INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Research Article

Emerging Therapeutic Strategies for Alzheimer's Disease: From Molecular Pathways to Novel Drug Development

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ARTICLE INFO

Published: 29 Nov 2026

Keywords:
Alzheimer's disease, Neurodegeneration, Amyloid-β, Tau protein, Neuroinflammation, Oxidative stress

DOI:
10.5281/zenodo.24645986

ABSTRACT

Alzheimer's disease (AD) is the most common type of dementia, posing serious and growing global difficulties. Its etiology is complex and varied, resulting from a confluence of environmental, genetic, and age variables. Many theories, including the cholinergic, amyloid, tau protein, inflammatory, oxidative stress, metal ion, glutamate excitotoxicity, microbiota-gut-brain axis, and aberrant autophagy, are involved in our current understanding of AD pathology. However, more clarification and confirmation are needed to identify the main causes of AD and to untangle the interactions between these pathological features. The majority of clinical medications have been withdrawn in recent decades because of their poor efficacy or side effects. The majority of the medications now on the market provide symptomatic relief, but they frequently have unfavorable side effects. However, the Food and Drug Administration (FDA) recently approved lecanemab and aducanumab, which may have disseminating effects. However, more research is required to confirm these medications' long-term safety and effectiveness. As a result, the search for safer and more potent AD medications continues to be a difficult and urgent undertaking. The current understanding of AD pathophysiology, developments in diagnostic biomarkers, the most recent clinical trial updates, and new technologies for AD medication development are all covered in this study. We highlight the latest advancements in the identification of selective. We discuss recent advancements in the identification of protein-protein interaction (PPI) modulators, selective inhibitors, dual-target inhibitors, allosteric modulators, covalent inhibitors, and proteolysis-targeting chimeras (PROTACs).

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

INTRODUCTION:

Dementia has become a worldwide health concern. An estimated 55.2 million people worldwide suffer from dementia, according to the World Health Organization's 2022 research agenda. Southeast Asia reports a frequency of 2.9%, Europe reports a prevalence of 6.5%, and other regions report rates ranging from 3.1% to 5.7% among persons over 60. The incidence of dementia is generally increasing, while some high-income countries are seeing a decline. By 2030, the estimated number of people living with dementia will surge to 78 million. Furthermore, the global financial burden associated with medical care, social services, and informal caregiving for those with dementia is expected to exceed US$ 2.8 trillion. This situation will have a profound impact on individuals, families, and societies.

Alzheimer's disease (AD), the predominant form of dementia, exhibits similar epidemiological trends and represents an urgent and escalating challenge worldwide. In the United States, approximately one in nine individuals (10.8%) age 65 and older suffer from AD, with an annual incidence of 1275 new cases per 100,000 persons.

Patients with AD exhibit a substantial accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs) within their brains, accompanied by a cascade of pathological processes such as neuroinflammation, synaptic dysfunction, mitochondrial and bioenergetic disturbances, as well as vascular abnormalities. Collectively these processes may ultimately lead to the death of neurons. Clinically, the primary hallmark of AD is amnestic cognitive impairment. Initially, symptoms may manifest as depression, anxiety, social withdrawal, and altered sleep patterns. As the disease progresses, symptoms worsen, leading to severe memory loss, neuropsychiatric symptoms such as hallucinations and delusions, and intensified behavioral and emotional issues in its advanced stages. Additionally, some patients with non-amnestic cognitive impairment may experience varying levels of dysfunctions in visual-spatial, language, executive functions, behavior, or motor skills. Additionally, comorbidities associated with AD may worsen patients' conditions, speeding cognitive deterioration and adding to clinical phenotypic variation. Hypercholesterolemia, hypertension, diabetes, obesity, depression, and cardiovascular illnesses are examples of such problems. Furthermore, thrombosis, mobility issues, dysphagia, malnutrition, and pneumonia (lung infections) are complications that can significantly lower a patient's quality of life and raise their risk of dying.

The connection between comorbidities and the pathological changes in AD is currently the subject of ongoing research. Unfortunately, there is yet no cure for AD, and patients are frequently diagnosed at a late and irreversible stage, facing an average survival period of 4–8 years. Nonetheless, pathological changes in the brain begin during the preclinical stage, decades before clinical symptoms. Typically, patients transit to mild cognitive impairment (MCI) around 6-10 years later, with approximately 15% progressing to AD within 2 years and one-third within 5 years. Therefore, it's crucial to concentrate on the preclinical and MCI stages, where early intervention and management of modifiable risk factors could potentially lower the risk of onset or delay the progression of disease. Evidence suggests that about one-third of AD cases worldwide are closely linked to modifiable risk factors. Encouragingly, due to improvements in risk factors such as vascular health, lifestyle choices, and education levels, the incidence of AD is on a downward trend in the United States, South Korea, Europe, and certain regions of Asia. In recent years, numerous articles have highlighted modifiable risk factors for AD, alongside the benefits of Multidomain Alzheimer Preventive Trials. These insights underscore the efficacy of early prevention strategies for AD.

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The etiology of AD is complex and diverse, and the precise mechanisms underlying its onset are not yet completely under- stood. Beyond the pivotal role of Aβ and tau, a spectrum of other factors may contribute to the pathology of AD, such as acetylcholine deficiency, neuroinflammation, oxidative stress, biometal dyshomeostasis, glutamate imbalance, insulin resistance, gut microbiome abnormalities, cholesterol homeostasis disruption, mitochondrial dysfunction, and autophagy abnormalities.

Numerous hypotheses have been proposed to unravel the pathogenesis of AD, yet a unified theory remains elusive, likely due to the complex nature of AD. AD can be categorized into two main types: familial (accounting for 1-5% of AD cases) and sporadic forms (over 95% of cases). Familial AD (FAD) is predominantly characterized by autosomal dominant genetic mutations in amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) genes, typically manifesting between 30-65 years and progressing rapidly. In contrast, sporadic AD (SAD), also known as late-onset AD, usually manifests after the age of 65 and is influenced by a combination of genetic risks, environmental factors, and various comorbidities. Genome-wide association studies (GWAS) and genome-wide meta-analyses have identified numerous genetic risk loci associated with SAD, implicating pathways in immune response, lipid metabolism, Aβ plaque, NFTs, and endocytosis, yet many loci remain undiscovered.

Non-genetic factors such as lifestyles, psychosocial factors, environment, and diseases related to AD (comorbidities and complications), may elevate the risk of developing AD. They may achieve this by altering biological pathways and genetic susceptibility, making it challenging to pinpoint a direct cause of clinical pathology in AD.

