Phosphatidylserine; Membrane Nutrient for Memory. A Clinical and Mechanistic Assessment

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Abstract

Working in the cell membrane milieu, phosphatidylserine (PS) is a nutrient that supports membrane proteins crucial for homeostasis, maintenance, and specialized cell functions. PS is found most concentrated in the brain, where its relative abundance reflects its involvement in specialized nerve cell functions such as chemical transmitter production and release, receptor action, and synaptic activity.

The fundamental contributions of PS to the structure and function of individual nerve cells are expressed in the performance of the brain as a whole. More than 35 human studies that span almost 3 decades, together with numerous animal studies, indicate PS supports EEG integration, the HPAA (hypothalamic-pituitary-adrenal axis), and circadian rhythms of hormone release. Some sixteen clinical trials indicate that PS benefits measurable cognitive functions which tend to decline with age; these include memory, learning, vocabulary skills and concentration, as well as mood, alertness, and sociability.

PS is a phospholipid, ubiquitous in membranes and obligatory for all the cells of the body. Present in common foods in small amounts, PS may be a semi-essential nutrient. Although it can be synthesized in vivo from precursors, its multistep biosynthesis is energetically costly.

Until recently, supplemental PS was available only from bovine brain. Now PS is available as a soy lecithin-based concentrate. With its proven benefits against age-related mental decline, phosphatidylserine might represent a truly safe and effective means for improving the quality of life of the elderly.
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The progressive loss of mental agility with age has become a major focus of basic and clinical research efforts. Beginning around midlife, the brain's higher functions of memory, learning, semantic manipulation, and concentration (collectively referred to as cognition) measurably begin to fade. The ancient writer Virgil put it best in 70 B.C.: "Age takes away all things, even the mind." An impressive body of human studies with PS, published over a span of almost 3 decades,[1-35] now makes possible an optimistic approach to conserving those brain functions that decline with age.

Over the adult life span, individuals who are otherwise healthy can lose as much as half of their cognitive capacities, as measured from tests related to everyday tasks that rely on cognitive skills.[36-38] Such progressive and insidious loss of the brain's higher functions can have a telling effect on personal productivity, damage self-esteem, and bring considerable distress to many aging adults.

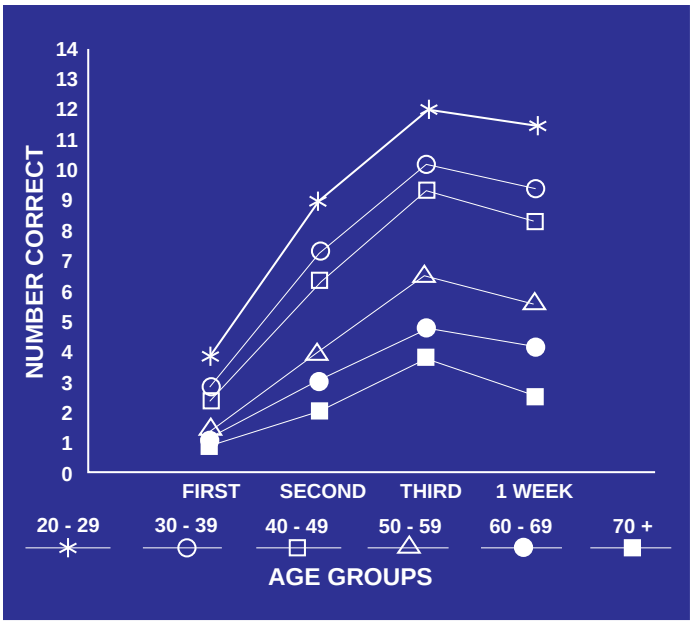

FIGURE 1. The age-related decline in name-face acquisition and recall, representing the ability to learn and recall 14 name-face combinations in 3 attempts on Day 1 and 1 week later. From Crook et al.[36]

Phosphatidylserine (PS) is one of the five phospholipids essential to the functionality of all the body's cells. All the phospholids contribute to the structural matrix of cell membranes,[39] but PS is unique in that it regulates the functional state of key proteins of cell membranes.[40-47] PS facilitates membrane-to-membrane fusion, a central process in nerve transmitter release;[48] and by activating cell surface receptors[49-51] supports signal transduction, the process through which the cell responds to chemical signalling substances.

