Therapeutic efficacy of plasmalogens for Alzheimer's disease, Mild Cognitive Impairment and Parkinson's disease in conjunction with a new hypothesis for the etiology of Alzheimer's disease

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Abstract

It has been reported in recent years that blood levels of plasmalogens (Pls) are decreased in various diseases. None of those reports, however, conducted any clinical trials to examine the effect of Pls on those diseases. This article describes our recent report on a therapeutic efficacy of orally administered Pls in mild cognitive impairment (MCI), mild to severe Alzheimer's disease (AD) and Parkinson's disease (PD). A 24-week, multicenter, randomized, double-blind, placebo-controlled trial was performed in patients with MCI (n=178) and mild AD (n=98). The study design for moderate AD (n=57) and severe AD (n=18) was 12-week open-labeled, and the design for patients with PD (n=10) was 24-week open-labeled. They showed a significant improvement in cognitive function and other clinical symptoms with elevation of the blood Pls levels. No adverse events were reported. The baseline levels of plasma ethanolamine plasmalogen and erythrocyte ethanolamine plasmalogen in MCI, AD and PD were significantly lower than those of normal aged. The degree of reduction in the blood Pls levels was in the order of MCI < mild AD < moderate AD < severe AD < PD. The findings suggest that the blood levels of Pls may be a beneficial biomarker for assessing AD severity. Based on these results, we have proposed a new hypothesis for the etiology of AD and other neuropsychiatric disorders.

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1. Background

A dramatic increase in the number of patients with cognitive impairment, especially Alzheimer's disease (AD), has emerged globally as an urgent issue to be addressed [1]. The measures taken up thus far are, however, not sufficient to control AD in the rapidly aging society, and effective therapeutic and preventive measures against AD remain to be established. A widely accepted hypothesis is that the pathological process of AD leading to cognitive deterioration is initiated by the accumulation of β-amyloid plaques and tau protein tangles in the brain, and pharmaceutical agents targeting the amyloid formation and clearance have been tested in the past decade [2]. However, clinical trials to demonstrate efficacy of these novel candidates have seen no success [2,3].

Recently published research has suggested a potential efficacy of plasmalogens (Pls), a special class of glycerophospholipids, in the treatment of AD, as noted in some reviews [4-9]. The levels of Pls have been found to be decreased in the postmortem AD brain and in the blood of AD patients [10-18]. Pls are found in the cell membrane of many mammalian tissues, especially of brain, heart, skeletal muscle, leukocytes, and sperm. Ethanolamine Pls (PlsPE) are abundant in the brain while choline Pls (PlsPC) are abundantly found in the heart. Out of their various functions, special attention is given to the antioxidant and anti-neuroinflammatory properties that are linked to the chemical structure of Pls characterized by the vinyl ether bond at the sn-1 position of glycerol backbone. Other well-known properties include ion transport, membrane fusion, cholesterol efflux, and precursor of biologically active substances. All these properties are essential to maintain life [4-9].

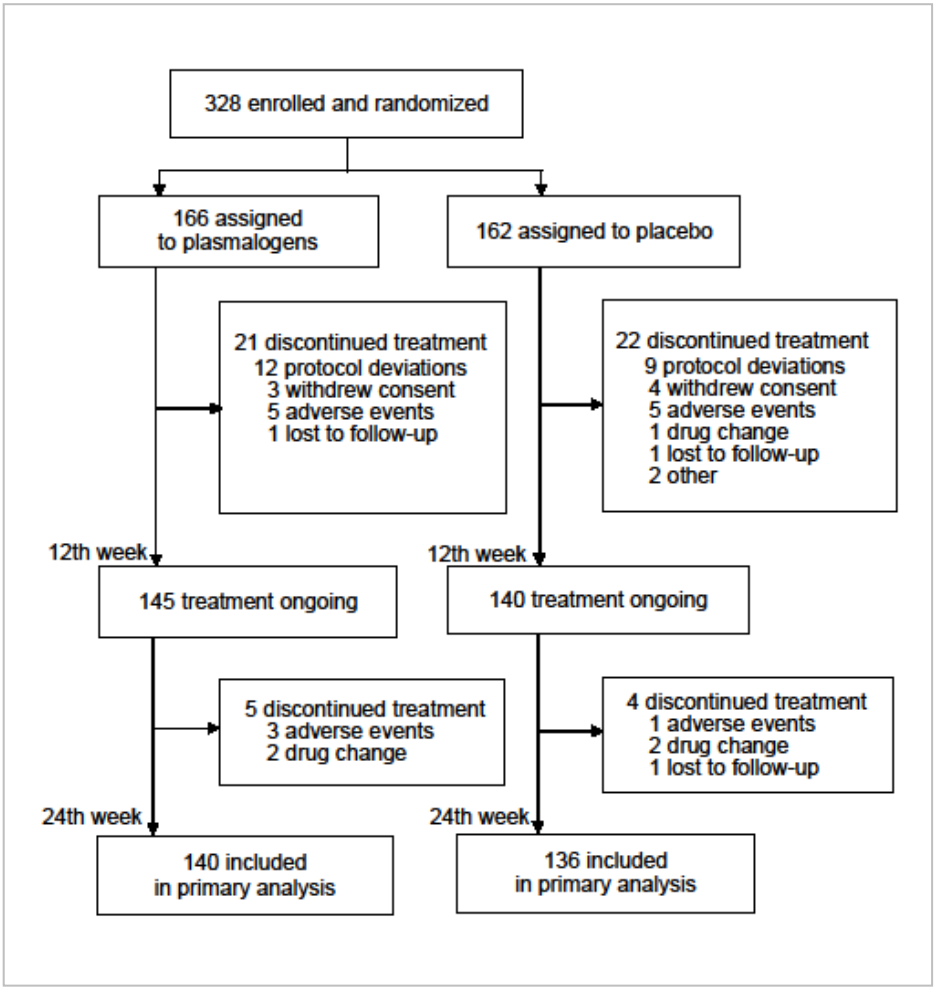
We developed a simple method to extract large amounts of Pls from animals, by which the research on Pls treatment and AD was accelerated [19,20]. Our studies using animal models demonstrated that Pls reduced the accumulation of β-amyloid and improved cognitive function by suppressing neuroinflammation [21-23]. Furthermore, we performed a 24-week placebo-controlled trial to examine the efficacy of orally administered Pls in patients with mild cognitive impairment (MCI) or mild AD [24,25]. We also investigated the effect of treatment with Pls on cognitive function in patients with moderate to severe AD and Parkinson's disease (PD) in open-label studies [26,27].

