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A β Oligomer-Induced Synapse Degeneration in Alzheimer's Disease

Kyle C. Wilcox,

Department of Neurobiology and Physiology, Northwestern University, Evanston, IL 60208, USA

Pascale N. Lacor,

Department of Neurobiology and Physiology, Northwestern University, Evanston, IL 60208, USA

Jason Pitt, and

Department of Neurobiology and Physiology, Northwestern University, Evanston, IL 60208, USA

William L. Klein

Department of Neurobiology and Physiology, Northwestern University, Evanston, IL 60208, USA

O.T. Hogan Biological Sciences 4-160, Northwestern University, 2205 Tech Drive, Evanston, IL 60208, USA

Kyle C. Wilcox: k-wilcox@northwestern.edu; William L. Klein: wklein@northwestern.edu

Abstract

A β oligomers cause a collection of molecular events associated with memory loss in Alzheimer's disease, centering on disrupting the maintenance of synapse structure and function. In this brief review of the synaptotoxic effects of A β oligomers, we focus on the neuronal properties governing oligomer targeting and toxicity—especially with respect to binding sites and mechanisms of binding. We also discuss ways in which mechanistic insights from other diseases offer clues in the pursuit of the molecular basis of Alzheimer's disease.

Keywords

Alzheimer's disease; Synapse degeneration; A β oligomers; mGluR5; Fragile X syndrome; Insulin dysfunction

Introduction

Marshall Nirenberg's career was emblematic of his drive to uncover the fundamental nature of information storage in biology. After his seminal studies on the genetic code, he focused on the storage of information in the brain—a process then and now theorized to result from the formation of stable synaptic connections. Thus, he sought to learn how and why synapses form as a result of our interaction with the world around us. At the opposite extreme, Alzheimer's disease (AD) is outwardly manifest as a debilitating inability to form new memories—and deficits in synapse formation and maintenance are now commonly thought to be its root cause.

The Initial Implication of Oligomeric A β in AD

The identification of the amyloid β peptide as the major component of senile plaques in AD brains (Masters and Beyreuther 1987; Glenner and Murphy 1989) spurred efforts to identify the mechanisms by which aggregates of A β might be capable of interfering with brain function. The amyloid cascade hypothesis predicted that reducing the buildup of amyloid plaques should reduce the memory impairment observed in AD (Hardy and Higgins 1992). However, experiments in animal models failed to attribute memory impairment to amyloid pathology—finding instead that plaque load does not dictate the severity of AD (Haass and Selkoe 2007). Soluble oligomeric forms of A β were first described in the early 1990s, but little thought was given to their being the primary toxic species in AD (Roher et al. 1991; Frackowiak et al. 1994; Kuo et al. 1996; Podlisny et al. 1995; Roher et al. 1993; Vigo-Pelfrey et al. 1993). Arising from the hypothesis that reducing amyloid fibrils would reduce A β toxicity, Oda et al. incubated A β peptides with clusterin, which prevented fibril formation but increased oxidative stress in PC12 cells treated with these preparations (Oda et al. 1994). In the wake of this finding, Lambert et al. (1998) showed that fibril-free soluble A β oligomers are neurotoxic and lead to rapid inhibition of long-term potentiation (LTP; an electrophysiological correlate of learning and memory) and eventually cell death. The name amyloid β -derived diffusible ligand (ADDL), coined in that work, was designed to emphasize the ability of these oligomers to act as specific toxins and was meant to differentiate those A β oligomers with dementing activity. That is, it was recognized that not every oligomer should be considered toxic. To this day, an exact assembly state and conformation of the toxin is still intensely sought after—if a single state exists—and the transient nature and heterogeneity of A β oligomers impedes efforts to define the structural basis of their toxic activity.

