Biochimica et Biophysica Acta xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

Amyloid fibrils compared to peptide nanotubes

Matjaž Žganec [a,b], Eva Žerovnik [a,c,*]

[a] Department of Biochemistry and Molecular and Structural Biology, Jožef Stefan Institute, Jamova 39, Ljubljana, Slovenia
[b] Faculty of Mathematics and Physics, University of Ljubljana, Jadranska 19, Ljubljana, Slovenia
[c] CipKeBip - Center of Excellence for integrated approaches in chemistry and biology of proteins, Jamova 39, 1000 Ljubljana, Slovenia

ARTICLE INFO

Article history:
Received 7 March 2014
Received in revised form 22 May 2014
Accepted 29 May 2014
Available online xxxx

Keywords:
Amyloid fibril
Oligomer
Optical property
Peptide nanotube
Quantum confinement
Toxicity

ABSTRACT

Prefibrillar oligomeric states and amyloid fibrils of amyloid-forming proteins qualify as nanoparticles. We aim to predict what biophysical and biochemical properties they could share in common with better researched peptide nanotubes. We first describe what is known of amyloid fibrils and prefibrillar aggregates (oligomers and protofibrils): their structure, mechanisms of formation and putative mechanism of cytotoxicity. In distinction from other neuronal fibrillar constituents, amyloid fibrils are believed to cause pathology, however, some can also be functional. Second, we give a review of known biophysical properties of peptide nanotubes. Finally, we compare properties of these two macromolecular states side by side and discuss which measurements that have already been done with peptide nanotubes could be done with amyloid fibrils as well.

1. Introduction

Amyloid fibrils are highly stable insoluble self-assembled protein deposits usually regarded as a characteristic of neural or systemic pathologies. Under diverse conditions they form an ordered β-sheet structure [1–3]. The phase states displayed by these deposits include liquid crystals, hydrogel, and nanotubes. Besides special mechanical properties each protein in amyloid fibril may also have a biological function. Therefore, the potential applications of amyloid fibrils exceed those of synthetic polymers.

Amyloid fibrils (Fig. 1) are associated with various diseases known as amyloidoses. Currently there are more than 25 proteins with non-homologous amino acid sequences that are known to form amyloid deposits extra- and/or intracellularly. This is a hallmark of neurodegenerative diseases such as Alzheimer's, Parkinson's and spongiform encephalopathies but also of type 2 diabetes mellitus. These diseases are progressive and associated with decreased quality of life and high mortality of the aging population.

In the scientific community there is now a consensus that it is not the amyloid fibrils themselves that are responsible for those diseases. Instead, smaller soluble aggregates, the prefibrillar and globular oligomers, of the order of 10–60 protein chains are thought to be responsible for cellular dysfunction and death [4–6]. However, at least in some species amyloid fibrils as such are known to have a physiological role [7].

Peptide nanotubes (Fig. 2)—an axially-symmetric ring-shaped system of protein molecules—have received a considerable amount of experimental interest in the recent years. Self-assembly, their ferroelectric and optical properties along with quantum confinement phenomena have been thoroughly studied [8,9]. A range of nanotechnological applications has been proposed, especially in the field of medicine and electrochemistry [9]. Here we review some of the studies that led to those applications and compare peptide nanotubes to amyloid fibrils.

2. Structure and properties of amyloid fibrils

Amyloid fibrils are ordered protein aggregates that are characterized by a β-sheet rich secondary structure, Thioflavin T dye binding, consequently enhanced fluorescence, and Congo red dye birefringence. The ability of proteins to form amyloid fibrils is not limited to specific range of peptide lengths or any particular primary structure. By choosing appropriate solution conditions, amyloid fibrils can also be produced efficiently in vitro.

2.1. Protein folding and misfolding

Native conformation of a protein is determined by its primary structure—the amino acid sequence. Natively folded proteins may occasionally partially unfold and adapt a non-native conformation. Mutations, metal interactions, acidic pH, elevated temperature, oxidation and

* Corresponding author at: Jožef Stefan Institute, Jamova 39, Ljubljana, Slovenia. Tel.: +386 1 477 3753; fax: +386 1 477 3984.
E-mail address: eva.zerovnik@ijs.si (E. Žerovnik).