Cognitive Decline, Stressors, and Lifestyle

Cognitive decline with aging is to some degree inevitable (see Figure 1). In the otherwise healthy person it is called Age-Related Cognitive Decline, or ARCD. This formally non-pathologic, "normal" condition, formerly termed Age-Associated Mental Impairment, in its severity correlates roughly with progressive decline of nerve net density in the hippocampus and the cortex. Some persons experience a decline that is accelerated over the "normal" ARCD situation, resulting in minimal cognitive function by the time life ends. By midlife, this population performs more poorly on cognitive tests and has lower than normal nerve net density. Such individuals are more likely to be at risk for pathologic dementia in later life.

Thomas Crook, PhD, and his collaborators at the Memory Assessment Clinics (MAC), pioneered over 20 years the non-pathologic definition of ARCD.[36,37] MAC currently has a battery of tests that are objective, statistically precise, and referrable to everyday, commonsense activities. These tests are completed by the subject with the help of video presentations that do not require computer sophistication. They have been validated across cultures, and are currently the "state of the art" in cognition assessment.

The MAC battery of cognitive assessment tests includes:

- **Name-Face Recall**. Learning and matching of names with faces

- **First-Last Names**. First and last names presented, then last names given for pairing with the first names. Also assesses verbal memory
- **Face Recognition**. A test of visual memory
- **Grocery List**. To help assess verbal learning and memory
- **Telephone Dialing**. Memorize and retaining a telephone number, under different conditions of delay and distraction
- **Misplaced Objects**. Placement and recall of keys, glasses, other common household objects—"verbal-visual associative memory"
- **Divided Attention**. Simulates driving a car, also recall of radio reports while driving. Reaction time and verbal-vocabulary memory

Total, or near-total, breakdown of mental functions is neither strictly age-related nor an inevitable accompaniment of aging.[52,53] Many negative lifestyle factors can adversely affect the brain and contribute to cognitive decline.[53] Heavy metals and free-radical stressors can destroy brain tissue. Smoking and alcohol intake are other major negative factors. Alcohol damage to memory is well documented: one drinking binge can initiate memory impairment that continues for days afterward, and drinkers can develop a dementia as debilitating as other dementias. Sustained emotional stress is known to impair memory. Nutrient deficiencies can impair the higher mental faculties, and food additives currently in widespread use can be sources of excitotoxins (e.g., monosodium glutamate, aspartame) that destroy neurons over the long term. Substance abuse (cocaine, amphetamines, psychedelics, and to some extent marijuana) also will impair the brain's higher functions.

More than 35 clinical trials and related human studies have been conducted with PS in the United States and in Europe; of this number, 16 were double-blind studies.[1-16] (see Table 1)The findings from the clinical trial data are promising: dietary supplementation with PS can alleviate, ameliorate, and sometimes reverse, age-related declines in memory, learning, concentration, and mood.

Double-Blinded Cognition Trials with Phosphatidylserine

To date (mid-1996), PS is the best-studied nutrient for prevention of cognitive decline. Most of the trials were on subjects who had experienced measurable losses in memory, judgment, abstract thought, and other higher mental functions, and sometimes also psychomotor deterioration and changes in personality and behavior. So far, 11 double-blind, randomized, placebo-controlled trials have been performed using PS for cognition.

Two of these double-blind cognition trials with PS were conducted primarily in the United States. Both were multicenter efforts, coordinated by Crook and collaborators of the MAC.[3,4] The 1991 trial focused on cognitive impairments associated with "normal" aging.[3] One hundred and forty-nine (149) subjects (ages 50-75 years) were studied. PS was given at 300 mg per day (100 mg 3 times per day), versus a placebo, for 12 weeks. Assessments were done at baseline, then at week 3 after beginning dosing, week 6, week 9, week 12, and lastly at week 16. Compliance was good, and PS was well tolerated. By week 3, trends in 3 of the 5 primary variables all favored PS:

- Learning names and faces (Name-Face Acquisition)
- Recalling names and faces (Name-Face Delayed Recall)
- Facial recognition (Delayed Non-Matching)

TABLE 1.

