Published in final edited form as:

J Mol Med (Berl). 2010 April ; 88(4): 331–338. doi:10.1007/s00109-009-0568-7.

β-amyloid oligomers and cellular prion protein in Alzheimer's disease

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Abstract

Prefibrillar oligomers of the β-amyloid peptide (Aβ) are recognized as potential mediators of Alzheimer's disease (AD) pathophysiology. Deficits in synaptic function, neurotoxicity, and the progression of AD have all been linked to the oligomeric Aβ assemblies rather than to Aβ monomers or to amyloid plaques. However, the molecular sites of Aβ oligomer action have remained largely unknown. Recently, the cellular prion protein (PrP^C) has been shown to act as a functional receptor for Aβ oligomers in brain slices. Because PrP^C serves as the substrate for Creutzfeldt–Jakob Disease (CJD), these data suggest mechanistic similarities between the two neurodegenerative diseases. Here, we review the importance of Aβ oligomers in AD, commonalities between AD and CJD, and the newly emergent role of PrP^C as a receptor for Aβ oligomers.

Keywords

Alzheimer's disease; Amyloid; Prion; Receptor; Neurodegeneration

Introduction

Worldwide, 35 million individuals suffer dementia and a majority of cases are due to Alzheimer's disease (AD) [1]. As first described in 1907 [2], the brain pathology of AD entails large extracellular Aβ peptide aggregates or “plaques,” plus intraneuronal “tangles” of hyperphosphorylated and polymerized tau protein. The histological findings are associated with neurodegeneration and cognitive decline, leading eventually to death.

Recent work has begun to reveal the mechanisms underlying this literally age-old affliction. Pathological, genetic, biochemical, and pharmacological lines of evidence all support the hypothesis that the Aβ peptide and in particular, the longer 42 aa residue form (Aβ₄₂), plays a causative role in AD. Both Aβ₄₀ and Aβ₄₂ are derived from the amyloid precursor protein (APP) by proteolytic processing involving α-, β-, and γ-secretases, but the Aβ₄₂ peptide is more prone to assemble into oligomeric and polymeric states than Aβ₄₀. The amyloid plaques of AD are comprised largely of fibrillary Aβ forms rich in β-pleated sheet. Human mutations in APP or the γ-secretase components, presenilin (PSen) 1, or 2 alter the production or fibrilization of Aβ₄₂ and cause early onset AD with highly penetrant, usually dominant inheritance. Transgenic expression in mice of the disease-causing mutant forms of the APP gene produces the deposition of Aβ plaque and progressive spatial memory defects

[3] (Fig. 1). Disease-causing mutant PSEN1 genes accelerate these phenotypes in transgenic mice. While APP mutations produce both plaques and tangles in human, they produce only plaques in mice for still unclear reasons. In support of a central role for A β , immunization against A β peptide reverses memory deficits in the mouse models [4,5]. The central role of A β in human AD is being explored by immunological methods. While such studies remain inconclusive, they have provided some caution regarding a simple correlation of A β plaque load with disease. It has been observed that among AD patients actively immunized with A β , some individuals had few plaques but severe end-stage dementia before death [6].

Oligomeric A β as the primary effector of AD

It is not immediately obvious which form of A β might interact with neuronal populations to cause disease. Monomeric A β peptide is present in both health and disease, arguing against a causative role. The insoluble A β plaques that characterize AD sequester aggregates of peptide in a β -pleated sheet conformation. The β -sheet conformation forms stable fibrillary structures that can be dispersed into aqueous solution only with nonphysiological denaturing reagents, such as formic acid. The insolubility limits direct exposure of aggregated plaque A β to responsive cells.

