

LE Magazine September 2002

COVER STORY

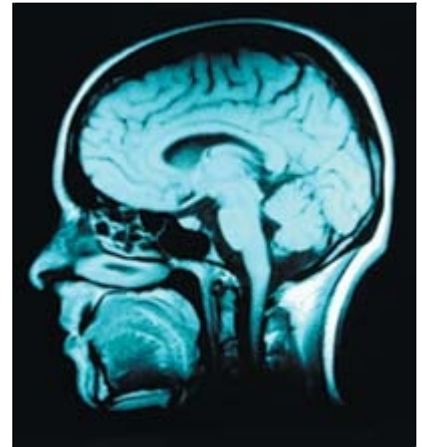
European Therapy Helps Prevent Brain Aging and Restore Neurologic Function

Page 1 of 2

Glycerylphosphorylcholine is a drug prescribed in Europe to treat neurological disease. It is sold in the United States as a dietary supplement to protect against age-related brain deterioration and memory loss.

In the November 2001 issue of *Mechanisms of Ageing and Development*, an extensive review was published about the multiple effects of glycerylphosphorylcholine (GPC).[1] The analysis covered thirteen published clinical trials examining a total of 4,054 patients with various forms of brain disorders including adult-onset cognitive dysfunction, Alzheimer's disease, stroke and transient ischemic attack. The overall consistent finding was that "administration of GPC significantly improved patient clinical condition."

The researchers stated that the effects of glyceryl-phosphorylcholine (GPC) were superior to the results observed in the placebo groups, especially with regard to cognitive disorders relating to memory loss and attention deficit. They noted that the therapeutic benefits of GPC were superior to those of acetylcholine precursors used in the past, such as choline and lecithin. What most impressed the researchers was data indicating that GPC helps facilitate the functional recovery of patients who have suffered a stroke.



Brain aging is characterized by cerebral circulatory deficit and neurotransmitter deficiency, along with structural deterioration to neurons and their connective transmission lines (axons and dendrites). A significant body of research indicates that glycerylphosphorylcholine (GPC) may be of benefit in helping to prevent every one of these pathological events. It may thus be possible to both protect against underlying causes of brain aging while partially restoring cognitive function.

This article describes the scientific studies that substantiate the benefits of glycerylphosphorylcholine.

Mechanisms of Ageing and Development is the official journal of the British Society for Research on Ageing.* This non-profit organization was the first scientific body to be concerned specifically with gerontology as a scientific discipline.

The aim of the Society is to foster an experimental approach to the problems of biological aging and to promote research to understand the causes of aging. Many of the now accepted molecular and medical concepts of aging were first introduced in the journal *Mechanisms of Ageing and Development*.

Note that "ageing" is the British spelling for aging. The British Society for Research on Ageing grew out of the "Club for Ageing" founded in the 1940's by Vladimir Korenchevsky.

Choline-fuelled signalling molecules are at the seat of learning, memory and behavior. As a result, there has been a lot of buzz around manipulating cholinergic neuronal transmission in order to slow or undo the neurologic effects of aging.

The tricky part is not how much choline can be pumped into the brain, but how efficiently this critical raw material can be transported to various regions of the brain. Otherwise, it's like gassing up a car that has a clunked out engine.

A large problem in aging and diseased brains is the slowing of cholinergic transport, while cholinergic neurons drop in number. In Alzheimer's disease, cholinergic cells shrivel up and die at a fast-forward pace. Scientists believe that even in healthy aging people, malfunctioning and decreased numbers of choline-powered neurons are somewhat to blame for short-term memory loss and cognitive decline.

The reason why choline has to get where it's going in the brain is that it has a big to-do list. In addition to being the precursor for the neurotransmitter acetylcholine, choline also synthesizes phosphatidylcholine. Brain cell membrane integrity is dependent on phosphatidylcholine. When choline levels are low, phosphatidylcholine can function to produce more acetylcholine. The problem with low choline is that it compromises the integrity of brain cell membranes, since boosting the production of acetylcholine diverts phosphatidylcholine away from its critical job of maintaining cell membranes. This all explains why the brain has such a voracious appetite for choline.

