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**REPORT****Preserving and Restoring Brain Function**

By Dale Kiefer



Protecting brain health is vital if the pursuit of a longer life is to have any meaning. According to current wisdom, some degree of cognitive impairment is all but inevitable as we age.<sup>1-6</sup> That is, unless steps are taken to prevent it.<sup>7-12</sup>

Scientists in Texas recently noted, “As life expectancy increases worldwide, pandemics of cognitive impairment and dementia are emerging as major public health problems.”<sup>2</sup> Another research team tried to inject humor into this sobering topic:

“Cognitive aspects of aging represent a grave challenge for our societal circumstances as members of the baby-boom generation spiral toward a collective ‘senior moment.’<sup>3</sup>

The encouraging news is that scientists have discovered methods to preserve and even restore neurological structure and function. These powerful weapons give aging adults unprecedented control over their cognitive health.

Recent data indicate that up to 9.4% of Europeans over the age of 65 suffer from some form of dementia.<sup>13</sup> A report from Great Britain notes that the incidence of cognitive impairment may increase dramatically with age.<sup>14</sup>

Cognitive impairment was detected in 18.3% of subjects in a study of more than 15,000 elderly in the United Kingdom, approximately half of whom were 75-79 years old.<sup>14</sup> French researchers noted recently, “In most countries, the prevalence of dementia varies between 6 and 8% for individuals aged 65 years or more. It then dramatically increases with each subsequent decade, reaching around 30% of the population aged over 85.”<sup>15</sup>



Unfortunately, these statistics fail to estimate the incidence of mild cognitive impairment (MCI). Subtler than dementia, MCI is also undoubtedly more prevalent. MCI, defined as an intermediate state between normal aging and dementia, is characterized by “acquired cognitive deficits, without significant decline in functional activities of daily living.”<sup>16</sup> In Australia, a small study attempted to identify the prevalence of MCI without dementia among community-dwelling elderly aged 70-79. One third of the subjects showed evidence of the condition.<sup>17</sup>

Researchers in Germany studied more than 1,000 elderly adults aged 75 and older. “Mild cognitive impairment is very frequent in older people,” they concluded. Prevalence rates ranged from 3% to 36%, depending on the diagnostic criteria applied. Over the course of about 30 months, up to 47% of those identified with MCI progressed to dementia.<sup>18</sup>

**STRATEGIES FOR PROTECTING THE BRAIN**

Cognitive decline is not inevitable with advancing age. It is possible to live a longer and healthier life, but preserving brain health is crucial to accomplishing this goal. Various factors conspire to rob us of mental acuity as we age. Recent studies suggest that inflammation (as determined by elevated levels of interleukin-6 or C-reactive protein), high blood pressure, high blood insulin, excessive body weight or obesity, arterial stiffness, and the increasingly common condition known as metabolic syndrome (characterized by a cluster of abnormal conditions such as insulin resistance, obesity, high cholesterol, and hypertension) are all independent risk factors for dementia.<sup>19-24</sup> Psychological health, including anxiety and depression, has recently been implicated as a risk factor as well.<sup>25</sup>

The ideal strategy for preserving brain function begins with preventing illnesses that may contribute to cognitive decline and dementia. Good nutrition—including dietary supplements—and a healthy lifestyle can keep many of these afflictions at bay. As a first step toward ensuring brain health, keep your blood pressure and weight in check, avoid metabolic syndrome and diabetes, and obtain treatment for depression or anxiety disorders. However, there is much more that can and should be done to protect the aging brain.

Scientists have advanced several theories regarding the causes of cognitive decline associated with advancing age. One familiar hypothesis proposes that toxic by-products of cellular metabolism known as free radicals slowly accumulate within cells, where they cause cumulative and eventually fatal damage.<sup>26</sup> Nerve cells (neurons) in the brain rely on the oxidative phosphorylation of glucose within the mitochondria to supply their considerable energy needs. Accordingly, the brain's appetite for glucose and oxygen is great.<sup>27</sup> As a result, the brain is particularly susceptible to oxidative stress. Free radicals are produced by the mitochondria at an accelerated rate. Supplemental antioxidants, therefore, are especially important to preserving healthy cognitive function.<sup>10</sup>

