

Alzheimer's disease: pathogenesis, diagnosis, and therapeutic strategies

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Abstract:

Presence of Alzheimer's disease (AD) is one of the main causes of progressive dementia. The pathophysiology of AD, a neurodegenerative disease, has been linked to intracellular neurofibrillary tangles composed of hyperphosphorylated τ -protein and extracellular aggregation of amyloid β ($A\beta$) plaques in the cortical and limbic regions of the human brain. Memory loss and increasing neurocognitive impairment are its hallmarks. Senile plaques are formed when $A\beta_{40}$ and $A\beta_{42}$ monomers are produced as a result of the aberrant processing of APP by β - and γ -secretases. These monomers then oligomerize and aggregate. Additionally, infectious infections such as HIV exacerbate the condition. Furthermore, microglial infiltration is triggered during disease pathogenesis by high quantities of $A\beta$ peptides in the central nervous system. When microglia come into contact with $A\beta$, they become activated, endocytose $A\beta$, and help to remove them through TREM2 surface receptors, all the while inducing an innate immune response to the aggregation. The current review covers the state of the art in AD therapies and diagnostics, including labeling and imaging techniques used as contrast agents for enhanced vision and sensing of the plaques. It also provides a full report on the causative elements leading to AD. The analysis highlights the critical need for nanotechnology as a successful therapeutic approach to boost medication bioavailability in the central nervous system.

Keywords: amyloid beta, amyloidogenesis, amyloid precursor proteins, β -secretases, tau phosphorylation

Introduction

The primary etiology of Alzheimer's disease (AD), a major protein conformational disease (PCD) with neurodegenerative symptoms, is abnormal protein processing and polymerization of usually soluble proteins [1, 2]. Soluble neuronal proteins can get misfolded as a result of aging, genetic mutation, or environmental influences. This can lead to aberrant conformations that accumulate and cause atypical neuronal functioning as well as loss [4]. Alois Alzheimer, a German neurologist, is credited with identifying AD as a neurodegenerative illness after studying Auguste Deter, a 51-year-old patient who had memory loss, language impairment, disorientation, and hallucinations. Plaques and tangles in the cerebral cortex were discovered during her autopsy, [5] which persuaded him that this was more than just ordinary dementia. Subsequent investigations of his findings demonstrated that dementia patients have neuritic amyloid β ($A\beta$) plaques [6]. Predisposition to the rare but powerful PS1 genetic mutation is thought to be the cause of the disease's early start [7]. Parkinson's disease, Creutzfeldt-Jakob disease, Huntington's disease, and Machado-Joseph disease are additional neurodegenerative diseases linked to aberrant protein conformations. These diseases stem from abnormalities in the α -synuclein, Cellular Prion protein (PrPc), Scrapie prion protein (PrPSc), Htt, and Ataxin3 proteins, respectively. It becomes crucial to address areas like AD mechanisms, pathogenesis, and diagnostics after learning the disease's causative factors and pathogenesis mechanism. Finally, it becomes important to figure out how to develop novel therapies to combat AD. Nanoparticle (NP)-based sensitive early-phase detection of AD biomarkers such as $A\beta$ and τ in patient cerebrospinal fluid (CSF) samples is one of the diagnostic and imaging approaches used. Additionally, aggregated $A\beta$ plaques can be seen using nanomaterials as contrast agents. It is critical to comprehend how NPs contribute to the drug's increased effectiveness and bioavailability through the blood-brain barrier (BBB) and into the central

nervous system (CNS). This study highlights the possible application of nanotechnology in therapies to prevent the advancement of AD, covers the present state of diagnostics and treatments, and provides a thorough understanding of the pathogenic route leading to full-blown AD.

