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# Mechanisms of Alzheimer's Disease Pathogenesis and Prevention: The Brain, Neural Pathology, N-methyl-D-aspartate Receptors, Tau Protein and Other Risk Factors

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The characteristic features of Alzheimer's disease (AD) are the appearance of extracellular amyloid-beta (Aβ) plaques and neurofibrillary tangles in the intracellular environment, neuronal death and the loss of synapses, all of which contribute to cognitive decline in a progressive manner. A number of hypotheses have been advanced to explain AD. Abnormal tau phosphorylation may contribute to the formation of abnormal neurofibrillary structures. Many different structures are susceptible to AD, including the reticular formation, the nuclei in the brain stem (e.g., raphe nucleus), thalamus, hypothalamus, locus ceruleus, amygdala, substantia nigra, striatum, and claustrum. Excitotoxicity results from continuous, low-level activation of N-methyl-D-aspartate (NMDA) receptors. Premature synaptotoxicity, changes in neurotransmitter expression, neurophils loss, accumulation of amyloid β-protein deposits (amyloid/senile plaques), and neuronal loss and brain atrophy are all associated with stages of AD progression. Several recent studies have examined the relationship between Aβ and NMDA receptors. Aβ-induced spine loss is associated with a decrease in glutamate receptors and is dependent upon the calcium-dependent phosphatase calcineurin, which has also been linked to long-term depression.

KEY WORDS: Alzheimer's disease; Amyloid β; N-Methyl-D-Aspartate; Neurodegeneration; Tau; Genetically modified animals.

## INTRODUCTION

Dementia in the elderly population is most commonly caused by Alzheimer's disease (AD). The characteristic features of AD are the appearance of extracellular amyloid-β (Aβ) plaques and neurofibrillary tangles in the intracellular environment, neuronal death and the loss of synapses, all of which contribute to cognitive decline in a progressive manner. AD is a terminal and incurable disease.[1] The most AD important risk factor is age, with the prevalence of AD rising exponentially after 65 years of age.[2,3] The overall prevalence of AD is expected to double within 20 years as average lifespan increases in developing nations.

Neurodegenerative conditions associated with cognitive decline, including AD, are frequently associated with changes in the number and shape of dendritic spines prior to neuronal death.[4,5] Neurodegeneration in AD patients is characterized by changes in neurotransmitter expression, reduced neutrophil numbers, synaptotoxicity, accumulation of Aβ-protein deposits (amyloid/senile plaques), and large scale neuronal death and neural atrophy in the final phase of the disease.[6-10] A number of studies have suggested that Aβ accumulation may contribute to dendritic spine loss.[4,5] Deficits in memory and other cognitive functions in the initial stages of the disease are associated with changes in the hippocamus and the entorhinal cortex.[11] As many as 80% of the neurons in the hippocampus may die over the course of AD, and this progressive loss is manifest in the cognitive changes and other symptoms seen in AD patients.[9,11]

In this review article, we will summarize the anatomy, pathogenesis, neural mechanisms, the role of tau, N-methyl-D-aspartate (NMDA) receptors and brain-derived neurotrophic factor (BDNF), animal models, risk factors, and prevention of AD. These topics are of critical importance due to the ever-increasing prevalence of AD.

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## BRAIN AND ANATOMY

Memory functions are primarily mediated by the hippocampus and it's associated structures (e.g., subiculum, dentate gyrus, parasubiculum, presubiculum, and entorhinal cortex).[12-14] Accelerated hipocampal atrophy that is especially marked in the frontal-temporal horn and atrophy of the cerebral cortex is associated with AD. Early-phase neurocognitive symptoms of AD include memory and spatial learning deficits, both functions associated with the hippocampus.[15-19] Application of Aβ oligomers reduces the density of spines in organotypic hippocampal slice cultures and dissociated cultured neurons.[20-24] Significant atrophy of the entorhinal cortex occurs in AD and histological evaluation reveals neuronal degenerations and the presence of neurofibrillary tangles within layers II-IV. Neuritic plaques are frequently seen in layer III, while layers V and VI have relatively fewer neurofibrillary tangles compared to layers II and IV.[14,25,26] In addition, neuronal loss in layer II damages the perforant pathway or the projection of the entothinal cortex into the hippocampus. Efferent connections from the hippocampus to the cortex are inhibited by the progressive degeneration of neurons from layer IV.[14,27] Furthermore, damage to layer IV and layer II within the entorhinal cortex has been associated with pathological alterations in the closely related hippocampal formation. Prominent neuronal atrophy and neurofibrillary tangle deposition are seen in the CA1 region of the hippocampus.[14,28]

