Mathematical Biosciences 278 (2016) 5–10

Contents lists available at ScienceDirect

Mathematical Biosciences

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

Mathematical aspects of the kinetics of formation and degradation of linear peptide or protein aggregates

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ARTICLE INFO

Article history:
Received 28 January 2016
Revised 19 March 2016
Accepted 24 April 2016
Available online 29 April 2016

Keywords:
Biokinetics
Subcellular processes
Aggregation
Feedbacks
Neurologic diseases

ABSTRACT

In cells, peptides and proteins are sometimes prone to aggregation. In neurons, for example, amyloid β peptides form plaques related to Alzheimer's disease (AD). The corresponding kinetic models either ignore or do not pay attention to degradation of these species. Here, the author proposes a generic kinetic model describing formation and degradation of linear aggregates. The process is assumed to occur via reversible association of monomers and attachment of monomers to or detachment from terminal parts of aggregates. Degradation of monomers is described as a first-order process. Degradation of aggregates is considered to occur at their terminal and internal parts with different rates and these steps are described by first-order equations as well. Irrespective of the choice of the values of the rate constants, the model predicts that eventually the system reaches a stable steady state with the aggregate populations rapidly decreasing with increasing size at large sizes. The corresponding steady-state size distributions of aggregates are illustrated in detail. The transient kinetics are also shown. The observation of AD appears, however, to indicate that the peptide production becomes eventually unstable, i.e., the growth of the peptide population is not properly limited. This is expected to be related to the specifics of the genetic networks controlling the peptide production. Following this line, two likely general networks with, respectively, global negative and positive feedbacks in the peptide production are briefly discussed.

1. Introduction

Kinetic processes are customarily described by a system of differential equations. The number of equations may be large or infinite. For example, chemical reactions are frequently described by using equations for populations of molecules with specific energies [1]. Two other typical example are aggregation and polymerization which are treated by employing equations for populations of aggregates or polymers with specific numbers of monomers [2–10]. Often, such systems of equations can be simplified and reduced to those containing only a few equations. Equally often, however, the choice of differential equations is far from trivial even at the conceptual level, equations themselves are complex, and a system of equations should be analyzed numerically. Good examples here are genetic networks [11,12] and neural networks [13,14]. Physically, the function of cells in general or neurons in particular and the communication between them are fairly complex, and the models aiming at such networks are inevitably highly coarse-grained. The kinetic models focused on the details of the neuron function or on the processes perturbing the normal function of neurons are much less abundant. An important example of such processes is peptide and protein aggregation.

In vivo, peptide and protein aggregation sometimes accompanies gene expression. The extent of aggregation may be different, and its role is not always clear. Extensive aggregation is usually believed to be harmful. A classical example is Alzheimer's disease (AD) characterized by accumulation of plaques formed of amyloid β (Aβ) peptides [15]. Mechanistically, the aggregation typically occurs via reversible association of monomers. Although this feature is similar to that implied in the classical nucleation theory (CNT) [10,16], the process runs under conditions far from full equilibrium, and the corresponding theoretical treatments are not reduced to CNT (reviewed in [17–20]). The focus is here customarily on the transient kinetics observed in basic experimental studies where a system contains initially monomers and eventually aggregates. In such experiments and related models, there are no degradation steps. In cells, however, the aggregation occurs under chemically reactive conditions in the presence of various enzymes which regulate the population of peptides and proteins in various ways including degradation, and accordingly the understanding of the

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http://dx.doi.org/10.1016/j.mbs.2016.04.009
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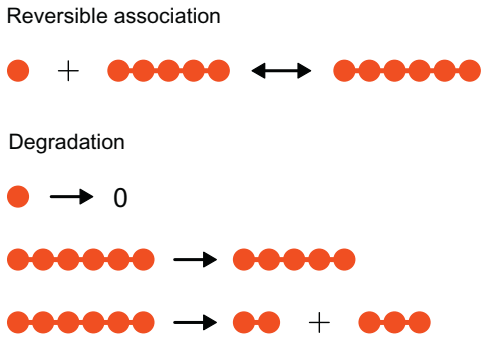

Fig. 1. Schematic illustration of the model reaction steps including (i) reversible association of a monomer to a 5-mer, (ii) degradation of a monomer, (iii) degradation of a terminal monomer in a 6-mer with formation of a 5-mer, and (iv) degradation of a monomer inside a 6-mer with formation of a dimer and 3-mer.

likely role of degradation in aggregation is of high interest. Referring again to AD, one can notice that the disturbance of Aβ clearance machinery appears to be a reason of Aβ accumulation in the brain [21,22] and targeting this machinery is one of the promising strategies for AD therapy [21–23]. In the literature, one can find a few kinetic models taking peptide or protein degradation into account [24–26]. The degradation is described there as a first-order process with the rate constant independent of the aggregate size, and the role of degradation in the kinetics is not scrutinized. In the studies focused on polymers (e.g., Refs. [4,5]), the degradation is associated with fragmentation, and its description is not identical to that of biodegradation.

