REVIEW ARTICLE

Neuroinflammation and a plasmalogen hypothesis of Alzheimer's disease

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Abstract
Recently, there has been an increased attention paid to the role of Plasmalogens (Pls) to the development of Alzheimer's Disease (AD). Pls are a kind of phospholipids and widely distributed in animal tissues (cell membranes). Pls account for about 18% of the total phospholipids in human, especially abundant in brain, heart, skeletal muscles, leukocytes, and sperms. Growing attention is now focused on the correlation between Pls and AD in the areas of biochemistry, physiology, and brain pathology. A 1995 report paved the way for subsequent studies, showing that Pls is decreased in postmortem brain of patients with AD. Another study has revealed a decrease in blood Pls. Some studies showed that oral administration of Pls improves cognitive function in AD animal models and inhibit amyloid-β accumulation. A multicenter double-blind randomized placebo-controlled trial (DB-RCT) was conducted in patients with mild cognitive impairment (MCI) and mild AD in Japan from 2014 to 2016. This review describes the progress of fundamental and clinical research on the correlation between Pls and AD. The review of these research also brings us to propose a new hypothesis to better understand the etiology of AD.

Key words: *Alzheimer's disease, plasmalogen, phospholipid, etiopathogenesis, biomarker*

INTRODUCTION

Alzheimer's disease (AD) is a growing concern in an aging global population with the number of persons with mild cognitive impairment (MCI) and AD increasing all over the world (Patterson, 2018; Wu, 2017). A limited number of anti-dementia drugs are used in clinical settings to slow down the rate of cognitive decline. However, no definitive medical guidance has been established for the prevention or treatment of AD (Anderson, 2017). According to systematic review, physical exercise has been evaluated as the only effective protective factor against cognitive decline. Supplements such as vitamin B, folic acid, vitamin C, beta-carotene, ginkgo leaf extract, and omega-3 unsaturated fatty acids have not been considered protective (Plassman, 2010; Anstey, 2019). In recent years, a growing number of publications, including several from Japan, have suggested that plasmalogens (Pls) are useful targets for the treatment of AD. A review of these studies on Pls, which include basic, animal, and clinical investigations, suggests that Pls are deeply involved in the development of AD (Goodenowe, 2017; Ginsberg, 1995; Guan, 1999; Han, 2001).

WHAT ARE PLASMALOGENS?

In recent years, a number of reviews on the role of Pls in AD have been published in international academic (Paul, 2019; Su, 2019; Wallner, 2011). Pls are a type of glycerophospholipid that was discovered 90 years ago. Generally, glycerophospholipids are classified into three types according to the way they bind to the first position (sn-1) of the glycerol backbone. Those linked by vinyl at sn-1 are called Pls. Most Pls are ethanolamine Pls or choline Pls. Pls decreases with aging and pathological process (Farooqui, 2001; Maeba, 2007; Lessig, 2009).

Pls are phospholipids present in many animal tissues, accounting for approximately 18% of all phospholipids in humans. Pls are distributed predominantly in the brain, heart, skeletal muscle, leukocytes, and spermatozoa. Ethanolamine Pls are abundant in the brain, and choline Pls are abundant in the heart and skeletal muscle. In cells, Pls are generated in the peroxisome (an organelle) and endoplasmic reticulum (Lizard, 2012; Braverman, 2012).

The physio-biochemical functions of PIs are diverse. PIs function as (1) components of the plasma membrane, (2) precursor substances or reservoirs for intracellular second messengers, such as prostaglandins and leukotrienes, (3) membrane fusion, (4) cholesterol excretory function from the plasma membrane, and (5) antioxidants. γ-secretase activity inhibitory effects and anti-neuroinflammatory effects are directly associated with AD (Zarrouk, 2018; Ifuku, 2012; Luoma, 2015; Walter, 2017; Katafuchi, 2012; Ali, 2019; Hossain, 2017).

BASIC PL RESEARCH

Studies on the postmortem brain of AD patients

The association between PIs and AD has been reported in various fields, including biochemistry, physiology, and brain pathology. The origin of this research focus was a report by Ginsberg et al. in 1995, in which they found that PI levels are reduced in the postmortem brains of AD patients (Ginsberg, 1995).

