Roles of Vitamins E and C on Neurodegenerative Diseases and Cognitive Performance

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Demographic changes, together with improvements in nutrition, general health, and life expectancy, will greatly change the social and economic structures of most industrialized and developing countries in the next 50 years. Extended life expectancy has increased the number of chronic illnesses and disabilities, including cognitive impairments. Inflammatory processes and vascular dysfunctions appear to play important roles in the pathogenesis of age-associated pathologies including Alzheimer’s and Parkinson’s disease. A large body of evidence shows that both vitamins E and C are important for the central nervous system and that a decrease in their concentrations causes structural and functional damage to the cells. Several studies reveal a link between diets rich in fruits and vegetables containing generous amounts of vitamins E and C and lower incidence of certain chronic diseases.

Key Words: α-tocopherol, ascorbate, cognition, neurodegeneration.

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Introduction

Both aging and age-associated neurodegenerative diseases are associated with various behavioral impairments that significantly decrease the quality of life and tax the current health care system. Age-associated pathologies, including Alzheimer’s disease (AD) and Parkinson’s disease (PD), are accompanied by considerable declines in cognitive performance.1–3 In the aged animal, as well as in elderly patients, loss of memory and cognitive function often accompany a prominent loss of cholinergic, noradrenergic, and dopaminergic neurons.4 Strikingly, 10 to 15% of the population over age 65, and approximately 50% of individuals over the age of 80, are afflicted by AD.5–7 The events leading to the development of neurodegenerative disease remain unclear, although inflammatory processes, free radical formation following the activation of glial cells (called reactive gliosis), organelles dysfunction, and exhausting metabolic changes may be among the major factors involved in pathogenesis. Researchers are examining genetic vulnerability factors in neurodegenerative diseases such as AD, yet only a small number of cases are familial; of these, only a small portion are genetically determined. Even though AD is the most frequent cause of dementia in elders, and the mechanisms underlying this disease are associated with aging, combined molecular and cellular neurobiology research efforts have not been able to generate sufficient information for the scientific community to completely understand the process. Formation and deposition of Aβ-amyloid protein, which forms a plaque, is the histopathologic hallmark of AD,3–8 and is considered a major etiologic factor in the pathogenesis and progression of AD; however, this hypothesis has not been validated.9

Cytokines, secreted molecules (proteins) that function as mediators of intercellular communication, have several roles in multicellular organisms, including host defense against microorganisms and inflammatory processes. Reactive gliosis is a prominent consequence of trauma and many other forms of injury to the central nervous system (CNS), and is a common feature in virtually every neurodegenerative disease including AD.10 Human astrocytes, in particular, respond to several forms of CNS lesions by proliferation and cytodifferentiation.11 Activated glia cells may lead to brain tissue damage in many ways, including enhanced production of free radicals, protein degradation mediated by proteases, cytokines, and changes in amyloid metabolism.12 Researchers have demonstrated that astrocytes...
can produce a variety of cytokines, including interleukin-1 (IL-1) and tumor necrosis factor-α (TNFα), as well as several adhesion molecules (which regulate the adhesion of leukocytes to the vascular wall). These compounds appear to underlie pathologic processes and functional disturbances in acute and chronic neurologic disease. Several cells of the body can produce TNFα after an appropriate stimulus, its activity is tightly regulated at the levels of secretion and receptor expression. Abnormalities in the production of these substances might contribute to the pathophysiology of immune and inflammatory processes in brain.

Recent studies suggest that following stress, tissues initiate an inflammatory cascade that includes acute-phase protein synthesis, up-regulation of inflammatory adhesion cell molecules, and proinflammatory cytokine release. Interestingly, data suggest that antioxidant vitamin therapy can provide tissue protection by inhibiting translocation of the transcription factor NF-κB and interrupting the secretion of inflammatory cytokines. Other proposed mechanisms by which increased intake and plasma concentrations of the antioxidants E and C may positively influence the development of pathologic disorders including maintaining the immune system (enhances lymphocyte proliferation and decreases production of immunosuppressive prostaglandin E2), platelet function (inhibits platelet adhesion), formation and repair of collagen and muscle, and brain function.

Taking generous amounts of both vitamins E and C in preparation for aging may help to limit the buildup of cellular damage associated with disease and promote and maintain health and cognitive performance. Vitamins E and C are scavengers of free radicals and play important roles, beyond their antioxidant properties, in cell function. These nutrients provide reducing equivalents within the cell for critical enzymatic functions and may be most important in oxidative injury following glial cell activation. In a study by Sram et al., daily oral supplementation with 300 IU vitamin E and 1000 mg vitamin C for 12 consecutive months improved short-term memory, psychomotor performance, and overall mood. Battisti et al. reported a case of early-onset ataxia with cerebellar atrophy and vitamin E deficiency; after the patient was treated with α-tocopherol, the authors observed a motor improvement directly related to vitamin E serum levels. These findings further support the hypothesis that a high tissue vitamin E concentration may be crucial for proper brain functions. In a study conducted among home-living patients with AD, researchers found that vitamin C plasma levels decreased in proportion with the severity of the cognitive impairment.

PD is another disease in which formation of free radicals appears to be involved, and when the capacity of scavenging free radicals in the brains of these patients increases, the progression of PD is slowed. Antioxidants, particularly vitamin E, have been tested for therapeutic efficacy in PD. Surveys of early-life food intake showed that subjects whose diets had high amounts of vitamin E were less likely to develop PD later in life. In a clinical study in which subjects received a high-dose supplement containing 3.0 g/day of vitamin C and 3200 IU of vitamin E, levodopa therapy was not required until 2.5 years later compared with the group not taking vitamins. Reducing the formation of dopamine-derived metabolites, which are formed by oxidative deamination via catalysis by monoamine oxidase, may be relevant because these metabolites are neurotoxic. Vitamin C, as suggested by some study results, can prevent dopamine-mediated toxicity. Findings from epidemiologic studies investigating the correlation between the intake of vitamin E and PD are mixed; some studies show that higher dietary vitamin E intake is associated with a decreased incidence of PD. Other studies failed to find an association between diets high in vitamin E and decreased incidence of PD. Clinical studies that used high doses of vitamins E and C observed a delay in the need for pharmacologic treatment, possibly owing to the retarded progression of catecholaminergic neuron degeneration. Although this type of intervention was not effective in altering motor or cognitive performance, a delay in the need to use drugs is an important result for patients with AD and PD.