Double-Blind Clinical Trials with Phosphatidylserine

1.	Amaducci et al, 1988	142 subjects	200 mg/day vs. placebo	Benefited memory, verbal ability, daily living
2.	Cenacchi et al, 1993	425 subjects	300 mg/day vs placebo	Benefited memory, learning, adaptability
3.	Crook et al, 1991	149 subjects	300 mg/day vs placebo	Benefited memory, global clinical in subgroup
4.	Crook et al, 1992	51 subjects	300 mg/day vs placebo	Benefited memory, global clinical in subgroup
5.	Delwaide et al, 1986	35 subjects	300 mg/day vs placebo	Benefited daily living
6.	Engel et al, 1992	33 subjects	300 mg/day pl/crossover	Gave global clinical benefit
7.	Funfgeld et al, 1989	62 subjects	300 mg/day vs placebo	Reduced anxiety, improved mood
8.	Gindin et al, 1995	72 subjects	300 mg/day vs placebo	Benefited memory, improved mood
9.	Maggioni et al, 1990	10 women	300 mg/day pl/crossover	Improved memory, anxiety, concentration, sociability
10.	Monteleone et al, 1990	8 men (exercising)	50, 75 mg iv vs placebo	Reduced stress hormone production
11.	Monteleone et al, 1992	9 men (exercising)	400/800 mg vs placebo	Reduced stress hormone production (at 800 mg/day)
12.	Nerozzi et al, 1987	48 subjects	300 mg/day vs placebo	Benefited memory
13.	Palmieri et al, 1987	87 subjects	300 mg/day vs placebo	Benefited memory, learning, sociability, daily living
14.	Ransmayr et al, 1987	39 subjects	300 mg/day vs placebo	Improved discrimination of flickering light
15.	Rosadini et al, 1991	8 men	25/50/75 mg iv vs placebo	Boosted EEG alpha rhythm (at 50, 75 mg)
16.	Villardita et al, 1987	170 subjects	300 mg/day vs placebo	Benefited memory, learning, verbal ability, concentration

A subgroup of 57 subjects who were relatively more memory-impaired, and slightly older (64.3 average age) seemed to benefit more from PS. This subgroup was markedly improved on the MAC battery at week 12, and showed global improvement in cognitive status, as assessed from detailed interviews conducted "blind" by trained interviewers. Four weeks after they were taken off PS, they were still performing better on 5 measures (all statistically significant, $p \leq 0.05$):

- Facial Recognition
- Misplaced Objects Recall
- Telephone Number Recall
- Paragraph recall
- Ability to concentrate

Encouraged by these findings, the investigators returned to their data to attempt to answer a crucial question: *What meaning, if any, do these findings have for the subjects' quality of life?* They took as their model the parameter name-face acquisition. They calculated that for the older, more affected subgroup, PS had "rolled back the clock" by roughly 12 years. In other words, from being at an average "cognitive age" equivalent to the average 64-year-old, these subjects were restored on average to a cognitive age of 52. This can scarcely be called a reversal of age-associated memory impairment by PS, but in the authors' words, "The magnitude of effect may be considered significant by many subjects and clinicians." [3]

The second U.S. trial by Crook and the MAC enrolled fifty-one (51) subjects.[4] They were older (55-85 years, average 71 years), and more severely afflicted than in the first study. This study was also conducted double-blind and randomized, with 300 mg PS given daily versus a placebo for 12 weeks. Assessments occurred at 3, 6, 9, and 12 weeks. No post-dosing followup assessment was done.

By week 12, the PS-treated subjects showed the following improvements (all statistically significant, $p < 0.05$):

- Memory for names of familiar persons; names of clinic staff
- Recall of the location of frequently misplaced objects
- Recall of details of events from the previous day
- Recall of details of events from within the past week

Using similar statistical sorting techniques as in the previous study, the authors again identified a subgroup of subjects who derived additional benefits from PS. These subjects had relatively mild cognitive impairment at the outset, as compared with the whole group entering the study. This less-afflicted subgroup benefited significantly on the 5 variables listed above, and on two others:

- Ability to maintain concentration
- Two measures of overall global improvement in cognitive status

To this group the benefits from PS were apparent as early as three weeks into the study. The findings from this trial suggest, as with the previous MAC trial, that PS can benefit cognitive functioning in subjects over the age of 50 who are in relatively early stages of cognitive decline.

The additional double-blind studies with PS on cognition were conducted in Europe. Delwaide and collaborators concluded, "...the changes observed reflect an improvement in behavior which can be useful for subjects and their families." [5] Palmieri and collaborators[13] stated, "Phosphatidylserine appears to exert an action in two distinct contexts: one relating to the cognitive effects of vigilance, attention, and short-term memory, and the other relating to behavioral aspects such as apathy, withdrawal and daily living.... The observed effects...improve the quality of life and contribute in keeping them within their own families and social background." Villardita and collaborators[16] concluded that PS can benefit both attention and arousal processes upon which might rest the more complex cognitive mechanisms.