Cholinergic hypothesis

The cholinergic hypothesis was the earliest to delineate the pathogenesis of AD. It describes the severe damage of cholinergic neurons in the nucleus basalis of meynert (NBM), leading to a marked decrease in choline acetyltransferase (ChAT) activity within the primary projection areas the cerebral cortex and hippocampus (regions associated with learning and memory). Additionally, this neuronal damage is accompanied by a significant increase in the density of senile plaques. The scenario in the cholinergic hypothesis suggests a close relationship between deficits of basal forebrain cholinergic and cognitive impairments observed in AD. Cholinergic neurons in the basal forebrain are crucial components of the central cholinergic system, significant contributing to the regulation of cognitive functions, attention, and memory. These cell bodies of neurons are predominantly located in the medial septal nucleus (MSN), diagonal band of broca (DBB), NBM, and substantia innominate (SI). It has been observed that cholinergic neurons in the NBM region are particularly susceptible to degeneration and loss in AD.

Amyloid hypothesis

The accumulation of Aβ is a hallmark pathological feature in both extensively studied autosomal dominant AD and sporadic late- onset AD patients. Aβ originates from the processing of the APP, a transmembrane glycoprotein, through its sequential cleavage by β-secretase and γ-secretase (a multiprotein complex with PS1 or PS2 as catalytic subunits). This process yields various lengths of Aβ fragments, with Aβ40 and Aβ42 being the predominant. The hydrophobic C-terminal of Aβ42 facilitates the β-sheet conformational transition and the aggregation and formation of the core component of senile plaques. Mutations in PS1, a typical mutation in FAD, potentially promote Aβ accumulation through multiple mechanisms, including increased Aβ production and impairment of autophagy functions. However, FAD mutations are not necessarily linked to an increase in Aβ42 levels or an elevation of Aβ42/Aβ40 ratio. The plaque formation in SAD is notably more intricate, related to a dynamic imbalance between Aβ production and clearance mechanisms. Apolipoprotein E (APOE), particularly the ε4 allele, stands out as the most crucial genetic risk factor for

SAD. Carrying one or two APOE ε4 alleles increases the risk of AD by 2-3 and 12-fold, respectively. Research indicates that APOE protein is detectable in neuritic plaques, and individuals with the APOEε4 allele also have a higher burden of Aβ plaques in their brains, highlighting its critical influences on Aβ deposition.

Tau protein hypothesis

As a major component of NFTs, tau protein exhibits a spatial and temporal distribution that Strongly correlates with Clinical symptoms, making it a highly specific pathological biomarker in AD patients. Tau is a microtubule-associated protein predominantly expressed in the axons of neurons, with lower expression levels in dendrites, soma, and glial cells. It hosts numerous phosphorylation sites across its N-terminal region, C-terminal region, and repeat region, which are regulated by a balance of various kinases and phosphatases to maintain normal neuronal physiological functions. Under pathological conditions, an imbalanced activity of phosphatases and kinases leads to hyperphosphorylation of tau. This process leads to he detachment of tau protein from microtubules, followed by conformational changes and mislocalization, accumulation of tau oligomers, paired helical filaments (PHFs), and NFTs within the cell body and dendrites. These changes ultimately impair neuronal function and cause cell death. Additionally, other post- translational modifications, including truncation, glycosylation, glycation, and sumoylation, play an active role in promoting tau aggregation and increasing its toxicity.

Neuroinflammation hypothesis

Neuroinflammation is generally characterized as a chronic inflammatory response in the central nervous system (CNS) that fails to resolve on its own. It often involves the activation of glial cells and the release of pro-inflammatory factors during neuroinflammation. Microglia, the CNS foremost innate immune cells, acts as an initial defense against danger-associated molecular patterns and pathogen-associated molecular pattern receptors. Microglia are elongated, branched cells that monitor their environment and secrete neurotrophic factors in a state of homeostasis. Once stimulation is detected, microglia undergo morphological changes and initiate a variety of responses. Aβ is a typical trigger for microglial activation. Activated microglia migrate towards senile plaques, engulf Aβ, and release enzymes to break down Aβ. Over prolonged periods, they might become less efficient at handling Aβ but continue to generate proinflammatory cytokines. Aβ also causes the formation and activation of the NLRP3 inflammasome within microglia, which releases ASC specks that bind rapidly to Aβ in promoting Aβ aggregates and the spread of Aβ pathology.

Oxidative stress hypothesis

During regular metabolic processes, the body produces reactive oxygen species (ROS), reactive nitrogen species, and other highly reactive and unstable substances. These substances are generally kept at low levels by an efficient antioxidant defense system to protect cells from oxidative damage. However, in the brain of AD patients, factors such as metal accumulation, overexpression of related enzymes (e.g., NADPH oxidase), and mitochondrial dysfunction are involved in producing excessive ROS, surpassing the ability of the endogenous antioxidant system and resulting in an oxidative imbalance. It will damage neuronal membrane lipids, proteins, and nucleic acids, ultimately causing neuronal cell death. The abnormality of the electron transport chain within mitochondria is particularly a significant contributor to free radical production. Aβ plays a crucial role in mitochondrial dysfunction by reducing the activities of key enzymes and disrupting the dynamics of mitochondria. Oxidative stress presented in the early stages of AD acts as a crosstalk between different hypotheses of AD. For example, oxidative stress modulates the process of APP and the activity of secretases, thereby promoting the amyloid pathway. Furthermore, it is instrumental in the phosphorylation of tau proteins and the subsequent formation of NFTs. The activation of microglia induced by ROS triggers a neuroinflammatory cycle. The presence of free metals and complexes of Aβ with metals act as catalysts for ROS production, ultimately leading to neuronal cell death. Given these connections between oxidative stress and other AD mechanisms, antioxidants have emerged as promising agents in AD treatment with positive outcomes observed in animal models. However, the efficacy of antioxidants in clinical trials for AD remains uncertain. Several studies

have indicated that standalone treatments or treatments in combination with cholinesterase inhibitors did not confer significant cognitive benefits to patients with AD.

