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Review Article

Impacts of Membrane Biophysics in Alzheimer's Disease: From Amyloid Precursor Protein Processing to Aβ Peptide-Induced Membrane Changes

Sholpan Askarova, Xiaoguang Yang, and James C.-M. Lee

Department of Biological Engineering, University of Missouri, Columbia, MO 65211, USA

Correspondence should be addressed to James C.-M. Lee, leejam@missouri.edu

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An increasing amount of evidence supports the notion that cytotoxic effects of amyloid-β peptide (Aβ), the main constituent of senile plaques in Alzheimer's disease (AD), are strongly associated with its ability to interact with membranes of neurons and other cerebral cells. Aβ is derived from amyloidogenic cleavage of amyloid precursor protein (AβPP) by β- and γ-secretase. In the nonamyloidogenic pathway, AβPP is cleaved by α-secretases. These two pathways compete with each other, and enhancing the non-amyloidogenic pathway has been suggested as a potential pharmacological approach for the treatment of AD. Since AβPP, α-, β-, and γ-secretases are membrane-associated proteins, AβPP processing and Aβ production can be affected by the membrane composition and properties. There is evidence that membrane composition and properties, in turn, play a critical role in Aβ cytotoxicity associated with its conformational changes and aggregation into oligomers and fibrils. Understanding the mechanisms leading to changes in a membrane's biophysical properties and how they affect AβPP processing and Aβ toxicity should prove to provide new therapeutic strategies for prevention and treatment of AD.

1. Introduction

The senile plaque composed of neurotoxic amyloid-β peptide (Aβ) is a pathologic characteristic of Alzheimer's disease (AD) [1–6]. Aβ is derived from the cleavage of a type I membrane protein, (AβPP), by β- and γ-secretases [7]. Alternatively, AβPP can be cleaved by α-secretase to produce a neurotrophic, neuroprotective α-secretase-cleaved soluble AβPP (sAβPP$_\alpha$) through a nonamyloidogenic pathway [8]. These two pathways compete with each other, and increasing sAβPP$_\alpha$ has been suggested as a potential therapy for AD [9]. The cleavage of AβPP by β-secretase (BACE), the primary step to produce Aβ [10, 11], occurs mainly in lipid rafts, which are highly ordered membrane microdomains enriched in cholesterol, sphingolipids and saturated phospholipids [12–17]. On the other hand, the activity of α-secretases is favored in nonraft domains [18]. Therefore, AβPP processing can be altered by manipulating membrane lipid composition, such as removal of cholesterol and sphingolipids [19–22]. Since AβPP, α-, β-, and γ-secretases are membrane proteins, AβPP processing can be also affected by the biophysical membrane properties such as membrane fluidity and molecular order [19–26].

Amyloidogenic cleavage of the AβPP leads to the production of Aβ peptides of different length [27]. An increasing amount of evidence supports the notion that cytotoxic effects of Aβ are strongly associated with its ability to interact with membranes of neurons and other cerebral cells, astrocytes, microglial, and cerebral endothelial cells. Aβ peptides in different forms can directly bind to membrane molecules and alter biophysical membrane properties [28–33]. Aβ can also indirectly affect membrane properties by binding to membrane receptors and triggering downstream signaling pathways. Moreover, there is evidence that Aβ_{1-42} oligomers can accelerate the amyloidogenic processing of AβPP by changing membrane physical properties and interacting with lipid raft-related ganglioside GM-1 [25]. Membrane properties and composition, and the presence of metal ions,

in turn, play critical roles in Aβ cytotoxicity associated with its conformational changes, aggregation into oligomers and fibrils, and ability to interact with membrane molecules [34–40].

In this paper, we summarize the effects of membrane composition and properties on AβPP processing and interactions of physiologically relevant $A\beta_{1-40}$ and $A\beta_{1-42}$ with membranes studied in membrane models, cell cultures, and *in vivo*. Understanding the mechanisms leading to changes in a membrane's biophysics and how they cause changes in AβPP processing and Aβ toxicity should provide insights into new therapeutic strategies for prevention and treatment of AD.

