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Soy Lecithin-Derived Phosphatidylserine Plus Phosphatidic Acid: Effects on Brain Functions in Elderly Patients with Alzheimer's Disease and Dementia

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Abstract

Phosphatidic acid (PA) and phosphatidylserine (PS) and are natural constituents of healthy brain cell membranes, which have been recognized since the 1970s as essential to normal neuronal functioning. PA is a precursor in the formation of other phospholipids, including PS and phosphatidylethanolamine (PE). Also, it has an impact on membrane rigidity/flexibility, which is important in modulating exo- and endocytosis. PS is also an important precursor for PE synthesis. Since PS predominantly occurs in brain cells, but normal diets do not include the consumption of brains, PS is available to our brains mostly via natural "production" in our bodies.

Here, we present a tabulated literature survey of clinical studies on PS and/or PA regarding brain function in elderly people. In addition we give a summary on two of our our already published pilot studies performed with a brain-health food supplement containing a proprietary blend of 100 mg PS and 80 mg PA produced from soy lecithin: A three-month double-blind, placebo-controlled study demonstrated the positive influence of three PS+PA capsules/day, (300 mg PS+240 mg PA per day; n=40)) or placebo (n=32) on memory and mood in functioning, non-depressive elderly people with memory problems. In a two-month randomized, double-blind, placebo-controlled study, three PS+PA capsules/day (300 mg PS+240 mg PA per day; n=56) or placebo (n=40) improved daily functioning, mental health, emotional state, and self-reported general condition in patients with Alzheimer's disease (AD).

Altogether there is encouraging clinical data that PS+PA supplementation could be beneficial to AD patients and other elderly people with memory or cognition problems. Long-term studies are, however, still lacking.

Keywords: Alzheimer's disease; Cognition; Daily functioning; Dementia; Elderly; Memory; Mood; Phosphatidic acid; Soy lecithin-derived phosphatidylserine; MemreePlus™

Phosphatidylserine (PS) and Phosphatidic Acid (PA) in Memory

The membrane phospholipids phosphatidic acid (PA) and phosphatidylserine (PS) are essential to cellular functioning, acting as a biological detergent, keeping fatty substances soluble and cell membranes flexible [1,2]. During the pathogenesis of several age-related neurodegenerative diseases, including Alzheimer's disease, the neuronal membrane lipid composition is altered in the brain [3,4]. Also, the lipid raft composition appears to be altered in neurodegenerative diseases [5].

PS (and PA), produced by enzymatic conversion of soybean lecithin, avoids possible regulatory and safety issues regarding bovine spongiform encephalopathy. Soy lecithin-derived PS is absorbed and metabolized, with elevated serum levels for at least 1.5 hours after an oral dose, as has been shown within a kinetic study on 8 human volunteers. The baseline serum level of PS in relation to the level of total serum phospholipids was around 2%. 30 minutes after ingestion, it started to increase, peaking at 90 minutes after intake at around 4%, and returning to the basal level 180 minutes after intake [23].

Recently, oral administration of phosphatidylcholine/phosphatidylethanolamine (PE) -transphosphatidylated PS has been shown to improve memory impairment in aged rats [6]. Also, other experiments have shown an improvement in memory, learning capacity, and other cognitive parameters in PS-supplemented rodents [7-11]. This is plausible, since PS was found to stimulate neurotransmitter release [7,12], increase brain glucose metabolism [13,14] and reduce oxidative stress in the brain [15].

In clinical studies, PS-containing preparations were found to selectively dampen stress levels [16-18], improve learning and perception parameters in children with attention deficit hyperactivity disorder (ADD) [19,20], and improve calculation speed of athletes [21]. Table 1 summarizes previously performed studies on PS and/or PA regarding brain function in the elderly.

Summary of Two Previously Published Pilot Studies on PS & PA

In the following, we summarize the clinical results from a recent publication on clinical effects of dietary soy lecithin-derived PS+PA supplementation (manufactured by Lipogen Ltd. (Haifa, Israel) within two placebo-controlled studies on elderly people with memory impairment or dementia [23]. These studies were performed between 1992 and 1999, and were, to our knowledge, the first studies performed with plant-derived PS. For both studies, informed consent of the participants was obtained, and the studies complied with the Helsinki Declaration of 1996. However, an ethics committee vote was omitted since it was not mandatory at the time.