Metal ion hypothesis

In physiological conditions, trace metals maintain homeostasis of the neuronal metal ion microenvironment. This balance can be disrupted by the inappropriate deposition or misdistribution of metal ions, with the dyshomeostasis of Fe2+, Cu2+, and Zn2+ closely associated with AD. The accumulation of these biometals in Aβ plaques and NFTs plays a critical role in pathological protein deposition. For instance, they may modulate the activity of essential enzymes, alter the conformation of proteins, or disrupt clearing pathways. When metals are sequestered in protein deposits, it may initiate a cascade of ROS production and accentuate toxicity. Specifically, iron-induced oxidative stress causes increased release of iron from ironcontaining proteins, converting Fe3+ to Fe2+ intracellularly. Fe2+ overload can induce ferroptosis and lipid peroxidation through the generation of ROS via the Fenton reaction, ultimately resulting in neuronal death. Similarly, Cu+ directly binds to lipoylated dihydrolipoyl transacetylase (DLAT), inducing lipoylated DLAT aggregation and ultimately leading to cuproptosis. The sequestration in protein deposits also causes functional metal loss, potentially contributing to the cognitive decline in AD. Zinc could interfere with signaling through N-methyl-D-aspartate (NMDA) receptors. Supplementation of zinc may promote the maturation of proBNDF, reducing synaptic dysfunction and neuronal death. Hence, zinc deficiency is crucial in the context of glutamate excitotoxicity and synaptic dysfunction in AD. Overall, metal dyshomeostasis is closely linked to various events in AD such as amyloidosis, tauopathy, oxidative stress, and neuronal death. This hypothesis provides an alternative approach to understanding the pathogenesis of AD and detecting pathological changes. Further research is necessary to elucidate its role in AD.

Glutamatergic excitotoxicity

Glutamate is the main excitatory neurotransmitter of glutamatergic neurotransmission in the CNS.206 Their receptors comprise ionotropic glutamate receptors, including NMDA receptors, αamino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, and kainate receptors, as well as metabotropic glutamate (mGlu) receptors. Glutamate mainly interacts with NMDA receptors to control the influx of sodium and calcium to neurons. Magnesium ions act to shut the NMDA receptor's cationic channel and block the entry of ions into neurons under physiological conditions. However, in AD, there is an overstimulation of NMDA receptors, which results in the dislodgement of magnesium and permits an excessive entry of sodium and calcium ions. The entry of sodium into neurons causes their temporary swelling, while an increase in calcium levels initiates various Ca2+-dependent processes. These processes include the creation of ROS, disruption of mitochondrial function, and the activation of necrotic/apoptotic pathways, ultimately resulting in permanent excitotoxic damage to the neurons. Overall, pharmaceutical validation of the glutamatergic excitotoxicity hypothesis demonstrates the effectiveness of neurotransmitter regulation in improving cognitive symptoms.

Microbiota-gut-brain axis hypothesis

In recent years, the microbiota-gut-brain axis hypothesis has attracted significant attention, unveiling potential pathways for novel therapeutic strategies. The microbiota predominantly consists of bacteria, with smaller populations of fungi, viruses, archaea, and protozoa. These microorganisms offer trophic and protective effects in metabolism and innate immunity and influence brain function via the gut-microbiota-brain axis. The microbiota-gut-brain axis refers to a bidirectional communication system between the gut and the brain, including metabolic, endocrine, neural, and immune pathways that can work independently or in concert. Alterations in the host's diet, use of antibiotics, exposure to psychosocial stress, or irregularities in the immune system may shift the relative proportions of bacterial species, resulting in a disruption of the microbiota's composition and functionality as dysbiosis. Subsequently, the intestinal epithelial barrier is compromised. Harmful substances and microorganisms in the intestinal tract could enter the bloodstream, triggering an immune response that may lead to systemic inflammation. The onset of systemic

inflammation may allow inflammatory mediators to cross over the BBB and impact microglia, further exacerbating neuroinflammation. This process is accompanied by imbalanced neurotransmission, which ultimately leads to neuronal degeneration and damage. Overall, the microbiota-gut-brain axis hypothesis establishes a connection between the peripheral immune system and the CNS, offering a fresh perspective for AD research Moreover, drugs and biomarkers related to the gut microbiome are potentially considered. However, the investigation of this mechanism is still in an early stage. The exact mechanisms by which the gut microbiome affects brain activity or its connections with other pathological features of AD remain unclear.

Abnormal autophagy

Autophagy, a highly conserved metabolic degradation process, maintains cellular homeostasis by delivering intracellular protein aggregates and damaged organelles to lysosomes for degradation and recycling. It primarily occurs via three types: microautophagy, chaperone-mediated autophagy, and macroautophagy (commonly referred to as autophagy). Microautophagy is the simplest pathway in which cytoplasmic substrates enter vesicles formed by morphological changes in lysosomal or endosomal membranes, and are ultimately degraded within the lysosome. Chaperone-mediated autophagy involves chaperone proteins recognizing and binding to specific protein sequences (KFERQ-like motifs), facilitating substrate transfer to lysosomes through interactions with lysosomal membrane proteins (LAMP2A). Macroautophagy, the main subtype, is primarily regulated by mTORC1 for activating the unc-51-like autophagy activating kinase 1 (ULK1) complex and dephosphorylating transcription factor EB (TFEB) to induce autophagy. Under the regulation of autophagy-related protein complexes, a phagophore forms and gradually expands to a sealed autophagosome. The autophagosomes then move retrogradely along microtubules to the microtubule organizing center, which is rich in lysosomes. They fuse with lysosomes to form autolysosomes, where substrate degradation occurs. In certain instances, autophagosomes could first merge with endosomes to form amphisomes, which then fuse with lysosomes. However, the abundant accumulation of autophagic vacuoles in swollen (malnourished) neurons is observed to have a linkage with Aβ/APP-βCTF, suggesting that autophagy clearance is severely disrupted under pathological conditions and is closely linked to amyloid pathology. This makes autophagy a focal point in recent AD pathogenesis research. There is increasing evidence indicating that genetic factors, reduced expression of related proteins, and defective vesicular transportation are potential causes of autophagy pathway disruptions. These disruptions interfere with clearance mechanisms involving substrate engulfment, autophagosome formation, autophagosome-lysosome fusion, and lysosomal structure and function. In AD, autophagy defects mediate the disruption of protein homeostasis networks (production and extracellular secretion of Aβ, abnormal aggregation of tau protein) and lead to the accumulation of damaged organelles, such as dysfunctional mitochondria. In summary, abnormalities of autophagy are intimately related to the onset and progression of AD. There is a growing emphasis on the involvement of chaperone-mediated autophagy, contributions of glial cell autophagy, and the precise causes of mitochondrial autophagy disorders. Autophagy-stimulating drugs including small molecule therapies and gene therapies, have shown significant neuroprotective potential in various AD animal models, suggesting a potential intervention option. However, the challenges posed by the broad targets of autophagy modulators, and lack of appropriate in vivo autophagic flux detection methods, hinder further clinical applications of these drugs.

