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Dilinoleoylphosphatidylethanolamine May Restrain the Progress of MCI into Alzheimer's Disease

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ABSTRACT

Phosphatidylethanolamine, a component of the plasma membrane, regulates diverse cellular processes. The present review shows the beneficial effect of 1, 2-dilinoleoyl-sn-glycero-3-phosphoethanolamine (DLPE), a phospholipid, on mild cognitive impairment (MCI), a preliminary group of Alzheimer's disease (AD). Neuronal death (apoptosis) causes brain atrophy and cognitive disorders such as AD and senile dementia. DLPE significantly inhibits PC-12 cell death induced by amyloid-$\beta_{1\text{-}40}$ (A$\beta_{1\text{-}40}$) or thapsigargin that triggers endoplasmic reticulum (ER) stress. Oral administration with DLPE for 7 months suppresses a decrease in the number of hippocampal neurons and ameliorates spatial memory decline in senescence-accelerated mouse-prone 8 (SAMP8) mice. These findings indicate that DLPE has the potential to protect neurons from ER stress- and senescence-induced apoptosis and to ameliorate senile dementia. In the follow-up surveys more than three years of 41 MCI patients, who took DLPE (~0.9 mg) everyday, thirty-five patients (85%) had no brain atrophy progression and improved or maintained the Mini Mental State Examination (MMSE) score. This indicates that DLPE may prevent MCI from developing into AD.

Introduction

Mild cognitive impairment (MCI), causing a slight but noticeable decline in cognitive abilities, is an intermediate stage between the expected cognitive decline of normal aging and the more-serious decline of dementia such as Alzheimer's disease (AD) [1]. The diagnosis of MCI is made if patients meet the following criteria: i) memory complaints, ii) normal activities of daily living, iii) normal general cognitive function, iv) abnormal memory for age, and v) not demented. Since then, several avenues of studies have applied the MCI criteria and focused on how likely and how fast people with MCI develop AD. All the persons with MCI do not progress AD; some persons never get worse or a few eventually get better [2]. Early diagnosis and early care of MCI, however, may be the most critical strategy to prevent the progress into AD.

AD is characterized by progressive and severe atrophy of the brain including the frontal and parietal lobes and the hippocampus. Amyloid deposition as a

single etiology for AD causes endoplasmic reticulum (ER) stress-induced apoptosis of neurons, responsible for brain atrophy [3,4]. So far, no promising drug for treatment of ER stress-induced neuronal apoptosis has been provided. We have earlier found that 1, 2-dilinoleoyl-sn-glycero-3-phosphoethanolamine (DLPE), a phospholipid, inhibits ER stress-induced neuronal cell death [5]. This raises the possibility that DLPE could be developed as an effective drug for treatment and prevention of AD.

1. DLPE protects neuronal cells from ER stress-induced apoptosis

Intraluminal accumulation of unfolded proteins in the ER triggers ER stress, to activate caspase-4 for humans (caspase-12 for mice and rats) followed by activation of the effector caspase-3, to induce apoptosis [6-8]. ER stress-induced neuronal apoptosis plays a central role in the pathogenesis of neurodegenerative diseases such as AD and Parkinson disease, senile dementia, and ischemic neuronal damage [9-14].

Amyloid-$\beta_{1\text{-}40}$ ($A\beta_{1\text{-}40}$) reduced PC-12 cell viability (Figure 1A). This implies that $A\beta_{1\text{-}40}$ induces neuronal cell death (apoptosis). DLPE inhibited $A\beta_{1\text{-}40}$-induced PC-12 cell death in a concentration (1-300 μM)-dependent manner, with the maximum at 30 μM [5] (Figure 1A,B). In contrast, other examined phospholipids such as 1-linoleoyl-2-palmitoyl-sn-glycero-3-phosphoethanolamine (LPPE), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-diheptadecanoyl-sn-glycero-3-phosphoethanolamine (DPPE), 1,2-diheptadecanoyl-sn-glycero-3-phosphoethanolamine (DHPE), 1,2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE), and 1,2-dilinoleoyl-sn-glycero-3-phosphocholine (DLPC) exhibited no effect [5] (Figure 1A).

