GlyceroPhosphoCholine (GPC), Mind-Body Nutrient for Active Living And Healthy Aging

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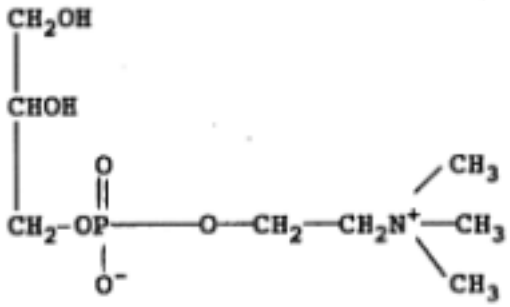
Figure 1. The chemical structure of GPC, glycero(3)phosphocholine. Note its zwitterionic nature (positive and negative charge on the same molecule).



Glycerophosphocholine (pronounced *gli-sero-fos-fo-ko-lean*) or GPC is a small nutrient molecule with a large place in the scheme of life. Its centrality to human life is suggested by its abundance in mother's milk.[1] GPC supports multiple facets of homeostasis—the body's maintenance of the conditions necessary for life. Its natural presence in all the body's cells makes it an orthomolecule (*molecule ortho*dox to the body).[2] Orthomolecules typically are safer and more clinically versatile than other nutrients.

There has been confusion over GPC's chemical name. The correct, most current name is glycerophosphocholine, as set by the authoritative International Union of Pure and Applied Chemists or IUPAC, acting together with the International Union of Biochemists or IUB (the IUPAC-IUB Nomenclature). Older names include choline alfoscerate (or alphoscerate), glycerylphosphorylcholine, and L-alpha-glycerylphosphorylcholine.

Hundreds of clinical and scientific studies document that GPC has a plethora of roles in human health, with proven benefits for people at all stages of life. As a dietary supplement, GPC has been extensively researched and has shown consistent benefits. It has excellent safety and tolerability, consistent with its orthomolecular status.

GPC's biochemical centrality in our cell processes becomes physiologically amplified into tissue growth and renewal, organ vitality, reproduction, and mind-body integration. GPC appears to be that rare nutrient which supports the mind, the body and their functional integration for the individual's ongoing survival.

At least twenty-three (23) clinical trials have been completed using GPC. All have had clinically meaningful positive outcomes. GPC significantly 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 asserted in a meta-analysis by the veteran clinician Lucilla Parnetti.[5] It has proven uniquely valuable for brain recovery following stroke or other circulatory injury.[6-8] Last but not least, preliminary findings indicate GPC can revitalize 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. Well-controlled trials prove GPC can benefit this population.

The drug scopolamine depletes the brain's acetylcholine stores, causing a transitory cognitive impairment similar to that observed in normal aging—"scopolamine amnesia."[10] Canal and collaborators at the University of Milan did 2 double-blind trials that assessed GPC's capacity to block this effect of scopolamine in young, healthy people.[3,4]

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, both given by intramuscular injection. In the first double-blind trial,3 the 32 subjects were randomly allocated to 4

different groups. They were then preloaded with either placebo or with GPC by mouth (1200 mg per day), for 10 days. On the eleventh day they were 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 of 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. Further, 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. 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 against scopolamine amnesia, to a degree superior to idebenone and aniracetam. "Working memory," a test of abstract reasoning carried out together with an interfering attentive task, also was significantly protected by GPC—it was virtually completely protected, never significantly dropping below baseline under the influence of scopolamine.[4]

Overall, these findings indicate that GPC has a truly rare ability to improve mental performance in young, healthy people. Its capacity to block scopolamine's detrimental effects on their attention, word recall, and working memory capacities were impressive, and even more impressive was that GPC could enhance their baseline mental performance.

Besides this marked enhancement of cognitive functions, in a randomized double-blind trial with healthy subjects aged 25-32 years GPC improved the EEG (electroencephalograph) patterns.[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. A double-blind EEG trial used subjects with AAMI (age-associated memory impairment), a condition diagnosed in subjects aged 50 years or older. As observed with the young healthy subjects, GPC achieved a lessening of the delta slow waves associated with accelerated aging.[12]

In controlled trials with subjects as old as 65 years, GPC improved a number of mental processing measures, including reaction time linked 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, in a direct comparison against 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 milliseconds 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] 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. When compared with other dietary "cholinergic precursors" such as choline, phosphatidylcholine or cytidine diphosphocholine (citicoline), GPC has superior benefits.[17] In 2001 Lucilla Parnetti published a meta-analysis of the data then available on GPC in this area of application.[5] Parnetti's analysis covered 10 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 7 trials with GPC against vascular dementia that altogether involved 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 scale quantifies cognitive decline, emotional-affective aspects, and problems with interpersonal relationships.

