

Advances in Our Understanding of the Pathophysiology of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most common age-related dementia, currently affecting more than 5 million patients in the US alone, and is characterized by the presence of both extracellular plaques and intraneuronal tangles in the brain of a patient with dementia. Alois Alzheimer first described the pathology associated with the disease over 100 years ago, and during the past three decades our understanding of the disease and of potential ways to treat it has increased tremendously. In this article we describe our current understanding of both the pathophysiology of Alzheimer's disease and current and future therapeutic interventions, including symptomatic relief, disease modification, and the reversal of synaptic and neuronal loss.

Keywords

Alzheimer's disease (AD), therapeutics, pathology, amyloid-beta peptide, plaques, neurofibrillary tangles

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Alzheimer's disease (AD) is a neurodegenerative age-related progressive disease and the most common cause of dementia in the elderly.¹ Current estimates hold that there are upwards of 5 million people with AD in the US.² This number is expected to almost triple over the next few decades, and the worldwide incidence of AD will reach even more staggering proportions.² As the prevalence of AD grows, the accompanying economic and psychosocial costs related to acute hospitalizations, nursing home care, and care-giver stress will also escalate. Therefore, it is not surprising that efforts to understand the pathophysiology of AD and thereby derive effective treatments for this devastating disease have never been greater.

Over the last few decades a great deal of information has been learned about the underlying cellular and molecular pathology of AD. Since the early 1900s it has been recognized that the major pathologic hallmarks of AD are senile or neuritic plaques and neurofibrillary tangles, composed primarily of amyloid-beta (A β) peptide and hyperphosphorylated tau protein, respectively.³ The pathologic consequences of these lesions are synaptic dysfunction, neuronal loss, and gross cerebral atrophy.⁴

Several other AD-related pathologies have been identified, including inflammation and microvascular deposition of A β (also known as amyloid angiopathy).⁴ These pathologic features are the targets of substantial drug development efforts that are aimed primarily at preventing the deposition of A β and/or abnormally phosphorylated tau, as described below.

A β Pathology

For at least two decades the primary focus of AD pathophysiology has been on the extracellular plaques containing a core of A β peptide that is 40–42 amino acids in length. Over the years a series of elegant studies have shown that the A β peptide is cleaved from a larger precursor molecule, the amyloid precursor protein (APP) (see *Figure 1*).⁵

Under normal conditions, cleavage of APP occurs in such a manner that formation of pathogenic A β is avoided. This pathway is the so-called non-amyloidogenic pathway resulting in soluble APP α (sAPP α). However, under pathologic conditions sequential cleavage of APP by β -secretase (also known as β -amyloid precursor protein site cleaving enzyme [BACE]) and γ -secretase enzymes results in A β formation.^{3,5} In its fibrillar form A β has a strong tendency to aggregate, hence the formation of A β -containing plaques that are toxic to surrounding structures, including neurons. While other APP cleavage products such as amyloid precursor protein intracellular domain (AICD) may be neurotoxic, experimental evidence supports the idea that A β plays a more predominant role in the pathophysiology of AD.⁵

A good deal of the evidence supporting the importance of A β in the pathophysiology of AD comes from genetic studies.⁶ While the majority of AD cases are sporadic, a small subset of cases are familial and occur in younger individuals with an autosomal dominant pattern of inheritance. In fact, familial AD (FAD) is now known to be caused by specific mutations in one of three genes: APP, presenilin 1 (PS1), or

presenilin 2 (*PS2*).^{6,7} Importantly, mutations in the *APP*, *PS1*, or *PS2* genes promote the production of A β peptides. In addition, an extra copy of the *APP* gene in trisomy 21 is likely responsible for the development of AD pathology in Down syndrome.⁸ Indirect evidence for the relevance of A β comes from studies of apolipoprotein E (*ApoE*). The presence of the ϵ 4 allele of the *ApoE* gene confers increased risk for the development of AD.⁹ While the link between *ApoE* and AD is not well understood, the presence of *ApoE* ϵ 4 also contributes to an increased deposition of A β in the brain.

