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Cellular Membrane Fluidity in Amyloid Precursor Protein Processing

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Abstract

The senile plaque is a pathologic hallmark of Alzheimer's disease (AD). Amyloid- β peptide ($A\beta$), the main constituent of senile plaques, is neurotoxic especially in its oligomeric form. $A\beta$ is derived from the sequential cleavage of amyloid precursor protein (APP) by β - and γ -secretases in the amyloidogenic pathway. Alternatively, APP can be cleaved by α -secretases within the $A\beta$ domain to produce neurotrophic and neuroprotective α -secretase-cleaved soluble APP (sAPP α) in the nonamyloidogenic pathway. Since APP and α -, β -, and γ -secretases are membrane proteins, APP processing should be highly dependent on the membrane composition and the biophysical properties of cellular membrane. In this review, we discuss the role of the biophysical properties of cellular membrane in APP processing, especially the effects of phospholipases A₂ (PLA₂s), fatty acids, cholesterol, and $A\beta$ on membrane fluidity in relation to their effects on APP processing.

Keywords

APP; Alzheimer's disease; Cellular membrane

Introduction

In Alzheimer's disease (AD) brains, there is an increased deposition of amyloid plaques which are mainly composed of neurotoxic amyloid- β peptide ($A\beta$). Recent research indicates that the soluble oligomeric form of $A\beta$ significantly contributes to the pathogenesis of the disease [1]. In the amyloidogenic pathway, $A\beta$ is derived from a proteolytic process of

amyloid precursor protein (APP), in which APP is cleaved sequentially by β - and γ -secretases [2, 3]. Alternatively, APP can be cleaved by α -secretases between amino acids 16 and 17 within the A β domain and produce neurotrophic and neuroprotective soluble APP (α -secretase-cleaved soluble APP, sAPP α) in the nonamyloidogenic pathway [4]. These two pathways compete with each other, and enhancing APP processing by α -secretases has been suggested as a potential therapeutic strategy for AD [5]. Since APP and α -, β -, and γ -secretases are membrane proteins, APP processing should be affected by the local membrane environment. For example, γ -secretase activity can be modulated by membrane thickness in a cell-free system [6]. The cleavage of APP by β -secretase, the primary step to produce A β [7, 8], occurs preferentially in lipid rafts, which are highly ordered membrane microdomains rich in cholesterol, sphingolipids, and saturated phospholipids [9–14]. On the other hand, the activity of α -secretases is favorable in nonraft domains [15].

Phospholipases A₂ (PLA₂s) are responsible for the maintenance of phospholipid homeostasis in cellular membranes and implicated in AD and APP processing [16–18]. Fatty acids, the hydrolyzed products of PLA₂s, alter membrane properties [19–21] which influence cellular functions. Moreover, A β in different forms directly bind to membrane and change its biophysical properties [22]; A β indirectly affects membrane properties by binding to membrane receptors and triggering downstream signaling pathways [23–26]. In this review, we discuss the evidence about the effects of PLA₂s, fatty acids, cholesterol, and A β on membrane properties in relation to their effects on APP processing. Understanding the mechanisms leading to changes of membranes biophysics and how they result in changes in APP processing should provide insights into new therapeutic strategies for the prevention and treatment of AD.

Phospholipases A₂ on Membrane Properties and APP Processing

PLA₂s are ubiquitous enzymes in mammalian cells that catalyze the hydrolysis of fatty acids from *sn*-2 position of phospholipids. PLA₂s are classified into three major families: calcium-dependent cytosolic PLA₂ (cPLA₂), calcium-independent PLA₂ (iPLA₂), and secretory PLA₂ (sPLA₂). These enzymes are responsible for the maintenance of phospholipid homeostasis in cellular membranes [27]. They are also important in the production of lipid mediators, such as arachidonic acid (AA), a precursor for the synthesis of eicosanoids [28]. Activation of PLA₂s has been implicated in diverse cellular responses such as mitogenesis, differentiation, inflammation, and cytotoxicity, and changes in activities of PLA₂s occur in many neurodegenerative diseases including AD [29–36]. For a comprehensive understanding of PLA₂, see the review by Dennis et al. [27].

