Plasmalogen in the brain: Effects on cognitive functions and behaviors attributable to its properties

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Highlights

- We review the correlation between plasmalogen and behavior.
- Effect of plasmalogens on vesicle trafficking and signal transduction in the brain.
- Aberrant behaviors led by alteration in the plasma and brain plasmalogen levels.
- Improvement of brain plasmalogen compositions to alleviating brain disorders.

Abstract

Ether phospholipid compositions are altered in the plasma or brain of patients with brain disorders, such as Alzheimer and Parkinson's disease, including those with psychiatric disorders like schizophrenia and bipolar disorders. Notably, plasmenyl ethanolamine has a unique chemical structure, i.e., a vinyl-ether bond at the sn-1 position, which mainly links with polyunsaturated fatty acids (PUFAs) at the sn-2 position. Those characteristic moieties give plasmalogen molecules unique biophysical and chemical properties that modulate membrane trafficking, lipid rafts, intramolecular PUFA moieties, and oxidative states. Previous reports suggested that a deficiency in plasmenyl ethanolamine leads to disturbances of the myelin structure, synaptic neurotransmission and intracellular signaling, apoptosis of neurons, and neuroinflammation, accompanied by cognitive disturbances and aberrant behaviors like hyperactivity in mice. Therefore, this review summarizes the relationship between the biological functions of plasmalogen. We also

proposed biophysical properties that alter brain phospholipid compositions related to aberrant behaviors and cognitive dysfunction. Finally, a brief review of possible remedial plasmalogen replacement therapies for neurological, psychiatric, and developmental disorders attributable to disturbed plasmalogen compositions in the organs and cells was conducted.

Keywords

Plasmalogen; neurological disorders; behavior; delivery

1. Introduction

Plasmalogens are a subclass of glycerophospholipids whose glycerol backbone is linked to an alkyl chain at the sn-1 position by a vinyl-ether bond and an acyl chain at the sn-2 position by an ester bond (Fig. 1). They form components of the biological membrane, including the plasma membrane and the membranes of intracellular organelles. Therefore, extensive studies on biophysical properties propose that plasmalogens not only change the curvature, fluidity, rigidity, thickness, and lateral pressure of planar cell membranes, but also modulate the activity of the integral membrane proteins by interacting with them. Furthermore, the glycerol backbone is mainly bonded to polyunsaturated fatty acids, such as docosahexaenoic acid (DHA) and arachidonic acid (AA) in plasmalogens, suggesting its role in anti-inflammatory and proinflammatory functions, respectively (Dorninger et al., 2020). These physical and chemical properties affect neurological and psychiatric disorders because ether phospholipids, including plasmalogens, are rich in the brain. It is worth noting that ethanolamine plasmalogen (PlsEtn) accounts for over 50% of the total ethanolamine phosphoglycerides in the gray matter and over 85% phosphoglycerides in myelin (Horrocks and Sharma, 1982). Studies reported that plasmalogen deficiency was linked to the pathology of Alzheimer's disease and rhizomelic chondrodysplasia puctata brain lesions (Berger et al., 2016; Grimm et al., 2011; Han et al., 2001; Hossain et al.,

2017). They also noted that serum or plasma ether phospholipids differed between healthy subjects and patients with psychiatric disorders, such as psychosis or bipolar disorder type I (Dickens et al., 2021; Ogawa et al., 2020). Recently, behavioral studies using rodents have supported the efficacy of ether phospholipids for restoring behavioral disturbances and cognitive dysfunctions (Hino et al., 2019). Ether phospholipids also play vital roles in neuropsychiatric disorders' brain function and pathology, accounting for their consideration as a medication for preventing and treating the disorders described above. Therefore, it is important to understand how ether phospholipids affect brain functions. This review discusses the relationship between biological functions and biophysical and biochemical properties of plasmalogens as a medication for managing neurological and psychological disorders.