## NEURAL MECHANISMS

Cell types affected by AD include: locus ceruleus, the nuclei of the brain stem (e.g., raphe nucleus), reticular formation, amygdala, substantia nigra, striatum, hypothalamus, thalamus, and claustrum, and select regions of the cerebral cortex. The neuronal types affected vary by region according to the expression of neurotransmitters, neuromodulators, and neuropeptides. The degenerative process results in cerebral atrophy and neuron loss.[29-32] Disease pathobiology affects non-neuronal cells as well; oligodendroglia, astrocytes, blood vessels, microglia, and the choroid plexus all undergo degenerative processes. Transgenic mouse models of AD indicated that amypoid plaques occur in the vicinity of structural changes capable of altering brain function, including neurite dystrophy and spine loss.[5,33-36] Synaptic loss strongly correlates with cognitive deficits in AD. Synapse loss is likely a morphological reflection of the synaptic dysfunction that begins early in the disease.[33,37-40] Early structural studies of post-mortem brain tissues demonstrated that AD patients exhibited a reduced number of dendritic spines and reduced synapse density in the hippocampus and cortex relative to age-matched control brain tissues. There was a direct correlation between increased dendritic spine loss and worsening mental status. The progressive atrophy of dendritic spines is therefore proportional to AD pathogenesis and may represent accurate indicator of advancing disease.[5,41]

