Lipidomics in Human Brain

Subjects: Physiology

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One of the richest tissues in lipid content and diversity of the human body is the brain. Glycerophospholipids are the main lipid category widely distributed in neural cell membranes, with a very significant presence for the ether lipid subclass. Ether lipids have played a key role in the evolution of the human brain compositional specificity and functionality. Ether lipids determine the neural membrane structural and functional properties, membrane trafficking, cell signaling and antioxidant defense mechanisms.

Keywords: antioxidants ; plasmalogens ; human brain ; lipidomics ; lipid

1. Introduction

A healthy adult human brain is one of the richest tissues in lipid concentration of the human body, accounting for about 12% of the fresh weight and 50% of the dry matter of the brain [1]. Brain lipids display a great deal of functional and structural diversity. The main lipid categories and classes are present in neurons and glial cells as an expression of the different structural and functional needs related to membrane composition and organization, signaling pathways, and homeostasis of oxidative stress [1][2][3][4]. The human brain accomplishes a broad range of functions, from motor to cognitive, which are dependent on the organization of groups of diverse neuronal and glial cell populations. The expression of specific lipid profiles contributes to the functional and morphological diversity among neuronal and glial cells [5][6][7].

2. Lipid Species and the Human Brain

The whole adult human brain comprises the largest diversity of lipid categories, classes, subclasses and molecular species. For instance, the brain contains a great diversity of glycerophospholipids (GPs) [1], as well as sphingolipids (SPs), with a very significant amount of molecular species [8]. Furthermore, cholesterol and its derivatives are also relevant in the brain, which contains a quarter of the human body total cholesterol [9].

GPs are the main lipid category extensively present in neural cell membranes, with a very significant presence for the ether lipid subclass. In the human brain, GPs represent approximately 5% of the wet weight in the whole brain, 4% of the gray matter (GM) and 7% of the white matter (WM). Diacylglycerophosphates (PAs), a central intermediary in the biosynthesis pathways of both neutral lipids and GPs, occurs in low concentrations in the brain (2% of total GPs). The predominant form of glycerophosphocholines present in the human brain is diacylglycerophosphocholines (PCs) (32.8%), with palmitic acid (16:0) and oleic acid (18:1n-9) as the most representative fatty acid (FA) components [10][11][12][13]. Its ether lipid forms, the 1-(1Z-alkenyl),2-acylglycerophosphocholines (PC plasmalogen, or PC(P-)) and the 1-alkyl,2-acylglycerophosphocholine (PC(O-)), are a minor fraction, representing only 2% of total glycerophosphocholines in the brain. Glycerophosphoethanolamines are quantitatively the main GPs in the human brain (35.6%) [13][14] and the predominant form is the 1-(1Z-alkenyl),2-acylglycerophosphoethanolamines (PE plasmalogen or PE(P-)), accounting for 50–60% of the glycerophosphoethanolamine class. The alkylacyl (PE(O-)) form content is low (3–7%), whereas diacylglycerophosphoethanolamines (PEs) make up the remaining amount of glycerophosphoethanolamines. Their total FA profile indicates a selective positional distribution. Thus, the position-1 of sn-glycerol is occupied mainly by saturated and monounsaturated fatty acids (16:0, stearic acid (18:0), and 18:1n-9), both in the WM and GM; whereas position-2 consists of the polyunsaturated fatty acids (PUFAs), and these are more abundant in the GM than in the WM. The content of glycerophosphoserines in the human brain is approximately 16.6% [13][14] of total GPs. They are mostly present as diacylglycerophosphoserines (PSs, more than 90%) and also as the 1-(1Z-alkenyl),2-acylglycerophosphoserine (PS(P-)), and contain FAs 18:0, 18:1n-9 and docosahexaenoic acid (DHA, 22:6n-3). Inositolphosphoglycerides represent about 2.6% of total GPs in the human brain [10]. Glycerophosphoinositols and glycerophosphoinositols trisphosphates are additional relevant GPs, with only trace amounts of glycerophosphoinositol bisphosphates. Notably, the highest

concentrations of glycerophosphoinositols among animal tissues are present in the neural tissue. The main FAs of this class are 18:0 and arachidonic acid (AA, 20:4n-6). Finally, Kahma et al. [15] found 0.2% of GPs as glycerophosphoglycerols (PGs) and 0.1% as glycerophosphoglycerophosphoglycerols (cardiolipins) in the human brain. The latter is mainly located in the brain mitochondria. The main FAs included in this minor, but relevant GP fraction, are 16:0, palmitoleic acid (16:1n-7), 18:0, 18:1n-9, linoleic acid (18:2n-6), linolenic acid (18:3n-3) and 20:4n-6.

