



“P.S.”:

Remember Your Citicoline!

Once thought to be little more than a sort of “bag” that kept the cell’s innards in one place, the cell membrane is now known to be a key player in the life of the cell. Like a castle wall, with its lookouts, drawbridge, and sentries, well-functioning cell membranes must simultaneously protect the cell from a hostile outer world, while allowing crucial raw materials in and letting wastes out. More: like a castle wall, the cell membrane may be used as an anchor for equipment necessary for the livelihood of the inhabitants. So proper cell membrane structure plays a crucial role in the health and functioning of cells.

In the case of the brain, membrane structure is even more crucial. Brain function depends on communication between brain cells (neurons). Although it happens at lightning speed, the process by which these brain cells talk to one another is amazingly complex -- and every step along the way is dependent on proper cell membrane structure and function. Part of the reason why the brain seems to go downhill with “normal” aging is changes to the amounts, balance, and chemistry of fatty molecules called phospholipids in the brain.^{1,2}

PS: The Lecithin with Limits

By now, almost anyone who’s sought out natural support against **Age-Related Cognitive Decline (ARCD)** knows about the brain phospholipid **phosphatidylserine** (*foss-fah-tie-dull-SEER-een*, or *foss-fah-tid-ull-sir-EEN*: abbreviated “**P.S.**” -- a cute, catchy name for a brain nutrient!). Phosphatidylserine has an earned reputation as a core nutrient for those looking to slow, and even to reverse, aspects of ARCD -- a reputation firmly founded on several clinical trials.^{3,5}

When we’re young, well-nourished, and healthy, our brains naturally produce their own phospholipids, creating exactly the fatty molecules it needs, in the ratios required. The failure to maintain the level and balance of new phospholipids is at the root of much of the decline in mental function that accompanies aging. That’s why taking PS can be so helpful with ARCD: it boosts the brain’s declining levels of PS back to more youthful levels, allowing the brain’s PS-dependent machinery to function more youthfully in turn.

But important as PS is for the healthy working of the brain, it isn’t the whole story on phospholipids and brain function. When a person takes a PS supplement, his or her brain becomes enriched with PS; however, the brain depends upon having *all* of its natural phospholipids present, at optimal levels and in a balanced ratio. So while taking PS alone can “top up” the level of *one* crucial phospholipid in neuron membranes, it can never completely restore the youthful phospholipid balance of the brain -- and thus, youthful brain structure and function.

Fill in the Gaps

Brain function relies on a wide spectrum of phospholipids -- not just PS. Of course, PS supplements contain small amounts of some of the other key brain phospholipids

(**phosphatidylcholine [PC]** and **phosphatidylinositol [PI]**), but not in the same proportions as are found in a healthy, functioning brain. And however important PS may be, these other phospholipids also play vital roles in proper brain function.

PI, for instance, is necessary for the normal functioning of 25 different proteins involved in relaying hormonal messages to the inner machinery of the cell, including the crucial **protein kinase C (PKC)**.⁴¹ PI-based signalling is vital to the functioning of every cell in the body; in fact, scientists recently discovered that **signalling using PI is required for the cell to send out instructions from its DNA.**⁴²

Citicoline boosts PS by 37.5%, PC by 22-30%, PI by 16%, and PE by 11-13% in brains and neurons.

It’s also known that **signalling via PI is inhibited in Alzheimer’s Disease**,⁴³ with specific signalling proteins showing reductions of 43-59% in their activity. These signalling systems are involved in a wide range of cellular functions, including normal cell growth and development, utilization of glucose as fuel, and the “cellular suicide” (**apoptosis**) of dysfunctional cells. The proper activation of PKC by PI is known to **reduce the formation of beta-amyloid peptide** from amyloid precursor protein,⁴⁴ plaques made from amyloid are one of the two key features of Alzheimer’s disease. And, in fact, **Alzheimer’s patients show significantly less PI (and phosphatidylethanolamine [PE]) than normal, healthy people.**⁴⁵

Another factor which must be considered is the effects of taking single phospholipids (like PS) on organs *other than* the brain. Different organs, and the various “factories” (**organelles**) within different cells, have different ratios of phospholipids required for optimal function. For instance, the membranes of the body’s cellular “power plants” (**mitochondria**) have much more **PE** than do other organelles.⁴⁸ Unlike the situation with the whole brain, **PS**

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actually *increases* with age in the mitochondria of the heart.⁴⁷ Supplementing with PS alone may thus be expected to further upset the healthy, youthful function of these cellular “power plants.”