2. Role of Physical Membrane Properties in AβPP Processing

2.1. Cholesterol on Physical Properties of Membranes and AβPP Processing. Cholesterol is an essential component of the cellular membrane and plays a vital role in the regulation of membrane functions. Distribution of cholesterol within the plasma membrane is not even: the highest level of free cholesterol inside the plasma membrane is found in cytofacial bilayer leaflet [41, 42]. The exofacial leaflet contains substantially less cholesterol, and it is mostly condensed in lipid rafts, which are more tightly packed than nonlipid raft domains due to intermolecular hydrogen bonding involving sphingolipid and cholesterol [43]. This asymmetric distribution of cholesterol is altered by aging: it is significantly increased in exofacial leaflet with increasing age [42, 44]. Membrane cholesterol levels can also be modulated by specific inhibitors of the cellular biosynthesis such as statins (3-Hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) inhibitors), or it can be selectively extracted from plasma membrane by methyl-β-cyclodextrin (MβCD) [41]. The percentage of cholesterol in phospholipid bilayers affects many biophysical parameters of lipid bilayers, such as thickness, thermomechanical properties, molecular packing, conformational freedom of phospholipid acyl chains and water, molecular oxygen permeability, membrane hydrophobicity, membrane excitability in neurons, internal dipolar potential, and membrane fluidity [45–51].

It has been shown that intracellular cholesterol homeostasis regulates AβPP processing [52]. A model of membrane compartmentalization has been suggested for AβPP present in two cellular pools, one associated with the cholesterol-enriched lipid rafts, where Aβ is generated, and another outside of rafts (i.e., nonraft domains), where α-cleavage occurs [13]. It has been reported that membrane cholesterol depletion decreased the content of AβPP in cholesterol and sphingolipid-enriched membrane microdomains and subsequently inhibited the amyloidogenic pathway to produce Aβ [19, 53]. In contrast, cholesterol accumulation in Niemann Pick type C (NPC) model cells has been shown to shift AβPP localization to lipid rafts [54]. Exposure of cholesterol to astrocytes, primary neurons, and glial cultures inhibited the secretion of $sAPP_\alpha$ and reduced cell viability [55–57]. It has been demonstrated that cholesterol decreased the secretion of $sAPP_\alpha$ by interfering with AβPP maturation and inhibiting glycosylation of the protein [56]. Furthermore, some studies showed that cholesterol levels in the membranes were positively correlated with β-secretase activity [58], while lovastatin enhanced the α-secretase activity [55].

The results of another study showed that the cholesterol transport inhibitor, U18666a, increased $sA\beta PP_\alpha$ secretion and intracellular $A\beta PP_\alpha$ levels and reduced secretion of $A\beta_{1-40}$ in N2aAPP "Swedish" cells [59]. Inhibition of intracellular cholesterol transport also altered presenilin localization and AβPP processing in neuronal cells [60]. Similarly, inhibition of Acyl-coenzyme A:cholesterol acyltransferase (ACAT) modulated AβPP trafficking and reversed diffuse brain amyloid pathology in aged AβPP transgenic mice [61–63]. Nevertheless, lowering cholesterol by treatment with statins was found to reduce [13, 21, 64] or enhance Aβ generation, depending on the condition of the study [65]. One possible explanation for the controversial results is that moderate reduction in cholesterol is associated with a disorganization of detergent-resistant membranes (DRMs) or lipid rafts, allowing more β-site AβPP cleaving enzyme (BACE) to contact AβPP and resulting in increased Aβ generation, whereas a strong reduction of cholesterol inhibits the activities of BACE and γ-secretase, resulting in a decrease in Aβ generation [14]. On the other hand, in the low-dose statin treatment conditions [65], enchanted Aβ production could be a result of feedback upregulation of HMG-CoA mPNA and increased cholesterol level.

Consistent with the membrane compartmentalization model, cellular cholesterol depletion results in an increase in membrane fluidity, a parameter which characterizes an average lateral motion of phospholipid molecules within the lipid bilayer [19, 66–69]. On the other hand, an increase in membrane fluidity has been demonstrated to shift AβPP processing to nonamyloidogenic cleavage by α-secretase [54–56, 65–68]. It has been reported that the removal of cholesterol with methyl-β-cyclodextrin or treatment with lovastatin increased membrane fluidity, which resulted in higher expression of the α-secretase and impaired internalization of AβPP [19]. At the same time, cholesterol enrichment has been shown to reduce membrane fluidity [70, 71]. Cholesterol enrichment that impeded membrane fluidity may lower $sA\beta PP_\alpha$ production by hindering the interaction of the substrate with its proteases [72]. Interestingly, substitution of cholesterol by the steroid 4-cholesten-3-one induces minor change in membrane fluidity and reduces $sA\beta PP_\alpha$ secretion, whereas substitution of cholesterol by lanosterol increases membrane fluidity and $sA\beta PP_\alpha$ secretion [19]. These results suggest reversible effects of cholesterol on the α-secretase activity depending on membrane fluidity.