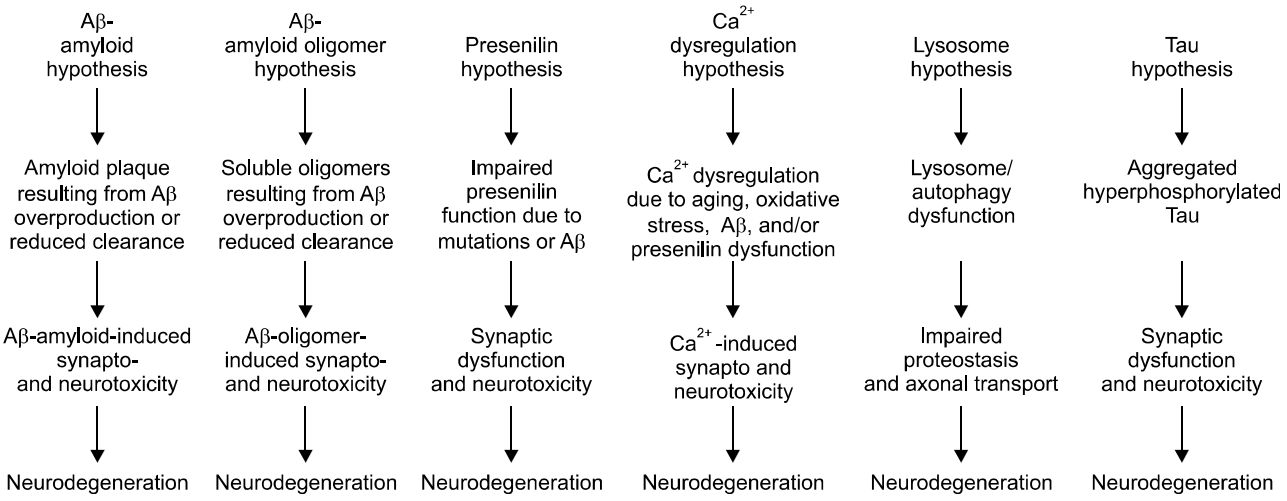


**Fig. 1.** Pathogenic hypotheses for synaptic and neuronal toxicity in Alzheimer's disease.

## PATHOGENESIS OF ALZHEIMER'S DISEASE

A number of hypotheses have been proposed that may explain AD pathogenesis: (a) the Aβ-amyloid hypothesis, (b) the Aβ-amyloid oligomer hypothesis, (c) the presenilin hypothesis, (d) the $Ca^{2+}$ dysregulation hypothesis, (e) the lysosome hypothesis, and (f) the tau hypothesis (Fig. 1). Although the amyloid hypothesis is the best-developed hypothesis,[42,43] multiple reports have suggested a weak correlation between Aβ deposition and neuronal atrophy and cognitive impairment.[43,44]

Aβ is the most widely studied component of AD pathogenesis. The isolation and partial sequencing of the meningovascular Aβ by George Glenner and Caine Wong in 1984 was a turning point for modern research of the fundamental mechanisms of AD.[45] Multiple forms of Aβ are derived by proteolytic cleavage from the type I cell-surface protein amyloid precursor protein (APP). The amyloid hypothesis broadly posits that excessive amounts of Aβ peptide in the brain (particularly Aβ42) are responsible for AD-related pathology, including amyloid plaques, neurofibrillary tangles, synapse loss, and eventual neuronal cell death.[2,3,46,47]

Imaging of amyloid plaques reveals the rapid formation of plaque structures over a 24 hour time period; dystrophic swelling of adjacent dendrites begins to appear within one week.[48,49] Instability of spines in the vicinity of Aβ plaques reflects dynamically dysfunctional plasticity in neuronal structures. These processes enhance functional deficit in the regions surrounding plaques.[48]

## ALZHEIMER'S DISEASE AND NMDA RECEPTORS

Glutamate is the principal excitatory neurotransmitter of the Central Nervous System (CNS). Glutamate mediates neuronal plasticity, neural transmission, memory processes, and learning.[50] The pathogenesis of AD is strongly associated with alterations in glutamate signaling and the tissues affected by AD contain high densities of glumatergic neurons.[9,51-56] Early degeneration occurs to the neocortex pyramidal neurons of layers V and III[57,58] and to the glutamate-innervated cortical and hippocampal neurons.[59] 'Excitotoxicity' occurs as a result of the chronic, moderate activation of NMDA receptors, leading to neurodegeneration.[9,60-63] The excitotoxicity hypothesis is supported by clinical evidence indicating that the NMDA receptor antagonist memantine slows AD progression.[64] Prolonged $Ca^{2+}$ elevation suppresses synaptic function, leading to subsequent synaptotoxicity and eventually atrophy; these events correlate with the loss of learning and memory functions in AD.[56,64,65] Multiple neurotrophic factors have been demonstrated to enhance defense against excitotoxicity. Fibroblast growth factor treatment alters expression of NMDA receptors in cultured cortical and hippocampal neurons, protecting against glutamate toxicity.[66]

NMDA receptors mediate synaptic plasticity, critical for memory and learning functions, through long-term potentiation (LTP).[67-69] Synaptic plasticity is an essential component of memory and learning.[5,70] LTP of synaptic transmission and permanently altered expression of post-synaptic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors occurs as a result of high levels of synaptic activity and open NMDA receptors.[71] However, mild synaptic stimulation elicits long-term depression (LTD) in active NMDA receptors.[5,72] Several recent studies have examined the relationship between Aβ and NMDA.[73] Aβ-induced spine loss is associated with a decrease in glutamate receptors, also required for LTD, in a calcineurin-dependent manner.[3,20,74-76] It is widely believed that the synaptic dysfunction and synapse loss contribute to the cognitive deficits of patients with AD.