Soluble A β oligomers have been described that adopt a variety of aggregation states as small as dimers and as large as protofibrillar structures comprising dozens A β monomers (for reviews, see Glabe 2008; Rahimi et al. 2008). While toxic agency has been ascribed to oligomer preparations enriched in high and low molecular weight oligomers, suggesting the possibility of dementing activity across a range of oligomer species, dodecameric and dimeric A β species have been a focal points for studies of A β oligomer toxicity. Oligomers of A β containing roughly 12 monomers were identified in human brain extracts and found to bind cultured neurons (Gong et al. 2003) in a manner similar to synthetic ADDLs, in which high molecular weight species preferentially target neurons (Lacor et al. 2004). The implication of these brain-derived dodecamers as pathophysiologically relevant A β oligomers is supported by the isolation of a similar 56 kDa species from APP-overexpressing AD transgenic mice that was capable of disrupting memory upon injection into young wild type rats (Lesne et al. 2006). Dodecamers have also been described by additional groups using synthetic A β oligomers (Barghorn et al. 2005; Bernstein et al. 2009). At the lower end of the oligomer spectrum, dimeric A β was recently purified from AD brains and also found to inhibit LTP in hippocampal slices (Shankar et al. 2008) and induce Tau hyperphosphorylation and other degenerative effects in cultured neurons (Jin et al. 2011). This finding follows the extensive use of cell culture-derived oligomers by Selkoe and others that are reported to be primarily dimers and trimers of A β (Selkoe 2008; Walsh et al. 2002, 2000).

Synaptic Effects of A β Oligomers

A β oligomers exert their toxicity through binding at synapses. As might be expected for a molecule that disrupts LTP, synthetic oligomers as well as AD brain- or CSF-derived soluble oligomers consistently show abundant binding to the dendritic arbors of select hippocampal neurons in culture (Gong et al. 2003; Lacor et al. 2004) and this dendritic

binding is evident in the form of punctate labeling that co-localizes with PSD-95 as visualized by high-resolution confocal fluorescence microscopy (Lacor et al. 2004). Oligomers also co-localize with PSD-95 in brain sections of AD transgenic mice (Koffie et al. 2009). Oligomer binding sites are enriched with postsynaptic proteins including calcium/calmodulin-dependent kinase II, Arc, spinophilin, drebrin and n-methyl-D-aspartate receptor (NMDAR), while the presynaptic marker, synaptophysin, is opposite these puncta (Lacor et al. 2004; Lacor et al. 2007). Excitatory synapses appear to be preferentially targeted, as oligomers co-localize with PSD-95 and Homer1b/c, scaffolding proteins that interact with glutamate receptors and Shank family proteins at excitatory synapses (Tu et al. 1999), while no colocalization is evident in the case of gephyrin, a scaffolding protein at inhibitory synapses (Renner et al. 2010). Immunoprecipitation of ADDL-binding complexes in synaptosomes results in the identification of several prominent glutamate receptors (NR1, NR2, GluR1, and mGluR5), EphB2, and neuroligin, but neither nicotinic acetylcholine receptors nor glycine receptors were present—further demonstrating excitatory synapse targeting (Lacor et al. 2007; Renner et al. 2010).

The effect of the synaptic association of A β oligomers is synapse loss, which is accompanied by a collection of effects on synapse size, shape, and composition (reviewed in Lacor 2007). Exposure to oligomers leads to a reduction in the stubby and mushroom spines found in healthy neurons and the transient formation of aberrant spines with slender filopodial or large, branched morphologies reminiscent of structures formed in mental retardation (Lacor et al. 2004; Lacor et al. 2007; Shrestha et al. 2006). In the early timescale prior to synapse loss, oligomers induce changes in the makeup of synaptic membranes, evident as a loss of surface glutamate receptors—both NMDA (Lacor et al. 2007; Snyder et al. 2005) and α -amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA; Hsieh et al. 2006) subtypes—as well as EphB2 (Lacor et al. 2007; Cisse et al. 2011) and insulin receptors (De Felice et al. 2009; Zhao et al. 2009). The trafficking-mediated surface loss of synaptic receptors prior to structural changes and spine loss is consistent with the postulated loss of synaptic plasticity without cell death in early-stage AD (Klein et al. 2007; Lambert et al. 1998).