AD pathogenesis

There is a lot of research being done to better understand AD pathophysiology and develop effective therapeutics. AD is a progressive neurodegenerative disease that is extremely complex [8]. It ranks among the main causes of dementia cases worldwide. Approximately 5.3 million Americans, 500,000 of whom have younger-onset AD and 5.1 million of whom are 65 years of age or older, suffer from AD in the US alone [9]. Extracellular aggregates of A β plaques and intracellular aggregations of neurofibrillary tangles (NFTs), which are made of hyperphosphorylated microtubule-associated τ , are described as histological features of AD. A β plaques begin to form in the brain's orbitofrontal, basal, and temporal neocortex areas before spreading to the hippocampus, diencephalon, amygdala, and basal ganglia. A β can also be detected in the cerebellar cortex, lower brain stem, and mesencephalon in severe situations. The locus coeruleus, transentorhinal, and entorhinal regions of the brain are the sites where τ -tangle development is initiated by this concentration of A β . It expands to the neocortex and hippocampal regions during the crucial stage [10]. The cause, pathophysiology, and factors linked to the progression of AD are the main topics of this review. A β and NFTs are thought to be the main players in the disease's evolution. Amyloid precursor protein (APP), an essential protein on the plasma membrane, is first alteredly cleaved by β -secretases (BACE1) and γ -secretases to form insoluble A β fibrils, which is the beginning of amyloid pathology. Subsequently, A β oligomerizes, diffuses into clefts in synapses, and tampers with synaptic transmission [11,12]. It then polymerizes into insoluble amyloid fibrils, which collect to form plaques. As a result of this polymerization, kinases are activated, which causes the microtubule-associated τ protein to become hyperphosphorylated and polymerize into insoluble NFTs. Microglia surrounding plaques are

recruited subsequent to the formation of plaques and tangles. This increases local inflammatory response and microglial activation while also increasing neurotoxicity.

Structure and function of APP

APP is a member of the same protein family as the amyloid precursor-like proteins (APLP1 and APLP2) found in mammals and the amyloid precursor protein-like (APPL) found in *Drosophila*. It is a transmembrane protein that is essential and has extracellular domains. When APP is sick, different enzymes cleave it differently, producing amyloidogenic fragments. There is still much to learn about APP's physiological roles. Research utilizing transiently transfected cell lines demonstrates that APP regulates neurite outgrowth and functioning, as well as cell survival, proliferation, and motility. These effects are linked to the release of soluble ectodomains that occur during normal APP cleavage [13, 14]. Studies showing neural defects in mice injected with APP RNAi [15] and increased cognitive performance and synaptic density following intracerebral injections of APP-ectodomain have demonstrated the relevance of APP [16]. Type 1 transmembrane glycoprotein, which is encoded by APP, can be cleaved through an amyloidogenic mechanism in a diseased condition or through a nonamyloidogenic pathway in a normal state [17]. Different polypeptides that may result from complicated proteolysis, glycosylation, phosphorylation, or alternative splicing are released by APP [18, 19]. Out of the 770 amino acids in APP, A β consists of 28 residues and 14 more residues from the transmembrane domain. The large soluble ectodomain APP α is released into the medium by α -secretase at the cleavage site, while the C-terminal fragment C83 remains in the membrane. γ -secretase then cleaves C83 at position 711, releasing the soluble P3 peptide. As an alternative, aberrant cleavage in a sick condition is caused by β -secretase, which releases shortened APP β , and C-terminal fragment C99, which is kept in the membrane and cleaves further to release insoluble A β peptides by γ -secretase. The APP intracellular domain is released into the cytoplasm upon γ -secretase's cleavage of both C83 and C99. This soluble domain then translocates to nuclei to facilitate further gene expression functions.

Amyloidogenic pathway

In the sick state, APP is cleaved differentially. A β is liberated from APP via consecutive cleavages by BACE-1, an intramembrane aspartyl protease composed of four proteins: presenilin, nicastrin, anterior pharynx-defective 1 (Aph1), and Psen2 complexed together [20]. BACE-1 is a membrane-spanning aspartyl protease with its active site located in lumen. This complex aids in the production of neurotoxic and insoluble A β fragments by γ -secretase. The first and rate-limiting step is β -secretase cleavage, which results in a cut at the N-terminus of A β . The protein's extracellular region is mostly removed, leaving only the C-terminal of APP [21], which is then further cleaved at the C-terminus of A β to create A β oligomers that subsequently polymerize to form aggregated plaques.