Subsequently, the level of PIs in various parts of the postmortem brain of AD patients with different severities was measured by Han et al. (2001). A reduction in PIs of up to 40% was reported in the cere-

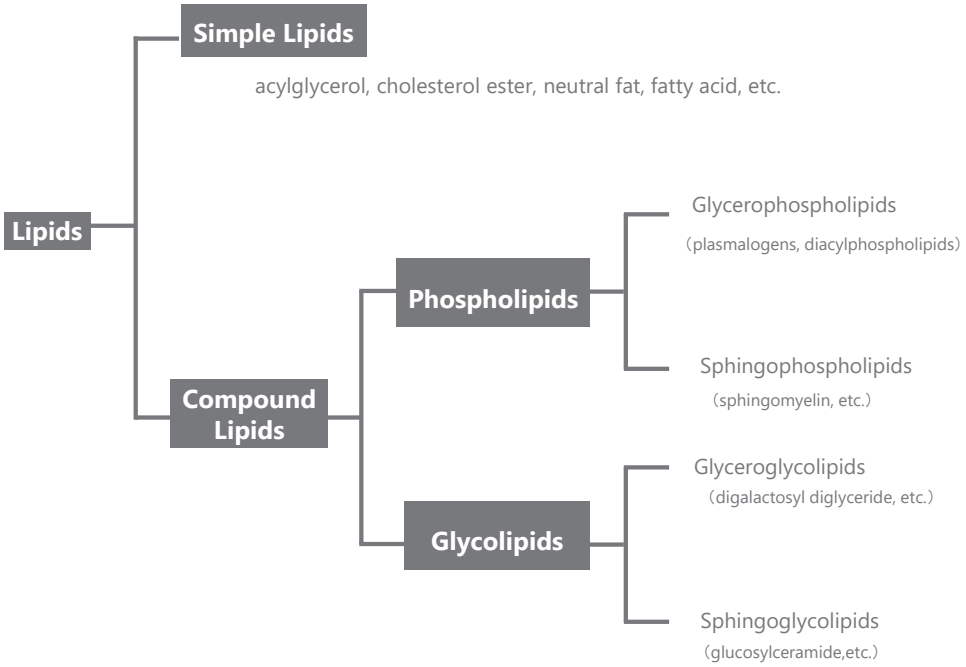

Figure 1. Classification of Lipids

- **existence in all mammalian tissues (membrane)**
- **about 18 % of the total human phospholipid**
- **abundant in the brain, retina, leukocytes (immune cells), sperm, heart, and skeletal muscle**
- **Ethanolamine-plasmalogen is ten times as much as choline-plasmalogen except in heart and skeletal muscle.**

Figure 2. Location and proportion of plasmalogen

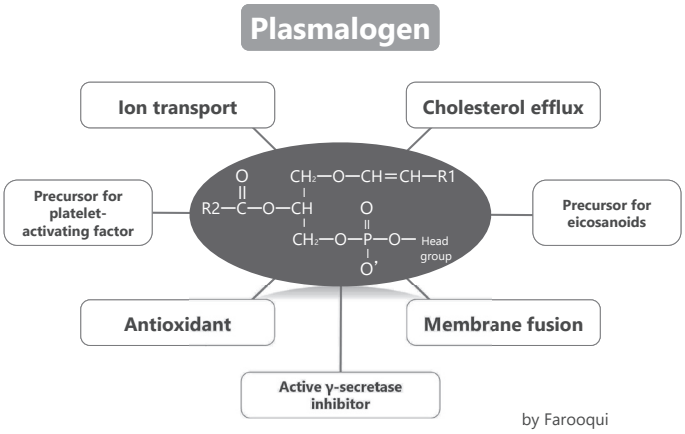

Figure 3. Functions of Plasmalogen

bral white matter of very-early AD patients. Pls in the cerebral gray matter region decreased by 10%–30% depending on the severity of AD. In the cerebellum, a decrease in Pls was observed in the white matter region, but no abnormalities were observed in the gray matter region. In addition, a 10% reduction in Pls was observed in the cerebrum of 18-month-old AD-model mice measured simultaneously, whereas no such change was observed in the cerebellum of these mice. These studies have indicated that the reduction in Pls is closely related to AD (Ginsberg, 1995; Han, 2001).

