Journal of Alzheimer's Disease 33 (2013) S67–S78
DOI 10.3233/JAD-2012-129001
IOS Press

Review

Molecular Mechanisms of Amyloid Oligomers Toxicity

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Abstract. Amyloid oligomers have emerged as the most toxic species of amyloid-β (Aβ). This hypothesis might explain the lack of correlation between amyloid plaques and memory impairment or cellular dysfunction. However, despite the numerous published research articles supporting the critical role Aβ oligomers in synaptic dysfunction and cell death, the exact definition and mechanism of amyloid oligomers formation and toxicity still elusive. Here we review the evidence supporting the many molecular mechanisms proposed for amyloid oligomers toxicity and suggest that the complexity and dynamic nature of amyloid oligomers may be responsible for the discrepancy among these mechanisms and the proposed cellular targets for amyloid oligomers.

Keywords: Alzheimer's disease, amyloid, amyloid oligomers, amyloid toxicity

INTRODUCTION

The aggregation and accumulation of amyloid-β (Aβ) plays a significant role in the pathogenesis of Alzheimer's disease (AD). Aβ oligomeric aggregates are believed to be the main toxic species and the causative agent underlying the pathological mechanism for AD, aggregating and accumulating within and around neurons. Excised from the amyloid-β protein precursor (AβPP) by β- and γ-secretases, the Aβ peptide has the intrinsic property of forming aggregates with β-pleated sheet structure [1]. The amyloid hypothesis has undergone several modifications, mainly concerning the type of Aβ thought to cause AD: initially this was the amyloid plaque, followed by increased concentrations of $A\beta_{42}$, then increased $A\beta_{42}:A\beta_{40}$ ratio, and finally oligomeric Aβ [2]. Results from clinical trials have shown that removing plaques will not reverse the damage or stop AD [3, 4]. Recent evidence suggests that this toxicity may be linked to the aggregation state of the peptide, implicating oligomers, rather than insoluble fibrils, as the primary toxic species [5, 6]. While both are found in the brains of postmortem AD patients, soluble Aβ oligomers are better correlated with disease severity than are the classic amyloid plaques containing insoluble Aβ fibrillar deposits [7–9]. Furthermore, oligomers are found both extracellularly and intracellularly, and are capable of moving between the interior of the cell and the extracellular space [10, 11]. However, Aβ oligomer structure, size, conformation, and interrelationships with other amyloid aggregates, as well as the exact mechanism of Aβ oligomer-induced neurotoxicity, remain elusive [12–14]. Monomeric Aβ undergoes conformation transitions and proceeds to form low molecular oligomers (dimer/trimer), and then soluble high molecular aggregates and progress to form

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ISSN 1387-2877/13/$27.50

spherical oligomers which are composed of 12 to 24 monomers, which prolong to protofibrils and finally become insoluble fibrils [15]. These various structures differ not only in aggregation state, but also in their toxic effects. Recently, many have reported that fibrils, which were once thought to exhibit the highest levels of toxicity, are actually second in toxicity to intermediate aggregates of Aβ (spherical oligomers and protofibrils) [14, 16, 17].

Our studies demonstrated the presence of a variety of Aβ oligomer conformations [15]. The different conformations can be produced by several pathways and simple manipulation of conditions in which Aβ aggregates, and underlines the complexity of the mechanism of oligomer formation [15, 16, 18–23]. Moreover, several studies suggest that oligomeric species differ not only in mechanism of formation, but also in mechanism of toxicity [24–26].

RECEPTOR-MEDIATED Aβ OLIGOMER NEUROTOXICITY

Extracellular Aβ oligomers bind the cell surface, leading to functional disruption of a number of receptors, including the N-methyl-D-aspartate receptor (NMDAR) [27] and others (Fig. 1A), resulting in synaptic dysfunction and neurodegeneration. A number of possible mechanisms and targets are under investigation, including the abnormal activation of signaling pathways.

Recently, Yamamoto et al. [28] suggested that Aβ oligomers induce nerve growth factor (NGF) receptor-mediated neuronal death. NGF can induce cell death through the p75 neurotrophin receptor (p75NTR), a member of the tumor necrosis factor receptor superfamily [29]. A previous report supports this concept, demonstrating that Aβ-derived diffusible ligands (ADDLs) potently alter NGF-mediated signaling in cultured cells [30]. Moreover, several studies suggested that Aβ toxicity is produced through the association with p75NTR [31–37]. Specifically, Aβ toxicity mediated by p75NTR depends on a death domain [38] in the cytoplasmic part of p75NTR molecules [37]. However, it has also been demonstrated that p75NTR promotes the survival and differentiation of vertebrate neurons, indicating that p75NTR might have diverse functions in both cell death and cell survival [39]. It should be noted that conflicting evidence also exists regarding the role of p75NTR against the toxicity of Aβ oligomers. Costantini and colleagues showed that soluble oligomers of Aβ exert cytotoxic activity independent of p75NTR and that the expression of p75NTR exerts a protective role against the toxic activity of soluble oligomers. The authors also concluded that this role is due to an active function of the juxtamembrane sequence of the cytoplasmic region of p75NTR and that the protective function is mediated by phosphatidylinositide 3-kinase (PI3K) activity [37]. In another study, it was observed that low levels of extracellular Aβ increase the levels of p75NTR in primary cultures of human neurons. Unexpectedly, it was found that p75NTR protects primary human neurons against Aβ-induced toxicity [40]. These opposite conclusions imply that the signaling pathways of p75NTR are complicated and that the functions of p75NTR vary depending on several factors.

Other reports on neuronal receptor-mediated toxicity mechanisms have shown that Aβ disturbs NMDAR-dependent long-term potentiation induction *in vivo* and *in vitro*. Furthermore, these studies suggest that Aβ specifically interferes with several major signaling pathways downstream of NMDAR, including the Ca^{2+}-dependent protein phosphatase calcineurin, Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), protein phosphatase 1, and cAMP response element-binding protein (CREB) (reviewed in [41]). In another study of downstream NMDAR effectors, Zhao et al. determined that low molecular weight oligomeric Aβ could also inhibit CaMKII and thereby disrupt the dynamic balance in place between protein kinase and phosphatase, presumed to be critical during synaptic plasticity [42]. In another study, it was found that ADDLs stimulated excessive formation of reactive oxygen species (ROS) through a mechanism requiring NMDAR activation. ADDL binding to neurons was reduced and ROS formation was completely blocked by an antibody to the extracellular domain of the NR1 subunit of NMDARs [43]. The authors showed that the mechanism of ADDL-stimulated ROS formation requires ADDL targeting and activation of NMDARs, leading to a rapid increase in neuronal calcium levels. Taken together, these observations suggest that dysregulation of NMDAR function induced by ADDL binding to neuronal synapses may lead to synaptic mitochondrial dysfunction and excessive ROS formation.

Shankar and coworkers found that Aβ oligomers decrease spine density through a pathway that requires NMDA-type glutamate receptors (NMDARs), calcineurin, and cofilin. These results suggest that Aβ oligomers mimic a state of partial NMDAR blockade, by reducing NMDAR activation, reducing