3. Ether Lipids and the Human Brain Evolution

The lipidome is a dynamic system strictly regulated and adapted to cell requirements. The human brain has evolved towards the complexity and structural/functional diversity of neural cells, and these adaptative mechanisms also include cell lipidomes. Effectively, lipidomic analyses have revealed that each human tissue and brain region possess distinctive lipid composition, and that the lipidome signature of the brain is significantly different from that of other non-neural tissues [5]. In particular, from the 5713 detected features, 4727 showed significant differences in the analyzed tissue concentrations, and 75% (3542 features) showed different profiles in the brain compared to non-neural tissues. Notably, these lipidome differences are assigned by specific lipid classes. Thus, the brain lipidome is characterized by an abundance of glycerophosphocholines, glycerophosphoethanolamines, neutral glycosphingolipids, glycerophosphoglycerols and glycosyldiradylglycerols; and a depletion in triacylglycerols, fatty amides and sterols. The enriched lipid species belong to specific lipid subclasses, namely diacylglycerols, dihydroceramides, ceramides and especially 1-(1Z-alkenyl), 2-acylglycerophosphoethanolamines (PE(P-)). Furthermore, within the human brain, the interregional comparison (between cerebellar cortex, primary visual cortex and prefrontal cortex) also showed region-specific differences. Consistent with this observation, additional studies also demonstrated the presence of specific interregional differences in the fatty acid profiles of the human brain [6][7]. Therefore, a general trait of the (human) brain is the high selectivity in lipid classes and subclasses present in their lipidome. The distinctive trait of lipids between the brain and other tissues also suggests that they are a specific adaptation, facilitating the unique structural and functional properties of the cell membranes in the brain tissue.

Other observations about the brain lipidome evolution give additional support to the above-expressed ‘rule’ [5]. Thus, when the human lipidome is compared to that of primates (macaque and chimpanzee) and mammalian (mouse) tissues, the existence of a species-specific and a brain-specific lipidome is corroborated. Lipids systematically distinguish the brain from other tissues for each animal species, suggesting a tissue-specific lipidomic trait conservation across animal species. Additionally, the lipid classes and subclasses that distinguish the brain and other tissues are shared among animal species, indicating a basic compositional specificity of the brain lipidome. Importantly, the magnitude of differences in the lipidome profile between the brain and other tissues increase parallelly with the gain in the brain’s functional capacity from mice to humans. Furthermore, the greatest expression of this change occurs at the level of the human neocortex, and is associated in a specific way with the high concentration of PE(P-) content. Taken together, these findings demonstrate the human brain-specific features, confirming that the brain lipid composition evolves rapidly, and suggesting that lipids, and especially ether lipids, played a key role in the evolution of brain functionality.

4. Basic Traits of Ether Lipids: Structure, Metabolism, and Function

Contrary to conventional GPs that have acyl chains joined by ester bonds, in both sn-1 and sn-2 positions, ether lipids have an alkyl chain linked by an ether bond in the sn-1 position. Specifically, ether lipids can contain both alkyl (1-O-alkyl, plasmanyl) and alkenyl (1-O-alk-1′-enyl, plasmenyl) residues (for review, see [16][17]). The “plasmenyl” forms are also known as plasmalogens, and they were described for first time in 1924 by Feulgen and Voit [18]. Plasmalogens are the most common form of ether lipids. The alkyl–ether linkage is represented by the “O-” prefix, and the (1Z)-alkenyl ether (plasmalogen) species by the “P-” prefix. The alkyl/alkenyl residues —usually palmitoyl, stearyl, and oleyl alcohols— are mainly located in the sn-1 position; whereas the sn-2 position is usually substituted by PUFAs, such as 20:4n-6 and 22:6n-3. In the human brain, ether lipids mainly belong to the lipid class PE, in a lesser degree to PC and 1-O-alkyl-2-acylglycerols (alkyl-DG), and occasionally to PSs or PIs.