In all these trials GPC improved the overall clinical symptoms, including cognition, affective (mood) symptoms, and somatic symptoms such as fatigue and dizziness. The findings, 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 citicoline 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's review[5] identified 6 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 scoring system.[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 acetylcarnitine.[25] And when compared 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 on this multicenter trial noted the degree of benefit from GPC was similar to 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, “possibly improving patients’ and caregivers’ quality of life.” This trial did not lose a single patient to adverse effects from GPC.[27]

GPC is Unmatched for Stroke Recovery

GPC has produced especially impressive benefits for brain trauma recovery. In all, five trials have been published in which GPC was successfully used to enhance stroke recovery in 2,972 patients.[6-8,28,48] In all these trials GPC

produced clinically meaningful results, providing benefits for stroke that are unique among nutraceuticals.

Parnetti's 2001 analysis[5] covered three of the 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 3 clinical trials altogether totaled 2,484 patients.[6-8] 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 included 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. The findings from the two others were similarly positive. Parnetti[5] summarized the outcomes from these 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.[5-8]

Two other large, multicenter stroke trials, not reviewed by Parnetti, followed a virtually identical design to the foregoing three.[28] As with the other trials, these patients were started on intramuscular GPC at 10 days after their stroke event, continued for 1 month, then switched over to oral for the subsequent 5 months. The benefits achieved were highly statistically significant.

Intramuscular GPC for the first month accelerated the expected recovery from focal neurological deficits, including space-time orientation, degree of consciousness, language, motor capacity, and general wellbeing. The second phase of treatment with oral GPC (1200 mg/day) consolidated the improvements.

The protocols and outcomes of the 5 stroke trials conducted to date with GPC are analyzed in my review of GPC as an injectable nutraceutical.[47] This review covers all studies and trials in which GPC was administered in injectable form, including GPC's pharmacokinetics and its applications for dementia, growth hormone release, craniocerebral injury, and postsurgical encephalopathy.

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. In some 45-50% of bypass patients mood and personality change, cognitive functions disappear, mental fatigue sets in earlier than normal. These symptoms can be transitory, or persist and 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.[29] 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 significant residual memory deterioration while the placebo group continued to exhibit significant memory impairment.

The trials that used GPC with success to treat craniocerebral injury are discussed in my review of GPC as an injectable, intended for qualified health professionals.[47] For this application GPC offers a precious option for patients so badly damaged as to be in coma.

To summarize, in 11 trials conducted on dementia, 5 on stroke, 2 on craniocerebral injury, and 1 on surgery-related cognitive damage, GPC produced clinically remarkable improvement and was extremely well tolerated. In her meta-analysis, Parnetti[5] concluded that GPC's degree of efficacy ranks it superior to other cholinergic agents. GPC, whether used via the oral, the intramuscular or even the intravenous routes, presents a remarkable opportunity for benefit to these patient populations. It is also very well suited for use in combination with drugs or other nutrients.

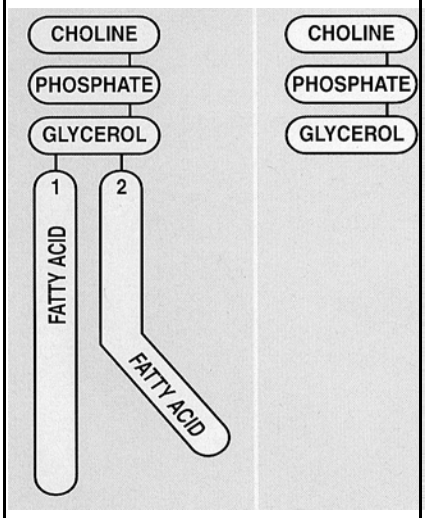
GPC may be so well tolerated because it is an endogenous, orthomolecular protectant for all the tissues. Being zwitterionic (having a positive and a negative charge on the same molecule), GPC is especially well suited for a range of buffer functions. Indeed, its concentration in the human brain was found to increase following stroke, also in neurological and psychiatric disorders such as Alzheimer's, schizophrenia, bipolar disorder, and cerebellar ataxia.[30] 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.