Signaling Pathways Linked to Ad Pathogenesis

Neuroinflammatory signaling

Several pathological factors in AD, such as Aβ, pro-inflammatory cytokines, and oxidative stress, activate microglia and initiate downstream signaling pathways such as MAPK, NF-κB, and PI3K/ Akt. The activation of these pathways further promotes the activation of microglia and the production of inflammatory mediators, exacerbating neurotoxicity. ERK, JNK, and p38 MAPK are three primary MAPK signaling pathways that may activate transcription factors such as AP-1 and NF-κB to release pro-inflammatory cytokines like TNF-α, IL-1β, and NO. NF-κB can be co-regulated by multiple pathways including MAPK and PI3K/Akt to

enhance transcriptional activity, thus promoting the expression of pro-inflammatory and pro-oxidant enzyme genes. A recently identified microRNA, miR-25802, found to be overexpressed in AD, likely plays a crucial role in exacerbating disease pathology. This microRNA may regulate the polarization of microglial cells towards a pro-inflammatory phenotype through the modulation of the KLF4/NF-κB signaling pathway. Such alterations can further aggravate key pathological features in the 5xFAD mouse model including increased deposition of Aβ plaques and deficits in learning and memory. The NFκB signaling pathway significantly impacts the expression of components related to the NLRP3 inflammasome, such as NLRP3 protein, ASC, pro-IL-1β, and pro-IL-18. The NLRP3 inflammasome activates caspase-1 through its assembly and activation processes. Activated caspase-1 can cleave gasdermin D (GSDMD), triggering pyroptosis and releasing IL-1β, IL-18, and ASC specks into the extracellular environment. This may exacerbate the spread of inflammation and neuronal death. Additionally, the connection between NF-κB signaling and NLRP3 inflammasome activation with AD tau pathology has garnered significant attention. Inactivated NF-κB pathways in microglia may reduce the seeding and amplification of tau proteins in microglia, thus rescuing cognitive deficits in young PS19 mouse models, yet the accumulation of tau inclusions in neurons of aged PS19 mice warrants further investigation According to recent studies, proinflammatory cytokines like IL-1β may induce an increase in tau transcription in human primary neurons by activating the NF-κB signaling pathway in neurons. Brain-derived tau proteins may activate the inflammatory response in microglia via the TLR2/ MyD88/NF-κB pathway. tau proteins can activate the NLRP3 inflammasome, which then promotes excessive tau phosphorylation and aggregation by affecting specific tau kinases and phosphatases. These findings reveal the complex interplay between inflammatory responses and tau pathology, providing a more comprehensive understanding of AD's molecular mechanisms. The activation of the cGAS-STING signaling pathway in AD also plays a crucial role in neuroinflammation.

Lysosomal dysfunction

Lysosomes rely on a rich array of acidic hydrolases to selectively degrade and recycle both intracellular and extracellular materials, playing a crucial role in maintaining cellular homeostasis. Lysosomal dysfunction is considered a critical factor in the development of many diseases, which may manifest as impaired acidification, abnormal expression of lysosomal enzymes, lysosomal membrane stability issues, transport defects, and defects in autophagosome/endosome-lysosome fusion. These issues may disrupt lysosomal degradation pathways, including the autophagy-lysosomal pathway and endosomal-lysosomal system, leading to the accumulation of pathological proteins and damaged organelles, further disrupting the cellular environment. A key factor affecting lysosomal function is the pH controlled by the vacuolar (H^+)-ATPase (V-ATPase), which uses the energy from ATP hydrolysis to drive H^+ from the cytoplasm into the lysosome. Other factors such as Cl^-, Ca^{2+}, and Na^+ ion channels/transporters also interact with the luminal pH and collectively regulate the lysosomal acidic environment. AD, lysosomal acidification deficits may weaken the clearance of Aβ, ultimately leading to the accumulation of extracellular Aβ plaques. This phenomenon indicates that lysosomal-related clearance system dysfunction might be one of the early events in the progression of AD and has become a focus of current AD research. It has been reported that the PS1 holoprotein may facilitate N-glycosylation of the V0a1 subunit of V-ATPase and its trafficking from the endoplasmic reticulum (ER) to lysosomes, thereby promoting the assembly and maturation of V-ATPase. However, there are inconsistent views on a series of events caused by defects in PS1, including impaired maturation of V0a1 in lysosomes, V-ATPase dysfunction, and lysosomal acidification defects.267,268 Calcium dysregulation associated with PS1 has been proposed as a potential cause of endolysosomal defects. once again affirmed the link between lysosomal acidification dysfunction and V-ATPase, further elucidating that aberrant lysosomal acidification mediates transient receptor potential cation channel mucolipin subfamily member 1 (TRPML1) overactivation, resulting in dysregulation of lysosomal calcium ions. Moreover, they demonstrated that solely reversing lysosomal calcium ion

levels in cellular models failed to impact lysosomal acidity and autophagic function beneficially.

Cholesterol metabolism

Cholesterol is abundant in the brain, serving as a critical component of the myelin sheath and the membranes of neural cells, including neurons and glial cells. The balance between cholesterol synthesis, transport, metabolism, and clearance is crucial for neuronal growth, synaptic plasticity, and learning and memory functions. In AD, cholesterol biosynthesis and catabolism are impaired, contributing to the progression of AD through mediation of Aβ, tau, inflammation, and other pathological changes. The connection between cholesterol and Aβ may be related to lipid rafts, which are cholesterol-rich microdomains on the plasma membrane. These rafts may facilitate the colocalization of APP with its cleaving enzymes, enhance the activities of β and γ secretases, and influence the endocytosis of APP, thereby mediating its amyloidogenic pathway. With the assistance of cholesterol transporter APOE, astrocyte-derived cholesterol could be transferred to neuronal membranes, regulating cholesterol-dependent lipid clusters (also known as lipid rafts) on neurons to promote Aβ generation. Differences in cholesterol levels caused by different APOE isoforms may be related to their cellular expression and regulatory mechanisms. Additionally, different APOE isoforms have varying impacts on Aβ pathology. Compared to APOE3 and APOE2, APOE4-mediated pathways of Aβ clearance are impaired, and APOE4 exhibits a higher affinity interaction with Aβ, potentially driving a more severe Aβ plaque burden, making it one of the strongest genetic risk factors for AD. Cholinergic dysregulation associated with ApoE4 also contributes to tau pathology. For instance, in chimeric human cerebral organoids (chCOs), astrocytes and neurons carrying the APOE4 genotype could jointly promote tau phosphorylation in neurons, closely linked to the role of APOE4 in increasing cholesterol levels and lipid droplet content, suggesting that APOE4 may affect tau phosphorylation in AD by influencing lipid metabolism.