The ether lipid biosynthesis initiates in the peroxisome and is completed in the endoplasmic reticulum. Its synthesis is regulated by a feedback mechanism, as a result of sensing the content of ether lipids (in particular, plasmalogens) and/or its metabolites at the membrane level [19]. Analogously to the brain cholesterol content, the brain has the capacity to tightly self-regulate their plasmalogen content, which is independent of circulating plasmalogen and its fluxes, and the transport through the blood-brain barrier [19]. Ether lipids have a short half-life, between 30 min and 3 h.

Although the full functional spectrum of ether lipids remains to be elucidated, researchers currently know that they are involved in a variety of biological functions in the brain tissue, including structural roles, membrane trafficking, cell

signaling and oxidative-stress homeostasis [20].

4.1. Structural Roles

Ether lipids are structural components of cell membranes and the subcellular compartments. The presence of an ether bond in the phospholipid structure provokes a conformational change, which produces a tighter packing of these lipids and alters the physical properties of the membranes. These properties facilitate a stronger intermolecular hydrogen bonding between the headgroups [21], promote close alignment [22][23] and decrease membrane fluidity. The importance of this distribution in structures such as myelin, is confirmed by the abundance of myelin in plasmalogens [24] and by the observation that ether lipid deficiency in both mouse models and human subjects often presents defects in myelination [25].

Another important observation is the high concentration of plasmalogens in lipid raft microdomains [26][27]. In line with this, the plasmalogen-deficient GNPAT knockout mice show aberrant lipid raft formation, along with alterations in cholesterol location [27].

4.2. Membrane Trafficking

An inverted hexagonal structure of the cell membranes is related to membrane fusion [28]. Ether lipids, especially plasmalogens, have inherent properties that affects membrane geometry. Specifically, plasmalogen-enriched membranes have a marked tendency to form non-lamellar, inverse hexagonal structures [29], thus facilitating the processes of membrane trafficking, which is particularly relevant, for instance, at a synaptic level and, consequently, neurotransmission. Effectively, the membrane of synapses, as well as synaptic vesicles, show a richness in ether lipids. In line with this, it has been previously described that the synapsis process is impaired in ether lipid-deficient mice [30]. Furthermore, plasmalogens are important components of exosomes [20], but their relevance for the brain function is currently unknown.

4.3. Cell Signaling

Ether lipids are a source of a wide spectrum of signaling mediators [20], some of which have not even been described at the brain level. Thus, the list of ether lipids and derivatives involved in signaling includes, for instance, compounds such as alkylglycerol, alkyl-lysophosphatidic acid (alkyl-LPA), alkenyl-LPA, ether-linked diglycerides, 2-halo fatty aldehydes, lysoplasmalogen, lyso-PAF, N-acyl ethanolamine plasmalogen (pNAPE), plasmalogens, platelet-activating factor (PAF), plasmanyl phospholipids and GPI anchor [20]. These ether lipid compounds have demonstrated to interact with components related to diverse signaling pathways such as AKT/PKB, PKC, PPAR, LXR, GPCR and MAPK [20]. As derived mostly from in vitro and animal models studies, these pathways are potentially involved in different neuronal and/or glial cell processes, such as energy metabolism, myelination, neurotransmission (synaptic plasticity), pro- and anti-inflammatory responses, cholesterol homeostasis and oxidative stress. However, the relevance of these compounds and signaling pathways in the human brain physiology and sAD still is thus far incomplete.

Due to the preferential presence of PUFA in the sn-2 position, ether lipids have also been proposed as a second-messenger precursor reservoir [31]. Among these PUFAs, 20:4n-6 and 22:6n-3 (DHA) must be highlighted due to their particular biological and physiological importance as precursors of eicosanoids and docosanoids, respectively. Interestingly, it has been suggested that the participation of DHA in diverse molecular events relates to synaptic plasticity, neuro- and synaptogenesis, neurite outgrowth and learning and memory-related processes, as well as neuroprotective antioxidant mechanisms [32][33]. Plasmalogens also act as a reservoir for AA. AA has been involved in both physiological (synaptic plasticity) and physiopathological (sAD) processes [34].