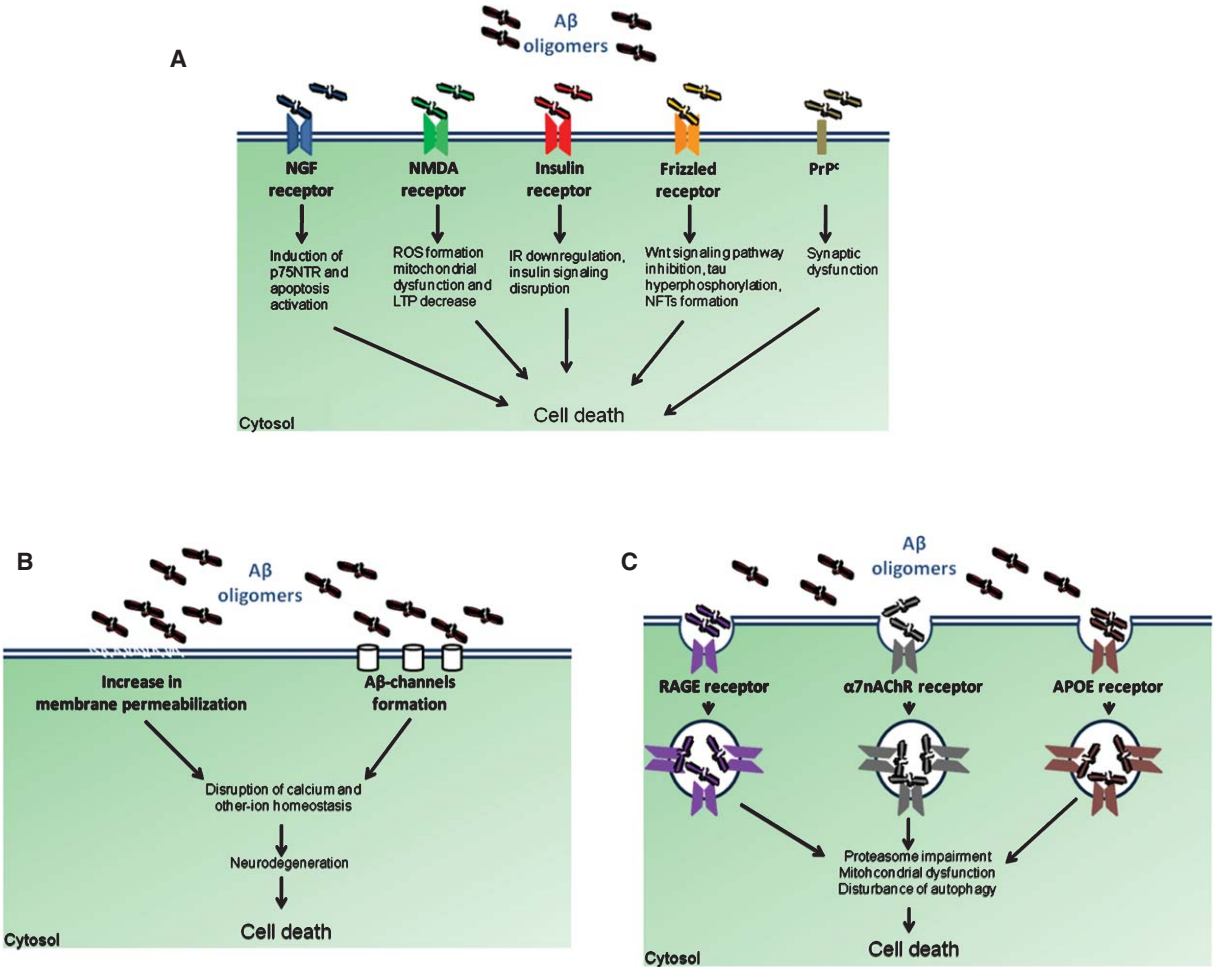

Fig. 1. A) Aβ oligomer neurotoxicity can be mediated through their ability to bind multiple receptors leading to the activation of various signaling pathways. Two possibilities may explain the lack of receptor specificity: 1) Aβ oligomers are indeed "sticky" as have been reported having a detergent-like quality, making it easier for them to be promiscuous in their interactions; and 2) oligomers are heterogeneous as indicated by colors and each oligomeric species has high affinity to a specific receptor or membrane protein. B) Aβ oligomers insertion in the membrane and the subsequent formation of ion channels or pores lead to neurodegenerative processes. C) The intracellular accumulation of Aβ oligomers and other aggregates cause many key pathological events of AD, including proteasome impairment, mitochondrial dysfunction, disturbance of autophagy, the production of reactive oxygen species, lipid peroxidation, disruption of lysosomal membrane, and breakdown of many cellular processes.

NMDAR-dependent calcium influx, or enhancing NMDAR-dependent activation of calcineurin [44]. It has also been shown that signal transduction by neuronal insulin receptors (IRs) is strikingly sensitive to disruption by soluble Aβ oligomers. In a recent study, it was found that ADDLs caused a rapid and substantial loss of neuronal surface IRs specifically on dendrites bound by ADDLs. Removal of dendritic IRs was associated with increased receptor immunoreactivity in the cell body, indicating redistribution of the receptors [45]. The results presented by the authors identify novel factors that affect neuronal IR signaling and suggest that insulin resistance in AD brain is a response to ADDLs, which disrupt insulin signaling. Townsend and colleagues found that soluble Aβ binds to IR and interferes with its insulin-induced autophosphorylation. Taken together, these data demonstrate that physiologically relevant levels of naturally secreted Aβ interfere with IR function and prevent the rapid activation of specific kinases required for long-term potentiation [46]. De Felice et al. also suggest that ADDLs caused major downregulation of plasma membrane IRs, via a mechanism sensitive to CaMKII and casein kinase II inhibition [47].

Magdesian et al. showed that Aβ oligomers bind to the Frizzled (Fz) cysteine-rich domain at or in close proximity to the Wnt-binding site and inhibit the canonical Wnt signaling pathway [48]. Wnts are secreted glycoproteins that bind to and signal through Fz receptors and mediate cell-cell communication [49]. Wnt signaling regulates a variety of critical biological processes, including development, cell movement, cell polarity, axon guidance, and synapse formation [50]. Magdesian and colleagues concluded that Aβ oligomers bind to Fz receptors, producing the inhibition of Wnt signaling, which causes tau phosphorylation and neurofibrillary tangles; that suggests a Wnt/β-catenin toxicity pathway [48].

A recent study by Lauren et al. [51] identifies the cellular prion protein (PrP^C) as an Aβ oligomers-receptor. The authors demonstrated that PrP^C is a mediator of Aβ oligomer-induced synaptic dysfunction and that Aβ oligomers bind with nanomolar affinity to PrP^C, but the interaction does not require the infectious PrP^{Sc} conformation. The binding of Aβ oligomers to PrP^C receptor may disrupt the interaction between PrP^C and co-receptor, such as NMDAR. Despite the fact that Aβ oligomers have been strongly implicated in neuronal dysfunction and neurotoxicity in AD, the signal transduction mechanisms involved in the neuronal impact of Aβ oligomers remain to be fully elucidated. A major unknown is the identity of the neuronal receptor(s) that binds Aβ oligomers and mediates neuronal dysfunction. As we described above, several studies postulate a great number of possible receptors involved in the toxicity of Aβ oligomers, but some of these studies are contradictory. The final identification of a highly specific receptor(s) for Aβ oligomers would provide considerable insight into mechanisms of pathogenesis and might reveal novel opportunities for the development of strategies to combat AD.

CELLULAR MEMBRANE AND Aβ OLIGOMERS TOXICITY

The maintenance of plasma membrane integrity is critical for cell viability, since the membrane controls the exchange of materials between the cell and its surrounding environment. An increase in membrane permeability and intracellular calcium concentration has long been associated with amyloid pathogenesis, although questions remain as to the mechanism underlying these observations [52, 53]. One explanation for the molecular mechanism of neurodegeneration induced by Aβ specifically is channel formation and disruption of calcium homeostasis. Arispe and coworkers demonstrated the incorporation of Aβ peptides into artificial lipid bilayers to form cation-specific channels [54, 55]. Furthermore, others reported cytosolic calcium elevations as a result of this channel formation by Aβ, but also by other amyloid-forming proteins [56]; the results of this study strongly suggest that incorporation of Aβ into membranes and the subsequent pore formation may be the primary events in Aβ neurotoxicity. Specifically, the authors suggested that after being incorporated into the membrane, Aβ will change its structure and accumulated Aβ become aggregated on the membranes. They also suggested the possibility that the ratio of cholesterol to phospholipids in the membrane alters membrane fluidity and therefore affects the process. Micro-circumstances on the membranes, such as the presence of rafts, may influence this process [56]. These data and other reports culminated in what came to be known as the "channel hypothesis", implicating amyloid peptide channels in the pathogenic ion dysregulation observed in degenerative disease [57, 58]. In this respect, Aβ may share this mechanism of toxicity with the similar mechanism underlying the toxicity of various antimicrobial or antifungal peptides, such as alamethicin, gramicidin, magainin 2, and melittin, which also exhibit channel forming ability and cell toxicity [59]. Once Aβ channels are formed on neuronal membranes, the disruption of calcium and other-ion homeostasis may promote numerous degenerative processes, including free radical formation [60] and phosphorylation of tau [61], thereby accelerating neurodegeneration. The free radicals also induce membrane disruption, by which unregulated calcium influx is amplified and a vicious circle is initiated. We recently demonstrated the presences of these Aβ pores in human cases of AD [62, 63].

