GPC (GlyceroPhosphoCholine), Ortho-Nutraceutical For Active Living and Healthy Aging

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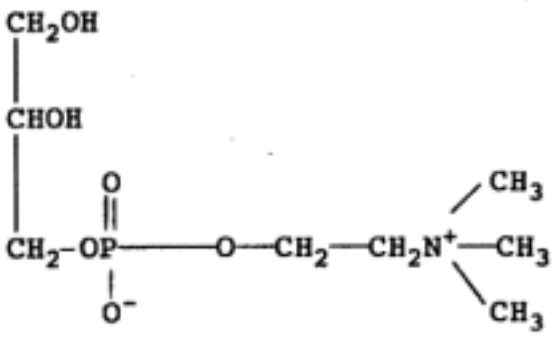
GPC or GlyceroPhosphoCholine (pronounced *gli-sero-fos-fo-ko-lean*) is a small molecule with a large place in the scheme of life. It is a cell protectant, a pro-phospholipid building block for cell membranes, a chemical transmitter source, and widespread in metabolism.

Figure 1. The chemical structure of GPC (glycerophosphocholine, L-alpha-glycerylphosphorylcholine).



Functionally, GPC is important at all levels: basic cell processes (homeostasis), tissue growth and renewal, organ vitality, and mind-body integration. A measure of its biochemical importance is that it is naturally present in mother's milk.1

GPC is naturally present in all the body's cells, and is therefore an orthomolecule (*molecule ortho*dox to the body).2 **But having clinical value proven to equal or exceed any other nutrient or drug, combined with its**

diverse functionalities and marked bioavailability, this small molecule deserves the unique classification of ortho-nutraceutical.

GPC, sometimes also called choline alfoscerate (or alphoscerate) has been extensively researched via basic science and clinical study. It has unique benefits as a nutraceutical while offering excellent safety and tolerability consistent with its orthomolecular status.

At least twenty-three (23) clinical trials have been done with GPC. All of them had positive outcomes: GPC benefits attention, mental focus, recall, and other higher mental functions (cognition), including in young healthy subjects.[3,4] **GPC offers marked benefit for individuals with memory decline, whether linked to poor brain circulation or of the Alzheimer's type, as recently reviewed.**[5] **It has proven uniquely valuable for brain recovery following stroke or other circulatory injury.**[6-8] **Last but not least, GPC seemingly revitalizes master hormone functions in the elderly.**[9]

GPC Has Impressive Benefits for the Healthy Young

Various nutraceuticals and pharmaceuticals have shown modest capacity to improve cognitive function at middle age. But agents that improve mental performance in the healthy young are practically unknown. But well-controlled trials proved GPC could benefit this population.

The drug scopolamine depletes the brain's acetylcholine stores, even in young healthy humans, causing a transitory cognitive impairment similar to that observed in normal aging.[10] **Canal and collaborators at the University of Milan assessed GPC for its capacity to block this "scopolamine amnesia."**[3]

The volunteers were men and women aged 19-38 years. The procedure was to start the subjects on either an inactive placebo or on GPC, then to treat them with scopolamine or a placebo given by intramuscular injection. In the first double-blind trial,[3] **32 subjects were randomly allocated to 4 different groups. They were then preloaded with by mouth (1200 mg per day for 10 days) and on the eleventh day injected with either scopolamine bromidrate or placebo. They were tested immediately before being injected (baseline) then again at 0.5 hrs, 1, 2, 3 and 6 hrs after injection. In the mnemonic (Free Recall) test, 20 words were read aloud to them three times, then they had two minutes to write down all the words they could remember. In the test for**

attention (Cancellation Test), they were given a matrix of 60 rows x 20 columns of randomly generated digits; 3 digits were designated as targets and these had to be located and eliminated within 3 minutes.

On the attention test, GPC pretreatment blocked the scopolamine effect for at least the first 3 hours. On the mnemonic word recall test, GPC pretreatment significantly protected against scopolamine all the way through the 6-hour trial. But GPC actually improved the *baseline* word recall performance in these healthy young subjects.[3]

The second double-blind trial involved 48 men and women aged 22-33 years.[4] **This time, pretreatment with GPC (1200 mg/day for 7 days) was compared against pretreatment with the drugs idebenone and aniracetam. More tests were used: learning capacity for verbal and nonverbal material; selective attention; divided attention; and working memory.**

Scopolamine without GPC pretreatment negatively impacted all these tests. But GPC pretreatment protected learning and long-term verbal memory (immediate and deferred recall of 20 words; facilitated recall; recognition) against scopolamine. GPC provided statistically significant protection, superior to idebenone and aniracetam. GPC also significantly benefited "working memory," a test of abstract reasoning carried out together with an interfering attentive task. Working memory was so well protected that it never significantly dipped below baseline.[4]

Overall, these findings indicate that GPC has that rare ability to improve mental performance in young, healthy people. Its capacity to block scopolamine's detrimental effects on attention, word recall, and working memory is impressive, but even more impressive is that GPC can enhance the baseline mental performance of healthy young people.

