ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Acta Neurobiol Exp 2004, 64: 41-52

Neurodegenerative aspects of protein aggregation

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Review

Abstract. Protein aggregation and amyloid fibril deposits are characteristic features of more than twenty pathologic conditions characterized by plaque deposition in the central nervous system. Recent studies point out relationships between protein misfolding and numerous serious diseases. Despite different origins (sporadic, familial or transmissible), they are sometimes called conformational diseases to emphasize aberrant conformations as the putative cause of deposits that precede or accompany the clinical manifestation of the disease. Neurological disorders such as Alzheimer's disease (AD), Prion disorders (PrD), Parkinson's disease (PD), and Huntington's disease (HD) are the most typical examples of protein-based dementias, characterized by protein conformational transitions (α-helix/random coil to β-sheet) that cause aggregation followed by fibrillization. Although it is very tempting to postulate a common mechanism of toxicity based on conformational and structural analogies, it should be noted that the factors responsible for conformational transition, oligomerization, aggregation, and plaque formation, are still subject of speculation and additional data is required to test the amyloid fibril hypothesis.

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Key words: protein aggregation, conformation, Alzheimer's disease, Parkinson's disease, prion disorders, Huntington's disease

INTRODUCTION

Considerable attention is currently focused on understanding how protein structure influences its function. More specifically, the propensity of some proteins to aggregate has spurred interest in this area due to its potential role in several neurodegenerative diseases.

Large numbers of intracellular and extracellular proteinaceous fibers have been observed in numerous neuropathies. At least 23 different amyloidoses and other proteinopathies characterized by aggregate formation have been defined (Stefani and Dobson 2003). The presence of protein aggregates in tissue serve as hallmarks of the above disorders and have been used to imply a causative relationship between the pathologies and the observed aggregates (Religa and Winblad 2003). The amyloid hypothesis has emerged in light of these correlations (Dobson 2001, Kelly 1998). Accumulation of protein aggregates, predominantly in the fibrillar form in brain parenchyma or vessels, is associated with signs of neurodegeneration caused by oxidative stress (Brzyska et al. 2001, Castellani et al. 2004, Mattson 2002, Pogocki 2003, Raina et al. 2004, Squier 2001, Van Der Vlies et al. 2003), disturbance of calcium homeostasis (Brzyska and Elbaum 2003, Mattson 1994, 2002), apoptosis, or necrosis (Offen et al. 2000, Rego and Oliveira 2003).

The aggregated proteins characteristic of AD, PrD, HD, and PD lack significant primary sequence homology, however, they share a high degree of similarity in their ability to undergo conformational changes, form fibrillar structures, and resist proteolysis *in vitro* and *in vivo*. Thus, despite major differences in amino acid composition, the cellular location and type of lesion generated by these proteins and the pathological mechanisms postulated for these proteins are similar (Hashimoto et al. 2003, Murphy 2002).

In addition to their structural resemblance, while in aggregated form, they might share comparable pathways of aggregation (Hashimoto et al. 2003, Murphy 2002, Stefani and Dobson 2003), making it very tempting to postulate a common mechanism of their neurotoxicity. Predictions of amyloid fibril-forming proteins have been forwarded based on their conformational analogy (Kallberg et al. 2001). As a result, given that the propensity to undergo conformational transition (α-helix$\rightarrow\beta$-sheet) appears to be responsible for aggregation and fibrillization leading to the neurotoxicity, stabilization of α-helix secondary structure to prohibit/delay deposit formation can be considered as a possible therapeutic approach in the putative conformational diseases (Kazantsev et al. 2002, Soto 2002, Soto et al. 1996, 2000).

In this review we focus on the most frequent neurodegenerative disorders to examine the possibility that, in spite of differences in the target cell, intracellular location, medical manifestations, and complicated etiology, these disorders might share common key step of pathogenesis.