Help on the way

Enter L-alpha glycerylphosphoryl-choline (GPC), a byproduct of phosphatidylcholine, and a precursor that's useful in stoking the cholinergic neurotransmitter system. More specifically, it aids in the synthesis of several brain phospholipids, which increases the availability of acetylcholine in various brain tissues. The GPC form of choline has been shown in studies to reverse the cognitive and behavioral glitches seen in aging, Alzheimer's disease (AD), stroke and memory loss.

Aging

Studies suggest that glyceryl-phosphorylcholine is effective in slowing the expression of structural changes that occur in the brain as a result of age. These changes result in the loss of neuronal function, as well as a decline in the number of neurons and their receptors. One study found that long-term treatment of rats with GPC in their drinking water was effective in countering the loss of neuro-connecting fibers and brain cells that are consistent with aging. In GPC-treated rats, both the area occupied by neuro-connecting fibers and their density were significantly higher than in age-matched controls. Moreover, the number of granule neurons of the hippocampus (nerve cells that transmit information to the cerebellum) was higher in GPC-treated animals than in control 24-month-old rats. The authors stated that it appears that "glycerylphosphorylcholine treatment counteracts some anatomical changes of the rat hippocampus occurring in old age."^[2]



More specifically, GPC aids in the synthesis of several brain phospholipids, which increases the availability of acetylcholine in various brain tissues. The GPC form of choline has been shown in studies to reverse the cognitive and behavioural glitches seen in aging.

Other research shows similar findings. Scientists looked at the density of nerve cells in the hippocampus and in the cerebellar cortex in adult (12-month-old) and old (24-month-old) rats. Results showed that a six-month treatment with GPC countered the age-dependent reduction of nerve cells.^[3]

A number of studies have also demonstrated the ability of GPC to help restore muscarinic M1 receptors in old rats. These are a type of acetylcholine receptor whose number of sites tend to decrease with age. Italian researchers assessed the effects of aging and of GPC treatment on the hippocampus of experimental rats. Treatment with GPC restored, in part, choline acetyltransferase immunoreactivity and acetylcholinesterase reactivity in the hippocampus of aged rats. The treatment also countered, in part, the age-related loss of M1 receptors in old rats.^[4]

In a later study, this scientific team examined specifically how six-month treatment with GPC would affect the density and pattern of M1 cholinergic receptors in rat brains. And again, they found that GPC treatment countered, in part, the loss of muscarinic M1 receptor sites in old rats. The authors suggest that the reduction in muscarinic M1 sites noticeable in aging rats may reflect a loss of nerve cells and/or terminals in these hippocampal fields, and that GPC increased the expression of muscarinic M1 cholinergic receptors.^[5] Likewise, other researchers concluded that chronic treatment of aged rats with GPC restored the number of M1 receptors to levels found in the striatum and hippocampus from young animals, and partially reversed membrane stiffness in both regions.^[6]

Dementia

The idea that cholinergic treatments might help dementia of the Alzheimer's kind goes back to what's known as the "cholinergic hypothesis" set forth about 20 years ago.^[7] That's when a U.S. researcher found and reported that the number of cholinergic neurons in the basal forebrain was substantially lower in Alzheimer's disease patients than in healthy individuals, and that the loss of cholinergic innervation from this area of the brain might be the basis of disease-related cognitive changes. Since then, research has characterized the Alzheimer's brain as having substantive degenerative loss of cholinergic receptors and a deficiency of acetylcholine, which could explain the breakdown in cholinergic transmission that leads to dementia, learning and memory impairment.

While certainly not an exclusive theory on the underpinnings of Alzheimer's disease and how to treat it, the theory has given rise to a number of cholinergic-based therapies aimed at bettering cholinergic transmission. Primarily, therapies have included the use of acetylcholine precursors, M1 muscarinic agonists, and acetylcholinesterase or cholinesterase inhibitors in order to restore cholinergic function in the Alzheimer's disease brain. Inhibiting the natural breakdown of acetylcholine through esterase inhibitors and stimulating acetylcholine release with cholinergic precursors, such as choline and phosphatidylcholine (lecithin), have been the focus of many clinical trials.