2. Efficacy in patients with Mild Cognitive Impairment (24≤MMSE-J≤27) [24,25]

2.1. Study methods

A multicenter, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy of scallop-derived Pls in 25 hospitals or clinics in Japan from November 2014 to April 2016, targeting patients aged 60 to 85 years with the scores of 20-27 on the Mini-Mental State Examination-Japanese version (MMSE-J). The participants who totaled 328 had no cerebrovascular dementia as confirmed by a CT scan or MRI, and they were given the clinical diagnosis of Alzheimer's disease or Mild Cognitive Impairment. The enrolled participants were randomly assigned to receive either Pls 1.0mg or matching placebo for 24 weeks. The processes of randomization, masking, and allocation concealment were strictly performed by the expert. Fig. 1 shows the study profile.

Fig. 1 Study profile of RCT (MCI and mild AD)



The primary endpoint was change in the MMSE-J score. Its total score ranges from 0 to 30 and a lower score indicates poorer cognitive function. The secondary endpoints were Wechsler Memory Scale-Revised (WMS-R), Geriatric Depression Scale Short Version in Japanese (GDS-S-J), the levels of phosphatidyl ethanolamine Pls (PlsPE) in plasma, and the relative concentration of PlsPE in erythrocyte membrane, shown as the percentage of Pls to the total phospholipids in erythrocyte membrane. Overall, 276 out of 328 participants completed the 24-week study period.

In this section, we described the efficacy of Pls in patients with Mild Cognitive Impairment (MCI) (24≤MMSE-J≤27). There were no statistically significant differences between the Pls-treated group (n=90) and the placebo group (n=88) on age and the baseline values for study outcomes as shown in Table 1.

Table 1 Baseline characteristics of RCT (MCI)

Variable	**Plasmalogen** (n=90)	**Placebo**(n = 88)	***P* value***
Male, n (%)	37 (41.1%)	26 (29.5%)	0.12
Age in year	75.8 (6.1)	75.9 (5.5)	0.90
MMSE-J	25.6 (1.3)	25.6 (1.1)	0.99
1. Orientation to time	4.1 (1.0)	4.1 (1.0)	0.75
2. Orientation to place	4.3 (0.6)	4.4 (0.6)	0.13

3. Three-word registration	3.0 (0.2)	3.0 (0.3)	0.98
4. Attention and calculation	4.2 (1.0)	3.9 (1.1)	0.07
5. Three-word recall	1.4 (1.0)	1.5 (1.1)	0.56
6. Language (naming)	2.0 (0.2)	2.0 (0.1)	0.99
7. Language (repeating)	1.0 (0.1)	1.0 (0.1)	0.55
8. Language (3-step command)	2.8 (0.5)	2.8 (0.4)	0.66
9. Language (reading)	1.0 (0.0)	1.0 (0.0)	-
10. Language (writing)	1.0 (0.2)	1.0 (0.2)	0.98
11. Visual construction	1.0 (0.2)	1.0 (0.2)	0.72
WMS-R（0 min)	5.39 (3.97)	5.49 (4.32)	0.87
WMS-R (30 min)	3.66 (4.13)	3.90 (4.61)	0.71
Erythrocyte PlsPE (%)†	8.07 (1.09)	8.17 (1.00)	0.53
Plasma PlsPE (mg/dl)	3.92 (1.34)	4.03 (1.29)	0.56

Values are mean (SD) unless otherwise specified.
MMSE-J=Mini Mental State Examination-Japanese
PlsPE= ethanolamine plasmalogens
* Chi-square test for proportion and unpaired t-test for mean.
† Number of the patients were 90 in the Pls-treated group and 87 in the placebo group.

2.2. Results

2.2.1. Change in Mini-Mental State Examination-Japanese and Wechsler Memory Scale-Revised

The MMSE-J total score increased at 24 weeks in both the Pls-treated group and the placebo group although no significant between-group difference was found in the change of the MMSE-J total score. Out of the 11 domains of the MMSE-J, the orientation to place improved significantly in the Pls-treated group, but not in the placebo group (Table 2). The change in the domain score was significantly different between the two groups. With regard to the orientation to time, the Pls-treated group showed no notable baseline-to-endpoint change while the placebo group showed a statistically significant decline at endpoint. However, the between-group difference in the change of the score for the orientation to time was not statistically significant (Fig. 2). Regarding the domains of calculation, registration and other domains, there was no significant change in either group, nor was there any significant between-group difference at endpoint.

The WMS-R (0min) and WMS-R (30 min) scores each showed a significant improvement in both groups, but with no statistically significant between-group difference.

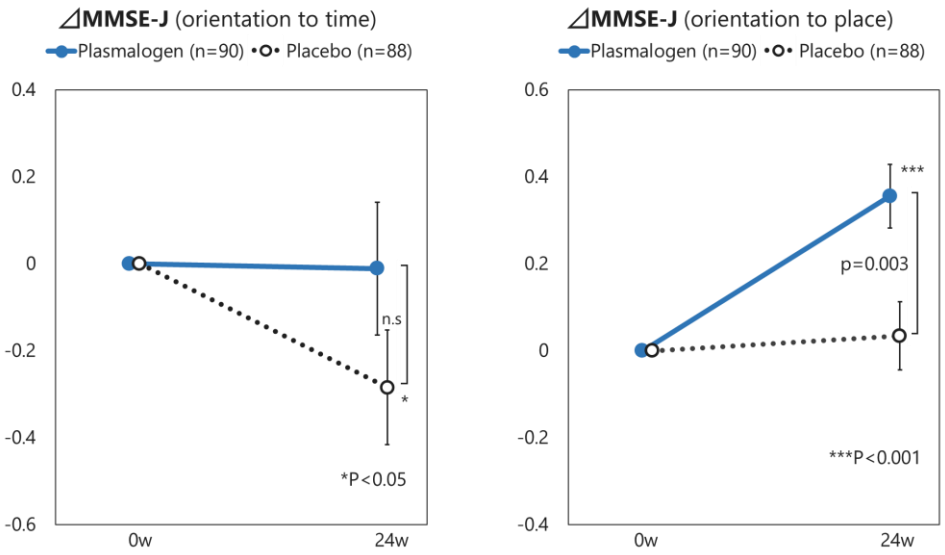
Table 2 Mean difference from baseline (MCI)

Variable	**Plasmalogen** (n=90)		**Placebo** (n=88)		***p*-value***
	mean	(95%CI)	mean	(95%CI)	
MMSE-J	0.59	(0.13 : 1.05)	0.39	(-0.18 : 0.95)	0.58
1. Orientation to time	-0.01	(-0.31 : 0.29)	-0.28	(-0.54 : -0.02)	0.18
2. Orientation to place	0.36	(0.21 : 0.50)	0.03	(-0.12 : 0.19)	0.003
3. Three-word registration	0.02	(-0.03 : 0.08)	0.05	(-0.01 : 0.10)	0.55

