Open Access

Amyloid Oligomer Structures and Toxicity

Charles G. Glabe*

Department of Molecular Biology and Biochemistry, University of California, Irvine, CA 92697, USA

Abstract: Amyloid accumulation is commonly associated with a number of important human degenerative diseases and recent findings indicate that soluble amyloid oligomers may represent the primary pathological species in degenerative diseases. Amyloid oligomers are structurally and morphologically diverse, raising the question on whether this diversity is pathologically significant and whether different types of oligomers may have different toxic activities. Many of the amyloids associated with neurodegenerative diseases form three immunologically distinct types of oligomers. Fibrillar oligomers are structurally related to fibrils and may represent small pieces of fibrils or fibril protofilaments. Prefibrillar oligomers are kinetic intermediates in fibril formation and annular protofibrils that resemble membrane pores. These three classes of oligomers share common structures and toxic activities. Focus on these common mechanisms of toxicity provides a means of simplifying the list of primary disease mechanisms and opens the possibility of developing broad spectrum therapeutics that target several amyloid related degenerative diseases.

Keywords: Amyloid structure, amyloid toxicity, amyloid oligomers, amyloid disease, pathogenesis.

INTRODUCTION

The accumulation misfolded proteins as amyloid fibrils is a key pathognomonic feature of many age-related degenerative diseases, including Alzheimer's (AD), Parkinson's, Huntington's diseases, type II diabetes and prion diseases. In most of these diseases, the end stage aggregation products that accumulate are amyloid fibers. Amyloids have traditionally been defined by their solubility, morphology and ability to bind dyes, like Congo red and thioflavin dyes. Although the common association of amyloids with neurodegenerative disease is a compelling argument for their causal association with pathogenesis, in many cases the presence of these fibrillar deposits in not obligately associated with disease. In AD, non-demented individuals have been reported that have same amount of insoluble amyloid deposits. This has led to a modification of the amyloid hypothesis to state that amyloid oligomers are causally related to disease [1]. There has been an increasing amount of evidence to support the hypothesis that amyloid oligomers represent the primary toxic species and that fibrils may be either inert, protective or toxic by distinct mechanisms.

AMYLOIDS HAVE COMMON, GENERIC STRUCTURES

Advances in our understanding of the structure of amyloid fibrils indicate that many of them share a common structural motif: Intermolecularly hydrogen bonded parallel strand where the sequence of the strands above and below are in register [2-8]. This structural motif gives rise to homogeneous tracts of amino acid side chains, known as "steric zippers" running up and down the ß sheets. Since the 20 amino acids are well distributed among various sequences, amyloid fibrils formed by different sequences will all display the same steric zippers, although the arrangement of the zippers will vary with the sequence. Amyloid oligomers also have common structures [9]. Conformation dependent, aggregation specific antibodies suggest that there are 3 general classes of amyloid oligomer structures than many types of amyloidogenic sequences form [10, 11]. These include "fibrillar oligomers", which may represent small pieces of fibrils or fibril protofilaments [12], "prefibrillar oligomers", which are kinetic intermediates that precede fibril formation [9, 13] and "annular protofibrils", which are pore like structures [11, 14] (Fig. **1**).

Fibrils and fibrillar oligomers react with the fibril specific antibody, OC [12]. This antibody recognizes a generic fibril epitope, as it reacts with several types of amyloid fibrils, including amyloid beta peptide (Aß), alpha synuclein, islet amyloid polypeptide and poly Q. This antibody also recognizes a number of natural peptide hormones stored as functional amyloids in pituitary secretory granules [15]. Monoclonal antibodies with similar generic fibril immunoreactivity have also been reported [16, 17]. OC stains all types of amyloid deposits in AD and islet amyloid in transgenic mouse models of type II diabetes, but it does not react with prefibrillar oligomers or annular protofibrils [11, 12]. A11 recognizes a generic epitope associated with prefibrillar oligomers, but it does not react with amyloid fibrils [9]. This indicates that prefibrillar oligomers have a common structural motif that is distinct from that displayed by fibrils. Anti-annular protofibril antibody recognizes a generic epitope that is specific to annular protofibrils [9]. This antibody also recognizes heptameric pores, but not monomers from the bacterial toxin, alpha hemolysin, suggesting that it recognizes a beta barrel motif. The fact that these antibodies recognize common structural features that are unique to specific amyloid aggregation states suggests that the aggregates may share a common mechanism of toxicity and pathogenesis. Indeed, amyloid oligomers from non-disease related proteins and peptides are intrinsically