Thapsigargin, an inhibitor of Ca^{2+}/ATP ase, releases and depletes calcium from the ER, causing ER stress-induced apoptosis [15]. Thapsigargin reduced PC-12 cell viability, and DLPE significantly inhibited the effect of thapsigargin [5] (Figure 1C). Taken together, these results indicate that DLPE has the potential to protect neuronal cells from ER stress-induced apoptosis (Figure 2).

2. DLPE suppresses senescence-induced neuronal cell death

Senescence-accelerated mouse-prone (SAMP) is a murine model of accelerated senescence, and senescence-accelerated mouse-resistant (SAMR), that reveals normal aging, is used as a control for SAMP [16,17].

The number of hippocampal neurons in SAMP8 mice significantly decreased as compared with that in SAMR1 mice (Figure 3), indicating that neurons are gone with aging. DLPE clearly inhibited a decrease in the number of hippocampal neurons in SAMP8 mice [5] (Figure 3). This indicates that DLPE has the potential to suppress senescence-induced neuronal death.

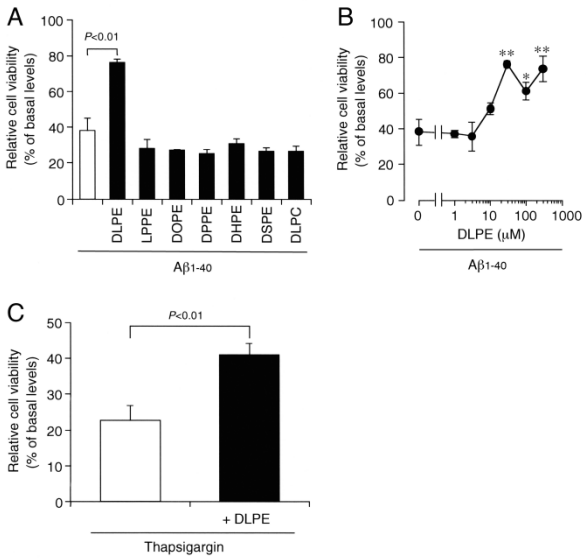

Figure 1: The protective effect of DLPE against ER stress-induced neuronal cell death. (**A**) PC-12 cells were treated with $A\beta_{1\text{-}40}$ (5 μM) in the absence (control) and presence of phospholipids (30 μM) as indicated for 48 h, followed by MTT assay. Data represent the mean (± SEM) percentage of basal levels (MTT intensities of cells untreated with $A\beta_{1\text{-}40}$) (n=6 independent experiments). P value, unpaired *t*-test.(**B**) Cells were treated with $A\beta_{1\text{-}40}$ (5 M) in the absence (control) and presence of DLPE at concentrations as indicated for 48 h, followed by MTT assay. Data represent the mean (± SEM) percentage of basal levels (MTT intensities of cells untreated with $A\beta_{1\text{-}40}$) (n=6 independent experiments). *P<0.1, **P<0.01 as compared with control, unpaired *t*-test. (**C**) In a different set of experiments, cells were treated with thapsigargin (100 nM) in the absence (control) and presence of DLPE (30 μM) for 24 h, followed by MTT assay. In the graphs, data represent the mean (± SEM) percentage of basal levels (MTT intensities of cells untreated with thapsigargin) (n=6 independent experiments). P value, unpaired t-test.

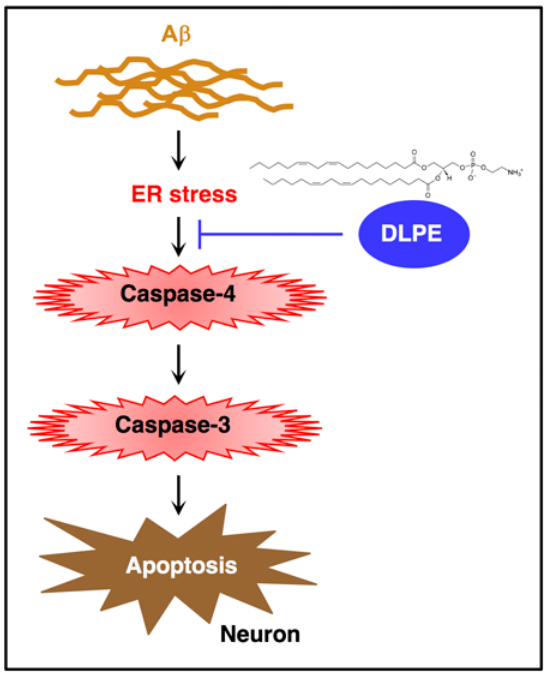

Figure 2: A schematic diagram underlying the protective effect of DLPE against Aβ-induced apoptosis of neurons.

