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Neurobiology of Aging 27 (2006) 570–575

NEUROBIOLOGY OF AGING

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Review

Common mechanisms of amyloid oligomer pathogenesis in degenerative disease

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Received 11 January 2005; received in revised form 13 April 2005; accepted 20 April 2005
Available online 14 February 2006

Abstract

Many age-related degenerative diseases, including Alzheimer's, Parkinson's, Huntington's diseases and type II diabetes, are associated with the accumulation of amyloid fibrils. The protein components of these amyloids vary widely and the mechanisms of pathogenesis remain an important subject of competing hypotheses and debate. Many different mechanisms have been postulated as significant causal events in pathogenesis, so understanding which events are primary and their causal relationships is critical for the development of more effective therapeutic agents that target the underlying disease mechanisms. Recent evidence indicates that amyloids share common structural properties that are largely determined by their generic polymer properties and that soluble amyloid oligomers may represent the primary pathogenic structure, rather than the mature amyloid fibrils. Since protein function is determined by the three-dimensional structure, the fact that amyloids share generic structures implies that they may also share a common pathological function. Amyloid oligomers from several different proteins share the ability to permeabilize cellular membranes and lipid bilayers, indicating that this may represent the primary toxic mechanism of amyloid pathogenesis. This suggests that membrane permeabilization may initiate a core sequence of common pathological events leading to cell dysfunction and death that is shared among degenerative diseases, whereas pathological events that are unique to one particular type of amyloid or disease may lie in up stream pathways leading to protein mis-folding. Although, these upstream events may be unique to a particular disease related protein, their effects can be rationalized as having a primary effect of increasing the amount of mis-folded, potentially amyloidogenic proteins.

Keywords: Alzheimer's disease; Amyloid oligomers; Pathogenic mechanisms; Membrane permeabilization; Intracellular calcium

1. Introduction

Therapeutic strategies that target disease mechanisms hold considerable promise for effectively treating or curing amyloid related degenerative diseases. The dilemma for medical scientists is to decide which of the pathological mechanisms to target for therapeutic development. Degenerative diseases share a striking number of common pathological features or events, such as evidence of membrane damage, oxidative stress, mitochondrial dysfunction up regulation of autophagy and cell death. Which mechanisms are primary and are they related in a causal sequence? In addition to the accumulation amyloid fibrils, these diseases also show evidence of oxidative damage, ion and metal dyshomeostasis, aberrant signal transduction, mitochondrial dysfunction and cell death. Recent evidence suggests that amyloid oligomers, which represent intermediates in the fibril formation process may be primarily responsible for amyloid pathogenesis, rather than the mature fibrils that accumulate as large aggregates [25,36]. The purpose of this review is to explore the hypothesis that these common disease mechanisms may be causally related to common properties of amyloid oligomers that are shared among degenerative disease.

2. Common pathway of amyloid fibril formation

Amyloid fibrils accumulate in degenerative diseases as a consequence of the intermolecular hydrogen bonding of

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doi:10.1016/j.neurobiolaging.2005.04.017

extended polypeptide strands that arise as a consequence of protein mis-folding. Amyloids from different diseases may share a common pathway for fibril formation. The initiating event is protein mis-folding or denaturation, which results in the acquisition of the ability to aggregate in an infinitely propagating fashion. Quasi-stable intermediate aggregates ranging from dimers up to particles of a million Dalton or greater have been observed by a variety of methods [12,21,26,28,55,58]. Soluble spherical aggregates of approximately 3–10 nm have been observed for many different types of amyloids by electron and atomic force microscopy [2,26,37] and these spherical oligomers appear to represent intermediates in the pathway of fibril formation. These spherical particles have also been called micelles, prefibrillar aggregates, protofibrils, and ADDLs [10,26,36,40,55,58]. At longer aggregation times, curvilinear fibers form that have a beaded appearance form. These structures have also been called "protofibrils" because they appear to be formed by the coalescence of the spherical subunits [26]. Finally, these structures either anneal or undergo a conformational change to form mature 6–10 nm cross-β fibrils that have either a smooth or helical morphology [22,26]. This same spectrum of aggregation intermediates and morphologies have been observed for many types of amyloids, such as α-synuclein [14], islet amyloid [30] and non-disease associated "neoamyloids" [11].

