

Review

Vitamin E and Neurodegenerative Disorders Associated with Oxidative Stress

D. ALLAN BUTTERFIELD^{a,*}, ALESSANDRA CASTEGNA^a, JENNIFER DRAKE^a, GIOVANNI SCAPAGNINI^b and VITTORIO CALABRESE^c

^aDepartment of Chemistry, Center of Membrane Sciences, and Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40506, USA;

^bBlanchette Rockefeller Neuroscience Institute, Rockville, MD 20850, USA; ^cDipartimento di Scienze Chimiche, Sezione di Biochimica e Biologia Molecolare, University of Catania, 95125 Catania, Italy

(Received 29 January 2002; Revised 12 March 2002; In final form 25 March 2002)

Several neurodegenerative disorders are associated with oxidative stress that is manifested by lipid peroxidation, protein oxidation and other markers. Included in these disorders in which oxidative stress is thought to play an important role in their pathogenesis are Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), tardive dyskinesia, Huntington's disease (HD), and multiple sclerosis. This review presents some of the chemistry of vitamin E as an antioxidant and summarizes studies in which vitamin E has been employed in these disorders and models thereof.

Keywords: Vitamin E; Oxidative stress; Neurodegenerative disorders; Protein oxidation; Lipid peroxidation

INTRODUCTION

Background on Vitamin E

Vitamin E is one of the most important lipid-soluble antioxidants. The term "vitamin E" was introduced in the year 1922 (Evans and Bishop, 1922), when a new dietary factor in animal nutrition considered important for reproduction was described. Isolation of two compounds with vitamin E characteristics, designated as α - and β -tocopherol, was performed in the year 1936 from wheat germ oil. Several other isomers were then isolated from plant, so that a total of eight isomers are known to occur in nature. The essentiality of this factor was confirmed in the year

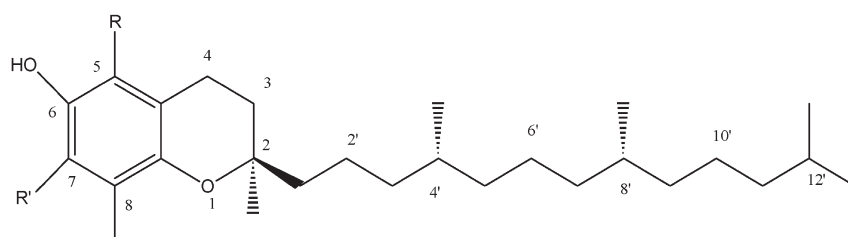
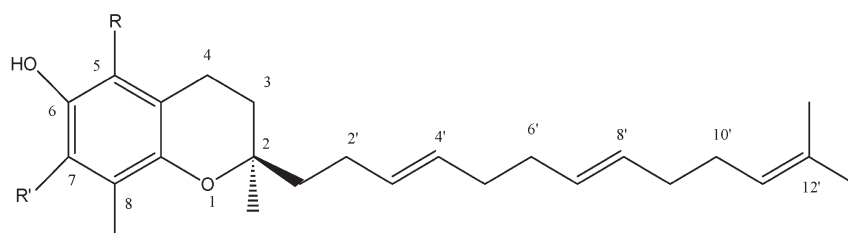
1968 by the American Food Nutrition Board, and since then, extensive studies have confirmed its role in protecting the integrity of tissues by acting as chain breaking antioxidant.

Vitamin E Isoforms and Chemistry

Natural vitamin E occurs as eight different isomers, classified in two groups of lipid-soluble compounds, tocopherols (α -, β -, γ - and δ -tocopherol) and tocotrienols (α -, β -, γ - and δ -tocotrienol) (Fig. 1), where α -, β -, γ - and δ - indicate the number and the position of the methyl groups attached to the aromatic ring. The difference between the first and the second group consists of the triple unsaturation on the tocotrienols side chain, at positions 3', 7' and 11'.

The antioxidant activity displayed by the tocopherols was investigated since their discovery, with particular attention to the mechanism of action and the structure of the metabolites. A study on the effect of chemical structure of phenolic compounds on the reactivity towards peroxy radicals (Burton *et al.*, 1983) demonstrated that α -tocopheroxyl radical displays an unusual stability due to resonance stabilization of the unpaired electron, and electron-donating substituents can increase this effect. The mechanism of electron trapping is shown in Fig. 2.