*Address correspondence to this author at the Department of Molecular Biology and Biochemistry, University of California, Irvine, California 92697, USA; Fax: +1 949 824 8551; E-mail: cglabe@uci.edu

1874-1967/09 2009 Bentham Open

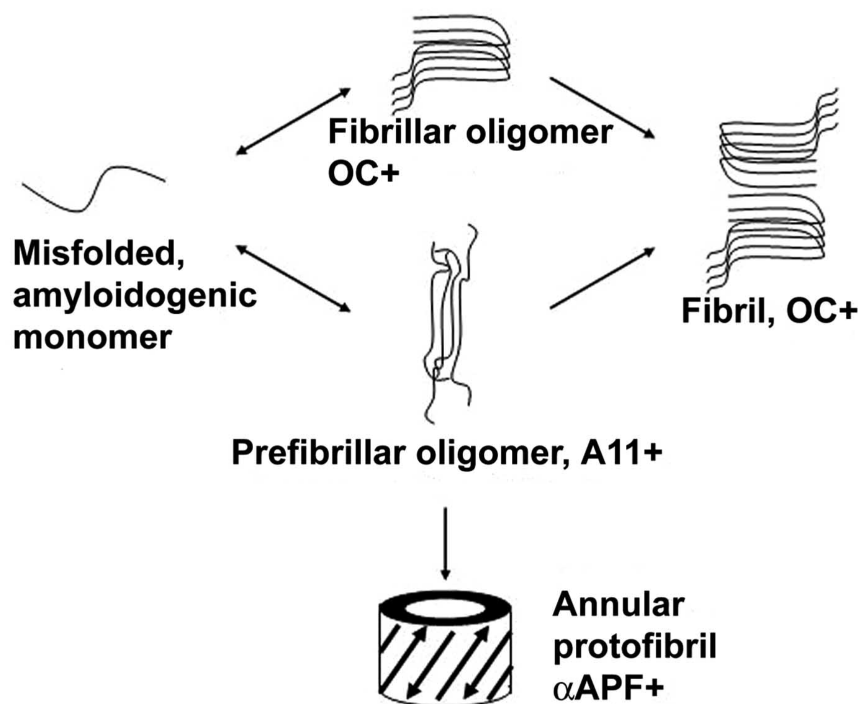

Fig. (1). Distinct assembly states of amyloids. Misfolded amyloidogenic monomers can adopt a fibrillar lattice structure that is recognized by the fibril specific antibody, OC. Fibrillar oligomers represent small pieces of a fibril protofilament, but they share immunoreactivity with OC. Alternatively, monomers may assemble into prefibrillar oligomers that are A11 positive and OC negative. Prefibrillar oligomers are precursors for the formation of annular protofibrils. Annular protofibrils are recognized by aAPF antibody.

toxic [18] and the toxicity shares features with disease related amyloid toxicity [19]. The fact that fibrils, prefibrillar oligomers and annular protofibrils display distinct generic epitopes suggests that have fundamental differences in the structural organization of their polypeptide backbones. If fibrils are parallel, in register structures and annular protofibrils are beta barrels, prefibrillar oligomers may be antiparallel beta sheets or alpha extended sheets [20, 21]. Alpha sheets are characterized by a unique pattern of bifurcated hydrogen bonding and can transition back and forth between ß-sheet through individual transitions of backbone ϕ,φ angles [21]. If fibrils, prefibrillar oligomers and annular protofibrils have distinct structures, their toxic activities may also be distinct.

AMYLOIDS ARE GENERIC TOXINS

Although disease associated amyloids have received the most attention, it has become increasingly apparent that the ability to form amyloid fibrils and oligomers is a widespread consequence of protein misfolding [22]. The SH3 domain of phosphatidylinositol 3' kinase and the N-terminal domain of HypF protein form amyloid fibrils and prefibrillar oligomers and the oligomers form by these non-disease related proteins display equivalent toxicity to disease related oligomers like Aß [13, 23]. Amyloid oligomers derived from cytosolic proteins and peptides, like alpha synuclein and polyQ are toxic to cells when they are applied externally, indicating that their toxicity does not depend on specific intracellular targets. The toxicity of amyloid does not appear to be stereospecific as the amyloid aggregates derived from D-amino acid peptide, like D-Aß42 are as toxic as the normal L-amino acid peptides [24, 25], although a more recent report indicates that D-Aß42 aggregates are not toxic [26]. The finding that amyloid oligomers are generically toxic is consistent with the observation that they form common generic structures, since one of the cannons of biochemistry is that the structure of proteins determines their function.