As opposed to the case for A β monomer or fibril, there is growing evidence that soluble oligomeric or prefibrillary intermediate species of A β peptide are responsible for neuronal dysfunction and degeneration. Oligomeric A β species have been linked to disease by both correlation and functional studies. In mouse models and in human disease, the correlation between the level of A β oligomers and functional impairment is stronger than that for either A β plaque deposition or total A β monomer concentration [7,8]. In functional studies, A β oligomers are reported to suppress synaptic plasticity to induce dendritic spine retraction and to impair memory function [7–16]. The A β ₄₂ peptide has a greater propensity to create higher order structure than does the A β ₄₀ peptide [17], and in a mixture of synthetic A β ₄₂ and A β ₄₀, A β ₄₀ inhibits A β ₄₂ oligomerization into putatively toxic dodecamers [18] consistent with the ability of specific human AD-causing mutations to increase the A β ₄₂:A β ₄₀ ratio [3].

Different A β oligomer species

A recent biophysical analysis of the early stages of A β ₄₀ and A β ₄₂ oligomerization using ion mobility coupled with mass spectrometry [17] characterized distinct pathways prior to fibril formation. Tetramers, likely assembled from dimers, assumed distinct respective geometries; A β ₄₀ exhibited a “closed” tetramer resistant to further addition of A β ₄₀ subunits, while a more “open” A β ₄₂ tetramer facilitated further assembly into a hexameric paranucleus, which in turn stacks into a more stable dodecamer of low beta sheet content with a mass of 55 kDa. While A β oligomerization is beginning to yield to biophysical analysis, there is less agreement as to which form(s) of peptide mediate(s) toxicity in AD. Complicating efforts to definitively identify the function of specific A β oligomeric species is the dynamic structure of oligomers as intermediates in potentially multiple oligomerization pathways (reviewed by [19]). Synthetic A β ₄₂ rapidly forms insoluble fibrils under most buffer conditions, such as in PBS solution. However, if the peptide is denatured and then diluted into F12 tissue culture medium, a relatively stable soluble A β “globulomer” is created over several hours or days [15,16]. This oligomeric species appears spherical (not fibrillary) by atomic force microscopy with a diameter of about 5 nm and a molecular weight of 100–500 kDa by size exclusion chromatography (SEC). This form has also been termed A β -derived diffusible ligand or ADDL. The ADDL form has been reported to prevent long-term potentiation (LTP) of the Schaffer collateral pathway from CA3 to CA1

in hippocampal slices [16,20]. Moreover, this A β -oligomer induces dendritic spine retraction in hippocampal cultures [13].

A second form of soluble A β -oligomer was identified in the medium of CHO cells (7PA2 cell line) expressing the V717F mutation of APP [11,21]. This cell-derived A β -oligomer also suppresses hippocampal (LTP) and exhibits a range of molecular weights by SEC, including dimer, trimer, and other oligomeric species. The calculated potency for the cell-derived A β in LTP suppression is strong in the low nM to high pM range. Initial evidence indicated that a range of oligomers in these preparations possess LTP-suppressing activity, but monomers were inactive. A third form of A β -oligomer, termed A β *56, was detected in APP_{swe} Tg2576 transgenic mouse brain and observed to correlate better with memory impairment than other forms of A β [7]. This species migrates with an apparent molecular weight of 56 kDa in the presence of SDS, suggesting that it may contain approximately 10–12 A β monomers, similar to the dodecamer described in the biophysical study by Bernstein et al. [17]. Moreover, A β *56 impairs hippocampal LTP and injection of A β *56 into the brain of healthy rats produced an impairment of memory retention. Recent fractionation studies of human brain samples have generated evidence that A β dimers may correlate best with disease [8]. Moreover, dimers fractionated by SEC inhibited LTP in hippocampal slices and when infused into mice, created memory deficits [3]. The secondary structure and cytotoxicity of stabilized isolated monomeric, dimeric, trimeric, and tetrameric synthetic A β ₄₀ oligomers has been studied after photoinduced cross linking of a mixture undergoing oligomerization with the finding that A β monomers are largely unstructured, while dimers, trimers, and tetramers exhibit order-dependent increases in β -sheet content and toxicity [22]. Common to all of these preparations is the existence of nonfibrillar oligomeric A β species with neuronal toxicity or potent ability to suppress synaptic function in vitro or in vivo.