A β 40 and A β 42 are the two primary subtypes of A β polymers that directly contribute to the development of plaque and produce neurotoxicity. Compared to A β 42, which functions as a toxic building block of A β assembly and is less abundant, highly insoluble, severely neurotoxic, and more aggregation-prone, A β 40 is more plentiful and less neurotoxic. A β 40/A β 42 aggregation leads to ion channel blockage, disrupted calcium homeostasis, increased oxidative stress in the mitochondria, and impaired glucose regulation and energy metabolism, all of which worsen neuronal health and ultimately cause neuronal cell death.

Epigenetics of AD

The study of gene-gene interactions, genotype expression, and different biological processes that translate genotype expression into corresponding phenotypes is known as epigenetics [22]. Neuroepigenetics, the branch of epigenetics that studies neurological diseases, has progressed quite well and has been extensively researched in CNS-associated diseases, including pathologies and disorders related to learning, movement, behavior, and cognition [23, 24]. Understanding epigenetics is crucial to comprehending the extent to which environmental factors, paternal genes, dietary practices, traumatic experiences, stress, learning

difficulties, chemical or drug addiction exposure, and the ensuing structural disruptions, mutations, or alterations in DNA are influenced [25, 26]. Recent research has investigated the role of epigenetics in AD, one of the most complicated aging-related neurological disorders [27]. Aging, genetic abnormalities, nutritional and metabolic problems, exposure to environmental variables, and—most importantly—the involvement of social factors all play intricate roles in the onset and progression of AD [28]. It's likely that variables including obesity, diabetes, hypertension, and inflammatory illnesses, in addition to aging, affect AD and cause epigenetic changes or perhaps cause AD-like pathogenesis in children. It is plausible [29] and has been documented in several brain regions [30] that there are correlations between DNA-methylation patterns in the brain and aging. It is hypothesized that an understanding of DNA epigenetic mechanisms is crucial to comprehending aging and the complications associated with Alzheimer's disease patients, as these mechanisms play a part in memory formation and maintenance, much as a decrease in DNA methylation deteriorates neuronal plasticity and causes memory loss [31]. Histone alterations might be just as significant as DNA methylation. Histone acetylation in APP-PSEN1 double-mutant transgenic mice has been studied; associative learning deficit was linked to a decrease in H4K14 histone acetylation [32]. Histone deacetylase (HDAC) inhibitors also impact the aggregation and synthesis of A β in AD animals. Promising research has been done with their inhibitors, including vorinostat, valproic acid, and trichostatin A. Thus, in order to target the mechanisms and complexities associated with AD, it becomes crucial to comprehend the epigenetic mechanisms involved in aging [33].

Diagnostics for AD: labeling and imaging

Neuropsychological testing is the main basis for the current diagnosis of AD. Neuroimaging and the monitoring of established biomarkers, such as A β peptide concentrations (A β 1-42:A β 1-40 ratio) and total and hyperphosphorylated τ (Thr181 and Thr231) proteins in the CSF, are necessary for a clinical diagnosis of AD. With 18F-florbetapir (or alternatively 11C Pittsburgh compound B) positron emission tomography

(PET), amyloid oligomers and plaque accumulation can also be visualized; nevertheless, nonlinear connection between A β concentration in CSF and PET scans is still a cause for worry. But for many older patients, CSF sample is not always practical or well tolerated due to its rather intrusive nature. Clinically useful noninvasive imaging techniques include fludeoxyglucose PET, which provides information on brain metabolism. Indeed, different stages of Alzheimer's disease have been linked to altered brain metabolism, including hyper- and hypometabolism. Another useful noninvasive method for identifying functional problems is magnetic resonance imaging (MRI) at increasing field strength and resolution. Iron oxide nanoparticles (NPs) are used as contrast agents in magnetic resonance imaging (MRI) to detect and identify amyloid plaques. To enhance detection efficiency, the NPs can be tagged with fluorescent probes [34]. It is said that these iron oxide nanoparticles bond to the N terminal of A β , facilitating their imaging. Furthermore, it has been observed that using an external magnetic field, nonfluorescent or fluorescent rhodamine-tagged γ Fe₂O₃ NPs may selectively identify A β fibrils and extract them from solubilized A β [35, 36]. Polystyrene-block-poly (n-butyl cyanoacrylate) NPs containing thioflavin T to target A β have also been reported, in addition to iron NPs [37]. Using fluorescent semiconductor nanocrystals (quantum dots) for labeling and gold NPs as contrasting agents to explore structural stages in A β self-assembly, MRI has been employed [38, 39]. An ultrasensitive NP-based biobarcode system that uses oligonucleotide (DNA barcode)-modified AuNPs and magnetic microparticles functionalized with monoclonal/polyclonal antibodies has been used to detect soluble forms of A β from CSF [40]. Additionally, electrochemical sensing using click chemistry, which uses AuNPs and assembled monolayers to interact with A β peptide [41], and ultrasensitive electrical detection for A β 1-42 using scanning tunneling microscopy [42] have also been employed. The ability to diagnose AD has significantly increased thanks to recent conceptual and technological advancements. Following an AD diagnosis, the available therapeutic options are limited to disease-modifying therapies with comparatively low efficacy.