Interestingly, new population-based, prospective cohort studies, have shown that high intake of vitamins E and C are associated with lower risk of Alzheimer’s disease and less cognitive decline with aging. Up-regulated inflammatory mediators—cytokines, complement proteins, and adhesion molecules—are neurotoxic, and may represent extracellular signals that initiate neuronal degeneration through several intracellular signals. Vascular disease is a common disorder among the elderly and, combined with AD, is the main cause of cognitive impairment. Recent evidence suggests that the two may be more closely linked than previously thought. Epidemiologic studies indicate that risk factors for vascular disease and stroke are associated with cognitive impairment and AD, and that the presence of cerebrovascular disease intensifies the severity of the clinical symptoms of AD. Sublethal damage to the endothelium appears to initiate a series of events that form the basis of “the endothelial injury hypothesis,” which plays a crucial role in the early stages of vascular...
dysfunction, cell activation, and secretion of inflammatory mediators, including cytokines and adhesion molecules.

Antioxidant vitamins E and C are important for vascular and brain function and may be capable of quieting activated glial cells in the brain, and/or reducing the oxidative-mediated damage; the latter may be relevant to ameliorate or delay the damage caused by inflammatory processes in neuronal cells. These two vitamins may therefore have important effects on the rate of progression of neurodegenerative disease and on cognitive performance. Several studies indicate that increased vulnerability to oxidative stress may be a major factor involved in the functional declines of the CNS in age-related neurodegenerative diseases, and that antioxidants such as vitamins E and C may ameliorate or prevent such decline.

In previous studies, we examined the effect of long-term feeding of Fischer 344 rats diets supplemented with vitamin E (500 IU/kg) or control diets (beginning when the rats were 6 months of age and continuing for 8 months) on age-related neuronal signal-transduction and cognitive behavioral deficits. We found that the diets supplemented with vitamin E prevented the cognitive declines associated with several receptor-mediated responses including dopamine release by the striatal cells, cerebellar activity, and the activity of the GTPase involved in the transmission of cell signals. Additionally, vitamin E postponed the onset of cognitive behavioral declines assessed via the rate of acquisition (learning) and memory retention. Results of this study suggest that an optimal intake of vitamin E may help to retard the age-related functional changes in the CNS associated with cognitive deficits. Interestingly, a significant depletion of specific chain-breaking antioxidants including vitamins E and C were observed in both AD and vascular dementia groups. Significantly reduced amounts of plasma vitamins E and C were found in malnourished subgroups of AD patients. Other studies have shown that dementia subjects with apparently normal nutritional status had significant deficiencies in antioxidants. These findings, together with a large body of in vitro and animal studies, suggest the oxidative stress hypothesis as an important factor in the pathogenesis of neurodegenerative processes such as AD and PD. The validity of this hypothesis, however, has come under question. New evidence, including our studies, has raised important questions about the relevance of this hypothesis to the pathogenesis of neurodegenerative processes. Oxidation may be a secondary event occurring in people with markedly incompetent antioxidant mechanisms. Researchers speculate, based on events occurring under in vitro conditions, that deposits of chemical compounds such as amyloid-beta protein, which may also occur under in vivo conditions, when the body is unable to contain them, may precipitate oxidative chain reactions. Interestingly, decreased levels of specific antioxidants such as vitamins E and C were not reflected in the overall measure of antioxidant capacity. In addition, whereas several researchers were unable to show changes in elderly patients with PD, studies that administered vitamins E and C showed beneficial effects including the slowing of the disease process. A table including some of the most relevant studies on the roles of vitamins E and C on vascular function and neurologic changes associated with cognitive performance has been incorporated (Table 1).

Vitamin E

The lipid-soluble antioxidant vitamin E is localized in the cell membrane and has been targeted for its relation to atherosclerosis and vascular function. Decreased concentration of antioxidants including vitamin E in the presence of stimuli such as infection, bacterial colonization, exposure to various toxins, and/or metabolic changes such as increased homocysteine, could increase free radical concentrations and alter normal brain vascular function. Various studies have assessed the effects of vitamin E intake on neurologic function and vitamin E concentration in different brain regions. Our study assessed the effect of a graded dietary vitamin E intake on brain levels and brain function following a 2-month feeding period with diets supplemented with 5, 30, 60, 250, or 500 mg α-tocopherol-acetate/kg diet. Animals on this diet exhibited a significant increase of vitamin E concentration in the brain and peripheral tissues. Interestingly, the CNS had increased vitamin E concentration in a dose-dependent manner only when the diet was supplemented with 5, 30, or 60 mg/kg diet. Vitamin E in food plus 60 mg E as a supplement, or 80 mg vitamin E/kg, was the optimum intake, meaning that CNS tissue was maximally enriched. Compared with the low vitamin E groups—the diets not supplemented with vitamin E—rats on diets supplemented with the 60 mg vitamin E/kg diet showed a significant enhancement on brain function as assessed by dopamine release from striatum, and this finding supports a previous study in which vitamin E supplementation prevented cognitive behavioral deficits in aged rats. Although the brain has a limited capacity to incorporate vitamin E, therefore, the optimal intake of this nutrient may provide significant benefits for brain performance.