In contrast to the amyloid channel hypothesis, recent data suggest that homogeneous solutions of amyloid oligomers increase the conductance of artificial lipid bilayers, but do not exhibit channel-like properties. Specifically, the conductance changes observed did not occur in discrete steps; rather, oligomers appeared to enhance ion mobility across the lipid bilayer independently [64]. This increased conductivity was not ion specific, and thus has the potential to depolarize the membrane and lead to cellular dysfunction. A growing body of evidence points to membrane permeabilization by amyloid oligomers as a common mechanism of pathogenesis in amyloid-related degenerative diseases [13, 19, 64–77]. These studies suggest that membrane permeabilization caused by amyloid oligomers is due

to defects in the lipid bilayer, rather than the formation of discrete proteinaceous pores. In accordance with this observation, a study by Demuro et al. showed that amyloid oligomers consistently produce rapid and dramatic elevations in Ca^{2+}, whereas equivalent concentrations of monomers or fibrils do not. The action of amyloid oligomers appears to involve a channel-independent disruption of the integrity of both plasma and intracellular membranes [68]. The authors propose that amyloid oligomers exert an immediate action by increasing the permeability of the plasma membrane and subsequently penetrate cells, as proposed previously [78], where they similarly disrupt intracellular membranes to cause leakage of sequestered Ca^{2+}. In another study we reported that soluble oligomers from several types of amyloid specifically increase lipid bilayer conductance regardless of the sequence, while fibrils and soluble low molecular weight species have no effect. The increase in membrane conductance occurs without any evidence of discrete channel or pore formation or ion selectivity [64]. The results presented in this study indicate that soluble oligomers from many types of amyloidogenic proteins and peptides increase membrane conductance in a conformation-specific fashion and suggest that this may represent the common primary mechanism of pathogenesis in amyloid-related degenerative diseases. The increase in membrane conductivity could lead to depolarization of the plasma membrane, which would be detrimental to the function of cells and especially so for neuronal function. The membrane conductance increase we reported can also account for a wide range of effects, such as defects of cytosolic ion homeostasis and signaling as a direct consequence of the membrane conductance increase [79]. Other experiments suggested that amyloid oligomers break down or reduce the normal dielectric barrier to ion translocation provided by the hydrocarbon region of the lipid bilayer [76]. The authors proposed that Aβ oligomers increase membrane conductance and permeability to charged species by spreading apart the lipid head groups and consequently thinning the bilayer and lowering the permeability barrier [80, 81]. More recently, Demuro and collaborators were able to image the formation of Ca^{2+} single-channel and pores formed by Aβ oligomers using total internal reflection fluorescence microscopy [82].

The formation of non-specific Aβ pores or channels (Fig. 1B) on neuronal membranes in AD brain cause the disruption of calcium and other-ion homeostasis may promote numerous degenerative processes, including free radical formation [60] and phosphorylation of tau [61], thereby accelerating neurodegeneration and cell death. The free radicals also induce membrane disruption, by which unregulated calcium influx is amplified and a vicious circle is initiated lipid oxidation and other modifications [83, 84].

INTRACELLULAR Aβ OLIGOMER TOXICITY

In addition to extracellular Aβ, there is a large body of evidence to demonstrate that Aβ accumulates intracellularly [85–87]. Intraneuronal Aβ accumulation has been identified in AD patients, transgenic mice, and cultured cells [88–94]. Intraneuronal Aβ accumulation appears prior to extracellular amyloid plaque formation and results in synaptic dysfunction [88, 93, 95–102]. A key question that remains to be addressed is whether the intracellular Aβ builds up because a portion of the generated Aβ is not secreted and consequently remains intracellular, or alternatively, whether secreted Aβ is taken back up by the cell to form these intracellular pools [103–106]. It is well known that is also localized in the trans-Golgi network [107], endoplasmic reticulum, and endosomal, lysosomal [108], and mitochondrial membranes [109]. The liberation of Aβ could potentially occur wherever AβPP and the β- and γ-secretases are localized, and it is likely that this occurs in several cellular compartments. In addition to Aβ being produced intracellularly, previously secreted Aβ that forms an extracellular Aβ pool can be taken up by cells and internalized into intracellular pools through various receptors and trasnporters. A recent study showed that, in mice with a toxin-induced compromise of the blood-brain barrier, fluorescently labeled Aβ that is injected into the tail vein can accumulate intracellularly in pyramidal neurons in the cerebral cortex [110]. The results presented by the authors provide direct evidence that neurons can take up extracellular Aβ, one of mechanisms that has been proposed is the endocytocis of Aβ oligomers [111].

It is well known that Aβ binds to the α7 nicotinic acetylcholine receptor (α7nAChR) with high affinity, and that this binding results in receptor internalization and accumulation of Aβ intracellularly [112, 113]. These findings were recently confirmed in a study using the mouse model 3xTg-AD, where the authors show a loss of the α7nAChRs restricted to brain regions that accumulate intraneuronal Aβ [114]. Recently, the analyses of a novel animal model A7KO-AβPP, revealed the significance of α7nAChR in AD and its protective role for Aβ oligomers toxicity in early

stage AD. Analysis in early stage pre-plaque cognitive decline revealed neurodegeneration in A7KO-AβPP hippocampus. These changes occurred concomitant with the appearance of a dodecameric oligomer of Aβ that was absent from all other genotypic groups [115].

Several studies have shown that apolipoprotein E (APOE) receptors, which are members of the low-density lipoprotein receptor family, modulate Aβ production and cellular uptake [116]. LDL receptor-related protein, which is another member of this family of receptors, binds to Aβ directly, or through ligands such as APOE, and undergoes rapid endocytosis, facilitating Aβ uptake [116]. It is well known that APOE ε4 is the major genetic risk factor for AD, and it is remarkable that one of its functions appears to be to directly mediate the accumulation of intracellular Aβ. It has been reported that Aβ is internalized through the scavenger receptor for advanced glycation end products (RAGE), in neurons and microglia [117–119]. The binding of Aβ to RAGE in neurons initiated a cascade of events that produces oxidative stress and nuclear factor-κ B (NF-κB) activation, which induce the production of macrophage colony-stimulating factor [120] and an enhanced microglial response. Additionally, it has been shown that RAGE-Aβ complexes are internalized and that they co-localize with the lysosomal pathway in astrocytes in AD patients [119].

The toxicity mechanism of intracellular Aβ oligomers remains unclear. Almeida et al. demonstrated that in AβPP mutant transgenic mice and in human AD brain, progressive intraneuronal accumulation of Aβ occurs, especially in multivesicular bodies (MVBs) [121]. The authors provided evidence that Aβ accumulation in neurons inhibits the activities of the proteasome and deubiquitinating enzymes. These data suggest a mechanism whereby Aβ accumulation in neurons impairs the MVB sorting pathway via the ubiquitin-proteasome system (UPS) in AD. Indeed, the authors hypothesize that the inhibition of the UPS by Aβ impairs the endocytic trafficking of neuronal receptors and thereby may be the cause of synaptic dysfunction in AD. Furthermore, several others studies suggest that an inhibition of the proteasome leads to an increase of Aβ levels [122, 123]. Recent studies by LaFerla's group have shown proteasome inhibition in the 3xTg-AD mice at ages at which oligomeric Aβ accumulation is seen within neuronal cell bodies [123, 124]. These findings show that oligomeric Aβ accumulation within neuronal cell bodies has pathological consequences, as proteasome impairment led to the build-up of tau protein. Another study, by Mousnier and colleagues, reported a possible prefolding-mediated proteasomal protein-degradation pathway [125]. This suggests that Aβ oligomers-prefolding complex could cause proteasome dysfunction and subsequent cell death.

Accumulation of Aβ has also been observed in mitochondria [126]. Progressive accumulation of intracellular Aβ in mitochondria is related to diminished enzymatic activity of respiratory chain complexes III and IV, and a reduced rate of oxygen consumption [127]. These observations correlated with the multiple mitochondrial defects reported in AD and mouse models of the disease [128]. A marked disturbance of autophagy has recently been appreciated in AD [129, 130], adding to evidence for extensive dysfunction of the lysosomal system in this disease [131]. Aβ can accumulate in lysosomes in the AD brain. Aβ within the lysosomal compartment destabilizes its membrane [132], which will lead to the release of Aβ in the cytosolic compartment.

The studies described in this section suggested that the toxicity mechanism of intracellular oligomers could be different from the one produced by extracellular oligomers (Fig. 1C). However, further studies are necessary to determine the exact mechanism of toxicity produced by Aβ oligomers in AD.