GPC also has measurable benefits at the physiologic level. In a randomized double-blind trial with healthy subjects aged 25-32 years, EEG (ElectroEncephaloGraphic) patterns were improved.[11] **GPC lessened the slow wave ("delta") activity that typically becomes more prevalent with aging or pathologic brain decline.**

GPC Enhances Mental Processing at Middle Age

Various physiologic tests indicate GPC improves mental performance at middle age, even in subjects with subnormal function. On the EEG, as with young healthy subjects a lessening of the delta slow waves was seen in a double-blind trial on subjects with AAMI (age-associated memory impairment, a condition diagnosed only in subjects aged 50 years or older).12

In controlled trials with subjects aged up to 65 years, GPC improved a number of mental processing measures, including reaction time which is related to acetylcholine nerve pathways,13,14 **and visual cortex performance related to dopaminergic pathways.**15

Reaction time evaluation has proven reliable in assessing age-related cognitive dysfunction. Abbati and collaborators compared GPC's effects on reaction time, versus the drug oxiracetam.13 **Forty male outpatients aged 55-65 years were diagnosed with senile organic brain syndrome of medium severity. Following evaluation via reaction time measurements, a clinical self-reporting scale, and two psychometric tests, they were randomized into two groups. One group received 1 gram oxiracetam and the other group 1 gram GPC, by daily intramuscular injection, for 12 weeks. Follow-up testing was done for a further 12 weeks.**

Both oxiracetam and GPC benefited the subjects' clinical status, psychometric performance, and central reaction times.13 **The respective degrees of benefit were comparable during the 12 weeks of daily dosing: a six-point improvement on the overall clinical assessment, about 5 points on the Mini Mental State Evaluation (MMSE), 22-23 points on Barthel's Index, 97 millisecs on central reaction time. But upon follow-up, 3 months after dosing had ended, the GPC group showed a more lasting effect than the oxiracetam group.**16

Visual evoked potential (VEP) is a physiologic response linked to cognitive performance. Sicurella and colleagues measured VEP in 5 subjects of ages 59-83 who presented clinically with chronic cerebral vasculopathy.15 **Baseline measurements were taken, then 3 grams of GPC was given i.m. and the measurements repeated over a total 5.5 hours. GPC increased VEP amplitude in all 5 patients, by more than 60% on average.**

GPC Helps the Elderly Resist Cognitive Deterioration

GPC has been subjected to a number of controlled trials against cognitive decline. Compared with other dietary "cholinergic precursors" such as choline, phosphatidylcholine or cytidine diphosphocholine (citicholine), GPC had superior benefits.[17] **In 2001 the noted researcher Lucilla Parnetti published a sweeping analysis of the data available on GPC from these trials.**[5] **In all, Parnetti analyzed ten clinical trials that included 1,570 patients with dementia, whether related to poor circulation (vascular dementia), of non-circulatory degenerative origin (Alzheimer's-type), or of possible mixed origin.**

Superior Performance Against Vascular Dementia

Parnetti identified seven trials with GPC against vascular dementia, involving 789 patients—431 received GPC orally at 1200 mg/day for 3 or 6 months, while 358 received GPC by intramuscular injection over 3 months.[14,18-23] **To assess these trials she used mainly the Sandoz Clinical Assessment Geriatric (SCAG) Scale.**[24] **The SCAG quantitates cognitive decline, emotional-affective aspects, and problems with interpersonal relationships.**

In all the trials GPC improved the overall clinical symptoms, including cognition, affective symptoms, and somatic symptoms such as fatigue and dizziness. In summary:

1. **Memory, attention, other cognitive measures, and mood all were significantly improved;**
2. **GPC achieved marked improvement of disorientation, irritability, emotional lability, and indifference to surroundings;**
3. **The overall SCAG improvement ranged from 8 to 30%. GPC outperformed the nutraceutical citicholine in three direct comparison trials,**[18-20] **and bested oxiracetam in a fourth.**[21]