Studies on the blood of AD patients

In 2007, Goodenowe et al. found that AD patients exhibited a decline in Pl levels (Goodenowe, 2007). Cognitive function progression and Pls were measured in a total of 324 patients with mild, moderate, or severe AD, and in 68 older adults aged 50–90 years with normal cognitive function. Simultaneously, 209 healthy older adults aged 50–95 years were divided into three groups (50–59, 60–69, and 70–95 years) to determine the effect of aging on Pls by measuring their serum values. Postmortem serum Pl levels were also measured in 20 patients who had died from AD and 19 patients who had died from other causes. The results showed that serum Pls decreased in all 324 AD patients, and that the degree of decrease was proportional to the severity of AD. A decrease in Pls in the healthy elderly due to age was not observed.

One of the authors (MT) was involved with the work by Dayan Goodenowe, Phenomenome Discoveries Inc. When they visited our research laboratory at Osaka University, their data were quite interesting to us, where we agreed with the possibility that the serum plasmologen level can be a useful peripheral biomarker of AD. Furthermore, the content of plasmologens is high in *Halocynthia roretzi* and in *Halocynthia aurantium*, unique local seafood in northern part of Japan, which could be supplemental remedy of AD for Japanese people if the decreased level of plasmalogens with AD is a significant finding. We supplied Phenomenome Discoveries 80 plasma samples from Alzheimer cases diagnosed with NINCDS-ADRDA criteria and 80samples from aged-matched control subjects. Since Osaka samples are used for confirmation of the findings, we sent the samples under blind and the plasma levels of plasmologen 16:0/22:6 were compared between AD and the control in our lab. The data clearly showed the significant difference between AD and the control ($p < 0.0005$) with 27% reduction of serum plasmologen levels in AD.

In 2007, Mawatari et al. succeeded in simplifying the method for detecting Pls (Mawatari, 2007).

In 2009, they developed a process for extracting highly pure Pls (Mawatari, 2009). This finding would enable Pl-dosing studies in animals and humans and contribute significantly to subsequent Pl studies.

In 2010, Wood et al. measured serum Pls in a group of 40 AD patients and 66 healthy individuals aged 67–89 years and re-measured serum Pl levels in patients with AD a year later (Wood, 2010). The AD Assessment Scale Cognitive Subscale (ADAS-Cog) was used to assess cognitive function. The aim of this study was to investigate the association between serum Pl levels in patients with AD and cognitive function using ADAS-Cog in comparison with healthy older adults. All patients with serum Pls ≤75% showed cognitive decline after 12 months. In healthy older adults with Pls ≥75% at baseline, ADAS-Cog scores had not changed after 1 year (Wood, 2010). Wood et al. also measured Pls and diacylglycerols in 2015 using liquid chromatography tandem spectrometry (LC/MS/MS) in late-onset AD patients (n = 90), MCI patients (n = 77), and control subjects (n = 51) (Wood, 2015). In the AD and MCI groups, decreased serum Pl levels and increased diacylglycerols were observed. Although changes were not detected in level of these lipids, serum Pls decreased as dementia progressed (Wood, 2015).

In 2012, Oma et al reported that erythrocyte Pls decreased in patients with AD (Oma, 2012).

Changes in Pls in erythrocyte cell membranes with lipid rafts similar to those in cranial nerve cell membranes upon oral administration suggested that oral Pls cross the blood-brain barrier. A decrease in the Pl concentration in the erythrocyte membrane is observed.

In 2012, Mawatari et al also reported that a dietary Pls increases erythrocyte membrane Pls in rats (Mawatari, 2012).

In 2016, Yamashita et al. measured the levels of serum amyloid-beta protein (Aβ protein), phosphatidylcholine hydroperoxide (PCOOH), serum Pls and erythrocyte cell membrane Pls in 28 AD patients and 28 healthy older adults (Yamashita, 2016). The aim of the study was to investigate correlations between the Aβ protein, PCOOH, and Pl values in patients with dementia. The results showed lower values of serum Pls in patients with AD, particularly Pl values, containing DHA. AD patients had lower Pl levels and higher PCOOH levels in the erythrocyte membranes. In the

blood of AD patients and control group, PCOOH levels in the erythrocyte membrane and Aβ40 serum levels tended to correlate. This may indicate that Pls correlate with Aβ protein levels (Yamashita, 2016). Taken together, these biochemistry studies indicated that the decline in Pls is related to cognitive decline.