GPC Works Through Diverse Mechanisms

GPC has truly profound involvement in human biochemistry. It provides a unique form of non-antioxidant protection for all our cells. It is a rare water-phase phospholipid, a building block for the membranes that drive all cells. Further, GPC is a major source of the key chemical nerve and muscle transmitter acetylcholine, and the body's main reservoir of the essential nutrient choline.

The small GPC molecule is well absorbed into the watery phase, soon to circulate with the blood and reach all the tissues. It readily crosses the blood-brain barrier to support numerous brain processes. GPC also has defined roles in the essential functions of the autonomic nervous system, reproductive system, endocrine system, skeletal muscles, kidneys, and liver. GPC supports human health through a variety of mechanisms, as detailed in the sections that follow.

Figure 2. Oil-phase versus water-phase phospholipids. Lt: PC (phosphatidylcholine). Rt: GPC, lacking the fatty acid "tails" of PC.



Effective Source of Choline, Essential Nutrient

Choline is a vitamin-like, essential nutrient. Its many functions include serving as (a) a methyl group source for gene-level and other metabolic regulation, (b) a precursor for the transmitter substance acetylcholine, (c) a resource for incorporation into the choline cell membrane phospholipids sphingomyelin and phosphatidylcholine (PC). But free choline is unstable in the water phase and potentially toxic. Thus the blood and tissues carry very little free choline. GPC is an effective and convenient source of metabolic choline, and a key choline buffer and reservoir in humans.

Whether injected or given by mouth, GPC effectively raises blood and brain choline levels for an extended period, without the shortcomings posed by dietary choline supplements.[31] In young, healthy human volunteers, oral GPC was well absorbed and markedly increased the plasma levels of choline for up to ten hours.[31] In rats, brain choline already was increased at one-half after oral administration; the brain uptake may involve active transport.[32] By 24 hours in the rat, all the brain regions are enriched with GPC but the

pituitary gland concentration is far above the plasma concentration an markedly exceeds any other brain region.

Resource for AcetylCholine, Chemical Transmitter

By readily elevating brain choline levels, GPC also is a major resource for brain production of acetylcholine (ACh).[33] This chemical transmitter is central to 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. Experiments with rats indicate that GPC given by mouth significantly raises brain ACh levels, but especially in the hippocampus.[33] This treatment also improves the animal's resistance to agents that deplete ACh. Scopolamine, the agent used by Canal's group to induce amnesia in humans,[3,4] also fails to induce amnesia in rats predosed by mouth with GPC.[33]

A Phospholipid Cell Membrane Builder

Life depends on cell membranes.[34] Membranes are dynamic microstructures built on a continuous matrix composed mostly of phospholipids. Within this matrix are arranged the large protein complexes that drive energetics and most of the other metabolic processes that support life. From the simplest to the most sophisticated life forms, membranes are basically the same in their structure and their importance for the continuation of life.[34]

Quantitatively, the main phospholipid of membranes is phosphatidylcholine (PC). Cells grow or renew themselves by making new membrane mass, and this creates demand for PC, which in its turn is most efficiently synthesized from GPC.[35]

GPC is unique in being a water-phase phospholipid. Technically it is a "de-acylated" PC—the PC molecule without its usual fatty acid tails (see Fig. 2). The GPC molecule is readily transformed to PC by simply adding back the fatty acid tails,[35] and enzymes exist to do this trick with very little energy cost. Therefore GPC has special value for our cells: in its native form it is a unique protectant that can attain high levels in the cytoplasm without doing damage. Then, this reservoir can be drawn upon to make PC for membrane

mass, notably without the major energy expenditure of energy needed to make PC from simpler precursors such as CDP-choline.[35]

Preferred Source for Omega-3 PhosphatidylCholine

GPC's utility as a convenient, cytoplasmic source for membrane PC has a more sophisticated aspect. Cells that are the most metabolically active require the most fluid membrane systems, and fluidity requires that more membrane phospholipids carry long-chain unsaturated fatty acids.[34] GPC is a preferred substrate for attachment with DHA (docosahexaenoic acid, omega-3) to make highly unsaturated DHA-PC molecules.

In such metabolically challenged cells—including nerve cells, skeletal myofibers, the retinal light-sensing cells, and the spermatozoon[34,36,37]—specialized enzymes transfer DHA as new "tails" onto GPC molecules (refer to Fig. 2). Enrichment of membranes with DHA-PC enables their proteins to "flip" or "spin" faster in the membrane environment.[34] The available evidence suggests GPC has a pivotal role in conjunction with DHA, for optimizing cell membrane performance.[36,38] The clinical implications are profound.