Many studies support the notion that Aβ production occurs in endosomes [22, 73–77]. Since AβPP is a transmembrane protein, its internalization from the plasma membrane is regulated by key regulators of endocytosis, such as Rab5, and this process has been found to enhance AβPP cleavage by β-secretase leading to increased Aβ levels [78]. In contrast, AβPP, lacking its cytoplasmic internalization motif, can

accumulate at the plasma membrane and undergo cleavage by α-secretase [10, 11]. Cholesterol has been demonstrated to increase clathrin-dependent AβPP endocytosis in a dose-dependent and linear manner [79]. There were also studies demonstrating that alterations in cholesterol transport from late endocytotic organelles to the endoplasmic reticulum had important consequences for both AβPP processing and the localization of γ-secretase-associated presenilins [60]. It has been suggested that cholesterol increase in AD could be responsible for the enhanced internalization of clathrin-, dynamin2-, Eps15-, and Rab5-dependent endocytosis of AβPP and the ensuing overproduction of Aβ [79]. Alternatively, AβPP internalization could be reduced by lowering cholesterol, which leads to an increase in membrane fluidity, AβPP accumulation on the cell surface, and increased sAβPP$_\alpha$ secretion [19].

2.2. Fatty Acids on Membrane Physical Properties and AβPP Processing. Fatty acids are other essential components of the cellular membranes. They are important ingredients in various dietary sources and play a central role in the normal development and function of the brain [80–83]. For example, long-chain polyunsaturated fatty acids (PUFAs) of the ω-6 and ω-3 series, the major polyunsaturated fatty acids in the central nervous system [84], are essential for prenatal brain development and normal brain functions [83, 85, 86]. Animals specifically deficient in dietary ω-3 fatty acids have been demonstrated to have reduced visual acuity and impaired learning ability [86, 87]. Diets enriched in long-chain ω-3 PUFA (DHA) have been shown to modulate gene expression for brain function, improve synaptic and neurotransmitter functions of neurons, enhance learning and memory performances, and display neuroprotective properties [86, 88–90]. Arachidonic acid (AA), another abundant fatty acid in the brain, is a second messenger [91] and a precursor for the synthesis of eicosanoids [92]. The presence of PUFAs in neuronal cells influences cellular function both directly, through effects on membrane properties, and indirectly by acting as precursors for lipid-derived messengers [93, 94].

In fact, the disturbed metabolism of fatty acids is associated with AD [95]. For instance, lower levels of DHA have been reported in serum samples taken from AD patient [96], while greater consumption of DHA has significantly reduced the likelihood of developing AD [97]. Dietary ω-3 PUFA depletion has been shown to activate caspases and decrease NMDA receptors in the brain of a transgenic mouse model of AD [98]. DHA and curcumin have been shown to suppress Aβ-induced phosphorylation of tau tangles and the inactivation of insulin receptors in primary rat neurons [99]. Recently, reduced expression of the neuronal sortilin-related receptor SorLA/LR11 (LR11), a sorting protein that regulates APP trafficking to β- and γ-secretases, was identified as a probable genetic risk factor for late-onset Alzheimer's disease [100]. DHA, in turn, has been found to increase LR11 expression in primary rat neurons, human neuronal line, and aged nontransgenic and DHA-depleted APPsw AD transgenic mice [101]. In 15-month-old AβPP/presenilin-1 mice, DHA supplementation improved spatial memory, decreased Aβ deposition, and slightly increased relative cerebral blood volume, indicating that a DHA-enriched diet can diminish AD-like pathology [102].