2. Chemical structure and biophysical properties of ether lipids

Glycerophospholipids are major components of the cell membrane. These phospholipids are classified into diacyl and ether glycerophospholipids, including alkyl acyl glycerophospholipids (plasmanyl phospholipids) and alkenyl acyl glycerophospholipids (plasmenyl phospholipids) (Fig. 1). An acyl chain is attached via an ester linkage to the sn-1 and sn-2 glycerol backbone positions in diacyl glycerophospholipids. However, an

alkyl or alkenyl chain instead of an acyl chain is linked to the sn-1 position of glycerol moieties in ether phospholipids. Among ether phospholipids, plasmenyl phospholipids, called plasmalogen, mainly possess an ethanolamine or a choline moiety in the sn-3 position of the glycerol backbone in humans. Furthermore, although saturated or monounsaturated carbon acyl chains are linked to the sn-1 position, polyunsaturated fatty acids are found at the sn-2 positions of plasmalogens (Han et al., 2001). Therefore, plasmalogens have characteristic biophysical features compared to the other phospholipids, in addition to protecting PUFA from oxidation in the gray matter (Hachem and Nacir, 2022).

Due to the amphipathic property of phospholipids, the hydrophobic effect influences the lipid bilayer, which is a fundamental structure of biological membranes in water (Yeagle, 2016b). In pure water, water molecules are randomly distributed. As a result, the dynamic hydrogen-bonding pattern among the water molecules is also random. However, when hydrophobic molecules are introduced into water, their hydrogen-bonding network is more ordered, surrounding the hydrophobic molecule (Yeagle, 2016b). With phospholipids, associations with hydrophobic portions and water lead to a more ordered water structure, decreasing entropy in this reaction; hence, the mixing of hydrophobic molecules with water is energetically unfavorable (Yeagle, 2016b).

The hydrophobic effect also allows phospholipids to aggregate in the lipid bilayer, favoring an interface between the water and hydrophobic portions by the hydrophilic portion of the phospholipids. Meanwhile, phospholipid assembly structures differ between phosphatidylcholine and phosphatidylethanolamine or between plasmalogen and ester-linked phospholipids based on their differences in the packing ratio (Yeagle, 2016a). Here, the packing ratio (P_r) is described using the following equation:

$$P_r = A_h/A_c$$

where A_h is the effective cross-sectional area of the hydrophilic portion, and A_c is the effective cross-sectional area of the hydrophobic phospholipid chain. Although similarities exist in the cross-sectional area between the hydrophilic and hydrophobic portions in phosphatidylcholine, the packing ratio is approximately one. Hence, most PCs form a lamellar bilayer structure. However, PE can form the hexagonal II structure ($P_r < 1$) due to the hydrophobic effect. In PE, the intermolecular hydrogen bonds (amine-phosphate hydrogen bonds) neutralize the charges on the hydrophilic portion. Subsequently, fewer water molecules can bind to the hydrophilic portion of PE using hydrogen bonds. This association proposes that more unbound and more ordered water molecules cover the surface of PE bilayer membranes, decreasing entropy. As a result, PE forms a hexagonal II structure to reduce the contact of the membrane surface with water

so that the hydrophobic effect is compensated (Yeagle, 2016a). Furthermore, a vinyl-ether bond, more hydrophobic than an ester bond, induces a closer packing of the sn-1 and sn-2 acyl chains at the proximal region to reduce the contact between water and the hydrophobic chains at the water-lipid interface (Koivuniemi, 2017; Rog and Koivuniemi, 2016). This reduced contact promotes the formation of the hexagonal-II phase of the membrane, simultaneously leading to more rigid bilayers through an increase in lateral packing, due to more ordered acyl chains in the hydrophobic portions. Thus, these biophysical properties are involved in various biological processes, including not only membrane trafficking including a vesicle fusion process but also signal transduction by mediating the sort and function of plasma membrane proteins. In fact, plasmalogens are rich in lipid rafts (Hossain et al., 2022), and the plasmalogen deficiency in lipid rafts causes reduced phosphorylation of protein kinase B (AKT) in the Schwann cell membrane by presumably affecting the correct compartmentalization of AKT (da Silva et al., 2014). In addition, the activation of glycogen synthase kinase 3β (GSK3β), led by reduced AKT phosphorylation, also inhibits the Schwann cell differentiation, impairing axonal sorting and myelination. Furthermore, reduction in glyceronephosphate *O*-acyltransferase (*GNPAT*) expression by lentiviral shRNA injection into bilateral hippocampus led to the depletion of TrkB protein, a target receptor of brain-derived

