Available online at www.sciencedirect.com
SCIENCE DIRECT
Chemistry and Physics of Lipids 141 (2006) 72–82
CPL
CHEMISTRY AND PHYSICS OF LIPIDS
www.elsevier.com/locate/chemphyslip

Review

The role of lipid–protein interactions in amyloid-type protein fibril formation

Galyna P. Gorbenko [a], Paavo K.J. Kinnunen [b,*]

[a] *Department of Biological and Medical Physics, V.N. Karazin Kharkiv National University, Kharkiv, Ukraine*
[b] *Helsinki Biophysics and Biomembrane Group, Institute of Biomedicine, P.O. Box 63, Haartmaninkatu 8, University of Helsinki, FIN-00014, Finland*

Received 12 December 2005; accepted 20 February 2006
Available online 10 March 2006

Abstract

Structural transition of polypeptide chains into the β-sheet state followed by amyloid fibril formation is the key characteristic of a number of the so-called conformational diseases. The multistep process of protein fibrillization can be modulated by a variety of factors, in particular by lipid–protein interactions. A wealth of experimental evidence provides support to the notion that amyloid fibril assembly and the toxicity of pre-fibrillar aggregates are closely related and are both intimately membrane associated phenomena. The present review summarizes the principal factors responsible for the enhancement of fibril formation in a membrane environment, viz. (i) structural transformation of polypeptide chain into a partially folded conformation, (ii) increase of the local concentration of a protein upon its membrane binding, (iii) aggregation-favoring orientation of the bound protein, and (iv) variation in the depth of bilayer penetration affecting the nucleation propensity of the membrane associated protein. The molecular mechanisms of membrane-mediated protein fibrillization are discussed. Importantly, the toxicity of lipid-induced pre-fibrillar aggregates is likely to have presented a very strong negative selection pressure in the evolution of amino acid sequences.

Keywords: Protein–lipid interactions; Membrane-induced protein aggregation; Amyloid fibrils

Contents

Abbreviations: CL, cardiolipin; DG, diacylglycerol; Chol, cholesterol; IAPP, islet amyloid polypeptide; PA, phosphatidic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PG, phosphatidylglycerol; PI, phosphatidylinositol; PIP, PI 4-phosphate; PIP_2, PI 4,5-P_2; PS, phosphatidylserine; SM, sphingomyelin

* Corresponding author. Tel.: +358 505404600; fax: +358 919125444.
E-mail address: paavo.kinnunen@helsinki.fi (P.K.J. Kinnunen).

0009-3084/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.chemphyslip.2006.02.006

1. Introduction

Lipid–protein interactions play a key role in a wide variety of cellular processes, including signal transduction, intracellular transport, enzyme catalysis, energy conversion in the cell, antimicrobial defense, and control of membrane fusion (Lee, 2004; Palsdottir and Hunte, 2004; Dowhan et al., 2004; Kinnunen et al., 1994). Critical for all these functions are unique structural features of the protein molecules representing an ensemble of rapidly interconverting conformational substates highly sensitive to various environmental factors. Lipid bilayer, the basic structural element of biological membranes, is commonly regarded as a two-dimensional liquid providing a variety of environments, which can affect protein structure and dynamics via both specific and non-specific interactions. Accordingly, these interactions are controlled not only by general physicochemical characteristics of a membrane, such as its phase state, bilayer curvature and elasticity, surface charge, and degree of hydration, but also by the exact chemical nature of membrane lipids, extent of acyl chain unsaturation, conformation and dynamics of lipid headgroups and acyl chains, and protein–lipid selectivity arising from factors such as the hydrophobic matching at the protein–lipid interface (Jensen and Mouritsen, 2004). Importantly, these factors can exert influence not only on protein conformation, but also on its oligomerization state, a number of studies providing evidence for substantial enhancement of protein and peptide aggregation in a membrane environment (Han and Tamm, 2000; Fernandes et al., 2003; Paquet et al., 2001).

During the last decade, one specific type of protein aggregates has drawn particular interest due to its involvement in the pathogenesis of the so-called conformational diseases. More specifically, these aggregates are featured by the presence of specific filamentous structures, amyloid fibrils, having a core cross-β-sheet structure in which polypeptide chains are oriented in such a way that the β-strands run perpendicularly to the long axis of the fibril, while the β-sheets propagate in its direction (Serpell, 2000; Sunde and Blake, 1998). Mature fibrils have diameters of 4–13 nm and usually contain 2–6 laterally associated or twisted protofilaments, each 2–5 nm in diameter (Jimenez et al., 1999; Khurana et al., 2003). Interestingly, the ability to form fibrils is not limited to proteins associated with conformational diseases. There are good grounds for believing that amyloid-forming propensity is a generic property of polypeptide chain since a number of disease-unrelated proteins and peptides have been demonstrated to form fibrils (Dobson, 2004; Srisailam et al., 2002).

Several lines of evidence suggest that the formation by the Aβ peptide of amyloid fibers and their cytotoxic action are membrane associated processes (Yip et al., 2001, 2002; Fernandez and Berry, 2003; Bokvist et al., 2004; Thirumalai et al., 2003; Stefani, 2004). Lipid bilayer may act as an effective catalyst of fibrillogenesis, providing a generic environment where protein molecules adopt conformation and orientation promoting their assembly into protofibrillar and fibrillar structures (Thirumalai et al., 2003; Stefani, 2004; Sparr et al., 2004; Zhao et al., 2004). Cell membrane is further thought to be the direct target mediating amyloid-induced cell death. Amyloid formation has been reported to induce membrane permeabilization resulting from alterations in bilayer structure and/or uptake of lipids into the forming fiber (Sparr et al., 2004; Zhao et al., 2004, 2005; Lin et al., 2001; Michikawa et al., 2001). It has also been hypothesized that extraction of membrane lipids by the forming amyloid (Sparr et al., 2004; Zhao et al., 2004) may be the direct cause for membrane permeabilization and cell death (Zhao et al., 2005).

2. Membrane-induced protein fibrillization

Vast majority of studies on membrane-mediated fibrillogenesis have been undertaken with model systems including amyloidogenic peptides or proteins and lipid vesicles of varying composition (Bokvist et al., 2004; Sparr et al., 2004; Sharp et al., 2002; Lindström et al., 2002; Terzi et al., 1997). An important conclusion reached is that the fibrillogenic properties of membrane-bound proteins are largely determined by the chemical nature of membrane lipids and the mode of protein–lipid interactions. Several studies have demonstrated anionic phospholipids to represent the main membrane component responsible for the enhancement of fibril formation, as shown for α-synuclein (Zhu et al., 2003; Jo et al., 2000, 2004; Narayanan and Scarlata, 2001;