4. Attention and calculation	0.10	(-0.15 : 0.35)	0.24	(-0.06 : 0.54)	0.48
5. Three-word recall	0.00	(-0.22 : 0.22)	0.24	(-0.02 : 0.50)	0.17
6. Language (naming)	0.02	(-0.02 : 0.07)	0.02	(-0.01 : 0.05)	0.99
7. Language (repeating)	0.01	(-0.01 : 0.03)	0.02	(-0.01 : 0.05)	0.55
8. Language (3-step command)	0.06	(-0.06 : 0.17)	0.07	(-0.04 : 0.18)	0.88
9. Language (reading)	0.00	(- : -)	0.00	(- : -)	-
10. Language (writing)	0.03	(0.00 : 0.07)	0.02	(-0.02 : 0.07)	0.72
11. Visual construction	0.00	(-0.04 : 0.04)	-0.02	(-0.08 : 0.03)	0.53
WMS-R (0 min)	1.51	(0.84 : 2.18)	1.98	(1.28 : 2.67)	0.34
WMS-R (30 min)	1.27	(0.60 : 1.93)	1.67	(0.97 : 2.37)	0.41
Erythrocyte PlsPE†	0.26	(0.07 : 0.45)	0.32	(0.12 : 0.53)	0.67
Plasma PlsPE	-0.47	(-0.70 : -0.23)	-0.41	(-0.68 : -0.13)	0.74

MMSE-J=Mini Mental State Examination-Japanese
PlsPE= ethanolamine plasmalogens
* unpaired t-test for mean
† Number of the patients were 90 in the Pls-treated group and 87 in the placebo group.

Fig. 2 Change in MMSE-J scores after Pls administration (MCI)



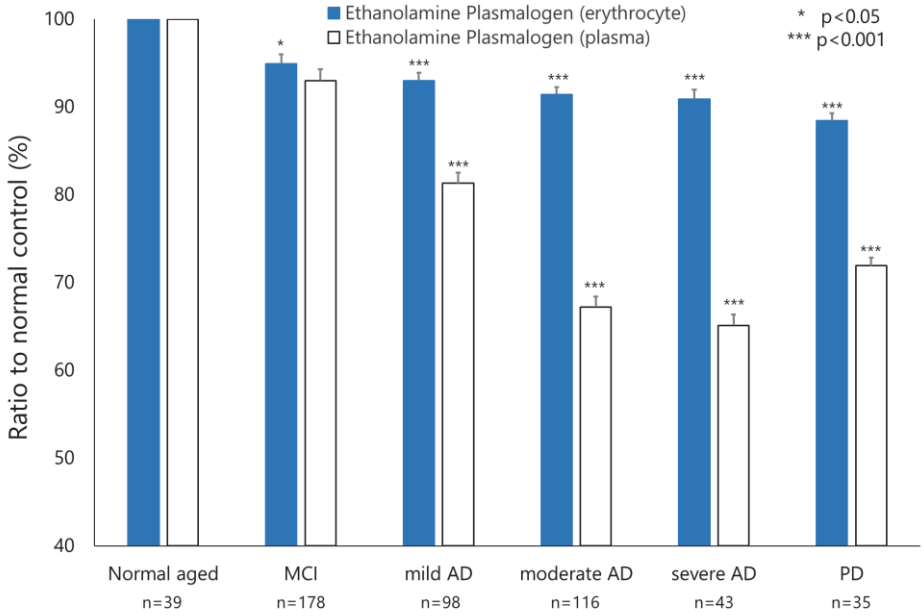
MMSE-J= Mini Mental State Examination-Japanese

2.2.2. Change in the blood level of ethanolamine plasmalogen

Both the Pls-treated group and the placebo group showed an improvement in the levels of erythrocyte PlsPE after Pls ingestion, but no significant difference was observed between the two groups. The levels of plasma PlsPE were decreased in both groups, producing no significant between-group difference (Table 2).

When compared to age-matched healthy controls, a slightly significant decrease was noted in baseline-erythrocyte PlsPE overall although there was no significant decrease in baseline-plasma PlsPE (Fig. 3).

Fig. 3 Comparison with healthy controls in the blood levels of PlsPE



MCI = mild cognitive impairment, AD = Alzheimer's disease, PD = Parkinson's disease
The number of moderate AD, severe AD and PD includes cases other than the study participants.

2.3. Discussion

The MMSE-J total score improved statistically significantly in the Pls-treated group while the change was not significantly different from the change in the placebo group. However, the analysis on each domain of the MMSE-J demonstrated that the orientation to place improved significantly and differentially in the Pls-treated group alone. This improvement of the orientation to place coincides with our preceding animal experiment, in which orally administered Pls improved learning and memory of mice using the Morris water maze test (manuscript in preparation). On the other hand, there was no significant between-group difference for the orientation to time. The finding is, however, not necessarily peculiar in view of the temporal occurrence of disorientation to time and place. Orientation to time is usually disturbed at first, and then orientation to place is lost during the progression form MCI to AD [28]. Hence, it is not a forced explanation that recovery of the late-disturbed orientation to place precedes that of orientation to time. Furthermore, the orientation to time in the placebo group significantly worsened after 24-week treatment in contrast to the Pls-treated group with no worsening. These findings indicate the possibility that Pls treatment may arrest the progression from MCI to AD.

3. Efficacy in patients with mild Alzheimer's disease (20≤MMSE-J≤23) [24]

3.1. Study methods

The study participants in this section were 98 patients with mild AD out of the 276 participants who completed the 24-week RCT described earlier in Section 2.1 (Fig. 1). There were no statistically significant differences between the Pls-treated group (n=50) and the placebo group (n=48) on age and the baseline values for study outcomes as shown in Table 3.

Table 3 Baseline characteristics of RCT (mild AD)

Variable	**Plasmalogen** (n = 50)	**Placebo** (n = 48)	***P* value***
Male, n (%)	25 (50.0%)	18 (37.5%)	0.23
Age in year	77.3 (5.9)	77.6 (5.6)	0.82
MMSE-J	21.4 (1.1)	21.7 (1.0)	0.30
1. Orientation to time	2.5 (1.1)	2.7 (1.4)	0.42
2. Orientation to place	4.0 (0.8)	3.8 (0.7)	0.24
3. Three-word registration	2.9 (0.3)	3.0 (0.0)	0.05
4. Attention and calculation	2.8 (1.5)	2.8 (1.5)	0.87
5. Three-word recall	0.6 (0.9)	0.8 (1.0)	0.38
6. Language (naming)	2.0 (0.0)	2.0 (0.1)	0.31
7. Language (repeating)	1.0 (0.2)	1.0 (0.2)	0.97
8. Language (3-step command)	2.8 (0.4)	2.9 (0.4)	0.86
9. Language (reading)	1.0 (0.0)	1.0 (0.0)	-
10. Language (writing)	0.9 (0.3)	0.9 (0.3)	0.95
11. Visual construction	0.9 (0.4)	0.9 (0.3)	0.83
WMS-R (0 min)	2.36 (2.20)	2.21 (2.17)	0.74
WMS-R (30 min)	0.66 (1.85)	0.60 (1.04)	0.83
Erythrocyte PlsPE (%)	8.01 (0.97)	7.96 (0.88)	0.77
Plasma PlsPE (mg/dl)	3.23 (1.13)	3.71 (1.22)	0.05

Values are mean (SD) unless otherwise specified.
MMSE-J= Mini Mental State Examination-Japanese
*Chi-square test for proportion and unpaired t-test for mean.