CONCLUSIONS

Based on the studies discussed here and the countless targets associated with toxicity of Aβ oligomers, it is conceivable that oligomers are not specific and interact with many targets, or it is possible that the toxicity is associated with the formation process rather than a specific oligomeric species, this (kinetic model of toxicity) model [133, 134] demonstrates that Aβ aggregation and the formation of the fibrils causes toxicity at low concentrations. Alternatively, we propose that Aβ oligomers possess a large number of exchangeable, still distinct conformational polymorphisms [135], similar to the structural polymorphisms described for Aβ fibrils [136–139], and that different subgroups of Aβ oligomers and fibrils induce neurotoxicity and may contribute to AD pathology via different mechanisms [15, 25, 140, 141]. The unique combination of size, hydrophobicity, and conformation of each oligomeric species determines both its toxicity and the final aggregation state (Fig. 2). The existence of polymorphisms in what are now known as oligomers may be analogous to the polymorphisms that exist within yeast prions [142, 143]. Identifying these subtle differences between oligomers both *in vitro* and *in vivo* represents

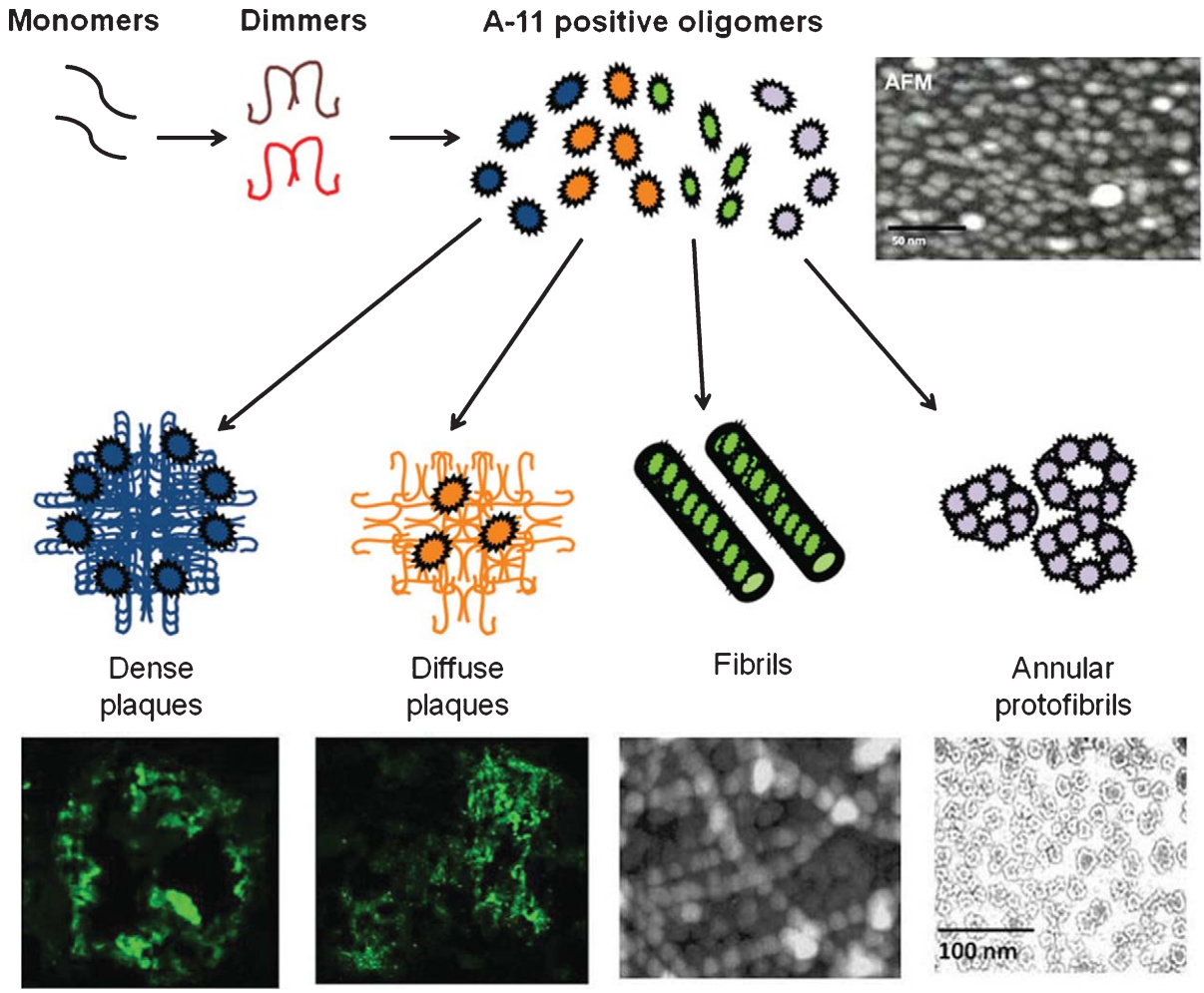

Fig. 2. Amyloid oligomers have different sizes and possess different conformations, and the structural diversity of Aβ oligomers shape the aggregation pathway of each species and determine their toxicity. This may explain the large number of toxic events associated with Aβ oligomers.

the next challenge facing the amyloid field and requires novel methods and reagents.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1246).

REFERENCES

[1] Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science* **297**, 353-356.

[2] Pimplikar SW (2009) Reassessing the amyloid cascade hypothesis of Alzheimer's disease. *Int J Biochem Cell Biol* **41**, 1261-1268.

[3] Hardy J (2009) The amyloid hypothesis for Alzheimer's disease: A critical reappraisal. *J Neurochem* **110**, 1129-1134.

[4] Cappai R, Barnham KJ (2008) Delineating the mechanism of Alzheimer's disease A beta peptide neurotoxicity. *Neurochem Res* **33**, 526-532.

[5] Baglioni S, Casamenti F, Bucciantini M, Luheshi LM, Taddei N, Chiti F, Dobson CM, Stefani M (2006) Prefibrillar amyloid aggregates could be generic toxins in higher organisms. *J Neurosci* **26**, 8160-8167.

[6] Haass C, Selkoe DJ (2007) Soluble protein oligomers in neurodegeneration: Lessons from the Alzheimer's amyloid beta-peptide. *Nat Rev Mol Cell Biol* **8**, 101-112.

[7] McLean CA, Cherny RA, Fraser FW, Fuller SJ, Smith MJ, Beyreuther K, Bush AI, Masters CL (1999) Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease. *Ann Neurol* **46**, 860-866.

[8] Lue LF, Kuo YM, Roher AE, Brachova L, Shen Y, Sue L, Beach T, Kurth JH, Rydel RE, Rogers J (1999) Soluble amyloid beta peptide concentration as a predictor of synaptic change in Alzheimer's disease. *Am J Pathol* **155**, 853-862.

