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Review

Kinetics of amyloid formation and membrane interaction with amyloidogenic proteins

Regina M. Murphy *

Department of Chemical and Biological Engineering, University of Wisconsin, Madison, 1415 Engineering Drive, Madison, WI 53706, USA

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Abstract

Interest in amyloidogenesis has exploded in recent years, as scientists recognize the role of amyloid protein aggregates in degenerative diseases such as Alzheimer's and Parkinson's disease. Assembly of proteins or peptides into mature amyloid fibrils is a multistep process initiated by conformational changes, during which intermediate aggregation states such as oligomers, protofibrils, and filaments are sampled. Although once it was assumed that the mature fibril was the biologically toxic species, more recently it has been widely speculated that soluble intermediates are the most damaging. Because of its relevance to mechanism of disease, the paths traversed during fibrillogenesis, and the kinetics of the process, are of considerable interest. In this review we discuss various kinetic models used to describe amyloidogenesis. Although significant advances have been made, construction of rigorous, detailed, and experimentally validated quantitative models remains a work in progress. We briefly review recent literature that illustrates the interplay between kinetics and amyloid–membrane interactions: how do different intermediates interact with lipid bilayers, and how does the lipid bilayer affect kinetics of amyloidogenesis?

Keywords: Kinetic; Amyloid; Beta-amyloid; Fibril; Lipid bilayer

Contents

* Tel.: +1 608 262 1587; fax: +1 608 262 5434.
E-mail address: regina@engr.wisc.edu.

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Interest in protein misfolding and aggregation in general, and amyloidogenesis in particular, has exploded in the past dozen years, as scientists recognize the role of protein aggregates in a number of degenerative diseases. Arguably, beta-amyloid peptide (Aβ) has received the most attention because of its importance in Alzheimer's disease pathology. Other amyloidogenic proteins of note include α-synuclein, the prion proteins, transthyretin, insulin, and polyglutamine-containing peptides or proteins. The difference in thermodynamic stability of folded, unfolded, and misfolded proteins is not large, and the same forces (e.g., hydrogen bonding, hydrophobic effect, electrostatics) control both native folding and non-native misfolding. Reasoning from this basis, and collating data from numerous experiments, it now appears that given modest disturbances (e.g., as seemingly innocuous as a single-point mutation [1], or a change in salt concentration [2]), nearly any polypeptide chain can be driven towards misfolding and aggregation [3]. Our focus in this review is particularly on the kinetics of amyloid formation. Given the enormous depth and breadth of the recent amyloid literature, this review is not encyclopedic but idiosyncratic.

1. Morphologies and methods

Kinetics is concerned with the pathway by which a monomeric protein or peptide converts to amyloid fibrils, and the rate at which fibrillogenesis proceeds. To address the question of the kinetic pathway, we need to answer the questions: What intermediates are observed? What are their size, structural, and morphological characteristics? These questions are not strictly academic, because there is considerable evidence that the size, structural features, and morphology of the aggregated species are the key determinants of toxicity [4]. An increasingly popular hypothesis is that intermediates in the aggregation pathway, rather than the mature insoluble fibrils, are the most toxic species [5–11]. If the kinetic intermediates are toxic, then clearly the link between amyloid formation and disease cannot be understood in the absence of an understanding of the kinetics of amyloidogenesis. Elucidation of the fibrillogenesis kinetics will contribute to the development of new therapeutic strategies based on altering rates of association. For example, if soluble aggregates but not monomer nor mature fibril are toxic, then compounds that sequester the monomer [12] and arrest oligomerization [13,14], or conversely that accelerate conversion of intermediates to mature fibril [15–17], may be of therapeutic interest.

1.1. Conformational and aggregation states

Several different conformational and aggregation states are observed with amyloid proteins. The casual reader is strongly cautioned: the field is littered with vague, inconsistent, and even contradictory nomenclature. The tasks of interpreting experimental data and of comparing outcomes from different studies are made more daunting by the fact that a plethora of experimental methods is used to detect and characterize various conformation and aggregation states. The definitions we have chosen should not be construed as "the last word", nor can it be assumed when reading the primary literature that the nomenclature is the same as what we have chosen.

Monomers may have native or non-native secondary structure. For some amyloidogenic peptides such as Aβ or α-synuclein, the monomeric peptide is disordered, but is likely not a true random coil. For example, solution NMR revealed that monomeric Aβ is mostly extended but possesses regions of β-strand and turn that appear to be retained in the fibrillar structure [18]. Similarly, residual order was detected in Raman spectra of a-synuclein [19], and molecular dynamic simulations predict that polyglutamine monomers adopt a restricted conformational ensemble that includes extended and compact populations [20]. The native fold of monomeric amyloidogenic proteins is not restricted to a particular structure: it may be α-helical (e.g., apomyoglobin [21] or prion protein [22]), β-sheet (e.g., immunoglobulin light chain [23]), or a mix. Several well-known amyloidogenic proteins exist stably as a defined native oligomer, for example, the homotetrameric protein transthyretin, or the zinc-stabilized insulin hexamer. Dissociation to the monomer is typically required for conversion to amyloid [24–26]; in these cases the monomer may be altered conformationally from the native fold and is generally not stable.

Oligomers are globular aggregates that generally lack a well-defined secondary structure. Some have argued that oligomers are akin to micellar structures, with cylindrical or spherical shape [27]. The sizes and conformational characteristics of oligomers are quite variable. For example, Aβ was observed to form both small spherical oligomers of about 5 nm in diameter with molar masses in the 20–50 kDa range [6] as well as large spherical oligomers with diameters around 15 nm and molar masses approaching 1 million Da [28]. Small spherical oligomers have also been reported with amyloidogenic peptides including insulin and prion peptide fragment [5]. Globular assembles, lacking defined structure and heterogeneous in size, have been observed in a variety of preparations of proteins containing polyglutamine domains [29,30]. Whether oligomers are a direct intermediate to structured fibrils, an off-pathway byproduct, or an intermediate towards amorphous aggregates, remains uncertain. With Aβ [27] and with polyglutamine-containing proteins [31], the evidence points towards these oligomers being on-pathway. On the other hand, β-sheet oligomers were detected in a study of prion protein assembly, but the authors suggested that the oligomer is "off-pathway"