

REPORT**Quenching the flames of inflammatory brain aging**

By Dale Kiefe

Natural agents block the brain's dual inflammatory pathways, improve circulation and restore acetylcholine. Clearly, any steps that can be taken to prevent cognitive decline – often viewed as the first step on the path to full-blown dementia – are well worth investigating.¹



That's why scientists around the world are intensively researching every aspect of the diseases associated with age-related dementia. Unfortunately, Alzheimer's disease, once it takes hold, has no known cure. But some scientists believe that it may be possible to prevent the disease from ever starting.² Although the exact causes of these dementias are not fully understood, there is reason for hope. Recent research has focused on some likely culprits and the natural agents that block them. Some of these agents treat symptoms of cognitive decline and early dementia. But the best news is that some of them may well provide a measure of prevention as well. While exact causes of some dementias remain elusive, the prevailing hypotheses hold that several factors may play a role in age-related neurodegeneration. It's believed that toxins - byproducts of cellular metabolism - accumulate within cellular structures, causing eventual damage. Interruptions in cerebral blood flow are also suspect. Furthermore, it's believed that inflammation plays a key role in triggering a cascade of events which eventually leads to the destruction of functional tissue.³ Elevation of a blood marker of chronic inflammation known as

C-reactive protein increases stroke risk two to three fold.⁴

Some of the cells that are lost as a result of this neurodegenerative cascade include cells of the cholinergic system. Their loss leads to a decline in levels of a vital messenger chemical called acetylcholine, a neurotransmitter responsible for important functions such as memory, sleep and cognition. In Alzheimer's disease, it's well established that the presence of a protein, beta-amyloid (A β), triggers inflammation.⁵ Early on, this inflammation and cholinergic dysfunction may be experienced as mild memory impairment or confusion.⁶ But left unchecked, it invariably leads to advancing cognitive decline, dementia and eventual death. Vascular dementia, most commonly caused by stroke, was once believed to be altogether different from Alzheimer's-type dementia. But recently scientists have postulated that vascular dementia may share common elements of its pathology with Alzheimer's, specifically, the disruption of normal cholinergic function, as mentioned above.^{7,8}

Preventive measures

The risk of dementia is relatively small in early old age, but the odds increase annually. In the developed world, dementia is estimated to strike about 1.5% of the population by 65 years of age. But it increases exponentially: by 80 years of age 30% will be afflicted.^{9,10} And there's evidence that some cognitive decline is inevitable in the elderly, even in the absence of other diseases such as Alzheimer's.¹⁰ Scientists have discovered natural agents that provide significant brain health benefits. They attack the presumptive causes of age-related brain decline at the source, by blocking both of the principal inflammation pathways, improving cerebral blood flow and reversing the loss of acetylcholine and its receptors, among other beneficial effects. The remainder of this article discusses the arsenal of natural agents available to fight age-related mental decline.

Alpha GPC-acetylcholine precursor

L-alpha glycerylphosphoryl choline, better known as GPC, is an acetylcholine precursor derived from soy. The brain uses GPC as a building block to create new acetylcholine. As mentioned above, acetylcholine is an essential neurotransmitter involved in muscular control, sleep and cognition. Acetylcholine levels are reduced with advancing age, resulting in neurodegeneration that manifests as cognitive decline, vascular dementia (e.g. loss of mental function subsequent to stroke) and Alzheimer's disease. GPC has been proven to partially reverse or slow the cognitive deficits associated with early memory loss and "senility."^{2,15} Available in Europe only by prescription, GPC is currently available in the United States as a dietary supplement. Studies have shown that it is well tolerated with few side effects.^{2,6}

GPC's mechanism of action somewhat resembles that of the cholinesterase inhibitor drugs, such as donepezil (Aricept®) and rivastigmine (Exelon®), which are presently prescribed in this country to combat acetylcholine deficits among presumed Alzheimer's and vascular dementia patients. Rather than interfering with a natural enzyme that breaks down acetylcholine, however, GPC provides a means for the body to manufacture new acetylcholine. This has a two-fold benefit. Normal neural transmission is restored, and cell membranes are left intact. When acetylcholine runs low, the body often raids stores of choline in the cell membranes in an effort to restore circulating acetylcholine to normal levels. In effect, the body is consuming itself, rendering cell membranes weak and potentially leading to nerve cell death. Please refer to Life Extension, July 2003, p.26 for a summary of GPC research.