3.2. Results

3.2.1. Change in Mini-Mental State Examination-Japanese and Wechsler Memory Scale-Revised

An intention-to-treat analysis yielded no significant difference between the Pls-treated and the placebo groups in the outcomes of cognitive function. The MMSE-J score showed a nearly significant improvement in the Pls-treated group versus no such improvement in the placebo group, producing no statistically significant between-group difference. The WMS-R (0min) and WMS-R (30 min) scores each showed a significant improvement in the Pls-treated group with no significant between-group difference (Table 4).

Table 4 Mean difference from baseline (mild AD)

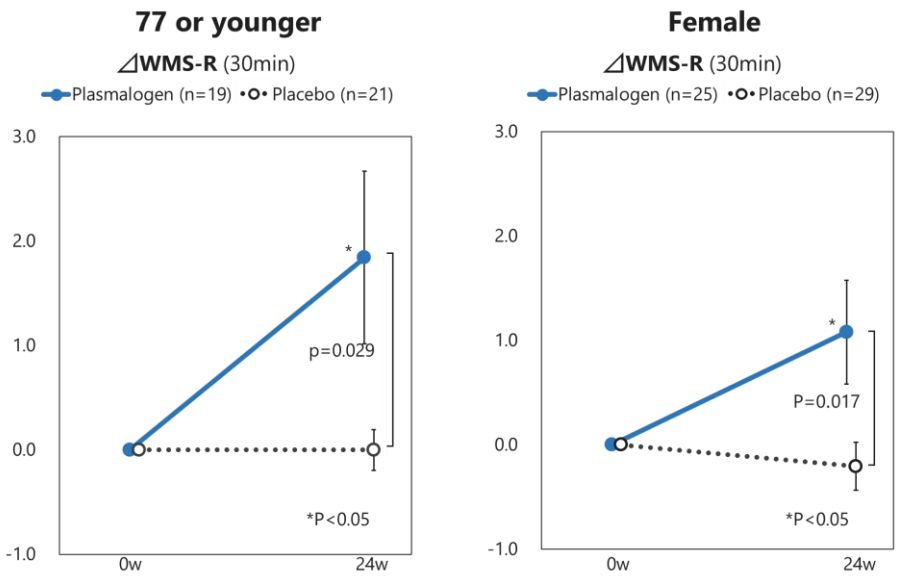
Variable	**Plasmalogen** (n=50)		**Placebo** (n=48)		***p*-value***
	mean	(95%CI)	mean	(95%CI)	
MMSE-J	0.06	(-0.76 : 0.88)	0.19	(-0.59 : 0.96)	0.82
1. Orientation to time	-0.18	(-0.65 : 0.29)	-0.15	(-0.52 : 0.23)	0.91
2. Orientation to place	-0.06	(-0.33 : 0.21)	0.10	(-0.21 : 0.42)	0.43
3. Three-word registration	0.02	(-0.07 : 0.11)	-0.02	(-0.06 : 0.02)	0.42

4. Attention and calculation	0.24	(-0.25 : 0.73)	0.48	(0.02 : 0.94)	0.48
5. Three-word recall	0.02	(-0.29 : 0.33)	-0.19	(-0.45 : 0.07)	0.30
6. Language (naming)	0.00	(- : -)	0.02	(-0.02 : 0.06)	0.31
7. Language (repeating)	0.04	(-0.02 : 0.10)	0.02	(-0.05 : 0.09)	0.68
8. Language (3-step command)	-0.04	(-0.17 : 0.09)	-0.10	(-0.25 : 0.05)	0.51
9. Language (reading)	0.00	(- : -)	0.00	(- : -)	-
10. Language (writing)	0.02	(-0.07 : 0.11)	0.04	(-0.04 : 0.13)	0.73
11. Visual construction	0.00	(-0.13 : 0.13)	-0.02	(-0.15 : 0.11)	0.82
WMS-R (0 min)	1.24	(0.49 : 1.99)	2.35	(-0.39 : 0.99)	0.07
WMS-R (30 min)	0.78	(0.04 : 1.52)	1.33	(-0.37 : 0.41)	0.08
Erythrocyte PlsPE†	0.24	(-0.03 : 0.52)	0.40	(0.11 : 0.69)	0.42
Plasma PlsPE	0.16	(-0.07 : 0.40)	-0.34	(-0.69 : 0.00)	0.02

MMSE-J=Mini Mental State Examination-Japanese
PlsPE= ethanolamine plasmalogens
* unpaired t-test for mean
† Number of the patients were 50 in the Pls-treated group and 49 in the placebo group.

We, furthermore, analyzed the WMS-R score by sex and age. Participants were divided into two groups based on the median value, 77 years or younger and 78 years or older. In the age group of 77 years or younger, WMS-R (30 min) increased statistically significantly in the Pls-treated group, showing a significant between-group difference. Focusing on the sex differences, the female of all ages in the Pls-treated group made a significant improvement in WMS-R (30 min) with a statistically significant between-group difference (Fig. 4).

Fig. 4 WMS-R improvement in 77 years or younger participants and female participants (mild AD)



WMS-R = Wechsler Memory Scale-Revised

3.2.2. Change in the blood level of ethanolamine plasmalogen

The levels of plasma PlsPE improved in the Pls-treated group after Pls ingestion in contrast to a decline in the placebo group, showing a statistically significant difference between the two groups. Regarding the levels of

erythrocyte PlsPE, there was no significance in between-group difference (Table 4).

When compared to age-matched healthy controls, the baseline levels of erythrocyte PlsPE were markedly significantly decreased overall while those of plasma PlsPE were significantly lower than the controls (Fig. 3).

3.3. Discussion

No statistically significant difference was observed in the MMSE-J score between the Pls-treated and the placebo groups. However, the Pls-treated group showed a significant improvement in the WMS-R score and the improvement seemed to be greater than that in the placebo group. Notably, there was a more remarkable improvement in WMS-R in the age group of 77 years or younger and in the female of all ages. These results indicate that oral administration of scallop-derived purified Pls might be effective in improving cognitive function of mild AD patients. This study did not confirm the efficacy of Pls ingestion in the age group of 78 years or older, or in the male of all ages. One reason for the lack of efficacy in these aged participants might be ascribed to age-related irreversible degenerative changes in the brain [29]. It is unknown why the efficacy was obvious in females but not in males.