PS can benefit cognition at daily intakes lower than 300 mg. In a multicenter trial in Italy, Amaducci et al[1] enrolled 142 subjects 40-80 years of age. The dosing period was only 3 months, but a major finding from this trial was that PS could "break through" after the subjects stopped taking it, to produce benefits that reached statistical significance as much as 3 months later despite a daily PS intake of only 200 mg per day (2 x 100 mg).

The trial by Cenacchi and collaborators, published in 1993,[2] was the largest and longest ever conducted with PS. It recruited at 23 institutions in northern Italy, and involved a large number of investigators. The 425 subjects, ages 65-93 (average age 77+ years), all had moderate to severe cognitive decline. They received PS at 300 mg per day or placebo for six months. After statistical analysis, the scores for Activities of Daily Living were not significant, while withdrawal and apathy were significant improved ($p \leq 0.01$). The memory and learning scores (BSRT) were also highly significant ($p < 0.01$) in favor of PS.

Cenacchi and his collaborators concluded, "The resulting improvements in adaptability to the environment can have an important impact on the quality of life of such patients." [2]

The other European trials with PS for cognitive function were not conducted double-blind, yet produced results consistent with the double-blind studies. In summary:

1. Cognitive decline, mild: improved short-term memory, mood and behavior (Caffara and Santamaria, open trial[17]);

2. Cognitive decline, mild: improved attentive function and social interest (Sinforiani et al, open trial[18]);

3. Cognitive decline, mild-moderate: improved memory and recall, improved socialization and participation (Granata and Michele, open trial[19]);

4. Cognitive decline, mild-moderate: improved cognition and behavior (Puca et al, exploratory open trial[20]);

5. Cognitive decline, moderate: global improvement (Allegro et al, open trial[21]).

In two small trials, Cocito and collaborators investigated PS in combination with GABA (gamma-amino-butyric acid) against epilepsy.[33,34] They concluded that epileptics could possibly benefit from PS, but only through chronic administration.

Global—Physiological Effects of PS on Brain Function

In a European double-blind trial, Ransmayr and collaborators[14] worked with elderly subjects and documented improved brain physiology (flicker-fusion frequency) from PS. This test parameter has been linked to improved vigilance, concentration, and motor reaction. Subsequent studies, particularly with EEG (ElectroEncephaloGraphy) indicate PS might globally enhance brain performance.

Quantitative EEG methods are now widely used to provide information about the brain as whole organ. Rosadini and collaborators[15] used EEG to study the effects of PS in eight male volunteers aged 21-28 years. Baseline EEGs were done, then PS was administered intravenously and double-blind. PS boosted the alpha rhythm an average 15-20 percent without detectable adverse affects. This EEG rhythm is most indicative of acetylcholine-cholinergic activity in the brain; in aging and cognitive deterioration it is often abnormally lowered.

EEG can be particularly informative when combined with neuropsychological testing. Engel and coworkers[6] did a double-blind study on 33 subjects with mild cognitive deterioration. Subjects were orally supplemented with 300 mg PS daily, or with placebo. The trial had a crossover design: both dosing phases lasted 8 weeks, with an 8-week "washout" period between. PS boosted EEG "power" values up towards the normal level, and more of the PS subjects benefited on the clinical global improvement ratings. The benefits of PS persisted through the ensuing washout and dosing phases.

PET (Positron Emission Tomography) and related "imaging" techniques, which measure regional energy states in parts of the brain, have been used to abjectively evaluate the effects of PS.[22-24] PET generates dramatic metabolic "maps" of the whole brain, complete with semi-quantitative color gradations. PET has now become sufficiently refined to detect subtle variations in glucose metabolism, and used correctly it can provide a semi-quantitative "map" of brain activity as a whole. PET

and other state-of-the-art imaging can help detect and "track" cognitive decline without invading the body or seriously inconveniencing the subject under study.

Heiss and collaborators[22] successfully employed PET to correlate clinical cognitive impairment with impaired brain metabolism. They did a controlled clinical trial on 40 subjects with mild to moderate cognitive impairment. After neuropsychological testing, brain metabolism was periodically mapped by PET. All the subjects began the trial with abnormally low resting brain metabolism; over the 6 months of the study only the group given PS (4 x 100 mg per day) did not decline further on their tests or in their resting brain metabolism, as mapped by PET.