Important Improvements in Alzheimer's Symptoms

For "non-vascular, degenerative dementia" involving both probable Alzheimer's and mixed vascular—Alzheimer's, Parnetti identified six trials

involving 565 patients with generally mild to moderate dementia—505 received GPC orally at 1200 mg/day for 3 or 6 months, and 60 were treated with 1000 mg i.m. for 3 months.13,14,22,23,25,26 **To assess these she used mainly the MMSE.**16 **As with vascular dementia, she concluded GPC had impressive benefit:**

1. **GPC significantly increased the MMSE score in all the trials, indicating marked improvement of cognitive functions such as orientation and language in addition to memory and attention. The overall MMSE improvement ranged from 10-26 percent.**

2. **In a direct comparison against advanced Alzheimer's, GPC performed roughly twice as well as the nutraceutical acetylcarnitine.**25 **And against organic brain syndrome GPC again bested oxiracetam.**13

A recently published double-blind trial further documented GPC's benefits against mild to moderate Alzheimer's dementia.27 **Oral GPC (1200 mg per day) was compared against placebo, in 261 patients for 6 months. GPC proved significantly superior on all the measures, including the MMSE, the GDS (Global Deterioration Scale, for cognitive decline), the ADAS (Alzheimer's Disease Assessment Scale-Total, Cognitive, Behavioral), GIS (Global Improvement Scale), and the CGI (Clinical Global Impression).**

The investigators noted the degree of benefit from GPC was similar to the donezepil and superior to rivastigmine, both of which are acetylcholinesterase inhibitor drugs. They noted the GPC patients improved not just on cognition but in behavior and activities of daily living, in their words "possibly improving patients' and caregivers' quality of life." No patient left the study due to adverse GPC effects.

GPC is Unmatched for Stroke Recovery

GPC has produced especially impressive benefits for brain trauma recovery. Parnetti's analysis5 **covered three clinical trials with GPC against stroke.**6-8 **To assess functional recovery in the acute post-stroke phase, all three trials used the Mathew's scale. This scale carefully assesses cognitive domains (awareness level, orientation) and neurological domains (language, cranial nerve function, motor and sensory function). In addition, two of the trials**6,7 **used the Global Deterioration Scale (GDS) to assess the severity of cognitive**

decline, and the Crichton Geriatric Rating Scale (CGRS) to assess behavioral functions.

These three clinical trials altogether totaled 2,484 patients. None included control groups because the patients were too ill to be denied treatment. All used the same protocol: GPC i.m. at 1,000 mg/day for the first month, then orally at 1,200 mg/day for 5 months.

The largest stroke trial used 176 hospital centers within Italy, and 2,044 patients.[7] **The investigators judged GPC significantly helped more than 95 percent of the patients. There were no life-threatening adverse effects, nor did blood analyses and other laboratory monitoring reveal any abnormal effects. Summary outcomes from the three stroke trials:**

1. **In the first phase of treatment (intramuscular), neurological functions recovered by 20-30%;**

2. **In the subsequent, oral phase of treatment, clinical improvement continued. All the tests gave comparable results: the MMSE improved 12-15%, the GDS 20%, the CGRS 19-21 percent.**

3. **The investigators concluded GPC offered unique benefits against acute cerebrovascular disease.**

A fourth stroke trial, not reviewed by Parnetti, followed a virtually identical design.[28] **In 34 centers 320 patients were followed for 6 months, beginning on GPC intramuscular then switching to oral. The benefits measured were highly statistically significant. The researchers observed that intramuscular GPC for the first month accelerated recovery from focal neurological deficits, including space-time orientation, degree of consciousness, language, motor capacity, and general wellbeing. Then oral GPC consolidated the improvements.**

Salvage of Cognitive Function Damaged by Surgery

One trial with GPC against acute cerebrovascular damage was conducted randomized and double-blind. It involved patients with cognitive deficit consequent to anesthesia for heart surgery.[29]

Bypass surgery often results in brain damage. Mood and personality change, cognitive functions disappear, mental fatigue sets in earlier than normal. Such symptoms can be transitory or become chronic. Auteri and collaborators in Italy studied 20 patients of both sexes, aged 45-65 years, who underwent open-heart surgery for coronary bypass. In the first test following surgery, 45% of the patients (9/20) showed reduced performance by neuropsychological testing (Benton Visual Retention Test and Wechsler Memory Scale). All 20 were then randomized to two groups: one received GPC intravenously for one month then intramuscularly for 5 months; the other received intravenous placebo for one month then no further treatment. At the end of the 6-month period, the GPC group had no remaining memory deterioration while the placebo group had significantly lost function.

