Review

The potential mechanism of plasmalogen reduction in Alzheimer's diseases and effect of plasmalogen supplementation to Alzheimer's disease

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Abstract

Plasmalogens are a kind of membrane glycerophospholipids with special properties. They are characterized by the inclusion of vinyl- ether linked alkyl chain at the sn-1 position of the glycerol backbone, and typically a polyunsaturated fatty acyl chain at the sn-2 position. These two characteristics provide new properties to these compounds. Plasmalogens are essential to human health, and play important roles in neuronal development, immune response and as an endogenous antioxidants. However, the mechanism of their related biological functions is still unclear.

Keyword

Plasmalogen、phosphatidylcholine (PC)、phosphatidylethanolamine (PE) 、Alzheimer's diseases、β-amyloid (Aβ)、reactive oxygen species（ROS）

Introduction:

Plasmalogens are a naturally occurring glycerophospholipid mainly in the form of phosphatidylcholine (PC) and phosphatidylethanolamine (PE)[1]. Plasmalogens are existed almost in all mammalian tissues and their average percentage is about 15–20% of total phospholipids. [2] Plasmalogens is thought to be related to membrane anti-oxidant function and bilayer formation. In addition, they have a variety of biological activities, including improving cognitive function, preventing neuroinflammation and inhibiting neuronal cell death.[3] Defective of plasmalogens synthesis or reduced levels of Plasmalogens have been associated with a range of neurodegenerative diseases. However, whether Plasmalogens play a causal role in these disease states or represent the outcome of a pathological process has not been fully established. In this review, the potential mechanism of the changes in Alzheimer's disease and the new progress in clinical trials of the treatment in Alzheimer's disease with plasmalogens are reviewed

Plasmalogens and Alzheimer's disease:

Alzheimer disease (AD) is a progressive neurodegenerative disorder characterized by brain deposition of senile (neuritis) plaque containing β-amyloid (Aβ), neurofibrillary tangles,

synaptic loss, neuroinflammation and overexpression of arachidonic acid (AA, 20:4N-6) metabolizing enzymes.[4] Studies have shown that the concentration of plasmalogens in the brains of AD , especially PC, is significantly reduced in the affected areas of the brain. The degree of reduction was associated with cognitive deficits .[4] Wood et al. reported that erythrocyte plasmalogen levels correlate with disease severity, suggesting a systemic etiology for the reduction of plasmalogen in AD.[5]

It is well known that oxidative damage is increased in the brain of AD due to age-related decreased energy supply, mitochondrial dysfunction, glutamateric neurotransmission, and accumulation of Aβ. Aβ itself has been described as an oxidizing agent.[6] Aβ also can further catalyze the production of reactive oxygen species (ROS).[7] It was found that the accumulation of amyloid beta precursor protein (APP) could lead to the increase in cellular ROS levels.[1] Therefore, oxidative stress caused by Aβ and ROS can accelerate the progression of AD. Compared with other glycerol phospholipids, plasmalogens are easily oxidized and have a different pathway of oxidation degradation due to the existence of α, β-unsaturated ether linkage. The inhibition effect of plasmalogens on lipid oxidation may be related to the direct reaction between plasminogen specific enol ether double bond and oxidant. Therefore one enol-ether double bond is able to scavenge two peroxy radicals.[8] It has been demonstrated that plasmalogen markedly delays the oxidative degradation of intrachain double bonds in polyunsaturated diacyl phospholipids as the products of enol ether oxidation do not propagate the oxidation of polyunsaturated fatty acids. Thus brain membrane plasmalogen is apparently a target for reactive oxygen species which are generated under various oxidative stress conditions in AD.[9] Because vinyl ethers are highly susceptible to ROS and oxidation, the decrease in plasmalogens levels is likely due to the increased oxidative stress that occurs in AD pathogenesis.[10] Thus, it is suggested that plasmalogens can act as a scavenger to protect other lipids, lipoproteins and endothelial cells from oxidative damage by scavenging peroxy radicals and other reactive oxygen species.[8]