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Publication	Study design	Duration	Participants	Oral dosage	Brief outcome summary
Zhang et al., 2015 [22]	Controlled study	12 weeks	57 AD patients	300 mg/d of PS or placebo	In AD patients, vocabulary and picture matching scores in the two treatment groups increased after treatment. Moreover, the scores in the treated group were significantly greater than the control group.
Moré at al., 2014 [23] (study in 1992), Study 1 summarized below	Randomized, placebo-controlled, double-blind study	3 months	72 functioning, non-depressive elderly (60–80 years)	Soy derived: 100 mg PS+80 mg PA in lecithin tid or placebo	Significant positive influence of PS on memory and mood in pre-post comparison
Moré at al., 2014 [23] (study in 1995), Study 2 summarized below	Randomized, placebo-controlled, double-blind study	2 months	96 patients with AD (50–90 years)	Soy derived: 100 mg PS+80 mg PA in lecithin tid or placebo	Significant positive effect on daily functioning, positive trends on emotional state and on self-reported general condition, no adverse effects
Moré at al., 2014 [23] (study 1991-1999)	Historical prospective data (discussed)	2 months to 13 years (mean 1.4 ± 1.8 years)	68 patients with AD, dementia, or memory loss (44–92 years)	Soy derived PS+PA supplementation	No adverse effects, significant positive influence of PS in most cognitive categories in pre-post-comparison
Richter et al., 2013 [24]	Open label	12-weeks	30 elderly volunteers with memory complaints (50-90 years)	Soy derived PS (100 mg tid)	PS showed favourable effects on cognitive function
Kato-Kataoka et al., 2010 [25]	Randomized, double-blind placebo-controlled study	6 months	78 elderly people with mild cognitive impairment (50–69 years)	Soy derived PS (100 mg tid) or placebo	The supplemented subgroup with low memory scores significantly improved regarding memory, compared to baseline, while elderly in the placebo group remained unchanged
Jorissen et al., 2001 [26].	Randomized, double-blind placebo-controlled study	12 weeks	120 aged patients with AAMI (>57 years) (*n*=41, PS-group)	100 mg soy derived PS 6 times daily or placebo	No significant cognitive improvements in any group
Schreiber et al., 2000 [27]	Open label	12-weeks	18 AAMI patients (65-78 years)	plant derived PS (100 mg tid)	Significant positive effects on cognition
Heiss et al., 1994 [13]	Controlled study	6 months	70 probable AD patients	2 x 200 mg/day PS +cognitive training or pyritinol 2 x 600 mg/day +cognitive training or cognitive training only, or social support only	PS treatment had an effect on different measures of brain function, with best effects after 8 and 16 weeks.
Cenacchi et al., 1993 [28]	Randomized, double-blind placebo-controlled study	6-month	494 cognitively-impaired elderly (65-93 years)	300 mg bovine brain-derived PS daily or placebo	Significant improvement in behavioural and cognitive parameters in the supplementation group
Engel et al., 1992 [29]	Double-blind cross-over study	8 weeks (8 week washout between treatments)	33 patients with mild primary degenerative dementia according to DSM-III	Bovine brain derived PS (300 mg/d) versus placebo	PS reduced the higher power values compared to placebo, shifting EEG power more towards the normal level.
Crook et al., 1991 [43]	Randomized, double-blind placebo-controlled study	12-week	149 aged patients with AAMI (50-75 years)	100 mg bovine brain-derived PS tid or placebo	Supplemented subgroup with low level performance improved, relative to placebo in daily life learning and memory tasks
Fünfgeld et al., 1989 [30]	Open label	Up to 18 months	Parkinsonian patients with senile dementia of Alzheimer's type (SDAT).	Bovine brain derived PS (300 mg/d) versus placebo	A therapeutic effect of PS was observed: acceleration of a slowed EEG
Villardita et al., 1987 [31]	Randomized, double-blind placebo-controlled study	3 months	170 aged patients with AAMI (55-80 years)	bovine brain-derived PS, 300 mg daily or placebo	Improvement on neuropsychological tests in the PS-supplemented subjects relative the placebo group
Delwaide et al., 1986 [32]	Randomized, double-blind placebo-controlled study	6 weeks	42 hospitalized demented patients	3 x 100 mg bovine brain derived PS versus placebo	There was a trend toward improvement in the PS treated patients; analysis of covariance showed a significant treatment effect on the Peri Scale

AD Alzheimer's disease, AAMI, Age associated memory impairment, PA Phosphatidic acid, PS Phosphatidylserine, tid Three times daily.