There are a variety of potential links between Aβ and the NMDA receptor: 1) NMDA receptor may bind Aβ directly or through indirect interactions; 2) NMDA receptors may mediate Aβ activity relative to plasticity and/or synaptic transmission; 3) NMDA may be a downstream target of Aβ, meaning that Aβ mediates the function of NMDA receptors; 4) NMDA signaling may influence the assembly of Aβ plaques (Fig. 2).

## TAU PROTEIN

The accumulation of the protein tau within the brain tissue of AD patients was first described in 1986.[77,78] Tau phosphorylation was also proposed as a potential contributor to the formation of neurofibrillary tangles in AD.[78-80] In patients with AD, hyperphosphorylation of certain amino acids in tau proteins causes the proteins to dissociate from the microtubules, disturbing the transport structure and resulting in starvation of neurons and, ultimately, cell death. Hyperphosphorylated tau thus has an important role in intracellular neurofibrillary changes and the pathogenesis of AD and related tauopathies.[81,82]

CNS dendrites primarily express the axonal protein tau.[83] Tau mediates transfer of Fyn, a Src kinase, to the dendritic compartment; Fyn subsequently phosphorylates

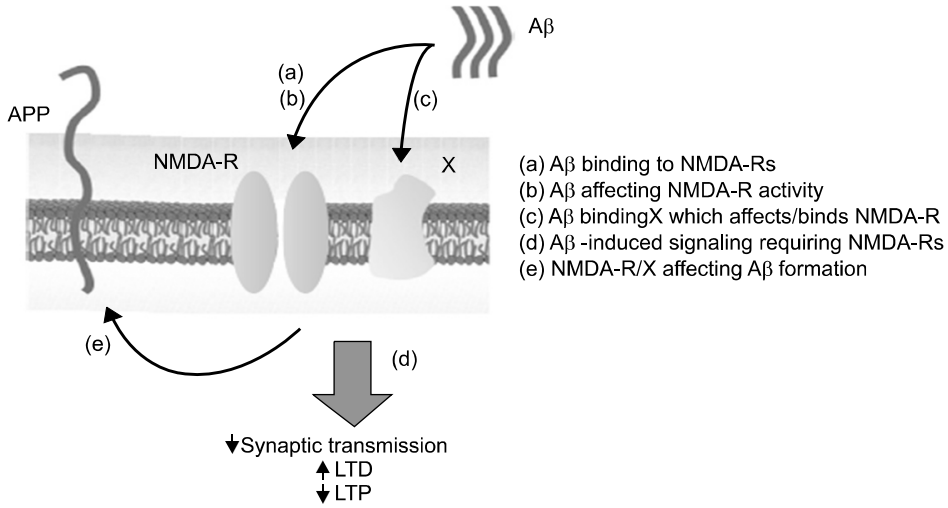


**Fig. 2.** Several potential roles for N-methyl-D-aspartate receptors (NMDA-Rs) in the amyloid-β (Aβ) cascade are depicted.
APP, amyloid precursor protein; LTD, long-term depression; LTP, long-term potentiation.

NMDA, facilitating an interaction with the post-synaptic density protein 95 (PSD95). In studies involving APP transgenic ($APP^{tg}$) APP23 mice, the PSD95 complex exerts toxic effects in concert with Aβ, resulting in as evidenced by marked functional deficits in memory, increased excitotoxicity, and death.[84] Reductions in fast axonal transport and microtubule density tau transgenic mice are associated with amyotrophy, axonopathy, and motor deficits.[84-86]

## BRAIN-DERIVED NEUROTROPHIC FACTOR AND ALZHEIMER'S DISEASE

BDNF, a growth factor included within the neurotrophin family, is a critical mediator of neuronal survival, synaptic plasticity, and cellular differentiation. In addition to these well-established cell survival functions, BDNF contributes to cognitive activity learning, behavior, and memory.[87,88] Low expression of BDNF mRNA in the nucleus basalis of Meynert, the neocortex, and the hippocampus has been reported in postmortem samples taken from AD patients.[89-92] Immediate, transient hippocampal elevation of BDNF mRNA levels occurs in mice during the execution of passive avoidance tests, hippocampus-dependent learning in the Morris water maze and contextual fear tests. Anti-BDNF antibodies induce impaired memory in mice during the passive avoidance and water maze tests.[93-95] Impaired LTP of the hippocampus occurs in mice deficient in neuronal BDNF; LTP can be restored in these animals following administration of BDNF. [96]