Immunoreactivity of cPLA₂ is upregulated in reactive astrocytes in AD patient brains [37, 38]. Increases of sPLA₂-IIA and cPLA₂-IVA expression were also found in the hippocampus of AD patients [29, 39, 40]. In addition, A β has been shown to activate cPLA₂ in primary rat and mouse brain endothelial cells, astrocytes, cortical neurons, and PC12 cells [41–45]. However, PLA₂ activity was significantly decreased in the parietal and, to a lesser degree, in the frontal cortex of AD brains [46]. Lower PLA₂ activity correlates 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 PLA₂ activity and a more severe form of the illness [47].

PLA₂s play key roles in the modulation of membrane properties under pathological and physiological conditions. PLA₂ activation affects membrane fluidity, which characterizes an average lateral motion of phospholipid molecules within the lipid bilayer, and APP processing [17, 18]. In AD brains, there is evidence for reduced membrane fluidity coupled with decreased PLA₂ activity [47, 48]. Similarly, inhibition of PLA₂ activity in rat hippocampus has been shown to reduce membrane fluidity and impair the formation of short- and long-term memory [18, 49]. In addition, nonspecific PLA₂ inhibitor partially suppressed muscarinic receptor-stimulated increases in sAPP α secretion in human neuroblastoma cells (SH-SY5Y) [50]. Our study showed that sPLA₂-III increased membrane fluidity and sAPP α secretion and decreased levels of A β in SH-SY5Y cells and primary neurons [51]. Moreover, AA increased fluidity of membranes in cultured cerebral endothelial cells [52, 53], SH-SY5Y cells [51], and hippocampal neurons in vivo [54]. Another hydrolyzed product of PLA₂, docosahexaenoic acid (DHA), has also been demonstrated to increase membrane fluidity and sAPP α secretion in human embryonic kidney (HEK) 293 cells and overexpressing APP cells [55]. Therefore, the effects of PLA₂ on membrane fluidity and APP processing may partially attribute to its hydrolyzed products, fatty acids, which will be reviewed in the following section. Interestingly, compounds capable of altering membrane fluidity also modulate sAPP α production. Benzyl alcohol (C₆H₅OH) increases, whereas pluronic F68 (PF68) decreases, membrane fluidity and sAPP α secretion [22]. In turn, A β itself accelerates the amyloidogenic processing of APP by reducing membrane fluidity [22]. The study by Kojro et al. [56] showed that treatment with methyl- β -cyclodextrin (M β CD) to reduce cellular cholesterol increased membrane fluidity, APP accumulation at the cell surface, and sAPP α secretion. Our study also showed that sPLA₂-III and AA treatment increased the accumulation of APP at cell surface [51]. These results are consistent with the notion that A β production mainly occurs in endosomes [57–62]. Increased membrane fluidity partially impairs the endocytosis of APP and subsequently increases sAPP α production. Since PLA₂ increases membrane fluidity and nonamyloidogenic cleavage of APP, PLA₂ activity modulation can be considered as a potential target for AD treatment.

Fatty Acids on Membrane Properties and APP Processing

Fatty acids are important ingredients in various dietary sources. They are essential components of cellular membrane and play a pivotal role in the normal development and function of the brain [63, 64]. Long-chain ω -3 and ω -6 polyunsaturated fatty acids (PUFAs), the major polyunsaturated fatty acids in the central nervous system [65], are essential for prenatal brain development and normal brain functions [64, 66, 67]. Diets rich in long-chain ω -3 PUFAs (e.g., 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 [67–71]. Animals with diets deficient in ω -3 fatty acids have reduced visual acuity and impaired learning ability [16, 67]. AA, another abundant fatty acid in the brain, is a second messenger [72] and a precursor for the synthesis of eicosanoids [28]. The presence of PUFAs in

neuronal cells influences cellular function both directly through their effects on membrane properties and indirectly by acting as precursors for lipid-derived messengers [19, 20].