Prion protein function

The neurodegenerative infectious prion diseases in humans (CJD) and other mammals (scrapie, bovine spongiform encephalopathy, chronic wasting disease) are characterized by the accumulation of abnormally folded scrapie prion protein (PrP^{Sc}), which is the essential constituent of infectious prions. (reviewed in [23–27]). The normally folded, GPI-linked cellular prion protein (PrP^C) is required for the pathogenesis of prion encephalopathies: mice with a targeted disruption of the PrP gene (*Prnp*) are resistant to infectious prions [28]. Grafting experiments [29], conditional cell-type-specific PrP knockout mice [30], and transgenic mice expressing an anchorless PrP mutant [31] indicate neuronal expression of PrP^C, which is required for the neurotoxic action of PrP^{Sc}. In addition to the infectious disease, various mutant forms of PrP can acquire neurotoxic function even in the absence of PrP^{Sc}/prion propagation (reviewed by [32]). Not unlike A β , monomeric PrP^{Sc} appears to have little toxicity or scrapie infectivity [33–36] with maximal infectivity corresponding to an oligomer of 14–28 PrP molecules [37]. These biochemical and functional studies support the idea that with protein folding/aggregation diseases, smaller subfibrillar particles may be much more pathological than larger amyloid fibrils or plaques [38]. Copper- and zinc-binding sites are located in the octarepeat region and the unstructured region between PrP residues 106–126 that is thought to be integral to the misfolding of PrP^C into the β -sheet rich, protease-resistant pathogenic isoform.

While the pathology of PrP dysfunction has been extensively studied, the normal physiological function of PrP^C is still emerging. In contrast to the toxic activity of pathological PrP^{Sc}, PrP^C appears to confer enhanced tolerance to stress in primary neurons [39]. In rats and mice, PrP^C has neuroprotective activity after ischemic insult [40–44]. In multiple cell culture systems, PrP^C can modulate stress pathways, in particular, Bax-mediated pathways (reviewed by [45]). PrP dimers have been reported [46,47] and

dimerization of PrP^C on a neuroectodermal cell line (1C11) with antibodies directed against the 139–155 PrP epitope was found to stimulate the activity of the nonreceptor tyrosine kinase, fyn, and extracellular regulated kinases [48,49], suggesting that trophic signaling through PrP involves dimerization. Presumably, the antibodies in this type of experiment are mimicking the action of naturally occurring, as yet uncharacterized PrP^C ligands. One class of toxic PrP mutants is characterized by deletions in an internal hydrophobic domain (HD) at residues 113–133 [50–52]. Initially identified as a putative dimerization domain [53], this HD was subsequently shown to mediate dimer formation of PrP^C in neuroblastoma cells and required for its protective activity against various stresses, while also conferring susceptibility to the toxic action of PrP^{Sc} [54]. Thus, much like some receptor tyrosine kinases, PrP^C appears to require dimerization for activation of trophic signaling pathways, the disruption of which may be the deleterious mechanism of PrP^{Sc} as well as inherited prion diseases.

Similarities between AD and CJD

AD and prion-mediated spongiform encephalopathies both occupy a spectrum of symptomatic pathologies with some overlap. They are dementing disorders involving deposition of extracellular protein aggregates with associated neurodegeneration. In AD, A β -containing plaques build up in the neuropil and are associated with neurofibrillary tangles composed of hyperphosphorylated tau protein. In CJD, PrP^{Sc} deposits are generally unassociated with tau pathology. However, in both transmissible variant Creutzfeldt–Jakob disease (vCJD) [55] and Gerstmann–Straussler–Scheinker disease, a familial prion disease caused by various mutations in the PrP gene [56–58], PrP^{Sc} deposits are associated with phospho-tau laden neurites and perikarya [55], albeit at lower overall levels than in AD brain. Treatment of rat cortical neurons with either synthetic A β ₄₀ or PrP 106–126 peptides results in increased tau protein phosphorylation at Ser202/Thr205 and cell death in a Cdk5-dependent manner [59].