MECHANISMS UNDERLYING THE ACTIONS OF PLS REVEALED BY BASIC STUDIES

Anti-neuroinflammatory effects of Pls

Pls protect internodal myelin from oxidative damage and reduce neuroinflammation (Kou, 2011; Bradburn, 2019). Neuroinflammation is a condition in which the production of various cytokines and radicals, such as active oxygen and hydrogen, is increased by the activation of glial cells in the brain and are observed in many neurodegenerative diseases such as AD. In animal models, when lipopolysaccharide (LPS), an endotoxin, is administered peripherally in adult mice, Aβ protein accumulation as well as neuroinflammation is observed in the brain (Honsho, 2008). Using this neuroinflammatory model, Katafuchi et al. found that concomitant administration of Pls suppressed LPS-induced glial activation, expression of cytokines such as IL-1β and TNF-α, and accumulation of the Aβ protein in adult mice brain (Katafuchi, 2012).

With regard to the mechanism underlying the inhibition of glial activation (neuroinflammation) of LPS by Pls, Ali et al. showed that Pls suppressed the intracellular uptake (endocytosis) of LPS and its receptor, the toll-like receptor (Ali, 2019) and subsequent activation of caspase-3 and NF-κB.

Inhibition of neuronal cell death by Pls

Among AD patients, PI content is significantly reduced in the hippocampus, where neuronal cell death is observed. Hossain et al. investigated the effects of Pls on neuronal cell death in serum-depleted media using primary cultures of mouse hippocampus and neuronal cell lines (Hossain, 2013). AKT and ERK1/2 were activated by PI administration, suppressing caspase-9 and caspase-3 (activated by serum-depletion). Protein phosphoenzymes, such as AKT and ERK1/2, activate mitochondrial Bcl-2 and survival signals that modify Bax, suggesting that Pls are involved in apoptotic signaling (Onodera, 2014).

To elucidate the Pls-induced signaling mechanism, we investigated the localization of Pls on the plasma membrane and found nearly ten-fold more Pls on lipid rafts. In addition to cholesterols and sphingolipids, lipid rafts contain many signaling molecules, including G protein-coupled receptors (GPCRs) and TrkB, a receptor for brain-derived neurotrophic factor (BDNF). Hossain et al. found that activation of AKT and ERK by Pls in cultured nerve cells was mediated by several orphan GPCRs expressed in nerve cells (Hossain, 2016).

PI-induced mechanisms for improvement of learning and memory

Hossain et al. showed the oral ingestion of Pls attenuated the LPS-induced memory loss and microglial activation (Hossain, 2018). Microinjections of shRNA lentiviral vectors, which knock down expression of GNPAT, a synthetase of Pls, into bilateral hippocampi reduced hippocampal PI content and impaired hippocampus-dependent spatial cognitive learning in the water-maze learning test. This suggests that Pls may act in a facilitative manner on learning and memory behaviors. Moreover, hippocampus-dependent memory was reduced in mice with LPS administration-induced neuroinflammation. Memory loss was only marginal in mice injected with Pls (Hossain, 2018).

Pls have been shown to activate the cAMP responsive element-binding protein in nerve cells and to strengthen the expression of BDNF in the nucleus. Lipid rafts are rich in TrkB (BDNF receptors), whereas Pls exert facilitative effects on learning and memory via lipid rafts. These findings suggest that Pls may be useful as a substance with therapeutic or preventive effects against dementia, such as that due to AD (De Strooper, 2018).

CLINICAL TRIALS OF PLS FOR AD

To date, there has been one trial each of a double-blind randomized trial (DB-RCT) and an open-label trial for AD that involved administration of Pls. Fujino et al. conducted a multicenter, DB-RCT study on orally administered, scallop-derived Pls in subjects with MCI and mild AD ranging in age from 60 to 85 years, from November 2014 to April 2016. The results were reported in 2017 (Fujino, 2017). A total of 25 medical institutions in Japan participated in a 24-week DB-RCT. The primary outcome survey items were the Mini-Mental State Examination (MMSE-J), Wechsler Memory Scale-Revised (WMS-R), erythrocyte Pls, and plasma Pls. PI levels of erythrocyte membranes and plasma at baseline in patients with MCI and mild AD were significantly reduced compared to those in healthy older adults. At 24 weeks