Evidence linking vitamin E deficiency and neurologic sequelae in humans is now firmly established. Several neuropathologic observations are associated with vitamin E deficiency in humans, indicating the importance of this nutrient in the CNS. Recent studies showed that increased vitamin E intake slows the progression of dementia in AD, enhances vascular function, and improves CNS function.
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<td>Sano et al.</td>
<td>27</td>
<td>Selegiline and/or vitamin E</td>
<td>341</td>
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<td>Clinical trial of vitamin E treatment (2000 IU/day) in patients with moderately advanced AD. Vitamin E group showed slower functional deterioration leading to nursing home placement.</td>
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<td>Riviere et al.</td>
<td>34</td>
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<td>Foy et al.</td>
<td>39</td>
<td>Vitamin E/vitamin C and AD, PD,</td>
<td>442, 65–69 yr</td>
<td>Significant reductions in individual antioxidants were found in all dementia groups displaying either AD, PD, VD, compared with matching controls.</td>
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<td>Fahn</td>
<td>40</td>
<td>Vitamin E, vitamin C, and PD</td>
<td></td>
<td>Administration of high vitamin E and vitamin C to PD patients extended the time that levodopa became necessary by 2.5 years compared with nonsupplemented control group.</td>
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<tr>
<td>Vatassery et al.</td>
<td>48</td>
<td>Large doses of vitamin E in the</td>
<td>Review</td>
<td>Studies indicate a beneficial effect of vitamin E in short period treatments. However, the role it plays when taken over a period of 2 years, remains unclear.</td>
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<td>de Rijk</td>
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<td>Antioxidants and PD the Rotterdam Study</td>
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<td>Englehart</td>
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<td>Morris</td>
<td>55</td>
<td>Vitamin E and cognitive decline in older persons</td>
<td>2889, 65–102 yr</td>
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<tr>
<td>Morris</td>
<td>56</td>
<td>Antioxidants and risk of AD</td>
<td>Prospective study (815), &gt;65 yr</td>
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Gokce et al. 63 Vitamin C and coronary artery disease 46 Long-term vitamin C supplementation (500 mg/day/month) reversed endothelial vasomotor dysfunction in patients with coronary artery disease.

Ross et al. 64 VaD the Honolulu-Asia Aging Study 3403 The most common stroke subtype associated with VaD was found to be the lacunar stroke. Supplementary vitamin E was protective against developing VaD.

Masaki et al. 65 Vitamin C and E and cognitive function 3385, 71–93 yr Findings suggest that both vitamin E and vitamin C supplements may protect against vascular dementia and may improve cognitive function in late life.

Schmidt et al. 67 Vitamin E and cognitive function 1979, 50–75 yr Subjects with no history or signs of neuropsychiatric disease, selected randomly from the community, their plasma vitamin E was significantly associated with cognitive functioning.

Ortega et al. 69 Dietary intake and cognitive function 260, 65–90 yr Consumption of a more satisfactory global diet—more vegetables, fruit, carbohydrate, fiber, folate, vitamin C—associated with better cognitive function in the elderly.

Jackson et al. 70 Vitamin E and AD in subjects with DS 24 Plasma vitamin E levels measured in 12 DS subjects with AD were significantly lower than in 12 DS controls; possible interaction between risk of AD and the protective action of vitamin E.

Feillet-Coudray et al. 78 Oxidative stress (8-epiPGF2) and AD Despite decreased antioxidant defenses with increasing age, in a healthy population, plasma 8-epiPGF2alpha levels were not correlated with age. AD patients presented no modification of plasma 8-epiPGF2alpha level and no alteration of the antioxidant status.

Sheen 82 The HOPE study 9000, >55 yr Not protection of vitamin E supplements at a dose of 400 UI/day in high-vascular risk patients (55 years and above), after a mean follow-up of 4.5 years.

Stampfer et al. 83 Vitamin E and the risk of coronary disease 87245, 34–59 yr Among middle-aged women the use of vitamin E supplements was associated with a reduced risk of coronary heart disease.

Rimm et al. 84 Vitamin E and the risk of coronary disease 39910, 40–75 yr Association between a high intake of vitamin E and a lower risk of coronary heart disease in men.