WHY ARE AMYLOID OLIGOMERS MORE TOXIC THAN AMYLOID FIBRILS?

A number of studies have provided evidence that soluble Aß oligomers are more toxic to cells than mature fibrils [9, 18, 27-31]. In some cases, fibril formation may actually be neuroprotective [32]. Although amyloid fibrils have also been reported to be toxic [33], there is evidence that fibrils and oligomers are toxic by distinct mechanisms [34]. The fact that prefibrillar oligomers and annular protofibrils have generic structures that are distinct from fibrils is consistent with the idea that they have distinct mechanisms of toxicity. For example, prefibrillar oligomers have been reported to permeabilize cell membranes while fibrils lack this activity [31, 35]. Prefibrillar oligomers can also bind to membranes and convert into annular protofibrils that may represent ß-barrel membrane pores [11]. It is more difficult to rationalize the differential toxicity of Aß fibrillar oligomers and Aß fibrils, as they share the same generic epitope recognized by fibril specific antibodies [12] and they exhibit the same parallel, in-register structure as fibrils [36]. One possibility is that fibrillar oligomers may be small pieces of a single protofilament and that they may have hydrophobic surfaces exposed on the surface of the ß-sheets that would otherwise by hidden by sheet stacking interactions between the

protofilaments in the mature fibril [37]. Another possibility is that the ends of fibrils and fibrillar oligomers are toxic and therefore the oligomers would be more toxic in relationship to the amount of Aß because the fibrils are considerably longer. Fibrillar oligomers may also be more toxic than fibrils because they are smaller and more capable of diffusing throughout the tissue than the fibrils that accumulate as insoluble deposits [27].

POTENTIAL MECHANISMS OF AMYLOID TOXICITY AND PATHOGENESIS

Many different mechanisms have been proposed for amyloid toxicity. Indeed, the pathogenic mechanism landscape is beginning to look like the elephant viewed by blind men, with many different and seemingly incompatible parts and functions. Soon after the identification of Aß as the major component of amyloid plaques in AD, reports of both toxicity and trophic activity appeared [38-40]. The toxicity was reported to be related to the aggregation state of Aß, with aggregation being required for toxicity [41, 42]. Several potentially pathogenic alterations were soon reported to be associated with Aß toxicity. A partial list includes elevated intracellular calcium [43], activation of complement [44], induction of apoptosis [45], formation of ion channels [46], altered ion channel function and oxygen radical production [47], potentiation of cytokine secretion [48], induction of tau phosphorylation [49], tau dependent microtubule disassembly [50], modulation of signal transduction pathways [51], binding of Aß to the receptor for advanced glycation end products (RAGE) [52], binding to synapses and inhibition of LTP [27, 29], binding to APP [53], binding to alpha7 nicotinic acetylcholine receptors (α7nAChR) [54], inhibition of synaptic function [55], loss of excitatory synapses [56], binding to mitochondrial alcohol dehydrogenase and mitochondrial dysfunction [57], endocytosis of N-methyl-D-aspartate (NMDA) receptors [58], membrane permeabilization [59] and loss of neuronal spines [60]. With so many different ways of damaging neurons and interfering with their function, Aß starts looking like the Swiss army knife of AD. These potential mechanisms are not mutually exclusive. Some of them may be proximal to Aß and some may be downstream events in a causal cascade. Understanding which of these mechanisms is the primary effect of amyloid oligomers is important for developing therapeutic strategies that target amyloid toxicity, but it also presents a serious experimental challenge in view of the many deleterious functions ascribed to amyloids.

WHICH MECHANISMS ARE PROXIMAL TO AMYLOID?

Understanding the primary pathogenic properties of amyloids is also critical for understanding how all the pathogenic pieces fit the puzzle. What does amyloid actually interact with and are these interactions specific to a particular amyloid sequence or are they specific to a particular assembly state or conformation? Aß oligomers are known to bind to cells and in neuronal cells, it binds to both synaptic and non-synaptic sites [27, 61]. The binding of Aß oligomers is restricted to a subset of 30-50% of neurons, suggesting that the binding is specific for certain types of neurons [62]. Some of the neuronal binding sites are sensitive to trypsin digestion, suggesting that they are proteins [27] and a variety of cell surface proteins have been reported to bind aggregated Aß, including amyloid precursor protein (APP) [53, 63], NMDA-receptors [64], integrins [64], RAGE [52], the α7nAChR [54] and the prion protein (PrP) [65]. If Aß does indeed bind to all of these different cell surface proteins, this would be an unusual specificity unlike typical ligands for cell surface receptors.