The Heiss trial[22] also utilized a new approach, namely *Activation PET*: mapping with PET while the subject is taking a test. As the subject proceeds with the test, the brain "lights up" on PET, its metabolism becoming increased or "activated." PS subjects showed a significantly greater degree of activation than did subjects not given PS. Also, the superior activation by the PS group was accompanied by significant improvements on their test performances. Data on a representative 10 subjects from each group indicated that PS stabilized cognitive decline for the six months of the study, while also stabilizing resting brain metabolism and boosting brain activation. However, another paper from the Heiss team reported that the PS effect faded after the 4-month timepoint. They suggested progressive pathological changes in this particular patient sample might have "overcome" the PS effect.[23]

Phosphatidylserine Effects on Adaptability and Mood

PS can benefit brain dysfunctions other than the strictly cognitive. In an exploratory open trial by Fünfgeld and Nedwidek[25] on subjects with dopamine transmitter deficiency, 8 of the 12 subjects given PS showed improvement. Another patient improved when the PS intake was increased. This trial lasted for only 3 weeks; a longer dosing period and customized dosing might have been more informative. In an earlier study, subjects with severe cognitive deficits along with motor impairments responded to intravenous PS (about 35 mg in 200 mg bovine brain cortex phospholipids) with improvements in motor performance and elevated levels of homovanillic acid (a dopamine marker) in their cerebrospinal fluid.[26]

PS can have beneficial effects on mood. In a double-blind trial conducted on elderly women, PS brought about consistent improvement of memory and behavior[9]. In an open trial, Manfredi's group[27] also obtained statistically significant improvement of various psycho-organic parameters in elderly women given 50 mg PS per day intramuscularly. Findings from the 1995 trial by Gindin et al[8] suggest PS can also improve mood parameters in elderly men.

PS might modulate the cortisol release that occurs in response to stressful conditions; this effect might not be restricted to the aged. Monteleone's group[11] reported on an open, placebo-controlled trial of young, healthy men subjected to exercise-induced stress. The oral intake of PS for 10 days prior to a session of bicycling to near-exhaustion lowered the stress hormone production normally associated with strenuous exercise. This confirmed findings from an earlier study by the same group[10] in which PS was given intravenously.

Supplementation with PS might also help conserve hypothalamic function and benefit the aging hypothalamus-pituitary-adrenal axis (HPAA). One example is the Early