## THE CHOLINERGIC SYSTEM AT RISK

Inflammation is also implicated in the development of various neurological disorders, including Alzheimer's disease and vascular dementia. It is believed that inflammation triggers a cascade of events that leads to the destruction of neurological tissues.<sup>28</sup> In Alzheimer's disease, the presence of a protein, beta-amyloid (A $\beta$ ), appears to trigger inflammation.<sup>29</sup> A decline in acetylcholine, an important messenger chemical or neurotransmitter, has also been observed in individuals with Alzheimer's disease.<sup>30</sup> Early on, this inflammation and cholinergic dysfunction may be experienced as mild memory impairment or confusion. Left unchecked, however, it invariably leads to advancing cognitive decline and dementia. Anti-inflammatory strategies thus make sense in protecting cognitive function.

Interruptions in cerebral blood flow have also been implicated in cognitive decline,<sup>31,32</sup> so optimizing blood flow is a logical strategy for protecting brain function. Vascular dementia was once considered distinctly different from Alzheimer's-type dementia, but scientists now believe that vascular dementia and Alzheimer's share a common pathology—namely, the disruption of cholinergic function.<sup>33</sup> Even decreasing psychological stress may be helpful. New research shows that older men who secreted the highest levels of epinephrine (a stress hormone) were more likely to suffer subsequent cognitive decline.<sup>34</sup> While body cells are easily replaced, the nerves and supporting tissues of the brain and spinal cord cannot yet be replaced once they are damaged or destroyed. Cells of the brain and nervous system are incapable of further division and renewal once they reach maturity.<sup>35,36</sup>

Various lifestyle factors contribute to healthy brain aging, including regular exercise and adequate sleep, routine mental stimulation, a positive outlook, and a healthy social network.<sup>7,37,38</sup> However, nutritional support for the aging brain likewise is of paramount importance. Supplements that combat inflammation, improve cerebral blood flow, and reverse the loss of acetylcholine and its receptors directly target the causes of age-related brain decline.

## GPC BENEFITS BRAIN HEALTH

Glycerophosphocholine, or GPC (formerly called L-alpha glycerylphosphorylcholine, or choline alfoscerate) is naturally present in all the body's cells. Its importance to life and safety as a supplement are evidenced by its substantial presence in human breast milk.<sup>39,40</sup> First discovered in the late 1990s, GPC is now regarded as essential to the healthy development of newborns, due to the great demand for choline, especially by the rapidly developing brain.<sup>40</sup>



Among aging adults, the rationale for GPC therapy goes back to the hypothesis, developed more than 30 years ago, that declining levels of acetylcholine—and a concurrent decrease in the number of neurons that are its intended target—are responsible for a range of cognitive deficits.<sup>29</sup> Acetylcholine is an essential neurotransmitter involved in muscle control, sleep, and cognition. Its decline coincides with advancing age, and is a hallmark of the neurodegeneration seen in cognitive decline, vascular dementia, and Alzheimer's disease. By boosting acetylcholine levels in the brain, the hypothesis proposes, it should be feasible to reverse these cognitive deficits and changes in brain structure.<sup>1</sup>

Early attempts to identify a suitable precursor for acetylcholine failed until scientists experimented with GPC.<sup>41-44</sup> Sold in Europe by prescription only, GPC is available in the US as a dietary supplement. GPC provides a crucial building block for the production of new acetylcholine in the brain. Numerous clinical trials have scrutinized the efficacy and safety of GPC in humans and in animal models of human neurological disorders.<sup>45-48</sup> These studies, large and small, controlled and informal, have universally demonstrated GPC's effectiveness, safety, and tolerability.<sup>1,49,50</sup> The studies have examined everything from changes in learning, memory, and brain structure in rats, to stroke-induced cognitive deficits in humans, to induced and restored memory deficits in laboratory animals.<sup>1,45-51</sup>

In early 2001, a retrospective analysis of published clinical data involving 4,054 patients concluded that, overall, GPC improved patients' clinical conditions. Of the 10 studies devoted to dementia disorders, a majority were controlled trials that compared the efficacy of GPC to either placebo or a reference drug. Dr. Lucilla Parnetti, a coauthor of the analysis, wrote, "Administration of [GPC] significantly improved patient clinical condition . . . results were superior or equivalent to those observed in control groups under active treatment and superior to the results observed in placebo groups."<sup>1</sup>

Early clinical trials with GPC used daily dosages of 1200 mg. After an initial two to four weeks at this dose, some people reduce their dose to 600 mg daily. A daily dose of 300 mg may be appropriate for healthy young people.