Until recently it was thought that the major pathogenic form of A β was as insoluble fibrils that are deposited in the extracellular space as amyloid plaques.⁵ However, recent work has implicated soluble A β oligomers in AD pathophysiology.¹⁰ Soluble A β is neurotoxic and has been correlated with cognitive decline in AD.⁴ However, the relative importance of soluble versus insoluble A β , and the role of recently discovered intraneuronal A β in the pathophysiology of AD remain unclear.⁴

Tau Pathology

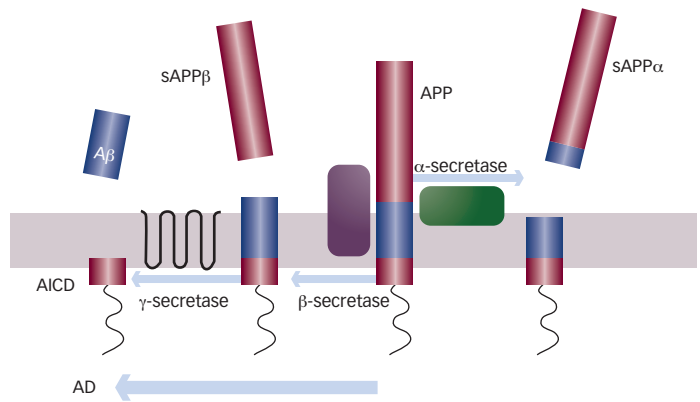
In addition to deposition of A β in the form of senile plaques, the other major pathologic hallmark of AD is neurofibrillary tangles, which are composed of hyperphosphorylated tau.³ Normally found in microtubules, tau protein plays an important role in microtubule stabilization.¹¹ It follows that tau indirectly regulates synaptic structure and function, which to a large extent are dependent on the integrity of microtubules. Evidence has shown that hyperphosphorylated tau dissociates from the microtubular network and forms intraneuronal aggregates that are neurotoxic.¹¹ Many species of phosphorylated tau have been identified, and several have been associated with AD. Specific tau kinases such as cyclin-dependent protein kinase 5 (*cdk5*) and glycogen synthase kinase-3 β (*GSK3 β*) likely play an important role in tau hyperphosphorylation.¹² However, the mechanisms responsible for triggering tau hyperphosphorylation are not well understood.

Relationship Between A β and Tau in Alzheimer's Disease

Although a great deal is known about the molecular pathology of AD, the functional relationship, if any, between the major pathologic hallmarks remains unknown. By the time AD is diagnosed with certainty at autopsy, both plaques and tangles are present in abundance. One approach to deciphering the relationship between A β and tau is through the use of transgenic mice. In particular, in triple transgenic mice that harbor mutations in *APP*, *PS1*, and tau, A β deposition in plaques precedes the appearance of neurofibrillary tangles.¹³ Whether a similar relationship holds for humans remains to be determined.

The relevance of deposition of A β and abnormal tau in the pathophysiology of AD has also been called into question. Accordingly, *post mortem* studies have shown that AD pathology may be present in the brain without clinical dementia.¹⁴ Explaining this paradox may significantly enhance the understanding of AD pathophysiology. New imaging modalities such as the use of the Pittsburgh compound B (*PIB*) to visualize A β *ante mortem* will help to clarify the role of A β in the process leading to cognitive impairment in AD.

Figure 1: Amyloid Precursor Protein Processing



Amyloid precursor protein (*APP*) may be processed by α -secretase, generating *SAPP α* and precluding *A β* generation. Alternatively, sequential cleavage by β -secretase followed by the γ -secretase complex results in *A β* generation. The *APP* intracellular domain (*AICD*), a byproduct of *A β* formation, is a nuclear signaling fragment.

Other Potential Processes Contributing to Alzheimer's Disease Pathophysiology

In addition to the major pathologic features discussed above, several other intracellular processes may contribute to AD pathogenesis. As noted previously, inflammatory changes in the form of microglial infiltrates have been demonstrated in the AD brain.¹⁵ Anti-inflammatory drugs have shown promise in animal models and are currently being investigated for efficacy in clinical trials.