Is the binding of Aß to these cell surface receptors stereospecific according to peptide sequence? Stereospecific binding would be very desirable from a therapeutic standpoint, as many drugs have been developed that are receptor antagonists. The typical controls used to demonstrate specificity include scrambled peptides and the reverse Aß sequence and the lack of binding or activity of these control peptides is often interpreted as a reflection of the specificity of the interaction. However, these peptides do not aggregate and it is known for most of these binding interactions that the binding depends on the aggregation state of Aß. Fibrillar prion peptide 106-126 and islet amyloid polypeptide bind to APP as well as Aß fibrils, so this binding interaction is independent of the amino acid sequence [66]. In addition, the all D amino acid variant of Aß42 binds to neuronal cell bodies, axons and dendrites to the same extent as L-Aß42, indicating that this binding interaction is not stereospecific [26]. In the cases where it has specifically been examined, the binding has been found to be aggregation specific, rather than sequence specific.

Membrane permeabilization is another fundamental and widely reported property of amyloid oligomers. The earliest findings reported the formation of ion channels in lipid bilayers [46, 67]. Later work reported the formation of pores [14, 68] and non-selective permeabilization of lipid bilayers and cell membranes caused by altering the dielectric properties of the membrane [35, 59, 69]. Regardless of the precise mechanism, the experiments with lipid bilayers demonstrate that amyloid oligomers interact with membranes and cause the dysregulation of ion homeostasis. Membrane permeabilization is also a common and generic property of many different types of amyloid oligomers including Aß, alpha synuclein, polyQ and IAPP have been widely reported to permeabilize membranes [70, 71]. Amyloid oligomers specifically increase lipid bilayer conductance regardless of the sequence, while fibrils and soluble low molecular weight species have no observable effect [19, 72]. Like toxicity, membrane permeabilization is a generic property of amyloid oligomers that may reflect their common structural foundations.

COMMON MECHANISMS OF AMYLOID OLIGOMER TOXICITY AND DISEASE PATHOGENESIS

One way of evaluating the potential significance and relationships of these mechanisms is to examine which of these mechanisms are specific to Aß and AD and which of the mechanisms are common to many amyloid related degenerative diseases. Since amyloids are believed to be causally related to pathogenesis in many degenerative diseases and they share common structural features, mecha-

nisms that are shared by these diseases have a broader base of experimental support. Of the mechanisms listed above, calcium dyshomeostasis, has been widely reported in other neurodegenerative diseases. As noted above elevated intracellular calcium levels may be the direct result of amyloid oligomers permeabilizing membranes [35, 59], forming ion channels or pores [67, 73] or activating endogenous calcium channels [74, 75]. Mitochondrial dysfunction, the production of oxygen radicals and apoptosis are also widely reported to be associated with amyloid-related degenerative diseases and are known to be caused by accumulation of excess Ca^{+2} in the mitochondrial matrix, so these common disease features may be downstream of elevated cytosolic Ca^{+2} levels [76]. Since elevated intracellular Ca^{+2} levels have been widely reported in neurodegenerative disease and it can regulate several of the key down stream pathological events, it is worth considering as a central mechanism.

CONCLUSIONS

The case for a common, shared mechanism of amyloid toxicity and pathogenesis is compelling. The accumulation of amyloids as fibrils or oligomers is commonly associated with neurodegeneration. Amyloid oligomers have common, intramolecularly hydrogen bonded ß structures that give rise to repetitive patterns of amino acid side chains on their surfaces. Amyloid oligomers are toxic *in vitro* and *in vivo* by a variety of mechanisms. Since structure determines the function of biological molecules, this common structure implies that amyloids have common toxic activities. Of the many mechanisms that have been proposed for amyloid toxicity, elevated cytosolic Ca^{+2}, production of reactive oxygen species and mitochondrial dysfunction have been widely reported to be associated with amyloid toxicity. These may represent key features of a common mechanism of amyloid pathogenesis in neurodegenerative disease. Targeting this common pathway may lead to the development of effective therapeutics for a broad spectrum of neurodegenerative diseases.