Table 1: Overview of clinical studies on PS and/or PA regarding brain function in elderly.

Study 1: Effect of PS+PA on memory and mood in functioning elderly

In 1992, elderly male and female residents (aged 60–80 years) of three Israeli rural collective communities (Kibbutzim Givat Brenner, Gat, and Galon), with memory problems in daily life were randomly included in this placebo-controlled study. The subjects were not demented, achieving at least 25 out of 30 on the Folstein Mini-Mental State Examination (MMSE) [33]. Also they were not depressed or suffering from any major disease, and were not taking medication with influence on memory.

For 3 months, the subjects took soy lecithin-derived PS (100 mg) and PA (80 mg) ("L-Telect", Lipogen Ltd., Haifa, Israel; similar to current Lipogen PS Plus™ & MemreePlus™) tid (40 ITT/31PP subjects) or placebo (500 mg lecithin) (32 ITT/26 PP subjects) to evaluate effects

on memory performance. The Wechsler Memory test (WMT; without age correction) was used to examine memory, learning, association, and information gathering as distinct from intelligence [34]. Both placebo and PS+PA group had (as expected) a significant test-retest improvement in total WMT scores in the testing at the end of the study (P<0.005). However, the PS+PA group, compared to the placebo group, reached a higher degree of significance, see Figure 1A. In pre- and post-comparison of components of the memory test, none of the placebo group's changes were statistically significant – in contrast, results for maintaining information, visual memory, and memorizing numbers improved with a statistical significance of P<0.05 within the PS+PA group.

When comparing the scores between groups, only trends in favour of the PS+PA group could be observed, possibly due to the rather small study size and its relatively short duration. However, subjects on PS+PA supplementation with a high initial WMT score showed more significant memory improvements, whereas those who had scored low did not, see Figure 1B.

Mood was additionally tested using the LDS [35]. The resulting score was also used to exclude those with a score of <17 during recruitment. Subjects in the PS+PA group did not have any significant mood changes from baseline (late summer/early fall) to the end of the study in (late fall/winter), however in the placebo group a seasonally expected mood deterioration was observed (P<0.001 in pre-post comparison). This is consistent with a different report that PS had a positive effect on geriatric depression [36].

Study 2: Effect of PS+PA on daily functioning and general condition in 96 patients with AD

A two-month double-blind, randomized, placebo-controlled trial was performed on patients diagnosed with definite-probable AD (Alzheimer's Disease and Related Disorders Association) in 1995. Men and women aged 50-90 years were recruited from the Kaplan Medical Centre (Rehovot, Israel), from kibbutzim near Rehovot, and the Israel Association of Alzheimer's Disease. 56 patients were allocated to 100 mg of PS+80 mg PA mixed with lecithin tid ("L-Telect", Lipogen Ltd., Haifa, Israel) (53 PP patients); 40 patients to placebo (starch) (39 PP patients). The two randomized groups were comparable at baseline.

PS+PA had clear beneficial effects in patients with dementia, especially if the expected gradual cognitive deterioration is taken into consideration:

The 7-ADLs functioning index includes general self-reporting and scoring of activities of daily living (Table 2) [48]. In the PS+PA group, no progression of the deterioration of daily functioning was observed, compared to a decline in the control group (P=0.039).

The Folstein MMSE [33] was used to examine the mental status before and after supplementation. A slight and non-significant improvement in both groups (P=0.872) could be detected. 23.5% of the PS+PA group showed an improvement from abnormal (≤ 23) baseline scores to normal scores (<23) following supplementation, compared to 4 of 35 (11.4%) in the placebo group. Also, a positive trend in favour of the PS+PA group (P=0.156) could be observed when comparing the means of the index of emotional state (simplified Tel-Aviv University Rosen Target Detection Test [35]).

Another positive trend was observed in the self-reported general condition: 49.0% of the PS+PA group reported an improvement compared to 26.3% in placebo group (P=0.084).

A post-trial (patient-funded) consumption rate of 42.9% of the PS+PA group (6 of 14 assessed patients) *versus* 0 of 11 placebo patients (P=0.010) additionally indicated the beneficial effects of PS+PA in patients with AD. It should be noted that another 3 assessed patients were unable to continue consumption because of inability to purchase PS+PA.