Dietary fatty acids may integrate into cell membranes to change their physical properties and subsequently alter cell functions. The ability of fatty acids to modulate membrane properties and functions [90, 94, 103–109] depends both on the saturation degree of the fatty acids and the trans/cis ratio of the unsaturated fatty acids [110–113]. For example, diets enriched in unsaturated PUFAs, DHA, and AA have been shown to increase membrane fluidity of neurons and other cells [71, 89, 114, 115]. DHA has been also capable of counteracting cholesterol-induced decreases in platelet membrane fluidity and modulating platelet hyperaggregation [71]. Similarly, cis-polyunsaturated linolenic, α-linoleic, and eicosatrienoic fatty acids increased membrane fluidity [110]. In contrast, membrane incorporation of saturated acids led to decreased membrane fluidity [109, 112, 116]. PUFAs have also been shown to affect many other membrane properties, such as molecular order, compressibility, permeability, fusion, and protein activity [117, 118].

Since AβPP, α-, β-, and γ-secretases are membrane protein molecules, AβPP processing can be altered by manipulating the membrane lipid composition. It was mentioned before that an increase in membrane fluidity has resulted in an increase in nonamyloidogenic cleavage by α-secretase to produce sAβPP$_\alpha$ [19, 25]. At the same time, enrichment of cell membranes with PUFAs increases membrane fluidity and, consequently, promotes nonamyloidogenic processing of AβPP [113]. It has been shown that a typical Western diet (with 40% saturated fatty acids and 1% of cholesterol) fed to transgenic AβPP/PS1 mice increased Aβ, while diets supplemented with DHA decreased Aβ levels compared to regular diet [119]. Similarly, DHA has been shown to decrease the amount of vascular Aβ deposition [120] and reduce cortical Aβ burden [121] in the aged Alzheimer mouse model. In this model, DHA modulated AβPP processing by decreasing both α- and β-AβPP C-terminal fragment products and full-length AβPP [121]. DHA has also been shown to stimulate nonamyloidogenic AβPP processing resulting in reduced Aβ levels in cellular models of Alzheimer's disease [122]. At the same time, the study of the effects of fatty acids on cell membrane fluidity and sAβPP$_\alpha$ secretion in relation to degrees of unsaturation has suggested that not all unsaturated fatty acids, but only those with 4 or more double bonds, such as arachidonic acid (20 : 4), eicosapentaenoic acid (20 : 5), and DHA (22 : 6), increased membrane fluidity and led to an increase in sAβPP$_\alpha$ secretion, while oleic acid (18 : 1), linoleic acid (18 : 2), and α-linolenic acid (18 : 3) did not [113]. Moreover, the results of another experiment have indicated that treatment of PSwt-1 cells with oleic acid and linoleic acid increased γ-secretase activity and Aβ production [123].

2.3. Phospholipases A_2 on Membrane Physical Properties and AβPP Processing. Phospholipases A_2 (PLA$_2$s) are ubiquitously distributed in mammalian cell enzymes that catalyze

the hydrolysis of fatty acids from *sn*-2 position of phospholipids. PLA_2s are classified into three major families: calcium-dependent cytosolic PLA_2 ($cPLA_2$), secretory PLA_2 ($sPLA_2$), and calcium-independent PLA_2 ($iPLA_2$). These enzymes are responsible for maintenance of phospholipid homeostasis in the cell membrane. They are also important in production of lipid mediators, such as arachidonic acid. Activation of PLA_2s has been implicated in diverse cellular responses such as mitogenesis, differentiation, inflammation, and cytotoxicity, and changes in PLA_2s' activities occur in many neurodegenerative diseases, including AD [124–136].

It has been shown that immunoreactivity of $cPLA_2$ (group IIA and IVA) increased in reactive astrocytes in severe AD patient brains [124–126]. Upregulations of $sPLA_2$-IIA and PLA_2-IVA were reported in the hippocampus of AD patients [126, 137, 138]. The levels of activated $cPLA_2$-IVA were also increased in the hippocampus of hAβPP mice [138]. Furthermore, Aβ has been shown to activate $cPLA_2$ in primary rat and mouse brain endothelial cells, astrocytes, cortical neurons, and in PC12 cells [139–143]. Contradictory, both increased and reduced PLA_2 activity has been reported in platelets of AD patients [144, 145]. At the same time, PLA_2 activity was significantly decreased in the parietal and, to a lesser degree, in frontal cortex of AD brains. Lower PLA_2 activity correlated significantly with an earlier onset of the disease, higher counts of neurofibrillary tangles and senile plaques and an earlier age of death, indicating a relationship between abnormally low PLA_2 activity and a more severe form of the illness [146].