3. Common structure of amyloid oligomers and fibrils

Amyloids also have a number of structural features in common. Amyloid fibrils have a "cross-β" structure, which indicates that the backbone hydrogen bonding is parallel to the fibril axis [18,34,35]. Amyloids also bind characteristic dyes, like Congo red and thioflavin dyes, which may be a reflection of their common cross-β structure [38]. More recent structural characterization indicates that amyloid fibrils represent a generic, intermolecular hydrogen bonded structural motif that is not commonly represented in native protein structures. Spectroscopic structural analysis of several different amyloids indicates that the polypeptide is commonly arranged as parallel-β strands in a sheet where the amino acid sequence is in exact register [3,6–8,17,41,56]. The findings that several major disease related fibril structures are parallel and in exact register suggest that this may represent a common structural motif for other amyloids as well.

Amyloid oligomers also display a common structural motif that is distinct from fibrils based on the observation that a conformation dependent antibody specifically recognizes a common epitope on amyloid oligomers, but not fibrils, monomers or natively folded proteins for many different types of proteins [32]. This indicates that the antibody recognizes a generic polypeptide backbone epitope that is independent of the amino acid sequence, but yet is shared in common among all types of amyloid oligomers. The anti-oligomer antibody also generically inhibits the toxicity of soluble oligomers examined in vitro.

4. Common primary mechanism of pathogenesis

Since different amyloid oligomers share a common structure and they are generically toxic to cells, this predicts that they have the same primary mechanism of toxicity in degenerative diseases. What is the primary mechanism of amyloid oligomer toxicity? If soluble oligomers have a common mechanism of toxicity, it predicts that they would act on the same primary target. This restricts number of potential targets to ones that are accessible to all of the different types of oligomers. Some amyloids arise from cytosolic proteins, while others are derived from secretary or extracellular proteins. This suggests that the primary target of oligomers must be accessible to both the cytosolic and extracellular compartments. The most obvious target that is accessible to both the cytosolic and extracellular compartments is the plasma membrane that forms the interface between the two compartments.

A growing body of evidence suggests that membrane permeabilization by amyloid oligomers may represent the common, primary mechanism of pathogenesis of amyloid related degenerative diseases. An increase in membrane permeability and intracellular calcium concentration has long been associated with amyloid toxicity, although there is some disagreement as to the mechanism by which amyloids increase intracellular calcium [42,44]. Amyloidogenic proteins and peptides, such as Aβ, α-synuclein, polyglutamine and IAPP have been widely reported to form discrete pores or single channels in membranes [4,5,29,37,47,48]. This has led to the formulation of the "channel hypothesis" to account for the mechanism of amyloid pathogenesis in degenerative disease [31]. Common properties of these channels include the irreversible insertion of discrete, single channels that display heterogeneous conductance levels and ion selectivity that are inhibited by Congo red and Zn^{2+} ions [31]. Amyloid oligomers specifically increase lipid bilayer conductance regardless of the sequence, while fibrils and soluble low molecular weight species have no observable effect [10,33]. Using homogeneous and pure populations of amyloid oligomers, we found that this increase in membrane conductance is not ion selective and we did not observe discrete pore or single channel formation [33]. The membrane permeabilizing activity of pure oligomers is reversible and can be inhibited by anti-oligomer antibody, but is not inhibited by Congo red [33]. Atomic force microscope images of oligomer-treated membranes are consistent with the interpretation that oligomers disrupt membranes without forming discrete pores [23]. The explanation for the discrepancy between the numerous reports of single channel insertion and our failure to observe discrete pores or single channels by amyloid

oligomers are not yet clear, but we are in general agreement on the points that amyloids permeabilize membranes and that the aggregation state of the peptide is important for this activity.

Amyloid oligomers also permeabilize cell membranes [10,16,46]. Extracellular applications of oligomeric forms several types amyloidogenic proteins and peptides cause a rapid and large increase in cytosolic free [Ca], whereas equivalent amounts of soluble monomer and fibrils have no detectable effect [16]. The Ca^{2+} influx is not blocked by cobalt, indicating that the effect is not due to activation of existing Ca channels. Amyloid oligomers also caused a rapid leakage of fluorescent dyes from cells loaded with fluo-3 and calcein, indicating that molecules other than ions are also mobilized in response to oligomers [16]. This is in agreement with reports of oligomer induced leakage of fluorescent dyes from phospholipid vesicles [2,30,50]. Oligomer treatment of cells results in an increase in cytosolic Ca^{2+} in Ca^{2+}-free medium and that this increase can be largely eliminated by pretreatment with thapsigargin to deplete endoplasmic reticulum calcium [16,46]. This suggests that external application of oligomers leads to liberation of Ca^{2+} from intracellular stores. This is consistent with reports that oligomers may subsequently penetrate into cells where they similarly disrupt intracellular membranes to cause leakage of sequestered Ca [10], but it could also result as a consequence of altered intracellular signaling.