Conversely, the reduction of plasmalogens may further enhance ongoing oxidative damage in AD and alter membrane properties to promote further damage.[11] Increased membrane free cholesterol increases the production of Aβ from amyloid precursor protein (APP). However cholesterol esters stimulate non-amyloidogenic APP degradation . Lack of plasmalogens lead to higher levels of membrane free cholesterol, which facilitates Aβ production. Therefore, the reduction of plasmalogens in AD may promote the production of Aβ. In addition an in vitro study has shown that Aβ aggregation can be modulated by plasmalogens.[12]

In addition, since PE are major endogenous lipid constituents that facilitate membrane fusion of synaptic vesicles associated with neurotransmitter release, the loss of PE may adversely affect synaptic structure and function. Thus this potentially contributing to the synaptic dysfunction and neurotransmitter depletion observed in AD.[11]

Regarding the possible mechanism of plasmalogen reduction in AD :

1. Plasmalogens synthesis is initiated in peroxisomes , and therefore changes/damages in peroxisome would result in alterations in plasmalogen synthesis. Peroxisome deficits have been reported in the liver and brain of AD subjects. [11]On the other hand, it has also been shown that increased Aβ and ROS reduced the expression of a rate-limiting enzyme, alkyl-dihydroxyacetone phosphate-synthase, for plasmalogens de novo synthesis, due to the dysfunction of peroxisomes where plasmalogens are biosynthesized, resulting in a decrease in plasmalogen level.[11]

2. Decreased levels of plasmalogen have been observed in neuroinflammation and that might lead to a diminished level due to the antioxidant properties of plasmalogens that protect cells from oxidative stress . Considerable evidence has suggested that there is a connection loop between Aβ accumulation, neuroinflammation, ROS production, and plasmalogen deficiency. In addition, plasmalogen-selective phospholipase A2 (Pls-PLA2) degrades PE by releasing DHA or arachidonic acid from the glycerol backbone at the sn-2 position. And this process is possibly activated by production of ceramide under inflammatory conditions which might contribute to the loss of PE in the brain.[11]

3. PKCδ is an isoform of protein kinase C (PKC) family proteins. Activation of PKCδ is associated with neuroinflammation and various neurodegenerative diseases, including AD. Studies have shown that there is a significant correlation between the decrease of PE and the increase of PKCδ expression in glial cells. Callop-derived plasmalogens (sPLs) can reduce PKCδ which possibly by inhibiting the expression of p38 and JNK proteins involved in the regulation of PKCδ in microglia.[13]

Possible mechanisms of plasmalogens in the treatment of AD :.

1. Cellular signaling experiments showed that plasmalogens prevent neurons death by enhancing phosphorylation of the phosphoinositide 3-kinase (PI3K)-dependent serine/threonine-specific protein kinase AKT and extracellular-signal-regulated kinases ERK1/2.[14] The mechanism is that PE activated orphan GPCR (G-protein coupled receptor) proteins to induce ERK signaling in neuronal cells. Overexpression of GPCRs enhanced PE-mediated phosphorylation of ERK and Akt in cells. When endogenous PE were reduced, GPCRs-mediated cellular signaling transduction was significantly reduced.

2. γ-secretase is a membrane-associated aspartic protease that catalyzes the final step in the production of Aβ. PE can decrease the activity of γ-secretase. In vitro studies showed that the increase of the phosphatidylethanolamine plasmalogen (PEPls)/ phosphatidylethanolamine (PE) ratio could inhibit the activity of γ-secretase and decrease the production of Aβ. The effect of PE/PEPls on γ-secretase activity may be due to the phospholipid head group and the existence of vinyl ether bond in PEPls.[16]

3. Caspase-9 is associated with intrinsic apoptosis pathway and has also been reported to be involved in neuronal cell death . Plasmalogens treatment was found to effectively reduce the activation of caspase-9, leading to the inhibition of apoptosis. The mechanism may be that Plasmalogens-mediated activation of