5. Plasmalogens as Endogenous Antioxidants in the Human Brain

The appearance and use of ether lipids (plasmalogen) by eukaryotic cells is directly related to the origin of the aerobic life [35] and the subsequent generation of free radicals (reactive oxygen species, ROS), which demanded the incorporation of antioxidant defense mechanisms to ensure cell survival. The biosynthesis pathway of plasmalogen in eukaryotic cells is accomplished using an oxidative mechanism that, similarly to the aerobic desaturation of fatty acids, needs a source of molecular oxygen. The result is the generation and incorporation of a vinyl ether bond in the plasmalogen structure which confers to its special properties. One of these properties is that this kind of bond confers a high ROS sensitivity to plasmalogens, generated physiologically during oxidative metabolism by cells. Thus, the oxidative metabolism that is needed for plasmalogen synthesis results in a molecule that, in turn, is sensitive to oxidative damage. This oxygen sensitivity of plasmalogens was described in 1972 [36]. Therefore, it may be suggested that plasmalogens, as targets of ROS, act as free radical scavengers [37][38][39][40][41] and may be considered as a potential endogenous antioxidant

mechanism inside lipid membranes. In line with this, the rich plasmalogen content observed in the brain [5] may be interpreted as an additional adaptive response to the high oxidative conditions present in the human brain [42][43], while protecting unsaturated membrane lipids from oxidation by free radicals [41]. Consistent with this concept, plasmalogen-deficient animal and cell models are more prone to oxidative damage than control models [37][44][45][46]. In the presence of ROS, plasmalogens are easily degraded with scission at the alkenyl ether bond [37]. In this situation, cells have the ability to acylate the resulting 2-monoacyl-glycerophosphatidylethanolamine, with the subsequent formation of diacylglycerophosphatidylethanoalmine, or to deacylate the resulting lysophospholipid.

References

1. Sastry, P.S. Lipids of Nervous Tissue: Composition and Metabolism. Prog. Lipid Res. 1985, 24, 69–176.
2. Thudichum, J.L. A Treatise on the Chemical Constitution of the Brain; Archon Books: Hamden, CT, USA, 1962.
3. Piomelli, D.; Astarita, G.; Rapaka, R. A Neuroscientist's Guide to Lipidomics. Nat. Rev. Neurosci. 2007, 8, 743–754.
4. Naudí, A.; Cabré, R.; Jové, M.; Ayala, V.; Gonzalo, H.; Portero-Otín, M.; Ferrer, I.; Pamplona, R. Lipidomics of Human Brain Aging and Alzheimer's Disease Pathology. Int. Rev. Neurobiol. 2015, 122, 133–189.
5. Bozek, K.; Wei, Y.; Yan, Z.; Liu, X.; Xiong, J.; Sugimoto, M.; Tomita, M.; Pääbo, S.; Sherwood, C.C.; Hof, P.R.; et al. Organization and Evolution of Brain Lipidome Revealed by Large-Scale Analysis of Human, Chimpanzee, Macaque, and Mouse Tissues. Neuron 2015, 85, 695–702.