Disturbed metabolism of fatty acids is associated with AD [73–76]. For example, lower levels of DHA were reported in serum samples taken from an AD patient [77], while greater consumption of DHA significantly reduced the likelihood of developing AD [78]. DHA and curcumin have been shown to suppress A β -induced phosphorylation of tau tangles and the inactivation of insulin receptors in primary rat neurons [79]. Recently, reduced expression of the neuronal sortilin-related receptor SorLA/LR11, a sorting protein that regulates APP trafficking to β - and γ -secretases, was identified as a probable genetic risk factor for late-onset AD [80]. DHA, in turn, has been found to increase LR11 expression in primary rat neurons, human neuronal line, and aged nontransgenic and DHA-depleted APP^{sw} AD transgenic mice [44]. In 15-month-old APP/presenilin-1 mice, DHA supplementation improved spatial memory, decreased A β deposition, and slightly increased relative cerebral blood volume, indicating that a DHA-enriched diet can diminish AD-like pathology [81]. One plausible explanation is that ω -3 PUFAs enhance phagocytosis of A β by microglia and decrease inflammation [82]. In addition, 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 [83].

PUFAs in neuronal cells influence cellular functions through their ability to integrate into cell membrane and change their physical properties [19, 20]. Not only can PUFAs be incorporated into membrane phospholipids but also are they able to associate with cellular membrane as free fatty acids. The ability of fatty acids to modulate membrane properties and functions [18, 70, 84–88] depends on both the saturation degree of the fatty acids and the *trans/cis* ratio of the unsaturated fatty acids [21, 89, 90]. For example, diets rich in PUFAs, including DHA and AA, have been shown to increase membrane fluidity of neurons and other cells [54, 69, 91, 92]. DHA is capable of counteracting a cholesterol-induced decrease in platelet membrane fluidity and modulating platelet hyperaggregation [91]. In contrast, membrane incorporation of saturated fatty acids led to decreased membrane fluidity [87, 90, 93, 94]. However, the fatty acids with short chain length (e.g., length=10) increase α -secretase activity [95]. *Trans* fatty acids accumulate in the cellular membrane and increase A β production and oligomerization [96]. Many other membrane properties including molecular order, compressibility, and permeability are also affected by PUFA [97].

It has been reported that an increase in membrane fluidity leads to an increase in nonamyloidogenic cleavage by α -secretase to produce sAPP α [22, 56]. Consistently, enrichment of cell membranes with PUFAs increases membrane fluidity and, subsequently, promotes nonamyloidogenic processing of APP [21]. A typical Western diet (with 40 % saturated fatty acids and 1 % of cholesterol) fed to transgenic APP/PS1 mice increases A β , while diets supplemented with DHA decrease A β levels [98]. Similarly, DHA decreases the amount of vascular A β deposition [99] and reduces cortical A β burden [100] in the aged mouse model of AD. In this model, DHA modulates APP processing by decreasing both α - and β -APP C-terminal fragment products and full-length APP [100]. DHA stimulates nonamyloidogenic APP processing resulting in reduced A β levels in cellular models of AD [101]. Meanwhile, our study of the effects of fatty acids on cell membrane fluidity and

sAPP α secretion in relation to degrees of unsaturation has suggested that not all unsaturated fatty acids but only those with four or more double bonds, such as AA (20:4), eicosapentaenoic acid (EPA, 20:5), and DHA (22:6), increased membrane fluidity and led to an increase in sAPP α secretion, while stearic acid (SA, 18:0), oleic acid (OA, 18:1), linoleic acid (LA, 18:2), and α -linolenic acid (ALA, 18:3) did not [21]. Moreover, another study indicated that treatment of PSwt-1 CHO cells with oleic acid and linoleic acid increased γ -secretase activity and A β production [102]. These studies suggest that modulation of PUFAs content in cellular membrane is essential in enhancing sAPP α production partially due to their effects on membrane fluidity.

Cholesterol on Membrane Properties and APP Processing

Cholesterol is an essential component of cellular membrane and plays a vital role in the regulation of membrane functions. Distribution of cholesterol within plasma membrane is not even: cholesterol is mostly condensed in lipid rafts, which are more tightly packed than nonlipid raft domains due to intermolecular hydrogen bonding involving sphingolipid and cholesterol [103,104]. Cholesterol distribution correlates with altered APP processing in mice treated with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) inhibitors) [105]. Levels of membrane cholesterol can be modulated by specific inhibitors of the cellular biosynthesis such as statins, or it can be selectively extracted from plasma membrane by M β CD [56, 106]. Chronic simvastatin treatment decreases cholesterol levels in mouse brains and affects cholesterol distribution within synaptosomal membranes [107]. Simvastatin also significantly increases the levels of insoluble A β but reduces levels of soluble A β in the brain [107]. The content 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 [104, 108–114].