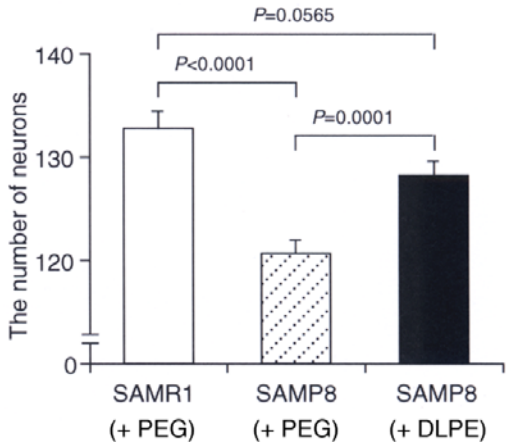

Figure 3: The effect of DLPE on the number of hippocampal neurons. After oral administration with PEG or DLPE (1 mg/kg body weight) for 7 months, coronal slices of the brain from SAMR1 and SAMP8 mice were prepared, and the number of neurons, immunoreactive to an anti-NeuN antibody, was counted in the consistent area (142 μm x 192 μm) of the hippocampal CA1 region both on the left and right sides from 8 sections per a mouse and summated. Values represent the mean (± SEM) number of hippocampal neurons (n=5 for SAMR1 mice with PEG administration, 10 for SAMP 8 mice with PEG administration, and 7 for SAMP8 mice with DLPE administration). *P* values, unpaired *t*-test.

3. DLPE ameliorates senescence-induced memory decline

SAMP 8 mice are shown to have learning and memory decline with age-related reduction of choline acetyltransferase activity [18-20]. In support of this notion, the retention latency for SAMP8 mice in the water maze test was significantly longer than the latency for SAMR1 mice [5] (Figure 4). The prolonged latency for SAMP8 mice was markedly shortened by oral administration with DLPE, reaching the level similar to that for SAMR1 mice [5] (Figure 4). This indicates that DLPE has the potential to ameliorate senescence-induced memory decline.

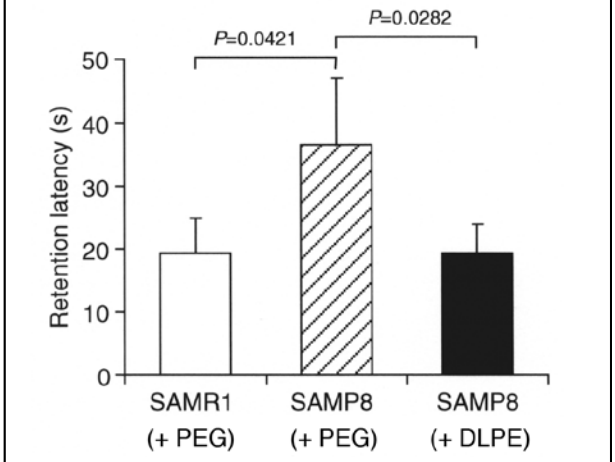

Figure 4: The effect of DLPE on age-related spatial memory decline. Water maze test was carried out in SAMR1 and SAMP8 mice after oral administration with PEG or DLPE (1 mg/kg body weight) for 7 months. Values represent the mean (± SEM) retention latency from 2-day block (n=5 for SAMR1 mice with PEG administration, 10 for SAMP8 mice with PEG administration, and 7 for SAMP8 mice with DLPE administration). *P* values, unpaired *t*-test.