The changes in the blood level of plasma Pls after treatment differed significantly between the Pls-treated and the placebo groups. Plasma PlsPE in the placebo group was significantly reduced after treatment, whereas that of the Pls-treated group remained unchanged. These findings may indicate that production of Pls in peroxisome was reduced concurrently with the progression of AD during the 24-week study period, and that oral administration of Pls may contribute to maintain the production of Pls in peroxisome.

4. Efficacy in patients with moderate Alzheimer's disease (11≤MMSE≤19) and severe Alzheimer's disease (MMSE≤10) [26]

4.1. Study methods

Efficacy of scallop-derived Pls was examined in an open-label study. A total of 103 participants aged 60 to 85 years were recruited from 23 hospitals or clinics in Japan from February 2015 to December 2015, consisting of moderate AD (n=57) and severe-AD (n=18). The baseline characteristics of completed participants are described in Table 5.

The enrolled participants received 1.0 mg of scallop-derived Pls for 12 weeks. Efficacy endpoints included change in the MMSE score, the levels of Pls in erythrocyte and plasma, and 5-item neurofunctional evaluation rated by caregivers. The degree of improvement in the MMSE was classified as remarkable improvement (ΔMMSE≥4), improvement (ΔMMSE 2 to 3), no change (ΔMMSE±1) and worsening (ΔMMSE≤-2).

Table 5 Baseline characteristics of Open Trial (moderate AD and severe AD)

Variable	**Moderate AD** (n = 57)	**Severe AD** (n = 18)	***P* value***
Male, n (%)	24 (42.1%)	8 (44.4%)	1.00

Age in year	77.2 (4.7)	74.9 (5.0)	0.09
MMSE	15.9 (2.5)	5.7 (2.4)	0.00
1. Orientation to time	1.2 (1.1)	0.1 (0.3)	0.00
2. Orientation to place	2.2 (1.4)	0.2 (0.4)	0.00
3. Three-word registration	2.9 (0.5)	1.6 (1.2)	0.00
4. Attention and calculation	1.2 (1.2)	0.1 (0.2)	0.00
5. Three-word recall	0.8 (1.0)	0.2 (0.5)	0.01
6. Language (naming)	1.9 (0.5)	0.9 (1.0)	0.00
7. Language (repeating)	0.8 (0.4)	0.0 (0.0)	0.00
8. Language (3-step command)	2.9 (0.4)	2.3 (1.0)	0.00
9. Language (reading)	0.9 (0.3)	0.3 (0.5)	0.00
10. Language (writing)	0.6 (0.5)	0.0 (0.0)	0.00
11. Visual construction	0.6 (0.5)	0.1 (0.2)	0.00
Erythrocyte PlsPE (%)	7.83 (0.91)	8.03 (1.20)	0.45
Plasma PlsPE (mg/dl)	3.05 (1.22)	3.15 (1.24)	0.76

Values are mean (SD) unless otherwise specified.
MMSE = Mini-Mental State Examination.
PlsPE = ethanolamine plasmalogen.
*Chi-square test for proportion and unpaired t-test for mean

4.2. Results

4.2.1. Change in Mini-Mental State Examination

The MMSE score in moderate AD made a significant improvement by 1.72 points. A MMSE domain-specific analysis showed a statistically significant improvement in orientation to time, orientation to place, and three-word recall. No significant improvement in the MMSE score was observed in severe AD (Table 6).

As illustrated in Fig. 5, more than half of moderate AD improved in the post-treatment MMSE score. According to the degree of improvement, 31% of moderate AD were classified as remarkable improvement, 21% as improvement, 36% as no change, and 12% as worsening. Although no remarkable improvement was noted in severe AD, 29% of them improved.

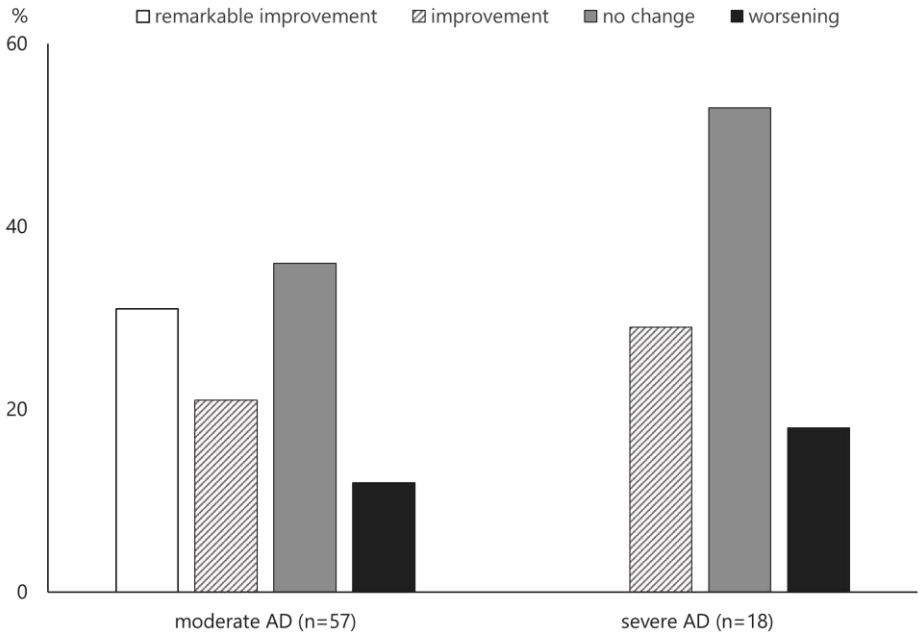
Table 6 Mean difference from baseline (moderate AD and severe AD)

Variable	**Moderate AD** (n=57)		**Severe AD** (n=18),		***p*-value***
	mean	(95% CI)	mean	(95% CI)	
MMSE	1.72	(0.88 : 2.56)	0.28	(-0.71 : 1.27)	0.07
1. Orientation to time	0.51	(0.15 : 0.87)	-0.11	(-0.27 : 0.05)	0.06
2. Orientation to place	0.37	(0.02 : 0.72)	0.17	(-0.18 : 0.52)	0.54
3. Three-word registration	0.04	(-0.12 : 0.19)	0.17	(-0.29 : 0.63)	0.47
4. Attention and calculation	0.23	(-0.13 : 0.59)	0.17	(-0.09 : 0.42)	0.85
5. Three-word recall	0.42	(0.08 : 0.76)	-0.17	(-0.42 : 0.09)	0.06
6. Language (naming)	0.04	(-0.08 : 0.15)	-0.11	(-0.56 : 0.34)	0.35