Intracellular cholesterol homeostasis regulates APP processing [115]. In membrane compartmentalization model, APP presents in two cellular pools, one is associated with the cholesterol-enriched lipid rafts, where A β is generated, and the other is outside of rafts (i.e., nonlipid raft domains), where α -cleavage occurs [10, 116]. It was reported that membrane cholesterol depletion decreased the content of APP in cholesterol and sphingolipid-rich membrane microdomains and subsequently inhibited the amyloidogenic pathway to produce A β [56, 117]. DHA decreases cholesterol de novo synthesis, shifts its distribution from raft to nonraft domains, and decreases β - and γ -secretase activity [118]. In contrast, cholesterol accumulation in Niemann-Pick type C (NPC) model cells has been shown to shift APP localization to lipid rafts [119]. Consistent with the membrane compartmentalization model, cellular cholesterol depletion leads to increased membrane fluidity [56, 120–122]. An increase in membrane fluidity shifts APP processing to nonamyloidogenic cleavage by α -secretase [119–121, 123, 124]. The removal of cholesterol with M β CD or treatment with lovastatin increased membrane fluidity, which resulted in higher expression of the α -secretase and impaired internalization of APP [56]. The increased membrane fluidity also correlates with a redistribution of cholesterol, sphingomyelin, and proteins involved in APP processing between raft and nonraft domains and enhances sAPP α production [125]. Local

cholesterol increase triggers APP-BACE1 (β -secretase) clustering in lipid rafts and rapid endocytosis [126]. Actually, APP has a flexible transmembrane domain and binds to cholesterol [127]. Titration of C99 fragment of APP reveals a binding site for cholesterol, providing a mechanistic insight into how cholesterol promotes APP accumulation in lipid raft and amyloidogenesis [127].

Meanwhile, cholesterol enrichment has been shown to reduce membrane fluidity [91, 128]. Exposure of cholesterol to astrocytes, primary neurons, and glial cultures inhibited the secretion of sAPP α and reduced cell viability [123,124,129]. Furthermore, some studies showed that cholesterol levels in the membranes were positively correlated with β -secretase activity [130], while lovastatin enhanced α -secretase activity [124]. Cholesterol enrichment that impeded membrane fluidity may lower sAPP α production by hindering the interaction of the substrate with its proteases [131]. Interestingly, substitution of cholesterol by the steroid 4-cholesten-3-one induces a minor change in membrane fluidity and reduces sAPP α secretion, whereas substitution of cholesterol by lanosterol increases membrane fluidity and sAPP α secretion [56]. These results suggest reversible effects of cholesterol on the α -secretase activity depending on membrane fluidity.

Many studies support the notion that A β production occurs in endosomes [58–62]. APP internalization from plasma membrane is regulated by key regulators of endocytosis, such as Rab5, and this process enhances APP cleavage by β -secretase to increase A β levels [132]. In contrast, APP, lacking its cytoplasmic internalization motif, accumulates at the plasma membrane and undergoes cleavage by α -secretase [7, 8]. Cholesterol increases clathrin-dependent APP endocytosis in a dose-dependent and linear manner [133]. Moreover, alterations in cholesterol transport from late endocytotic organelles to the endoplasmic reticulum had important consequences for both APP processing and the localization of γ -secretase-associated presenilins [134]. It has been suggested that cholesterol increase in AD could be responsible for the enhanced internalization of clathrin-dependent endocytosis of APP and the overproduction of A β [133]. Alternatively, APP internalization could be reduced by lowering cholesterol, which leads to an increase in membrane fluidity, APP accumulation on the cell surface, and increased sAPP α secretion [56].