[9] Tomic JL, Pensalfini A, Head E, Glabe CG (2009) Soluble fibrillar oligomer levels are elevated in Alzheimer's disease brain and correlate with cognitive dysfunction. *Neurobiol Dis* **35**, 352-358.
[10] Gaspar RC, Villarreal SA, Bowles N, Hepler RW, Joyce JG, Shughrue PJ (2010) Oligomers of beta-amyloid are sequestered into and seed new plaques in the brains of an AD mouse model. *Exp Neurol* **223**, 394-400.
[11] Takahashi RH, Almeida CG, Kearney PF, Yu F, Lin MT, Milner TA, Gouras GK (2004) Oligomerization of Alzheimer's beta-amyloid within processes and synapses of cultured neurons and brain. *J Neurosci* **24**, 3592-3599.
[12] Ross CA, Poirier MA (2005) Opinion: What is the role of protein aggregation in neurodegeneration? *Nat Rev Mol Cell Biol* **6**, 891-898.
[13] Caughey B, Lansbury PT (2003) Protofibrils, pores, fibrils, and neurodegeneration: Separating the responsible protein aggregates from the innocent bystanders. *Annu Rev Neurosci* **26**, 267-298.
[14] Glabe CG (2006) Common mechanisms of amyloid oligomer pathogenesis in degenerative disease. *Neurobiol Aging* **27**, 570-575.
[15] Glabe CG (2008) Structural classification of toxic amyloid oligomers. *J Biol Chem* **283**, 29639-29643.
[16] Glabe CG, Kayed R (2006) Common structure and toxic function of amyloid oligomers implies a common mechanism of pathogenesis. *Neurology* **66**, S74-S78.
[17] Meier JJ, Kayed R, Lin CY, Gurlo T, Haataja L, Jayasinghe S, Langen R, Glabe CG, Butler PC (2006) Inhibition of human IAPP fibril formation does not prevent beta-cell death: Evidence for distinct actions of oligomers and fibrils of human IAPP. *Am J Physiol Endocrinol Metab* **291**, E1317-E1324.
[18] Lesne S, Koh MT, Kotilinek L, Kayed R, Glabe CG, Yang A, Gallagher M, Ashe KH (2006) A specific amyloid-beta protein assembly in the brain impairs memory. *Nature* **440**, 352-357.
[19] Kayed R, Pensalfini A, Margol L, Sokolov Y, Sarsoza F, Head E, Hall J, Glabe C (2009) Annular protofibrils are a structurally and functionally distinct type of amyloid oligomer. *J Biol Chem* **284**, 4230-4237.
[20] Kayed R, Head E, Sarsoza F, Saing T, Cotman CW, Necula M, Margol L, Wu J, Breydo L, Thompson JL, Rasool S, Gurlo T, Butler P, Glabe CG (2007) Fibril specific, conformation dependent antibodies recognize a generic epitope common to amyloid fibrils and fibrillar oligomers that is absent in prefibrillar oligomers. *Mol Neurodegener* **2**, 18.
[21] Kayed R, Head E, Thompson JL, McIntire TM, Milton SC, Cotman CW, Glabe CG (2003) Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. *Science* **300**, 486-489.
[22] Kayed R, Glabe CG (2006) Conformation-dependent anti-amyloid oligomer antibodies. *Methods Enzymol* **413**, 326-344.
[23] Necula M, Kayed R, Milton S, Glabe CG (2007) Small molecule inhibitors of aggregation indicate that amyloid beta oligomerization and fibrillization pathways are independent and distinct. *J Biol Chem* **282**, 10311-10324.
[24] Chong YH, Shin YJ, Lee EO, Kayed R, Glabe CG, Tenner AJ (2006) ERK1/2 activation mediates Abeta oligomer-induced neurotoxicity via caspase-3 activation and tau cleavage in rat organotypic hippocampal slice cultures. *J Biol Chem* **281**, 20315-20325.
[25] Cizas P, Budvytyte R, Morkuniene R, Moldovan R, Broccio M, Losche M, Niaura G, Valincius G, Borutaite V (2010) Size-dependent neurotoxicity of beta-amyloid oligomers. *Arch Biochem Biophys* **496**, 84-92.
[26] Zako T (2010) Amyloid oligomers. *FEBS J* **277**, 1347.
[27] Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, Nairn AC, Salter MW, Lombroso PJ, Gouras GK, Greengard P (2005) Regulation of NMDA receptor trafficking by amyloid-beta. *Nat Neurosci* **8**, 1051-1058.
[28] Yamamoto N, Matsubara E, Maeda S, Minagawa H, Takashima A, Maruyama W, Michikawa M, Yanagisawa K (2007) A ganglioside-induced toxic soluble Abeta assembly. Its enhanced formation from Abeta bearing the Arctic mutation. *J Biol Chem* **282**, 2646-2655.
[29] Hansma HG, Laney DE, Bezanilla M, Sinsheimer RL, Hansma PK (1995) Applications for atomic force microscopy of DNA. *Biophys J* **68**, 1672-1677.
[30] Chromy BA, Nowak RJ, Lambert MP, Viola KL, Chang L, Velasco PT, Jones BW, Fernandez SJ, Lacor PN, Horowitz P, Finch CE, Krafft GA, Klein WL (2003) Self-assembly of Abeta(1-42) into globular neurotoxins. *Biochemistry (Mosc)* **42**, 12749-12760.
[31] Rabizadeh S, Bitler CM, Butcher LL, Bredesen DE (1994) Expression of the low-affinity nerve growth factor receptor enhances beta-amyloid peptide toxicity. *Proc Natl Acad Sci U S A* **91**, 10703-10706.
[32] Yaar M, Zhai S, Pilch PF, Doyle SM, Eisenhauer PB, Fine RE, Gilchrest BA (1997) Binding of beta-amyloid to the p75 neurotrophin receptor induces apoptosis. A possible mechanism for Alzheimer's disease. *J Clin Invest* **100**, 2333-2340.
[33] Yaar M, Zhai S, Fine RE, Eisenhauer PB, Arble BL, Stewart KB, Gilchrest BA (2002) Amyloid beta binds trimers as well as monomers of the 75-kDa neurotrophin receptor and activates receptor signaling. *J Biol Chem* **277**, 7720-7725.
[34] Kuner P, Schubenel R, Hertel C (1998) Beta-amyloid binds to p57NTR and activates NFkappaB in human neuroblastoma cells. *J Neurosci Res* **54**, 798-804.
[35] Perini G, Della-Bianca V, Politi V, Della Valle G, Dal-Pra I, Rossi F, Armato U (2002) Role of p75 neurotrophin receptor in the neurotoxicity by beta-amyloid peptides and synergistic effect of inflammatory cytokines. *J Exp Med* **195**, 907-918.
[36] Tsukamoto E, Hashimoto Y, Kanekura K, Niikura T, Aiso S, Nishimoto I (2003) Characterization of the toxic mechanism triggered by Alzheimer's amyloid-beta peptides via p75 neurotrophin receptor in neuronal hybrid cells. *J Neurosci Res* **73**, 627-636.
[37] Costantini C, Rossi F, Formaggio E, Bernardoni R, Cecconi D, Della-Bianca V (2005) Characterization of the signaling pathway downstream p75 neurotrophin receptor involved in beta-amyloid peptide-dependent cell death. *J Mol Neurosci* **25**, 141-156.
[38] Bothwell M (1996) p75NTR: A receptor after all. *Science* **272**, 506-507.
[39] Dechant G, Barde YA (2002) The neurotrophin receptor p75(NTR): Novel functions and implications for diseases of the nervous system. *Nat Neurosci* **5**, 1131-1136.
[40] Zhang Y, Hong Y, Bounhar Y, Blacker M, Roucou X, Tounekti O, Vereker E, Bowers WJ, Federoff HJ, Goodyer CG, LeBlanc A (2003) p75 neurotrophin receptor protects primary cultures of human neurons against extracellular amyloid beta peptide cytotoxicity. *J Neurosci* **23**, 7385-7394.
[41] Yamin G (2009) NMDA receptor-dependent signaling pathways that underlie amyloid beta-protein disruption of LTP in the hippocampus. *J Neurosci Res* **87**, 1729-1736.

[42] Zhao D, Watson JB, Xie CW (2004) Amyloid beta prevents activation of calcium/calmodulin-dependent protein kinase II and AMPA receptor phosphorylation during hippocampal long-term potentiation. *J Neurophysiol* **92**, 2853-2858.

[43] De Felice FG, Velasco PT, Lambert MP, Viola K, Fernandez SJ, Ferreira ST, Klein WL (2007) Abeta oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine. *J Biol Chem* **282**, 11590-11601.

[44] Shankar GM, Bloodgood BL, Townsend M, Walsh DM, Selkoe DJ, Sabatini BL (2007) Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. *J Neurosci* **27**, 2866-2875.

[45] Zhao WQ, De Felice FG, Fernandez S, Chen H, Lambert MP, Quon MJ, Krafft GA, Klein WL (2008) Amyloid beta oligomers induce impairment of neuronal insulin receptors. *FASEB J* **22**, 246-260.

[46] Townsend M, Mehta T, Selkoe DJ (2007) Soluble Abeta inhibits specific signal transduction cascades common to the insulin receptor pathway. *J Biol Chem* **282**, 33305-33312.

[47] De Felice FG, Vieira MN, Bomfim TR, Decker H, Velasco PT, Lambert MP, Viola KL, Zhao WQ, Ferreira ST, Klein WL (2009) Protection of synapses against Alzheimer's-linked toxins: Insulin signaling prevents the pathogenic binding of Abeta oligomers. *Proc Natl Acad Sci U S A* **106**, 1971-1976.