Findings from post-mortem analyses of AD tissues have also shown an oligomer association with AD. A loss of specific synaptic proteins has been observed that is correlated with AD severity and regionally specific neurodegeneration (Proctor et al. 2010) and post-mortem staining of early stage AD brains using oligomer-selective antibodies (Lacor et al. 2004) show diffuse immunostaining reminiscent of the synaptic-type deposits observed in prion-associated diseases (Kovacs et al. 2002). Other experiments using oligomer-specific antibodies have identified a 70-fold increase in the concentration of A β oligomers in AD brains (Gong et al. 2003), an increase that is also detectable in the CSF of individuals with AD, although to a lesser degree (Georganopoulou et al. 2005). Oligomer staining using conformationally specific antibodies was also shown to be spatially distinct from fibrillar deposits in human brain slices (Kayed et al. 2003), implying that these species can form independently of amyloid fibrils.

Effect of A β Oligomers on Memory

The early discovery of LTP impairment by synthetic soluble A β oligomers (Lambert et al. 1998) has been supported by experiments using oligomers released by hAPP-transfected cells (Walsh et al. 2002) and with soluble extracts from the brains of AD subjects and transgenic mice (Lesne et al. 2006; Shankar et al. 2008). Oligomers also impede the reversal of long-term depression (LTD) (Hsieh et al. 2006; Wang et al. 2002), indicating a net shift of synaptic activity in favor of inhibition suggesting instability in synaptic composition and morphology (Klein et al. 2001; Lacor et al. 2004). LTP impairment in AD transgenic mice

correlates with accumulation of soluble oligomers (Chang et al. 2003) but precedes A β deposition into plaques (Larson et al. 1999; Oddo et al. 2006). The temporal correlation of LTP with oligomer accumulation is borne out by behavioral testing for memory in animal models (Cleary et al. 2005; Lesne et al. 2006).

Various animal models have proven useful in defining the biological presence and dementing activity of A β oligomers. Early work by Mucke demonstrated that A β overexpression in transgenic mice causes AD-like synapse loss without the production of amyloid plaques (Mucke et al. 2000). Oligomeric A β was positively identified in transgenic animals in 2003 (Chang et al. 2003), and oligomers corresponding roughly to 12-mers were isolated from AD transgenic mice and found to impair memory upon injection into wild type rats (Lesne et al. 2006). The behavioral influence of oligomeric A β rather than plaques is further supported by experiments using transgenic mice in which soluble oligomers accumulate without plaque formation at any age tested, up to 24 months (Tomiyama et al. 2010). Similar mice lacking fibrils while at the same time producing oligomeric A β species have also been described (Gandy et al. 2010). These different lines of transgenic animals were made by altering the same amino acid residue in the amyloid precursor protein. In the former study, glutamic acid 693—corresponding to position 22 in the A β peptide—was deleted based on a similar deletion found in a Japanese family that develop a form of AD with decreased levels of A β , and studies of this mutated peptide reveal a propensity to form oligomers but not fibrils (Tomiyama et al. 2008). In the latter mice, the same residue was mutated to a glutamine (E693Q). It is interesting to note that despite the apparent lack of amyloid plaques in E693Q mice, the mutation in humans is responsible for a form of hereditary cerebral hemorrhage with amyloidosis (Levy et al. 1990), which is accompanied by A β deposition.

How Do A β Oligomers Target Neurons?

When considering the basis of oligomer attachment to neurons, three competing hypotheses dominate the landscape. One hypothesis is that oligomeric A β interacts directly with membranes—perhaps to form toxic pores. Findings that A β peptides and oligomers can insert into model membranes of varying compositions support this hypothesis (Lashuel and Lansbury 2006), which has been proposed to constitute a general gain-of-function underlying the toxicity of multiple proteins involved in neurodegenerative disease (Kayed et al. 2003). Studies using both model membranes and intact cells have identified an effect of negatively charged phospholipids in mediating the interaction of A β peptides with neuronal membranes (Alarcon et al. 2006; Hertel et al. 1997; McLaurin and Chakrabarty 1997; Wong et al. 2009), perhaps even catalyzing oligomer formation (Wong et al. 2009).