AKT and ERK can inhibit caspase-9 probably by targeting Bad protein.[14]

Therapeutic effect of plasmalogens on AD:

1. It has been reported in animal experiments that peripheral intravenous injection of plasmalogens in rats can increase plasmalogens content in the brain and inhibit lipopolysaccharide (LPS) -induced microglial activation, resulting in reduced neuroinflammation and accumulation of β-amyloid protein (Aβ).[17] A more recent study in rats demonstrated the potential of oral administration Eicosapentaenoic acid (EPA)-enriched PE plasmalogen (150 mg/kg body weight per day) isolated from sea cucumbers (Cucumaria frondosa) to ameliorate Aβ-induced neurotoxicity by restraining oxidative stress, neuronal injury, apoptosis and neuro-inflammation.[1]

2. In a 24-week multicentric, randomized, double-blind, placebo-controlled human trial, oral administration of purified scallop-derived plasmalogens (1mg/day) significantly improved memory function in women with mild AD and in patients under 77 years of age, but only in patients with mild cognitive impairment.[18]

Conclusion:

Many studies have shown a link between a deficiency of plasmalogens and AD, but it is not clear whether reduced plasmalogens in the brain of AD patients are a cause or consequence of the disease. Therefore, further studies are needed to determine the relationship between plasmalogens and AD. At present, the number of literature on the clinical efficacy of plasmalogens for AD is not enough. Due to some promising results in animal studies, studies on the molecular mechanisms of plasmalogens' action in patients with AD and further clinical trials will help determine whether plasmalogens can be used as novel agents for the treatment of AD.

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References:

[1] Paul S, Lancaster GI, Meikle PJ. Plasmalogens: A potential therapeutic target for neurodegenerative and cardiometabolic disease. Prog Lipid Res. 2019 Apr;74:186-195. doi: 10.1016/j.plipres.2019.04.003. Epub 2019 Apr 8. PMID: 30974122.

[2] Koivuniemi A. The biophysical properties of plasmalogens originating from their unique molecular architecture. FEBS Lett. 2017 Sep;591(18):2700-2713. doi: 10.1002/1873-3468.12754. Epub 2017 Aug 1. PMID: 28710769.

[3] Hossain MS, Mawatari S, Fujino T. Biological Functions of Plasmalogens. Adv Exp Med Biol. 2020;1299:171-193. doi: 10.1007/978-3-030-60204-8_13. PMID: 33417215.

[4] Igarashi M, Ma K, Gao F, Kim HW, Rapoport SI, Rao JS. Disturbed choline plasmalogen and phospholipid fatty acid concentrations in Alzheimer's disease

prefrontal cortex. J Alzheimers Dis. 2011;24(3):507-17. doi: 10.3233/JAD-2011-101608. PMID: 21297269; PMCID: PMC3175096.

[5] Wood PL, Mankidy R, Ritchie S, Heath D, Wood JA, Flax J, Goodenowe DB. Circulating plasmalogen levels and Alzheimer Disease Assessment Scale-Cognitive scores in Alzheimer patients. J Psychiatry Neurosci. 2010 Jan;35(1):59-62. doi: 10.1503/jpn.090059. PMID: 20040248; PMCID: PMC2799506.

[6] Hartmann T, Kuchenbecker J, Grimm MO. Alzheimer's disease: the lipid connection. J Neurochem. 2007 Nov;103 Suppl 1:159-70. doi: 10.1111/j.1471-4159.2007.04715.x. PMID: 17986151.

[7] Cheignon C, Tomas M, Bonnefont-Rousselot D, Faller P, Hureau C, Collin F. Oxidative stress and the amyloid beta peptide in Alzheimer's disease. Redox Biol. 2018 Apr;14:450-464. doi: 10.1016/j.redox.2017.10.014. Epub 2017 Oct 18. PMID: 29080524; PMCID: PMC5680523.