A β on Membrane Properties and APP Processing

Many studies showed direct interactions of A β with components of the plasma membrane, which disrupts the membrane properties consequentially [135–144]. Several types of A β -membrane interactions were suggested. A β peptide can be retained in a membrane upon APP cleavage and thus be prevented against release and aggregation [145]. A β can also be released as soluble monomers into the extracellular environment and then be removed [145, 146]. After releasing, on the other hand, A β can reinsert into a membrane and form ion-conducting pores or undergo accelerated aggregation on a membrane surface and form nonspecific structures, which causes thinning and deformation to the membrane [145, 147–151]. A simulation study showed that a highly asymmetric cholesterol distribution which is depleted on the exofacial leaflet but enhanced on the cytofacial leaflet of the model lipid membrane thermodynamically favors membrane retention of a fully embedded A β peptide [152]. However, in the case of cholesterol redistribution that increases concentration of

cholesterol on the exofacial layer, typical of aging or AD, the free energy favors peptide extrusion of the highly reactive N-terminus into the extracellular space that may be vulnerable to aggregation, oligomerization, or deleterious oxidative reactivity [152]. The insertion of the peptide into the artificial membrane bilayers alters membrane lipid packing and induces molecular disorder (more water molecules were partitioned into the membrane core), as shown by the fluorescence microscopy of the environmentally sensitive probe laurdan [153–155]. The membranes of immortalized rat astrocytes become more molecularly ordered upon incubation with A β in a time-dependent manner, which is due to the signaling pathway involving NADPH oxidase and cPLA₂ triggered by A β [153]. The incorporation of A β into the membranes and formation of cation-selective channels lead to the alteration of membrane permeability and electrical conductance [138, 151, 156–164]. It has been suggested that A β -induced membrane depolarization and increased ion influx in neurons were not just due to forming of cation-selective pores but rather resulted from downstream pathways involved with metabotropic glutamate receptor and G-proteins [164].

A β has been shown to reduce membrane fluidity and accelerate the amyloidogenic processing of APP [22, 140, 165–169]. A β stimulates the amyloidogenic processing of APP by reducing membrane fluidity and complexing with GM-1 ganglioside [22]. This dynamic action of A β may start a vicious circle, where endogenous A β stimulates its own production [22]. Interestingly, DHA has protective effect against impaired learning in A β -infused rats, which is associated with increased synaptosomal membrane fluidity [170]. It was shown that, in vivo, A β administration caused a decrease in membrane fluidity of synaptosomes isolated from frontal and hypothalamic neurons of 3-month-old mice [168]. In a model system of liposomes, decreased fluidity reduced membrane permeabilization [171]. By using in situ atomic force microscopy and fluorescence spectroscopy, randomly structured A β 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-rich samples [166]. DPH (1,6-diphenyl-1,3,5-hexatriene) fluorescence study has shown a similar effect of A β on membrane fluidity of unilamellar liposomes with a strong correlation to A β aggregation state and pH [167]. Unaggregated peptides at pH 7 do not affect membrane fluidity, while aggregated A β at pH 6 or 7 decreased membrane fluidity in a time- and dose-dependent manner [167]. Studies of SH-SY5Y human neuroblastoma cells have shown some contradictory results. In this study, A β monomers increased fluidity of cell membranes, and A β -aluminum complex promoted even a greater effect [172]. Another study showed A β significantly increased annular and bulk fluidity in synaptic plasma membranes (SPM) of rat cerebral cortex and hippocampus, while A β had no effect on fluidity of SPM of cerebellum [173]. The differences in the effects of A β on fluidity could result from the tissue source and preparation, the amounts of cholesterol and phospholipid, whether A β is soluble or aggregated, and the age of the organism. The differences could also be due to the different locations of fluorescent probes in the membrane environment and the lifetime of the fluorescent probes.

A β also alters composition of cellular membrane lipids [174], causes oxidative lipid damage [175], increases membrane fusion [176], impairs membrane redox system [177], stimulates trafficking of cholesterol from plasma membrane to the Golgi complex in mouse primary astrocytes [178], reduces the cell membrane roughness [179], and disrupts membrane