PLA_2s play key roles in modulation of membrane properties under pathological and physiological conditions. For instance, in immortalized rat astrocytes (DITNC cells), $cPLA_2$ mediated the Aβ-induced membrane molecular order increase (biophysical parameter which characterizes molecular packing of lipids and water in lipid bilayers) [147]. In primary rat cortical astrocytes, ROS induced by menadione, a redox active agent, also altered astrocyte's membrane molecular order through activation of $cPLA_2$ [148]. PLA_2 activation has been shown to affect lipid membrane fluidity and AβPP processing as well [149, 150]. In AD brains, there is evidence for reduced membrane fluidity coupled with decreased PLA_2 activity [146, 151, 152]. Similarly, inhibition of PLA_2 activity in rat hippocampus has been shown to reduce membrane fluidity and impair the formation of short- and long-term memory [150, 153]. Arachidonic acid (AA), PLA_2-hydrolyzed product, increased fluidity of membranes in cultured cerebral endothelial cells [154, 155] and hippocampal neurons *in vivo* [114]. Secretory $sPLA_2$-III and AA have been shown to increase membrane fluidity and $sA\beta PP_\alpha$ secretion and decrease levels of $A\beta_{1-42}$ in SH-SY5Y cells [156]. Another hydrolyzed product of PLA_2, DHA, has also been demonstrated to increase membrane fluidity and $sA\beta PP_\alpha$ secretion in HEK cells and in neuronal SH-SY5Y overexpressing AβPP cells [157]. In addition, it has been reported that nonspecific PLA_2 inhibitor partially suppressed muscarinic receptor-stimulated increases in $sA\beta PP_\alpha$ secretion in SH-SY5Y [23]. Since PLA_2 increases membrane fluidity and nonamyloidogenic cleavage of AβPP, PLA_2 activity modulation can be considered as a potential target for AD treatment.

3. Role of Membrane Physical Properties in Aβ-Membrane Interaction and Aβ Cytotoxicity

3.1. Aβ-Membrane Interactions Studied in Membrane Models and in Cell Cultures. Cleavage of AβPP leads to the production of Aβ peptides of different length, of which $A\beta_{1-40}$ is the major species and $A\beta_{1-42}$ is the most fibrillogenic and toxic component in AD plaques [27]. Numerous studies have demonstrated direct interaction of $A\beta_{1-40}$ and $A\beta_{1-42}$ with components of the plasma membrane, which consequentially disrupts the membrane properties [28–33, 158–160]. There are several suggested types of Aβ-membrane interactions. Aβ peptide can be retained in a membrane upon AβPP cleavage, thus being prevented against release and aggregation [161]. It also can be released as soluble monomers into the extracellular environment and then be removed [161, 162]. On the other hand, Aβ can reinsert into a membrane and form ion-conducting pores or bind to a membrane surface by undergoing accelerated aggregation and form nonspecific structures, which causes thinning and deformation to the membrane [161, 163–166].

$A\beta_{1-42}$ has been shown to reduce membrane fluidity and accelerate the amyloidogenic processing of AβPP [25, 33, 167–172]. *In vivo*, a decrease in membrane fluidity of synaptosomes isolated from frontal and hypothalamic neurons of 3-month-old mice, administrated with Aβ, has been demonstrated [171]. By using *in situ* atomic force microscopy and fluorescence spectroscopy, randomly structured $A\beta_{1-42}$ has been reported to decrease membrane fluidity of planar bilayers composed of total brain lipids, and this effect is cholesterol-content dependent: the most dramatic effect has been seen for cholesterol-enriched samples [168]. DPH (1,6-diphenyl-1,3,5-hexatriene) fluorescence study has shown a similar effect of $A\beta_{1-40}$ on membrane fluidity of unilamellar liposomes with a strong correlation to Aβ aggregation state and pH [170]. It has been reported that unaggregated peptides and pH 7 do not affect membrane fluidity, while aggregated Aβ at pH 6 or 7 decreased membrane fluidity in a time- and dose-dependent manner [170]. Studies of SH-SY5Y human neuroblastoma cells have shown some contradictory results. In this observation, $A\beta_{1-42}$ monomers increased fluidity of cell membranes, and Aβ-Aluminium complex promoted even a greater effect [172]. Differences in effects of Aβ on fluidity could result from the tissue source and preparation, whether Aβ is soluble or aggregated, and the age of the organism. The differences in effects of Aβ on fluidity could also be the result of differences in the location of the fluorescent probes in the membrane environment and the lifetime of the fluorescent probes.