*Corresponding author. Tel.: +1-859-257-3184. Fax: +1-859-257-5876. E-mail: dabcs@uky.edu

RRR-Tocopherol**R-Tocotrienol**

Isoform	R	R'
α	CH ₃	CH ₃
β	CH ₃	H
γ	H	CH ₃
δ	H	H

FIGURE 1 Naturally occurring components of vitamin E.

Among the four tocopherols, the α -form is the most important one. α -tocopherol is the only isomer that is retained by the organism once absorbed and the only isoform included in the current dietary intake recommendations (Food and Nutrition Board, 1992). However, recently the importance of the γ -isomer, as the major form of vitamin E in the US diet, was reviewed (Jiang *et al.*, 2001).

In nature, the most abundant form of vitamin E is called RRR- α -tocopherol, that has the highest biological activity and accounts for the 90% of the vitamin E in animal and human tissue, including blood plasma (Cohn, 1997). The synthetic stereoisomers (*all-rac*- α -tocopherol) show lower biological activity compared to the natural form, indicating that the biological properties of α -tocopherol is strictly related to its stereochemical structure.

Bioavailability and Absorption of Vitamin E

Vitamin E is a necessary nutrient that must be provided by food. The primary source is edible oil originating from plants (Azzi and Stocker, 2000), such as sunflower, wheat germ, safflower and peanut oil, followed by butter and cereals.

The fat soluble nature of the vitamin E indicates that its absorption and transport in the body is very

complex and regulated by the level of fat intake. In humans, its absorption occurs in the proximal part of the intestine and requires bile acid secretion and micellarization. Vitamin E is mainly distributed in adipose tissue, and in the subcellular membrane fractions, the major concentration of α -tocopherol is found in the Golgi apparatus and lysosomes (Buttris and Diplock, 1988). The transport of tocopherol involves specific proteins in tissues. Three α -tocopherol binding proteins have been isolated from the cytosol of mammalian tissue and studied (Dutta-Roy, 1997). One is a hepatic protein that specifically transports α -tocopherol from lysosomes to the endoplasmic reticulum. The second is a 15 kDa protein that is present not exclusively in liver and is capable of transporting the δ - and γ -isomers, although the α -form is the preferred. The third protein is a plasma membrane α -tocopherol binding protein, which is specifically found in human erythrocytes and liver, where it is thought to regulate α -tocopherol levels.

Oxidative Stress in Neurodegenerative Disorders

Increasing evidence supports the notion that oxidative stress is important in the pathogenesis of

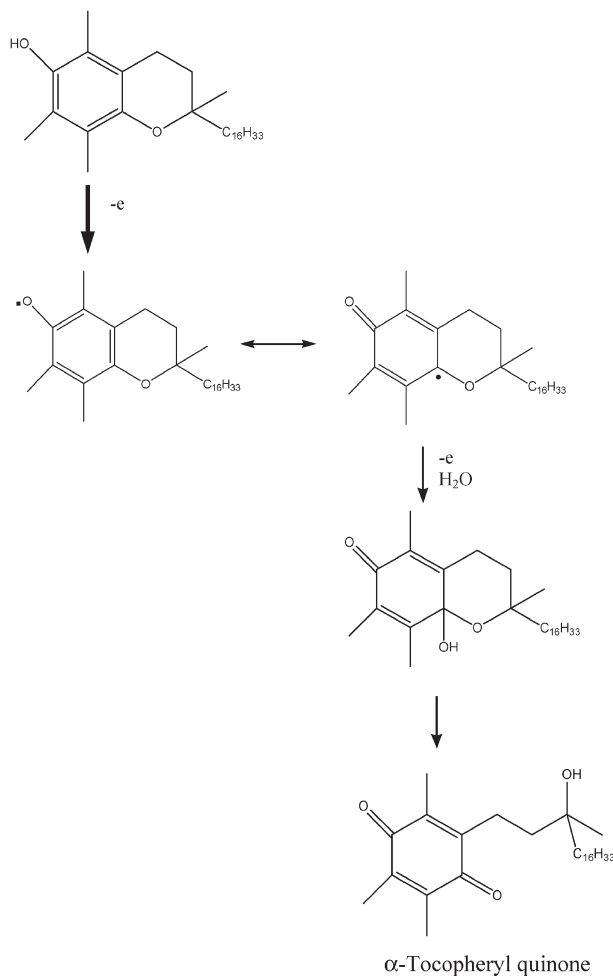


FIGURE 2 Mechanism of electron trapping of α -tocopherol.

several neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and others. Oxidative stress is defined as the overproduction of reactive oxygen (ROS) and/or reactive nitrogen (RNS) species, a decrease in the defense systems against such ROS and RNS, or a combination of both effects (Halliwell and Gutteridge, 1990; Butterfield and Stadtman, 1997).

In each neurodegenerative disorder listed above, evidence for one or more markers of oxidative stress, manifested as protein oxidation, lipid peroxidation, ROS generation, DNA oxidation, have been described (Browne *et al.*, 1999; Butterfield and Kanski, 2001; Butterfield *et al.*, 2001). Hence, one therapeutic strategy in these disorders has been to use approved antioxidants to determine if amelioration of signs and symptoms occurs. Vitamin E is a known lipid-soluble, chain-breaking antioxidant. This review summarizes research on the use of vitamin E in some neurodegenerative disorders.

VITAMIN E AND ALZHEIMER'S DISEASE (AD)

AD is characterized symptomatically by progressive cognitive and memory decline, speech loss, and personality changes. Pathologically, AD is characterized by deposition of amyloid β -peptide ($A\beta$) in senile (neuritic) plaques and the presence of neurofibrillary tangles, and synapse loss (Katzman and Saitoh, 1991). Strong evidence of oxidative damage in AD brain exists, and $A\beta$ and its sequelae may be associated with this oxidative stress (Butterfield *et al.*, 2001). $A\beta$ causes oxidative damage to and neurotoxicity of neurons (Varadarajan *et al.*, 2000). Vitamin E blocks these effects *in vitro* (Koppal *et al.*, 1998; Behl, 1999; Butterfield *et al.*, 1999; Yatin *et al.*, 2000). The glutamate transporter, Glt-1, is oxidatively modified in AD brain (Lauderback *et al.*, 2001a,b), consistent with the decreased activity of this transporter in AD brain and with increased opportunity for excitotoxic mechanisms to lead to oxidative stress and neurodegeneration.

Low concentrations of vitamins E and C are reported in AD CSF. This finding was not confirmed but is consistent with a recent study of plasma from AD and control subjects (Bourdel-Marchasson *et al.*, 2001). Interestingly, the level of malondialdehyde (as a marker of lipid peroxidation) was inversely correlated with the level of vitamin E. The lower levels of vitamin E in CSF and plasma might reflect their consumption as antioxidants in the face of inexorable oxidative stress. Antioxidant supplementation conceivably could play a role in AD in combating this oxidative damage and compensating for the decreased level of endogenous vitamin E. Hence, although little is known about dietary antioxidants on development and progression of neurodegenerative disorders, especially AD (Halliwell, 2001), vitamin E has been used in clinical trials in this dementing disorder. In one study (Kontush *et al.*, 2001), AD subjects were divided into two groups, one of which received 400 IU of vitamin E and 1000 mg of vitamin C daily for one month, and the second of which received 400 IU of vitamin E alone. Two major findings of this study were reported. (1) Plasma and CSF levels of both vitamins E and C were significantly elevated in AD patients given both vitamins relative to baseline; the group that received vitamin E alone also had increased CSF vitamin E levels. (2) In the group given both vitamins, this increased CSF level of antioxidant vitamin E was correlated to decreased susceptibility of lipoproteins to *in vitro* oxidation. The authors suggest that a combined approach of vitamins E and C is better than vitamin E alone in protecting central nervous system tissue from oxidative insult. This result may reflect the relative stability of the tocopheroxyl radical that would normally require the presence of a reducing agent such as vitamin C to regenerate vitamin E.