neurotrophic factor (BDNF), in the hippocampus raft fraction in mice, whereas a plasmalogen-rich diet consumption caused an increase in TrkB protein levels in the raft fraction (Hossain et al., 2022). The BDNF–TrkB signaling pathway has crucial roles in synaptic plasticity, neuronal survival, learning, and memory; plasmalogen diet-induced enhancement of learning and memory was suggested to be dependent on the BDNF–TrkB signaling pathway (Cunha et al., 2010; Hossain et al., 2022; Lu et al., 2014; Peng et al., 2009). Thus, plasmalogens contribute to the biological function of cells, mediating alterations in the biophysical and biochemical properties of the membrane.

3. Biological functions and clinical relevance of plasmalogens

3.1.Neurodegenerative diseases

A study reported that PlsEtn levels were dramatically decreased in the cerebral and cerebellar white matter and cerebral gray matter of patients with Alzheimer's (Han et al., 2001). Similarly, the loss of plasmalogens has been reported in patients with Parkinson’s disease and multiple sclerosis (Gitler et al., 2017). These observations imply that plasmalogens play a critical role in brain function. In Alzheimer’s model mice, PlsEtn deficiency was also observed in the cerebral cortex (Han et al., 2001) and hippocampus (Azad et al., 2021). In another study, to account for the pathological conditions of

Alzheimer's disease, an increased level of amyloid β, composing amyloid plaques, increased reactive oxidative species production. It also reduced the protein stability of alkylglycerone phosphate synthase (AGPS), one enzyme that synthesizes ether phospholipids, thus decreasing PlsEtn levels (Grimm et al., 2011). Plasmalogens function as scavengers of radical species through the oxidation of their vinyl-ether bond (Mangold and Weber, 1987). Specifically, a study reported that PlsEtn alleviated amyloid β-induced neurotoxicity by inhibiting oxidative stress, neuronal injury, apoptosis, and neuroinflammation in rats, proposing the vinyl-ether bond responsible for these effects (Che et al., 2018). Thus, the vinyl-ether linkage can play a critical role in preventing and improving neurodegenerative disorders.

3.2 Psychiatric disorders

Another recent study revealed that serum ether phospholipid levels decreased in subjects at clinical high risk (CHR) for psychosis who developed psychosis than their counterparts who did not (Dickens et al., 2021). Moreover, plasma PlsEtn levels were significantly lower in patients with BP I in a different study than in healthy controls. Plasma PE levels in patients with BP I were lower than those in controls and patients with BP II (Ogawa et al., 2020). Altered activities of neurons, i.e., serotonergic, dopaminergic, and glutaminergic neurons, including aberrant gene expression related to calcium signaling

and PUFAs have also been suggested in bipolar disorders (Kato, 2019).

In patients with schizophrenia (SCZ), assessment of the erythrocyte membrane lipidome revealed that the total concentration of ether phospholipids, especially the total amount of plasmalogen, was significantly reduced in both PC and PE (Li et al., 2022). Concurrently, most of the PUFAs in PE were reduced in the erythrocyte membrane, and saturation indices (% saturated fatty acid [SFA]/% monosaturated fatty acid and % SFA/% PUFA) and the lipophilic index (a mean measure of fatty acid melting points) were higher in the SCZ group, suggesting lower cell membrane fluidity in patients with SCZ (Li et al., 2022).