Duchenne Muscular Dystrophy, the most common muscular dystrophy in humans, is a progressive muscle fiber dysfunction that destroys the capacity to walk and often causes premature death. Duchenne is based in mutation of a protein (dystrophin) closely linked to the cell membrane system of the skeletal myofiber—the sarcoplasmic reticulum.[36] Analyses of skeletal muscles from patients document a relative deficiency of GPC in the affected muscle fibers.[37]

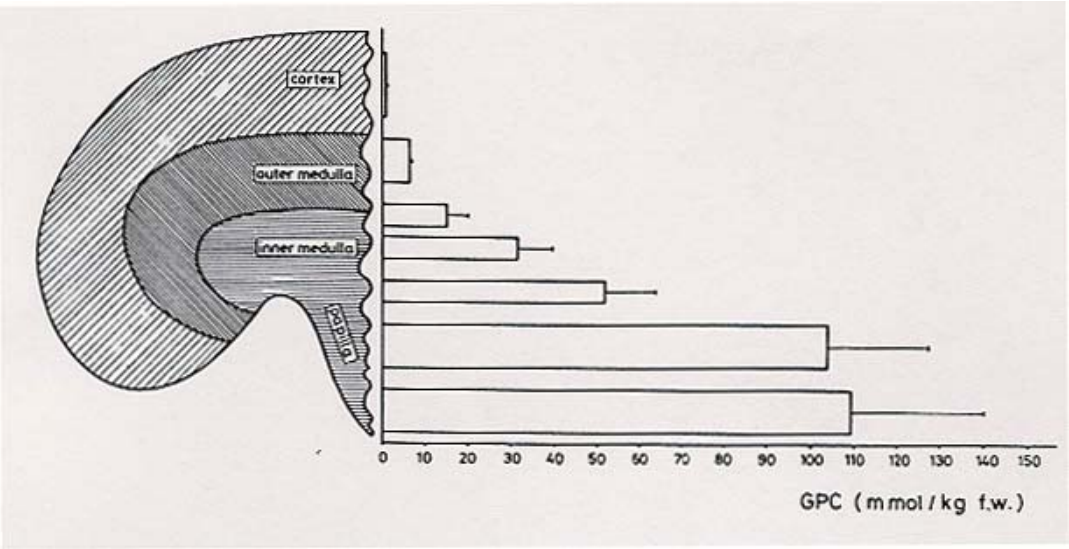
Infante and Huszagh[36] suggested that Duchenne may be, in whole or part, a GPC deficiency disease. They noted that the fastest-contracting skeletal fibers have high levels of DHA-PC in their membranes, to support the high fluidity necessary for rapid transfer of calcium across the membrane. GPC is used to make such DHA-PC for the sarcoplasmic reticulum membranes. As a rule, the faster-contracting a fiber, the more active the reticulum and the higher the content of GPC and DHA-PC. Infante and Huszagh noted that in Duchenne patients, those muscles with the least GPC are the first to break down.

Further research is needed, but recent findings support this GPC deficiency scenario as a contributor to Duchenne muscular dystrophy.[37]

Osmotic Protectant and Osmoregulator

All cells have an osmotic pressure with respect to their external fluid environment. The osmotic pressure is a tendency to draw water into the cell, and is proportional to the total content of molecules in the cell's water-phase ("cytoplasm"). For the cell to survive it must keep its water-phase molecular content in balance with the exterior. GPC is prominently used for this purpose. It is an important osmotic protectant ("osmolyte"[39]) in all the organs, and very likely is used to regulate osmotic pressure wherever osmotically stressful buildup occurs.[39-42]

Figure 3. Proceeding from the outermost cortex of the kidney to the inner papilla, GPC concentration rises in parallel with the rising concentration of urea. From Wirthenson G, et al.[42]



In the nephron cells of the kidney, GPC has unique value to protect against the metabolic buildup of the amine urea.[39-42] This metabolic waste product can become toxic as it accumulates prior to being cleared with the urine. The presence of GPC in high concentration shields the proteins of the cell against damage from urea, without itself posing any threat—GPC is a "nonperturbing osmolyte." In the kidney, GPC can attain concentrations that match or exceed other crucial cell protectants such as glutathione.[42]

Under some circumstances the kidney nephron cells accumulate urea to very high concentrations. The GPC concentrations in these cells rise in parallel with the increasing urea concentrations.[41] Also, moving from the kidney cortex zone to the papilla zone, urea becomes progressively more concentrated and so also does GPC, as illustrated in Fig. 3.[42]

Essential to Sperm Maturation and Fertility

GPC reaches extremely high levels in semen, the highest being a remarkable 100 millimolar in the ram.[39] In human males semen GPC does not even approach this level, but numerous studies conducted over decades have linked poor semen GPC status to male infertility.