Nexrutine®— nature's COX-2 inhibitor

Nexrutine® is a novel plant extract derived from the bark of the phellodendron tree of Asia. Nexrutine®'s action resembles that of the newest class of inflammation-fighting drugs, the COX-2 inhibitors, such as Celebrex®, Vioxx® and Bextra®. These blockbuster prescription drugs have been extensively researched in human trials and are proven effective at reducing inflammation by interfering with the activity of COX-2 (cyclooxygenase-2).



COX-2 is a villain. It is an intermediary enzyme: a link in a cascading chain of compounds which eventually trigger release of prostaglandins, resulting in inflammation. In Alzheimer's disease this inflammatory damage spreads to neighboring cells in the brain. As they become inflamed they release stress chemicals in turn, which trigger more inflammation, setting into motion an accelerating spiral of decline.

Although scientists do not unanimously agree that halting inflammation may prevent the onset of Alzheimer's and vascular dementia, many researchers continue to investigate the possibility. In one study on the effects of COX-2-inhibitor therapy, researchers concluded: "Our findings further support the importance of these disease-modifying drugs in the prevention and treatment of Alzheimer's disease."¹¹ Other studies have also linked inflammatory processes with other neurodegenerative

diseases, such as Lou Gehrig's and Parkinson's diseases.^{12,13}

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The COX-2 inhibitors are easier on the stomach than commonly available over-the-counter NSAID medications, such as aspirin and ibuprofen, which can cause gastric bleeding when taken in high doses. NSAIDs block both COX-2 and its more benevolent cousin, COX-1, which is necessary for stomach lining protection. Thus, compounds that block COX-2 selectively are at least as effective as NSAIDs at relieving inflammation, but are supposedly better tolerated by the body. While the makers of COX-2 inhibiting drugs claim they are safe for the stomach, reports published after the drugs were approved show that they can cause gastric side effects in certain individuals. One reason is that so-called COX-2 inhibitor drugs also suppress some COX-1.



Unlike expensive prescription COX-2 inhibitors, plant-derived Nexrutine® inhibits the gene expression of COX-2 rather than directly inhibiting the enzyme, in effect cutting the problem off at the source, rather than intervening once COX-2 is released. This difference in mechanism of action also explains the rapid onset of Nexrutine®'s anti-inflammatory action. Seventy-nine percent of subjects who used Nexrutine® for two weeks agreed that Nexrutine® helped relieve or avoid the general aches and pains associated with overexertion and physical activity, and there was no evidence of side effects at recommended dosages.¹⁴ Although the neurological anti-inflammatory effect of Nexrutine® has not been tested in human subjects under tightly controlled conditions, such human trials have been completed on the COX-2 inhibitor Vioxx®(rofecoxib). Researchers concluded that Vioxx® "significantly prevented [experimentally] induced brain inflammation and cholinergic degeneration."¹¹

Another trial looked at a different COX-2 inhibitor's effect on the progression of Lou Gehrig's disease (amyotrophic lateral sclerosis, or ALS). Researchers declared: "Evidence provides strong support for the therapeutic use of COX-2 inhibitors in ALS."¹³ Inflammation has been implicated in a variety of diseases, and may play a role in everything from heart disease to cancer and Alzheimer's disease. Leading edge research points to dual inflammatory pathway blockade as the most effective strategy for combating inflammation related degenerative disease. In the next section we turn to the other inflammatory pathway, 5-lipoxygenase (5-LOX).

5-Loxin — Nature's 5-LOX inhibitor

For thousands of years natives of India, North Africa and the Near East have gathered and traded in herbal products obtained from *Boswellia serrata*, a tree that yields aromatic gum resins when stripped of its bark. In India practitioners of Ayurvedic medicine have traditionally used extracts from the gummy portion of the tree's sap to treat symptoms of arthritis, which is, after all, an inflammation of the joints. It was this application that prompted Western scientists to investigate *Boswellia's* potential as a treatment for inflammation.

They discovered through rigorous laboratory testing that one component, β -boswellic acid, acts as a specific inhibitor of a key enzyme involved in the inflammation pathway: 5-lipoxygenase (5-LOX). Having isolated and concentrated the most active of the Boswellic acids, it is now possible to derive the benefits of 5-LOX inhibition without consuming large amounts of ordinary *Boswellia serrata* extracts.