An alternative hypothesis is that toxic A β oligomers act within the cell (Takahashi et al. 2004; Walsh et al. 2000) to exert a toxic effect on synapses. Intracellular A β , though not necessarily oligomers, is observed in AD brains (Gouras et al. 2000) and there is evidence of intracellular A β generation (reviewed in LaFerla et al. 2007). Recent AD transgenic rat models feature intracellular oligomers as detected by an oligomer-specific monoclonal antibody, suggesting that A β oligomers are present inside neurons (Leon et al. 2010; Tomiyama et al. 2010). Whether oligomers form extracellularly, intracellularly, or both is not agreed upon in the literature. Oligomeric A β may form within neurons prior to export (Walsh et al. 2000), but the demonstration that A β monomer concentrations in the interstitial fluid of the brain undergo a circadian cycle in living mice highlights the likelihood that oligomer formation is also occurring extracellularly (Kang et al. 2009). The toxicity of intracellular A β may also depend on the aggregation state, as an inverse correlation was reported between intracellular A β monomers and nucleic acid oxidation—hypothesized to be a protective mechanism against oxidative stress (Nunomura et al. 2010).

Finally, the loss of synaptic activity associated with A β oligomers may be triggered by oligomer binding to specific sites on the neuronal surface—an attractive model because it immediately offers a basis for therapeutic intervention against toxic oligomers. All regions of the AD brain are not equally affected (Braak and Braak 1991), and this holds true at the cellular level, where the cultured hippocampal neurons are highly targeted by A β oligomers, while cerebellar neurons are not affected (Gong et al. 2003; Klein et al. 2001). Further evidence of specific susceptibility of different neuronal populations is the triggering of mitochondrial dysfunction in cortical, but not cerebellar preparations by A β oligomers (Eckert et al. 2008). Dramatic cell-to-cell differences in oligomer binding exist in hippocampal cultures, illustrating that even in a targeted region there is some determining factor that enables oligomers to bind a given cell (Lacor et al. 2007). Similar to these cell-to-cell differences, A β oligomers seem to be specific for a subset of synapses within a single cell. While 90% of oligomers co-localize with synaptic markers, only half of the excitatory synapses bind oligomers (Lacor et al. 2004). This fractional synaptic targeting increases upon neuronal activation (Deshpande et al. 2009), which may reflect changes in synaptic receptor regulation. The trypsin sensitivity of oligomer binding and observations that these molecules preferentially affect mature neurons—developing the ability to bind oligomers around 14 days in vitro—suggest the presence of a developmentally regulated proteinaceous receptor (Lacor et al. 2007; Lambert et al. 1998; Shughrue et al. 2010).

Proposed Binding Sites for A β Oligomers

As yet, no single protein seems to recapitulate all of the necessary characteristics of a true oligomer receptor. Even non-protein binding sites have been proposed, including GM1 gangliosides and the lipid rafts they inhabit, which have been implicated in multiple aspects of AD pathophysiology including APP processing (Fonseca et al. 2010) and A β oligomer binding (Gong et al. 2003; Zampagni et al. 2010). In fact, GM1 gangliosides were reported to directly mediate the binding of toxic calcitonin oligomers (Malchiodi-Albedi et al. 2010). Ganglioside removal by neuraminidase treatment caused the complete elimination of calcium influx in the presence of calcitonin oligomers, but lipid raft disruption by ganglioside removal may also disorganize other receptors prominent in these membrane domains.

Many proteinaceous receptors for A β oligomers have been reported in the past several years. Among them are the P75 neurotrophin receptors, the antibody-based blockade of which prevents cell death after exposure to relatively high doses of A β oligomers (Knowles et al. 2009); the receptor for advanced glycation endproducts, or “RAGE” (Sturchler et al. 2008); the frizzled receptor (Magdesian et al. 2008), and nicotinic acetylcholine receptors (Magdesian et al. 2005), which were shown to bind monomeric A β peptides.