[48] Magdesian MH, Carvalho MM, Mendes FA, Saraiva LM, Juliano MA, Juliano L, Garcia-Abreu J, Ferreira ST (2008) Amyloid-beta binds to the extracellular cysteine-rich domain of Frizzled and inhibits Wnt/beta-catenin signaling. *J Biol Chem* **283**, 9359-9368.

[49] Dann CE, Hsieh JC, Rattner A, Sharma D, Nathans J, Leahy DJ (2001) Insights into Wnt binding and signalling from the structures of two Frizzled cysteine-rich domains. *Nature* **412**, 86-90.

[50] Gordon MD, Nusse R (2006) Wnt signaling: Multiple pathways, multiple receptors, and multiple transcription factors. *J Biol Chem* **281**, 22429-22433.

[51] Lauren J, Gimbel DA, Nygaard HB, Gilbert JW, Strittmatter SM (2009) Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers. *Nature* **457**, 1128-1132.

[52] Mattson MP, Cheng B, Davis D, Bryant K, Lieberburg I, Rydel RE (1992) beta-Amyloid peptides destabilize calcium homeostasis and render human cortical neurons vulnerable to excitotoxicity. *J Neurosci* **12**, 376-389.

[53] Mattson MP (1994) Calcium and neuronal injury in Alzheimer's disease. Contributions of beta-amyloid precursor protein mismetabolism, free radicals, and metabolic compromise. *Ann N Y Acad Sci* **747**, 50-76.

[54] Arispe N, Pollard HB, Rojas E (1993) Giant multilevel cation channels formed by Alzheimer disease amyloid beta-protein [A beta P-(1-40)] in bilayer membranes. *Proc Natl Acad Sci U S A* **90**, 10573-10577.

[55] Arispe N, Rojas E, Pollard HB (1993) Alzheimer disease amyloid beta protein forms calcium channels in bilayer membranes: Blockade by tromethamine and aluminum. *Proc Natl Acad Sci U S A* **90**, 567-571.

[56] Kawahara M, Kuroda Y, Arispe N, Rojas E (2000) Alzheimer's beta -Amyloid, human islet amylin, and prion protein fragment evoke intracellular free calcium elevations by a common mechanism in a hypothalamic GnRH neuronal cell line. *J Biol Chem* **275**, 14077-14083.

[57] Kagan BL, Azimov R, Azimova R (2004) Amyloid peptide channels. *J Membr Biol* **202**, 1-10.

[58] Kagan BL, Hirakura Y, Azimov R, Azimova R, Lin MC (2002) The channel hypothesis of Alzheimer's disease: Current status. *Peptides* **23**, 1311-1315.

[59] Bechinger B (1997) Structure and functions of channel-forming peptides: Magainins, cecropins, melittin and alamethicin. *J Membr Biol* **156**, 197-211.

[60] Yatin SM, Aksenova M, Aksenov M, Markesbery WR, Aulick T, Butterfield DA (1998) Temporal relations among amyloid beta-peptide-induced free-radical oxidative stress, neuronal toxicity, and neuronal defensive responses. *J Mol Neurosci* **11**, 183-197.

[61] Takashima A, Noguchi K, Sato K, Hoshino T, Imahori K (1993) Tau protein kinase I is essential for amyloid beta-protein-induced neurotoxicity. *Proc Natl Acad Sci U S A* **90**, 7789-7793.

[62] Lasagna-Reeves CA, Glabe CG, Kayed R (2011) Amyloid-beta annular protofibrils evade fibrillar fate in Alzheimer disease brain. *J Biol Chem* **286**, 22122-22130.

[63] Lasagna-Reeves CA, Kayed R (2011) Astrocytes contain amyloid-beta annular protofibrils in Alzheimer's disease brains. *FEBS Lett* **585**, 3052-3057.

[64] Kayed R, Sokolov Y, Edmonds B, McIntire TM, Milton SC, Hall JE, Glabe CG (2004) Permeabilization of lipid bilayers is a common conformation-dependent activity of soluble amyloid oligomers in protein misfolding diseases. *J Biol Chem* **279**, 46363-46366.

[65] Klein WL, Stine WB Jr, Teplow DB (2004) Small assemblies of unmodified amyloid beta-protein are the proximate neurotoxin in Alzheimer's disease. *Neurobiol Aging* **25**, 569-580.

[66] Stefani M, Dobson CM (2003) Protein aggregation and aggregate toxicity: New insights into protein folding, misfolding diseases and biological evolution. *J Mol Med* **81**, 678-699.

[67] Walsh DM, Selkoe DJ (2004) Oligomers on the brain: The emerging role of soluble protein aggregates in neurodegeneration. *Protein Pept Lett* **11**, 213-228.

[68] Demuro A, Mina E, Kayed R, Milton SC, Parker I, Glabe CG (2005) Calcium dysregulation and membrane disruption as a ubiquitous neurotoxic mechanism of soluble amyloid oligomers. *J Biol Chem* **280**, 17294-17300.

[69] Porat Y, Kolusheva S, Jelinek R, Gazit E (2003) The human islet amyloid polypeptide forms transient membrane-active prefibrillar assemblies. *Biochemistry* **42**, 10971-10977.

[70] Canale C, Torrassa S, Rispoli P, Relini A, Rolandi R, Bucciantini M, Stefani M, Gliozzi A (2006) Natively folded HypF-N and its early amyloid aggregates interact with phospholipid monolayers and destabilize supported phospholipid bilayers. *Biophys J* **91**, 4575-4588.

[71] Butterfield SM, Lashuel HA (2010) Amyloidogenic protein-membrane interactions: Mechanistic insight from model systems. *Angew Chem Int Ed Engl* **49**, 5628-5654.

[72] Lashuel HA, Lansbury PT Jr (2006) Are amyloid diseases caused by protein aggregates that mimic bacterial pore-forming toxins? *Q Rev Biophys* **39**, 167-201.

[73] Volles MJ, Lee SJ, Rochet JC, Shtilerman MD, Ding TT, Kessler JC, Lansbury PT Jr (2001) Vesicle permeabilization by protofibrillar alpha-synuclein: Implications for the pathogenesis and treatment of Parkinson's disease. *Biochemistry* **40**, 7812-7819.

[74] Valincius G, Heinrich F, Budvytyte R, Vanderah DJ, McGillivray DJ, Sokolov Y, Hall JE, Losche M (2008) Soluble amyloid beta-oligomers affect dielectric membrane

properties by bilayer insertion and domain formation: Implications for cell toxicity. *Biophys J* **95**, 4845-4861.

[75] Green JD, Kreplak L, Goldsbury C, Li Blatter X, Stolz M, Cooper GS, Seelig A, Kistler J, Aebi U (2004) Atomic force microscopy reveals defects within mica supported lipid bilayers induced by the amyloidogenic human amylin peptide. *J Mol Biol* **342**, 877-887.

[76] Sokolov Y, Kozak JA, Kayed R, Chanturiya A, Glabe C, Hall JE (2006) Soluble amyloid oligomers increase bilayer conductance by altering dielectric structure. *J Gen Physiol* **128**, 637-647.

[77] Hannig J, Zhang D, Canaday DJ, Beckett MA, Astumian RD, Weichselbaum RR, Lee RC (2000) Surfactant sealing of membranes permeabilized by ionizing radiation. *Radiat Res* **154**, 171-177.

[78] Bucciantini M, Calloni G, Chiti F, Formigli L, Nosi D, Dobson CM, Stefani M (2004) Prefibrillar amyloid protein aggregates share common features of cytotoxicity. *J Biol Chem* **279**, 31374-31382.

[79] Mattson MP, Barger SW, Cheng B, Lieberburg I, Smith-Swintosky VL, Rydel RE (1993) beta-Amyloid precursor protein metabolites and loss of neuronal Ca2+ homeostasis in Alzheimer's disease. *Trends Neurosci* **16**, 409-414.

[80] Neumcke B, Lauger P (1969) Nonlinear electrical effects in lipid bilayer membranes. II. Integration of the generalized Nernst-Planck equations. *Biophys J* **9**, 1160-1170.

[81] Parsegian A (1969) Energy of an ion crossing a low dielectric membrane: Solutions to four relevant electrostatic problems. *Nature* **221**, 844-846.

[82] Demuro A, Smith M, Parker I (2011) Single-channel Ca(2+) imaging implicates Abeta1-42 amyloid pores in Alzheimer's disease pathology. *J Cell Biol* **195**, 515-524.