after administration, blood Pl levels were elevated in the Pls administration group compared to those in healthy older adults. However, Pl levels were significantly decreased in the placebo-treated group. With regards to MMSE-J and WMS-R, both the Pl- and placebo-treated groups showed marked improvements in the primary analysis, with no statistically significant differences between the two groups. However, secondary stratified analyses revealed some interesting findings. WMS-R scores significantly improved among women and participants below 77 years of age. This DB-RCT had some limitations. It had 300 or fewer individuals completing the study, and the follow-up time was as short as 6 months. However, the study provides hope for the future development of new substances to prevent AD. RCT-DB showed no serious side effects in the clinical use of Pls. Therefore, it is desirable to conduct DB-RCT and follow-up studies on AD and Pls in more than one country. It would also be desirable to accumulate data on its use in clinical practice in the future. Moreover, this DB-RCT suggests that blood levels of Pls are potential candidates for new biomarkers for MCI and AD (Fujino, 2017). In a separate analysis, Pls decreased hallucination among persons with MCI (Fujino, 2018). In 2019, Fujino et al. reported on the effects of scallop-derived Pls in moderate and severe AD with an open-label study and reported marked improvements in cognitive function (Fujino, 2019).

NEUROINFLAMMATION/PL HYPOTHESIS

The reduction in Pl levels is strongly associated with the onset of AD. This is supported by findings that include anatomicopathological findings of the AD brain, biochemistry studies on Pls and animal experiments on Pls (Goodenowe, 2007; Ginsberg, 1995; Guan, 1999; Han, 2001).

Accumulation of Aβ proteins in brain nerve cells has been considered as the main cause of AD (Janelidze, 2016; Nakamura, 2018). For the treatment of dementia, acetylcholinesterase inhibitors such as donepezil are often prescribed when AD is diagnosed (Birks, 2018). However, they have been no obvious ameliorative or preventive effects although they were expected to slow down disease progression (Walsh, 2019). The development of new drugs based on the present mainstream Aβ protein onset hypothesis has been attempted many times. Every dementia drug aimed at eliminating the Aβ protein has failed (Egan, 2018; Lawlor, 2018). Reliable amyloid biomarkers in AD are yet to be developed (Blennow, 2015). The relationship between Aβ protein levels and the progression of cognitive impairments and dementia has not been clearly demonstrated (Dang, 2018). In addition, there were many patients who did not develop any AD symptoms despite high Aβ deposition in the post-mortem brain, and in contrast, some patients with serious AD symptoms were diagnosed at autopsy to be mild (Latimer, 2017; Roberts, 2018; Snowdon, 2001).

These reports demonstrate that the Aβ protein onset hypothesis has a fundamental flaw. These results thus indicate that it is time to reevaluate the Aβ protein hypothesis as a hypothesis for AD onset (Selkoe, 2016). In the present century, various risk factors contributing to cognitive decline have been revealed (Prince, 2014; WHO, 2019). These include stress, lack of exercise, sleep disturbance (Bubu, 2017), unbalanced diet, reduced stimulation of the brain (such as with decreased hearing) (Loughrey, 2018), brain injury (Fann, 2018), diabetes (Vagelatos and Eslick, 2013), and arteriosclerosis. Smoking (Chang, 2012), alcohol use (Rehm, 2019), and air pollution are also considered risk factors. These risk factors cause neuroinflammation and reduce Pl levels. Various risk factors are likely to cause neuroinflammation and decrease Pls at the cranial nerve cell membrane, resulting in the disruption of neural networks (Parbo, 2017). The investigation of various risk factors holds promise for the prevention of AD. A wide range of risk factors have been identified, and protective measures for AD have been proposed (Prince, 2014; WHO, 2019). However, it is not clear why, in any case, these risk factors cause AD or what the underlying mechanisms are. There is a missing link between risk factors and the onset of AD.

Fujino et al. proposed the neuroinflammation and Pl hypothesis (Fujino, in press) as an alternative to the Aβ protein hypothesis. This hypothesis is based on basic and clinical research findings cited in the previous chapter and encompasses the Aβ protein hypothesis (Figure 4).

According to the new hypothesis, the Aβ protein is a part of the AD process rather than the main cause of AD onset. Future testing is required, but it is considered a valuable hypothesis to be explored.