ALZHEIMER'S DISEASE

AD is the leading cause of dementia in the elderly. The etiology of AD is complex with the same clinical symptoms and neuropathological profile being observed in both sporadic and familial forms (Duara et al. 1993). Extracellular amyloid plaques and intracellular neurofibrillary tangles are two proteinaceous pathological lesions observed in the brains of Alzheimer's patients. Amyloid plaques consist of heterogeneous peptides 39-42 amino acids long, with the 42 amino acid peptide responsible for plaque formation (Iwatsubo et al. 1994). Amyloid-β (Aβ) is one of the proteolytic products of a multiple processing of a larger, approximately 70 kDa, membrane-bound amyloid-β protein precursor (APP). Aβ results from the consecutive cleavage of APP by two endopeptidases: β- and γ-secretases. The first is a membrane aspartyl protease (BACE1) (Hussain et al. 1999, Sinha et al. 1999, Vassar et al. 1999, Yan et al. 1999). The second, γ-secretase, has not been yet clearly defined, although presenilin 1 and 2 (PS-1 and PS-2), two transmembrane proteins seem to be required to generate Aβ (Price et al. 1998, Sisodia and St George-Hyslop 2002). Mutations in APP and in the multiple transmembrane domains of PS-1 and PS-2 are linked to familial AD (Citron et al. 1992). More specifically, these mutations can shift the membrane cleavage to generate $A\beta_{1\text{-}42}$ rather than $A\beta_{1\text{-}40}$, thus favoring a more amyloidogenic peptide. The above observations are consistent with a primary causal role of Aβ in plaque formation and AD pathology.

AMYLOID-β

In solution, Aβ is capable of adopting several different conformations depending on the solvent type. Generally, mixture of β-sheet and random coil structures is observed in physiological buffers. However, conditions of high peptide concentration favor self-aggregation

and enrichment of the β-sheet structure is observed (Barrow et al. 1992). Membrane-like environments render the amyloid peptide more prone to adopt α-helix conformation (Shen and Murphy 1995).

It is presumed that Aβ peptides contain two regions of higher hydrophobicity; C-terminal residues 32-42 and the short span of residues 17-21 creating regions of increased probability for β-sheet formation. Additionally, residues 9-21 can undergo α→β conformational transition (Soto et al. 1994) and replacement of any residue within the sequence residues 17-23 by proline increases solubility of Aβ and diminishes the β-sheet content and fibril formation (De Strooper et al. 1995). Thus fibrillogenesis has been shown to be linked to α→β conversion.

Insoluble aggregates, when examined by electron microscope, revealed the presence of long, unbranched fibrils up to 10 nm in diameter (Fraser et al. 1991, Serpell et al. 1995), consistent with several laterally aggregated fibers. Solid state NMR determinations performed on a short amyloid peptide 10-35 suggested that the peptide forms a parallel β-sheet structure (Benzinger et al. 1998). This result was confirmed by a quantum solid state NMR of β-amyloid 1-40 peptide pointing to parallel β-sheet arrangements (Benzinger et al. 2000). Interestingly, results obtained through atomic force microscopy (Stine et al. 1996), and indirectly by x-ray diffraction (Inouye et al. 1993), suggest the presence of thin aggregates, which could play a role in protofilaments formation. To this end, using molecular modeling, Chaney and colleagues (1998) suggested that three protofilaments intertwine to create the fibril-form structure, composed of six units in cross-section (Chaney et al. 1998).