The fluorescence microscopy of a membrane with the environmentally sensitive probe Laurdan has demonstrated the ability of $A\beta_{1-42}$ oligomers to affect the membrane molecular order [147, 173, 174]. It has been shown that an interaction of $A\beta_{1-42}$ with artificial membranes made them molecularly disordered (more water molecules were

partitioned into the membrane core) due most likely to the insertion of the peptide into the bilayer and the direct alteration of membrane lipid packing. In the same study, the effect of $A\beta_{1-42}$ oligomers on immortalized rat astrocytes (DITNC cells) membranes was opposite. DITNC membranes become more molecularly ordered upon incubation with Aβ in a time-dependent manner, and it was consistent with activation of $cPLA_2$. At the same time, in the presence of NADPH oxidase inhibitor, the membranes of the cells remained molecularly disordered. These results suggested an indirect effect of Aβ through the signaling pathway involving NADPH oxidase and $cPLA_2$ [147].

The study of the interaction of $A\beta_{1-42}$ with unilamellar lipid vesicles has demonstrated increased vesicle fusion and a thinning of the lipid bilayer and enhancing of these effects at pH 7 and at a high Aβ/lipid ratio [175]. The micropipette manipulation of giant unilamellar vesicles has shown the ability of $A\beta_{1-42}$ to affect the membrane lysis tension depending on artificial membrane lipid composition. It has been found that neither $A\beta_{1-42}$ nor $A\beta_{1-40}$ changed mechanical properties of glycerophospholipid-cholesterol vesicles, while partial substitutions of cholesterol with 7β-hydroxycholesterol that contained additional dipole of oxysterol led to a dramatic reduction of the lysis tension upon Aβ treatment. The results of this experiment strongly suggest that a negative bilayer surface charge is required for Aβ-membrane interaction [176].

The Aβ-membrane interaction may also be followed by the incorporation of Aβ into the membranes and formation of cation-selective channels, which lead to alteration of membrane permeability and electrical conductance [31, 177–186]. The study of the effects of soluble $A\beta_{1-42}$ oligomers on planar lipid and tethered lipid bilayers has indicated that Aβ oligomers were inserted into the hydrophobic core of the bilayer, affecting both membrane leaflets and significantly increasing membrane ion current [31, 178]. It has been demonstrated that Aβ-induced ion conductance was different from ion transfer through water-filled pores and depended on peptide concentration and membrane lipid composition [178]. Similarly, $A\beta_{1-40}$ caused a dose-dependent increase in the Na^+, Ca^{2+}, and K^+ influx in the lumen of liposomes formed from the acidic phospholipids but did not change cation conductance in a case of liposomes formed from the neutral phospholipids [179]. There was also evidence that Aβ induced an increase in membrane conductance, which was dependent on the area compressibility of the lipid bilayer. Membranes with a large area compressibility modulus were almost insensitive to $A\beta_{1-42}$ oligomers, while membranes formed from soft, highly compressible lipids were very sensitive to the presence of oligomers [31].

In vitro, after $A\beta_{1-42}$ treatment, the membranes of human neuronal hNT cells and neuron-like differentiated PC12 cells depolarized and exhibited enhanced membrane permeability [183, 186]. Patch-clamp studies of a cell line derived from hypothalamic gonadotrophin-releasing hormone GnRH neurons have demonstrated spontaneous formation of Zn^{2+}-sensitive channel pores upon $A\beta_{1-40}$ monomers treatment [184]. Similarly, $A\beta_{1-40}$ aggregates induced perforation of hippocampal neuronal synapses, causing an increase in membrane conductance, intracellular calcium, and ethidium bromide influx [185]. It has been suggested that Aβ-induced membrane depolarization and increased ions influx in neurons was not just due to forming of cation-selective pores but rather was a consequence of events resulting from downstream pathways with involvement of metabotropic glutamate receptor and G-proteins [186].