In the 10 trials conducted on dementia and 4 on stroke, GPC produced clinically remarkable improvement and was extremely well tolerated. Parnetti concluded that GPC's degree of efficacy ranks it superior to other cholinergic agents. Since there is no panacea for dementia or stroke, GPC's proven safety and orthomolecular status makes it highly suitable for application in combination with drugs or other nutrients.

GPC concentration in the human brain was found to increase following stroke, and in neurological and psychiatric disorders such as Alzheimer's, schizophrenia, bipolar disorder, and cerebellar ataxia. Previously this was attributed simply to phospholipid breakdown occurring as a result of cell damage. Recently it has become apparent that GPC and its counterpart GPE (glycerophosphoethanolamine) may be protecting the embattled brain tissue by blocking phospholipid breakdown, and conceivably also by enhancing phospholipid synthesis.30

GPC Works Through Diverse Mechanisms

Well absorbed by mouth, circulating with the blood, and entering numerous metabolic pathways, GPC has pro-homeostatic, growth-supportive and restorative clinical benefits. GPC has proven roles in the essential functioning of the brain, liver, kidneys, muscle, testes, and endocrine system. GPC supports human health through a variety of mechanisms:

Source of Active Choline, Essential Nutrient

Choline is a vitamin-like, essential nutrient. But free choline is poorly bioavailable, unstable in the water phase, and potentially toxic. Thus the blood and tissues carry very little free choline. GPC is an "active choline" source, able to raise blood and brain choline levels more safely and efficiently than choline itself.

In humans, GPC taken by mouth is well absorbed and increases plasma levels of choline for up to ten hours. Research with animals using radiolabeled GPC suggests GPC becomes incorporated into the choline phospholipids phosphatidylcholine (PC) and sphingomyelin.

Choline from GPC is available (a) as a methyl group source for gene-level and other metabolic regulation, (b) as an essential component of the chemical transmitter acetylcholine, (c) for incorporation into choline phospholipids such as phosphatidylcholine and sphingomyelin. GPC is readily processed to choline by enzymes, at minimal energy cost to the body. It is the body's main choline buffer and reservoir.

Resource for AcetylCholine, Chemical Transmitter

GPC is also the major choline reservoir for the biosynthesis of acetylcholine. This chemical transmitter is involved in brain circuit maturation, expansion, renewal, and repair, as well as in the "plasticity" adjustments of the brain circuitry that occur throughout the lifespan. Acetylcholine is also employed by the nerves to stimulate the skeletal muscles, and by the autonomic nervous system to manage the other organs.

"Pro-Phospholipid" Source for Cell Membranes

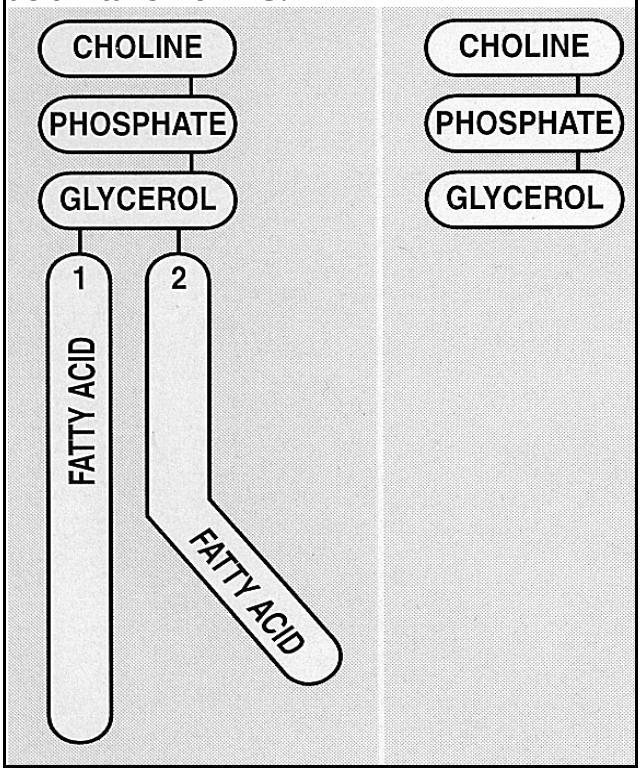
Life depends on cell membranes. Membranes are the dynamic matrix supporting virtually all the energy exchanges and molecular transformations of life. Virtually all the proteins that drive the life processes are located on or within membranes.