7. Language (repeating)	0.05	(-0.05 : 0.16)	0.11	(-0.05 : 0.27)	0.57
8. Language (3-step command)	0.00	(-0.13 : 0.13)	0.11	(-0.50 : 0.72)	0.58
9. Language (reading)	0.04	(-0.04 : 0.11)	-0.06	(-0.17 : 0.06)	0.20
10. Language (writing)†	-0.02	(-0.13 : 0.09)	0.00	-	0.85
11. Visual construction†	0.05	(-0.07 : 0.17)	0.00	-	0.61
Erythrocyte PlsPE	0.20	(0.00 : 0.40)	0.14	(-0.33 : 0.61)	0.79
Plasma PlsPE††	0.30	(0.02 : 0.58)	0.42	(-0.20 : 1.04)	0.68

MMSE = Mini Mental State Examination
PlsPE = ethanolamine plasmalogens
* unpaired t-test for mean
†Number of patients: n = 56 in moderate AD and n=18 in severe AD
††Number of patients: n = 45 in moderate AD and n=18 in severe AD

Fig. 5 Categorical distribution of MMSE improvement in moderate and severe Alzheimer's disease



MMSE = Mini Mental State Examination, AD = Alzheimer's disease
remarkable improvement (ΔMMSE≥4), improvement (ΔMMSE 2 to 3),
no change (ΔMMSE±1), worsening (ΔMMSE≤-2)

4.2.2. Change in the blood level of PlsPE

Orally administered Pls to moderate AD resulted in a significant elevation of the PlsPE levels in both plasma and erythrocyte whereas there was no significant change after 12-week treatment in severe AD (Table 6).

When compared to age-matched healthy controls, the baseline levels of erythrocyte PlsPE were markedly significantly decreased while those of plasma PlsPE were significantly lower than the controls (Fig. 3).

4.3. Discussion

These results provide a strong indication that Pls administration could enhance cognitive function in moderate AD. However, this study was open-labeled without a control group, and some of the observed improvement may have been due to the placebo effect. In this regard, it could be presumed that the placebo effect is unlikely to occur

in moderate-to-severe AD in such a way as observed in general physical illnesses and symptoms. If based on the premise that the placebo effect is brought about by patients' *expectation* and *hope,* those suffering from moderate-to-severe AD are less likely to develop the conceptions of *expectation* and *hope* because of their cognitive dysfunction.

To deal with the magnitude of placebo effect, we searched and retrieved relevant studies from PubMed and CiNii database. The placebo group in each study targeting moderate-to-severe AD presented cognitive deterioration consistently. One of them reported a decrease of 0.3 points in MMSE after 24-week placebo treatment period [30]. It is unlikely that the natural course of MMSE deterioration in AD patients is altered by the placebo effect although no direct evidence is available that placebo does not make improvement of the MMSE score with 12-week treatment duration. Putting together these findings, it could be concluded that scallop-derived Pls had therapeutic efficacy for moderate-to-severe AD.

Only 1.0 mg/day of Pls showed efficacy on cognitive function in AD and MCI. It is unclear how its physiological mechanism with such a small amount of administered Pls works. One hypothesis is that Pls may act through some receptors like hormones. Lipid rafts in the cell membrane are considered to be associated with cell signaling [23,31]. Some studies reported that lipid rafts are abundant in PlsPE [32]. G-protein coupled receptors (GPCR) are also localized to lipid rafts and caveolae [33]. These findings may indicate the possibility of Pls functioning as a ligand of GPCR. The concentration of PlsPE in human plasma is about 100 μmol/l, but plasma PlsPE may circulate as lipoproteins. It is unlikely that Pls in lipoproteins solely act as a ligand of receptors, but it is possible for free Pls derived from oral administration, even in a small amount, to work as a ligand of some receptors at intestinal cells before becoming lipoproteins. It is well-known that the intestine is in close communication with the brain through neural, endocrine, and immune pathways [34].

There are naturally concerns that orally administered Pls might be destroyed by stomach acid because of their sensitivity to it. Despite such concerns, our experiments in mice [35] and clinical trials in human [24,26,27] showed that the levels of Pls were increased in plasma and erythrocyte membrane by oral administration of Pls (1 mg/day/person). These results suggest that Pls might reach the intestines without being destroyed by stomach acid in an effective amount as a hormone when being ingested with a meal.

Interestingly enough, after a 12-week of treatment, the improvement of the MMSE total score in moderate AD was more remarkable than that in mild AD and MCI with the same dosage of Pls (MCI: 0.32 points, mild AD: 0.50 points, moderate AD: 1.72 points) [24]. It could be possible that patients with moderate AD have relatively less normal brain tissue and more damaged tissue due to the brain atrophy than those with mild AD and MCI. Therefore, the former may demand and consume less hormone-like substance, Pls, than the latter. Additionally, the brain activity of the latter is almost as high as that of healthy individuals, and thus consumes as much Pls as healthy individuals do. On the other hand, the brain activity of moderate AD is lower and consumes less Pls than that of healthy individuals. This hypothetical reasoning leads to a conclusion that even a very small amount of Pls is effective for moderate AD. The reason for no significant improvement in severe AD is presumably that they have a smaller number of normal brain tissue than other diseases and therefore do not respond to small doses of Pls. If a

larger amount of Pls (i.e., 2–3 mg per day) is administered to mild AD, MCI and severe AD, the same effect as moderate AD might be obtained. Further research on the dose-response effect are needed to determine the influence of severity.

5. Efficacy in patients with Parkinson's disease [27]

5.1. Study methods

To assess the efficacy of Pls in patients with Parkinson's disease (PD), 14 participants were recruited, of which 7 had a history of deep brain stimulation (DBS) treatment. Finally, 10 of them completed the trial. The baseline characteristics are summarized in Table 7. The participants taking anti-Parkinson drugs (including dopamine agonists) had no regimen changes in the preceding one month and kept unchanged during the study period. Participants ingested 1mg/day of scallop-derived Pls for a 24-week treatment period followed by a 4-week observation period. Parkinson's Disease Questionnaire-39, which evaluates PD-specific health-related quality of life with a higher score indicating lower quality of life, and the levels of Pls in plasma and erythrocyte were checked at 0, 4, 12, 24, and 28 weeks of treatment. The blood levels of Pls in patients with PD were compared with those of 39 age-matched normal controls.

Table 7 Baseline characteristics of Open Trial (PD)

Variable	**Parkinson's disease** (n=10), mean	**Normal control** (n=39), mean	***p* value***
Male, n (%)	3 (30.0%)	13 (33.3%)	1.000
Age in year	67.80 (7.41)	71.87 (5.50)	0.058
MMSE	28.56 (2.13)	29.90 (0.31)	0.000
Plasma PlsPE	2.97 (0.76)	4.27 (1.07)	0.001
Erythrocyte PlsPE (%)	7.67 (0.78)	8.56 (0.94)	0.008

Values are mean (SD) unless otherwise specified.
MMSE = Mini-Mental State Examination
PlsPE; ethanolamine plasmalogen
*Chi-square test for proportion and paired t-test for mean

5.2. Results

5.2.1. Change in Parkinson's Disease Questionnaire-39

Oral administration of Pls improved some clinical symptoms in patients with PD concomitantly with an increase of Pls in peripheral blood (Table 8). This clinical improvement was almost parallel to the increase of erythrocyte PlsPE (Fig. 6).