ACKNOWLEDGEMENT

This work was supported by a grant from the NIH AG00538 and grants from the Cure Alzheimer Fund and The Larry L. Hillblom Foundation. C.G. is a consultant for Kinexis, Inc.

REFERENCES

[1] Walsh DM, Selkoe DJ. A beta oligomers - a decade of discovery. J Neurochem 2007; 101(5): 1172-84.

[2] Benzinger TL, Gregory DM, Burkoth TS, *et al.* Propagating structure of Alzheimer's beta-amyloid(10-35) is parallel beta-sheet with residues in exact register. Proc Natl Acad Sci USA 1998; 95(23): 13407-12.

[3] Antzutkin ON, Balbach JJ, Leapman RD, Rizzo NW, Reed J, Tycko R. Multiple quantum solid-state NMR indicates a parallel, not antiparallel, organization of beta-sheets in Alzheimer's beta-amyloid fibrils. Proc Natl Acad Sci USA 2000; 97(24): 13045-50.

[4] Luhrs T, Ritter C, Adrian M, *et al.* 3D structure of Alzheimer's amyloid-beta(1-42) fibrils. Proc Natl Acad Sci USA 2005; 102(48): 17342-7.

[5] Török M, Milton S, Kayed R, *et al.* Structural and dynamic features of Alzheimer's Abeta peptide in amyloid fibrils studied by site-directed spin labeling. J Biol Chem 2002; 13: 13.

[6] Der-Sarkissian A, Jao CC, Chen J, Langen R. Structural organization of alpha-synuclein fibrils studied by site-directed spin labeling. J Biol Chem 2003; 278(39): 37530-5.

[7] Jayasinghe SA, Langen R. Identifying structural features of fibrillar islet amyloid polypeptide using site-directed spin labeling. J Biol Chem 2004; 279(46): 48420-5.

[8] Sawaya MR, Sambashivan S, Nelson R, *et al.* Atomic structures of amyloid cross-beta spines reveal varied steric zippers. Nature 2007; 447(7143): 453-7.

[9] Kayed R, Head E, Thompson JL, *et al.* Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. Science 2003; 300(5618): 486-9.

[10] Glabe CG. Structural classification of toxic amyloid oligomers. J Biol Chem 2008; 283(44): 29639-43.

[11] Kayed R, Pensalfini A, Margol L, *et al.* Annular protofibrils are a structurally and functionally distinct type of amyloid oligomer. J Biol Chem 2009; 284(7): 4230-7.

[12] Kayed R, Head E, Sarsoza F, *et al.* Fibril specific, conformation dependent antibodies recognize a generic epitope common to amyloid fibrils and fibrillar oligomers that is absent in prefibrillar oligomers. Mol Neurodegener 2007; 2(18): 1-11.

[13] Baglioni S, Casamenti F, Bucciantini M, *et al.* Prefibrillar amyloid aggregates could be generic toxins in higher organisms. J Neurosci 2006; 26(31): 8160-7.

[14] Lashuel HA, Hartley D, Petre BM, Walz T, Lansbury PT, Jr. Neurodegenerative disease: amyloid pores from pathogenic mutations. Nature 2002; 418(6895): 291.

[15] Maji SK, Perrin MH, Sawaya MR, *et al.* Functional amyloids as natural storage of peptide hormones in pituitary secretory granules. Science 2009; 325 (5938): 328-32.

[16] Hrncic R, Wall J, Wolfenbarger DA, *et al.* Antibody-mediated resolution of light chain-associated amyloid deposits. Am J Pathol 2000; 157(4): 1239-46.

[17] O'Nuallain B, Hrncic R, Wall JS, Weiss DT, Solomon A. Diagnostic and therapeutic potential of amyloid-reactive IgG antibodies contained in human sera. J Immunol 2006; 176(11): 7071-8.

[18] Bucciantini M, Giannoni E, Chiti F, *et al.* Inherent toxicity of aggregates implies a common mechanism for protein misfolding diseases. Nature 2002; 416(6880): 507-11.

[19] Bucciantini M, Calloni G, Chiti F, *et al.* Prefibrillar amyloid protein aggregates share common features of cytotoxicity. J Biol Chem 2004; 279(30): 31374-82.