http://dx.doi.org/10.1016/j.bbagen.2014.05.019
0304-4165/

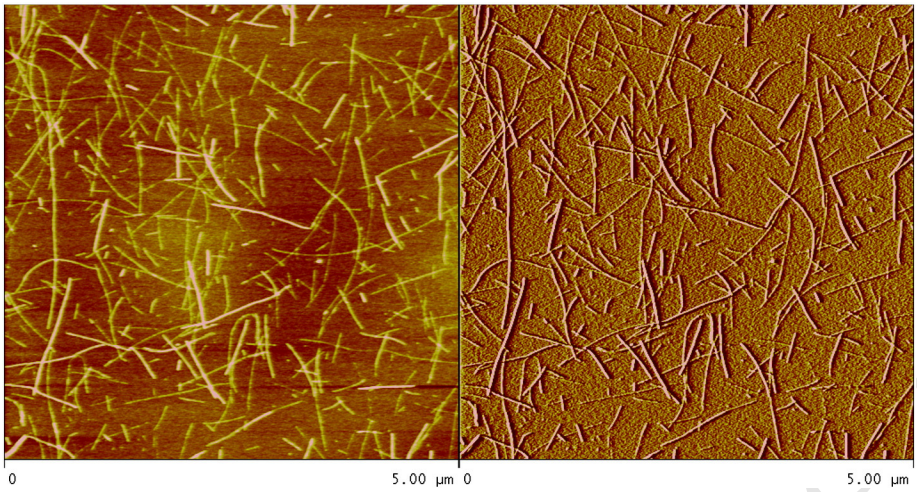

Fig. 1. An AFM image of amyloid fibrils formed by human stefin A (at pH 2.4 upon heating to about 90 °C for 2 h). Melting temperature of stefin A is 94 °C. We can see thicker and thinner type of amyloid fibrils of heights 2.8 and 5.6 nm [103]. We thank Dr. Miha Škarabot from Soft-Matter Physics (JSI) for his help in acquiring the image.

proteolysis or increase in protein concentration can all drive protein misfolding [10]. A set of protein structures, however, is natively unfolded (NUP), intrinsically disordered (IDP) [11]. These too, among them α-synuclein and tau, are prone to form amyloid fibrils [12].

With or without assistance of chaperone proteins misfolded proteins eventually refold back to their native conformation, get labeled for degradation via the ubiquitin proteasome pathway or start to oligomerize. Oligomerization is thermodynamically favorable either because of formation of new intermolecular hydrogen bonds of the edge strands or due to hydrophobic effect, which shields hydrophobic parts of protein chains from the solvent. Additionally, lipid bilayers of cell membranes can change protein conformation and increase the propensity of amyloid-forming proteins to aggregate [13].

2.2. Structure and morphology of amyloid fibrils

The main structural characteristics of amyloid fibrils is the cross β structure, where β-strands run penperdicularly to the fibril axis, which is revealed by the double concentric pattern in X-ray diffraction, where characteristic lengths can be observed: a meridional signal at Q3 4.76 Å 4.7 Å (represents the distance between β-strands connected by hydrogen bonds) and an equatorial signal at 10.6 Å (represents the distance between β-sheets). The antiparallel β-sheets are zipped together by π-bonds between adjacent phenylalanine rings and salt-bridges between charge pairs (glutamic acid–lysine), thus controlling and stabilizing the structure [14]. Whereas the strands are parallel or anti-parralel depends on each case. For example, solid-state NMR studies [15–17] of amyloid-β peptide usually gave an in register, parralel arrangement of the β-strands. An in-register parallel β-sheet seems more favorable as it maximizes favorable hydrophobic interactions for any amino acid sequence. It also aligns Gln and Asn residues with themselves, maximizing favorable "polar zipper" interactions. Antiparallel β-sheets have also been found in some amyloid fibrils, but until recently only in fibrils formed by short peptides. From 2005 many solid-state structures of amyloid fibrils have been solved as reviewed in Tycko [16]. Of interest, HET-$s_{218-289}$, formed a β-helix resembling motif that has been observed in crystal structures of certain monomeric proteins, such as the pertactin [18]; supporting suggestions that β-helices might be important structural motifs within amyloid fibrils [16 and refs therein].

An amyloid fibril (if it grows not agitated) appears to be made of several filaments (4–6), twisting helically around the fibril axis [2]. However, before the filaments or fibrils form (several micrometers long), usually less ordered and shorter structures (200 nm), the so called protofibrils, which are slightly bended, form. Also, smaller globular oligomers, which compose the granular aggregate, already have similar structural features [16].

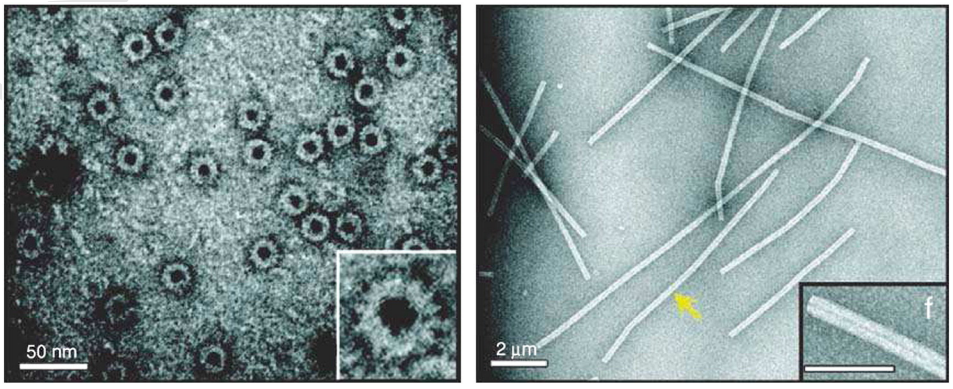

Fig. 2. Transmission electron microscope (TEM) image of representative peptide nanodisks (left) and nanotubes (right) generated from modified TMV coat protein. TMV nanodisks are layered heptadecameric structures. (Copyright 2007 American Chemical Society), web page: http://wires.wiley.com/WileyCDA/WiresArticle/articles.html?doi=10.1002%2Fwnan.1180.

Please cite this article as: M. Žganec, E. Žerovnik, Amyloid fibrils compared to peptide nanotubes, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbagen.2014.05.019