Table 8 Improvement of clinical symptoms of Parkinson's disease after oral administration of scallop-derived ether phospholipids

PDQ-39	**Before (n=10),** mean scores	**After 24 weeks (n=10)**, mean scores	***p* value***

Total	273.5 (145.2)	188.8 (93.8)	0.02
Mobility	50.5 (29.0)	48.8 (22.9)	0.66
Daily activity	48.8 (23.7)	35.4 (16.3)	0.05
Emotional well-being	40.4 (27.5)	26.3 (19.1)	0.07
Stigma	23.1 (17.9)	15.0 (17.7)	0.05
Social support	17.5 (18.2)	6.7 (12.3)	0.03
Cognitions	40.7 (19.8)	25.0 (16.4)	0.02
Communication	35.8 (33.8)	22.5 (26.4)	0.07
Bodily discomfort	16.7 (11.1)	9.2 (10.0)	0.03

Values are mean (SD) unless otherwise specified.
*Paired t-test for mean

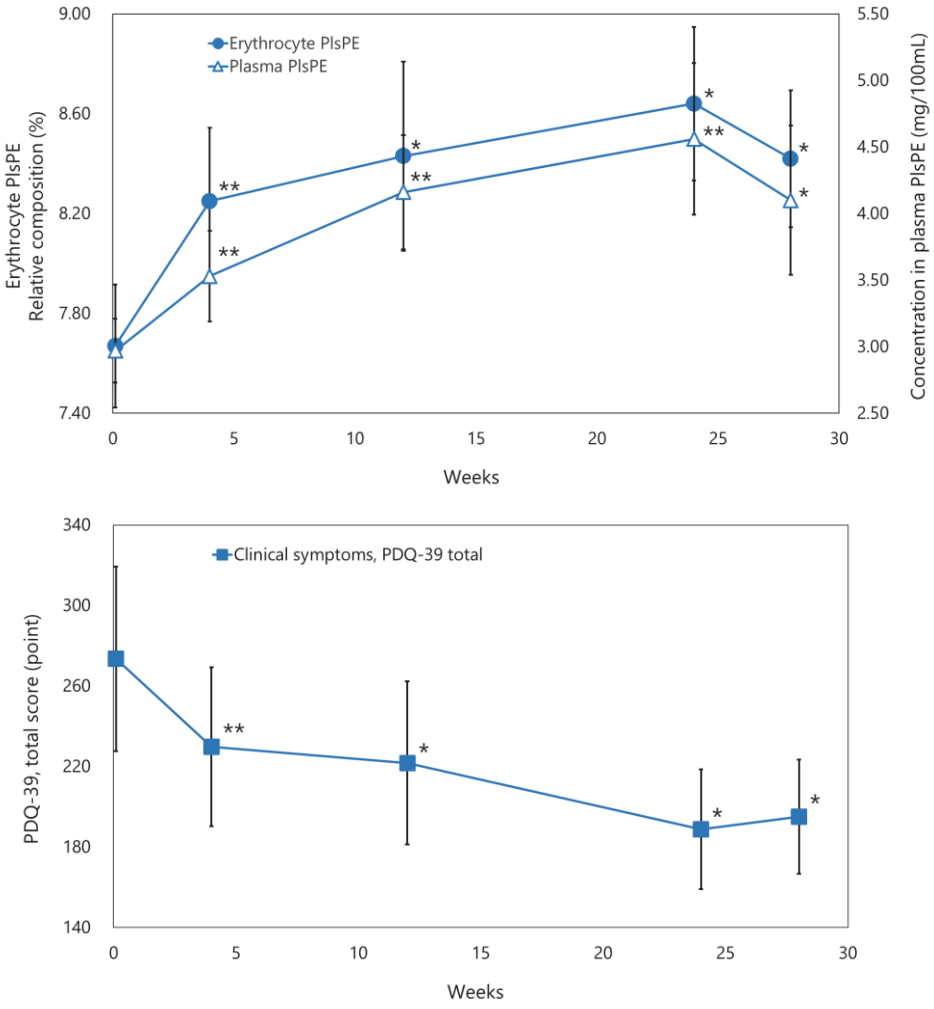


Fig. 6 Increase in erythrocyte PlsPE (relative composition) and plasma PlsPE (concentration), and improvement in clinical symptoms of PD (PDQ-39)

**p<0.01, *p<0.05 Error bars indicate standard error.
PlsPE = ethanolamine plasmalogen
PDQ-39 = Parkinson's Disease Questionnaire-39
Last 4 weeks (24 to 28 weeks) were the observation period without administration.
Differences from immediate before trial

5.2.2. Change in the blood level of ethanolamine plasmalogen

Baseline levels in plasma and erythrocyte PlsPE in patients with PD were significantly lower than those of normal elderly controls (Fig. 3). The levels in both plasma and erythrocyte PlsPE, however, increased rapidly after ingestion of Pls, reached almost the normal range at 12 weeks, and were maintained until 24 weeks. Four weeks after the end of the administration period, the levels of both plasma PlsPE and erythrocyte PlsPE showed a tendency to decrease (Fig. 6).

5.3. Discussion

It is well-known that the vinyl ether bond at the sn-1 position makes Pls more susceptible to oxidative stress than corresponding ester-bonded glycerophospholipids [6,36-38]. Therefore, Pls may act as an antioxidant and protect cells against oxidative stress [37,38]. Some studies suggested that increased oxidative stress might be present in the peripheral blood of PD [39]. The increase in oxidized form of coenzyme Q10 in the plasma of PD may indicate elevated systemic oxidative stress in PD [40]. Actually, Dragonas et al. reported that a decrease in plasma Pls served as a marker of increased systemic oxidative stress in PD [41]. In their study, plasma Pls were measured by transesterification of plasma phospholipids and Pls-derived dimethyl acetal (DMA) was measured with gas chromatography. Several reports indicated that the presence of neuroinflammation in PD [42] and α-synuclein dimerization in erythrocyte in PD [43]. The decrease of Pls in the peripheral blood of PD might be in part due to high oxidative stress in PD.

This study showed that oral administration of purified Pls derived from scallop increased plasma and erythrocyte Pls in patients with PD as well as concomitant improvement in some PD-specific clinical symptoms. Some studies using animal models of PD have suggested efficacy of Pls for symptoms of PD. Gregoire et al. reported that Pls precursor analog treatment reduced levodopa-induced dyskinesia in parkinsonian monkeys [44], and that Pls augmentation with a Pls precursor reversed striatal dopamine loss in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-(MPTP-) treated mice [45].