Membranes are sheet – like molecular assemblies built on a foundation of phospholipids, of which phosphatidylcholine (PC) is the most abundant. Cells grow or renew themselves by making new membrane mass, and this

creates demand for PC that in turn is most efficiently synthesized from GPC.

GPC is a pro-phospholipid, a "de-acylated" PC—the PC molecule without its usual fatty acid tails (see Fig. 2). Though it is a water-phase substance, GPC is transformed to membrane-phase PC at very little energy cost. GPC can attain high levels in the cytoplasm without doing damage, and be available to make PC as necessary.

Figure 2. Left: Molecular organization of PC (phosphatidylcholine). Right: Molecular organization of GPC. Note the GPC molecule lacks the two fatty acid "tails" of PC.



Preferred Source for Omega-3 PhosphatidylCholine

As a pro-phospholipid GPC is a key substrate for the attachment of DHA (docosahexaenoic acid, omega-3) "tails" (see Fig. 1) to make PC-DHA. Enzymes are readily available that accomplish this task. The highly unsaturated DHA-PC is used in highly active cell types — nerve cells, muscle fibers, retinal light-sensing cells, and the spermatozoon — to increase membrane fluidity and thereby facilitate metabolic efficiency.[31] **Membrane**

systems enriched in PC-DHA enable their proteins to "flip" or "spin" faster in the membrane environment. GPC helps guarantee optimal membrane performance.

Duchenne Muscular Dystrophy, the most common muscular dystrophy in humans, is a muscle fiber dysfunction that destroys the capacity to walk. Duchenne is known to be membrane-based, and features a relative deficiency of GPC in the affected muscle fibers. Here also GPC serves as a pro-phospholipid for making PC-DHA, which is very important for skeletal fiber membrane function. In Duchenne patients, those muscles with the least GPC are the first to break down. Duchenne may be partly or wholly a GPC deficiency disease.31

<u>Osmotic Protectant and Osmoregulator</u>

All cells have an osmotic pressure with respect to their external fluid environment, proportional to the total content of molecules in their watery cytoplasm. Survival calls for keeping this molecular content appropriately in balance with the exterior. GPC is an important osmotic pressure regulator in the brain, liver, kidney, bladder, and probably all the organs.32 **It is also an osmotic protectant, sparing the activity of proteins as it builds in concentration around them.**33 **In the kidney and liver, it specifically protects against urea buildup which can become toxic. GPC reaches concentrations within cells that match or exceed other key cell protectants such as glutathione.**

The kidney nephron cells can concentrate urea to very high concentrations. GPC concentrations in these cells rises in parallel with the increasing urea concentrations. As urea becomes progressively more concentrated moving from the kidney cortex to the papilla, so also does GPC. The synthesis and breakdown of GPC are tightly regulated by the kidney cells to protect against urea toxicity.33

<u>Essential to Sperm Maturation and Fertility</u>

Membrane fluidity is also important for spermatozoal function. The maturing spermatozoa become enriched in PC-DHA as they move down the epididymis. Their membranes become highly fluid due to the increasing

endowment of PC-DHA. The epididymal cells that nurture the sperm cells apparently draw on GPC to make PC-DHA.34

GPC reaches extremely high levels in semen, the highest being a remarkable 110 millimolar in the ram (by comparison, GPC reaches 11 millimolar in human kidney cells and glutathione rarely exceeds 10 millimolar in human cells). In men, the lower the levels of PC-DHA and GPC in the semen, the greater the likelihood of poor sperm motility.34

GPC May Revitalize Brain Growth Hormone Release

GPC may also be valuable for hormonal restoration. Several studies were done, using healthy old and young subjects, to assess GPC's effects on growth hormone (GH) secretion by the pituitary gland. GPC was found to enhance physiologic GH release, particularly in the older subjects.

The pituitary is the body's "master" hormone-producing gland: it cyclically releases GH and other hormones that coordinate organ maintenance and renewal. But as humans reach middle age their GH production falls. Poor GH production likely predicts an unhealthy aging process.

Normally GH is released from the pituitary under the control of growth hormone releasing hormone (GHRH) produced by the hypothalamus. The administration of GPC (i.v.) prior to stimulation with GHRH (i.v.) was found to enhance growth hormone release. The GPC effect was proportionately greater in the old volunteers than in the young. This apparent brain revitalization by GPC is consistent with GPC's other marked benefits for brain function.