Mitochondrial dysfunction

Mitochondria are the primary source of cellular energy and mediate a multitude of biological processes including biosynthesis, redox balance, calcium signaling, and apoptosis, serving as the core drivers of vital activities. Observations in AD afflicted brains of regionally reduced glucose metabolism and alterations in several mitochondrial enzyme activities suggest mitochondrial dysfunction. This is primarily manifested by defects in energy metabolism, increased oxidative stress, calcium ion imbalance, and abnormal mitochondrial dynamics, all potentially leading to neuronal dysfunction and even apoptosis, exacerbating the neurodegenerative changes in AD. Moreover, AD pathological biomarkers could directly impact mitochondrial function, creating a vicious cycle. Aβ inhibits the activity of key mitochondrial enzymes such as electron transport chain enzyme complex IV, pyruvate dehydrogenase (PDH), and αketoglutarate dehydrogenase (αKGDH), reducing the efficiency of electron transfer, diminishing ATP synthesis, and stimulating the production of ROS. Additionally, Aβ interacts specifically with mitochondrial Aβ-binding alcohol dehydrogenase (ABAD), impeding the binding of NAD to ABAD and inducing ROS production. The generation of ROS and the imbalance of the antioxidant system further damage mitochondrial DNA, lipids, and proteins, aggravating mitochondrial dysfunction and cellular apoptosis. As the most common secondary messenger in cells, the importance of calcium ions is self-evident, and their homeostatic disruption is a significant factor in mitochondrial damage. Aβ may increase cytosolic calcium levels and impair mitochondrial calcium buffering functions through various pathways including plasma membrane receptors and calcium channels, enhanced ER calcium release, and the mitochondrial inner membrane calcium channel MCU. This leads to mitochondrial calcium overload, causing cyclophilin D (CypD) to relocate from the mitochondrial matrix to the inner membrane, promoting the formation of the mitochondrial permeability transition pore (mPTP), further inhibiting ATP synthesis, activating oxidative stress, and apoptosis. Moreover, tau is also associated with mitochondrial calcium imbalance, and due to the critical role of tau in microtubule structure and function, its abnormal phosphorylation and aggregation may adversely affect mitochondrial axonal transport, impacting local metabolic needs and overall neuronal function. Impairments in mitochondrial fission and

fusion mechanisms, as well as mitophagy, are also areas of concern in AD.

Calcium signaling

Intracellular calcium could originate from the opening of plasma membrane calcium channels, such as voltage-gated and ligand gated calcium channels, and the release of organelles like the ER and mitochondria. Calcium plays a multifaceted role in regulating gene expression, neurotransmitter release, membrane excitability, and inducing synaptic plasticity. Additionally, plasma membrane calcium ATPases (PMCA), the sarco/ER calcium ATPase (SERCA), the sodium-calcium exchangers (NCX), and Ca2+- binding proteins also regulate cytosolic calcium concentration. Maintaining this calcium homeostasis is fundamental to calcium signaling, and disruption in cytosolic calcium concentration gradients, as well as abnormalities in calcium signaling pathways, may lead to neurodegenerative diseases such as AD and Parkinson's disease (PD), cardiovascular diseases, and metabolic disorders. In AD, enhanced activity of L-type VGCCs, potentially related to their interaction with Aβ/tau, promotes excessive calcium influx into cells. Studies have shown that using L-type calcium channel blockers could mitigate the upregulation of L-type VGCCs and abnormal calcium influx induced by Aβ. Ligand-gated calcium channels such as NMDAR and α7nAChR, highly permeable to Ca2+, are closely associated with Aβ. 308 Overactivation of NMDARs by Aβ leads to abnormal calcium influx, triggering a cascade of downstream signaling events, resulting in dendritic spine loss, reduced distribution of NMDARs on neuronal membranes, impaired synaptic plasticity, and ultimately, cognitive decline. Complexes formed by Aβ with α7-nAChR efficiently promote Aβ internalization and increased calcium influx, further affecting extracellular Aβ plaque accumulation and synaptic transmission. Abnormal intracellular calcium signaling could also impact various organelles such as the ER, mitochondria, and lysosomes. The impaired function of SERCA and/or overactivation of calcium release channels (InsP3R and ryanodine (RyR) receptors) on the ER could facilitate the activation of the ER stress response.

Insulin signaling

Insulin regulates glucose metabolism, neuronal growth and survival, synaptic plasticity, and cognition, functions closely linked to two main insulin signaling pathways: phosphatidylinositol 3-kinase (PI3K)-Akt and Ras/Raf-MAPK. The PI3K-Akt pathway is a crucial component of insulin signaling, and in AD brains, there is observed a decrease in IRS-associated PI3K activity and reduced phosphorylation of Akt kinase. Lower levels of Akt activation weaken the inhibition of glycogen synthase kinase3 (GSK-3), which in turn positively affects the phosphorylation of tau protein and the production of Aβ. mTORC1, a downstream molecule of Akt, also serves as a critical nexus linking insulin signaling with the autophagy system. Its role in the inhibitory phosphorylation of IRS1, synaptic protein synthesis, synaptic plasticity, and autophagy regulation is significantly correlated with the accumulation of pathological protein aggregates and impaired learning and memory functions in AD. Some drugs targeting mTORC1 have been demonstrated in animal studies to effectively inhibit abnormal mTORC1 activation, thereby enhancing autophagy, reducing Aβ and tau pathology, and helping to delay cognitive decline. However, some studies express divergent views on the activity of mTORC1 in AD. Furthermore, the increased production of inflammatory mediators like TNF-α and the activation of stress kinases such as JNK, PKR, and IKK could promote the inhibitory serine phosphorylation of IRS-1, downregulate insulin signaling in the brain, and induce AD neurological dysfunction.

Dysregulated neurotrophic signaling pathway

Neurotrophic factors not only promote the survival, growth, and differentiation of neurons but are also crucial for maintaining synaptic plasticity and neuronal signaling functions. In AD, key neurotrophic factors include NGF and brain-derived neurotrophic factor (BDNF), which exert their effects through specific receptors such as tropomyosin-related kinase (Trk) and p75NTR. In AD, there is a reduction in the conversion of proNGF to mature NGF and an enhancement in the degradation of mature NGF, leading to a deficiency in mature NGF and accumulation of proNGF in the brain. The lack of mature NGF may promote the

phosphorylation of APP at T668, reducing its binding to TrkA and affecting its subcellular localization, thus increasing amyloidogenic processing of APP and Aβ production. The accumulation of proNGF and downregulation of TrkA (pro-survival signal) levels favor the predominance of pro-apoptotic signaling mediated by p75NTR, further promoting the degeneration of basal forebrain cholinergic neurons. Downregulation of BDNF expression leads to weakened BDNF signaling in AD. This weakened signaling triggers the activation of JAK2/STAT3 and C/EBPβ signaling pathways in the AD brain and inhibits downstream Akt signaling molecules, thereby promoting the activation of asparagine endopeptidase (AEP; also called δ-secretase) to cleave APP and tau proteins. The cleaved tau fragments could bind to TrkB receptors, further inducing neuronal apoptosis. A study suggested that impaired BDNF nutritional signaling also stimulated the expression of APP and PS1 to exacerbate amyloidogenesis. Similarly, Aβ can interfere with common neuroprotective signaling pathways, such as the Raf-MAPK/ERK pathway and the PI3K-Akt pathway, initiated by the binding of BDNF to TRKB, inducing cortical neurons into a dysfunctional state. According to recent research, microglial repopulation/self-renewal contributed to the restoration of BDNF expression and activation of the BDNF/TrkB neurotrophic signaling pathway, significantly reversing cognitive deficits in 5xFAD mice. This suggests that BDNF may provide potential benefits for AD treatment through its positive modulation of impaired synaptic plasticity and cognitive memory.