6. Naudí, A.; Cabré, R.; Ayala, V.; Jové, M.; Mota-Martorell, N.; Portero-Otín, M.; Pamplona, R. Region-Specific Vulnerability to Lipid Peroxidation and Evidence of Neuronal Mechanisms for Polyunsaturated Fatty Acid Biosynthesis in the Healthy Adult Human Central Nervous System. Biochim. Biophys. Acta-Mol. Cell Biol. Lipids 2017, 1862, 485–495.
7. Mota-Martorell, N.; Andrés-Benito, P.; Martín-Gari, M.; Galo-Licona, J.D.; Sol, J.; Fernández-Bernal, A.; Portero-Otín, M.; Ferrer, I.; Jove, M.; Pamplona, R. Selective Brain Regional Changes in Lipid Profile with Human Aging. GeroScience 2022, 44, 763–783.
8. Merrill, A.H.; Sullards, M.C.; Allegood, J.C.; Kelly, S.; Wang, E. Sphingolipidomics: High-Throughput, Structure-Specific, and Quantitative Analysis of Sphingolipids by Liquid Chromatography Tandem Mass Spectrometry. Methods 2005, 36, 207–224.
9. Dietschy, J.M.; Turley, S.D. Cholesterol Metabolism in the Brain. Curr. Opin. Lipidol. 2001, 12, 105–112.
10. Rouser, G.; Yamamoto, A. Curvilinear Regression Course of Human Brain Lipid Composition Changes with Age. Lipids 1968, 3, 284–287.
11. Rouser, G.; Galli, C.; Kritchevsky, G. Lipid Class Composition of Normal Human Brain and Variations in Metachromatic Leucodystrophy, Tay-Sachs, Niemann-Pick, Chronic Gaucher's and Alzheimer's Diseases. J. Am. Oil Chem. Soc. 1965, 42, 404–410.
12. Rouser, G.; Feldman, G.; Galli, C. Fatty Acid Compositions of Human Brain Lecithin and Sphingomyelin in Normal Individuals, Senile Cerebral Cortical Atrophy, Alzheimer's Disease, Metachromatic Leucodystrophy, Tay-Sachs and Niemann-Pick Diseases. J. Am. Oil Chem. Soc. 1965, 42, 411–412.
13. O'brien, J.S.; Sampson, E.L.; Brien, O.; Fillerup, D.L.; Mead, J.F.; Lz, J. Lipid Composition of the Normal Human Brain: Gray Matter, White Matter, and Myelin. J. Lipid Res. 1965, 5, 329.
14. Panganamala, R.V.; Horrocks, L.A.; Geer, J.C.; Cornwell, D.G. Positions of Double Bonds in the Monounsaturated Alk-1-Enyl Groups from the Plasmalogens of Human Heart and Brain. Chem. Phys. Lipids 1971, 6, 97–102.
15. Kahma, K.; Brotherus, J.; Haltia, M.; Renkonen, O. Low and Moderate Concentrations of Lysobisphosphatidic Acid in Brain and Liver of Patients Affected by Some Storage Diseases. Lipids 1976, 11, 539–544.
16. Dean, J.M.; Lodhi, I.J. Structural and Functional Roles of Ether Lipids. Protein Cell 2018, 9, 196–206.
17. Koch, J.; Watschinger, K.; Werner, E.R.; Keller, M.A. Tricky Isomers—The Evolution of Analytical Strategies to Characterize Plasmalogens and Plasmanyl Ether Lipids. Front. Cell Dev. Biol. 2022, 10, 768.
18. Snyder, F. The Ether Lipid Trail: A Historical Perspective. Biochim. Biophys. Acta-Mol. Cell Biol. Lipids 1999, 1436, 265–278.
19. Honsho, M.; Fujiki, Y. Plasmalogen Homeostasis—Regulation of Plasmalogen Biosynthesis and Its Physiological Consequence in Mammals. FEBS Lett. 2017, 591, 2720–2729.