Another study of vitamin E and vitamin C observed that those AD patients who received high vitamin E and C supplements had a lower risk of AD (Morris *et al.*, 1998). However, a different study of vitamin E and C supplementation indicated that those who took vitamin E and C supplements were protected against vascular dementia but not against AD (Masaki *et al.*, 2000).

A placebo-controlled, clinical trial of vitamin E (2000 IU per day) in moderate AD patients was conducted by the AD Cooperative Study (Sano *et al.*, 1997). These large doses of vitamin E appeared to pose little risk over an approximately two-year period. The authors reported that high-dose vitamin E slowed the progression of AD in these patients as measured by delayed institutionalization into a nursing home relative to the placebo group. Although criticized by others (Tabet *et al.*, 2000), who suggest that the Sano *et al.* (1997) study did not show efficacy of high dose vitamin E in moderate AD patients, based on the apparent success of this study, similar investigation of early AD and mild cognitive impairment subjects have been undertaken (Grundman, 2000; Thal, 2000).

A risk factor for AD is the presence of allele 4 of apolipoprotein E (apoE) (Roses, 1996). Synaptosomes from knock-in mice containing human apoE4 with no mouse background show significantly increased susceptibility to oxidative stress induced by A β relative to apoE2 or apoE3 (Lauderback *et al.*, 2002). Synaptosomes from apoE knock-out mice, containing no gene for apoE, likewise have increased susceptibility to oxidative stress induced by A β (Lauderback *et al.*, 2001a,b). Both studies suggest that apoE may serve an antioxidant function, but that apoE4 is less able to do so than apoE2 or apoE3. To test this idea, 1-month old control and apoE deficient mice received dietary vitamin E for 12 months. Vitamin E-fed animals performed significantly better on tests of spatial motor activity and decreased levels of lipid peroxidation relative to apoE deficient mice fed a normal diet (Veinbergs *et al.*, 2000). Based on these and other studies, it has been proposed that prospective studies are needed to determine if people at high risk of developing AD due to the presence of apoE4 might benefit from antioxidant intervention at an early and asymptomatic age (Dreon and Peroutkal, 2001).

Taken together, the effects of increased oxidative stress under which the AD brain exists appears to be ameliorated with vitamin E supplementation. That studies showed that increased CSF levels of α -tocopherol could be found in patients given vitamin E supplements suggests that blood-brain barrier penetration does occur if sufficiently high vitamin E dose is given for an extended period, even though the kinetics for penetration by vitamin E are slow. However, more easily penetrable vitamin E

analogues may be desirable. Although controversy still exists over vitamin E and vitamin E/C supplementation, future studies may help to elucidate the synergism of vitamin E and C supplementation and the effectiveness of vitamin E against brain oxidative stress in AD.

VITAMIN E AND PARKINSON'S DISEASE (PD)

There is strong evidence indicating association between neurodegeneration in PD and free radical-mediated cell death (Ebadi *et al.*, 1996). Findings such as increased basal concentrations of malondialdehyde and other products of lipid peroxidation, decreased levels of antioxidant molecules, such as glutathione, increased mitochondrial SOD activity, modified iron metabolism, and increased activity of neuronal phagocytes, suggest a possible role for oxidative stress in brain nigral degeneration in PD. It is thus conceivable that substances with antioxidant capabilities, such as vitamin E, might protect against the development of PD.

Several results support the use of vitamin E as a treatment against the progression of this progressively disabling disease. Studies on vitamin E deficient mice showed that animals placed in a vitamin E-free diet for 52 weeks presented progressive nigral dopaminergic cell loss, assessed by staining of tyrosine hydroxylase (TH) immunopositive neurons. In addition, persons with vitamin E deficiency due to abetalipoproteinemia show a reduced uptake of ^{18}F DOPA, a finding also observed in PD.