In addition to the effect of PUFA at the sn-1 and sn-2 positions on membrane fluidity, PlsEtn alters the fusogenicity of vesicles via its incorporation into the bilayer membrane. Vesicles comprising equimolar mixtures of PC and PlsEtn fused with phosphatidylserine vesicles were three times more rapid than the corresponding vesicles where PlsEtn was replaced with its diacyl phospholipid counterpart, i.e., PE (Glaser and Gross, 1994). A study also observed that vesicles containing PlsEtn in physiologic ratios with other phospholipids, i.e., PC and PS, underwent fusion six times more rapidly than the corresponding vesicles containing PE instead of PlsEtn (Glaser and Gross, 1994). These PlsEtn effects on membrane fluidity and fusogenicity indicate that plasmalogens possibly

contribute to the release and reuptake of neurotransmitters in the synapses. In agreement, a biological study reported that release of norepinephrine by electrical and chemical stimuli was decreased in the hippocampal and cortical slices of the glyceronephosphate O-acyltransferase (*Gnpat*) KO mouse, an ether lipid-deficient mouse, supporting this finding (Dorninger et al., 2019b). Alternatively, dopamine hyperactivity at D2 dopamine receptors in the mesolimbic pathway, NMDA receptor hypoactivity at GABAergic interneurons, and serotonin hyperactivity at 5-HT2A receptor on glutamate neurons are linked to hallucinations and delusions in psychosis (Stahl, 2018). Lower membrane fluidity and altered fusogenicity may affect these symptoms through alterations in vesicle trafficking and neurotransmitter release in patients with SCZ.

3.3 Neurodevelopmental disorder

In addition to neurodegenerative and psychiatric disorders, phospholipid and cholesterol metabolism is disturbed in the neurodevelopmental disorder Rett syndrome, which predominantly affects females; almost all cases result from mutations in methyl-CpG-binding protein 2 (*MECP2*) on the X chromosome (Percy, 2011). Patients with Rett syndrome have profound cognitive impairment, poor communication skills, loss of fine motor skills, stereotypic hand movements, and pervasive growth failure (Percy, 2011). Decreased levels of phospholipids and ether phospholipids including plasmalogens in

cerebrospinal fluid, but not plasma, are relevant in patients with Rett syndrome in addition to the reduction of sphingomyelin (Zandl-Lang et al., 2022). A recent study illustrated that decreased levels of phospholipids is one of the factors leading to the characteristic features of Rett syndrome. Supplementation of choline, a raw component of phosphatidylcholine, rescued deficits in motor coordination, anxiety-like behavior, and reduced social preference in *Mecp2*-conditional knockout mice (Chin et al., 2019). Moreover, dendritic length in MeCP2-depleted neurons can be rescued *in vitro* through the phosphatidylcholine synthesis pathway (Chin et al., 2019). Thus, phosphatidylcholine, including ether-linked phosphatidylcholine, may have clinical importance in behavioral, cognitive, and motor functions in neurodevelopmental diseases as well.

With regard to phosphatidylcholines, ether-linked phosphatidylcholines show an inverse correlation with melancholia in patients with major depressive disorder (MDD) (Brydges et al., 2022). Furthermore, selective serotonin reuptake inhibitors, first-line treatment for MDD, upregulated several plasma phosphatidylcholine and ether phosphatidylcholine in participants with MDD (MahmoudianDehkordi et al., 2021). Further, the plasma levels of 1-*O*-alkyl-2-acyl-phosphatidylethanol, an ether PEs, are significantly decreased in patients with MDD (Liu et al., 2016); therefore, ether PCs and PEs are considered to be candidate biomarkers for screening MDD and evaluating the response to treatment.