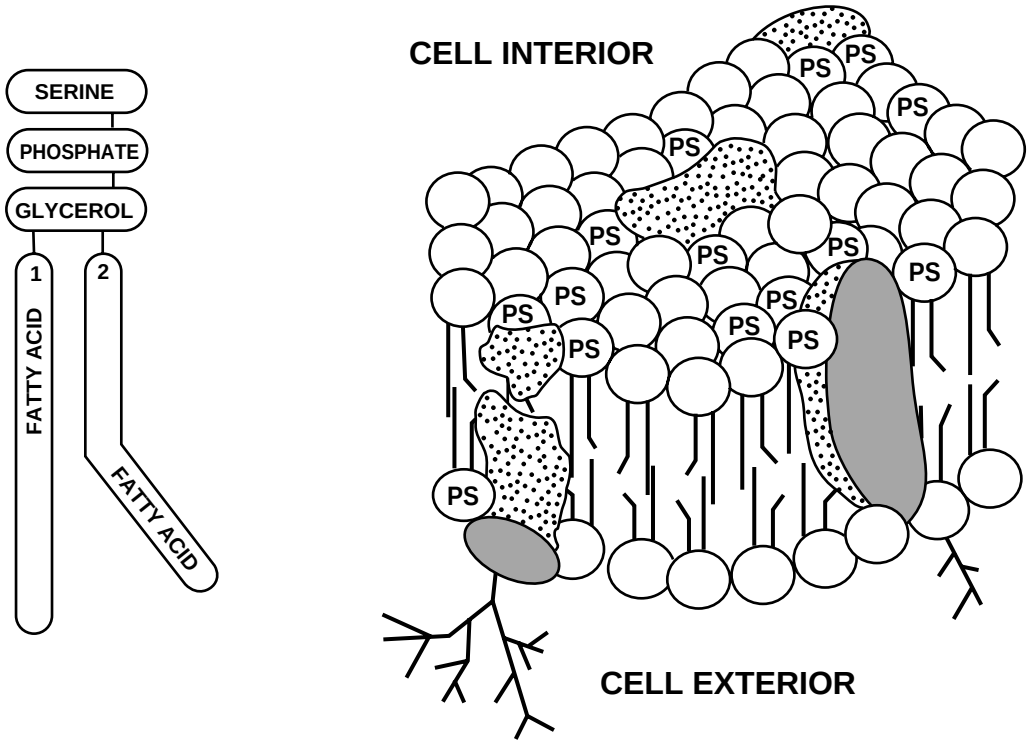

FIGURE 2. Left: Molecular organization of phosphatidylserine (PS). Right: PS is concentrated in the inner layer of the cell membrane, and is preferentially associated with proteins.

Cortisol Escape Phenomenon. In young, healthy people the oral administration of 1 mg of dexamethasone (DEX, a synthetic glucocorticoid) normally suppresses the production of cortisol and other adrenal steroids for more than 24 hours. In contrast, many older people do not show this suppression by DEX- a phenomenon called Early Cortisol Escape, and such lack of DEX suppression likely reflects dis-integration of the HPAA in the elderly. Oral supplementation of PS restored DEX suppression in a group of 14 institutionalized elderly (ages 66-78; $p \leq 0.02$).[28]

Further evidence that PS can benefit the aging HPAA comes from Masturzo and collaborators,[29] who did an open, placebo-controlled trial on institutionalized elderly men (ages 65-85, average age 73.7) with disturbed 24-hour circadian rhythm of thyrotropin (TSH) hormone secretion. While those on placebo deteriorated further, PS restored the daily rhythm of TSH secretion to a level comparable with the young male adult controls (mean age 22.3 years; $p \leq 0.001$). In another human study,[30] intravenous administration of PS in liposome form led to "spikes" of growth hormone release. This effect was interpreted as a likely result of activation of dopamine metabolism in the pituitary gland by PS.

Mechanisms of Action of Phosphatidylserine

The consistent clinical findings from the extensive research on PS indicate that by working in nerve cell membranes, PS helps optimize a variety of functions indispensable at the level of the single nerve cell. These

encompass homeostatic (basic, survival-type) processes; maintenance (renewal, repair, "housekeeping"); and specialized processes unique to the nerve cell. It is possible that cognitive performance might benefit as the health of the individual nerve cells is improved.

PS and the other phospholipids (PL) are large molecules that hold together the cell's membranes.[39] The PL pack together side-to-side, in a two-layer molecular structure, creating a membrane matrix into which proteins and other membrane constituents are inserted and secured (see Figure 2). The PS phospholipids are one of five phospholipid classes, the others being phosphatidyl- -cholines (PC), -ethanolamines (PE), and -inositols (PI); and the sphingomyelins.

The phosphatidyl PL molecules are organized along the same basic lines.[39] Each has a head group that contains phosphorus and one other chemical subgroup, which in the case of PS is serine. A 3-carbon backbone, structurally identical to glycerol, is attached to the head group. Extending out from the glycerol backbone are two tails, each of which is a fatty acid. The sphingomyelin phospholipids have a different molecular structure: they do not have the glycerol backbone, and carry only one fatty acid tail.

PS seems to function exclusively in cell membrane systems.[39-50] The outermost membrane, called the cell membrane, functions as a master switch for the cell. It controls:[39]

- Entry of nutrient substances into the cell; clearance of wastes
- Movements of charged atoms for impulse conduction
- Reception of molecular messages from outside the cell
- Transformation of messages into metabolic response
- Cell movement, shape changes, flattening or expansion
- Cell-to-cell recognition and communication

The ion pumps, transport molecules, enzymes, and receptors which manage these master-switch activities are all primarily protein in nature.[41-50] All are built into or onto the phospholipid membrane matrix, and all require PL for full functional capacity and optimal activity. The list of membrane proteins known to require PS:

- Sodium-potassium ATPases, regulating Na/K flux[41]
- Calcium and Magnesium ATPases, others[42,43]
- Protein kinases, mediating one type of signal transduction[44]
- Adenyl cyclases, regulating another type of transduction[45]
- NADPH-cytochrome reductase and other mitochondrial complexes[46]
- Proteins of secretory vesicles[47]
- Receptors for N-Methyl-D-Aspartic acid and other nerve transmitters[49-51]

PS is ubiquitous not only in the outer cell membrane, but also in membranes of secretory vesicles[47] and in the mitochondrial membrane system, where it also serves as a metabolic reservoir for PE and PC via enzymatic decarboxylation.[46,54] By acting as a metabolic backup for other structural PL in the cell's energy factories, PS may support the energy generation processes that are so essential to cell survival.