In animal models, vitamin E has shown neuroprotective activity against free radical-mediated injury caused by 6-hydroxydopamine (6-OHDA), a neurotoxin whose effects mimic the nigrostriatal lesions characterizing unilateral Parkinsonism (Ungerstedt, 1971). The mechanism of neurodegeneration of 6-OHDA, which causes loss in dopamine (DA) neurons and reduction of DA in the striatum (Jonsson, 1980) once injected in the nigrostriatal system, is suggested to involve the production of free radicals. The toxin is taken up by the catecholamine (CA) terminals via the CA reuptake process, thus generating hydrogen peroxide via a non-enzymatic reaction with oxygen (Cohen and Heikkila, 1974) and depleting the endogenous antioxidant pool (Perumal *et al.*, 1992). Several results demonstrate that vitamin E attenuates the toxicity of 6-OHDA. Biochemical evidence shows that α -tocopherol can prevent the toxin-induced destruction of striatal DA terminals (Cadet *et al.*, 1989) and counteract the depletion of antioxidant defenses such as glutathione and superoxide dismutase (Perumal *et al.*, 1992). In addition, behavioral and histochemical studies on 6-OHDA-lesioned rats show that vitamin E reduces the atrophy

and degeneration of the TH-positive terminals in the brain targeted regions and ameliorates the rotational behavior after addition of apomorphine (Roghani and Behzadi, 2001), which causes rotations that are considered reliable indicators of nigrostriatal degeneration (Schwartz *et al.*, 1991; Schwartz and Huston, 1996). All these data together demonstrate the beneficial effect of vitamin E in this model of induced injury, commonly used to elucidate the mechanism of degeneration in PD and suggest the possibility of a clinical use of this antioxidant in the treatment of PD neurodegeneration.

The effect of vitamin E on the progression of PD has been tested in several epidemiological studies. The Rotterdam study (de Rijk *et al.*, 1997) investigated the association between dietary antioxidant intake and PD, discovering a dose-dependence inverse association between vitamin E dietary consumption and PD incidence. These findings suggest a protective effect of vitamin E against the development of PD, and are in accordance with previous studies (Golbe *et al.*, 1988) showing low incidence of PD associated with a high intake of vitamin E-containing food items. However, another population-based study did not observe any significant difference with intake of vitamins with antioxidant activity (Logroscino *et al.*, 1996). Further, it is reported that the concentration of α -tocopherol (α -TOH) remains unchanged in brain and plasma of PD patients (Satya-Murti *et al.*, 1986; Nicoletti *et al.*, 2001).

Consistent with these results, vitamin E was used as a therapeutic agent in the DATATOP (deprenyl and tocopherol antioxidant therapy of PD) study. The investigation enrolled 800 untreated patients with early PD from the United States and Canada between 1987 and 1988, using daily administration of 2000 IU of vitamin E. The end point of the study was the subject's level of disability sufficient to start levodopa therapy. The investigators did not find any beneficial effect associated with vitamin E in delaying the onset of degeneration, slowing intellectual decline, and decreasing death rate (Shoulson, 1998). Vatassery *et al.* (1999) reported a linear correlation between vitamin E concentration in cerebrospinal fluid (CSF) and the number of days of ingestion, suggesting that long-term treatment with α -tocopherol might ameliorate antioxidant deficiency by increasing its concentration in the brain. Others (Fahan, 1992) reported a positive effect of a long-term, high-dose (3000 IU) vitamin E treatment in postponing the use of levodopa, suggesting that the concentration of brain vitamin E is highly regulated and large intake in conjunction with long term treatment is required to increase brain vitamin E level to the point where neuroprotection can be demonstrated. Taken together, the results are not compelling on the benefit of vitamin E in PD therapy.

VITAMIN E AND AMYOTROPHIC LATERAL SCLEROSIS (ALS)

ALS is a neurodegenerative disorder that affects motor neurons in the cortex, brainstem, and spinal cord. This devastating disease typically results in death 3–5 years after diagnosis. Of the familial ALS cases, which account for 10% of all cases, 20% are associated with a mutation in the SOD1 gene that encodes for CuZn-SOD (Rosen *et al.*, 1993). The mutation in CuZn-SOD is a gain-of-function alteration, resulting in more production of H_2O_2 (Gurney *et al.*, 1994). Through Fenton chemistry, H_2O_2 can produce the reactive hydroxyl radical, permitting indiscriminate attack on surrounding molecules, i.e. proteins, lipids, etc. Protein carbonyls, an indicator of oxidative stress (Butterfield and Stadtman, 1997), in red blood cell membranes and supernatants were correlated with the onset of clinical symptoms in sporadic ALS patients (Oteiza *et al.*, 1997).

