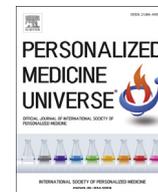


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Review

DL-/PO-phosphatidylcholine may shed light on the treatment of Alzheimer dementia

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ABSTRACT

Purpose: Thus far, no promising drug for Alzheimer disease has been developed. Previously, we documented the beneficial effects of 1,2-dilinoleoyl-*sn*-glycero-3-phosphocholine (DL-PC) and/or 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (PO-PC), which enhanced learning and memory abilities and improved cognitive disorders in both animals and humans. The present study reviews the usefulness of DL- and PO-PC for the treatment of Alzheimer dementia.

Study section and results: The anti-dementia effect of DL-PC, PO-PC, or DL-PC plus PO-PC was assessed in patients with cognitive decline and dementia by using the Mini-Mental State Examination (MMSE) test. The initial MMSE score for the patients was 17.4 ± 0.3 ; however, 1 month after taking DL- and/or PO-PC the score increased to over 20, corresponding to normal cognitive functions, and the effect was still evident in some subjects 5 years after taking DL- and/or PO-PC. Among the subjects in this study, 20 patients with Alzheimer disease had taken donepezil hydrochloride for more than 1 year. The MMSE score for those 20 patients was 11.8 ± 1.1 , and the score significantly improved to 19.9 ± 1.6 one year after stopping donepezil medication and instead taking DL- and PO-PC.

Conclusion: The results of the present study demonstrate that DL-/PO-PC could be an effective therapeutic agent for Alzheimer dementia.

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1. Introduction

Alzheimer disease is a tragic disease that is characterized by severe dementia in association with rapidly progressing brain atrophy. Several therapeutic approaches for Alzheimer disease have been attempted, yet no promising drug has resulted. Acetylcholinesterase inhibitors (AChEIs), such as donepezil, galantamine, and rivastigmine, have been clinically used for Alzheimer disease, but their effectiveness is limited only to an alleviation of Alzheimer disease symptoms [1]. Similarly, there is no evidence that memantine, a partial antagonist of *N*-methyl-D-aspartate (NMDA) receptor, is more effective than AChEIs in treating Alzheimer disease symptoms [1].

Abbreviations: DL-PC, 1,2-dilinoleoyl-*sn*-glycero-3-phosphocholine; PO-PC, 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine; MMSE, Mini-Mental State Examination; ACh, acetylcholine; AChEIs, acetylcholinesterase inhibitors; NMDA, *N*-methyl-D-aspartate; PLA₂, phospholipase A₂; PLD, phospholipase D; nACh, nicotinic ACh; LTP, long-term potentiation; LTD, long-term depression; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid.

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Accumulating evidence has pointed to the critical role of lipids in cognitive functions. The present study investigated whether the phospholipids 1,2-dilinoleoyl-*sn*-glycero-3-phosphocholine (DL-PC) and/or 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (PO-PC) are useful for the treatment of Alzheimer dementia.

2. Implication of DL- and/or PO-PC in cognitive functions

Phospholipids, which include phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol, are members of cell membrane components. Phosphatidylcholine is hydrolyzed into lysophosphatidylcholine and *cis*-unsaturated free fatty acids, such as arachidonic, oleic, linoleic, linolenic, and docosahexaenoic acid, by phospholipase A₂ (PLA₂) [2] (Fig. 1). Alternatively, phosphatidylcholine can be hydrolyzed into choline and phosphatidic acid by phospholipase D (PLD), followed by further hydrolysis of phosphatidic acid into lysophosphatidic acid and *cis*-unsaturated free fatty acids by PLA₂ [2] (Fig. 1). Among other effects, these hydrolysis products interact with nicotinic ACh (nACh) receptors. For example, *cis*-unsaturated free fatty acids potentiate nACh receptor responses to facilitate hippocampal