PRION DISORDERS

PrD are fatal neurodegenerative disorders of an infectious (Cervenakova et al. 2003, Marsh et al. 1974, Pattison et al. 1972), genetic (Bianca et al. 2003, Gajdusek and Gibbs Jr. 1975, Gambetti et al. 2003, Orge et al. 2003), or sporadic (Gajdusek and Gibbs Jr. 1975, Gambetti et al. 2003) origin, that are caused by a pathogenic isoform (PrP^{Sc}) of a normal cellular protein (PrP^{C}) (Weissmann and Flechsig 2003). PrD differ in the age of onset (Centers for Disease Control and Prevention 2003), incubation period (Kingsbury et al. 1983, Valleron et al. 2001), duration of clinical disease (Spencer et al. 2002), neurophysiological features (Merino-Ramirez and Escudero-Torella 2000), and PrP^{Sc} deposit localization in the tissue (Head et al. 2004). However, the only component and key agent in their pathogenesis is a small (50-150 kDa) proteinaceous infectious particle (prion) PrP^{Sc} (Alper et al. 1966), which is found in an abnormal oligomeric form that is protease resistant (Prusiner 1982). Even though neuronal loss, astrogliosis and spongiosis are characteristic for late stages of the pathologies (Budka et al. 1995, Jamrozik et al. 1997), they can also be characterized as transmissible spongiform encephalopaties (TSE). TSE agents can cross the species barrier (Bruce 2003), and this is strongly associated with the degree of homology in the *PRNP* gene between the infected donor and the recipient (Dormont 1999). In humans *PRNP* is located on the chromosome 20 (Sparkes et al. 1986), with the coding region found in exon 3 (Kretzschmar et al. 1986).

The most common of the human TSE is sporadic Creutzfeldt-Jakob disease (CJD), accounting for approximately 80% of all cases (5 variants were defined), while autosomal dominant transmission accounts only for approximately 10% of all CJD cases (Masters et al. 1981). The other human genetic forms include familial fatal insomia (FFI), Gerstmann-Straussler-Scheinker syndrom (GSS), and prion protein cerebral amyloid angiopathy (PrP-CAA). Interestingly, over 20 mutations of the prion gene have been reported, thus pointing to the complex nature of the pathology. Forms acquired by infection include kuru, iatrogenic CJD, and possibly, a new variant of CJD (nvCJD) (Young et al. 1999). TSE are rare and the majority of human PrD are sporadic, though even genetic forms of the disorders are transmissible (Dormont 1999).

Although the nature of the infectious agent has been a subject of intensive investigation for more than half a century (Gajdusek and Zigas 1957), the mechanism of PrP or PrP^{Sc} infectivity remains to be elucidated.

PrP STRUCTURE

The cellular prion protein, PrP^{C}, is a water soluble membrane glycoprotein with a high α-helix content (Liberski 2003, Pan et al. 1993). According to the "protein only" hypothesis (Alper et al. 1967, Griffith 1967) TSE results from conversion of a ubiquitous cellular PrP^{C} form into a β-sheet enriched "scrapie"-conformation PrP^{Sc} that is protease resistant and insoluble in several detergents. The above hypothesis assumes that the protein's conformational change is mainly responsible for the onset of TSE.

Using solution NMR, the conformation of PrP^C obtained from the mouse $mPrP_{121-231}$ and hamster $hsPrP_{90-231}$ has revealed a well defined globular domain from residue 124 to 228 and a disordered N-terminal flexible tail (23-133). The PrP^C globular region consisted of a pair of anti-parallel β-sheets and several α-helix segments (Riek et al. 1996). More recently, Zahn and colleagues (2000) reported the solution NMR structure of recombinant human protein, $hPrP_{23-230}$, and observed that within the globular segment there are three α-helices formed by residues 144-154, 173-194, and 200-228 and anti-parallel β-sheet segments 128-131, and 161-164 (Zahn et al. 2000).

Under physiological buffered conditions, the full length PrP is soluble, but in acidic, low salt conditions a conversion to β-sheet aggregates could be triggered by a low concentration of denaturants (Thompson et al. 2000). The hydrophobic C-terminal domain of the $PrP_{106-126}$ peptide and its His residue could participate in the observed α-helix to β-sheet conversion and subsequent aggregation (Salmona et al. 1999). The presence of the disulfide bond in PrP_{91-231} contributes to the peptide stability, its reduction generates a conversion of the native α-helix to β-sheet conformation. The above results are further supported by x-ray diffraction measurements which point to the possibility that conversion of the central core PrP region facilitate the transformation of α-helix to the β-sheet conformation (Inouye et al. 2000). Thus it is likely that short β-segments located in the core proximity could gain structural stability by self-aggregation.