GPC's potential to revitalize the aging brain is amply supported by animal research. In rats, GPC countered the age-associated losses of neural networks and neuron numbers in the hippocampus and frontal cortex.35 **GPC conserved the granule neurons and the pyramidal CA-1 and CA-3 neurons of the hippocampus; the Purkinje neurons of the cortex; and the granule neurons of the cerebellum. It conserved hippocampal acetylcholine receptors in aged (24-month) rats, while improving their learning and memory.**36

GPC also is regenerative. When the rat frontal cortex is surgically damaged, administration of GPC can repair the lesions.37 **It conserves cerebellar**

receptors for nerve growth factor (NGF), a foremost factor encouraging recovery in response to damage.38

Physiologically, GPC has numerous effects that could help slow brain aging. GPC blocks scopolamine's amnesic effect in animals,39 **as it does in humans, and enhances basal acetylcholine release in the rat brain.**40 **GPC also supports other transmitter systems such as dopamine, norepinephrine, and GABA.**41 **And it supports the signal transduction functions of the nerve cell membrane, which carry the receptor signals into the cell.**42

In rats, as in humans, GPC modifies EEG (ElectroEncephaloGraphic) patterns, reducing the delta or "slow waves" which are increased during aging or accelerated cognitive deterioration.43

Dosing, Safety, Tolerability, Compatibility

The oral intake level of GPC used in the clinical trials was usually 1,200 milligrams (mg) per day. Half that intake—600 mg GPC per day—approximately doubles brain choline levels. A reasonable dosing strategy for dietary supplementation with GPC is 1200 mg/day in divided doses (AM and PM) between meals for one month, then 600 mg/day for maintenance. Symptomatic subjects may stay on 1200 mg/day indefinitely or until adequate improvement is noted.

GPC is naturally distributed throughout the body's cells, tissues and organs, It reaches very high concentrations, but protects biomolecules rather than doing harm. Biochemically, GPC works in concert with the vitamins and the other orthomolecular nutraceuticals. It is also freely compatible with pharmaceuticals. Of the more than 4,000 patients who received GPC by mouth, i.m., or i.v. in clinical trials, not one was reported to experience an adverse effect serious enough to cause withdrawal from a trial. No adverse drug – GPC interactions were noted in elderly patients who continued to take their variety of medications during the trials.

Unlike the fat-soluble phospholipids, GPC has a pleasant taste and can be supplemented in liquid form; intramuscular and intravenous preparations are safe and well tolerated.

GPC, Ortho-Nutraceutical for All Ages

A large body of human research suggests GPC is a beneficial ortho-nutraceutical for individuals of all age groups. In well-controlled trials GPC improved mental performance in the healthy young, the middle-aged, and the elderly. In direct, head-to-head comparisons GPC's benefits surpassed pharmaceuticals (oxiracetam, aniracetam, idebenone) and nutraceuticals (acetylcarnitine, CDP-choline). Its apparent capacity to boost growth hormone release9 **boosts GPC above other nutraceuticals.**

GPC is not a vitamin — human cells have the capacity to produce it. Rather, it is one of an elite group of substances that the body becomes challenged to produce at short notice, as adaptation to biochemical stress. Many of these are classed as conditionally essential nutrients, since the body's capability to make them can be compromised by genetic conditioning, lack of metabolic vitamin cofactors, virus load, general ill-health, aging, or other adverse conditions; consequently they must come from the diet. GPC may well be conditionally essential, for example in patients with Duchenne muscular dystrophy.44 **Its ample presence in human mother's milk bolsters the case for conditional essentiality.**1

The ideal of active living suggests the organ systems are functioning at or near full capacity. GPC's diverse biochemistry as pro-phospholipid membrane building block, choline reservoir, parent molecule for acetylcholine and PC-DHA, and osmoprotectant illustrate how it supports a vast array of organ functions. GPC supports not just mental performance via the brain and nervous system, but physical performance through nerve-muscle integration (including via the sympathetic system).

The dream of healthy aging evokes images of experiencing the aging process with high quality of life, free of crippling degenerative disease. GPC with its marked clinical efficacy and safety, its multifaceted support for organ homeostasis, and its revitalizing effects on the brain, affords potent nutritional support for healthy aging. Rather than being an "anti-aging" panacea, GPC is a remarkably effective and safe ortho-nutraceutical for healthy aging with active living.

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