[20] Armen RS, DeMarco ML, Alonso DO, Daggett V. Pauling and Corey's alpha-pleated sheet structure may define the prefibrillar amyloidogenic intermediate in amyloid disease. Proc Natl Acad Sci USA 2004; 101(32): 11622-7.

[21] Daggett V. Alpha-sheet: The toxic conformer in amyloid diseases? Acc Chem Res 2006; 39(9): 594-602.

[22] Dobson CM. The structural basis of protein folding and its links with human disease. Philos Trans R Soc Lond B Biol Sci 2001; 356(1406): 133-45.

[23] Bucciantini M, Giannoni E, Chiti F, *et al.* Inherent toxicity of aggregates implies a common mechanism for protein misfolding diseases. Nature 2002; 416(6880): 507-11.

[24] Cribbs DH, Pike CJ, Weinstein SL, Velazquez P, Cotman CW. All-D-enantiomers of beta-amyloid exhibit similar biological properties to all-L-beta-amyloids. J Biol Chem 1997; 272(11): 7431-6.

[25] Pastor MT, Kummerer N, Schubert V, *et al.* Amyloid toxicity is independent of polypeptide sequence, length and chirality. J Mol Biol 2008; 375(3): 695-707.

[26] Ciccotosto GD, Tew DJ, Drew SC, *et al.* Stereospecific interactions are necessary for Alzheimer disease amyloid-beta toxicity. Neurobiol Aging 2009; March 24 [Epub ahead of print].

[27] Lambert MP, Barlow AK, Chromy BA, *et al.* Diffusible, nonfibrillar ligands derived from Abeta1-42 are potent central nervous system neurotoxins. Proc Natl Acad Sci USA 1998; 95(11): 6448-53.

[28] Dahlgren KN, Manelli AM, Stine WB Jr, Baker LK, Krafft GA, LaDu MJ. Oligomeric and fibrillar species of amyloid-beta peptides differentially affect neuronal viability. J Biol Chem 2002; 277(35): 32046-53.

[29] Walsh DM, Klyubin I, Fadeeva JV, *et al.* Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation *in vivo*. Nature 2002; 416(6880): 535-9.

[30] Gosavi N, Lee HJ, Lee JS, Patel S, Lee SJ. Golgi fragmentation occurs in the cells with prefibrillar alpha-synuclein aggregates and precedes the formation of fibrillar inclusion. J Biol Chem 2002; 277(50): 48984-92.

[31] Janson J, Ashley RH, Harrison D, McIntyre S, Butler PC. The mechanism of islet amyloid polypeptide toxicity is membrane disruption by intermediate-sized toxic amyloid particles. Diabetes 1999; 48(3): 491-8.

[32] Arrasate M, Mitra S, Schweitzer ES, Segal MR, Finkbeiner S. Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. Nature 2004; 431(7010): 805-10.

[33] Lorenzo A, Yankner BA. Beta-amyloid neurotoxicity requires fibril formation and is inhibited by congo red. Proc Natl Acad Sci USA 1994; 91(25): 12243-7.

[34] Deshpande A, Mina E, Glabe C, Busciglio J. Different conformations of amyloid beta induce neurotoxicity by distinct mechanisms in human cortical neurons. J Neurosci 2006; 26(22): 6011-8.

[35] Demuro A, Mina E, Kayed R, Milton SC, Parker I, Glabe CG. Calcium dysregulation and membrane disruption as a ubiquitous neurotoxic mechanism of soluble amyloid oligomers. J Biol Chem 2005; 280(17): 17294-300.

[36] Chimon S, Shaibat MA, Jones CR, Calero DC, Aizezi B, Ishii Y. Evidence of fibril-like beta-sheet structures in a neurotoxic amyloid intermediate of Alzheimer's beta-amyloid. Nat Struct Mol Biol 2007; Dec 2 [Epub ahead of print].

[37] Paravastu AK, Leapman RD, Yau WM, Tycko R. Molecular structural basis for polymorphism in Alzheimer's beta-amyloid fibrils. Proc Natl Acad Sci USA 2008; 105(47): 18349-54.

[38] Yankner BA, Dawes LR, Fisher S, Villa-Komaroff L, Oster-Granite ML, Neve RL. Neurotoxicity of a fragment of the amyloid precursor associated with Alzheimer's disease. Science 1989; 245: 417-20.

[39] Yankner BA, Duffy LK, Kirschner DA. Neurotrophic and neurotoxic effects of amyloid beta protein: reversal by tachykinin neuropeptides. Science 1990; 250: 279-82.