4. DLPE inhibits the progression of brain atrophy and cognitive deterioration in patients with MCI

The effects of DLPE on the brain atrophy and cognitive function were examined in 41 MCI patients at ages from 59 to 89 years old (average, 77 years old) (18 males and 23 females), who took lecithin containing DLPE (~0.9 mg) every day. In the Mini Mental State Examination (MMSE) score at the time of the first medical examination, over 27, between 20 and 26, and below 19 were regarded as normal, MCI, and AD, respectively. This study was approved by Institutional Review Board at Ohyama Hospital (Nishiwaki, Japan) and informed consent was obtained from all the participants. To see the progression of hippocampal atrophy, the areas of the hippocampus at the similar slice of the coronal CT images were measured and compared. To see the progression of cerebral atrophy, the length of the space between the cranial bone and

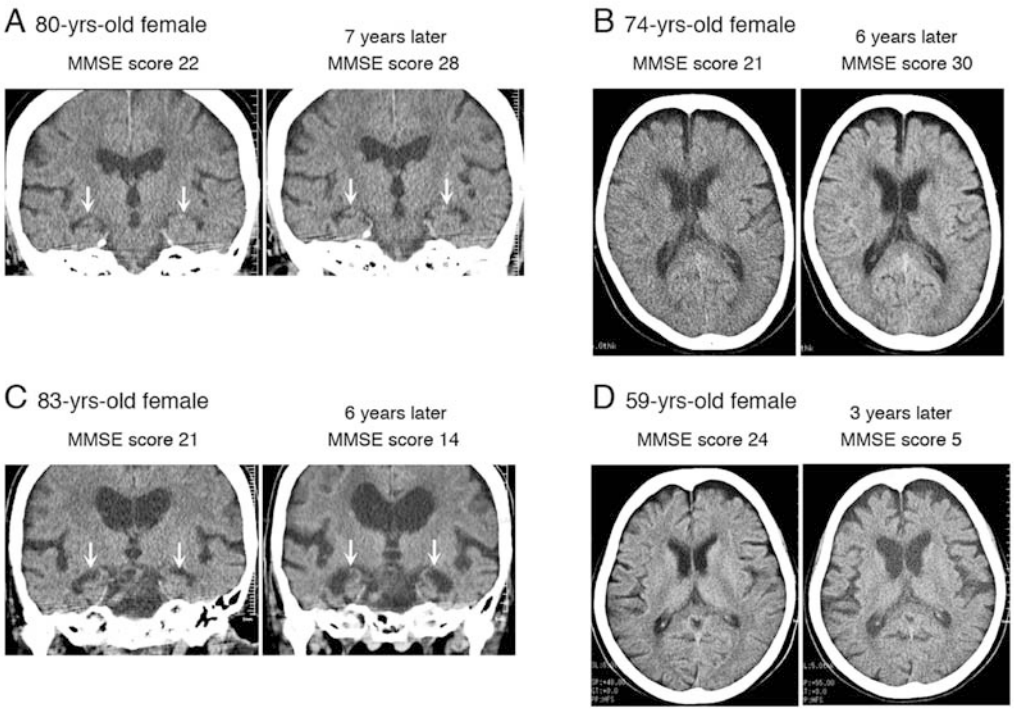

Figure 5: CT imaging. (**A**) (**C**) Coronal sections of CT imaging. The hippocampus is indicated by the white arrows. (**B**) (**D**) Axial sections of CT imaging. Progression of hippocampal atrophy (**A**) or cerebral atrophy (**B**) is not found, and the MMSE score rises 7 or 6 years after DLPE intake, respectively. Marked progression of hippocampal atrophy and decrease in the MMSE score are found 6 years after DLPE intake (**C**). Mild progression of front otemporal atrophy and relative dilatation of anterior horn of the lateral ventricle are seen, and the MMSE score is extremely worsened 3 years after DLPE intake (**D**).

cerebral cortical surface at the similar slice of the axial CT images was measured and compared.

In the more than three years' follow-up surveys, thirty-five of 41 patients (85%) had no brain atrophy progression and improved/maintained the MMSE score throughout during DLPE intake (unpublished data) (Table1, Figure 5A,B). The brain atrophy progression well correlated to the decrease of the MMSE score. In six of 41 patients (15%), the MMSE score was worsened in parallel with brain atrophy progression (unpublished data) (Table1, Figure 5C,D).