Numerous experimental studies have been conducted with PS in aged rodents. The findings [55-58,64] are consistent with those from the clinical trials, and add another dimension to the understanding of how PS works:

- Maze learning, other adaptive behaviors were partially rejuvenated
- Glucose utilization efficiency, synaptic efficiency improved
- Abnormal EEG patterns were reversed. Other phospholipids, oleic acid, serine amino acid did not substitute for PS [55, 64]
- Structurally, decline of nerve network density was reversed
- Nerve transmitters were boosted—acetylcholine, catecholamine turnover, tyrosine hydroxylase activity, dopamine release
- Lagging circadian and estrus rhythms were reset.

Findings from *in vitro* experiments with PS on cultured nerve cells indicate PS can confer protection from toxic free-radical attack. The researchers suggest PS may have antioxidant effects.[34] However, their data is also consistent with an enhancement of cellular detoxification capacity by PS due to its overall enhancement of membrane-based cell functions.

PS is present in every cell type in the body, and though it is currently best documented in nerve cells it also is involved in immunity, where it facilitates the recycling of old cells. Red blood cells in the circulation eventually become rigid and less able to squeeze through the narrow capillaries, and must be replaced. Membrane enzymes (amino-PL translocases) "transpose" PS from its usual position in the inner half of the membrane to the outer half. This apparently acts as a signal to circulating immune cells to remove the aged red cell from the circulation.[59] PS is also involved in membrane phenomena linked to bone matrix formation,[60] testicular function,[61] signal transduction in the heart,[62] and secretion by the adrenal glands.[63]

The Safety, Metabolism, and Bioavailability of PS

PS is an orthomolecule, a nutrient present in most common foods in small amounts. Though not strictly a vitamin, PS is very likely a semi-essential nutrient, since the body can make this phospholipid only through a complex series of reactions and with substantial investment of energy. Lecithins are normally a good dietary source of phospholipids, but until recently, PS occurred in commercial lecithins only in trace amounts. A plant-source PS has recently become available.

As studied in rodents,[65] phosphatidylserine has good bioavailability by the oral route. Following oral dosing, radioactively-labeled PS appears in the blood at about 30 minutes, and immediately also begins to build up in the liver and the brain. As PS is being absorbed into the intestinal lining cells, the PS headgroup remains intact but some of the tails (particularly those at position 2) are removed. Similar to the pattern with PC, which is very well documented, in the case of PS the fatty acid "tails" in the 2 position are hydrolysed away by digestive enzymes. Directly following absorption the tails are re-added by "re-acylation" enzymes. Thus, the exact fatty acid profile of the PS that is ingested is unlikely to limit its final disposition in the nerve cells, and *in situ* the most active form of PS in membranes is the lyso-form, which lacks a tail in the 2-position.

The available evidence indicates that it is the headgroup that gives PS its distinctive functional identity, and that the 2-position tail is important for function but differs depending on the tissue where the headgroup becomes located. Thus, the PS that circulates in the blood has exclusively C18:1 or C20:4 in the 2 position.[66] The 2-position tails may or may not be removed before PS can cross the blood-

brain barrier, and in the brain C18:1 or C22:6 occupy the 2-position.[67] In the testes, it is C14:0 or C20:4 which predominate.[61]

In the brain's gray matter, much of position 2 is occupied by the long-chain, omega-3 fatty acid DHA (docosahexaenoic acid, C22:6).[67] DHA is unquestionably important for the brain, and deficiency of DHA/omega-3 fatty acids impairs visual development as well as cognition. Those who are hypertensive, diabetic, or alcoholic may be impaired in making DHA from omega-3 precursors, and such individuals should probably supplement their diet directly with DHA. However, the close functional parallelism between DHA and PS in the brain does not mean that PS must have DHA attached in order to be effective. Lyso-PS reportedly can act synergistically with NGF (nerve growth factor), a small protein which enhances nerve cell renewal in the brain.[66]