Perhaps the most notable and controversial recent example of a receptor for A β oligomers is the cellular prion protein, PrP^C, identified in a gene expression screen in a non-neuronal cell line for proteins allowing ADDL binding, which the cells normally lack (Lauren et al. 2009). The prospect that PrP^C is the binding site for A β oligomers was quickly and alternately refuted (Callella et al. 2010; Kessels et al. 2010; Balducci et al. 2010) and supported (Gimbel et al. 2010; Chen et al. 2010) by multiple follow-up studies. Inconsistent or system-specific findings of PrP^C-independent oligomer toxicity and memory deficits may require a mechanism by which PrP^C participates in the clustering of oligomers with other receptors, allowing a stronger response to low oligomer concentrations (Laurén et al. 2010).

As mentioned above, loss of EphB2 receptors accompanies A β oligomer binding to neurons in culture (Lacor et al. 2007). Recent investigations of the mechanism of oligomer-mediated receptor internalization point to a direct interaction of dimers and trimers of A β with EphB2,

leading to its internalization and proteasomal degradation and a surface reduction in NR1—a subunit of NMDA receptors (Cisse et al. 2011). Treatment of cultured neurons with antibodies against NR1 leads to only a 50% reduction in oligomer binding while eliminating oligomer-induced generation of reactive oxygen species, and oligomer-induced effects can also be reduced using the NMDAR antagonist, memantine (De Felice et al. 2007; Lacor et al. 2007). The AMPA receptor subunit GluR2 may also contribute to oligomer binding but, as with other receptor candidates, reduction in AMPA receptor surface expression incompletely reduces synaptic oligomer binding (Zhao et al. 2010).

Finally, experiments using a mouse knockout of mGluR5 implicate this receptor in oligomer-induced synaptic pathology (Renner et al. 2010). While the approaches used in this study did not permit a direct analysis of whether mGluR5 interacts with oligomeric A β , the work demonstrates an essential role of mGluR5 in oligomer-induced synaptic reorganization as described in the next section.

Receptor Clustering: A Mechanism for Oligomer Toxicity in AD

How can so many receptors play a role in oligomer binding and synaptotoxicity? One hypothesis is that because A β oligomers likely comprise a distribution of states, they bind to multiple receptors. Another is that a single oligomer can alternately bind to different, low-affinity receptors. If either of these models were true, then the sum of the contributions of each receptor should equal the observed oligomer binding. While it appears that when each of the proposed receptors is ablated through some means, only a fractional decrease in oligomer binding is typically observed (De Felice et al. 2009; Lauren et al. 2009; Renner et al. 2010; Zhao et al. 2010), a combination of PrP^c, mGluR5, and NR1 antibodies applied simultaneously to cultured hippocampal neurons does not augment the fractional reduction in oligomer binding achieved using any of the individual receptor antibodies (Renner et al. 2010). This non-additivity suggests that a more complex mechanism is controlling the synaptic targeting of A β oligomers.

A new mechanism (Fig. 1) that may explain the implication of multiple receptors in oligomer toxicity is based on findings that oligomers undergo a progressive shift from an extrasynaptic, freely diffusive state toward the formation of static synaptic clusters. This clustering was monitored through the real-time single-particle tracking of quantum dot-labeled oligomers on the surface of live neurons (Renner et al. 2010). The reduced oligomer diffusion observed in these experiments mirrors the reduced diffusion accompanying transmembrane protein recruitment to specific sites (Douglass and Vale 2005; Geng et al. 2009), suggesting that oligomer clustering and immobilization may depend on specific receptors. Specifically, tracking mGluR5 diffusion following oligomer treatment reveals a diffusional restriction at synapses—reminiscent of oligomer tracking data (Renner et al. 2010). Even in the absence of A β oligomers, antibodies to an extracellular mGluR5 epitope artificially reduce mGluR5 diffusion and induce its clustering at synaptic sites, suggesting that oligomeric A β acts as an extracellular scaffold to bring together clusters of mGluR5—and likely other proteins—at the synapse. Interestingly, oligomer treatment has no effect on the surface diffusion of AMPA-type glutamate and GABA_A receptors, suggesting a specificity of A β oligomers for mGluR5-associated binding sites (Renner et al. 2010). Though there is currently no evidence that the receptor responsible for oligomer-induced clustering is mGluR5, its signaling activity following artificial clustering could be responsible for NR1 surface withdrawal and the rise in intracellular calcium levels in response to A β oligomers.