### Table 1. Effects of Vitamins E and C on Cognitive Function (Cont’d)

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<td>Jackson et al.</td>
<td>70</td>
<td>Vitamin E and AD in subjects with DS</td>
<td>24</td>
<td>Plasma vitamin E levels measured in 12 DS subjects with AD were significantly lower than in 12 DS controls; possible interaction between risk of AD and the protective action of vitamin E.</td>
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<td>Feillet-Coudray et al.</td>
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<td>Oxidative stress (8-epiPGF2) and AD</td>
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<td>Despite decreased antioxidant defenses with increasing age, in a healthy population, plasma 8-epiPGF2alpha levels were not correlated with age. AD patients presented no modification of plasma 8-epiPGF2alpha level and no alteration of the antioxidant status.</td>
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<td>Gale et al.</td>
<td>85</td>
<td>Vitamin C and risk of death from stroke and CHD</td>
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<td>In an elderly population vitamin C concentration, whether measured by dietary intake or plasma concentration, was strongly related to subsequent risk of death from stroke.</td>
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<td>Vitamin C, oxidative stress, and EC dysfunction</td>
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<td>Vitamin C supplementation (2 g) increased plasma vit-C concentration by 2.5-fold 2 hours after and reversed endothelial vasomotor dysfunction in patients with coronary artery disease.</td>
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<td>Dror et al.</td>
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<td>Vitamin needs: riboflavin, vitamin B₆, vitamin C in elders</td>
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<td>Vitamins (mg/day) based on regression lines needed to maintain cognitive and behavioral parameters: &gt;150 for ascorbic acid, &gt;3 for riboflavin, &gt;3 for vitamin B₆.</td>
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<td>Diaz et al.</td>
<td>88</td>
<td>Antioxidants and heart disease Review</td>
<td></td>
<td>Epidemiologic studies strongly indicates the presence of an inverse association between coronary artery disease and antioxidant intake, in particular vitamin E.</td>
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<td>Perrig et al.</td>
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<td>Cognitive function and vitamin E vitamin C</td>
<td>442, 65–94 yr</td>
<td>Higher vitamin C and beta-carotene plasma levels were associated with better memory performance; important role of antioxidants in brain aging among people aged 65 and older.</td>
</tr>
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<td>Paleologos et al.</td>
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<td>Vitamin C intake and cognitive impairment</td>
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<td>Elders in a community of Sydney, Australia. No association between vitamin C intake and verbal tests scores was observed. However, vitamin C supplements were associated with lower prevalence of more severe cognitive impairment on Mini-Mental State Exam.</td>
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<tr>
<td>Prasad et al.</td>
<td>91</td>
<td>Antioxidants/NSAID and AD Review</td>
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<td>Studies suggest that a combination of multiple antioxidants and NSAIDs may be more beneficial in the prevention of AD than when given individually.</td>
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<tr>
<td>Grundman et al.</td>
<td>92</td>
<td>AD Review</td>
<td></td>
<td>Roles of antiinflammatory agents (cyclooxygenase inhibitors) and antioxidant approaches (vitamin E) are currently being proposed or utilized in ND disease prevention trials.</td>
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The recently reported effects of nutrients such as vitamin E and the drug selegiline in prolonging time to institutionalization, or in significantly decreasing the disease process, exemplify the feasibility of this approach.27,34,100–102 Several prospective studies, including the U.S. Nurses-Health Study and the U.S. Health Professionals-Follow-up Study, found a significant reduction (≈40%) in risk of having a cardiac event for those taking vitamin E supplements.103 The Iowa Women’s Health Study found a 47% reduction in cardiac mortality. However, results of randomized, controlled clinical trials have not been consistent with previous studies.104 Although researchers for the Cambridge Heart Antioxidant Study observed a 47% reduction in fatal and nonfatal myocardial infarction in patients who received 400 or 800 IU vitamin E/day, no effect on mortality was detected.104 Several epidemiologic studies have suggested that inadequate antioxidant status is related to the development of vascular disease, particularly cardiovascular disease, but results from intervention trials have been contradictory.105 A recent trial did not find that vitamin E supplements provided cardiovascular protection at a dose of 400 UI/day in high-risk patients.82 However, vitamin E has shown some promise in the treatment of AD and cardiovascular disease.27,83,84,101,106,107 Although strong data suggest the potential benefit of vitamin E on vascular function,84 no clear consensus has been reached for primary prevention of cardiovascular disease. Animal studies have provided further evidence for the benefits of vitamin E by suggesting that free radical-mediated sublethal changes in endothelial cells may promote thrombosis, directly damage vascular cells, and interfere with vasomotor regulation.108–110 Thus, a generous intake of this nutrient could play a beneficial role in human health, and may contribute to the prevention or delay of neuro-pathologic processes. Interestingly, the Food and Nutrition Board, in addition to increasing its recommended dietary allowances (RDA) by 50%, set an upper limit of 1000 mg vitamin E/day. Vitamin E, through dietary supplementation alone or in combination with anti-inflammatory drugs, may therefore provide valuable protection against the vascular diseases and neurodegenerative changes associated with cognitive impairment.

### Vitamin C

Vitamin C is a water-soluble vitamin that participates in a large number of cell functions. All animal species appear to require vitamin C, but for humans, guinea pigs,
monkeys, bats, certain fish, and perhaps certain reptiles, it is a dietary requirement. These species lack the enzyme L-gulonolactone oxidase, which is necessary for vitamin C synthesis from 6-carbon sugars. Vitamin C is rapidly absorbed into the circulatory system in the upper part of the small intestine. Approximately 80 to 95% is absorbed when the intake is 100 mg/day and absorption decreases with larger intake: only about 50% is absorbed when the total intake is 1500 mg. In addition to the antioxidant role in cell injury, vitamin C has specific and well-defined roles in the activation of two classes of enzymes: the copper-containing hydroxylases (e.g., dopamine-hydroxylase and peptide glycine hydroxylase) and the iron-containing hydroxylases (e.g., procollagen proline 4-hydroxylase, which is involved in collagen synthesis; aspartate-hydroxylase, a precursor of protein C that is involved in the clotting cascade; and carnitine synthase, used by mitochondria for electron transfer in ATP synthesis). In addition, other enzymes, including tryptophan dioxygenase and tyrosine hydroxylase, have been found to be ascorbate-dependent.

The average body pool of vitamin C in adults is about 1500 mg with a fractional turnover rate of 3 to 4% daily; this suggests a need for approximately 60 mg/day. Considering the absorption variability factor, food viability, and a catabolism rate that varies with intake, a reference intake of 80 to 100 mg/day was recommended. Based on the RDA, 75 mg of vitamin C/day (before 2000, the RDA was 60 mg), a substantial number of people (20–30%) in the United States ingest vitamin C at or below recommendations. Researchers estimate that our Paleolithic ancestors ingested approximately 4000 mg of vitamin C/day. Although optimal vitamin C requirements are unknown, Levine et al. estimated they should be approximately 200 mg/day, based on concentrations in plasma and tissues, optimal vitamin C intake, and epidemiologic observations. Some researchers believe that human requirements for vitamin C are considerably higher than those previously discussed, scaling up to 1 to 3 g/day. Vitamin C is highly concentrated in the brain; it is estimated at between 100 and 500 µmol/L. Although vitamin C concentration in the brain changes rapidly in response to neural activity, its physiologic functions are not well understood. Vitamin C has been shown to significantly improve endothelium-dependent vasodilation in diabetics, perhaps by reducing excess superoxide production and thereby decreasing levels of nitric oxide inactivation. Higher vitamin C plasma concentrations have been significantly associated with better memory performance in patients with dementia. Cognitive performance in normal older people, as well as cognitive decline in Alzheimer patients, appears to be positively associated with vitamin C intake. Interestingly, the Food and Nutrition Board modified the dietary reference intake in April of 2000 and, in addition to increasing the RDA by 25 to 50%, set an upper limit for this nutrient of 2000 mg/day. Vitamin C treatment, through dietary supplementation alone or in combination with anti-inflammatory drugs and/or other antioxidants, may provide valuable protection against the neurodegenerative changes associated with cognitive impairment. High intakes of vitamin C, from which no toxic effects have been found, may cause diarrhea and abdominal bloating for some people, and is not recommended to patients who have iron overload, hemochromatosis, thalassemia major, sideroblastic anemia, or other diseases requiring multiple red blood cell transfusions. Whether vitamin C induces iron overabsorption in healthy people is not known.