5. Common pathogenic pathways

The permeabilization of membranes by amyloid oligomers that has been reported as a common component of amyloid toxicity may represent the primary common mechanism of amyloid pathogenesis (Fig. 1). It may initiate a series of downstream pathological events that represents a common pathway of degeneration in amyloid-related diseases. These events that may lie immediately downstream from membrane permeabilization may constitute a core group of common pathological events that ultimately result in cell dysfunction and death. All of the pathological events that are held in common by amyloid-related degenerative diseases may be part of this core group. A wide variety of transmembrane signaling processes and the production of reactive oxygen species could be directly related to membrane perturbation by soluble oligomers [43,51]. Even though soluble oligomers may not be acutely toxic in vivo as they are in vitro, the chronic leakage of ions across the plasma membrane may be sufficient to disrupt normal neuronal function, long term potentiation [57] and serve as a source of chronic stress in maintaining a normal membrane potential.

Membrane permeabilization by amyloid oligomers and the concomitant increase in intracellular calcium may be the proximate initiator of several pathogenic pathways, including reactive oxygen species (ROS) production [52], altered

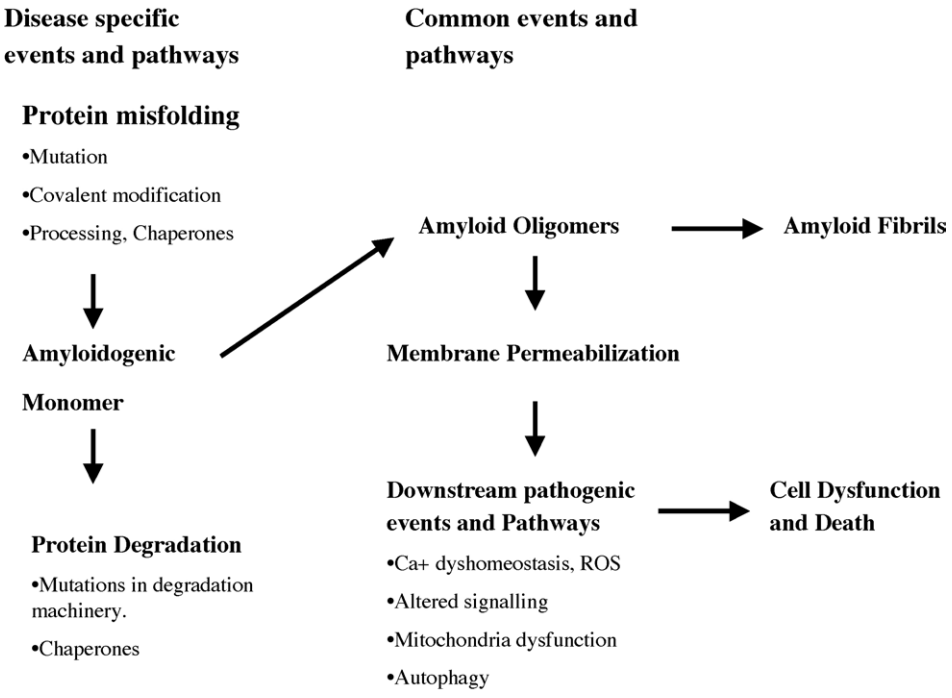

Fig. 1. Common and disease-specific pathways in degenerative diseases. According to this scheme, the permeabilization of membranes by amyloid oligomers is the primary pathogenic event common to amyloid-related degenerative diseases. This initiates a series of pathogenic pathways that are common to most, if not all amyloid diseases. It is not yet clear whether these common pathways are related in a causal sequence or whether they constitute parallel, synergistic pathways. Disease specific events and pathways are postulated to lie upstream from amyloid oligomerization and have the primary effect of increasing the amount of mis-folded, amyloidogenic proteins.