Meanwhile, plasmalogens serve as reservoirs for polyunsaturated fatty acids, e.g., docosahexaenoic acid (DHA) and AA, mostly occupying the sn-2 position. In particular, DHA possesses anti-inflammatory and anti-apoptotic effects, proposing that PUFAs released from plasmalogen exhibit neuroprotective effects and may improve psychiatric disorders such as MDD through decreases in production of proinflammatory cytokines and enhancement of neurogenic and anti-apoptotic effects by their metabolites (Borsini et al., 2021; Ciappolino et al., 2019; Dorninger et al., 2020).

4. The role of the ether phospholipids in the behavior

4.1. Ether phospholipid deficiency

The *Gnpat* KO model mouse, used in assessing complete deficiency in ether lipid biosynthesis, showed that the mouse exhibited hyperactivity, impaired social interaction, disturbed execution, impaired release, and vesicular uptake of monoamines (Dorninger et al., 2019a; Dorninger et al., 2019b). It was recently demonstrated that reductions in endogenous plasmalogen synthesis induced by *GNPAT* depletion via lentiviral shRNA injection in the bilateral hippocampus leads to learning and memory impairment in the Morris water maze test and novel object recognition test (Hossain et al., 2022). This study also suggested that the enhancement of Akt and ERK phosphorylation by ethanolamine plasmalogen induced the phosphorylation of cAMP-regulated element-binding proteins

(CREB), and the recruitment of CREB to the *Bdnf* promoter region increased BDNF protein expression (Hossain et al., 2022). As a result, activation of the BDNF–TrkB signaling pathway by a plasmalogen-rich diet improved learning and memory in mice (Hossain et al., 2022). Further, plasmalogen deficiency is also caused by a mutation of PEX7, which is responsible for the transport of AGPS into the peroxisome (Buchert et al., 2014). In an open-field test, hyperactivity was observed in the $Pex7^{hypo/null}$ mice, which were generated by the homozygous hypomorphic mice to mice heterozygous for the *Pex7* null allele and exhibit reduced plasmalogen levels in the plasma and organs, including the brain, lung, kidney, liver, skeletal muscle, heart, small intestine, and erythrocytes (Fallatah et al., 2020). However, PPI-1040 treatment normalized the hyperactivity in these mice (Fallatah et al., 2020). PPI-1040 is a synthetic PlsEtn compound, conjugating palmitic alcohol at the sn-1 position, DHA at the sn-2 position, and a cyclic phosphoethanolamine group at the sn-3 position. PPI-1040 readily converts to endogenous plasmalogen species by exposure to an aqueous or acidic environment, increasing plasmalogen levels in the plasma, liver, small intestine, erythrocytes, skeletal muscle, heart, but not the brain, lung, or kidney (Fallatah et al., 2020). In contrast, the endothelial knockout of PexRAP, a peroxisomal enzyme required for ether lipid synthesis, caused decreased ambulation and rearing, limited awareness of objects and environmental

changes, and decreased arousal, accompanied by reduced plasma PlsEtn in mice (Spears et al., 2021).

Alternatively, in astrocyte-like C8-D1A cells, although glycogen synthase kinase-3 (GSK3) phosphorylation decreased when cocultured with PexRAP knockdown endothelial cells, adding alkylglycerol to this coculture system rescued the decreased GSK3 phosphorylation in C8-D1A cells (Spears et al., 2021). Another study also observed that while the astrocyte end-feet continuously surround the cerebral microvessels, astrocytes directly communicate with endothelial cells and neurons, functioning as intermediates between neuronal and endothelial cells in communication (Menaceur et al., 2021). These reports propose that behavioral disturbance phenotypes depend on types of the cells with deficiency of plasmalogens. Furthermore, they propose that it is critical to appropriately deliver plasmalogens to target cells to maximize the therapeutic efficacy of behavioral disturbances.