One Size Won't Fit All

So PS, alone, is not the whole story on the role of brain phospholipids in declining mental function. Indeed, it's not clear that any *one* combination of specific phospholipids would work to simultaneously elevate the *total amount* of brain phospholipids, while also *maintaining them in their proper proportions* -- or whether such a supplement would be of help or hindrance to the function of membranes elsewhere in the body. Combine this with the role of “biochemical individuality” in health and the aging process, and it quickly becomes clear **there can be no “one size fits all” phospholipid combination:** the perfect mix might have to be “tailor made” for each individual.

Because of this, **taking PS can only be a partial -- and even unbalanced -- way to restore the health of the brain.** Taking PS *alone* -- or PC, or lecithin supplements -- corrects part of the problem, while leaving other parts unaddressed, and may even upset the harmony of the whole. In other words, when your martini runs low, topping it up with straight gin is likely to be a disappointment. Needless to say, the same goes for simple PC or lecithin supplements: they provide some of the pieces, but not the balance of the synergistic whole.

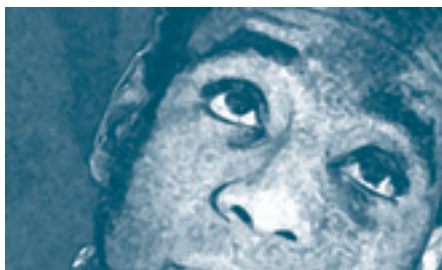
If we were to dream up the ideal supplement for whole-brain phospholipid balance, it would not be a simple “top-up” of a single, isolated phospholipid, or even an amalgamation of several phospholipids, but **a supplement which helps to restore the brain's *own* ability to maintain optimal phospholipid balance.**

The dream supplement is available. It's been used in Europe for decades. And

clinical trials prove that it works.

Citicoline

Cytidine diphosphate choline (CDP-choline or Citicoline) is a remarkable brain nutrient with a proven track record. Although it does contain choline, which is an important nutrient for brain function in its own right, **Citicoline's** real “business end” is the **cytidine** group.



Cytidine is a **nucleoside** -- a molecule in the same class as ATP, the “universal energy molecule,” and similar to the **nucleotides** which make up the DNA genetic code. Taking **Citicoline** delivers cytidine to the brain, where it is transformed into **cytidine diphosphate (CDP)**. CDP plays a key role in the body's production of the brain's phospholipids. Studies in middle-aged⁶⁷ or old⁸ lab animals show that cytidine itself, or cytidine delivered as **Citicoline, boosts PS by 37.2%, PC by 22-30%, PI by 16%, and PE by 11-13%** in brains and neurons.⁶⁹ By supporting the brain's ability to make its *own* phospholipids, the *total* brain phospholipid content is increased, yet the brain's normal, natural phospholipid proportions are retained.⁶

And, at the same time, new research suggests that **Citicoline allows the body to make better use of phospholipids derived directly from the diet or supplements.** A study using radiolabelled PS⁴⁶ shows that the fatty acid “tails” of phospholipids have to be changed as they are taken from the blood, then brought into the cell's outer membrane, and ultimately nestled into their final “home” in the cell. That's how the brain is able to use PS

derived from soy, even though its fatty acid “tails” are different from those in the human brain. Studies in isolated neuron precursor cells show that **Citicoline** selectively enhances the ability of phospholipids to incorporate a variety of fatty acids into their “tails,” facilitating this “customization” process. As well, **Citicoline increases the manufacture or release of key brain messenger molecules, such as acetylcholine,^{9a} norepinephrine, dopamine, and serotonin.⁹**

And it Works!

Extensive test-tube and animal studies have been performed to establish **Citicoline's** mechanisms of actions. But biochemistry is one thing, and results in real people's lives are another. **Double-blind, controlled studies prove that Citicoline delivers effective nutritional support in a broad variety of cognitive disorders,** including cognitive impairment associated with **Parkinson's disease,^{11,12} stroke,^{13,14} head trauma,^{16,17} and Alzheimer's Disease,¹⁸** and that it improves the odds of a good outcome after **high-risk brain surgery.¹⁹** These trials are evidence *in addition to* the many successful human studies which have been run with less formal structure.²²⁻³⁵ The fact that **Citicoline** -- unlike PS -- has been proven to be effective in providing support against such a sweeping range of mental impairments is a testament to its powers as an universal “phospholipid booster.”