[83] Ellis G, Fang E, Maheshwari M, Roltsch E, Holcomb L, Zimmer D, Martinez D, Murray IV (2010) Lipid oxidation and modification of amyloid-beta (Abeta) *in vitro* and *in vivo*. *J Alzheimers Dis* **22**, 593-607.

[84] Murray IV, Sindoni ME, Axelsen PH (2005) Promotion of oxidative lipid membrane damage by amyloid beta proteins. *Biochemistry* **44**, 12606-12613.

[85] Glabe C (2001) Intracellular mechanisms of amyloid accumulation and pathogenesis in Alzheimer's disease. *J Mol Neurosci* **17**, 137-145.

[86] LaFerla FM, Green KN, Oddo S (2007) Intracellular amyloid-beta in Alzheimer's disease. *Nat Rev Neurosci* **8**, 499-509.

[87] Gouras GK, Tampellini D, Takahashi RH, Capetillo-Zarate E (2010) Intraneuronal beta-amyloid accumulation and synapse pathology in Alzheimer's disease. *Acta Neuropathol* **119**, 523-541.

[88] D'Andrea MR, Nagele RG, Wang HY, Peterson PA, Lee DH (2001) Evidence that neurones accumulating amyloid can undergo lysis to form amyloid plaques in Alzheimer's disease. *Histopathology* **38**, 120-134.

[89] Gouras GK, Tsai J, Naslund J, Vincent B, Edgar M, Checler F, Greenfield JP, Haroutunian V, Buxbaum JD, Xu H, Greengard P, Relkin NR (2000) Intraneuronal Abeta42 accumulation in human brain. *Am J Pathol* **156**, 15-20.

[90] Gyure KA, Durham R, Stewart WF, Smialek JE, Troncoso JC (2001) Intraneuronal abeta-amyloid precedes development of amyloid plaques in Down syndrome. *Arch Pathol Lab Med* **125**, 489-492.

[91] LaFerla FM, Troncoso JC, Strickland DK, Kawas CH, Jay G (1997) Neuronal cell death in Alzheimer's disease correlates with apoE uptake and intracellular Abeta stabilization. *J Clin Invest* **100**, 310-320.

[92] Langui D, Girardot N, El Hachimi KH, Allinquant B, Blanchard V, Pradier L, Duyckaerts C (2004) Subcellular topography of neuronal Abeta peptide in APPxPS1 transgenic mice. *Am J Pathol* **165**, 1465-1477.

[93] Skovronsky DM, Doms RW, Lee VM (1998) Detection of a novel intraneuronal pool of insoluble amyloid beta protein that accumulates with time in culture. *J Cell Biol* **141**, 1031-1039.

[94] Wirths O, Multhaup G, Czech C, Blanchard V, Moussaoui S, Tremp G, Pradier L, Beyreuther K, Bayer TA (2001) Intraneuronal Abeta accumulation precedes plaque formation in beta-amyloid precursor protein and presenilin-1 double-transgenic mice. *Neurosci Lett* **306**, 116-120.

[95] Almeida CG, Tampellini D, Takahashi RH, Greengard P, Lin MT, Snyder EM, Gouras GK (2005) Beta-amyloid accumulation in APP mutant neurons reduces PSD-95 and GluR1 in synapses. *Neurobiol Dis* **20**, 187-198.

[96] Casas C, Sergeant N, Itier JM, Blanchard V, Wirths O, van der Kolk N, Vingtdeux V, van de Steeg E, Ret G, Canton T, Drobecq H, Clark A, Bonici B, Delacourte A, Benavides J, Schmitz C, Tremp G, Bayer TA, Benoit P, Pradier L (2004) Massive CA1/2 neuronal loss with intraneuronal and N-terminal truncated Abeta42 accumulation in a novel Alzheimer transgenic model. *Am J Pathol* **165**, 1289-1300.

[97] Moolman DL, Vitolo OV, Vonsattel JP, Shelanski ML (2004) Dendrite and dendritic spine alterations in Alzheimer models. *J Neurocytol* **33**, 377-387.

[98] Mori C, Spooner ET, Wisniewsk KE, Wisniewski TM, Yamaguch H, Saido TC, Tolan DR, Selkoe DJ, Lemere CA (2002) Intraneuronal Abeta42 accumulation in Down syndrome brain. *Amyloid* **9**, 88-102.

[99] Mucke L, Masliah E, Yu GQ, Mallory M, Rockenstein EM, Tatsuno G, Hu K, Kholodenko D, Johnson-Wood K, McConlogue L (2000) High-level neuronal expression of abeta 1-42 in wild-type human amyloid protein precursor transgenic mice: Synaptotoxicity without plaque formation. *J Neurosci* **20**, 4050-4058.

[100] Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, Metherate R, Mattson MP, Akbari Y, LaFerla FM (2003) Triple-transgenic model of Alzheimer's disease with plaques and tangles: Intracellular Abeta and synaptic dysfunction. *Neuron* **39**, 409-421.

[101] Spires TL, Meyer-Luehmann M, Stern EA, McLean PJ, Skoch J, Nguyen PT, Bacskai BJ, Hyman BT (2005) Dendritic spine abnormalities in amyloid precursor protein transgenic mice demonstrated by gene transfer and intravital multiphoton microscopy. *J Neurosci* **25**, 7278-7287.

[102] Takahashi RH, Milner TA, Li F, Nam EE, Edgar MA, Yamaguchi H, Beal MF, Xu H, Greengard P, Gouras GK (2002) Intraneuronal Alzheimer abeta42 accumulates in multivesicular bodies and is associated with synaptic pathology. *Am J Pathol* **161**, 1869-1879.

[103] Yang AJ, Chandswangbhuvana D, Shu T, Henschen A, Glabe CG (1999) Intracellular accumulation of insoluble, newly synthesized abetan-42 in amyloid precursor protein-transfected cells that have been treated with Abeta1-42. *J Biol Chem* **274**, 20650-20656.

[104] Bahr BA, Hoffman KB, Yang AJ, Hess US, Glabe CG, Lynch G (1998) Amyloid beta protein is internalized selectively by hippocampal field CA1 and causes neurons to accumulate amyloidogenic carboxyterminal fragments of the amyloid precursor protein. *J Comp Neurol* **397**, 139-147.

[105] Burdick D, Kosmoski J, Knauer MF, Glabe CG (1997) Preferential adsorption, internalization and resistance to

degradation of the major isoform of the Alzheimer's amyloid peptide, A beta 1-42, in differentiated PC12 cells. *Brain Res* **746**, 275-284.

[106] Yang AJ, Knauer M, Burdick DA, Glabe C (1995) Intracellular A beta 1-42 aggregates stimulate the accumulation of stable, insoluble amyloidogenic fragments of the amyloid precursor protein in transfected cells. *J Biol Chem* **270**, 14786-14792.

[107] Xu H, Greengard P, Gandy S (1995) Regulated formation of Golgi secretory vesicles containing Alzheimer beta-amyloid precursor protein. *J Biol Chem* **270**, 23243-23245.

[108] Kinoshita A, Fukumoto H, Shah T, Whelan CM, Irizarry MC, Hyman BT (2003) Demonstration by FRET of BACE interaction with the amyloid precursor protein at the cell surface and in early endosomes. *J Cell Sci* **116**, 3339-3346.

[109] Mizuguchi M, Ikeda K, Kim SU (1992) Differential distribution of cellular forms of beta-amyloid precursor protein in murine glial cell cultures. *Brain Res* **584**, 219-225.

[110] Clifford PM, Zarrabi S, Siu G, Kinsler KJ, Kosciuk MC, Venkataraman V, D'Andrea MR, Dinsmore S, Nagele RG (2007) Abeta peptides can enter the brain through a defective blood-brain barrier and bind selectively to neurons. *Brain Res* **1142**, 223-236.

[111] Yu C, Nwabuisi-Heath E, Laxton K, Ladu MJ (2010) Endocytic pathways mediating oligomeric Abeta42 neurotoxicity. *Mol Neurodegener* **5**, 19.

[112] Nagele RG, D'Andrea MR, Anderson WJ, Wang HY (2002) Intracellular accumulation of beta-amyloid(1-42) in neurons is facilitated by the alpha 7 nicotinic acetylcholine receptor in Alzheimer's disease. *Neuroscience* **110**, 199-211.