Excitotoxic mechanisms have been implicated in ALS as a significant increase in CSF glutamate levels was found in ALS patients compared to control (Shaw *et al.*, 1995); however, this increase was highly heterogeneous among the ALS patients, with the majority of cases within normal glutamate ranges. Further, glutamate uptake appears to be altered, evidenced by a decrease in total GLT-1 protein and glutamate transport (Bristol and Rothstein, 1996). Additionally, GLT-1 is modified by 4-hydroxynonenal, a lipid peroxidation end-product, in spinal cords of ALS patients (Pedersen *et al.*, 1998). The glutamate excitotoxicity observed in ALS can activate calcium-dependent type I nitric oxide synthetase, producing excess nitric oxide (Al-Chalabi and Leigh, 2000). It is thought that some mutant SOD1 increases the steady-state concentration of superoxide, allowing more superoxide to be available for reaction with nitric oxide to form the toxic anion, peroxynitrite ($ONOO^-$) (Al-Chalabi and Leigh, 2000). In fact, 3-nitrotyrosine has been shown to be elevated in motor neurons of the spinal cord (Abe *et al.*, 1995) and in the CSF (Tohgi *et al.*, 1999) of sporadic ALS patients compared to controls.

Even before there was evidence of oxidative stress in ALS patients, vitamin E was proposed as therapy, with Lou Gehrig being a famous recipient of vitamin E therapy (Reider and Paulson, 1997). The idea of vitamin E therapy in ALS patients declined as studies indicated that megadoses of vitamin E were not helpful in delaying the progression of the disease (Dorman *et al.*, 1969). However, when SOD was linked to ALS, vitamin E again was proposed as therapy for ALS.

In the well described transgenic ALS mouse model (Gly93 \rightarrow Ala mutation in Cu, Zn SOD) (Gurney *et al.*, 1994; Gurney, 1997), diets were supplemented with Vitamin E (Gurney *et al.*, 1996). Vitamin E delayed

the onset of the clinical disease and disease progression in the transgenic ALS mouse model, as determined by wheel activity. However, vitamin E had no effect on survival. Further, these transgenic mice show a blunted accumulation of vitamin E in the spinal cord and increased malondialdehyde levels over the lifetime of the mouse compared to the nontransgenic mice (Hall *et al.*, 1998), suggesting that vitamin E is consumed by the increased lipid peroxidation.

Plasma and serum levels of vitamin E in ALS patients appear to be the same as control (Iwasaki *et al.*, 1995; Oteiza *et al.*, 1997; de Bustos *et al.*, 1998; Bonnefont-Rousselot *et al.*, 2000). α -Tocopherol and α -tocopherol quinone (oxidized form of vitamin E, see Fig. 2 above) levels in CSF are reported to be lower in patients with sporadic ALS (Tohgi *et al.*, 1996). It is unclear why levels of both reduced and oxidized vitamin E are decreased and emphasize the need to understand the degradation and generation of vitamin E in ALS.

Various cell culture experiments indicate that vitamin E is beneficial in ALS models. Vitamin E protected against neurotoxicity of CSF from ALS patients in rat cortical cell cultures (Terro *et al.*, 1996), against loss in glucose and glutamate transport caused by FeSO_4 in NSC-19 motor neuron cells (Pedersen *et al.*, 1999), and against Fe^{3+} /ascorbate toxicity in cultured motor neurons (Kaal *et al.*, 1998). However, recent studies with vitamin E supplements given to patients have not been as clear. Patients with sporadic ALS were given an array of antioxidants including *N*-acetylcysteine, vitamin C, vitamin E, *N*-acetylmethionine, and dithiothreitol or dithioerythritol (Vyth *et al.*, 1996). The median survival of patients who received the antioxidant supplement increased by six months over the untreated group, but the researchers believe this difference to be a result of selection factors of the patients included in the study. In a recent study, ALS patients who were already receiving riluzole were additionally given α -tocopherol or placebo for one year (Desnuelle *et al.*, 2001). Though vitamin E treatment did not extend lifespan, patients who received vitamin E supplements did stay in a milder state of ALS longer than placebo recipients. These vitamin E supplemented patients also had higher plasma glutathione peroxidase activity and lower plasma TBARS.