A limited amount of research and small clinical trials have demonstrated that GPC boosts acetylcholine availability, its release, and even slightly improves cognitive dysfunction.[8] Moreover, a larger, multicenter, randomized, controlled study echoed the results of smaller studies. Researchers compared the efficacy of GPC and acetyl-L-carnitine among 126 patients with probable senile dementia of Alzheimer's type of mild to moderate degree. Results showed significant improvements in most neuropsychological parameters in the GPC recipients that was greater than improvements in the acetyl-L-carnitine group.[9]



Continued on Page 2 of 2

[click here for more information on Cognitex without Pregnenolone](#)

[click here for more information on Cognitex with Pregnenolone](#)

[Back to the Magazine Forum](#)

COVER STORY

Page 2 of 2

Stroke

Researchers have found that GPC can be useful in the treatment of cognitive deficits that often arise from cerebrovascular (stroke) events. When blood flow is disrupted by a stroke, the result is a cascade of events involving glutamate flooding NMDA receptors (excitotoxicity), which then leads to neuron death in the affected region of the brain.

An Italian multicenter trial looked at GPC in 2,044 patients suffering from recent stroke or transient ischemic attacks. GPC was administered, in phase 1, after the attack at the daily dose of 1 gram intramuscularly for 28 days and, in phase 2, orally at the dose of 400 mg during the next five months. Using a series of different standard measuring scales, a positive association was found in all parameters. According to one scale that measured deterioration (Global Deterioration Scale), "no cognitive decline" or "forgetfulness" was reported for 71% of the patients.[10]

A review of 13 published clinical trials comprising 4,054 patients in all, set out to weigh the benefits of GPC treatment for various forms of dementia disorders, including senile dementia of the Alzheimer's type or vascular dementia, and in acute cerebrovascular diseases, such as transitory ischemic attack (TIA) and stroke. Results from 10 controlled trials comparing GPC to a reference drug or placebo showed that GPC's clinical results were better or equal to those observed in control groups under active treatment and superior to the results observed in placebo groups. Meanwhile, three uncontrolled trials examining the use of GPC in acute cerebrovascular stroke and transient ischemic attack ("mini stroke") demonstrated promise that it could help with the functional recovery of patients with cerebral stroke, but would require further investigation.[1]



Memory loss

Another area of research has focused on the loss of memory function that occurs due to any number of causes, including disease, trauma or infection. Since amnesia (partial memory loss) has been related to decreased or blocked acetylcholine, researchers have set out to examine reversing this damage using GPC.

In one study, GPC was injected for 20 days into aged male rats (24 months old) with learning and memory capacity deficits. It was also administered to rats with amnesia, which was experimentally induced by scopolamine, a drug that works by blocking acetylcholine receptors. Results indicated that learning and memory capacity improved in both groups.[11]

Other researchers found that oral GPC reverses pharmacologically induced amnesia and partially counteracts the decrease of brain acetylcholine levels elicited by scopolamine administration. Additionally, in experiments that involved analyzing hippocampus slices from rats, scientists found that GPC was able to increase the amount of acetylcholine released.[12] Another study showed that administering oral GPC to rats prevented the learning impairment and reversed amnesia induced by scopolamine. This study showed that GPC increased acetylcholine release and resulted in acetylcholine formation. The authors concluded that the behavioral effects of GPC's ability may relate to its ability to increase hippocampal acetylcholine synthesis and release.[13]

Explaining the effects

Scientists have homed in on a number of means by which GPC may elicit its various brain fortifying effects. It is believed that GPC's mode of action may involve the release of free choline, which then aids in the synthesis of acetylcholine and phosphatidylcholine. A study involving 12 volunteers compared GPC to CDP-choline and showed that plasma choline was higher after GPC. [14] Some researchers have suggested that GPC "may result in an increased rate of phospholipid synthesis, including the phosphoinositides available for signal transduction at central nervous system level." [15]

Another area of research has focused on the loss of memory function that occurs due to any number of causes. Since amnesia has been related to decreased or blocked acetylcholine, researchers have set out to examine reversing this damage using GPC.

In other research, investigators demonstrated how GPC increased gamma-aminobutyric acid (GABA) release.[16] This amino acid acts as an inhibitory neurotransmitter in the central nervous system. Decreased amounts of GABA have been shown to contribute

to the dementia, mood disorders and psychoses related to Huntington's and Alzheimer's disease.[17]

GPC has also been called a growth hormone sensitizer, which basically means that it has the ability to potentiate the effects of growth hormone releasing hormone (GHRH) and increase human growth hormone (hGH) secretion, as one study showed.[18] Researchers wanted to assess what effect GPC would have on growth hormone secretion, so they administered growth hormone-releasing hormone (GHRH) to young and old human volunteers, either in combination with GPC or exclusively. Results revealed a greater growth hormone response to the GHRH plus GPC than to GHRH alone, and the effect was more pronounced in elderly subjects.