GPC is secreted into the seminal fluid from the epididymal cells and probably also from other testicular sources. In men, low levels of GPC in the semen correlate with poor sperm motility.[43] Furthermore, it seems that in newly-impregnated women GPC from the semen may be utilized as an energy source by the endometrial lining cells.[44]

Membrane fluidity is also essential to spermatozoal function—these cells require highly fluid membranes in order to swim. Maturing spermatozoa become enriched in DHA-PC as they move down the epididymis, which likely is produced by combining DHA with GPC.[38] This steadily increasing endowment of DHA-PC results in the spermatozoal membranes being highly fluid as the cells mature, enabling them to swim with high efficiency.

GPC May Revitalize Brain Growth Hormone Release

Supplementation with GPC may also be valuable for mental revitalization at the hormonal level, most specifically by elevating growth hormone (GH) secretion from the pituitary gland. Several studies have been done that used both old and young healthy 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. Abnormally low GH levels are linked with adverse changes in body composition and other hallmarks of unhealthy aging.[45] An orthomolecular intervention that would enhance pituitary GH secretion “from the inside

out," and without significant adverse effects could be a valuable contribution in this area.

Normally GH is released from the pituitary under the control of growth hormone releasing hormone (GHRH) produced by the hypothalamus. In studies by Ceda and collaborators,[9,46] the administration of GPC (i.v.) prior to stimulation with GHRH (i.v.) was found to enhance growth hormone release. Their various intravenous protocols are discussed in my review of GPC as an injectable.[47] The GPC effect of co-stimulating GH release 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, as described here and in the other review.[47]

GPC may also stimulate GH release on its own. In a small double-blind trial conducted by Schettini and collaborators,[26] GPC (1,000 mg per day) or a placebo were administered by once-daily intramuscular injection over a 3-month period. At baseline and the end of the test period, the researchers measured blood levels of the stress hormones cortisol and ACTH, also prolactin and growth hormone (GH).

Schettini and colleagues found that the group given daily i.m. GPC had a significant lowering of cortisol and ACTH and a significant increase of GH, after 3 months.[48] These findings corroborate those of Ceda's group with i.v. GPC,[46] and they further indicate that supplemental GHRH may not be essential to generate this benefit from GPC

There still is no unequivocal published finding that GPC raises blood GH when given by mouth, although this could be reasonably predicted from the positive outcomes with GPC given i.v. and i.m. The Schettini trial[26] also used SPECT scanning (single-photon emission computed tomography) to establish that GPC could elevate cortical energetic activity, in almost half the patients (four of nine). For additional details, refer to my review on injected GPC.[47]

Animal Research Supports GPC's Human Benefits

GPC's capacity to partially revitalize the aging human brain is amply supported by animal research. In rats, GPC blocked the usual age-associated losses of neural networks and neuron numbers in the hippocampus and frontal cortex.[49] In the hippocampus of these aged rats GPC conserved the

granule neurons and the pyramidal CA-1 and CA-3 neurons; in the cortex, the Purkinje neurons; and in the cerebellum, the granule neurons.[49] GPC also conserved hippocampal acetylcholine receptors in aged (24-month) rats, while improving their learning and memory.[50]

GPC also can has displayed regenerative capacity in animal experiments. Following surgical damage of the rat frontal cortex, administration of GPC speeded repair of the lesions.[51] GPC also was found to conserve cerebellar receptors for nerve growth factor (NGF), a foremost factor in mediating brain circuit recovery following damage.[52]

Physiologically, GPC has numerous effects in animal that indicate it slows brain aging. GPC blocks scopolamine's amnesic effect in animals,[53] as it does in humans,[3,4] and when administered by mouth enhanced acetylcholine release within the rat brain.[54] GPC also supports other transmitter systems such as dopamine, norepinephrine, and GABA.[55] GPC supports the signal transduction functions of the nerve cell membrane, which carry the receptor signals into the cell.[56] In rats, as in humans, GPC modifies EEG patterns. It reduces the “slow waves” that can become increased during aging or cognitive deterioration.[57]