Evidence is mounting for the effectiveness of such a proactive strategy. Although 5-LOX is only beginning to receive the attention it deserves among medical science researchers, some pioneering work on the nature of this powerful enzyme suggests that levels tend to increase as we age. And it's becoming clear that 5-LOX may also trigger cell death in the brain.¹⁵ "Thus," say the authors of one study, "the 5-LOX pathway could become a promising target of neuroprotective therapies for the aging brain."¹⁵

The rationale for 5-Loxin's use is based on clinical research into its benefits. Scientists at the University of British Columbia, for instance, investigated the potential neuroprotective benefits of dual inflammatory pathway blockade. They assessed the effects of both a COX-2-inhibitor and a 5-LOX inhibitor working in concert against brain inflammation. Their results speak for themselves: "Combinations of COX and 5-LOX inhibitors were more effective than single inhibitors," write the researchers. "The data suggest that both COX inhibitors and 5-LOX inhibitors may be neuroprotective... and that combinations of the two might have greater therapeutic potential than single inhibitors of either class."³

They found that inclusion of a 5-LOX inhibitor actually improved the effectiveness of COX inhibitors. "This synergism between 5-LOX and COX inhibitors indicates that inhibition of 5-LOX could be a promising new way to slow inflammation by reducing production of pro-inflammatory leukotrienes... 3"

Thus, 5-Loxin's ability to synergize with the COX-2 inhibitor Nexrutine® suggests that these supplements should be taken simultaneously for maximum effectiveness through dual inflammatory pathway blockade.

Quercetin— anti-thrombotic, anti-inflammatory flavonoid

We've all heard the time-honored adage; 'An apple a day keeps the doctor away.' While such a prescription for health may seem simplistic in our modern age of sophisticated medical technology, the presence of beneficial quercetin in apples may be the kernel of truth at the heart of this familiar folk wisdom.



Water-soluble quercetin belongs to a class of plant pigments known as flavonoids, which are often subdivided into isoflavones, anthocyanins, flavones, etc. Quercetin, which is present in varying amounts in vegetables and fruits such as apples, onions and tea, is one of the best-known and best-researched of the flavonoids. Quercetin has demonstrated anti-inflammatory, anti-histamine and potent antioxidant properties. It has been implicated in cancer prevention and the prevention of heart disease. But its most relevant brain-health effect is its anti-coagulant activity.¹⁶

In response to stress, blood in the brain becomes more prone to clotting, especially among the aged.^{17,18} Clotting can cause ischemia or stroke, which is responsible for the majority of cases of vascular dementia. Indeed, new research indicates that a series of barely detectable strokes may contribute to vascular dementia. This assault on the brain's integrity is known as multi-infarct dementia.¹⁹ It stands to reason, then, that a mild anti-coagulant, from a natural source, is likely to improve blood flow and help prevent strokes, by preventing clots from forming.

Phosphatidylserine —nature's cell membrane stabilizer

Phosphatidylserine (PS) is another weapon in the anti-brain aging arsenal. Sold in Europe and Japan as a regulated drug, where it is often prescribed to combat memory loss and learning deficits, PS is a natural and integral component of every cell membrane. It is available as a nutritional supplement in the United States, and serves as a key component of many brain function-enhancing formulas.

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This particular phospholipid's importance is underscored by the fact that the body manufactures it in order to insure its continual supply. Unfortunately, as with so many other vital functions, aging slows production of PS. Given that PS's functions include everything from boosting vital acetylcholine levels, to reducing levels of the stress hormone cortisol and prompting the release of mood-regulating dopamine, PS is clearly an important player in brain health.

PS also helps the brain use its fuel more efficiently. By boosting blood glucose metabolism and stimulating production of acetylcholine, PS has been shown to improve the condition of patients in cognitive decline.²⁰⁻²³ Clinical trials involving small groups of presumed Alzheimer's patients showed significant improvements with PS supplementation, especially among patients in the early stages of the disease. Positron emission tomography (PET) brain-imaging scans verified that patients taking PS experienced significant increases in glucose uptake compared to patients in the study who received social support or cognitive training, but no PS.