HUNTINGTON'S DISEASE

HD is a late onset hereditary neurodegenerative disorder generated by the expansion of the CAG/polyglutamine (polyQ) repeat located in exon 1 of the gene encoding huntingtin protein (htt) mapped to the chromosome 4 (Gusella et al. 1983, The Huntington's Disease Collaborative Group 1993). The disease is one of nine autosomal dominant neurodegenerative disorders generated by this type of genetic change. These disorders are manifested by uncontrolled movements, motor impairments and dementia. While aggregated polyQ are the main deposits in the patient's cerebral cortex and striatum (MacDonald 2003) and aggregation of htt in neurones has been linked to HD (Busch et al. 2003), the molecular mechanism responsible for this pathology remains unclear. The correlation between the number of CAG repeats and the risk of developing HD has been noted. Individuals with 40 or more CAG repeats will always develop the neuropathology, while presence of 35 CAG repeats or fewer will not result in the pathology (Penney Jr. et al. 1997).

In contrast to AD and PD, where presence of protein aggregates are pathological hallmarks, the link of the aggregates and HD is much more controversial (Bates 2003). *Postmortem* brains of HD patients reveal aggregated htt in neuronal intranuclear inclusions and dystrophic neurites (DiFiglia et al. 1997). The polyQ aggregates are observed in brains of HD transgenic mice and are seen as nuclear inclusions (Davies et al. 1997).

HUNTINGTIN STRUCTURE

Due to the low solubility of polyQ htt fragments and some difficulties in the polypeptide synthesis, its structure has not been completely defined. Moreover, molecular modeling (Masino and Pastore 2001), biophysical characterization and antibody-binding studies (Ko et al. 2001) have provided conflicting results concerning its structure. The htt protein was predicted as α-helical/random coil except for the N-terminus neighboring the polyQ segment (Masino and Pastore 2001). Circular dichroism (CD) studies of normal (Altschuler et al. 1997) and expanded polyQ containing 5-49 Q, bound to different flaking peptides (Chen et al. 2001), as well as NMR data (Masino et al 2002), suggested random coil structures. For these segments, interestingly, low resolution CD studies indicate that synthetic polyQ has a β-sheet conformation in acidic solution. This conformation is present even in trifluoroethanol, a high α-helix promoting solvent (Perutz et al. 1994). Studies of htt aggregation reveal globular and protofibrillar intermediates, the last high in β-structure (Poirier et al. 2002). Furthermore, Congo Red binding prevents formation of mature fibrils. Additionally, the exon-1 peptide of htt with 51 Q repeats has been shown to polymerize into fibers that yield an x-ray diffraction pattern suggesting formation of β-sheet and β-strands characteristic for the fibers (Perutz et al. 2002). The physiological relevance of the above studies on polyQ and their aggregates remains to be proven.

PARKINSON'S DISEASE

PD is the most frequent neurodegenerative movement disorder. Motoric disabilities, rest tremor, postural

instability, anxiety, depression, autonomic and dementive abnormalities are the most common clinical manifestations for this disease (Błaszczyk 1998, Delwaide and Gonce 1988, Peterson et al. 1988). PD has a multifactorial etiology involving genetic susceptibility (Kruger et al. 1998, Polymeropoulos et al. 1997) and environmental factors (metals and pesticides) (Manning-Bog et al. 2002, Tanner 1989). Dopamine deficiency caused by loss of dopaminergic neurons in substantia nigra pars compacta is responsible for the motor dysfunction symptoms (Narabayashi 1995). The presence of Lewy bodies (LB) in surviving dystrophic neurites are some of the major pathological manifestations of PD (Lewy 1912). Interestingly, LB have been found not only in PD, but also in other neurodegenerative dementias such as AD (Jensen et al. 1995), dementia with LB (DLB) (Baba et al. 1998, Okazaki et al. 1961), and multiple system atrophy (MSA) (Spillantini et al. 1998b, Tu et al. 1998). LB are composed of aprox. 10 nm amyloidogenic fibrils (Giasson et al. 1999). Their main structural component, α-synuclein, is able to form fibers similar in their secondary structure to those observed in the PD brain (Spillantini et al. 1998a).