AD therapeutics

Misfolding of proteins in AD causes cellular processes to become distorted and results in neuronal death. A protein that has misfolded can lose its function or gain it in a harmful way. This could happen as a result of aberrant protein aggregation, which renders the protein unable to carry out its intended function and prevents it from being eliminated by the cellular environment, which can have detrimental biological effects. In order to reduce the toxicity brought on by aberrant proteins, there are ongoing AD investigations focused on blocking the synthesis of misfolding proteins as well as their aggregation and dissemination [43]. Since a wide range of neurodegenerative mechanisms underlie both early- and late-stage AD, most AD treatment strategies concentrate on lowering toxic forms of $A\beta$ and τ . After analysis, a number of medications have advanced to Phase I, II, and III clinical trials.

None of the current treatment targets (such as galantamine, donepezil, and rivastigmine) are believed to be causally linked to the development of AD; instead, they all appear secondary. Unfavorable medication pharmacokinetics and pharmacodynamics frequently lead to therapy failure. Inadequate drug physical chemistry (hydrophobicity, for example), unfavorable biological membrane absorption, unfavorable pharmacokinetic parameters (intense and plasma metabolism), unstable drug chemistry (oxidation, hydrolysis, or photolysis), and tissue toxicity (hepatotoxicity, neurotoxicity, or kidney toxicity) are all causes of pharmacotherapy failure. A number of therapy approaches have been put out and tried in an effort to remove $A\beta$. There are a number of medications used to treat $A\beta$ breakdown, but most of them that performed well in in vivo experiments failed in human clinical trials, thus new approaches are desperately needed. Many of the medications on the market have low brain bioavailability and lose effectiveness as they cross the blood-brain barrier. This calls for fresh research that delves into effective CNS-specific neuroprotective tactics. Because of their capacity for multifunctionalization, which allows them to imitate the physiological mechanisms of transport across

the blood-brain barrier, NPs are attractive candidates for this use. This crucial cell-based physical barrier shields the brain from potentially dangerous compounds in the bloodstream, but it also blocks the passage of 98% of neuropharmaceuticals and diagnostics currently on the market.

Conclusion

Alzheimer's disease (AD) remains one of the most complex and devastating neurodegenerative disorders, characterized by progressive cognitive decline and neuronal loss. The disease is primarily driven by the aberrant processing of amyloid precursor protein leading to amyloid- β plaque formation, along with tau hyperphosphorylation and neurofibrillary tangle development. These pathological events initiate synaptic dysfunction, neuroinflammation, mitochondrial impairment, and ultimately neuronal death. In addition to classical genetic and molecular mechanisms, emerging evidence highlights the significant role of epigenetic modifications and environmental factors in disease onset and progression. Current diagnostic strategies rely on neuropsychological evaluation, cerebrospinal fluid biomarkers, and advanced imaging techniques; however, early and noninvasive detection remains a major clinical challenge. Therapeutic options available today are largely symptomatic and fail to halt disease progression, mainly due to poor drug bioavailability and limited penetration across the blood-brain barrier. In this context, nanotechnology-based approaches offer promising solutions for improved diagnosis and targeted drug delivery to the central nervous system. Overall, a deeper understanding of AD pathogenesis combined with innovative diagnostic tools and advanced therapeutic strategies is essential for developing effective disease-modifying interventions and improving patient outcomes in the future.

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