20. Dorninger, F.; Forss-Petter, S.; Wimmer, I.; Berger, J. Plasmalogens, Platelet-Activating Factor and beyond–Ether Lipids in Signaling and Neurodegeneration. Neurobiol. Dis. 2020, 145, 105061.
21. Lohner, K. Is the High Propensity of Ethanolamine Plasmalogens to Form Non-Lamellar Lipid Structures Manifested in the Properties of Biomembranes? Chem. Phys. Lipids 1996, 81, 167–184.
22. Han, X.; Gross, R.W. Plasmenylcholine and Phosphatidylcholine Membrane Bilayers Possess Distinct Conformational Motifs. Biochemistry 1990, 29, 4992–4996.
23. Paltauf, F. Ether Lipids in Biomembranes. Chem. Phys. Lipids 1994, 74, 101–139.
24. Farooqui, A.A.; Horrocks, L.A. Book Review: Plasmalogens: Workhorse Lipids of Membranes in Normal and Injured Neurons and Glia. Neuroscientist 2016, 7, 232–245.
25. Ferreira Da Silva, T.; Eira, J.; Lopes, A.T.; Malheiro, A.R.; Sousa, V.; Luoma, A.; Avila, R.L.; Wanders, R.J.A.; Just, W.W.; Kirschner, D.A.; et al. Peripheral Nervous System Plasmalogens Regulate Schwann Cell Differentiation and Myelination. J. Clin. Investig. 2014, 124, 2560–2570.
26. Pike, L.J.; Han, X.; Chung, K.N.; Gross, R.W. Lipid Rafts Are Enriched in Arachidonic Acid and Plasmenylethanolamine and Their Composition Is Independent of Caveolin-1 Expression: A Quantitative Electrospray Ionization/Mass Spectrometric Analysis†. Biochemistry 2002, 41, 2075–2088.
27. Rodemer, C.; Thai, T.P.; Brugger, B.; Kaercher, T.; Werner, H.; Nave, K.A.; Wieland, F.; Gorgas, K.; Just, W.W. Inactivation of Ether Lipid Biosynthesis Causes Male Infertility, Defects in Eye Development and Optic Nerve Hypoplasia in Mice. Hum. Mol. Genet. 2003, 12, 1881–1895.
28. Marrink, S.J.; Mark, A.E. Molecular View of Hexagonal Phase Formation in Phospholipid Membranes. Biophys. J. 2004, 87, 3894.
29. Glaser, P.E.; Gross, R.W. Plasmenylethanolamine Facilitates Rapid Membrane Fusion: A Stopped-Flow Kinetic Investigation Correlating the Propensity of a Major Plasma Membrane Constituent To Adopt an HII Phase with Its Ability To Promote Membrane Fusion. Biochemistry 1994, 33, 5805–5812.
30. Brodde, A.; Teigler, A.; Brugger, B.; Lehmann, W.D.; Wieland, F.; Berger, J.; Just, W.W. Impaired Neurotransmission in Ether Lipid-Deficient Nerve Terminals. Hum. Mol. Genet. 2012, 21, 2713.
31. Nagan, N.; Zoeller, R.A. Plasmalogens: Biosynthesis and Functions. Prog. Lipid Res. 2001, 40, 199–229.
32. Dorninger, F.; Forss-Petter, S.; Berger, J. From Peroxisomal Disorders to Common Neurodegenerative Diseases–the Role of Ether Phospholipids in the Nervous System. FEBS Lett. 2017, 591, 2761–2788.
33. Díaz, M.; Mesa-Herrera, F.; Marín, R. DHA and Its Elaborated Modulation of Antioxidant Defenses of the Brain: Implications in Aging and AD Neurodegeneration. Antioxidants 2021, 10, 907.
34. Katsuki, H.; Okuda, S. Arachidonic Acid as a Neurotoxic and Neurotrophic Substance. Prog. Neurobiol. 1995, 46, 607–636.
35. Goldfine, H. The Appearance, Disappearance and Reappearance of Plasmalogens in Evolution. Prog. Lipid Res. 2010, 49, 493–498.
36. Yavin, E.; Gatt, S. Oxygen-Dependent Cleavage of the Vinyl-Ether Linkage of Plasmalogens. Eur. J. Biochem. 1972, 25, 437–446.
37. Morand, O.H.; Zoeller, R.A.; Raetz, C.R.H. Disappearance of Plasmalogens from Membranes of Animal Cells Subjected to Photosensitized Oxidation. J. Biol. Chem. 1988, 263, 11597–11606.
38. Khaselev, N.; Murphy, R.C. Susceptibility of Plasmenyl Glycerophosphoethanolamine Lipids Containing Arachidonate to Oxidative Degradation. Free Radic. Biol. Med. 1999, 26, 275–284.
39. Maeba, R.; Sawada, Y.; Shimasaki, H.; Takahashi, I.; Ueta, N. Ethanolamine Plasmalogens Protect Cholesterol-Rich Liposomal Membranes from Oxidation Caused by Free Radicals. Chem. Phys. Lipids 2002, 120, 145–151.
40. Skaff, O.; Pattison, D.I.; Davies, M.J. The Vinyl Ether Linkages of Plasmalogens Are Favored Targets for Myeloperoxidase-Derived Oxidants: A Kinetic Study. Biochemistry 2008, 47, 8237–8245.
41. Broniec, A.; Klosinski, R.; Pawlak, A.; Wrona-Krol, M.; Thompson, D.; Sarna, T. Interactions of Plasmalogens and Their Diacyl Analogs with Singlet Oxygen in Selected Model Systems. Free Radic. Biol. Med. 2011, 50, 892–898.
42. Halliwell, B. Reactive Oxygen Species and the Central Nervous System. J. Neurochem. 1992, 59, 1609–1623.
43. Cobley, J.N.; Fiorello, M.L.; Miles Bailey, D. 13 Reasons Why the Brain Is Susceptible to Oxidative Stress. Redox Biol. 2018, 15, 490–503.
44. Zoeller, R.A.; Morand, O.H.; Raetz, C.R.H. A Possible Role for Plasmalogens in Protecting Animal Cells against Photosensitized Killing. J. Biol. Chem. 1988, 263, 11590–11596.

45. Reiss, D.; Beyer, K.; Engelmann, B. Delayed Oxidative Degradation of Polyunsaturated Diacyl Phospholipids in the Presence of Plasmalogen Phospholipids in Vitro. Biochem. J. 1997, 323, 807–814.
46. Luoma, A.M.; Kuo, F.; Cakici, O.; Crowther, M.N.; Denninger, A.R.; Avila, R.L.; Brites, P.; Kirschner, D.A. Plasmalogen Phospholipids Protect Internodal Myelin from Oxidative Damage. Free Radic. Biol. Med. 2015, 84, 296–310.