PS+PA had an excellent tolerability: 88.2% of the patients on PS+PA and 91.1% on placebo did not report any side effects. The remaining could either not remember or had sensations which could not be correlated to the supplementation.

Altogether, the published results [23] suggest that PS+PA can

Before-after comparison			
	PS+PA	**Placebo**	***P* value**
Baseline	6.23 ± 1.98	5.62 ± 2.42	0.433
After 2 months	6.23 ± 2.19	4.90 ± 3.00	0.021
Difference	0.00 ± 0.52	-0.72 ± 2.05	0.039
Change pattern analysis			
	PS+PA	**Placebo**	***P* value**
Deterioration	3.8%	17.9%	0.066 *(positive trend in favour of PS+PA)*
Stability	90.6%	79.5%	
Improvement	5.6%	2.6%	
7-ADL 7 activities of daily living, PA Phosphatidic acid, PS Phosphatidylserine.			

Table 2: Comparison of 7-ADL functioning index (Study 2), adapted from [23].

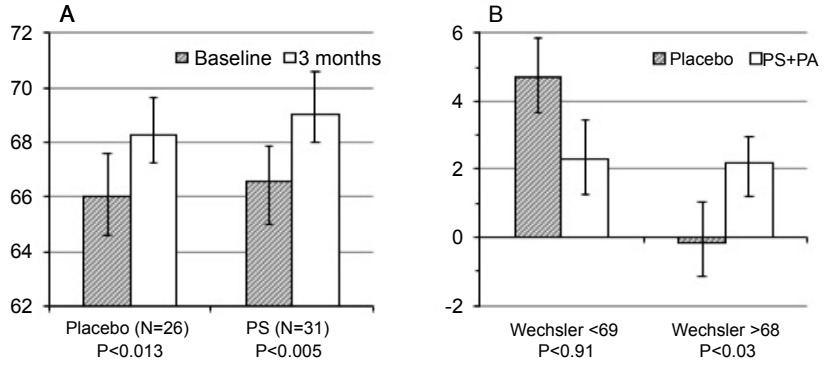

Figure 1: a) The PS+PA group, compared to the placebo group, reached a higher degree of significance, b) Subjects on PS+PA supplementation with a high initial WMT score showed more significant memory improvements. Study 1, adapted from [23]. Study 1, adapted from [23].

support memory and cognitive function, especially in people with cognition and memory deficiencies. Possibly, significance in some of the parameters was not reached due to the short study duration and the limited sample size. Similarly, encouraging results were also published in a number of other studies (Table 1).

Discussion

Regarding elderly people with memory impairment or dementia, there are promising clinical data, especially for the supplementation of PS (Table 1). In addition, there is an emerging understanding on how the phospholipid pattern is linked to brain function, or its decline: Mild cognitive impairment and AD have been linked to oxidative stress and corresponding lipid peroxidation within the brain [37]. Oxidative stress on neuronal membranes also has a detrimental effect on synaptosomal PS asymmetry, which is normally maintained by the ATP-requiring enzyme flippase [38]. Accordingly, the appearance of PS in the outer membrane leaflet is a signal of synaptosomal apoptosis, which was also observed in brain post-mortem autopsies of patients with mild cognitive impairment and AD [39]. Next to the PS distribution, also its overall level is likely to have an impact: In PC12 cells with induced apoptosis, a reduction in the level of PS was detectable before the detection of apoptosis [40].

The supplementation of PS may also have an impact on PE levels, since in mammalian cells PE is synthesized also by PS decarboxylation in the mitochondria [41]. PA is not only a precursor for other phospholipids, but also plays a pivotal role by influencing membrane fluidity, which is especially important for vesicle formation, e.g. during neurotransmission [42]. However there is only limited clinical evidence regarding PA supplementation in elderly people with dementia or age associated memory impairment.

Altogether, long-term investigations on PS+PA supplementation are needed. In most countries, regulatory issues prevent the supplementation of PS+PA for patients with AD, since this is a medical indication – this problem could only be solved by adapting regulations, or by including PS and PA into a drug product, and filing a full drug dossier, which in turn will require more extensive clinical studies.

Author Contributions and Conflict of Interest

The results on plant derived PS+PA were previously reported [23].

Here, we summarize our main findings and give an update on related literature. The authors cooperated on writing this article. D. Rutenberg in an employee of Lipogen Ltd (Haifa, Israel), M. I. Moré, is an employee of analyze & realize GmbH, Berlin, Germany.

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