**Inflammatory Factors Involved in Cognitive Impairment**

Increasing evidence shows that inflammatory processes, and the generation of cytokines and free radicals, are important factors in the pathogenesis of dementia associated with AD. Several inflammatory mediators have been observed in the brains of patients with AD over the last two decades. Although these mediators are typically undetectable in samples from non-demented elderly patients, they are prominent in the AD patients’ brain. Multiple endogenous sources including microglia, astrocytes, and brain endothelial cells can produce these inflammatory mediators in neurodegenerative pathologies. A number of studies have demonstrated the association between cytokines and the production of oxygen species, changes in cell membrane composition, regulation of adhesion molecules, and apoptosis. The importance of cytokines is emphasized in the propagation and maintenance of a CNS inflammatory response or unusual up-regulation of inflammatory mediators. Researchers have proposed that changes in the permeability of the blood-brain barrier, adhesion of blood-borne leukocytes to cerebral vessels, activation of chemoattractants and their receptors, and migration of inflammatory cells into the CNS, are regulated by cytokines, prostaglandins, and reactive oxygen species.

Following brain injury and inflammation, investigators have observed an astrocyte-mediated secretion of neurotrophic substances and cytokines underlying pathologic processes and functional disturbances in acute and chronic neurologic disease and injury. Adhesion molecules enable leukocytes to communicate and adhere to vascular endothelial cells, and are essential in immunologic and inflammatory responses in inflammatory disorders of the CNS. Researchers have detected adhesion of leukocytes to endothelium, and the release of oxygen radicals from monocytes, in brain...
vessels in patients with multiple sclerosis and AD, but not in the vasculature of normal controls. Polyunsaturated fatty acids are precursors in situ of prostaglandins that appear to have a significant impact on brain cell dysfunction associated with aging, and complications associated with neurodegenerative processes. Arachidonic acid (AA), incorporated within cell membrane phospholipids, plays a major role in the biophysical status of membrane properties such as fluidity, and is a source of leukotrienes and prostaglandins (PG) (Figure 1). After AA is synthesized, it is stored in the acylated form in the membrane phospholipids, and is released from the phospholipid molecule via the acyl hydrolases. One of the main pathways by which AA is liberated from the membrane is via phospholipase A2. Synthesis of prostaglandins and leukotrienes is mediated by the enzymes lipooxygenase (LIPOX) and cyclooxygenase (COX), respectively. Vitamin E has multiple roles in AA metabolism, and vitamin E’s concentration may be crucial for neuronal function. Vitamin E has been shown to modulate both LIPOX and COX, reducing the synthesis of eicosanoids. This inhibition appears to be unrelated to its antioxidant function. Binding studies with 14C-labelled α-tocopherol have revealed that vitamin E strongly interacts with LIPOX. Recent studies showed that vitamin E is also capable of modulating the activity of COX-2 by reversing the age-associated increase in PGE2 production. Supplementation with pharmacologic doses of vitamin E has detectable effects on lipid peroxidation and thromboxane biosynthesis in healthy subjects. Thus, these studies suggest that cellular vitamin E levels may have profound influence on the formation of leuko-

**Figure 1.** Effect of antioxidants and anti-inflammatory drugs on eicosanoid synthesis.

- **AA = Arachidonic Acid (20:4n-6)**
- **NSAID = Nonsteroidal anti-inflammatory drugs**
- **PG = Prostaglandins**
triienes and PGs. Nonsteroidal anti-inflammatory drugs are presumed to act by inhibiting COX, decreasing or preventing the formation of AA-derived prostaglandins.\textsuperscript{141} (Figure 1) Vitamin E also minimizes motor disturbance associated with spinal injury by maintaining normal metabolism of AA, as a result of a reduction in lipid peroxidation and/or sustained efficient blood flow.\textsuperscript{158} Using in vitro neurons, vitamin E protected against AA-induced down-regulation of acetylcholine receptor activity,\textsuperscript{159,160} which may have important implications for cognition because declines in acetylcholine neurotransmission can result in cognitive impairment\textsuperscript{161–164} and have been implicated in AD pathology.\textsuperscript{165} In human brains, inverse correlations between the neuronal tissue concentrations of AA metabolites and vitamin E have been reported.\textsuperscript{166–168} Greenberg-Levy et al.\textsuperscript{169} reported increased PG endoperoxide synthetase as well as higher PLA\textsubscript{2} activity in the cerebella and cerebra of chicks exhibiting nutritional encephalomalacia induced by a vitamin E–deficient diet. Increased levels of PGE\textsubscript{2} have also been observed in various brain regions of rats fed a vitamin E–deficient diet.\textsuperscript{170} Direct evidence of the benefits of vitamin E on AA metabolism has been reported in a small number of studies, and evidence obtained from studies performed on other peripheral tissues and cell models highlights the role of vitamin E in this regard,\textsuperscript{171} which, hypothetically, could also be extended to neuronal cells. Metabolites of AA are involved in cellular signaling events such as NFkB transcription factor activation\textsuperscript{171,172} and in the expression of certain cytokines. This is an important phenomenon because the synthesis of several cytokines, such as IL-1 and IL-6, is implicated in the etiopathology of various inflammatory and degenerative disorders, including AD and PD.\textsuperscript{173–175}