Dosing, Safety, Tolerability, Compatibility

The oral intake level of GPC used in the clinical trials was usually 1,200 milligrams (mg) per day, but one trial used 800 mg per day for its oral phase.[58] A reasonable therapeutic dosing strategy for GPC is to begin with 1200 mg/day in divided doses between meals for one month, then drop to 600 mg/day for maintenance. Symptomatic subjects may stay on 1200 mg/day indefinitely or until adequate improvement is noted. The best time to take GPC is early in the day, between meals and preferably before breakfast.

As a dietary supplement for general pro-homeostatic support, GPC can be given at 600 mg/day for the first month, then lowered to 300 mg per day. Here again, the capsules are best taken early in the day, between meals and preferably before breakfast.

GPC is very safe to take. 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 a life-threatening adverse effect.[5,27,47] No adverse drug – GPC interactions

were noted in elderly patients, who continued to take a wide variety of medications during the trials. Adverse effects most often reported from GPC in trials include dizziness, nausea, and sometimes a sensation of over-excitation. Often these can be ameliorated by lowering the daily intake. For some individuals a maintenance intake as low as 300 mg per day would likely provide noticeable benefit.

GPC's safety is attributable to its status as an orthomolecule. It is naturally present in all the body's cells, tissues and organs. It reaches very high concentrations, as part and parcel of its many pro-homeostatic functions. Metabolically, as shown from the numerous human and animal studies, GPC functions in harmony with the vitamins and the other orthomolecular nutraceuticals. It is also freely compatible with pharmaceuticals.

Unlike the fat-soluble phospholipids, GPC has a pleasant taste and can be consumed with pleasure as a liquid supplement.

Conclusions: GPC, Orthomolecule for All Ages

The substantial body of human research reviewed herein, and in my allied review exclusively for health professionals,[47] establishes GPC as a markedly beneficial orthomolecule (and nutraceutical) for individuals of all age groups. In many well-controlled clinical trials, GPC improved mental performance in the healthy young, the middle-aged, and the elderly. In head-to-head comparisons GPC's benefits surpassed those of pharmaceuticals (oxiracetam, aniracetam, idebenone) and nutraceuticals (acetylcarnitine, CDP-choline). Its capacity to boost growth hormone release[9,45-47] further elevates GPC to a category all its own.

GPC is not a vitamin — human cells have the capacity to produce it. But the evidence suggests that under stress, the organs can be called upon to rapidly make new GPC in large amounts, for its protective and other metabolic attributes. Under such biochemical – metabolic challenge, dietary GPC availability makes a clinically measurable contribution to quality of life. GPC's fundamental importance to life is predicted from its universal occurrence down to the simplest life forms, and in particular for its relative abundance in mother's milk.

For *Homo sapiens sapiens*, GPC appears to be important from cradle to old age. GPC's diverse benefits as cell membrane fluidizer, choline and acetylcholine reservoir, osmoprotectant and osmoregulator, fertility support substance, and brain revitalizer, underscore its benefits for people of all ages.

From the available evidence, dietary GPC supplementation benefits:

1. Development and maintenance of attention, concentration, recall
2. Speed and overall sharpness of mental processing
3. Mood, including positive attitude and sociability
4. Recovery of brain function following circulatory deprivation
5. Revitalization of declining mental function
6. Skeletal muscle integrity, including growth and regeneration
7. Kidney and liver functions, including renewal and detoxification
8. Fertility, both for sperm performance and for fertilization.

The many documented successes of GPC as an injectable nutrient add a literally lifesaving dimension to its efficacy.[47] For patients afflicted with stroke, cognitive problems that often follow surgery, or traumatic head injury, GPC offers safe and effective intervention that could make all the difference to quality of life if not to survival itself. Its promise as a growth hormone releaser and possible pituitary gland revitalizer remains to be more fully explored.

Besides its amply proven support for the mind and mental performance via the brain and nervous system, GPC also supports the body and physical performance via the skeletal muscles and the autonomic nervous system. GPC is a truly unique orthomolecular supplement for active living, through optimal integration of mind with body.

Most of us wish for an active life well into old age, and to experience the aging process with freedom from crippling disease. GPC may not be an "anti-aging" panacea, but as a unique mind-body nutrient it points the way to a healthy aging experience.

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