But most people taking brain boosting nutrients are not Alzheimer's patients, or persons on a waiting list for risky neurosurgery. Instead, most “smart nutrient” users are either proactively working to *prevent* the onset of cognitive decline in the first place, or are already beginning to feel the effects of what is often referred to in defeatist terms as the “normal” loss of brain function with age. We'd expect that a supplement with such global effects on brain function, and which is effective in such a wide array of severe conditions, would also be useful for this

age-related cognitive decline. And, indeed, **placebo-controlled clinical trials have found Citicoline to be effective in ARCD.**^{20,21}

In one such trial,²⁰ older subjects who were experiencing problems with their memories, but who were not suffering dementia, were tested on a battery of memory tests, and found to perform more poorly than young controls. Then the subjects were given each of four treatments, for four weeks each, at different times. All volunteers underwent three periods with different **Citicoline** regimens (a high (1000 mg) or moderate (500 mg) dose of **Citicoline**, or a lower (300 mg) dose combined with **nimodipine** (a blood pressure drug also used to treat some neurological deficits)). Subjects also underwent a dummy-pill phase. The results showed that **Citicoline significantly improved performance on several memory tasks**, including the free recall of word lists and the ability to remember a set of objects (either immediately after seeing them or later on). All **Citicoline** groups showed some improvement over the course of the trial. The only side effects were a decrease in blood pressure, and immunomodulatory effects shown as minor changes in the populations of white blood cells.

Citicoline was also tested in ARCD in a randomized, double-blind, placebo-controlled trial²¹ run by MIT in conjunction with US Army Research Institute of Environmental Medicine. In the first phase, ninety-five older volunteers with no active psychiatric or neurological disorders, and who had scores on tests of mental status which put them within the normal range, were randomly assigned to take either a dummy pill or **Citicoline** for three months. **Those subjects with poorer memories at baseline showed improvements in recall** (remembering details of a story heard one half hour previously).

Subjects who began the study with poorer memories were then used in an additional study, in which they received one of two high doses of **Citicoline** for two months each. The higher dosage of **Citicoline** was **“clearly associated with improved immediate and delayed logical memory.”** While side effects such as constipation, insomnia, and chest pain did occur, no one side effect was more commonly reported in patients receiving **Citicoline** than those receiving the dummy pill. In fact, the *total* incidence of side effects was actually *higher* in the placebo group!

Citicoline delivers effective support in a broad variety of cognitive dysfunctions.

Neurons Beyond the Brain

Of course, the proper functioning of neurons is required for a lot more than just the workings of the brain. Since **Citicoline** so effectively supports the healthy functioning of the nerves of the brain, and has been found so helpful in cognitive functioning, you might expect that **Citicoline** would be helpful with many non-brain conditions grounded in neurological dysfunction.

The final word isn't in, but preliminary evidence suggests that you'd be right.

Glaucoma, for instance, is caused by the buildup of pressure from the fluid in the eye (**intraocular pressure**), which literally *squeezes* the nerves that leave the eyeball, causing them to lose their supply of nutrients and slowly starve. In an open trial,³⁶ patients with glaucoma were given one gram of **Citicoline** daily for ten days. While the study was too short to assess any improvement in symptoms, the researchers did find that **Citicoline “acts positively on the glaucomatous optic nerve damage” and led to “favorable neurotrophic [nerve-nourishing] effects.”**

While these results were obtained using injected **Citicoline**, it is now known³⁷ that **Citicoline** is so well-absorbed that **the bioavailability of Citicoline is the same**

when taken in a capsule as when it is injected. Obviously, what is called for is a large, longer-term trial to prove that the nerve-nourishing positive action of **Citicoline** on nerve damage from glaucoma will translate into clinical results; so far, however, no one seems to have taken up the baton presented by this study.

Likewise, **amblyopia**, or **“lazy eye,”** is ultimately a neurological disorder, although always associated with some other problem with visual function (such as a misalignment of the focus of the two eyes). Amblyopia develops when the nerve cells which connect one eye to the brain are literally *turned off*, because the sensory messages the poorer eye is sending don't match up with those being sent by the dominant eye. After years of being deactivated, the nerves leading to the amblyopic eye can ultimately cause that eye to go fully blind.

Again, **Citicoline** may offer hope. Italian researchers have performed several trials in patients with amblyopia³⁸⁻⁴⁰ which have confirmed that **Citicoline significantly improves both symptoms and neurological function**, and can be used to increase the effectiveness of **occlusion** (the standard therapy for “lazy eye,” which involves covering up the dominant eye to encourage the “deactivated” eye to begin functioning again).

With ongoing research, we may expect the fulfillment of some present promises, and the discovery of new applications for this remarkable nutrient.

Bring the Balance Back

Our minds are what make us who we *are*. Memories are our connection to our history, and the foundation of who we are today. The workings of the mind reflect the structure of the brain, and phospholipids play a vital part in that structure. **Citicoline** restores more youthful levels and balance of brain phospholipids, carrying us from our past into a clear future.

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