[8] Farooqui AA, Horrocks LA. Plasmalogens, phospholipase A2, and docosahexaenoic acid turnover in brain tissue. J Mol Neurosci. 2001 Apr-Jun;16(2-3):263-72; discussion 279-84. doi: 10.1385/jmn:16:2-3:263. PMID: 11478381.

[9] Han X, Holtzman DM, McKeel DW Jr. Plasmalogen deficiency in early Alzheimer's disease subjects and in animal models: molecular characterization using electrospray ionization mass spectrometry. J Neurochem. 2001 May;77(4):1168-80. doi: 10.1046/j.1471-4159.2001.00332.x. PMID: 11359882.

[10] Grimm MOW, Michaelson DM, Hartmann T. Omega-3 fatty acids, lipids, and apoE lipidation in Alzheimer's disease: a rationale for multi-nutrient dementia prevention. J Lipid Res. 2017 Nov;58(11):2083-2101. doi: 10.1194/jlr.R076331. Epub 2017 May 20. PMID: 28528321; PMCID: PMC5665674.

[11] Su XQ, Wang J, Sinclair AJ. Plasmalogens and Alzheimer's disease: a review. Lipids Health Dis. 2019 Apr 16;18(1):100. doi: 10.1186/s12944-019-1044-1. PMID: 30992016; PMCID: PMC6466717.

[12] Braverman NE, Moser AB. Functions of plasmalogen lipids in health and disease. Biochim Biophys Acta. 2012 Sep;1822(9):1442-52. doi: 10.1016/j.bbadis.2012.05.008. Epub 2012 May 22. PMID: 22627108.

[13] Sejimo S, Hossain MS, Akashi K. Scallop-derived plasmalogens attenuate the activation of PKCδ associated with the brain inflammation. Biochem Biophys Res Commun. 2018 Sep 5;503(2):837-842. doi: 10.1016/j.bbrc.2018.06.084. Epub 2018 Jun 21. PMID: 29920240.

[14] Hossain MS, Ifuku M, Take S, Kawamura J, Miake K, Katafuchi T. Plasmalogens rescue neuronal cell death through an activation of AKT and ERK survival signaling. PLoS One. 2013 Dec 20;8(12):e83508. doi: 10.1371/journal.pone.0083508. PMID: 24376709; PMCID: PMC3869814.

[15] Hossain MS, Mineno K, Katafuchi T. Neuronal Orphan G-Protein Coupled Receptor Proteins Mediate Plasmalogens-Induced Activation of ERK and Akt Signaling. PLoS One. 2016 Mar 2;11(3):e0150846. doi: 10.1371/journal.pone.0150846. PMID: 26934370; PMCID: PMC4775022.

[16] Onodera T, Futai E, Kan E, Abe N, Uchida T, Kamio Y, Kaneko J. Phosphatidylethanolamine plasmalogen enhances the inhibiting effect of phosphatidylethanolamine on γ-secretase activity. J Biochem. 2015 May;157(5):301-9. doi: 10.1093/jb/mvu074. Epub 2014 Nov 18. PMID: 25409699.

[17] Ifuku M, Katafuchi T, Mawatari S, Noda M, Miake K, Sugiyama M, Fujino T. Anti-inflammatory/anti-amyloidogenic effects of plasmalogens in lipopolysaccharide-induced neuroinflammation in adult mice. J Neuroinflammation. 2012 Aug 13;9:197. doi: 10.1186/1742-2094-9-197. PMID: 22889165; PMCID: PMC3444880.

[18] Fujino T, Yamada T, Asada T, Tsuboi Y, Wakana C, Mawatari S, Kono S. Efficacy and Blood Plasmalogen Changes by Oral Administration of Plasmalogen in Patients with Mild Alzheimer's Disease and Mild Cognitive Impairment: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial. EBioMedicine. 2017 Mar;17:199-205. doi: 10.1016/j.ebiom.2017.02.012. Epub 2017 Feb 24. PMID: 28259590; PMCID: PMC5360580.