Moreover, other researchers have been able to show that GPC treatment may increase the expression of nerve growth factor receptors in the rat cerebellar cortex. Nerve growth factor is important for regulating the growth and maturation process of cholinergic neurons in the central nervous system, as well as their repair, survival and regeneration. Unfortunately, the receptors for these vital proteins fall prey to the ravages of age, making them less effective over time at performing their neuroprotective work. However, findings from one study suggest that GPC can undo these age-related effects, after the daily administration of GPC to rats for six months.[19]

Other researchers have demonstrated that GPC increases protein kinase C activity after just one hour following oral administration. And in vitro, GPC promoted protein kinase C translocation in cortical slices from rats at concentrations.[20]

GPC also increases the release of the neurotransmitter dopamine, a chemical messenger in the brain that regulates emotions, sensation of pain and pleasure and physical movement. This may be useful in the treatment of Parkinson's disease, which has been found to involve an imbalance between dopaminergic and cholinergic transmission. In Parkinson's disease, dopamine-transmitting neurons die. That's why patients are given L-DOPA, a drug that produces dopamine in the brain as a replacement for endogenous dopamine. If GPC can perform a similar task, it may become another way to ameliorate Parkinson's.[21]



Safety profile

At a glance, GPC seems to have much to offer the aging brain by increasing the bioavailability of choline, restoring the number of acetylcholine receptors and decreasing progressive cell membrane stiffness that occurs with cognitive aging. But as anyone knows, the most effective drug therapy in the world won't work if patients do not, or cannot, take it.

GPC has been shown in numerous human studies to have high tolerability and safety. In one study, side effects, such as heartburn, nausea-vomiting, insomnia-excitation and headache were reported by just 2% (44) of patients, and only four patients dropped out of the study due to unwanted effects. The authors conclude that, "The trial confirms the therapeutic role of GPC on the cognitive recovery of patients with acute stroke or TIA, and the low percentage of adverse events confirms its excellent tolerability." [22]



An open clinical trial was carried out to compare the efficacy and the tolerability of 1 gram/day GPC with 1 gram/day CDP-choline, both given intramuscularly for 90 days in 120 patients with mild to moderate vascular dementia. Besides reporting good symptomatic relief and tolerability with both treatments, results suggested GPC tested more highly on both accounts, according to clinical measurements and patients reports, compared with CDP-choline.[23] Other studies have echoed the same kind of positive reports.

Conclusion

Given the growing evidence that suggests glycerylphosphorylcholine's (GPC) usefulness in preventing and treating many conditions that tax our mental faculties, coupled with a vote for its safety and tolerability, it would not be surprising to see this neuroceutical gaining more ground in neuropsychiatry circles and popularity among people who want to preserve their brain power for as long as possible.