3.2. Membrane-Associated Conformational Modifications and Aggregation of Aβ. In a previous section, we discussed the ability of Aβ to alter biophysical properties of membranes and the dependence of these processes on membrane environment. These studies suggest that membrane property and composition, in turn, play a critical role in conformational changes and aggregation of Aβ. The aggregation of Aβ is a complicated multistep process consisting of several phases: monomers → soluble oligomers (clusters of small numbers of peptide molecules without a fibrillar structure) → protofibrils (aggregates of isolated or clustered spherical beads made up of ~20 molecules with β-sheet structure) → mature fibrils [187]. Although the mechanism which initiates Aβ aggregation is not fully understood, it has been shown to be modulated by several factors, including concentrations of monomers and their conformational transitions, sequential changes in the Aβ primary structure, and interactions with metal ions and membrane molecules [35, 37, 40, 169].

In vitro studies have demonstrated that Aβ monomers can exist in three major conformation forms: α-helix, β-sheet, or random coil depending on physical properties and chemical composition of the environment [188, 189]. Since the toxic Aβ mostly consists of β-sheets, even though the original hydrophobic component of Aβ is a part of a transmembrane α-helix of AβPP, the conformational transition of Aβ from α-helix or random coil to β-sheet is most likely the very first step in the formation of oligomers and fibrils [190]. Multidimensional NMR spectroscopy and circular dichroism (CD) studies have demonstrated that alterations in the membrane structure and biophysics can trigger the conversion of soluble α-helical monomeric $A\beta_{1-40}$ into the oligomeric β-sheet conformation [161, 189]. It has been shown that, in an ordered membrane system, Aβ adopted a single α-helical confirmation, while in disordered micelles Aβ rather adopted soluble β-sheet oligomeric conformation [189]. At the same time, study of the neutral and negatively charged bilayers showed an increase in β-sheet content as the negative charge on the lipid membrane increased [161, 191].

In situ atomic force microscopy and total internal reflection fluorescence microscopy studies have indicated that the size and the shape of $A\beta_{1-40}$ and $A\beta_{1-42}$ aggregates, as well as the kinetics of their formation, depended on the physicochemical nature of the surface [192, 193]. For example, on hydrophilic surfaces (mica) $A\beta_{1-42}$ formed particulate, pseudomicellar aggregates, while on hydrophobic surfaces (graphite) Aβ formed uniform, elongated sheets with dimensions consistent with the dimensions of β-sheets. The results of this study suggested that Aβ fibril formation may be driven by interactions at the interface of aqueous

solutions and hydrophobic substrates, which occurs in membranes and lipoprotein particles *in vivo* [192]. Similarly, $A\beta_{1-40}$ fibril growth was especially prominent on chemically modified negatively charged quartz surfaces, while no fibril formation was observed on the positively charged surfaces [193].

Numerous *in vitro* and *in vivo* studies have demonstrated that lipid bilayer composition, as well as membrane-associated proteins, can regulate Aβ aggregation in both enhancement and inhibition manner [37–40]. It has been suggested that binding of Aβ to the ganglioside-containing membranes can induce a structural transition from random coil to β-sheet in Aβ40/42 and accelerate fibril formation [194–196]. Electron microscopy studies have demonstrated that interaction of Aβ40/42 with plasma, lysosomal, and endosomal membranes accelerated fibrillogenesis of Aβ, while the presence of Golgi membranes hindered the process [169].

4. Conclusion

An increasing amount of evidence demonstrates that a lot of cellular processes in AD are intimately associated with physical properties and organization of membranes. The primary step in Aβ accumulation, the amyloidogenic cleavage of AβPP, is affected by the membrane properties such as membrane fluidity and molecular order and can be modulated by removal of cholesterol and manipulation of membrane lipid composition. Aβ-membranes interaction, in turn, affects biophysical membrane properties and accelerates the amyloidogenic processing of AβPP. Aβ has been reported to reduce membrane fluidity, affect molecular order and membrane lysis tension, induce thinning of the lipid bilayer, and increase membrane conductance. Aβ can also indirectly affect membrane properties by binding to membrane receptors and triggering downstream signaling pathways leading to oxidative stress and inflammation. On the other hand, the ability of Aβ to interact with membranes of neurons and other cerebral cells depends on physical properties and organization of membranes, such as cholesterol content, lipid composition and Aβ/lipid ratio, pH, the presence of metal ions, and bilayer surface charge. Membrane properties and composition play critical roles in Aβ cytotoxicity associated with its conformational changes and aggregation state as well. Therefore, understanding how membrane properties and organization are related to cellular pathways in AD should prove to provide insights into the mechanisms of the pathogenesis in AD.

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