α-SYNUCLEIN

This small, 14 kDa protein, is a highly conserved presynaptic macromolecule abundant in various regions of the brain (Jakes et al. 1994, Quilty et al. 2003). The name "synuclein" was selected as a result of the protein's location within synapses and the nuclear envelope (Maroteaux et al. 1988). α-Synuclein belongs to the family of intrinsically unstructured (natively unfolded) proteins, that have low content of ordered structure (mainly random coil as determined by CD) under physiological conditions (Kim 1997). This property is a consequence of a low overall hydrophobicity and large net charge leading to a strong electrostatic repulsion (Uversky et al. 2000). Based on the α-synuclein primary structure the following three regions of the protein have been postulated: (i) residues 1-60 of the N-terminal end composed of α-helix forming ability; (ii) residues 61-95, hydrophobic region, highly amyloidogenic; (iii) residues 96-140, acidic region rich in proline residues (Davidson et al. 1998, George et al. 1995, Mannig-Bog et al. 2002). A triplet of tyrosine residues, a unique fingerprint of α- and β-synucleins, is confined to this region (Hedge and Jagannatha Rao 2003). Presence of highly conservative hexamer motif (KTKEGV) (four repeats in region I, two repeats in the central region) suggests similarity of α-synuclein to α-helical domains of apolipoproteins, able to bind lipids (Clayton and George 1998, George et al. 1995). Consistently with this structural similarity a significant increase in α-helix content was reported upon α-synuclein binding to synthetic vesicles formed by acidic phospholipids (Davidson et al. 1998). However, the protein undergoes aggregation leading to fibrillar structures in PD brain, which adopt a β-sheet secondary structure (Serpell et al. 2000).

The familial PD mutations A30P and A53T as well as rat and zebra finch synucleins carry threonine at position 53. These synucleins have faster rates of fibril formation than native protein (Serpell et al. 2000). Fibril formation from native as well as mutated proteins involved nucleation dependent mechanism with formation of the seeds that preceded fibril elongation (Conway et al. 2000, Wood et al. 1999).

PROTEIN AGGREGATION

Based on observations that protein structure is associated with the cellular processes, it could be postulated that failure to fold correctly is responsible for biological malfunction resulting in different forms of pathologies. "Misfolded" proteins could therefore possess biological activity generating impairment of cell's viability. It is very tempting to speculate, based on previously published reports, that the above neurodegenerative diseases could share common pathways of protein aggregation, protease resistance, and fibrillar structure thus making it a generic property of several polypeptide chains (see Table I).

The kinetics of protein self-aggregation gives two distinctive models. The nucleation mechanism suggests that the rate limiting step is the initial step of nucleus formation, followed by a rapidly growing elongation step (Jarrett et al. 1993). The template model postulates that presence of aggregate induces conformational changes of the non-β monomer to aggregate prone β conformer.

The observed spontaneous Aβ pH-dependent self aggregation (Pallitto and Murphy 2001) takes place in several distinct steps: (i) refolding of monomers or dimers to unstable β-sheet conformers; (ii) filament initiation by cooperate aggregation into nuclea consisted of several monomers; (iii) filament elongation taking place by intermediate addition and end to end association; (iv) fi-

Table I

Properties of neurodegenerative proteins

pathology	protein	aggregation	conformation in aggregates	oligomerization	fibrillar morphology
Alzheimer's disease	β-amyloid	+	β-sheet	+	+
Prion disorders	prion protein	+	β-sheet	+	+
Huntington's disease	huntingtin	+	β-sheet	?	+
Parkinson's disease	α-synuclein	+	β-sheet	+	+

bril formation and growth by lateral aggregation and end to end association.