BBB dysfunction

The BBB is formed by components such as endothelial cells, astrocytes, and pericytes, along with the basement membrane, and together with other cells like microglia and neurons, they constitute the neurovascular unit (NVU). The BBB not only allows highly selective permeability of substances entering and exiting through specialized structures (seal off adjacent BECs) but also dynamically regulates cerebral blood flow through theprocess of neurovascular coupling, maintaining homeostasis and neuronal function in the CNS. Dysfunction of the BBB includes disruption of BBB integrity (or BBB leakage), changes in BBB transport functions, reduced cerebral blood flow, and neuroinflammation. Some evidence suggests that in AD, dysregulation of tight junction proteins, increased matrix metalloproteinase signaling, and degeneration and loss of pericytes may all contribute to BBB leakage, leading to the accumulation of numerous blood-derived neurotoxic proteins in the brain, causing neuroinflammation and oxidative stress. Disruption of the BBB may also lead to ischemic/hypoxic brain damage and increase Aβ production. Abnormal expression of transport proteins/receptors in the BBB, such as downregulation of LRP1 which exports Aβ from the brain to the blood, impaired function of Pgp, and upregulation of RAGE that facilitates the entry of Aβ from the blood into the brain, could be potential reasons for impaired Aβ clearance and substantial accumulation in the brain. Reduced activity and expression of the GLUT-1 transporter in the BBB suggest decreased glucose uptake and utilization by the brain, which may further exacerbate cerebrovascular degeneration, BBB breakdown, and Aβ pathology in models overexpressing APP, inducing neurodegeneration and cognitive deficits.

Clinical Trials of AD

Biomarkers for AD diagnosis

The National Institute on Aging and Alzheimer's Association (NIAAA) proposed a research framework to define the biology of AD using Aβ deposition, pathologic tau, and neurodegeneration AT (N) biomarkers. The current established biomarkers mainly include imaging biomarkers, cerebrospinal fluid (CSF) biomarkers, and blood biomarkers. Molecular imaging techniques like magnetic resonance imaging (MRI) and positron emission tomography (PET) are commonly used to detect structural and functional brain activity in vivo. Specifically, structural MRI (sMRI) assesses hippocampal and entorhinal cortex atrophy in the medial temporal lobe, 18fluorodeoxyglucose (18FDG)-PET detects reduced glucose metabolism in the posterior cingulate and temporoparietal lobes, and PET imaging shows Aβ and tau deposition. However, sMRI and (18FDG)-PET indicate neurodegeneration or neuronal injury in the AT (N) framework with limitations in specifically diagnosing AD. They cannot accurately differentiate AD from other neurodegenerative

diseases with similar pathologies, such as frontotemporal degeneration and TDP-43 proteinopathies with medial temporal lobe atrophy. Additionally, the atypical AD and cerebrovascular diseases may also complicate the diagnosis. Therefore, these methods typically need to be combined with other clinical information and assessment tools for a comprehensive evaluation of AD pathology. Amyloid PET and tau PET not only reflect the overall accumulation and spatial distribution of amyloid plaques and NFTs but may also detect abnormal brain changes earlier than neurodegeneration, thus providing opportunities for early intervention in the disease. Studies have reported that amyloid PET exhibits 90% sensitivity and specificity in diagnosing AD, and tau PET can specifically identify AD dementia from other neurodegenerative diseases, showing higher diagnostic accuracy than MRI markers.

Clinical drugs

Traditional AD drugs are categorized into two classes: AChEIs (tacrine (3), donepezil (4), rivastigmine (5), galantamine (6)) and NMDA receptor antagonists (memantine (7)). AChEIs boost postsynaptic stimulation by increasing both the level and the action duration of ACh, thereby enhancing cognitive and behavioral functions in patients. Tacrine (3) was approved for AD treatment in 1993 and pulled from the market in 2013 due to its liver toxicity. Nevertheless, it has potential in the study of multitarget-directed ligands. Second-generation AChEIs, including donepezil (4), rivastigmine (5), galantamine (6), are more selective. They exhibited fewer side effects or improved pharmacokinetic profiles, establishing them as first-line drugs for AD. Although these drugs have been widely used, ongoing research focuses on optimizing dose, dosage form, routes of administration, and combination therapies to minimize adverse effects and improve patient compliance as much as possible. The donepezil (4) transdermal patch, named Adlarity, was FDA-approved in 2022 for treating mild, moderate, and severe dementia of the Alzheimer type. Its weekly dosing frequency showed bioequivalence to daily oral administration at the same dosage while presenting fewer gastrointestinal adverse events than oral administration. This also offers greater convenience compared to the once-daily rivastigmine (5) patch. The application of nanocarriers is also being explored to deliver these cholinesterase inhibitors through intranasal administration, intravenous injection, and other methods. Nanocarriers play a crucial role in increasing drug concentrations, slowing drug release, and achieving excellent bioavailability. Furthermore, the combination use of appropriate cholinesterase inhibitors, such as donepezil (4) and galantamine (6), or the combination of cholinesterase inhibitors with other neurologic drugs, metal chelators, or antioxidants, may yield surprising effects in the management of cholinergic drugs in AD, including efficacy, tolerability, and safety. Memantine (7) is an FDA-approved NMDA receptor antagonist for the treatment of moderate to severe stages of AD. It modulates glutamate transmission and dopamine receptors, exhibiting certain efficacy in improving patients' cognitive function, daily living abilities, and behavior. Namzaric (8), fixed-dose combination memantine (7) extended-release/donepezil (4)) also provides another treatment option for patients with moderate to severe AD. These drugs primarily function by modulating neurotransmitter levels but cannot alter the course of the disease,409,411 which are instructive for designing new drugs. In 2017, a review proposed "disease modifying therapy for AD", which aims to intervene in the fundamental biological mechanisms to halt the disease's progression and provide enduring therapeutic benefits to patients.