signaling pathways [43,51] and mitochondrial dysfunction [54]. Many signaling pathways are regulated directly or indirectly by intracellular Ca^{2+} levels or membrane depolarization, including pathways leading to up regulation of autophagy and cell death. Membrane permeabilization by amyloid oligomers may also induce an oxidative stress response in cells [1,52]. Accumulation of Ca^{2+} in the matrix of mitochondria leads to an increase in ROS production, cytochrome *C* release and apoptosis [9]. Amyloid oligomers may also directly permeabilize the mitochondrial membrane [27]. Thus, the increase in energy demand necessary to maintain ion homeostasis and membrane polarization may also be a source of mitochondrial stress. Mitochondrial dysfunction may also feed back to upstream pathways that regulate the level of mis-folded proteins because many chaperones and the proteasome system utilize ATP. Chronic inflammation may also be a component of the core degenerative pathway as it is frequently observed in neurodegenerative diseases [19,20,45].

The accumulation of autophagic vesicles has been increasingly recognized as a common component of degenerative diseases [13,39]. The up regulation of autophagy may be a protective response to sequester and degrade toxic amyloid aggregates. Up regulation of autophagy reduces polyglutamine pathogenesis in transgenic fly and mouse models of HD [49]. The fact that amyloid aggregates and autophagic vesicles accumulate in degenerative diseases suggests that this response is not entirely successful. The failure to efficiently clear amyloid aggregates may also contribute to pathogenesis by stimulating autophagic programmed cell death [15,53].

6. Disease specific pathways

In addition to a common core of pathogenic pathways, unique, disease-specific events and pathways also characterize degenerative diseases. The simplest way of rationalizing their effects is to postulate that they lie upstream of the common pathways and have the common net effect of increasing the amount of mis-folded, aggregation competent proteins (Fig. 1). The most obvious class of disease specific events is mutations in the proteins that accumulate as amyloids in disease. These mutations are often associated with inherited, early onset forms of disease. Mutations destabilize the native folded structure of proteins, so the primary effect of these mutations may be to favor the accumulation of mis-folded proteins. Other disease-specific mutations occur in genes that do not encode proteins that accumulate as amyloids, such as the presenilins in AD and parkin in PD. These second site mutations may also have the primary effect in increasing the concentration of aggregation prone proteins and peptides. Presenilin mutations alter the proteolytic processing of APP, favoring the production of the longer and more aggregation prone Aβ-42 isoform [24]. Covalent modification of proteins, like oxidation, glycation and racemization may also promote mis-folding to give rise to amyloid oligomers. ROS production may also facilitate the mis-folding of proteins by covalent adduct formation.

One of the most striking examples of disease specific pathways is the cell type specificity of amyloid related degenerative diseases. In many cases, the cells at risk represent only a small fraction of the cells in which a particular amyloidogenic protein is expressed. This is often interpreted as an indicating that these particular cells are uniquely sensitive to degeneration by a specific mechanism, but the reason for this specificity is not entirely clear. It may also reflect differences in the synthesis, trafficking and metabolism of proteins in ways that uniquely give rise to mis-folded protein accumulation. It is also possible that the cell type specificity may be a reflection of whether a particular cell has an effective stem cell population. Amyloid toxicity may be inconsequential if a cell dies and is replaced by another perfectly functional cell and if the production of new cells can keep up with cell loss. This factor may explain why the majority of amyloid-related diseases are neurodegenerative.

7. Implications for therapeutic development

Understanding the relationships between pathological events pathways has significant implications for therapeutic development. Which pathways are primary and are they ordered in a causal sequence? Targeting downstream pathways may not be effective if there are multiple, parallel pathways or if the target is downstream from a significant source of pathogenesis. Targeting disease specific pathways, like Aβ-production, may be effective, but their effectiveness may be restricted to that specific disease. Focusing on the primary mechanism may be the most effective strategy if multiple downstream pathways ensue from a single stimulus, even if this target is difficult to approach. If the primary mechanism of pathogenesis is common to degenerative diseases as recent evidence suggests, therapeutics that target this common mechanism have the added benefit of being effective treatments for a broad range of age-related human disease.

Acknowledgements

I sincerely thank the Larry L. Hillblom Foundation and the National Institutes of Health for support. The author is a consultant for Kinexis Inc.

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