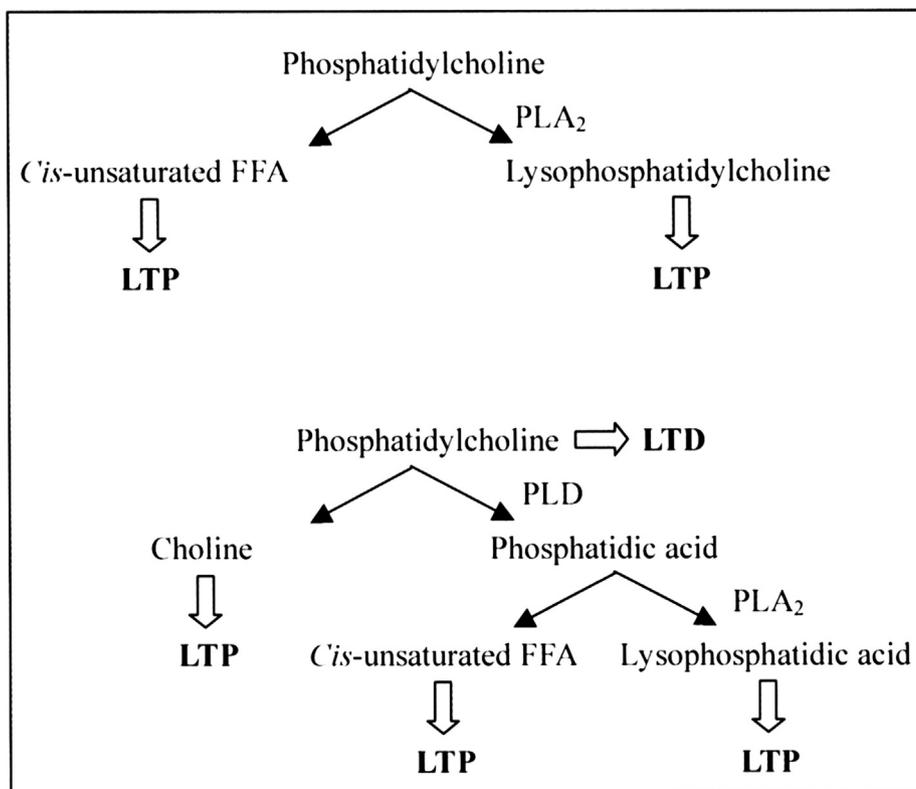


Fig. 1. Metabolic pathways for phosphatidylcholine and the role of phosphatidylcholine and metabolites in cognitive functions. FFA, free fatty acid.

synaptic transmission [3–6], while lysophosphatidylcholine and lysophosphatidic acid enhances the activity of nACh receptors [7,8] and choline serves as an $\alpha 7$ nACh receptor agonist [9].

$\alpha 7$ nACh receptor is preferentially localized on presynaptic terminals in the brain, where the receptor stimulates the release of neurotransmitters, including glutamate, and participates in the expression of long-term potentiation (LTP), a cellular model of learning and memory [10–16]. Accordingly, *cis*-unsaturated free fatty acids, lysophosphatidylcholine and lysophosphatidic acid could induce LTP by enhancing the activity of presynaptic $\alpha 7$ nACh receptor or activating the receptor (Fig. 1). Additionally, arachidonic acid serves as a retrograde messenger for LTP expression [17].

DL-PC potentiates $\alpha 7$ nACh receptor responses and induces LTP in an $\alpha 7$ nACh receptor-dependent manner [18]. This indicates that DL-PC could improve learning impairments. In contrast, PO-PC enhances long-term depression (LTD), another cellular model of learning and memory, in concert with decreased expression of the α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor subunit GluR1 on the plasma membrane [19] (Fig. 1). This indicates that PO-PC could improve memory disorders by enhancing LTD.