The neuroinflammation and Pl hypothesis is useful for explaining how risk factors for AD may adversely affect cognitive function. The Aβ protein hypothesis is not directly linked to risk factors for AD. The increase in the Aβ protein within cranial nerve cells may be a consequence of neuroinflammation caused by various risk factors and the associated decrease in

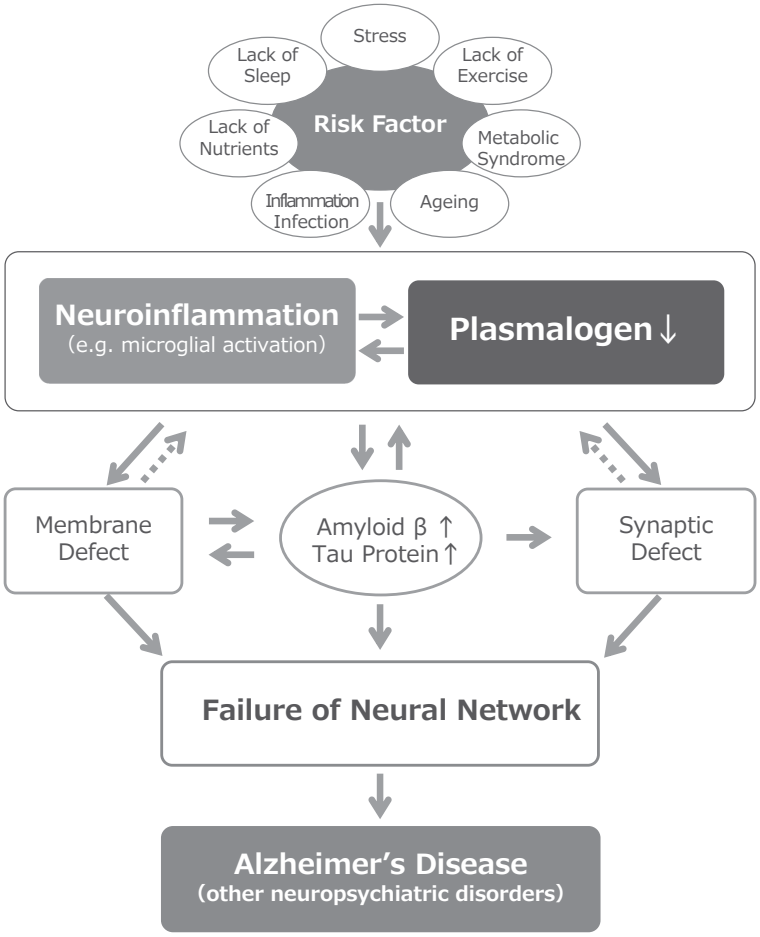

Figure 4. Hypothetical scheme of neuroinflammation and plasmalogen in Alzheimer pathogenesis

Pls at the plasma membrane. The neuroinflammation and Pl hypothesis proposes that the main cause of AD is not intracellular but membranous. The role of lipids should be further studied as major contributing factors to AD (Di Paolo, 2011; Florent-Bechard, 2009; Selkoe, 2011). According to the neuroinflammation and Pl hypothesis, the development of AD can be prevented by reducing the risk factors responsible for neuroinflammation. AD onset can be prevented by preventing the deficiency of lipid components, such as Pls, which are important constituents of the nerve cell membrane.

Pls, as an indispensable component of nerve cell, are likely to be involved in other neuropsychiatric diseases. Mawatari et al. (2020) reported improvements in blood Pl levels and clinical symptoms in Parkinson disease by oral administration of Pls. In addition, impaired Pls was observed in persons with chronic fatigue syndrome (Komaroff, 2017), depression (Hashioka, 2018; Felger, 2013), and schizophrenia (Kaddurah-Daouk, 2012; Wood, 2015).

CONCLUSIONS

A considerable body of basic research on AD and Pls has been conducted. A review of basic research, animal studies, and clinical trials on Pls suggests that Pls are deeply involved in the development of AD. The neuroinflammation and Pl hypothesis was proposed as an AD onset hypothesis based on various action phase mechanisms of Pls to the nerve cell membrane. A paradigm shift from the Aβ protein hypothesis to the neuroinflammation and Pl hypothesis is recommended. Such a paradigm shift is likely to improve the understanding and prevention of AD.

Only a few clinical studies linking Pls to AD are currently available. The reason for the efficacy of micro-dose administration (1 mg/day) is yet to be fully understood. The reason why Pls are not destroyed by gastric juices upon oral administration has not been sufficiently determined. The application of Pls for the treatment of dementia is still at an inception stage. However, the administration of lipids, such as Pls, which are important components of the nerve cell membrane, can prevent AD onset. So far, many of the

clinical trials on Pls have been disseminated from Japan to several other countries.

There is an urgent need for DB-RCTs to be conducted in many countries. In addition, it would be desirable to have increased experience of its use not only in Japan but also in other countries as Pls have no serious side effects.

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