Other processes for which there is experimental evidence supporting a role in AD pathogenesis are mitochondrial dysfunction and oxidative stress.^{16,17} In addition to AD, oxidative stress and mitochondrial dysfunction can be demonstrated in many other neurodegenerative diseases. Further studies will be necessary to establish causative roles for these processes in AD pathophysiology.

Current and Future Therapeutics for Alzheimer's Disease

Given the complexity of pathogenesis in the AD brain and the multiple layers of pathology that exist, it is not surprising that effective therapies to treat or prevent the disease have proved elusive. AD is an age-related disease, suggesting that possibilities exist to prevent the occurrence of the disorder during the aging process. AD is characterized by extensive neuronal and synaptic loss, which is thought to occur as a consequence of the accumulation of synaptotoxic A β peptides and hyperphosphorylated tau tangles, and underlies the memory loss associated with the disease. As AD is ultimately characterized by neuronal and synaptic loss, treatment will fall into three main categories: symptomatic relief, neuronal/synaptic loss reversal, and disease modification.

Symptomatic relief agents compensate for some of the cognitive decline caused by the disease but do nothing to address the underlying disease progression of accumulation of pathologies and subsequent synaptic and neuronal loss. As such, they provide temporary relief against the disease but ultimately become overwhelmed by the underlying pathology. Symptomatic relief therapies have been identified and are currently

prescribed as acetylcholine esterase inhibitors¹⁸ and a partial N-methyl D-aspartate (NMDA)-receptor antagonist known as memantine.¹⁹

Other potential symptomatic relief agents are now being developed, including histone-deacetylase inhibitors,^{20,21} $\alpha 7$ nicotinic receptor agonists,²² 5HT-6 receptor antagonists,²³ H₃ receptor antagonists,²⁴ and phosphodiesterase inhibitors.^{25,26}

Less research is being undertaken in trying to reverse the synaptic neuronal loss, perhaps due to a lack of animal models that show neuronal loss, but some progress is being made with stem cell implantation²⁷ and neurotrophins.²⁸ Both of these approaches appear to promote synaptogenesis and recover learning and memory deficits in numerous transgenic mouse models,²⁷⁻²⁹ including a novel model of hippocampal neuronal loss³⁰ as well as nerve growth factor (NGF) in humans.³¹ However, stem cell injections require surgery, and the vast area of the human brain affected by AD pathology makes stem cell therapy an unlikely treatment for AD, not to mention the logistic problems associated with potential stem cell rejection by the patient. As neural stem cells appear to promote recovery and synaptogenesis in transgenic mouse brains through the secretion of neurotrophins such as brain-derived neurotrophic factor (BDNF),²⁷ therapies that augment these neurotrophins may offer a more practical approach.

Disease modification through the inhibition of A β generation is the ultimate goal of AD therapeutics research, as prevention of the generation of A β is thought to be able to prevent the occurrence of AD. A β is sequentially cleaved from its parent protein APP, first by BACE 99 amino acids from the C-terminal of APP and then by the γ -secretase complex, of which presenilin forms the catalytic core that liberates A β from the membrane most commonly as a 40 or 42 amino acid peptide. Inhibition of either of these APP cleavages prevents A β generation. However, despite more than 10 years of compound screening, no effective inhibitor has been found that is bioactive in the brain but also safe. Highly potent γ -secretase inhibitors have been developed, but have been shown to be toxic to neurons³² as well as to potentially promote skin cancer³³ due to the extremely large list of substrates for the γ -secretase complex.³⁴ γ -secretase modulators have also been described that alter the way the complex cleaves APP to generate shorter, less toxic A β peptides and hence avoid the side effects associated with inhibition of the γ -secretase complex. However, these current modulators have low efficacy and have since failed in clinical trials.³⁵ Several companies are currently testing γ -secretase inhibitors in the clinic, and it is hoped that these new-generation inhibitors will have more specificity for APP and hence fewer side effects.