GPC works in a manner roughly similar to prescription cholinesterase inhibitor drugs such as donepezil (Aricept®) and rivastigmine (Exelon®), which are used to combat acetylcholine deficits in Alzheimer's and vascular dementia patients.<sup>52</sup> However, GPC tackles the problem of too little acetylcholine from a different angle. Rather than interfering with the enzyme that breaks down acetylcholine, GPC provides a means for the body to manufacture new acetylcholine.



Ashwagandha (*Withania somnifera*)

## ASHWAGANDHA AND THE BRAIN

Ashwagandha is a medicinal plant used in India to treat a wide range of age-related disorders.<sup>53-63</sup> Its most remarkable effect may involve its ability to preserve the health of the aging brain.

Ashwagandha offers myriad neuroprotective benefits. For example, one study showed that when given to mice, ashwagandha extract promotes memory retention, even when amnesia has been induced experimentally.<sup>60</sup> Another study found that ashwagandha extract is capable of protecting the brains of laboratory rats against experimentally induced stroke.<sup>61</sup> Ashwagandha constituents have also been shown to inhibit acetylcholinesterase (AChE), an enzyme responsible for breaking down acetylcholine, the neurotransmitter that is in dangerously short supply in the brains of Alzheimer's disease sufferers.<sup>62</sup> This AChE-blocking action is similar to that of prescription drugs such as Aricept® that are currently used to treat Alzheimer's symptoms.

Exciting new research indicates that ashwagandha extract is capable of halting and even repairing damage to brain cells in an experimentally induced model of Alzheimer's disease.<sup>63</sup> Scientists in Japan induced Alzheimer's-type brain cell atrophy and loss of synaptic function in mice by exposing them to the toxic protein Aβeta, which has been implicated in the genesis of Alzheimer's disease in humans. "Subsequent treatment with [a constituent of ashwagandha] induced significant regeneration of both axons and dendrites, in addition to the reconstruction of pre- and postsynapses in the neurons," according to the scientists.<sup>63</sup>

## PHOSPHATIDYLSERINE MAINTAINS BRAIN CELL MEMBRANES

Phosphatidylserine, a natural and integral component of every cell membrane, is a powerful weapon in the fight against brain aging. Phosphatidylserine is sold in Europe and Japan as a regulated drug, where it is often prescribed to combat memory loss and learning deficits. Available as a nutritional supplement in the United States, phosphatidylserine serves as a key component of many brain function-enhancing formulas.

The body manufactures phosphatidylserine to ensure its continual supply, underscoring the importance of this natural phospholipid. Unfortunately, however, aging slows production of this crucial contributor to brain health.

Phosphatidylserine helps the brain use its fuel efficiently. By boosting glucose metabolism and stimulating production of acetylcholine, supplemental phosphatidylserine has been shown to improve the condition of patients experiencing age-associated memory impairment or cognitive decline.<sup>8,64-67</sup> Clinical trials using small groups of patients with cognitive decline demonstrated significant improvements with phosphatidylserine supplementation, especially among patients in the early stages. Positron emission tomography (PET) brain-imaging scans verified that patients taking phosphatidylserine experienced significant increases in glucose uptake compared to subjects who received social support or cognitive training but not phosphatidylserine.<sup>68</sup>

A large multicenter trial examined the use of phosphatidylserine to combat the effects of moderate to severe age-related cognitive decline. Patients were drawn from 23 general medicine or geriatric units. Compared to patients who received dummy placebo pills, phosphatidylserine-supplemented patients demonstrated significant behavioral improvements, including increased socialization, motivation, and initiative.<sup>69</sup>

Phosphatidylserine is generally safe and well tolerated, with no significant drug interactions reported.<sup>70</sup>

## REPORT

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#### GRAPE SEED COUNTERS BRAIN CELL AGING

Wine has always been popular, but its health benefits are now the subject of intense scientific scrutiny. Wine is an excellent source of beneficial polyphenol compounds. For those unwilling or unable to imbibe regularly, the remarkable benefits of grape polyphenols are available through grape seed extracts. Scientific studies have shown that the antioxidant power of these natural compounds—known as proanthocyanidins—is 20 times greater than vitamin E and 50 times greater than vitamin C.<sup>71</sup>