Potential Therapeutic Drugs

The multifactorial nature of AD onset, coupled with the complex interactions among these factors, poses significant challenges to drug development. The limited efficacy of traditional medications, combined with the high failure rates in clinical drug development due to insufficient efficacy or adverse effects, has raised the bar for the development of the next generation of AD drugs. These drugs aim to furnish a repertoire of diverse and precise treatments tailored to individual patients and their distinct pathological processes. Progress in understanding the pathophysiological mechanisms, combined with advancements in drug development technologies, has paved the way for the discovery of novel drugs. Details of next-generation compounds in AD.

Selective inhibitors

Given the association of pan-inhibitors with cytotoxicity and adverse events, coupled with a deepening understanding of the physiological functions of pathological proteins, the development of selective inhibitors has advanced significantly. These inhibitors are capable of specifically targeting categories, subtypes, and structural domains, potentially providing more pronounced benefits in terms of efficacy, safety, and tolerability. Kadsuranin [(+)-2] and gomisin N [(−)-2], which are two stereoisomers of schisandrin B extracted from the fruits of S. chinensis, have been shown to effectively inhibit GSK-3β in an ATPcompetitive manner. Administering these compounds has been shown to effectively mitigate memory deficits and markedly reduce the expression of phosphorylated tau in the hippocampus in the APP/PS1 double-transgenic mice. Targeting less conserved substrate binding sites, as opposed to ATP binding sites, might offer advantages in terms of drug specificity, functional regulation, and safety. For example, compound 34 demonstrated these benefits. As the role of GSK-3α in promoting Aβ production and tau phosphorylation in AD models is recognized, selective inhibition of GSK-3α has emerged as a promising therapeutic strategy. The GSK-3α ATP-competitive inhibitor 35 could cross the BBB and significantly reduce tau phosphorylation at pThr231 in neonatal rat brains, potentially delaying early pathological progression in AD. It is noteworthy that simultaneous inhibition of both GSK-3α and GSK-3β could excessively activate the wnt/β-catenin pathway, leading to abnormal cell proliferation and other detrimental effects. Therefore, the ideal state for selective drugs is to ensure efficacy while providing a suitable therapeutic window for safety. For instance, the selective GSK3β inhibitor OCM51 (36) could achieve a beneficial balance between reducing tau phosphorylation and preventing overactivation of the β-catenin signaling pathway at appropriate doses. Additionally, leveraging the dynamic changes of targets may be a potential strategy for developing selective inhibitors. Given that overexpression of dualspecificity tyrosine phosphorylation-regulated kinase 1 A (DYRK1A) may influence the initial progression of AD through mechanisms including the hyperphosphorylation of pathologically relevant substrates such as tau, APP, PS1, regulation of axonal transport of APP, and participation in the selective splicing of tau prem RNA. the compound dp-FINDY (37) effectively targets the spatial dynamic changes in the ATP-binding site between the DYRK1A folding intermediate and the folded state, specifically acting on the folding intermediate. The development of selective inhibitors benefits the understanding of the roles played by different targets and their subtypes in AD, and it may also reduce the risk of side effects. Some adverse effects may originate from the off-target proteins. Differences in amino acids, explicit water molecules, spatial conformation and dynamics between the target and other proteins binding sites could serve as the basis for drug selectivity. However, in AD drug development, designing inhibitors with high selectivity poses significant challenges when faced with highly conserved or homologous binding pockets. The discovery of additional pockets on the target enzyme, target optimization (identifying substitutable targets), and the use of computational tools may offer new strategies. Nevertheless, the complexity and diversity of AD mechanisms suggest the difficulties of targeting specific targets and their limited impact on the disease progression.

Allosteric modulators

Allosteric modulators typically attach to regions distinct from the orthosteric site of receptors, inducing conformational changes to regulate the affinity and/or efficacy of orthosteric ligands, or to directly modulate receptor activity with positive, negative, or neutral effects. This precise tuning of receptor activity has revitalized the development of anti-γ-secretase drugs in the field of AD. Allosteric modulators of γ-secretase encourage the production of shorter, less toxic Aβ subtypes, and even potentially minimize effects on Notch and some other substrates. Some γsecretase modulators (GSMs) also exhibited promising safety outcomes in preclinical studies and clinical trials. Compared to orthosteric sites, allosteric sites often have lower conservation and greater diversity, providing new avenues for drug development targeting highly homologous subtypes, such as nAChR and mAChR. The α7 nAChR subtype presents a potential approach for treating AD due to its high expression in cognitive

functionrelated brain areas and interaction with Aβ. Selective positive allosteric modulators (PAMs) targeting the α7 nAChR subtype, such as compound 52, slowed the decline of episodic/working memory in amnesia mouse models. Unlike orthosteric agonists, 52 did not cause receptor desensitization even with repeated dosing, and is currently being evaluated in clinical trials for its efficacy and safety in mild to moderate AD patients. M1-mAChR positive allosteric modulators (M1-PAMs), such as BQCA (53) and PF06764427 (54), achieve subtype selectivity through allosteric effects but have significant agonistic activity that may lead to side effects like diarrhea.

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Covalent inhibitors

Covalent inhibitors, which form covalent bonds with their target proteins, rely on the specificity and stability of these interactions to exhibit superior potency, selectivity, and duration of action. This mechanism offers patients a convenient therapeutic option. Based on experiences in cancer treatment and other diseases, the development of AD covalent drugs also has a broad prospect. In cancer therapy, covalent inhibitors often target cysteine residues with acrylamide warheads. Based on this, which features an acrylamide warhead, can covalently bind to cysteine in GSK-3β. It significantly reduced the expression of APP and p-tau in the hippocampus of AD mice and improved spatial learning and memory abilities. A widely studied Ru (III) anticancer drug, KP1019, reveals a unique anti-Aβ strategy. Unlike conventional methods that inhibit Aβ production and aggregation, KP1019 counteracted Aβ toxicity to neuronal cell models by promoting the formation of soluble high-molecular-weight Aβ aggregates. This suggests that metal-based covalent inhibitors have promising potential in AD drug development. The electrophilic warheads and targeting residues of covalent inhibitors are continuously being developed. For example, the 6H8 fragment, obtained through NMR screening from the Maybridge library, may act as a covalent warhead targeting the pathological substrate APP of γ-secretase, thereby hindering Aβ production.