The shift in mGluR5 toward synapses in the presence of oligomers is significant in that mGluR5 is involved in the mechanisms of synaptic plasticity underlying learning and

memory (Simonyi et al. 2005) and contributes to oligomer-induced synaptotoxicity (Hsieh et al. 2006; Li et al. 2009; Wang et al. 2004). The involvement of mGluR5 also suggests a mechanism for how oligomers affect LTP/LTD and calcium homeostasis, especially given that mGluR5 antagonists prevent these cellular responses to oligomer treatment (Renner et al. 2010; Shankar et al. 2008; Townsend et al. 2007; Wang et al. 2004).

Mechanistic Clues from Other Diseases

As details of the molecular basis of AD emerge, it is becoming clear that AD shares aspects of other brain diseases. We wish to highlight two examples of diseases that appear to share some of the phenomenological and molecular details of AD.

mGluR5 as a connection to Fragile X syndrome

While AD-related deficits in learning and memory have a strong connection to aging, a possible parallel can be found in Fragile X syndrome—an autism spectrum disorder and the leading hereditary cause of mental retardation in children. As with AD, Fragile X appears to be the result of synaptic deficiencies leading to decreased mental capabilities. Many of the synaptic effects mirror those discussed above in AD, including aberrant spine morphology (Irwin et al. 2001), AMPA and NMDA receptor dysfunction (Yun and Trommer 2010; Zalfa et al. 2007), Arc overexpression and elevated LTD (Park et al. 2008), and the activation of the protein phosphatase PP2A and subsequent inactivation of MAPK1/2 (Kim et al. 2008)—also impaired in oligomer-exposed neurons (Wang et al. 2004).

Mechanistically, the most relevant commonality between Fragile X and oligomer synaptotoxicity is the involvement of mGluR5 receptors. In normal neurons, mGluR5 mobilization of calcium leads to dephosphorylation of fragile X mental retardation protein (FMRP), a protein that regulates the trafficking of specific mRNA transcripts to synaptic spines and their subsequent translation. FMRP phosphorylation downstream of mGluR5 relieves the translational repression of FMRP on its mRNA cargo (Bear et al. 2004). Excessive mGluR5 signaling activity is prevented by FMRP itself, through a negative feedback loop (Bear et al. 2004). A reduction in FMRP—whatever the cause—is thus expected to have a 2-fold effect on neurons: a loss of transcriptional control over synaptic mRNA pools and an inability to suppress hyperactive mGluR5 signaling. In Fragile X syndrome, FMRP activity is reduced at the level of translation (Jin and Warren 2000). In AD, on the other hand, it is possible that oligomer-induced clusters of mGluR5 stimulate a feedback-insensitive loss of FMRP activity. Functionally, this potential impact of oligomers would be equivalent to eliminating FMRP protein, as in Fragile X. Two expected AD-like consequences of the hypothesized mGluR5 cluster-mediated repression of FMRP activity are (i) the upregulation of Arc, which is under direct FMRP repression (Iacoangeli et al. 2008; Zalfa et al. 2003) and (ii) the alteration of synapse morphology through destabilization of PSD-95 mRNA, which is stabilized through a direct interaction with FMRP (Zalfa et al. 2007). Finally, because mGluR5 stimulates FMRP to permit translation of APP (Westmark and Malter 2007) an oligomer-induced loss in FMRP activity would also be expected to reinforce the effects of mGluR5 clustering by increasing APP translation and subsequent A β production.