Blom and coworkers,\textsuperscript{176} using human post-mortem astrocyte cultures and an astroglia cell line, identified a significant increase of PGE\textsubscript{2} and IL-6 upon stimulation with IL-1\textbeta. Interestingly, this induction was reduced when cells were treated with anti-inflammatory drugs such as dexamethasone or indomethacin, or with an experimental specific COX-2 inhibitor.\textsuperscript{92,171} Thus, the beneficial effects of these drugs observed in AD may be mediated by reducing IL-6 and/or PGE\textsubscript{2} expression in glial cells. The detrimental impact that IL-1 may have on neuronal function has been further highlighted by a number of comprehensive studies performed by Murray and coworkers.\textsuperscript{73,168,177} These authors argued that IL-1 induces the formation of reactive oxygen species and lipid peroxidation, both in vivo and in vitro, causing a large decline in the membrane’s AA composition that correlates with impaired postsynaptic activation (long-term potentiation [LTP]).\textsuperscript{172} Interestingly, LTP has been found in many areas of the brain including the hippocampus, and is thought to be important for spatial mem-

ory.\textsuperscript{168,177,178} The importance of vitamin E, therefore, as a modulatory compound in these processes has been demonstrated in different animal studies in which rats receiving diets supplemented with vitamin E exhibited significantly lower levels of IL-1,\textsuperscript{19} and lesser marked age-related deficits in LTP.\textsuperscript{73} Furthermore, using a human astrocytoma cell model derived from patients with AD, it has been possible to show the involvement of AA metabolites, in particular PGE\textsubscript{2}, in the regulation of cytokines.\textsuperscript{179,180} Thus glial cells appear to be a premier source of PGE\textsubscript{2} and may play a central role in the pathogenesis of neurodegenerative diseases.\textsuperscript{181} An intra-hippocampal infusion of 80 ng IL-6 markedly increased PGE\textsubscript{2} secretion into hippocampal dialysates, and PGE\textsubscript{2} secretion was suppressed by indomethacin administration. A positive association between the levels of PGE\textsubscript{2} and cytokine mRNA concentration in neuronal cells from patients diagnosed with AD has been detected, and increased levels of PGE\textsubscript{2} have been correlated with high levels of amyloid precursor protein.\textsuperscript{131} Increased expression of amyloid precursor protein is involved in the neurodegeneration pathology and cognitive impairment observed in transgenic mice.\textsuperscript{182,183} Interestingly, reactive glial cell astrocytes, showing increased glial fibrillary acid protein levels, are associated with aging and are found to be particularly elevated in the brain of patients with AD, in which they play a relevant role in β-amyloid formation.\textsuperscript{184} It has been postulated that prostaglandin production mediates activation of astrocyte cells during injury or inflammation. Thus, generous vitamin E intake or a combination of both E and non-steroidal anti-inflammatory drugs may be important to reduce AA metabolites involved in the etiology of various neurodegenerative diseases.

**Antioxidant Vitamins E and C and Cognitive Performance**

Decreases in motor function and memory are two main behavioral parameters observed in aging humans and animals.\textsuperscript{185} Evidence implicates oxidative stress as a cause of age-related neurodegenerative diseases, and a number of studies have examined the putative positive benefits of antioxidants in altering, reversing, or forestalling these neuronal/behavioral decrements, with varying degrees of success.\textsuperscript{49,186–188} Studies that have examined the roles of vitamins E and C in cognitive function in aging are of particular relevance. It is important to determine whether the neuronal protection provided by vitamins E and C translates into improvements in behavioral function by minimizing age-related decrements in cognitive and motor performance. For a recent review of the effects of vitamin E on behavior see Cantuti-Castelvetri et al.\textsuperscript{53} A number of pertinent studies are briefly discussed below.
Several human studies have investigated the role of supplementation with vitamins E and/or C on cognitive performance. The effects of vitamin C (1000 mg/day) and vitamin E (300 mg/day) were tested following long-term supplementation (24 months) in elderly (aged 60–90) nursing home patients.\(^{31}\) DNA synthesis, lipid peroxidation, assessment of vitamin levels, and psychological tests (digit span memory, verbal memory, psychomotor performance, subjective symptoms, and scores on the Crichton Geriatric Rating Scale) were examined after 0, 3, 6, 12, 18, and 24 months of intervention. A continual increase in vitamin E and vitamin C levels was detected. The increased vitamin E and vitamin C levels were associated with improvement on psychological tests; at 12 months, subjects improved on the digit span test (short-term memory), verbal memory, and motor performance, and scores on the Crichton Scale increased. Data from the Rotterdam study suggest that a high vitamin E intake may protect against the occurrence of PD.\(^{49}\) Thus antioxidant supplements for more than 6 months may improve cognitive and emotional functions in elderly populations.