[40] Whitson JS, Selkoe DJ, Cotman CW. Amyloid beta protein enhances the survival of hippocampal neurons *in vitro*. Science 1989; 243: 1488-90.

[41] Pike CJ, Walencewicz AJ, Glabe CG, Cotman CW. *In vitro* aging of beta-amyloid protein causes peptide aggregation and neurotoxicity. Brain Res 1991; 563: 311-4.

[42] Busciglio J, Lorenzo A, Yankner BA. Methodological variables in the assessment of beta amyloid neurotoxicity. Neurobiol Aging 1992; 13: 609-12.

[43] Mattson MP, Cheng B, Davis D, Bryant K, Lieberburg I, Rydel RE. beta-Amyloid peptides destabilize calcium homeostasis and render human cortical neurons vulnerable to excitotoxicity. J Neurosci 1992; 12: 376-89.

[44] Rogers J, Cooper NR, Webster S, *et al.* Complement activation by beta-amyloid in Alzheimer disease. Proc Natl Acad Sci USA 1992; 89: 10016-20.

[45] Loo DT, Copani A, Pike CJ, Whittemore ER, Walencewicz AJ, Cotman CW. Apoptosis is induced by beta-amyloid in cultured central nervous system neurons. Proc Natl Acad Sci USA 1993; 90(17): 7951-5.

[46] Arispe N, Rojas E, Pollard HB. Alzheimer disease amyloid beta protein forms calcium channels in bilayer membranes: blockade by tromethamine and aluminum. Proc Natl Acad Sci USA 1993; 90: 567-71.

[47] Behl C, Davis JB, Lesley R, Schubert D. Hydrogen peroxide mediates amyloid beta protein toxicity. Cell 1994; 77: 817-27.

[48] Gitter BD, Cox LM, Rydel RE, May PC. Amyloid beta peptide potentiates cytokine secretion by interleukin-1 beta-activated human astrocytoma cells. Proc Natl Acad Sci USA 1995; 92: 10738-41.

[49] Busciglio J, Lorenzo A, Yeh J, Yankner BA. beta-amyloid fibrils induce tau phosphorylation and loss of microtubule binding. Neuron 1995; 14: 879-88.

[50] King ME, Kan HM, Baas PW, Erisir A, Glabe CG, Bloom GS. Tau-dependent microtubule disassembly initiated by prefibrillar beta-amyloid. J Cell Biol 2006 20; 175(4): 541-6.

[51] Zhang C, Lambert MP, Bunch C, *et al.* Focal adhesion kinase expressed by nerve cell lines shows increased tyrosine phosphorylation in response to Alzheimer's A beta peptide. J Biol Chem 1994; 269: 25247-50.

[52] Yan SD, Chen X, Fu J, *et al.* RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease [see comments]. Nature 1996; 382(6593): 685-91.

[53] Lorenzo A, Yuan M, Zhang Z, *et al.* Amyloid beta interacts with the amyloid precursor protein: a potential toxic mechanism in Alzheimer's disease. Nat Neurosci 2000; 3(5): 460-4.

[54] Wang HY, Lee DH, D'Andrea MR, Peterson PA, Shank RP, Reitz AB. beta-Amyloid(1-42) binds to alpha7 nicotinic acetylcholine receptor with high affinity. Implications for Alzheimer's disease pathology. J Biol Chem 2000; 275(8): 5626-32.

[55] Kamenetz F, Tomita T, Hsieh H, Seabrook G, Borchelt D, Iwatsubo T, *et al.* APP processing and synaptic function. Neuron 2003; 37(6): 925-37.

[56] Koffie RM, Meyer-Luehmann M, Hashimoto T, *et al.* Oligomeric amyloid beta associates with postsynaptic densities and correlates with excitatory synapse loss near senile plaques. Proc Natl Acad Sci USA 2009; 106(10): 4012-7.

[57] Lustbader JW, Cirilli M, Lin C, *et al.* ABAD directly links Abeta to mitochondrial toxicity in Alzheimer's disease. Science 2004; 304(5669): 448-52.

[58] Snyder EM, Nong Y, Almeida CG, *et al.* Regulation of NMDA receptor trafficking by amyloid-beta. Nat Neurosci 2005; 8(8): 1051-8.