[113] Wang HY, Lee DH, D'Andrea MR, Peterson PA, Shank RP, Reitz AB (2000) beta-Amyloid(1-42) binds to alpha7 nicotinic acetylcholine receptor with high affinity. Implications for Alzheimer's disease pathology. *J Biol Chem* **275**, 5626-5632.

[114] Oddo S, Caccamo A, Green KN, Liang K, Tran L, Chen Y, Leslie FM, LaFerla FM (2005) Chronic nicotine administration exacerbates tau pathology in a transgenic model of Alzheimer's disease. *Proc Natl Acad Sci U S A* **102**, 3046-3051.

[115] Hernandez CM, Kayed R, Zheng H, Sweatt JD, Dineley KT (2010) Loss of alpha7 nicotinic receptors enhances beta-amyloid oligomer accumulation, exacerbating early-stage cognitive decline and septohippocampal pathology in a mouse model of Alzheimer's disease. *J Neurosci* **30**, 2442-2453.

[116] Bu G, Cam J, Zerbinatti C (2006) LRP in amyloid-beta production and metabolism. *Ann N Y Acad Sci* **1086**, 35-53.

[117] Deane R, Du Yan S, Submamaryan RK, LaRue B, Jovanovic S, Hogg E, Welch D, Manness L, Lin C, Yu J, Zhu H, Ghiso J, Frangione B, Stern A, Schmidt AM, Armstrong DL, Arnold B, Liliensiek B, Nawroth P, Hofman F, Kindy M, Stern D, Zlokovic B (2003) RAGE mediates amyloid-beta peptide transport across the blood-brain barrier and accumulation in brain. *Nat Med* **9**, 907-913.

[118] Yan SD, Chen X, Fu J, Chen M, Zhu H, Roher A, Slattery T, Zhao L, Nagashima M, Morser J, Migheli A, Nawroth P, Stern D, Schmidt AM (1996) RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. *Nature* **382**, 685-691.

[119] Sasaki N, Toki S, Chowei H, Saito T, Nakano N, Hayashi Y, Takeuchi M, Makita Z (2001) Immunohistochemical distribution of the receptor for advanced glycation end products in neurons and astrocytes in Alzheimer's disease. *Brain Res* **888**, 256-262.

[120] Du Yan S, Zhu H, Fu J, Yan SF, Roher A, Tourtellotte WW, Rajavashisth T, Chen X, Godman GC, Stern D, Schmidt AM (1997) Amyloid-beta peptide-receptor for advanced glycation endproduct interaction elicits neuronal expression of macrophage-colony stimulating factor: A proinflammatory pathway in Alzheimer disease. *Proc Natl Acad Sci U S A* **94**, 5296-5301.

[121] Almeida CG, Takahashi RH, Gouras GK (2006) Beta-amyloid accumulation impairs multivesicular body sorting by inhibiting the ubiquitin-proteasome system. *J Neurosci* **26**, 4277-4288.

[122] Oh S, Hong HS, Hwang E, Sim HJ, Lee W, Shin SJ, Mook-Jung I (2005) Amyloid peptide attenuates the proteasome activity in neuronal cells. *Mech Ageing Dev* **126**, 1292-1299.

[123] Tseng BP, Green KN, Chan JL, Blurton-Jones M, LaFerla FM (2008) Abeta inhibits the proteasome and enhances amyloid and tau accumulation. *Neurobiol Aging* **29**, 1607-1618.

[124] Rosario ER, Carroll JC, Oddo S, LaFerla FM, Pike CJ (2006) Androgens regulate the development of neuropathology in a triple transgenic mouse model of Alzheimer's disease. *J Neurosci* **26**, 13384-13389.

[125] Mousnier A, Kubat N, Massias-Simon A, Segeral E, Rain JC, Benarous R, Emiliani S, Dargemont C (2007) von Hippel Lindau binding protein 1-mediated degradation of integrase affects HIV-1 gene expression at a postintegration step. *Proc Natl Acad Sci U S A* **104**, 13615-13620.

[126] Manczak M, Anekonda TS, Henson E, Park BS, Quinn J, Reddy PH (2006) Mitochondria are a direct site of A beta accumulation in Alzheimer's disease neurons: Implications for free radical generation and oxidative damage in disease progression. *Hum Mol Genet* **15**, 1437-1449.

[127] Caspersen C, Wang N, Yao J, Sosunov A, Chen X, Lustbader JW, Xu HW, Stern D, McKhann G, Yan SD (2005) Mitochondrial Abeta: A potential focal point for neuronal metabolic dysfunction in Alzheimer's disease. *FASEB J* **19**, 2040-2041.

[128] Keil U, Hauptmann S, Bonert A, Scherping I, Eckert A, Muller WE (2006) Mitochondrial dysfunction induced by disease relevant AbetaPP and tau protein mutations. *J Alzheimers Dis* **9**, 139-146.

[129] Chyung JH, Raper DM, Selkoe DJ (2005) Gamma-secretase exists on the plasma membrane as an intact complex that accepts substrates and effects intramembrane cleavage. *J Biol Chem* **280**, 4383-4392.

[130] Nixon RA, Wegiel J, Kumar A, Yu WH, Peterhoff C, Cataldo A, Cuervo AM (2005) Extensive involvement of autophagy in Alzheimer disease: An immuno-electron microscopy study. *J Neuropathol Exp Neurol* **64**, 113-122.

[131] Nixon RA, Cataldo AM (2006) Lysosomal system pathways: Genes to neurodegeneration in Alzheimer's disease. *J Alzheimers Dis* **9**, 277-289.

[132] Yang AJ, Chandswangbhuvana D, Margol L, Glabe CG (1998) Loss of endosomal/lysosomal membrane impermeability is an early event in amyloid Abeta1-42 pathogenesis. *J Neurosci Res* **52**, 691-698.

[133] Wogulis M, Wright S, Cunningham D, Chilcote T, Powell K, Rydel RE (2005) Nucleation-dependent polymerization is an essential component of amyloid-mediated neuronal cell death. *J Neurosci* **25**, 1071-1080.

[134] Jan A, Adolfsson O, Allaman I, Buccarello AL, Magistretti PJ, Pfeifer A, Muhs A, Lashuel HA (2011) Abeta42 neurotoxicity is mediated by ongoing nucleated polymerization

process rather than by discrete Abeta42 species. *J Biol Chem* **286**, 8585-8596.

[135] Kayed R, Canto I, Breydo L, Rasool S, Lukacsovich T, Wu J, Albay R 3rd, Pensalfini A, Yeung S, Head E, Marsh JL, Glabe C (2010) Conformation dependent monoclonal antibodies distinguish different replicating strains or conformers of prefibrillar Abeta oligomers. *Mol Neurodegener* **5**, 57.

[136] Petkova AT, Leapman RD, Guo Z, Yau WM, Mattson MP, Tycko R (2005) Self-propagating, molecular-level polymorphism in Alzheimer's beta-amyloid fibrils. *Science* **307**, 262-265.

[137] Luhrs T, Ritter C, Adrian M, Riek-Loher D, Bohrmann B, Dobeli H, Schubert D, Riek R (2005) 3D structure of Alzheimer's amyloid-beta(1-42) fibrils. *Proc Natl Acad Sci U S A* **102**, 17342-17347.

[138] Kodali R, Williams AD, Chemuru S, Wetzel R (2010) Abeta(1-40) forms five distinct amyloid structures whose beta-sheet contents and fibril stabilities correlate. *J Mol Biol* **401**, 503-517.

[139] Miller Y, Ma B, Nussinov R (2010) Polymorphism in Alzheimer Abeta amyloid organization reflects conformational selection in a rugged energy landscape. *Chem Rev* **110**, 4820-4838.

[140] Wu JW, Breydo L, Isas JM, Lee J, Kuznetsov YG, Langen R, Glabe C (2010) Fibrillar oligomers nucleate the oligomerization of monomeric amyloid beta but do not seed fibril formation. *J Biol Chem* **285**, 6071-6079.

[141] Deshpande A, Mina E, Glabe C, Busciglio J (2006) Different conformations of amyloid beta induce neurotoxicity by distinct mechanisms in human cortical neurons. *J Neurosci* **26**, 6011-6018.

[142] Tanaka M, Collins SR, Toyama BH, Weissman JS (2006) The physical basis of how prion conformations determine strain phenotypes. *Nature* **442**, 585-589.

[143] Toyama BH, Kelly MJ, Gross JD, Weissman JS (2007) The structural basis of yeast prion strain variants. *Nature* **449**, 233-237.