However, several survey studies have shown that vitamin E and vitamin C intake does not prevent age-related cognitive decline.\(^{84,189}\) In the Rotterdam Study, the cross-sectional relationship between cognitive functioning, as assessed by the Mini-Mental State Examination, which tests orientation, memory, attention, language, and visuospatial construction, and dietary intake (food frequency questionnaire) of vitamins C and E was tested in a population-based sample of community-dwelling persons (aged 55–95) between 1990 and 1993;\(^{189}\) no significant associations between cognitive function and the intake of vitamins C and E were found. Other studies have supported previous observations.\(^{93,190–192}\) In the Zutphen Elderly study (aged 69–89), the relationships between polyunsaturated fatty acids, antioxidants, and cognitive functioning in men was examined, and an inverse association between fish consumption and cognitive function was observed.\(^{94,193}\)

Food intake was established through a crosscheck dietary history method and global cognitive functioning was assessed using the Mini-Mental State Examination. Intake of vitamins E and C did not offer any protective effects for cognitive impairment or decline.\(^{94}\) However, the level of dietary intake of vitamins E and C, even when the diets were well balanced (four servings of vegetables and two servings of fruits), barely provided what is considered a generous amount of these vitamins: 200 IU of vitamin E and about 200 mg of vitamin C/day. Consumption of a more satisfactory global diet containing more vegetables, fruits, folate, vitamin C, and other B vitamins was associated with better cognitive function in the elderly.\(^{62,95,96}\) The selection and preparation of the foods has a significant effect on the total amount of vitamins E and C ingested. In most diets, in fact, particularly in those of elders (because the total caloric intake is reduced), the total amount of these vitamins provided—in only 2 to 4 servings of fruits and vegetables—is low. The length of time that supplementation is used appears to be crucial, as several epidemiologic studies have documented significant correlations between intake of vitamins E and C and cognitive performance in aging.\(^{39,89}\) Plasma antioxidant vitamin levels in healthy subjects (aged 65 to 94) were examined with respect to cognitive performance as part of the Basle Longitudinal Project IDA (Interdisciplinary study on Aging). Plasma vitamin E and C levels were measured in 1971 and 1993; memory was also tested in 1993. Those who performed better on tests of free recall, recognition, and semantic memory, but not priming and working memory, had higher plasma levels of vitamin C; even ascorbic acid measured in 1971 was predictive for performance data in 1993. However, those who took vitamin E did not show a significant correlation with the semantic long-term component of memory in this study. Assessment between current and past nutritional status and cognitive performance was also examined in community residents (aged 66–90) who were free of significant cognitive impairment in the New Mexico Aging Process Study.\(^{96}\)

This study found that diets supplemented with vitamin C (median was 257 mg/day) led to higher scores on a measure of visuospatial skills and a test of nonverbal memory, whereas vitamin E (median was 29.3 mg/day) supplement users scored higher on tests of visuospatial recall, which measures nonverbal learning and memory, and abstract reasoning. Interestingly, long-term (6 years) supplementation with vitamin E led to higher scores than those who were nonusers of vitamin E on four of the cognitive measures analyzed (visuospatial skills, nonverbal learning, nonverbal memory, and abstract reasoning), whereas chronic vitamin C was found to improve visuospatial skills. Additionally, Paleologos and colleagues\(^{90}\) conducted a cohort study that attempted to assess the protective properties of vitamin C against cognitive impairment. The study included a subset of subjects (aged 69–91), enrolled in the Western Sydney Stroke in the Elderly Study, who regularly took extremely high levels of vitamin C. Assessment of cognitive functioning was measured 4 years following a baseline assessment (using food frequency questionnaires) in a follow-up home visit. The results indicated that high vitamin C intake (mean intake >200 mg/day) was associated with a lower prevalence of severe cognitive impairment, as measured by the Mini-Mental State Examination. Verbal and category fluency scores showed no differences in cognitive functioning between groups.

The protective properties of vitamin E and C have
also been tested on dementias and deterioration in cognitive functioning. Subjects (aged 71–93) from the Honolulu-Asia Aging Study\(^8^1\) were given a questionnaire on vitamin E and C intake in 1988, and dementia prevalence was assessed in 1991 and 1993. Cognitive performance was tested using the Cognitive Abilities Screening Instrument, which tests attention, concentration, orientation, short- and long-term memory, language ability, visual construction, word list generation, abstraction, and judgment. Subjects were divided into four groups after Cognitive Abilities Screening Instrument testing: low, low-normal, mild-normal, and high-normal, and then further divided into five mutually exclusive dementia groups: AD, vascular dementia, mixed/other types of dementia, low cognitive test scores without dementia, and cognitively intact. The most significant protective results were obtained for the vascular dementia group that had been taking both vitamin C and vitamin E supplements. The study found an 88% reduction in the frequency of subsequent vascular dementia. Protective effects were also found in the mixed/other dementia group, but not for AD. Those taking vitamin C or vitamin E supplements scored significantly better in cognitive test scores (among nondemented participants), but the use of both vitamin E and vitamin C showed only borderline significance. As such, long-term use of vitamin E and vitamin C supplements may be required to protect against vascular dementia and to improve cognitive function in late life.

Dror and coworkers\(^8^7,194\) examined supplements of micronutrients, including vitamins E and C, at a level of 100% RDA in 12 elderly people (aged 65–87). Medical, biochemical, nutritional, functional, cognitive, and behavioral parameters were established at baseline and 42 days following supplementation with retinol, thiamin, riboflavin, vitamin B\(_6\), vitamin B\(_{12}\), folic acid, niacin, pantothenic acid, vitamin C (45 mg/day), vitamin D, vitamin E (12 mg/day), and microelements. Following supplementation, functional independence measures and Tinetti Balance Evaluation values increased, whereas the Folstein Mini Mental State showed no consistent effects, and values for the Geriatric Depression scale decreased. The authors recommended a vitamin C intake of 150 mg/day for optimal performance in the elderly.

A number of experiments have examined the therapeutic use of vitamins E and C in neurodegenerative disorders in order to prevent or forestall their progression. For example, Sano and coworkers\(^2^7,10^0\) examined the effects of 2 years of treatment with vitamin E and/or selegiline in patients with AD of moderate severity, recruited from centers participating in an AD Cooperative Study. The primary outcome measure was the time to death, institutionalization, loss of ability to perform daily activities, or severe dementia, whereas secondary outcome measures included cognition levels, and functional, behavioral, and neurologic evaluations. After adjusting for baseline group differences, the study found significant delays in primary measures, but cognitive decline was unaffected by treatment conditions. Significant delays in institutionalization, as well as delays in the deterioration of the ability to perform daily activities and the need for care, were observed in the vitamin E group, which suggests that AD patients with moderate dementia might slow the progression of the disease if their diets contain generous amounts of vitamin E (200–400 mg/day). Early intervention with vitamin E therapy can delay the progression of AD and improve the symptoms and function of those affected with neurologic processes.\(^1^9^5\) This suggests that the time of initiation of the treatment may be of crucial importance to achieve the greatest benefits. Unfortunately these points have not been assessed in rigorous examinations to date.