References

1. Parnetti L, et al. Choline alfoscerate in cognitive decline and in acute cerebrovascular disease: an analysis of published clinical data. *Mech Ageing Dev* 2001 Nov;122(16):2041-55.
2. Ricci A et al. Oral choline alfoscerate counteracts age-dependent loss of mossy fibres in the rat hippocampus. *Mech Ageing Dev* 1992;66(1):81-91.
3. Amenta F, et al. Long term choline alfoscerate treatment counters age-dependent microanatomical changes in rat brain. *Prog Neuropsychopharmacol Biol Psychiatry* 1994 Sep;18(5):915-24.
4. Amenta F, et al. Cholinergic neurotransmission in the hippocampus of aged rats: influence of l-alpha-glycerolphosphorylcholine treatment. *Ann N Y Acad Sci* 1993 Sep 24;695:311-3.
5. Amenta F, et al. Muscarinic cholinergic receptors in the hippocampus of aged rats: influence of choline alfoscerate treatment. *Mech Ageing Dev* 1994 Oct 1;76(1):49-64.
6. Muccioli G, et al. Effect of l-alpha glycerylphosphorylcholine on muscarinic receptors and membrane microviscosity of aged rat brain. *Prog Neuropsychopharmacol Biol Psychiatry* 1996 Feb;20(2):323-39.
7. Whitehouse PJ, et al. Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. *Science* 1982 Mar 5;215(4537):1237-9.
8. Amenta F, et al. Treatment of cognitive dysfunction associated with Alzheimer's disease with cholinergic precursors. Ineffective treatments or inappropriate approaches? *Mech Ageing Dev* 2001 Nov;122(16):2025-40.
9. Parnetti L et al. Multicentre study of l-alpha-glycerolphosphorylcholine vs ST200 among patients with probable senile dementia of Alzheimer's type. *Drugs Aging* 1993 Mar-Apr;3(2):159-64.
10. Barbagallo Sangiorgi G, et al. Alpha-glycerophosphocholine in the mental recovery of cerebral ischemic attacks. An Italian multicenter clinical trial. *Ann N Y Acad Sci* 1994 Jun 30;717:253-69.
11. Drago F, et al. Behavioral effects of l-alpha-glycerolphosphorylcholine: influence on cognitive mechanisms in the rat. *Pharmacol Biochem Behav* 1992 Feb;41(2):445-8.
12. Lopez CM, et al. Effect of a new cognition enhancer, alpha-glycerolphosphorylcholine, on scopolamine-induced amnesia and brain acetylcholine. *Pharmacol Biochem Behav* 1991 Aug;39(4):835-40.
13. Sigala S, et al. L-alpha-glycerolphosphorylcholine antagonizes scopolamine-induced amnesia and enhances hippocampal cholinergic transmission in the rat. *Eur J Pharmacol* 1992 Feb 18;211(3):351-8.
14. Gatti G, et al. A comparative study of free plasma choline levels following intramuscular administration of L-alpha-glycerolphosphorylcholine and citicoline in normal volunteers. *Int J Clin Pharmacol Ther Toxicol* 1992 Sep;30(9):331-5.
15. Aleppo G, et al. Chronic l-alpha-glycerolphosphoryl-choline increases inositol phosphate formation in brain slices and neuronal cultures. *Pharmacol Toxicol* 1994 Feb;74(2):95-100.
16. Ferraro L, et al. Evidence for an in vivo and in vitro modulation of endogenous cortical GABA release by alpha-glycerolphosphorylcholine. *Neurochem Res* 1996 May;21(5):547-52.
17. Cummings JL, et al. Neurobiological basis of behavior. In: Coffey CE, Cummings JL, eds. *Textbook of Geriatric Neuropsychiatry*. American Psychiatric Press;1994:72-96.
18. Ceda GP, et al. Alpha-glycerolphosphorylcholine administration increases the GH responses to GHRH of young and elderly subjects. *Horm Metab Res* 1992 Mar;24(3):119-21.
19. Vega JA et al. Nerve growth factor receptor immunoreactivity in the cerebellar cortex of aged rats: effect of choline alfoscerate treatment. *Mech Ageing Dev* 1993 Jun;69(1-2):119-27.
20. Govoni S, et al. PKC translocation in rat brain cortex is promoted in vivo and in vitro by alpha-glycerolphosphorylcholine, a cognition-enhancing drug. *Ann N Y Acad Sci* 1993 Sep 24;695:307-10.

21. Trabucchi M, et al. Changes in the interaction between CNS cholinergic and dopaminergic neurons induced by l-alpha-glycerylphosphorylcholine, a cholinomimetic drug. *Farmaco [Sci]* 1986 Apr;41(4):325-34.

22. Barbagallo Sangiorgi G, et al. Alpha-glycerophosphocholine in the mental recovery of cerebral ischemic attacks. An Italian multicenter clinical trial. *Ann N Y Acad Sci* 1994 Jun 30;717:253-69.

23. Di Perri R, et al. A multicentre trial to evaluate the efficacy and tolerability of alpha-glycerylphosphorylcholine versus cytosine diphosphocholine in patients with vascular dementia. *J Int Med Res* 1991 Jul-Aug;19(4):330-41.

For more information on Cognitex *without* Pregnenolone, click here:

For more information on Cognitex *with* Pregnenolone, click here:

[Back to the Magazine Forum](#)

All Contents Copyright © 1995-2009 Life Extension Foundation All rights reserved.

LifeExtension®

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.