4.2. Alterations in brain plasmalogen composition

In our previous study, PlsEtn (18:0p-22:6) as well as gene expression of the enzyme-related phospholipid synthesis increased in the prefrontal cortex (Hino et al., 2019) associated with locomotor activity (Fritts et al., 1998; Jinks and McGregor, 1997; Ohmura

et al., 2019), in the male rat offspring subjected to prenatal undernutrition. An increase in the frequency of crossing across the areas, time spent at the center, and total distance traveled in the open-field test was observed in these rats subjected to prenatal undernutrition (Hino et al., 2019). The two former behaviors were accompanied by increased PlsEtn (18:0p-22:6) in the prefrontal cortex after intravenous injection of liposomes consisting of PlsEtn (18:0p-22:6) and egg PC into normal male rats (Hino et al., 2019). The hyperactive behavior of rats with PlsEtn (18:0p-22:6) rich brain in our study was inconsistent with the hyperactive behavior of the *Gnpat* knockout and $Pex7^{hypo/null}$ mice, which were systemically deficient in ether phospholipids (Fallatah et al., 2020). However, in PexRAP endothelial knockout mice, movements in the X + Y axes, i.e., ambulation, quantified using laser beam breaks, reduced with a decrease in plasma PlsEtn (Spears et al., 2021). Therefore, endothelial cells and astrocytes might be key mediators, modulating behavior when PlsEtn is intravenously incorporated into liposomes. Moreover, it was reported that prenatal undernutrition, which disturbs brain plasmalogen composition (Hino et al., 2019), reduces dopamine concentration, increases serotonin concentration, and alters norepinephrine, dopamine, and serotonin turnovers in the brain (Ono et al., 2022). Hence, alterations in brain phospholipid composition might cause aberrant release and uptake of monoamines, presumably due to aberrant vesicle

trafficking.

5. Therapeutic phospholipid-based approaches for managing neurological and developmental disorders.

Various methods have been attempted to treat Alzheimer's disease, developmental disorders, and psychiatric disorders. Here, oral administration and liposome delivery to achieve plasmalogen replacement therapy are discussed.

5.1. Oral administration

Oral administration is common and one of the most convenient therapeutic strategies to alleviate symptoms of disorders. A previous study reported that although little plasmalogen was degraded under pH 3–5, the vinyl-ether bond was cleaved at a pH 2 or less (Fallatah et al., 2020; Nishimukai et al., 2003) because that bond was acid/oxidation labile (Bozelli and Epand, 2021). Furthermore, while fasted gastric pH was less than 2, intragastric pH reached approximately 3–5 during the meal (Pantoflickova et al., 2003; Russell et al., 1993). Therefore, plasmalogens are proposed to be less cleaved when plasmalogens are present in the meal, and clinical trials on oral administration have been conducted to examine the effect of plasmalogens on neurological disorders. Results showed that oral administration of scallop-derived purified plasmalogen increased plasma

or erythrocyte PlsEtn compared to placeboic administration in mild Alzheimer's disease and Parkinson's disease (PD) with improvement of clinical symptoms (Fujino et al., 2017; Mawatari et al., 2020). Recently, synthetic plasmalogen analogs, PPI-1011, PPI-1025, and PPI-1040, were also used in model mice for RDCP and PD. Among these synthetic plasmalogen precursors, PPI-1040 is converted to PlsEtn (16:0/22:6), which has a vinyl-ether bond at sn-1; moreover, it is stable under pH 3–5. Similar to the oral administration of scallop-derived plasmalogen in humans, the oral administration of PPI-1040 increased plasma or serum plasmalogens in RDCP and PD model mice (Fallatah et al., 2020). In another study, while PlsEtn was not increased in the brain after injecting these plasmalogen analogs, they reduced aberrant behavior or brain monoamine disturbances (Fallatah et al., 2020; Miville-Godbout et al., 2016; Miville-Godbout et al., 2017); however, a correlation between PlsEtn deficiency in gray matter and AD clinical dementia ratings was observed (Han et al., 2001); phospholipid composition in the white matter of the frontal lobe was altered in bipolar disorder and schizophrenia (Ghosh et al., 2017). Hence, it is important to develop strategies to restore brain plasmalogen composition to remedy neurological disorders.