Prior to the advent of soy PS, clinical studies were done with a PS-enriched phospholipid fraction extracted from bovine brain. In 1995, a clinical trial with soy PS was concluded in Israel,[8] and its outcome was similar to the pattern set by the earlier clinical trials with bovine PS. Given the considerable shuffling at the 2 position of PS that occurs during absorption, circulation, and organ delivery, it should not be essential to supplement with PS that already carries DHA in position 2; co-supplementation of DHA along with PS ought to be sufficient. Also, safety has to be a major consideration—the only source of PS linked with DHA is bovine brain, and with the "mad cow" disease epidemic in Great Britain, the dietary consumption of bovine brain might be deemed a questionable practice.

PS appears to be safe as a dietary supplement. Preclinical toxicological studies on rats and dogs indicated PS was safe when taken by the oral route.[68] Dogs tolerayed 70 grams per day of PS for one year without apparent damage. The animal studies suggest that IM administration of PS may cause burning and itching, and IV administration may not be routinely advisable.

A minimum 35 clinical studies have been conducted with PS, and more than 800 subjects have received PS under controlled clinical conditions. To date, this nutrient has a good safety record. Rarely, stomach upset has been reported, and if a large dose (600 mg) is taken just before going to bed sleeplessness can result.

In addition to laboratory documentation of safety from earlier trials with PS, Cenacchi and collaborators[35] reviewed laboratory findings from 130 subjects given 300 mg of PS daily for up to 60 days during clinical trials. They found lowering of uric acid levels and (liver) SGPT, which though statistically significant were clinically negligible. Cenacchi's group also reported from their large 6-month trial that... "adverse events were very few, and clinically unimportant. These observations are remarkable in the light of the large number of subjects enrolled in this study, who represent a sample of the geriatric population commonly encountered in clinical practice."[35] Throughout the course of this clinical trial, the use of drugs for other diseases was allowed. No interactions were noted between PS and the wide variety of pharmaceuticals typically used by the elderly.

Conclusions: The Potential of PS as a Dietary Supplement

PS has been the most studied nutrient for cognitive decline. Very substantial amounts of mechanistic, experimental and clinical data are available on PS, and the

findings indicate PS is safe to take and highly effective. Intakes in the trials ranged from 200-500 mg daily; a reasonable supplementation strategy would be to take 200-300 mg per day (in 2 or 3 divided doses, with meals) for the first month, then lower the intake to 100-200 mg per day.

PS is far more abundant in the brain than in the other organs, and has the most clinical significance as a brain nutrient. Nerve cell homeostasis, maintenance, and specialized functions all involve membrane-based processes that rely on membrane phosphatidylserine. Major factors likely to contribute to cognitive impairment in later life all cumulatively damage cell membrane: heavy metals, free radicals (smoking, drinking, pollutants), chronic emotional stress (catecholamine auto-oxidation), and nutrient deficiencies, all of which continue to be widespread. Dietary supplementation with PS can help slow the loss of some brain functions, and partially rejuvenate others—in one U.S. double-blind trial, on name-face recall PS reversed more than a decade of decline.[3]

The 16 clinical trials completed with PS for cognition (11 double-blind, 5 less stringently controlled) consistently indicate PS provides metabolic support for memory, learning, concentration, and behavior. Crook and the MAC group have modernized and streamlined tests for cognitive function, and their findings indicate cognitive decline is already well underway by the 5th decade of life. It is likely that the earlier PS can be started, the more completely it might ameliorate progressive loss of the higher brain functions.

While PS appears to be a highly effective substance for conserving the intellect, it is not a magic bullet, and may not accomplish miracles by itself. Rather, its membrane-based action mechanisms lend PS to compatibility with other nutrients that are safe and have different mechanisms of action, such as *Ginkgo biloba* extract and acetyl-L-carnitine. PS is also fully compatible with vitamins, minerals, antioxidants, and other nutrients, all of which are likely to facilitate its action. PS is not contraindicated with respect to drugs, and is unlikely to interfere with the actions of the few pharmaceuticals available for cognitive decline and should complement their actions.

As a safe and effective dietary supplement, particularly in conjunction with exercise and lifestyle revision PS has proven potential to improve the quality of life for the elderly. PS might be an important tool aimed at conserving memory, learning, concentration, and other higher mental capacities in the face of advancing age.

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