A large multi-center trial examined the use of PS 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 receiving placebo, PS patients demonstrated significant improvements in behavior, including increased socialization, motivation and initiative.

PS is generally safe and well tolerated, with no significant drug interactions reported.²⁴ While there are no specific studies relating to the combined use of Coumadin® and PS, you should consult with your physician before taking PS, as it may enhance the anti-coagulant effect.

Vinpocetine — the brain cell oxygenator

Vinpocetine is a semi-synthetic derivative of the Vinca minor, or periwinkle plant. Developed more than two decades ago, vinpocetine has been hailed as an important neuroprotective agent with several key mechanisms of action. It has been widely used to treat symptoms of senility throughout Europe, where it is available only by prescription.

One of vinpocetine's most powerful effects is its ability to increase blood circulation and enhance oxygen utilization in the brain. This is especially important, given that blood flow in the brain tends to diminish with advancing age. Vinpocetine improves cerebral blood flow by inhibiting an enzyme that degrades the cellular messenger cyclic GMP. The degradation of cyclic GMP causes blood vessel constriction. Preventing degradation, therefore, allows cerebral arteries to relax, improving blood flow.



Vinpocetine's therapeutic effects may be mediated at the cellular level by its ability to enhance the electrical conductivity of cells comprising the neural network. It also protects the brain from damage caused by the excessive release of calcium ions intracellularly.

Vinpocetine's effects on human subjects have been studied under controlled conditions in a variety of clinical trials. Vinpocetine has even been studied in newborn babies who suffered brain damage due to birth trauma. Vinpocetine significantly reduced or eradicated seizures and caused a decrease in abnormally high pressure within the brain.

These studies reveal that vinpocetine's therapeutic effects compare favorably with prescription drugs of the acetylcholinesterase inhibitor class, such as Aricept®, which is used extensively in the United States and abroad to treat symptoms of Alzheimer's disease and vascular dementia. Human trials, and others using rodent models, reveal that vinpocetine is safe, effective and well tolerated.^{25,26}

Vinpocetine also exhibits some anti-clotting activity. While there are no specific studies relating to the combined use of Coumadin® and vinpocetine, you should consult with your physician before taking vinpocetine, as it may enhance the anti-coagulant effect.

Pregnenolone — the mother hormone

Pregnenolone is a powerful natural hormone that is synthesized by the body (in the mitochondria) directly from cholesterol.

Mitochondria are important structures within the cells that function as “power plants.”



Pregnenolone has been called the “mother” hormone because the body converts it into a variety of other important hormones, including dehydroepiandrosterone (DHEA), estrogens, progesterone and testosterone. Aging causes a sharp decline in pregnenolone production. It stands to reason, then, that levels of its daughter hormones also decline with age.

Unfortunately, research into pregnenolone’s mechanisms of action and effects has been relatively scant. Because it is a naturally occurring substance, and thus cannot be patented, pharmaceutical companies have had little incentive to invest in costly human trials. However, intriguing studies in rodent models have suggested that enhanced levels of pregnenolone may play an important role in neuronal protection.¹⁶

Pregnenolone is not recommended for men with prostate cancer, as androgenizing hormones such as DHEA and testosterone may exacerbate this condition. Conversely, pregnenolone may actually confer some protection against other types of cancer by helping the body regulate estrogen levels.

Pregnenolone has been credited with alleviating symptoms of menopause, reducing the incidence of osteoporosis and decreasing levels of “bad,” or LDL cholesterol.

Get proactive

The bad news is that a variety of factors conspire to rob us of mental acuity as we age. The good news is that modern science has worked hard to investigate and identify natural agents (some of which come to us from ancient herbal traditions) with potential to slow or even reverse the progression of this once-inevitable decline. They may represent the best available proactive option for maintaining or improving brain health as we age.

