Biochemical Pharmacology 88 (2014) 468–478

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Review - Part of the Special Issue: Alzheimer's Disease – Amyloid, Tau and Beyond

Therapeutic approaches against common structural features of toxic oligomers shared by multiple amyloidogenic proteins

Marcos J. Guerrero-Muñoz [a,b], Diana L. Castillo-Carranza [a,b], Rakez Kayed [a,b,*]

[a] Mitchell Center for Neurodegenerative Diseases, University of Texas Medical Branch, Galveston, TX, USA
[b] Departments of Neurology, Neuroscience and Cell Biology, University of Texas Medical Branch, Galveston, TX, USA

ARTICLE INFO

Article history:
Received 18 November 2013
Accepted 19 December 2013
Available online 7 January 2014

Chemical compounds studied in this article:
Methylene blue (PubChem CID: 6099)
Epigallocatechingallate (PubChem CID: 65064)
Curcumin (PubChem CID: 969516)
Resveratrol (PubChem CID: 445154)
Oleuropein (PubChem CID: 5281544)
Baicalein (PubChem CID: 5281605)
Phenol Red (PubChem CID: 4766)
Silibinin (PubChem CID: 31553)
CLR01 (http://www.med-chemist.com/2012/11/clr01-effectively-inhibits.html)
Anle138b (http://www.cipsm.de/en/publications/researchAreaA/2013/Anle138b_a_novel_oligomer_modulator_for_disease-modifying_therapy_of_neurodegenerative_diseases_such_as_prion_and_Parkinson_s_disease/index.html?style = 1)

Keywords:
Amyloid oligomers
Immunotherapy
Anti-amyloid small molecules

ABSTRACT

Impaired proteostasis is one of the main features of all amyloid diseases, which are associated with the formation of insoluble aggregates from amyloidogenic proteins. The aggregation process can be caused by overproduction or poor clearance of these proteins. However, numerous reports suggest that amyloid oligomers are the most toxic species, rather than insoluble fibrillar material, in Alzheimer's, Parkinson's, and Prion diseases, among others. Although the exact protein that aggregates varies between amyloid disorders, they all share common structural features that can be used as therapeutic targets. In this review, we focus on therapeutic approaches against shared features of toxic oligomeric structures and future directions.

Contents

* Corresponding author.
E-mail address: rakayed@utmb.edu (R. Kayed).

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http://dx.doi.org/10.1016/j.bcp.2013.12.023

More information is available at: http://www.elsevier.com/PubChem.

1. Introduction

Proteins are important macromolecules that perform essential processes in all living organisms. Protein folding determines the stability and function of proteins or peptides. However, when proteostasis is impaired, amyloidogenic proteins misfold and aggregate to form insoluble, fibrillar deposits called amyloids, which are a common hallmark of amyloid diseases like Alzheimer's disease (AD) [1]. Although there are reports about the toxicity of amyloid deposits [1–6], increasing evidence suggests a protective role for these structures, including the finding that amyloid plaques are present in individuals without clinical symptoms of AD [7]. Furthermore, poor correlation was observed between amyloid deposits and the progression of the disease in AD patients [8,9]. Removal of amyloid plaques in clinical trials did not reverse the damage or prevent the increase in dementia associated with AD [10,11]. Moreover, soluble Aβ levels correlated better with disease severity than amyloid plaques containing insoluble Aβ fibrils [12–14]. Recent evidence suggests that soluble Aβ aggregates, known as oligomers, are the primary toxic species [8,9]. These aggregates represent early stage intermediates characterized by spherical morphology and diameters ranging between 3 and 50 nm [15–18]. However, this is a transitory stage that is followed by the formation of late stage intermediates (protofibrils) characterized by curvilinear fiber morphology with diameters below 10 nm and lengths up to 400 nm [19]. Finally, these structures continue aggregating to form straight and highly regular fibrils with diameters between 6 and 20 nm [19–21]. These various structures differ not only in aggregation state, but also in their toxic effects. Many reports have shown that fibrils are less toxic than intermediate aggregates of Aβ (spherical oligomers and protofibrils) [22–25], thus Aβ oligomers have emerged as the most toxic species in AD.

2. Oligomer conformation is common to proteins involved in amyloid diseases

A key issue in the investigation of amyloid structures is the description of both the growth mechanism from monomeric precursors and the structural features of toxic oligomers. However, it is difficult to get solid data from structural features due to their intrinsically disordered nature. One strategy to stabilize these structures is to prepare constrained peptides that mimic β-sheet oligomer conformation [22,26–28]. These preparations were very useful in the generation of conformational anti-oligomer antibodies. When Aβ40 mimic was used to generate rabbit polyclonal A11 antibody, A11 not only recognized toxic Aβ oligomers, but also recognized oligomers from many different peptides and proteins related to amyloid diseases such as Aβ, α-synuclein (α-syn), lysozyme, insulin, polyglutamine (poly-Q), islet amyloid polypeptide (IAPP), prion protein (PrP) and p53, among others [22,29–33]. These results indicated a common epitope in toxic oligomers from different peptides or proteins. Another rabbit polyclonal anti-oligomer antibody, I11, was generated using an IAPP oligomimic preparation, rather than Aβ40 mimic, but no differences from A11 were observed, reinforcing the idea that oligomers from different peptides have common structural features [27]. However, another explanation is that IAPP and Aβ40 form similar antigenic epitopes in oligomer conformation due to the sequence similarities between these two peptides [34,35]. For this reason we made a preparation using an amyloidogenic peptide with higher sequence variability compared to Aβ and IAPP which still has common features of oligomers [28]. This preparation was useful for the generation of F11G3 mouse monoclonal antibody (mab) that recognizes Aβ, α-syn, IAPP, PrP and TDP-43 oligomers in human and synthetic samples [36]. Conformational antibodies have provided a more rational means of classifying amyloid oligomers based on their underlying structural organization and conformations *in vitro* and *in vivo* rather than on differences in size or sample preparation [22,27,36–38].

3. Oligomers: The most toxic species in amyloid diseases

Toxic oligomers are transient structures formed during fibrillogenesis. Amyloid proteins misfold and aggregate to form oligomers in an early stage, later form protofibrils and finally stabilize as fibril structures [39–47]. In AD and Huntington's disease (HD), amyloid deposits were poorly correlated with cytotoxicity in cell culture models [48]. Moreover, in Lewy body (LB)-associated disorders [49] and in an HD cell culture model [50], neurons with amyloid deposits were healthier than those without amyloid deposits, suggesting that cells may be dying before amyloid formation. Finally, AD and HD mouse models showed pathology before amyloid appearance [51–58]. It has been shown that soluble oligomers from different amyloidogenic proteins are more toxic than fibrils [22]. Furthermore, recent data showed that soluble amyloid oligomers are generally toxic, because oligomers from proteins both related and unrelated to disease are equally toxic [59]. While there are reports about toxicity related to fibrils, this phenomenon may be explained by the leakage of toxic oligomers resulting from fibril breakage [60,61].

4. General mechanisms of toxicity of oligomers and pathogenesis

Despite differences in the specific mechanisms of toxicity of oligomers from related disease proteins, it is clear that oligomers affect general pathways leading to cell death. Amyloid oligomers cause various pathological events, including endoplasmic reticulum stress, proteasome impairment, mitochondrial dysfunction, distur-