While vitamin E may be a potential therapy in the treatment of motor neuron disease, there are many quandaries with vitamin E treatment. Vitamin E appears to delay symptoms but does not extend life span, which may be attributed to the slow delivery of vitamin E, the point in the disease process when vitamin E is given, the amount of vitamin E given as a supplement, or the delayed kinetics for blood brain barrier penetration by this antioxidant. Additional studies of vitamin E in ALS are warranted to try to

resolve the utility of this compound in the treatment of ALS.

VITAMIN E AND TARDIVE DYSKINESIA

Tardive dyskinesia is a movement disorder that occurs in 20–25% of patients on traditional long-term neuroleptic drugs. The free radical hypothesis of tardive dyskinesia asserts that long-term administration of neuroleptics alters DA by increasing DA turnover, DA metabolism, and the number of DA receptors in the basal ganglia (Bischot *et al.*, 1993). DA is mainly processed by monoamine oxidase yielding DA quinones and H_2O_2 , resulting in oxidative stress (Elkashef and Wyatt, 1999). Increased TBARS and conjugated dienes have been found in the CSF of tardive dyskinesia patients, indicative of lipid peroxidation (Lohr *et al.*, 1990).

Vitamin E as a chain-breaking, lipid-soluble antioxidant has been studied in the treatment of tardive dyskinesia. Trials using vitamin E as therapy for tardive dyskinesia have been performed since the first in 1988 (Lohr *et al.*, 1988). Many of these trials have been reviewed extensively elsewhere (Lohr and Caligiuri, 1996; Boomershine *et al.*, 1999; Elkashef and Wyatt, 1999). In the majority of these trials, patients have shown an improvement in the Abnormal Involuntary Movement Scale (AIMS) score, but some trials have not shown statistical significance. These studies varied greatly in the amounts of vitamin E given daily (400–1600 IU), duration of treatment, number of participants, and duration of tardive dyskinesia symptoms.

A large multi-center, longer study was performed, known as the Veterans Affairs Cooperative Study (CS 394) (Adler *et al.*, 1999). In this study, nine sites were involved treating 73 patients with 1600 IU/day compared to 85 placebo patients, all of whom had tardive dyskinesia for less than 10 years. Forty-nine and fifty-five patients completed treatments for one year in the vitamin E and placebo therapies, respectively. Though the largely negative results of this study seem to refute prior studies, the authors suggest that their investigation may be different because of differences in study design and the patient population (Lohr and Lavori, 1998; Adler *et al.*, 1999). Among the differences in patient population is the prescribing of atypical antipsychotic drugs, which may have decreased patients' response to vitamin E therapy. The preponderance of evidence suggests only modest benefit from vitamin E therapy in this disorder. However, given the wide disparity in methodology in these trials, it is imperative to adopt a uniform paradigm to determine if vitamin E is beneficial in tardive dyskinesia.

VITAMIN E AND HUNTINGTON'S DISEASE (HD)

HD is an inherited neurodegenerative disease that affects the medium spiny neurons in the striatum and is clinically characterized by ataxia, choreiform movements, and dementia. The principal neuropathological features of the disease are marked atrophy, neuronal loss, and astrogliosis in the neostriatum. The genetic defect in HD has been recognized in an abnormal expanded trinucleotide (CAG) repeat in a gene located on the short arm of chromosome 4 which encodes a protein termed "huntingtin" (Huntington's Disease Collaborative Research Group, 1993), whose function, so far, remains to be elucidated. Several lines of evidence indicate that a defect in mitochondrial energy metabolism might underlie the pathogenesis of the selective neuronal death occurring in HD. Although full-length huntingtin is predominantly distributed in the cytoplasm, N-terminal fragments of huntingtin with expanded polyglutamine tracts are able to accumulate in the nucleus and kill neurons through apoptotic pathways.