PROTACs

The ubiquitin-proteasome system (UPS) is one of the primary protein degradation pathways within the cell. However, in AD, the dysfunction of this clearance pathway becomes a significant contributor to the accumulation of pathological proteins. The PROTACs exploit the UPS system to precisely target specific proteins, improving the accuracy and speed of protein degradation. Various reviews have consolidated information on PROTACs with potential applications in AD. These PROTACs target tau protein, phosphokinase GSK-3β, HDACs, BET proteins, and transthyretin (TTR)-Aβ interaction, exhibiting characteristics such as low dosage requirements, high efficacy, and high target selectivity. As technology continues to advance, PROTACs undergo continuous refinement. For

example, the GSK-3 degrader PT-65, developed through click chemistry, exhibited a more prolonged effect on p-tau than its GSK-3 warhead (a GSK-3 inhibitor). This may help reduce dosing frequency. Additionally, phosTAC7 and tau2-8 ingeniously leverage the flexibility of PROTACs to create targeted dephosphorylation strategies. In summary, PROTACs represent a burgeoning technology in AD drug development, specifically targeting dysfunctional enzymes, misfolded proteins, and even PPI in AD through the rational utilization of the UPS clearance system. However, PROTACs are still facing challenges. Limitations include the restricted choices of E3 ligases, primarily CRBN and VHL, and the considerable molecular weight of compounds that cause poor BBB penetration. Notably, while PROTACs can alter the existing pathological phenotype of AD, they cannot reverse the damage that has already occurred, particularly in addressing the genetic mutations associated with FAD.

Targeting the PPI network

Protein-protein interactions (PPIs) are fundamental in maintaining cellular functions, while aberrant interactions between proteins are implicated in the pathogenesis of numerous diseases. For instance, AD is characterized by the misfolding and aggregation of Aβ and tau proteins, involving a variety of molecular mechanisms and complex networks of PPIs. Thus, disrupting these interactions may block some critical signaling pathways and potentially mitigate the pathological process of AD. Although large and flat PPI interfaces may be more conducive to peptide and protein drug targeting, small molecule inhibitors also play a role in some AD-related PPIs due to their unique advantages.

CONCLUSIONS AND PROSPECTS

AD is a progressive neurodegenerative disease characterized by declining memory and cognitive dysfunction. Pathological features such as Aβ plaques and NFTs in patients have been well documented. However, the existing hypothesis fails to fully elucidate the precise impact of these alterations on the onset and development of AD or the complex interactions among various pathological events. The focus on inflammatory responses and the immune system has led to speculation that certain pathogens such as Porphyromonas gingivalis, herpes simplex virus 1 (HSV1), and SARS-CoV-2 may play a role in AD, and the antimicrobial activity of Aβ may also partially supports the mechanism. Some animal studies suggested that Porphyromonas gingivalis could translocate to the brain, closely linked to the deposition of Aβ and tau and the occurrence of neuroinflammation. While some epidemiological data and preclinical studies suggest the association between HSV1 and AD, more research is needed to further validate and understand the relationship. Research of both HSV1-infected mice and AD mouse models has revealed the gene MAM domain containing 2 (MAMDC2) exhibits significant expression in microglia, which results in high levels of I-IFNs to enhance antiviral responses in HSV1-infected mice and neuroinflammation in the AD animal model. HSV1 may also impact Aβ pathology through mechanisms, such as continuous production and aggregation of Aβ within infected neurons via the activation of caspase 3,600 and altering γsecretase activity.601 Many COVID-19 patients diagnosed with some long or post-acute sequelae of COVID-19 such as brain atrophy and memory decline, greatly increasing the risk of AD. AD patients are also more susceptible to COVID-19, with higher risks of hospitalization and mortality in the patients with dementia and COVID-19. This suggests a correlation between the two diseases. From a genetic perspective, some genes such as APOE4 and oligoadenylate synthetase 1 (OAS1) play important roles in susceptibility to both COVID-19 and AD. APOE4 as a significant genetic risk factor for AD also interacts with angiotensin-converting enzyme 2 (ACE2) to hinder SARS-CoV-2 infection and influence inflammation levels. Some variants in the interferon-responsive gene OAS1 may lower its expression and potentially increase the likelihood of AD and severe COVID-19, through excessive release of pro-inflammatory signals in myeloid cells such as microglia and macrophages, further leading to cell death. SARS-CoV-2 affects key pathological changes, such as Aβ, tau, and neuroinflammation, promoting cognitive impairment. Interaction between the SARS-CoV-2 Spike S2 subunit and γsecretase could regulate γ-secretase cleavage of APP and increase Aβ production. SARS-CoV-2 may facilitate the intercellular spread of tau aggregates by

forming extracellular vesicles modified with spike S protein. Upon entry into the host cell, it may cause cytokine storms and immune dysregulation, disrupt the BBB, and reduce Aβ clearance, ultimately resulting in neuroinflammation and Aβ aggregation. Additionally, the upregulation of shared pathogenic kinases in COVID-19 and AD, such as epidermal growth factor receptors, vascular growth factor receptors, Bruton tyrosine kinase, spleen tyrosine kinase, c-ABL, and JAK/STAT, suggests potential interactions between immunological and neurological mechanisms.

The current approaches to addressing AD focus on three main aspects: prevention, early diagnosis, and treatment. Managing modifiable risk factors provides a pathway for AD prevention, which may help reducing cognitive decline and the risk of AD. In early diagnosis, various biomarkers of CSF, blood, urine, saliva, and retina, may contribute to comprehensively reflecting the AD pathological process, serving as potential auxiliary tools that are more convenient, cost-effective, or less invasive. Pharmacotherapy is broadly employed in AD treatment; however, the efficacy or safety of most investigational and clinical drugs is not ideal. Factors such as dose-dependent adverse reactions, the inability to penetrate the BBB and achieve effective therapeutic concentrations, and variations in patient sensitivity and metabolic capacity may all influence outcomes. Here, we elucidate the issue from the perspective of the AD nature and drug development technologies. Firstly, the nature of AD may affect the choice of medication. For instance, the deficiency or mutation in aldehyde dehydrogenase (ALDH2) may influence melatonin administration, which could potentially benefit AD patients experiencing cardiac dysfunction. A study found that in APP/PS1 mutant mice, the decrease in ALDH2 activity could lead to a cascade of downstream events, including disruption of mitochondrial integrity, accumulation of mitochondrial DNA in the cytoplasm, downregulation of the cGAS-STING-TBK1 signaling pathway, and inhibition of autophagy and mitophagy, ultimately resulting in cardiac disorders. Moreover, the beneficial effects of melatonin on mouse hearts, which depend on the regulation of ALDH2 activity, could not be assessed due to mutations or deficiencies in ALDH2. Secondly, appropriate drug development strategies provide the possibility of safe and effective drugs.

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HOW TO CITE: Peddawad Bhagyashri, Mhaske Payal, Murkute Pratiksha, Khambait Lalita, Emerging Therapeutic Strategies for Alzheimer's Disease: From Molecular Pathways to Novel Drug Development, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 11, 6044-6059. https://doi.org/10.5281/zenodo.24645986