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Review

Physicochemical interactions of amyloid β-peptide with lipid bilayers

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Abstract

The aggregation and deposition onto neuronal cells of amyloid β-peptide (Aβ) is central to the pathogenesis of Alzheimer's disease. Accumulating evidence suggests that membranes play a catalytic role in the aggregation of Aβ. This article summarizes the structures and properties of Aβ in solution and the physicochemical interaction of Aβ with lipid bilayers of various compositions. Reasons for discrepancies between results by different research groups are discussed. The importance of ganglioside clusters in the aggregation of Aβ is emphasized. Finally, a hypothetical physicochemical cascade in the pathogenesis of the disease is proposed.

Keywords: Alzheimer's disease; Amyloid β-peptide; Lipid bilayer; Lipid raft; Ganglioside; Fibril formation

Contents

1. Introduction

Alzheimer's disease (AD), a progressive cognitive decline, is the most common form of dementia. The pathological hallmarks of AD brains are extracellular senile plaques and intracellular neurofibrillary tangles. It is widely accepted that the amyloid β-peptide (Aβ), which exists in fibrillar forms as a major component of senile plaques, is central to the development of AD [1,2]. Aβ is a peptide composed of 40–42 amino acids and generated from proteolytic cleavage of amyloid precursor

Abbreviations: Aβ, amyloid β-peptide; AD, Alzheimer's disease; APP, amyloid precursor protein; CD, circular dichroism; DAC-Aβ, Aβ-(1–40) with the diethylaminocoumarin dye at the N-terminus; L/P, lipid-to-peptide ratio; GSL, glycosphingolipids; PC, phosphatidylcholine; PG, phosphatidylglycerol; PI, phosphatidylinositol; PS, phosphatidylserine; SM, sphingomyelin

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protein (APP), a type I integral membrane glycoprotein (695–770 residues depending on the isoform), by β- and γ-secretases (Fig. 1). Aβ is present at a very low concentration ($<10^{-8}$ M) in biological fluids [3], and its physiological role is unknown. According to the so-called Aβ hypothesis, the conversion of soluble, nontoxic Aβ to aggregated toxic Aβ rich in β-sheet structures ignites the neurotoxic cascade(s) of Aβ [4]. Accumulating evidence suggests that the most neurotoxic species are soluble, nonfibrillar oligomers acting as intermediates during the formation of aggregates (fibrils) [5–11], although fibrils also exert mild toxicity including neuritic dystrophy and synaptic abnormality [8,11–16]. Jarrett and Lansbury, Jr. suggested that Aβ fibrillizes by the nucleation-dependent polymerization mechanism and lipids could act as heterogeneous seeds for the polymerization [17]. Aβ–membrane interactions have been extensively investigated to elucidate the molecular mechanisms of the Aβ-induced cellular dysfunctions underlying the pathogenesis of AD. It is naturally conceivable that Aβ interacts with membranes because it is an enzymatic product of the transmembrane protein APP. This review article mainly summarizes physicochemical Aβ–membrane interactions in most physiologically relevant systems, i.e. the interaction of full-length Aβ-(1–40) or Aβ-(1–42) with lipid bilayers, although many studies also use fragment peptides or other model membrane systems, such as monolayers and detergent micelles. In particular, the importance of ganglioside clusters in the fibrillization of Aβ is emphasized. Aβ also chemically or biochemically interacts with lipids. For example, lipid oxidation products chemically modify Aβ, enhancing its aggregation [18]. Conversely, Aβ oxidizes other molecules including lipids by generating reactive oxygen species in the presence of copper or iron [19,20]. Aβ also affects lipid metabolism [21], while lipids regulate the production of Aβ [21–24].