Taking the important role of Aβ degradation in AD into account (Refs. [21–23]), it is instructive to construct kinetics models describing this process in more detail compared to how it was done in the studies mentioned above. Herein, following this line, we present and analyze a model focused on the formation and degradation of linear aggregates (this motif is often believed to be typical for Aβ fibrils at least at the initial stage of their formation [19]). It specifies the likely mechanism of degradation of aggregates and the dependence of the corresponding rate constants on the aggregate size. The dependence of the steady-state and transient kinetics on the model parameters is clarified by using analytical approximations and illustrated numerically. In fact, our study describes one of the likely scenarios the formation and degradation of linear Aβ fibrils. The understanding of such kinetics is still limited due to their complexity related to biochemistry and also to mathematical formalism with an infinite number of equations describing the populations of different aggregates. In our study, we complement the analysis of the aggregation kinetics by brief general discussion of global negative and positive feedback in the peptide production. The clarification of what may happens in such situations is one of the prerogatives of mathematical bioscience. Bearing this in mind and taking into account that the problems we scrutinize are of high current interest, we keep the presentation on the level suitable for general readership and choose the tools for the analysis from this perspective.

2. Model

Our model is focused on the initial stage of aggregation occurring in solution with participation of monomers and liner aggregates (i-mers with $i \geq 2$) as schematically shown in Fig. 1. Aggregation is assumed to occur via reversible association of monomers and attachment of monomers to or detachment from terminal parts of aggregates. Monomers are considered to be generated with the constant rate, w. Degradation of monomers is described as a first-order process. Degradation of aggregates is assumed to occur at their terminal and internal parts with different rate constants. In the former case, the size of an aggregate is reduced from i to $i-1$. In the latter case, the destruction of one of the fragments is considered to result in splitting or, in other words, fragmentation of an aggregate into two parts so that the sum of their sizes is $i-1$. In principle, aggregates may associate. *In vivo*, however, this process is expected to be slowed down due to crowding, and we do not take it into account.

All the degradation steps introduced are considered to be performed by various special enzymes, e.g., proteases (concerning the degradation of Aβ peptides, see e.g. Refs. [27,28]; for a wider view, see also Refs. [29,30]). Different enzymes may function in slightly different ways, but anyway their function results in degradation of single monomers or monomers forming aggregates. The specific details of these processes are still poorly understood. In our model, as already noted, an enzyme is considered to process a monomer or one of the monomers forming an i-mer. In both cases, the monomer processed is assumed to disappear. Describing the degradation steps, we include the enzyme concentration into the degradation rate constants. This is possible if monomers and aggregates do not influence the enzyme formation and degradation.

With the specification above, the equation for the population of monomers is as follows

$$dN_1/dt = w - rN_1 - k_a N_1 \sum_{i=1}^{\infty} N_i + k_d \sum_{i=2}^{\infty} N_i + rN_2 + 2\nu \sum_{i=3}^{\infty} N_i. \quad (1)$$

The first two terms on the right-hand side describe monomer formation and degradation (r is the degradation rate constant). The third and fourth terms represent association and dissociation (k_a and k_d are the corresponding rate constants). The fifth term is related to degradation of dimers (to reduce the number of model parameters, the corresponding rate constant is set to be equal to that for monomers). The last sixth term takes degradation of the internal part of aggregates into account (ν is the corresponding rate per an internal monomer, and 2 is the coefficient corresponding to the fact that an i-mer can be formed on both sides).

For the populations of i-mers with $i \geq 2$, we have

$$dN_i/dt = k_a N_1 (N_{i-1} - N_i) + (k_d + r)(N_{i+1} - N_i) - (i-2)\nu N_i + 2\nu \sum_{j=i+2}^{\infty} N_j. \quad (2)$$

Here, the first term corresponds to monomer attachment. The second term describes monomer detachment and degradation of the terminal parts of aggregates. The third term represents the rate of degradation of the internal part of an aggregate (this rate is proportional to the number of fragments forming this part). The fourth term takes into account the increase of the population of i-mer due to degradation-induced splitting of aggregates with sizes larger than $i+2$ (2 is the coefficient corresponding to the fact that an i-monomer can be formed on both sides).

To integrate Eqs. (1) and (2) and present the results, it is convenient to use dimensionless variables. Bearing this in mind, we introduce the monomer population,

$$N_* = w/r, \quad (3)$$

corresponding to the steady-state reaction regime in the absence of aggregation, and normalize all the populations as

$$n_i \equiv N_i/N_*. \quad (4)$$

In addition, we employ dimensionless time,

$$\tau \equiv rt, \quad (5)$$