Studies of prion peptide $PrP_{106-126}$ and recombinant human prion proteins, PrP_{90-231} aggregation, as determined by turbidity measurements (Pallitto and Murphy 2001), are consistent with the nucleation model and the accompaniment of conformational conversion to β-sheet.

α-Synucleins (wild-type and mutants) are capable of concentration and time dependent self-aggregation resulting in fiber formation (Hashimoto et al. 1997, Hoyer et al. 2002). The fibers are similar to those isolated from LB obtained from PD patients (Conway et at. 1998). Nucleation dependent elongation with fibril formation has been reported for several forms of α-synuclein (Conway et al. 2000, Wood et al. 1999). Presence of intermediate, partially folded or "misfolded" proteins, correlates with the efficiency of fibrils formation (Uversky et al. 2001).

Self-association of monomeric htt proteins into aggregates depends on polyQ domain length. High molecular weight, fibrillar aggregates has been reported to form with nucleation limited lag-time kinetics. Addition of "seeds" containing preformed htt fibers can abolish the time delay (Scherzinger et al. 1999).

Several reports have suggested the template mode of protein aggregation. The time limited step required to form prion proteins aggregates (Cohen and Prusiner 1998) have been postulated to be limited by the conformational transition time. Conformational flexibility could regulate βA aggregation by a template-dependent dock-lock propagation mechanism (Esler et al. 2000a,b). Interestingly, proteins containing long polyQ regions have been reported to attract normal length polyQ macromolecules to form protein aggregates, thus inducing conformational transition from monomers to β-sheet filaments (Kazantsev et al. 1999).

It should be noted that these two modes of protein aggregation are not mutually exclusive, it is very likely that βA, PrP, α-synuclein and htt could undergo both spontaneous and induced conformational change, leading to aggregate formation. The clear definition which mechanism or mechanisms are responsible for the observed protein aggregation remains to be defined.

AGGREGATION AND NEUROTOXICITY

Understanding how the above proteins induce brain damage is one of the main focuses of neuropathology. Due to the fact that a substantial part of neurodegenerative diseases are manifested by inappropriate protein deposits, it was postulated that the aggregated proteins are linked to the diseases. Deposits can be extracellular, intracellular, or can be present in the nucleus. Peripheral tissues and organs are not free of proteinaceous aggregates. In the context of selected neuropathologies, it is of importance to note that the ability to form amyloid structure is a general property of a peptide chain, not confined to the few selected diseases. In addition, there are other protein fibrilar aggregates not related to amyloid diseases.

It was reported that oligomeric intermediates, rather than the fibrils, are the main toxic species (Hartley et al. 1999). Dimers and trimers of βA derived from neuropile and vascular amyloid deposits have been reported to contribute to the toxicity in rat hippocampal neuronal and glial cell cultures (Roher et al. 1996).

Infectivity of scrapie prion fragments has not been correlated with aggregates (as judged by amyloid staining properties) or presence of β-sheet conformation (Wille et al. 2000). No correlation has been observed between htt aggregation and cell death (Kuemmerle et al.

1999). In addition, misfolded or only partially folded α-synuclein could be more toxic to cells than its aggregates and formation of deposits could have protective properties resulting from cellular self-defense (Hedge and Jagganatha Rao 2003).

The hypothesis that the amyloid toxicity is confined to predominantly early aggregates rather than to mature fibrils supports findings of poor correlation between clinical symptoms of AD patients and number of plaques observed in their brains (Dickson et al. 1995).

However, a hypothesis attributing involvement of small oligomeric species in early stages of neurological changes, followed by plaque formation responsible for serious devastation of neuronal tissue could bridge the toxicity theories of soluble and aggregated forms of amyloidogenic protein species (Klein 2002).

Clearly, the overall image of the toxic forms of the above proteins and their actions still remains undefined and awaits experimental verification.

ACKNOWLEDGMENT

This work was financed by KBN as a research project 3 PO5F 005 24 in 2003-2006.

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Received 12 January 2004, accepted 22 February 2004