfully decreased by minocycline. It is said to block the kinases involved in tau production, such as CDK5, Akt/GSK-3, and p38. [119]

Lycopene (natural antioxidant)

Lycopene is a red stain that is primarily present in natural sources (tomatoes and apricots). It is a powerful antioxidant with a single-oxygen quenching capability that is between 47-100 times greater than that of beta-carotene and Phytonadione. The strong antioxidant lycopene can help mitigate ROS damage to DNA, cellular proteins, and lipids. When combined, the vitamin E, lycopene Ser262, and Ser396 epitopes of the tau protein were phosphorylated less frequently than each compound alone. [120]

Antibody Therapy in AD

Bapineuzumab was introduced in the early 2000s as the inaugural anti-Aβ antibody examined in phase 3 clinical trials. It was designed to eradicate Aβ plaques from the brain by binding to the N-terminus of Aβ. Initial clinical trials of bapineuzumab indicated potential; however, later trials failed to exhibit significant therapeutic effects, potentially attributable to suboptimal patient selection or insufficient dosage.[121] Solanezumab, another anti-Aβ antibody that is no longer under investigation, was designed to inhibit Aβ aggregation by targeting its mid-region. Clinical trials of solanezumab have yielded contradictory results; some indicate a deceleration of cognitive deterioration in people with moderate Alzheimer's disease, while others demonstrate no significant benefits. [122, 123] The US FDA has presently sanctioned two disease-modifying treatments (DMTs), five cognitive-enhancing medications, and one agent for alleviating agitation in Alzheimer's disease (AD), signifying advancements in AD treatment. Anti-amyloid monoclonal antibodies (mAbs) are the only DMTs now authorised for the treatment of AD. One of the two approved drugs, aducanumab, was granted rapid approval because it significantly reduced the amount of β-amyloid (Aβ) plaques visible on amyloid positron emission tomography (PET), which is considered a reliable indicator of therapeutic efficacy. [124-125] Lecanemab received standard approval based on clinical and biomarker results from a phase III study, following its accelerated approval from a phase II research study. [126] Aducanumab (BIIB037; Aduhelm™), a human immunoglobulin G1 monoclonal auto-antibody (IgG1-mAb), exhibits a higher affinity for fibrillar aggregates compared to monomers and interacts with an N-terminal epitope composed of amino acids from the Aβ42 peptide. In June 2021, the FDA conferred accelerated approval for Aducanumab, marking it as the inaugural approved disease-modifying therapy for Alzheimer's disease and the first approved amyloid-beta-targeting monoclonal antibody. Shortly after, the United Arab Emirates (UAE) also approved it. The medication is recommended for early-stage AD patients with moderate dementia or MCI who exhibit brain Aβ via amyloid PET or CSF investigations. According to data from clinical trials, the target dose of Acanthocephalus, which is administered intravenously every four weeks, is 10 mg/kg. [124] Based on information from phase II and III clinical trials, donanemab is presently being reviewed for standard approval. [126]

Conclusion

AD is a chronic neurological illness that is becoming more common each year. However, the pathophysiology of AD is complicated and still not entirely understood. Animal models are only partially reflective of the disorders being studied because no single model fully combines all of the traits found in humans. Therefore, similar symptoms in animal models to AD should not be referred to as Alzheimer's disease. These models are handy for researching several alterations associated with the pathophysiology of AD.

Therapeutic medication research for AD is continuously ongoing. It can take up to 20 years for pathological alterations to manifest as diagnostically significant symptoms in AD, as the disease progresses slowly. Consequently, managing AD early on is essential to halting its progression. Thus, to provide substantial benefits for AD patients, future research should examine the connection between decreased Aβ plaques and Tau levels. With aducanumab's expedited FDA approval, there is now optimism for the development of AD drugs, and we anticipate more affordable and efficient treatments for AD patients.

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