Though the symptoms of AD and Fragile X are by no means identical, the loss of FMRP activity through either transcriptional or functional mechanisms could account for the similarities between these diseases with respect to synapses. To advance this hypothesis a step further, the significant similarities between Fragile X syndrome and the oligomer-induced synaptic deficits in AD may warrant the consideration of AD as an adult-onset oligomer-induced manifestation of an autism spectrum disorder.

Connection between AD and diabetes

Insulin signaling (i.e., the series of intracellular signaling cascades initiated by insulin receptor activation) in the aging brain is another area that may provide a mechanistic link between a healthy brain and one that develops AD. Given the positive effect of insulin signaling on synaptic function (Chiu et al. 2008; van der Heide et al. 2006) and memory (Marks et al. 2009), there is a burgeoning interest in a role for insulin in dementia. Epidemiological studies reveal an increased prevalence of dementia in individuals with diabetes, including an approximately 2-fold increase in the risk for developing AD (Leibson et al. 1997; Ott et al. 1999). Aberrant insulin signaling in the absence of diabetes also increases the risk of dementia (Peila et al. 2004). Mouse models of diabetes exhibit AD-like pathology, including elevated levels of A β and tau phosphorylation, which can be reduced by insulin treatment (Jolivald et al. 2008), while inducing Type 1 or 2 diabetes in AD transgenic mice exacerbates AD and diabetic phenotypes (Jolivald et al. 2010; Ke et al. 2009; Plaschke et al. 2010; Takeda et al. 2010), indicating that common underlying mechanisms such as insulin dysfunction link diabetes and AD.

Oligomeric A β antagonizes insulin signaling, as oligomer-bound neurons exhibit reduced insulin receptor activity and a reduction in synaptic insulin receptors (De Felice et al. 2009; Zhao et al. 2008). On the other hand, cognitive impairment by A β oligomers in a mouse model can be protected against by inhibiting the PI3K-Akt-mTOR pathway (Caccamo et al. 2010), while insulin activation of this signaling pathway mediates several processes integral to synapse function, including receptor trafficking (Huang et al. 2004), synaptic plasticity (van der Heide et al. 2006), and protein synthesis (Lee et al. 2005). Consistent with a co-antagonistic relationship between oligomer toxicity and protective insulin signaling, pretreatment of neurons with insulin protects against oligomer binding and toxicity (De Felice et al. 2009; Zhao et al. 2009).

The age-dependent decline in insulin signaling (Fernandes et al. 2001) could therefore increase the susceptibility of neurons to oligomer toxicity, providing a possible mechanism for the development of sporadic AD. In this mechanism, oligomeric A β could further hinder the already-waning neuroprotective effect of insulin signaling, resulting in synapse loss and neuronal death. This hypothesis for the induction of sporadic AD predicts that methods of strengthening insulin signaling could potentially stave off AD pathogenesis if administered during the appropriate phase of disease development.

Conclusion

At a fundamental level, developing an understanding of how specific molecules and events create brain states in which memory storage cannot occur will allow us to gain great insight into the mechanisms of normal information storage in the human brain. To this end, the evolution of the amyloid cascade hypothesis to focus on the toxic action of oligomeric A β has highlighted the importance of determining the molecular mechanisms by which these species contribute to AD. As details emerge regarding the toxic pathways actuated by A β oligomers, shared mechanisms between AD and other diseases affecting the organization of the brain can be recognized. We expect these forthcoming connections to promote both theoretical and experimental inroads into the oligomeric basis of AD and potential disease-modifying therapies.

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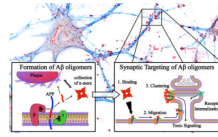


Fig. 1.

Formation and synaptic targeting of A β oligomers. A neuron is represented with *blue* neurites and *red* dendritic spines (background image). Following APP cleavage at the neural membrane by β - and γ -secretase, the 42-residue A β peptide (*red*) can be deposited into senile plaques or can alternatively form a collection of oligomeric species (*left inset*). Some component of this collection of oligomers interacts with neurons to form synaptic clusters which are associated with a variety of synaptic pathologies including the internalization of receptors involved in synapse function and maintenance and the initiation of toxic signaling cascades (*right inset*)