References

1. Burns A, Zaudig M. Mild cognitive impairment in older people. *Lancet* 2002; 360: 1963-1965.
2. Parnetti L et al. Choline alphoscerate in cognitive decline and in acute cerebrovascular disease: an analysis of published clinical data. *Mech Ageing Dev* 2001 Nov; 122(16): 2041-2055.
3. Klegeris A, McGeer P. Cyclooxygenase and 5-lipoxygenase inhibitors protect against mononuclear phagocyte neurotoxicity. *Neurobiol Aging* 2002; 23: 787-794.
4. Life Extension magazine, May 2001 pg.11., The Silent Stroke Epidemic.
5. Paris D, et al. AB vasoactivity: an inflammatory reaction. *Ann NY Acad Sci* 2000, Apr; 903: 97-109.
6. Bartus RT, et al. The cholinergic hypothesis of geriatric memory dysfunction. *Science* 1982; 217: 408-414.
7. Ritchie K, et al. Is senile dementia age-related or ageing-related? – evidence from a meta-analysis of dementia prevalence in the oldest old. *Lancet* 1995; 346: 931-934.
8. Ritchie K, Lovestone S. The dementias. *Lancet* 2002; 360: 1759-1766.
9. Hofman A, et al. The prevalence of dementia in Europe: a collaborative study of 1980-1990 findings. *Int J Epidemiol* 1991; 20: 736-748.
10. Jorm AF, et al. The prevalence of dementia: a quantitative integration of the literature. *Acta Psychiatr Scand* 1987; 76: 465-479.
11. Scali C, et al. The selective cyclooxygenase-2 inhibitor rofecoxib suppresses brain inflammation and protects cholinergic neurons from excitotoxic degeneration in vivo. *Neuroscience* 2003;117: 909-919.
12. Teismann P, et al. Cyclooxygenase-2 is instrumental in Parkinson’s disease neurodegeneration. *PNAS* 2003; 100 (9):5473-5478.



13. Pompl PN, et al. A therapeutic role for cyclooxygenase-2 inhibitors in a transgenic mouse model of amyotrophic lateral sclerosis. *FASEB J.* 2003; Apr;17(6):725-7.
14. Dennis and Company Research. Nexrutine® human trial report. Next Pharmaceuticals, Inc. 2002; 13.
15. Manev H, et al. Putative role of neuronal 5-lipoxygenase in an aging brain. *FASEB J* 2000; Jul;14(10):1464-9.
16. Pignatelli P, et al. The flavonoids quercetin and catechin synergistically inhibit platelet function by antagonizing the intracellular production of hydrogen peroxide. *Am J Clin Nutr* 2000; 72: 1150-1155.
17. Yamamoto K, et al. Plasminogen activator inhibitor-1 is a major stress- regulated gene: Implications for stress- induced thrombosis in aged individuals. *Proc Natl Acad Sci* 2002; 99 (2): 890-895.
18. Breteler M. Vascular involvement in cognitive decline and dementia: Epidemiologic evidence from the Rotterdam study and the Rotterdam scan study. *Ann N Y Acad Sci* 2000, Apr;903:457-465.
19. Iadecola C, Gorelick P.B. Converging pathogenic mechanisms in vascular and neurodegenerative dementia. *Stroke* 2003; 34: 335-337.
20. Schreiber S, et al. An open trial of plant- source derived Phosphatidylserine for the treatment of age-related cognitive decline. *Isr J Psychiatry Relat Sci* 2000; 37 (4): 302-307.
21. Palmieri G, et al. Double-blind controlled trial of phosphatidylserine in patients with senile mental deterioration. *Clin Trials J* 1987; 24:73-83.
22. Delwaide PJ, et al. Double-blind randomized controlled study of phosphatidylserine in senile demented patients. *Acta Neurol Scand* 1986; 73(2):136-40.
23. Fungfeld EW, et al. Double-blind study with Phosphatidylserine (PS) in parkinsonian patients with senile dementia of Alzheimer's type (SDAT). *Prog Clin Biol Res* 1989;317: 1235-1246.
24. Van den Besselaar AM. Phosphatidylethanolamine and Phosphatidylserine synergistically promote heparin's anticoagulant effect. *Blood Coagul Fibrinolysis* 1995; 6: 239-244.
25. Vas A, et al. Clinical and non-clinical investigations using positron emission tomography, near-infrared spectroscopy and transcranial Doppler methods on the neuroprotective drug vinpocetine: A summary of evidences. *J Neurol Sci* 2002; 203-204: 259-262.
26. Laszy J, Gyertyan I. Comparison of cognitive enhancer activity of acetylcholinesterase inhibitors and vinpocetine. *Neurobiology of Aging*; 2002 Jul-Aug, Suppl 1; 23(1):357.

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