trafficking of α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor contributing to early synapse dysfunction [180]. These perturbing effects may contribute to amyloidogenic processing of APP. Metal ions, pH, fatty acids, and cholesterol affect interactions of A β with membrane lipid and membrane insertion of A β and potentially inhibit fibril formation and the membrane perturbing effects of A β [170, 181–183]. A β polymers have a higher affinity for cholesterol than phosphatidylcholine or saturated fatty acids [184]. Aggregated A β may affect lipid transport between cells or remove specific lipids from membranes, and such effects could contribute to neuronal dysfunction. Actually, in C99/APP, membrane-buried GXXXG motifs (G, Gly; X, any amino acid) play a key role in cholesterol binding [127]. Association of C99/APP with cholesterol may favor partitioning of the protein into membrane domains rich in the proteases of the amyloidogenic pathway [127]. The linear fragment 22–35 of A β is a functional cholesterol-binding domain that could promote the insertion of β -amyloid peptides or amyloid pore formation in cholesterol-rich membrane domains [185]. Molecular dynamic simulations suggest that cholesterol induces a tilted α -helical topology of A β _{22–35}. This facilitates the establishment of an interpeptide hydrogen bond network involving Asn-27 and Lys-28, a key step in the octamerization of A β _{22–35} which proceeds gradually until the formation of a perfect annular channel in a phosphatidylcholine membrane [186].

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 A β accumulation, the amyloidogenic cleavage of APP, is affected by the membrane properties such as membrane fluidity and can be modulated by removal of cholesterol and manipulation of membrane lipid composition. PLA₂s and their hydrolyzed products, such as AA and DHA and other fatty acids, play important roles in the modulation of membrane properties in relation to their effects on APP processing. A β -membrane interactions, in turn, affect biophysical membrane properties and accelerate the amyloidogenic processing of APP. We review the role of the biophysical properties of cellular membrane in APP processing, especially the effects of PLA₂s, fatty acids, cholesterol, and A β on membrane fluidity in relation to their effects on APP endocytosis and processing, which are summarized in Table 1. Understanding how membrane properties and organization are related to cellular pathways including APP processing in AD should provide insights into the mechanisms of AD pathogenesis.

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Summary of the effects of PLA₂, fatty acids, cholesterol, and Aβ on membrane fluidity, accumulation of APP at cell surface, and secretion of sAPPα and Aβ

Table 1

Treatment	Membrane fluidity	APP at cell surface	Secretion of sAPPα	Aβ
PLA ₂ ^a	↑ [17, 18, 51]	↑ [51]	↑ [50, 51]	↓ [47, 51]
sPLA ₂ III	↑ [51]	↑ [51]	↑ [51]	↓ [51]
DHA	↑ [21]	NA	↑ [21]	↓ [81, 99–101], NC [21]
EPA	↑ [21]	NA	↑ [21]	NC [21]
AA	↑ [21, 51]	↑ [51]	↑ [21, 51]	NC [21, 51]
ALA	NC [21]	NA	NC [21]	NA
LA	NC [21]	NA	NC [21]	↑ [102]
OA	NC [21]	NA	NC [21]	↑ [102]
SA	NC [21]	NA	NC [21]	NA
PA	NC [51]	NC [51]	NC [51]	NC [51]
LPC	NC [51]	NC [51]	NC [51]	NC [51]
MβCD	↑ [56]	↑ [56]	↑ [56]	↑ [56]
Cholesterol	↓ [120–122, 128]	↓ [126, 133]	↓ [123, 124]	↑ ^b [133]
C ₆ H ₅ OH	↑ [22]	NA	↑ [22]	↓ [22]
PF68	↓ [22]	NA	↓ [22]	↑ [22]
Aβ	↓ ^b [22, 165, 166, 168, 169]	NA	NC [22]	↑ [22]

↑ increase, ↓ decrease, NC no change, NA data not available, sPLA₂-III secretory phospholipase A₂ type III, DHA docosahexaenoic acid (22:6), EPA eicosapentaenoic acid (20:5), AA arachidonic acid (20:4), ALA α-linolenic acid (18:3), LA linoleic acid (18:2), OA oleic acid (18:1), SA stearic acid (18:0), PA palmitic acid (16:0), LPC lysophosphatidylcholine, MβCD methyl-β-cyclodextrin, C₆H₅OH benzyl alcohol, PF68 pluronic F68, Aβ amyloid-β

^aResults partially come from studies with nonspecific inhibitor of PLA₂

^bThere are some contradictory results [172, 173, 187]. The discrepancy between different studies may be due to tissue and cell source and preparation, cholesterol content, whether Aβ is soluble or aggregated, locations, and lifetime of fluorescent probes