Cognitive decline occurs as the result of acetylcholine inhibition brought on by atrophy of cholinergic neurons in the forebrain of AD patients. BDNF enhances differentiation and survival of cholinergic neurons in the basal forebrain. Importantly BDNF induces the secretion of acetylcholine in basal forebrain neurons; acetylcholine is deficient in AD.[97,98] Cumulatively, preclinical observations have suggested that deficient BDNF synthesis contributes to neuronal dysfunction in AD.

## ANIMAL MODELS AND BEHAVIOR

Memory and learning are dependent upon alterations in synaptic transmission within the hippocampus and other areas of the brain. Transgenic animals that over-express Aβ accurately model familial-type AD and may contribute to increased understanding of the pathogenesis of cognitive and memory deficits.[5,99] Synaptic function and plasticity have been extensively studied in transgenic APP and APP/PS mice, with a focus on the dentate gyrus and CA1 subfields of the hippocampus. AD transgenic mice show abnormal synaptic transmission and impaired LTP, often well in advance of plaque formation.[3,100-102] Memory and learning deficits may occur within 3 months in mouse models, suggesting that soluble Aβ contributes to AD pathogenesis.[103,104] Alternate studies report later onset of symptoms at more advanced ages, implicating insoluble Aβ plaques.[100,104-109] The specific structure of Aβ that is responsible for cognitive deficits has been the subject of great debate. Amygdala-dependent learning is strongly inhibited with increasing age in Tg2576 mice models, suggesting that the amygdala is susceptible to Aβ toxcicity.[35,110,111]

## RISK FACTORS

Several risk factors of AD development have been reported, including psychosocial, genetic, and vascular parameters. AD may be classified as early (< 65 years) and late (60 to 65 years) onset disease. Late-onset AD is associated with strong genetic heritability, perhaps as high as 58-79%. Autosomal dominant mutations in the genes for presenilin 1 and 2 and APP are found in earl-onset, familial disease. Vascular risk factors (e.g., obesity, tobacco use, and blood cholesterol) and vascular diseases (e.g., diabetes mellitus, hypertension, and stroke) dare linked to an elevated risk of AD. Psychosocial factors such as low educational level, lack of social engagement, and poor social networking have also been associated with increased risk of AD.[1,112,113]

## COGNITIVE RESERVE AND PREVENTION

The quantitative function known as brain reserve has wide ranging biological implications for the pathogenesis of AD. For example, environmental stimuli trigger upregulation of BDNF and neurogenesis,[114-116] encouraging neural plasticity.[116,117] Cognitive and brain reserves, enhance our understanding of the differences in the clinical pathology of the brains of AD patients.[114,116] A number of studies have evaluated the association between leisure activities and AD incidence.[114] Engagement in intellectual activities (e.g., games, reading, or coursework) or social activities (e.g., maintaining close relationships with friends and relatives) was assessed in a large cohort of elderly New Yorkers who had not been diagnosed with AD; individuals engaged in numerous leisure activities had a dramatically reduced risk of developing AD during follow-up evaluation.[118,119]

## CONCLUSIONS

The principle aim this review article was to discuss the neuronal impairments associated with AD. A variety of interesting theories are emerging, including different perspectives on hypotheses such as the Aβ cascade, $Ca^{2+}$ dysregulation, tau hyperphosphorylation, and lysosome hypotheses. Various hypotheses related to AD play key roles in developing remedies and treatments. The use of animal models can shed light on research. The available evidence indicates that glutamatergic system, including NMDA receptors, contributes significantly to neuronal atrophy and synaptic dysfunction triggered by Aβ. Results have demonstrated low brain BDNF mRNA expression in patients with AD, including the hippocampus, which is responsible for learning and memory.

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