[59] Kayed R, Sokolov Y, Edmonds B, *et al.* Permeabilization of lipid bilayers is a common conformation-dependent activity of soluble amyloid oligomers in protein misfolding diseases. J Biol Chem 2004; 279(45): 46363-6.

[60] Shankar GM, Bloodgood BL, Townsend M, Walsh DM, Selkoe DJ, Sabatini BL. Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. J Neurosci. 2007; 27(11): 2866-75.

[61] Gong Y, Chang L, Viola KL, *et al.* Alzheimer's disease-affected brain: presence of oligomeric A beta ligands (ADDLs) suggests a molecular basis for reversible memory loss. Proc Natl Acad Sci USA 2003; 100(18): 10417-22.

[62] Lacor PN, Buniel MC, Chang L, *et al.* Synaptic targeting by Alzheimer's-related amyloid beta oligomers. J Neurosci 2004; 24(45):10191-200.

[63] Wagner MR, Keane DM, Melchor JP, Auspaker KR, Van Nostrand WE. Fibrillar amyloid beta-protein binds protease nexin-2/amyloid beta-protein precursor: stimulation of its inhibition of coagulation factor XIa. Biochemistry 2000; 39(25): 7420-7.

[64] Bi X, Gall CM, Zhou J, Lynch G. Uptake and pathogenic effects of amyloid beta peptide 1-42 are enhanced by integrin antagonists and blocked by NMDA receptor antagonists. Neuroscience 2002; 112(4): 827-40.

[65] Lauren J, Gimbel DA, Nygaard HB, Gilbert JW, Strittmatter SM. Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers. Nature 2009; 457(7233): 1128-32.

[66] White AR, Maher F, Brazier MW, *et al.* Diverse fibrillar peptides directly bind the Alzheimer's amyloid precursor protein and amyloid precursor-like protein 2 resulting in cellular accumulation. Brain Res 2003; 966(2): 231-44.

[67] Arispe N, Pollard HB, Rojas E. Giant multilevel cation channels formed by Alzheimer disease amyloid beta-protein [A beta P-(1-40)] in bilayer membranes. Proc Natl Acad Sci USA 1993; 90(22): 10573-7.

[68] Lashuel HA, Hartley DM, Petre BM, *et al.* Mixtures of wild-type and a pathogenic (E22G) form of Abeta40 in vitro accumulate protofibrils, including amyloid pores. J Mol Biol 2003; 332(4): 795-808.

[69] Sokolov Y, Kozak JA, Kayed R, Chanturiya A, Glabe C, Hall JE. Soluble amyloid oligomers increase bilayer conductance by altering dielectric structure. J Gen Physiol 2006; 128(6): 637-47.

[70] Kagan BL, Hirakura Y, Azimov R, Azimova R, Lin MC. The channel hypothesis of Alzheimer's disease: current status. Peptides 2002; 23(7): 1311-5.

[71] Caughey B, Lansbury PT. Protofibrils, pores, fibrils, and neurodegeneration: separating the responsible protein aggregates from the innocent bystanders. Annu Rev Neurosci 2003; 26: 267-98.

[72] Kayed R, Sokolov Y, Edmonds B, *et al.* Permeabilization of lipid bilayers is a common conformation-dependent activity of soluble amyloid oligomers in protein Mis-folding diseases. J Biol Chem 2004; 279(45): 46363-6.

[73] Arispe N, Pollard HB, Rojas E. The ability of amyloid beta-protein [A beta P (1-40)] to form Ca^{2+} channels provides a mechanism for neuronal death in Alzheimer's disease. Ann NY Acad Sci 1994; 747: 256-66.

[74] Etcheberrigaray R, Ito E, Kim CS, Alkon DL. Soluble beta-amyloid induction of Alzheimer's phenotype for human fibroblast K+ channels. Science 1994; 264: 276-9.

[75] Weiss JH, Pike CJ, Cotman CW. Ca^{2+} channel blockers attenuate beta-amyloid peptide toxicity to cortical neurons in culture. J Neurochem 1994; 62: 372-5.

[76] Brookes PS, Yoon Y, Robotham JL, Anders MW, Sheu SS. Calcium, ATP, and ROS: a mitochondrial love-hate triangle. Am J Physiol Cell Physiol 2004; 287(4): C817-33.

Received: April 30, 2009 Revised: July 03, 2009 Accepted: July 07, 2009

© Charles G. Glabe; Licensee *Bentham Open*.

This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/), which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.