3. Anti-dementia action of DL- and/or PO-PC in humans

There is evidence to support the anti-dementia effect of DL- and/or PO-PC in humans [19,20]. While evaluating the MMSE score (maximum score, 30), a score of less than 20 corresponds to mild cognitive impairment and dementia. The MMSE test was carried out on 310 patients (135 males and 175 females) with cognitive decline and dementia aged 59–95 years (average, 76 ± 1 years). The initial MMSE score was 17.4 ± 0.3 (Fig. 2), and the score increased to over 20, corresponding to normal cognitive functions, 1 month after oral intake of DL-PC (100 mg/day), PO-PC (90 mg/day), or DL-PC

(50 mg/day) and PO-PC (45 mg/day), the effect being still evident in some subjects 5 years after taking DL- and/or PO-PC (Fig. 2). This indicates that DL- and/or PO-PC has the potential to ameliorate cognitive disorders. Notably, taking both DL- and PO-PC (DL/PO-PC) had a more beneficial effect on cognitive impairment than taking either DL- or PO-PC alone [20] (Fig. 3).

4. DL/PO-PC is more effective than donepezil at treating Alzheimer dementia

Here, we introduce data supporting the benefits of DL/PO-PC. Twenty patients (11 males and 9 females) aged 59–87 years (average, 77 ± 2 years) with Alzheimer disease had taken donepezil hydrochloride (3 mg/day) for more than 1 year, and the MMSE score at the first test ranged from 0 to 18 (Fig. 4A). Donepezil medication for those patients was stopped, and instead, patients took a combination of DL-PC (50 mg/day) and PO-PC (45 mg/day).

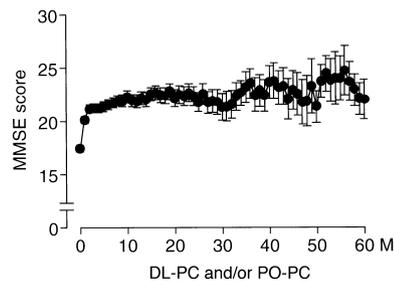


Fig. 2. Effect of DL- and/or PO-PC on cognitive disorders in humans. MMSE test was carried out before and after oral intake of DL-PC (100 mg/day), PO-PC (90 mg/day), or DL-PC (50 mg/day) and PO-PC (45 mg/day). In the graph, each point represents the mean (\pm SEM) MMSE score at the periods as indicated ($n = 310$).

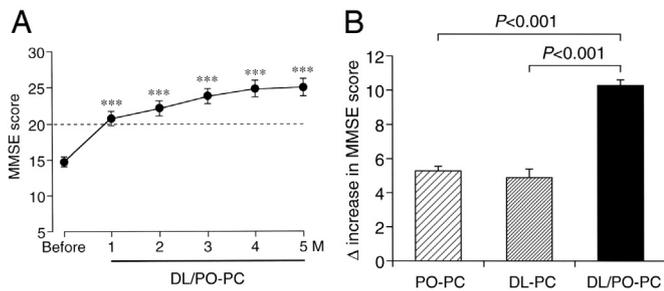


Fig. 3. Beneficial effect of DL-PC plus PO-PC (DL/PO-PC) on cognitive disorders in humans. MMSE test was carried out once a month before and after oral intake of DL-PC, PO-PC, or DL/PO-PC once daily after breakfast. (A) Each point represents the mean (\pm SEM) MMSE score at the periods as indicated for 75 subjects taking DL-PC (50 mg/day) and PO-PC (45 mg/day). *** $P < 0.001$ as compared with the score before DL/PO-PC (paired t -test). (B) An increase in MMSE score was calculated 5 months after taking DL-PC (100 mg/day) alone (21 subjects), PO-PC (90 mg/day) alone (214 subjects), and DL-PC (50 mg/day) plus PO-PC (45 mg/day) (75 subjects). Each column represents the mean (\pm SEM) MMSE score increase. P values, Dunnett's test.

Oral intake of DL/PO-PC significantly raised the MMSE score from 11.8 ± 1.1 to 19.9 ± 1.6 one year after beginning the treatment (Fig. 4B), but a smaller effect was observed for patients with an initial MMSE score below 10 (Fig. 4A). This implies that DL-/PO-PC has a more beneficial effect than donepezil in patients with Alzheimer dementia.