As with AD, CJD risk is increased by the APOE4 allele [60,61], while the age of onset of Gerstmann–Straussler–Scheinker disease is paradoxically delayed by 10 years in carriers of APOE4 [62]. The APOE2 allele lowers the risk of both AD and CJD [63]. In biochemical studies, APOE possesses binding affinity for several amyloidogenic proteins, including PrP and A β [51]. In histological studies, APOE is associated with A β plaques of AD brain and the kuru-like plaques of some CJD cases [64]. Furthermore, it copurifies with the protease-resistant core of PrP (PrP27-30) extracted from brains of hamsters with experimental scrapie [65].

Functionally, PrP^C is a negative regulator of β -secretase [66] and localizes in specialized membrane regions in close association with APOE, APP, amyloid beta precursor protein-like 2, amyloid precursor protein-binding family member 1, and a disintegrin and metalloprotease domain 23, which is a member of the α -secretase a disintegrin and metalloprotease family [67]. Oligomeric A β also possesses infectious prion-like features under certain situations. Intra-cerebral administration of exogenous A β -containing brain extracts from humans with AD or APP transgenic mice induces cerebral β -amyloidosis and associated pathology in APP transgenic mice in a time- and concentration-dependent manner [68,69].

Genetically, there is an association between homozygosity at *PRNP* codon 129 (Met versus Val) and early onset AD [70,71], as well as long-term memory [72], and early cognitive decline in the general population [73]. Though these findings have not been born out in all studies, a meta-analysis of published studies available at AlzGene supports an association of the Val allele with AD <<http://www.alzforum.org/res/com/gen/alzgene/>>. In a large-scale

genome-wide SNP study of candidate risk loci for late onset Alzheimer's Disease (LOAD), a focused analysis of some 25 previously reported LOAD risk genes was conducted, and only *PRNP* achieved statistical significance [74].

PrP^C is a receptor for oligomeric A β ₄₂

The potent action of oligomeric A β on neuronal cells suggests the presence of one or more neuronal high-affinity receptors for A β (Fig. 2). To identify candidates for this receptor, we conducted an unbiased expression-cloning screen of a brain cDNA library for binding sites with an oligomeric preparation of synthetic biotinylated A β ₄₂ [75]. This preparation consisted principally of oligomeric A β ₄₂ in the form of 50–100-mers and monomers. Of more than 200,000 expressed genes, only PrP^C expression supported binding of oligomeric A β ₄₂. The 50–100 nM affinity of A β oligomers for PrP^C expressing COS-7 cells matches its affinity for binding to hippocampal neurons. If this measured affinity is corrected for the extent of oligomerization, the estimated affinity of oligomeric A β ₄₂ is close to 1 nM. The interaction does not require the presence of PrP^{Sc}. When applied to hippocampal brain slices *in vitro*, A β oligomers suppress CA1 hippocampal LTP. This suppression is not observed in slices genetically lacking PrP^C or in the presence of an anti-PrP antibody that inhibits binding of oligomeric A β ₄₂ to PrP^C. Deletion mutants and competition studies with epitope-specific PrP antibodies indicate that A β ₄₂ oligomer binding involves PrP residues 95–105, which are adjacent to residues 106–126 that facilitate PrP amyloidogenesis and proximal to the dimerization-mediating HD residues at 113–133. One previous study reported that bivalent antibodies directed against PrP residues 95–105 injected into the mouse brain induce focal neuronal apoptosis [76]. These antibodies may interrupt endogenous trophic signaling through PrP^C or induce apoptotic signaling in a manner not inducible by their monovalent Fab fragments or an antibody to PrP residues 133–157.