BACE is one of the primary targets for blocking generation of A β , and BACE inhibitors have also been developed.³⁶ BACE has no other known function in the adult brain, and BACE knockout mice are perfectly viable with few obvious deficits.³⁷ However, the large binding pocket of BACE combined with its membrane location have proved a challenge in designing effective inhibitors that can cross the blood-brain barrier in sufficient concentrations to be useful, and, to date, no effective compounds have been fully developed.

An alternate approach to prevent A β generation is to stimulate the cleavage of APP at different sites, which then preclude it from becoming a substrate for BACE. These pathways are known as non-amyloidogenic and, to date, a single non-amyloidogenic pathway has been described in detail whereby APP is cleaved by an α -secretase. In fact, the vast majority of APP molecules are cleaved by the α -secretase processing pathway rather than by BACE. Several α -secretases have been identified that cleave APP 83 amino acids from the C-terminal.³⁸ This cut exists within the A β sequence and thus precludes A β generation. It is possible to stimulate further α -secretase cleavage of APP using phorbol esters or M1 agonists,³⁹ leading to reductions in pathology in mouse models of the disease. Central nervous system (CNS) permeable M1 agonists as well as forms of retinoids that promote α -secretase processing of APP have been developed that could potentially be moved into the clinic.⁴⁰⁻⁴²

Alternatively, rather than preventing the production of A β in the first place, it has been established that A β can be cleared from the brain via immunotherapy, aggregation blockers (i.e. plaque busters), or via modulation of the ApoE system. The most developed of these, and for that matter of any disease-modifying strategy, is immunotherapy.⁴³ It was first demonstrated in 1999 in an APP-overexpressing transgenic mouse that active immunization with A β led to robust clearance of plaques in the brain.⁴⁴ Since then, immunotherapy has been widely studied in mouse models of the disease, with both passive and active immunization proving effective.⁴⁵

Furthermore, it has been shown that removal of A β via immunotherapy also leads to the removal of tau pathologies in transgenic mice.⁴⁶ However, results of clinical trials have thus far been mixed, with meningoencephalitis occurring in a number of patients and no robust improvements in cognition.⁴⁷ Despite analyses showing statistically significant reductions in plaque load,⁴⁸ the lack of effects on cognition may be because immunotherapy does nothing to address the existing loss of both synapses and neurons. Hence, immunotherapy (and any A β -targeting strategy) may prove to be a powerful way to prevent the occurrence and progression of the disease, rather than a way to reverse the disease.

Other disease-modifying approaches available include targeting the hyperphosphorylated-tau-laden tangles with specific kinase inhibitors, strengthening the microtubule network that breaks down as a result of tau hyperphosphorylation, or directly breaking up tau aggregates with compounds such as methylene blue.⁴⁹ In addition, it may be possible to protect neurons and synapses from the effects of either the A β peptide or hyperphosphorylated tau, such that synaptic and neuronal loss does not occur even in the presence of plaques and tangles. For example, it is known that many cognitively normal people have plaques and tangles in their brains,¹⁴ which could be a form of pre-symptomatic AD, or these people may harbor some innate protection against these pathologies, such as a muted inflammatory response.⁵⁰

Such therapies will likely target either the inflammatory system, as chronic elevated inflammation can lead to neurodegeneration, or neuronal calcium signaling, as increased localized calcium levels could lead to both synaptic and neuronal degeneration and have been

measured in transgenic mouse models of the disease.⁵¹ As a partial NMDA receptor antagonist, memantine may protect against synaptic toxicity in AD and confer relief against the disease through a reduction in synaptic calcium levels.⁵²

Conclusions

It is becoming increasingly apparent that treatments for AD must be administered as early in the disease process as possible in order to be effective. Unfortunately, until pre-clinical biomarkers for AD are discovered and developed, this remains a difficult feat. It is also unlikely that such a complex disease will be treated or prevented with a single therapy. More likely, combinations of treatments will prove most effective either through additive effects, for example by reducing A β generation, or through combining disease modification with symptomatic relief and perhaps neurotrophin therapies. ■



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