6. Proposal of a new hypothesis for the etiology of Alzheimer's disease and a future study

It is common knowledge that AD is characterized pathologically by senile plaques which are mainly composed of amyloid-beta (Aβ) protein. The amyloid cascade hypothesis, widely supported at the present time, proposes that deposition of Aβ is a hallmark pathological lesion observed at the earliest stage of AD, that aggregated Aβ induces neuronal toxicity, and that deficiency in production and deposition of Aβ correlates well with the onset of AD based on the genetic analysis of familial AD.

Aβ, fragments of amyloid precursor protein (APP), is produced and secreted when cleaved by β- and γ-secretase. It is, therefore, considered essential to regulate the activity of secretase, and activate the pathway of Aβ degradation as an AD treatment strategy. Meanwhile, some studies reported that there were many patients who did not develop any AD symptoms despite high Aβ deposition in the postmortem brain, and that by contrast some patients with serious AD symptoms turned out at autopsy to be mild cases [46]. Thus far major pharmaceutical companies have been enthusiastic about developing new antidementia drugs, none of which works. To take an

example of Aβ-targeting AD drugs, no beneficial effects were achieved by administration to human patients [47,48]. From these results, it seems reasonable to conclude that the amyloid cascade hypothesis of AD has problems in itself.

Amid such circumstances, strong evidence supporting the neuroinflammation hypothesis is gradually accumulating. Our animal studies demonstrated that neuroinflammation-induced Aβ deposition caused AD and, furthermore, that Pls administration inhibited the deposition of Aβ and prevented the onset of AD as detailed in the former chapter. These findings strongly suggest that neuroinflammation is one of the main causes of AD.

Shamim et al. revealed that Pls administration to AD animal models improved spatial memory and concurrently increased the number of dendrites and spines in the hippocampus (manuscript in preparation), which indicates that Pls are effective for the improvement of neural network failure. Actually, improvement in cognitive function was observed among patients ranging from MCI to severe AD as described above. It is worth noting that spatial memory improvement in animal models is well consistent with significant improvement in orientation to place (one of the MMSE domains) among MCI patients in the Pls-treated group compared to the placebo group.

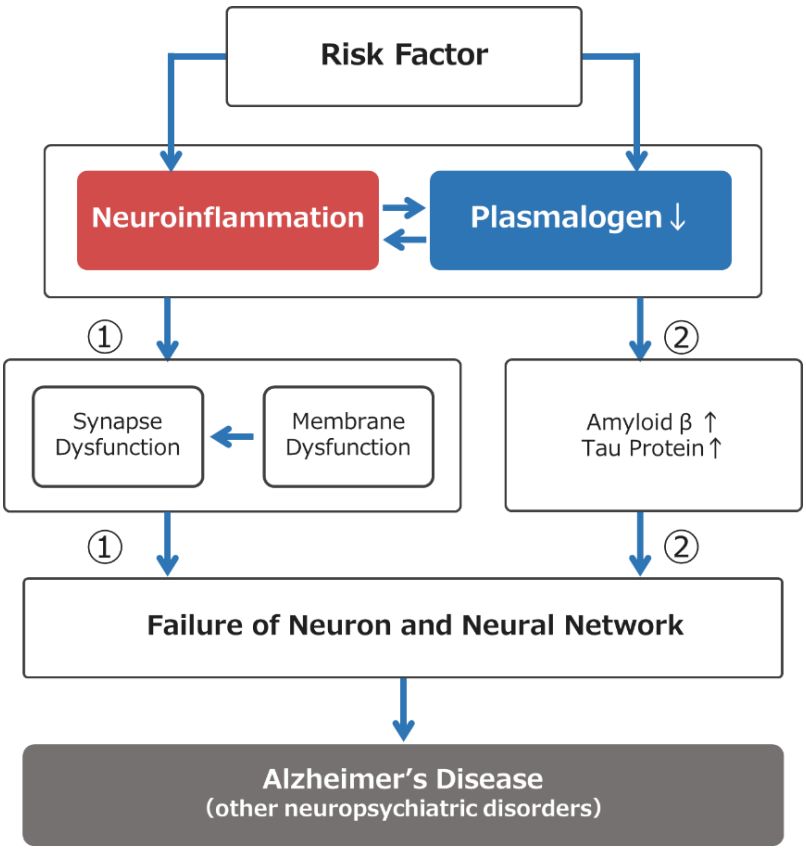


Fig. 7 A new hypothesis for the etiology of AD pathogenesis

Taken together, a new hypothesis is proposed here to explain AD pathogenesis as illustrated in Fig. 7.

When the brain is exposed to risk factors including mental stress, infection, metabolic syndrome and aging, neuroinflammation (microglial activation) is caused. This neuroinflammation leads to the malfunction of peroxisome and endoplasmic reticulum, and then causes an immediate decrease in Pls. Conversely, if Pls continue to be consumed more than produced (overconsumption caused by overstress, reduced production of peroxisome and

endoplasmic reticulum due to aging), neuroinflammation develops. To put it differently, physiological phenomenon "neuroinflammation" and biochemical phenomenon "decreased Pls" are opposite sides of the same AD pathogenesis. Such interactivity between "neuroinflammation" and "decreased Pls" results in functional and structural defects in neuronal membrane and synapse [49]. On the other hand, microglial activation causes activation of γ-secretase, accumulates Aβ, and then increases tau proteins [50].

Such membrane dysfunction and synapse dysfunction causes the failure of neurons, and disturbs the neural network through Route 1. Likewise, accumulation of Aβ and tau proteins affects the neurons and neural network through Route 2. Consequently, AD occurs. Route 1 and Route 2 presumably progress in parallel. Route 2, however, may not be a main route, because it has been reported that no accumulation of Aβ was observed in some patients with AD as results of an autopsy [46] and any inhibitor of Aβ accumulation has little effect in development of new drugs [47,48].

It is not difficult to imagine that failure of neuron and neural network, which occurs in various areas of the brain, causes other different diseases than AD (e.g. PD, schizophrenia, or depression) [51]. As stated in Section 5, some clinical symptoms of PD were significantly improved by Pls administration concomitantly with an increase of the Pls levels. Some other studies reported that Pls were decreased in patients with schizophrenia [52,53], which is mainly considered to occur as a result of neuroinflammation. These findings strongly support our new hypothesis of pathogenesis.

Thus far we have examined the efficacy of Pls, which reduce neuroinflammation, in patients with MCI, AD and PD. Further clinical trials by other research teams are required to verify the effects on these diseases. In addition to that, new trials are highly needed in patients with neuropsychiatric disorders including schizophrenia, depression, and others. Moreover, the measurement of blood Pls should be also investigated in the clinical trials from now on, because our present study and other reports suggest [18,54] that the blood levels of Pls are a new biomarker for the severity of diseases including MCI, AD, PD and other neuropsychiatric disorders [51]. We strongly hope that this new hypothesis will make a contribution to the elucidation of the pathogenesis of neuropsychiatric disorders, and to the establishment of their therapeutic and preventive methods.

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