5.2. Delivery of plasmalogens to the brain by liposomes

Small lipophilic molecules are suitable for brain delivery, and liposomes have been the most extensively explored for delivery to the brain through the blood-brain-barrier (BBB). (Lamptey et al., 2022). The penetration of nanocarriers, such as liposomes, through the BBB depends on the size, chemical modifications of the surface, and polarity (Lamptey et al., 2022). Dos Santos Rodrigues et al. developed liposomes with a diameter of ca. 130 nm, composed of 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine (DOPE), 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), cholesterol, and conjugated transferrin and rabies virus glycoprotein peptide. (Dos Santos Rodrigues et al., 2020). *In vitro*, these compositions more efficiently crossed the BBB model and transfected primary neurons *in vitro* than liposomes without surface modifications. Nevertheless, liposomes without surface chemical modifications could also cross the BBB (Dos Santos Rodrigues et al., 2020). Recently, exosome-like nanoparticles of 30–130 nm have been expected to deliver therapeutic agents to the brain through the BBB (Conlan et al., 2017; Katakowski and Chopp, 2016; Kim et al., 2022). A study reported that exosome-like liposomes with a diameter of less than 200 nm, composed of cholesterol, dipalmitoylphosphatidylcholine, Sphingomyelin, and polyethylene glycol (PEG)-ceramide, protected their cargo from external threats, successfully penetrated the cell membrane and delivered their cargo at the cytoplasm (Fernandes et al., 2021). These reports propose that liposomes less than

200 nm can cross the BBB and be incorporated into neuronal and glial cells. In addition, intravenous injection of liposomes, composed of PlsEtn (18:0p-22:6) and egg PC, resulting from frequent crossing, increased time spent at the center in the open-field test in rats, and the amount of PlsEtn (18:0-22:6), was more significant in the prefrontal cortex of the rat injected with those liposomes than the rats injected with vehicle liposomes (Hino et al., 2019). Therefore, PlsEtn (18:0-22:6) incorporated into liposomes can cross the BBB and exhibit its function in the brain since its size is suitable, i.e., 100 nm, including its hydrophobic surface due to PlsEtn, as described above. Thus, the delivery of PlsEtn by liposomes is considered an effective way for plasmalogen replacement therapy targeting the brain.

6. Conclusions

Ether phospholipids, including plasmalogens, have different biological functions ascribable to their biophysical properties. For instance, plasmalogens can modulate membrane trafficking, cell signaling, transporter functions, oxidative status, and storage of PUFA eventually affecting cognitive functions and behavior. Therefore, plasmalogen deficiency and phospholipid composition in the organs can be the causal factors to the onset of neurodegenerative, developmental, and psychiatric disorders. As a result,

plasmalogen replacement therapies have attempted to improve those disorders. However, although orally administering extracted plasmalogens and synthetic analogs replenish circulating and organ-specific plasmalogens, the brain's plasmalogen content was not restored. Thus, novel strategies to restore the brain's phospholipid composition are warranted to alleviate neurodegenerative, developmental, and psychiatric disorders.

Acknowledgements

This work is dedicated to Mr. Kodai Hino, who considerably contributed to our research related to plasmalogens and passed away in 2018.

Funding

This work was supported by the Japan Society for the Promotion of Science KAKENHI (Grant Number JP 16K08441 and 20K07918) and the Food Science Institute Foundation (Ryoushoku-kenkyukai) to JU.