Recent research indicates that grape seed extract may play a specific role in protecting the brain by preventing the kind of neuronal toxicity experienced by Alzheimer's disease patients. Korean scientists pre-treated rat brain cells with a grape seed extract in the laboratory before exposing the cells to beta-amyloid (Abeta), a toxic protein implicated in the formation of senile plaques in the brains of Alzheimer's patients. Untreated cells exposed to Abeta accumulated damaging reactive oxygen species (free radicals) and underwent programmed cell death. However, rat brain cells pre-treated with the grape seed extract were significantly protected from the toxic effects of Abeta.<sup>72</sup>

New research from China suggests that grape seed polyphenols offer protection by preventing oxidative damage to cellular DNA.<sup>73</sup> In the US, scientists analyzed the brain proteins of rats that were fed grape seed extract for six weeks, and identified 13 proteins that were positively altered by the supplement. The scientists stated that grape seed extract may confer "neuroprotective actions."<sup>74</sup>

#### VINPOCETINE ENHANCES BRAIN CIRCULATION

Vinpocetine is a semi-synthetic derivative of the periwinkle (*Vinca minor*) plant. Developed more than three decades ago, vinpocetine has been hailed as an important neuroprotective agent with several key mechanisms of action.<sup>75</sup> It has been widely used to treat symptoms of cognitive decline throughout Europe, where it is available only by prescription. Vinpocetine's ability to increase blood circulation and enhance glucose utilization in the brain is one of its most powerful effects.<sup>76-79</sup> This is particularly helpful to the aging brain, given that blood flow in the brain (and thus, oxygenation) tends to diminish with advancing age.

Vinpocetine's therapeutic effects include its ability to enhance the electrical conductivity of cells composing the neural network. It protects the brain from damage caused by the excessive release of calcium ions intracellularly. Vinpocetine improves cerebral blood flow by inhibiting an enzyme that degrades cyclic GMP, a cellular metabolite. Degradation of cyclic GMP causes blood vessel constriction. Preventing degradation, therefore, allows cerebral arteries to relax, improving blood flow.<sup>76-78,80-82</sup>

Scientists have studied vinpocetine's effects on human subjects under controlled conditions in various clinical trials. Three studies of older adults with memory problems associated with poor brain circulation or dementia-related disease have shown that vinpocetine confers significantly more improvement than a placebo in performance on comprehensive cognitive tests reflecting attention, concentration, and memory.<sup>83</sup> Vinpocetine has even been studied in newborn babies who suffered brain damage due to birth trauma. Vinpocetine significantly reduced or eradicated seizures and elicited a decrease in abnormally high pressure within the brain.<sup>84</sup>

These studies reveal that vinpocetine's therapeutic effects compare favorably with acetylcholinesterase inhibitor drugs such as Aricept®, which is used extensively in the US and abroad to treat Alzheimer's symptoms and vascular dementia. Human trials and others using rodent models reveal that vinpocetine is safe, effective, and well tolerated.<sup>81,85-87</sup>

There have been some reports that vinpocetine in combination with the prescription drug Coumadin® (warfarin) may slightly influence prothrombin time, a measure of the clotting time of blood plasma.<sup>88,89</sup> Although vinpocetine is unlikely to have a clinically meaningful effect on prothrombin time in patients who are also taking Coumadin®, please consult with your doctor if you plan to use a vinpocetine-containing supplement concomitantly with Coumadin® (warfarin).

#### PREGNENOLONE PROMOTES NERVE GROWTH

Pregnenolone is a powerful natural hormone that is synthesized directly from cholesterol in the mitochondria, the "power plants"

contained in all human cells. Pregnenolone for supplemental use is derived from a compound that occurs naturally in wild yams. In the body, pregnenolone is converted into other important hormones, including dehydroepiandrosterone (DHEA), estrogens, progesterone, and testosterone.<sup>90</sup>

Aging causes a sharp decline in pregnenolone production, and levels of the hormones for which it is a precursor tend to decline with age as well.<sup>91-93</sup> Progesterone, for example, is synthesized in the brain, spinal cord, and peripheral nerves from its direct precursor, pregnenolone.<sup>94</sup> Recent research suggests that progesterone plays a role in promoting the viability of nerve cells and in the formation of myelin sheaths, the fatty layers of “insulation” that allow electrochemical signals to propagate rapidly from one nerve to another. A recent clinical report summed up the potential implications of increasing progesterone: “Synthesis of progesterone in the brain, and the neuroprotective and promyelinating effects of this neurosteroid, offer interesting therapeutic possibilities for the prevention and treatment of neurodegenerative diseases, for accelerating regenerative processes, and for preserving cognitive functions during aging.”<sup>94</sup>