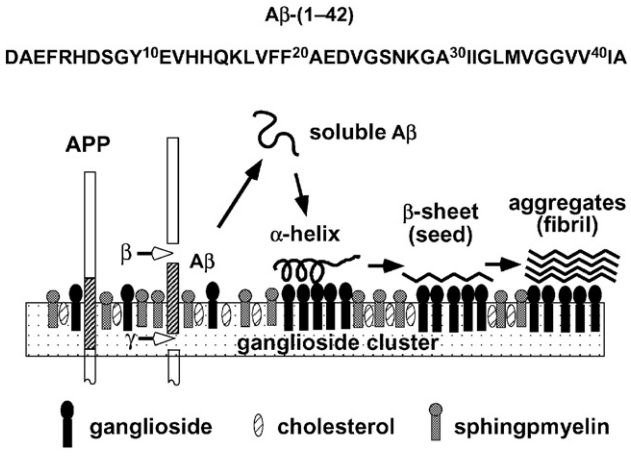

Fig. 1. The amino acid sequence of Aβ-(1–42) and a hypothetical model of the aggregation of Aβ induced by ganglioside clusters. Aβ is generated, at least partly, in lipid rafts composed of sphingolipids and cholesterol by the enzymatic cleavage (β- and γ-secretases) of APP. Aβ is soluble, and takes an unordered structure. Once ganglioside clusters are generated in a cholesterol-dependent manner, Aβ binds to the clusters, forming an α-helix-rich structure at lower peptide-to-ganglioside ratios, whereas the peptide changes its conformation to a β-sheet at higher ratios. The β-sheet form facilitates the aggregation (fibrillization) of Aβ, leading to cytotoxicity.

2. Aβ in solution

To understand Aβ–membrane interactions, the structures and properties of Aβ in solution should be elucidated, because different species of Aβ would interact differently with membranes. Aβ is amphipathic: The N-terminal 28 residues corresponding to the extracellular part of APP is hydrophilic, whereas the C-terminal remainder corresponding to the membrane-spanning domain is hydrophobic (Fig. 1). The hydrophilic part has 6 acidic amino acids (D^1, E^3, D^7, E^{11}, E^{22}, and D^{23}) with pKa values of 4.3–4.5 in D_2O, whereas the number of basic amino acids is only 3 (R^5, K^{16}, and K^{28}), although there are 3 His residues with pKa values of 6.5–6.6 [25,26]. Thus, Aβ is negatively charged at physiological pH, and electrically neutral at weakly acidic pH (~5.5), where the formation of Aβ fibrils is most accelerated [27].

The amphipathic Aβ is surface active, and lowers the surface tension of water [28–30]. Above a critical concentration of 15.5–17.5 μM, Aβ-(1–40) forms micellar aggregates at pH 7.4 [29,31]. Aβ-(1–42) forms a stable trimer or tetramer at concentrations above ~12.5 μM [32]. At lower concentrations, the peptide was previously reported to exist as a dimer, as determined by gel filtration analysis using globular proteins as molecular weight standards [28,33,34]. However, a recent study showed that this apparent dimeric species can be regarded as a monomer using dextrans as standards [35].

The state of Aβ in solution depends on various factors, and this may be a reason for discrepancies between results by different research groups. Aβ, especially Aβ-(1–42), tends to easily self-aggregate, forming oligomers in solution [32]. This tendency is dependent on the production lot [36] as well as the salt form (trifluoroacetic acid or HCl) [37] of the synthetic peptide. Contamination by trace amounts of metals such as zinc, copper, and iron promotes self-aggregation of Aβ [38]. Commercially available Aβ may contain nontrivial amounts of impurities [39]. Furthermore, the method by which the solution is prepared significantly affects the state of Aβ in solution. Dissolution into dimethylsulfoxide or hexafluoroisopropanol is often used to obtain monomeric Aβ [40]. However, some researchers use other solvents, such as trifluoroethanol, to make a stock solution of Aβ. The use of organic solvents may result in another complication. Aβ takes a random coil in aqueous solution whereas it assumes secondary structures in organic solvent-containing media [41,42]. The initial conformation of Aβ in stock solution may affect subsequent peptide–lipid interactions. One of the most reliable ways to prepare monomeric Aβ is to dissolve Aβ in 0.02% ammonia on ice and remove any large aggregates by ultracentrifugation [43]. The Aβ solution prepared by this method does not form fibrils upon incubation at 37 °C for a few days.

3. Interaction of Aβ with phospholipids and cholesterol

3.1. Zwitterionic phospholipids

Phosphatidylcholine (PC) and sphingomyelin (SM) are major zwitterionic phospholipids in mammalian cells. Most studies