**Conclusion**

From the literature reviewed above, it appears that vitamins E and C have some protective effects on age-related deficits in behavioral function, particularly when vitamin use is steady and started early in life. It is interesting to note that the studies that did not find a correlation between antioxidants and cognitive performance used only 30-point mini-mental evaluations to determine cognitive performance in the subjects.\(^5^2,9^4,1^8^9\) However, the studies in which an effect was observed employed a more in-depth analysis of cognitive performance and found that antioxidants had significant beneficial effects on cognitive performance, in that semantic memory was more sensitive to the treatment than working memory.\(^4^9,5^0,8^9\) The involvement of inflammatory mediators and AA metabolites in the etiology of neurologic disorders has been further supported by several studies in which nonsteroidal anti-inflammatory drugs or the application of specific inhibitors of COX, LIPOX, or phospholipase provide significant protective benefits.

New studies strongly support the role of inflammatory mediators in the pathogenesis of neurodegenerative disease, and an increased expression of these mediators has been found in the brains of patients with AD and other neurologic processes compared with patients without dementia. It is highly possible that modulation of the reactivity of glial cells, which appear to play a central role in the immunopathologic response in neurologic conditions, will generate a better understanding of these processes, and open new avenues for primary intervention. A rationale for the possible clinical benefits of antioxidants for several degenerative conditions has arisen from the many years of basic science, including clinical and epidemiologic studies. Substantial evidence
implicates nutrition in the pathogenesis of neurodegenerative diseases.

Both in vitro and in vivo studies show that vitamins E and C act both as antioxidants and as modulators of cell function. A large body of evidence has shown that these nutrients reduce the changes associated with cell degeneration following exposure to chemical or physical insults. To provide effective dietary intakes of vitamins E and C, nutritionists and clinicians should consider the varying needs and priorities of different age groups, particularly the elderly, and if regular diets do not provide the desirable amounts of vitamins E and C, a supplement is recommended.

For the first time in history, the Food and Nutrition Board, in addition to increasing the RDA by 50% for vitamin E and 25 to 50% for vitamin C, has set upper limits for these nutrients: 1000 mg/day for vitamin E and 2000 mg/day for vitamin C. Therefore, based on the literature cited in this manuscript and our own studies, we conclude, in addition to the dietary recommendations, additional vitamin E and/or vitamin C supplementation is a valid choice that should be considered. Vitamin supplements containing 200 to 400 mg α-tocopherol acetate/day, depending on the patient’s micronutrient status, appear to be the optimum intake to increase brain levels of vitamin E and to obtain the best possible benefits. Regarding vitamin C, recent studies have shown that 200 mg/day appears to be necessary to increase blood levels maximally and consequently increase tissue levels. Since this nutrient is aqueous, and no toxic effects have been observed, even when its intake was large (several grams/day), we believe that a supplement of 200 to 500 mg/day could be recommended. A good diet that contains an average of three servings of fresh vegetables and two servings of fruits may provide an average of 105 and 70 mg of vitamin C from vegetables and fruits respectively, and approximately 20 mg vitamin E. This diet would provide two times the RDA on average, and barely what is considered by some studies a generous intake of these nutrients to convey healthy benefits. Unfortunately, it is estimated that 45% of the population have no servings of fruit or juice and 22% have no servings of vegetables a day. Only 27% consumes three or more servings of vegetables and 29% have the two or more servings of fruit recommended by the U.S. Department of Agriculture and of Health and Human Services; approximately 9% have both.196,197 In addition, consumption of fruits and vegetables is lower among blacks than whites. Therefore, vitamin E and C treatment, through dietary supplementation alone or in combination with anti-inflammatory drugs, may be necessary to provide valuable protection against the neurodegenerative changes associated with cognitive impairment.

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**Immune-stimulating and Gut Health-promoting Properties of Short-chain Fructo-oligosaccharides**

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*Short-chain fructo-oligosaccharides are a group of linear fructose oligomers with a degree of polymerization ranging from one up to five (oligosaccharides).* Recent observations in animal models demonstrate that prebiotics and probiotics may exert beneficial effects on gut health by enhancing gut-associated lymphoid tissue responses either directly or indirectly through the production of short-chain fatty acids and the enhanced growth of lactic bacteria such as bifidobacteria and lactobacilli. Demonstration of the potential health benefits of short-chain fructo-oligosaccharides on colon cancer risk is an active field of research in animal and human nutrition.

Key Words: short-chain fructo-oligosaccharides, prebiotics, probiotics, colon cancer risk

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**Introduction**

Short-chain fructo-oligosaccharides (sc-FOS) have aroused widespread interest in the past decade, mostly because of their nutritional properties. By definition, oligosaccharides have a degree of polymerization (DP) lower than nine. Sc-FOS is a group of linear glucosyl α(1 → 2)(fructosyl)_nα(2 → 1) fructose polymers with a DP ranging from one up to five (Figure 1).

Short-chain fructo-oligosaccharides occur in small amounts in a number of plants such as onions, Jerusalem artichokes, asparagus, wheat, rye, and garlic. They are also produced commercially from sucrose as starting carbohydrate material, using a food-grade fungal fructosyltransferase.*

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* (US patent 46811771) (ACTILIGHT® Béghin Meiji—France) or MEIOLIGO® (Meiji Seika Kaisha—Japan) or NUTRAFLORA (GTC—USA).