The questions raised by these observations are numerous. To what extent, if any, are the neurodegenerative mechanisms of AD and CJD in common? Is the A β -induced LTP suppression via PrP^C in slices directly related to memory impairment by A β *in vivo*? Is A β binding to PrP^C a proximal step in the AD neurodegenerative pathway? To what extent is this AD neurodegenerative pathway similar to that induced by the interaction of PrP^{Sc} with PrP^C in CJD? The findings that both PrP^{Sc} and A β preferentially bind PrP^C as oligomers, and both are principle suspects in progressive neurodegenerative disorders, raise suspicion of a common downstream mechanism. With this hypothesis in mind, the finding that PrP^{Sc}-infected patients with high A β ₄₂ load exhibit lower levels of PrP^{Sc} and longer disease duration before death than patients with low A β ₄₂ load (10.1 months versus 3.8 months, respectively) [77] suggests these two neurodegenerative stimuli may compete for pathway modulation. Similarly, decreased cerebrospinal fluid PrP levels correlate with increased disease severity in Alzheimer's disease as well as other neurodegenerative disorders [78,79]. How oligomeric A β ₄₂ relates to dimerization-dependent PrP trophic or apoptotic signaling will inform models of this system's role in AD.

Mouse genetic models expressing familial AD mutant APP with or without familial AD mutant PSEN1 are useful tools for the laboratory study of AD. However, in these models cognitive decline occurs without the widespread neurodegeneration observed in human AD. Although the mice exhibit histological changes such as a reduction in serotonin immunoreactivity [80], the central human AD pathologies of reduced brain volume, hyperphosphorylated tau tangles, and widespread neuronal death do not result from expression of these transgenes. The reason for this is unclear, but it would tend to suggest that at least in mice, the early stages of cognitive decline are mechanistically decoupled from severe neurodegeneration. If neurodegeneration is not required for memory impairment, two mechanistic alternatives present themselves:

- The memory impairment of AD is due at least in part to synaptic impairment that is upstream in a pathway leading to neuronal death (Fig. 2) only under permissive or cooperative circumstances not present in transgenic murine physiological or temporal conditions. In support of this model, neutralization of the neuroprotective effects of secreted amyloid precursor protein in APP_{swe} mice results in tau phosphorylation and loss of hippocampal neurons [81], presumably by unmasking the neurotoxic effects of A β ₄₂.
- Neurodegeneration and A β ₄₂-mediated memory impairment, respectively, occupy two distinct, independently inducible pathways, only one of which is active in mice. Potentially consistent with this model, recent findings point to a toxic role for a cleaved amino-terminal fragment of APP via binding to death receptor 6 (DR6 or TNFRSF21) [82], suggesting that distinct pathological pathways may be independently inducible by signals other than A β ₄₂ originating from APP processing, though it is not clear why the transgenic murine brain should be insensitive to this putative action.

It will be useful to learn which of these two possibilities is predominant. For the present, these mouse models provide a means to specifically examine the memory deficit mechanisms of AD in the absence of attendant neurodegeneration and will be valuable tools for exploring the function of A β ₄₂ oligomer/PrP^C interaction as it relates to the onset of memory impairment in AD.

Acknowledgments

We thank Haakon B. Nygaard, M.D. for providing Fig. 1. S.M.S. is a member of the Kavli Institute for Neuroscience at Yale University. We acknowledge support from the National Institutes of Health, the Falk Medical Research Trust, an anonymous donor, and the Cure Alzheimer's Fund to S.M.S.

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Fig. 1. A β plaque deposition in transgenic mouse brain. Cerebral cortex sections of 12 month old APP^{sw}/PSen1 Δ E9 transgenic mice [83] (Jackson Laboratories) were stained for A β (green; anti-A β polyclonal antibody, Cell Signaling Technologies, Inc., number 2545), nissl (red), and nuclei (blue, DAPI). Note the amyloid plaques (arrows). Scale bar is 100 μ m

Fig. 2.

Model of A β_{42} action through PrP^C receptor. APP processing yields A β monomers, which undergo oligomerization eventually forming amyloid plaques. A β oligomers bind to PrP^C, inducing LTP inhibition [84]. We hypothesize that the same mechanism may lead to dendritic spine retraction via synaptotoxic action, with subsequent neuritic dystrophy and neurodegenerative pathology. These later steps are coupled to tauopathy and memory impairment in humans. The oligomeric infectious form of PrP and PrP^{Sc} independently induces neurodegeneration in a PrP^C-dependent fashion. See text for discussion