The mean MMSE score in 41 patients before DLPE intake was 23, and the score did not fall throughout during DLPE intake at least for three years (unpublished data) (Figure 6). Taken together, these results indicate that DLPE has the potential to inhibit the progression of brain atrophy and cognitive deterioration in patients with MCI. Accordingly, DLPE may restrain the progress of MCI into AD. It is presently unknown why DLPE had no beneficial effect on six patients (15%) with MCI. To address this question, further investigations need to be carried out.

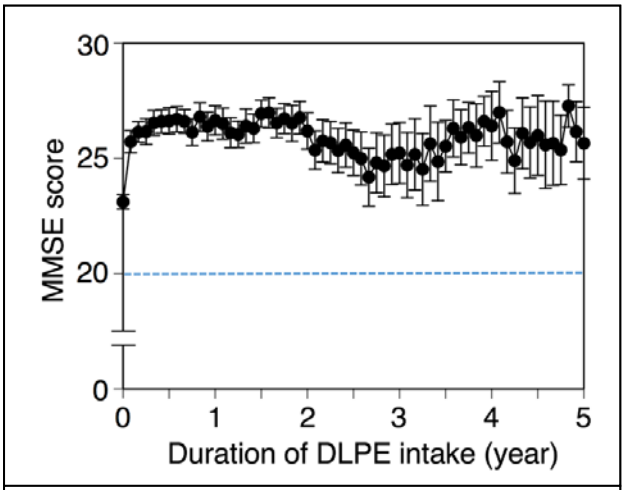

Figure 6: Time-course of the MMSE score. MMSE test was carried out before and after oral intake of lecithin containing DLPE (~0.9 mg) every day. In the graph, each point represents the mean (± SEM) MMSE score at the periods of time as indicated (n=41).

Conclusion

DLPE protected neuronal cells from ER stress- and senescence-induced apoptosis and ameliorated senescence-induced cognitive decline in cultured cells and an animal model. In the more than three years' follow-up surveys, the CT images showed no brain atrophy progression in thirty-five of 41 MCI patients (85%), who continuously took DLPE. This, in the light of

Table 1: Relation of MMSE score and brain atrophy.

Age/Sex	MMSE score		brain atrophy progression	Age/Sex	MMSE score		brain atrophy progression
74/M	21	30 (7 years later)	_	75/F	21	27 (4 years later)	_
80/F	22	28 (7 years later)	_	59/F	24	5 (3 years later)	+
81/F	26	29 (7 years later)	_	71/M	22	27 (3 years later)	_
75/M	26	29 (6 years later)	_	81/F	23	27 (3 years later)	_
74/F	20	30 (6 years later)	_	72/F	26	30 (3 years later)	_
70/M	21	27 (6 years later)	_	78/M	22	14 (3 years later)	+
75/M	22	29 (6 years later)	_	78/F	20	15 (3 years later)	+
74/M	24	24 (5 years later)	_	81/M	24	30 (3 years later)	_
69/F	21	14 (5 years later)	+	83/F	26	29 (3 years later)	_
76/F	25	26 (5 years later)	_	81/F	26	18 (3 years later)	_
71/M	23	29 (5 years later)	_	86/F	24	29 (3 years later)	+
77/F	23	26 (5 years later)	_	84/F	23	28 (3 years later)	_
82/F	22	18 (5 years later)	+	76/F	21	30 (3 years later)	_
80/M	20	28 (4 years later)	_	86/M	22	29 (3 years later)	_
72/M	20	28 (4 years later)	_	76/F	25	26 (3 years later)	_
78/M	25	30 (4 years later)	_	80/M	25	27 (3 years later)	_
83/F	21	30 (4 years later)	_	89/M	22	27 (3 years later)	_
81/M	24	30 (4 years later)	_	85/F	22	24 (3 years later)	_
61/F	26	29 (4 years later)	_	74/M	23	24 (3 years later)	_
85/F	25	25 (4 years later)	_	78/M	22	21 (3 years later)	_
78/F	21	24 (4 years later)	_				_

the fact that brain atrophy is attributed to neuronal cell death, indicates that DLPE has the potential to prevent neuronal cell death and brain atrophy progression. A rise or maintenance of the MMSE score was also found in thirty-five of 41 MCI patients (85%) without brain atrophy progression, who continuously took DLPE. This indicates that DLPE has the potential to prevent senescence-induced dementia. DLPE, thus, could become a promising preventive drug against the progress of MCI into AD.

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