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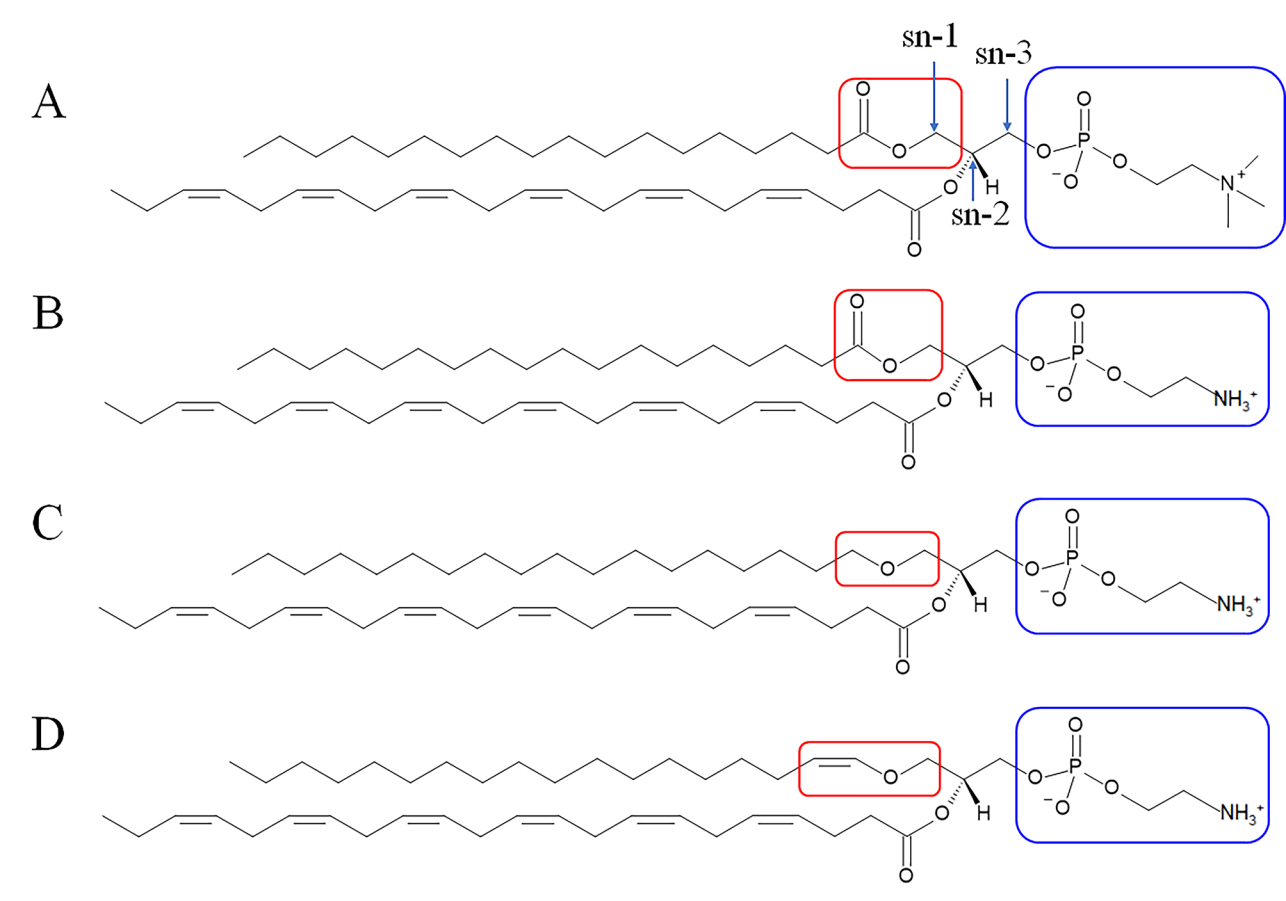
Figure legends

Figure 1 Chemical structure of the phospholipids. Diacy (A) and ether (B, C, D) phospholipids are shown. Phosphatidylcholine (A) and phosphatidylethanolamine (B)

have an ester bond at the sn-1 and sn-2 glycerol backbone positions (A), plasmanylethanolamine has an ether bond at the sn-1 postion (C), and plasmenylethanolamine has a vinyl-ether bond at the sn-1 position (D). Red rectangles indicate an ester, ether, or vinyl-ether bond at the sn-1. Blue rectangles indicate hydrophilic head groups.


A
sn-1
sn-3
sn-2
B
C
D