Finally, we present two very impressive cases. The first case was of an 86-year-old woman who had no history of donepezil medication. Initially, she could not draw a clock correctly and her MMSE score was 10. Surprisingly, after only 1 month of taking DL-PC (50 mg/day) and PO-PC (45 mg/day) she showed drastic

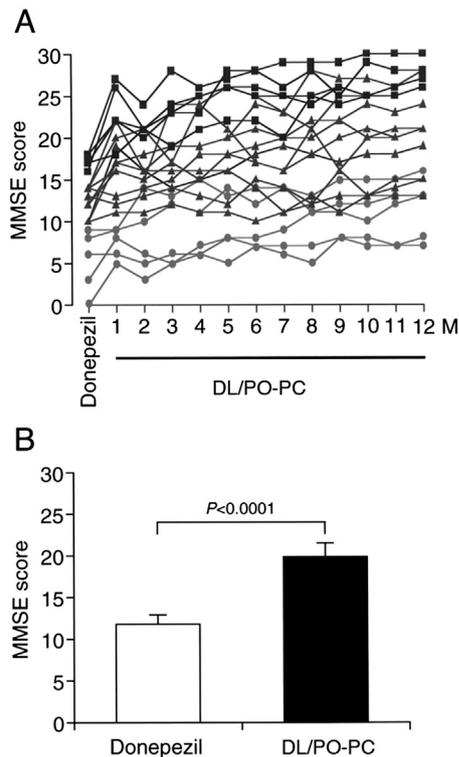
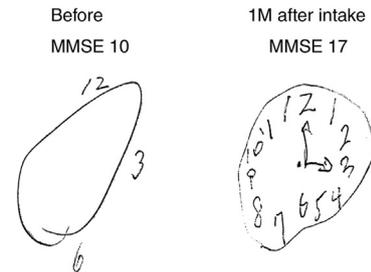


Fig. 4. DL-/PO-PC is more effective than donepezil in treating Alzheimer dementia. Donepezil medication for Alzheimer patients was stopped, and instead, patients took a combination of DL-PC (50 mg/day) and PO-PC (45 mg/day). (A) In the graph, each point represents the mean (\pm SEM) MMSE score at the periods as indicated ($n = 20$). (B) In the graph, each column represents the mean (\pm SEM) MMSE score before (Donepezil) and 12 months after taking DL-PC (50 mg/day) and PO-PC (45 mg/day) orally ($n = 20$). P value, unpaired t -test.

A. Case 1 (86 years old, female)



B. Case 2 (71 years old, male)

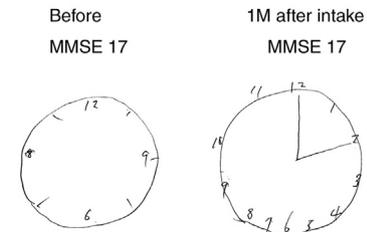


Fig. 5. Example drawings of a clock from two patients who exhibited a drastic improvement after taking a combination of DL-PC (50 mg/day) and PO-PC (45 mg/day) orally.

improvement; she was able to draw a clock correctly, and her MMSE score increased to 17 (Fig. 5A). The second case was of a 71-year-old man who also had no history of donepezil medication. In the initial test, he arranged the numbers of a clock counterclockwise and scored a 17 on the MMSE. Again, after 1 month of taking DL-PC (50 mg/day) and PO-PC (45 mg/day) orally, he could draw a clock correctly, and scored 17 on the MMSE (Fig. 5B). These cases further support the notion that DL-/PO-PC is useful for the treatment of Alzheimer disease.

5. Conclusion

There is definite evidence that DL-/PO-PC is capable of improving dementia including Alzheimer dementia. Accordingly, DL-/PO-PC could be a promising therapeutic agent for Alzheimer dementia.

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