Researchers in France have documented a significant correlation between cognitive performance and levels of pregnenolone sulfate, a neurosteroid. The scientists recently established that pregnenolone directly influences acetylcholine release in several key brain areas involved in memory and learning, cognition, and the sleep-wakefulness cycle. The research team has also shown that pregnenolone reverses declining neurogenesis, or new nerve growth. Such declines are associated with disorders such as Alzheimer’s disease. “Our data demonstrate that [pregnenolone sulfate] central infusions dramatically increase neurogenesis . . . furthermore, our recent data suggest a critical role for neurosteroids in the modulation of cerebral plasticity, mainly on hippocampal neurogenesis.”<sup>95,96</sup>

Pregnenolone is not recommended for men with prostate cancer, as androgenizing hormones such as DHEA and testosterone may exacerbate this condition. Conversely, pregnenolone may confer some protection against other types of cancer by helping the body regulate estrogen levels. Pregnenolone has also been credited with alleviating symptoms of menopause, reducing the incidence of osteoporosis, and decreasing levels of LDL (low-density lipoprotein).

## GINGER AND ROSEMARY: NATURAL ANTI-INFLAMMATORIES

The next time you need relief from pain or inflammation, consider heading for the spice rack rather than the medicine cabinet. Some of nature’s most potent anti-inflammatories are found in ginger and rosemary. Ginger has been used for thousands of years as a remedy for the pain and inflammation of arthritis,<sup>97</sup> and research has confirmed its effects.<sup>97-103</sup> A recent study conducted at Johns Hopkins University examined ginger’s ability to suppress inflammatory compounds in cells obtained from the joints of arthritis patients, which had been cultured in the laboratory. “We discovered that the ginger extract blocks activation of pro-inflammatory mediators and its transcriptional regulator . . . [ginger extract] offers a complementary and alternative approach to modulate the inflammatory process involved in arthritis,” the researchers concluded.<sup>101</sup>



Rosemary (*Rosmarinus officinalis*)

Because inflammation is implicated in the development of certain degenerative neurological disorders such as Alzheimer’s disease, controlling it is crucial to preserving brain health. While ginger has demonstrated anti-inflammatory properties, especially in arthritis, it has also been shown to block activation of brain cells that are involved in the inflammatory cascade implicated in the development of Alzheimer’s.



Ginger (*Zingiber officinale*)

When brain cells are exposed to beta-amyloid peptides (A $\beta$ ), microglial cells surround the A $\beta$ -containing neuritic plaques and produce proinflammatory cytokines, chemokines, and neurotoxic mediators. It is believed that when this inflammatory process continues unabated, nerve cells are destroyed, contributing to the development of Alzheimer’s.<sup>103,104</sup> Scientists wondered whether ginger extract could suppress activation of these brain cells by proinflammatory substances. By incubating cells with ginger extract and various inflammation-provoking substances, they demonstrated that “ginger can inhibit activation of human monocytic THP-1 cells by different pro-inflammatory stimuli and reduce the expression of a wide range of inflammation-related genes in these microglial-like cells.” The scientists concluded that ginger extract “may be useful in delaying the onset and the progression of neurodegenerative disorders.”<sup>103</sup>

Like ginger, rosemary has long enjoyed a reputation as a venerable healing herb. One of its chief active constituents, carnosol, functions as an antioxidant and anticarcinogen. Researchers in Taiwan reported recently that their findings suggest that carnosol inhibits nuclear factor-kappa beta activation, and provide possible mechanisms for its anti-inflammatory action.”<sup>105</sup> Another rosemary constituent, ursolic acid, has also been shown to interrupt the pathway that leads to activation of pro-inflammatory nuclear factor- kappa beta.<sup>106</sup>

## **NEW BEGINNINGS**

While various factors threaten us with “brain drain” as we age, the good news is that modern science has identified nutrients that can slow or even reverse the progression of this once-inevitable decline. These supplements offer a smart option for maintaining brain health throughout life.

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## REPORT

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