Oxidative stress has been implicated in the pathogenesis of this disease though the cause of the oxidative stress is uncertain (Browne *et al.*, 1999). In the 3-nitropropionic acid animal model of HD, protein carbonyls were found in striatal synaptosomes, preceding lesion formation (La Fontaine *et al.*, 2000). Because of the evidence of oxidative stress in HD, vitamin E was been proposed as therapy in these patients. High doses of vitamin E or placebo were given to HD patients (Peysers *et al.*, 1995). Though vitamin E did not change the neurologic or neuropsychiatric symptoms in the overall group, motor decline was slowed for those patients receiving vitamin E early in the disease. The authors conclude that vitamin E may be beneficial to slow the progression of the disease if given in early stages. While studies are few, vitamin E may potentially be a therapeutic strategy in HD; however, more trials with vitamin E supplementation in humans need to be performed, and especially early in this disorder to determine if benefit can be obtained.

VITAMIN E AND MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a disease characterized by perivascular infiltrates and demyelination of the white matter in the central nervous system. Although evidence indicates that MS is a complex trait caused by interaction of genetic and environmental factors, little is known about its cause or the factors that contribute to its unpredictable course (Trojano and Paolicelli, 2001). It is generally accepted that vascular factors, metabolic alterations, virus

infections of the CNS and/or disturbed immune mechanisms are responsible for the cause and course of MS.

The clinical symptoms of MS result from inflammatory damage to the insulating myelin sheath of axons in the CNS and at later stages to axons themselves. A local autoimmune process involving activation of helper T cells against CNS protein components is likely to be crucial in this development. Once triggered, the immune system attacks and destroys myelin and the myelin-forming cell (Storch *et al.*, 1998). Evidence exists indicating that oligodendrocytes respond to the attack by immune cells and their secreted products through modulation of its metabolism and gene expression (Lindsey *et al.*, 1997). It has been also suggested that inappropriate stress response within the CNS could influence both the permeability of the blood-brain barrier and the expression of heat-shock proteins, thereby initiating the MS lesion (van Noort *et al.*, 1998).

Although the precise cause of MS remains unknown, some investigations have been carried out on antioxidant mechanisms in these patients (Mehindate *et al.*, 2001). Free radicals contribute significantly in the modification of immune processes and inflammatory reactions, since they facilitate production of cytokines, which are important determinants in inflammatory reactions. Accordingly, the DNA-binding activity of nuclear factor (NF- κ B) is induced in the spinal cord of rats with experimental allergic encephalomyelitis (EAE), an animal model of MS (Pahan and Schmid, 2000). This activation of NF- κ B persisted throughout the disease period and decreased thereafter in the recovery phase. Pyrrolidine dithiocarbamate (PDTC), an inhibitor of NF- κ B activation, markedly inhibited the *in vivo* activation of NF- κ B in the spinal cord of EAE rats and attenuated the clinical symptoms of EAE, suggesting that activation of NF- κ B plays an important role in the pathogenesis of EAE, while inhibitors of NF- κ B activation may have therapeutic importance in MS. This finding poses intriguing implications in view of the recent evidence that vitamin E blocks NF κ B activation in different cell types (Hattori *et al.*, 1995; Lee *et al.*, 2001). Cytokines, immunoglobulins and complement complexes may also elicit a survival response in the oligodendrocytes, involving the induction of endogenous heat shock proteins and other protective molecules which indicates that redox systems and therefore the oxidant/antioxidant balance in these cells are of great importance in MS (van Noort, 1996).

Possible links between MS and lipid peroxidation are suggested by: the increased incidence of MS in population consuming high proportions of animal fat, since vitamin E is predominantly associated with plant lipid in the diet (Swank, 1991); decreased levels

of easily oxidizable linoleic acid in MS serum, platelets, erythrocytes, leukocytes and brain (Thompson, 1975); significantly increased malonaldehyde levels in blood as well as in the CSF of MS patients associated with significant changes in antioxidant enzymes in erythrocytes, granulocytes and lymphocytes (Szeinberg *et al.*, 1981; Calabrese *et al.*, 1994; 1998). Increased serum peroxide levels have been demonstrated in MS relative to control (Calabrese *et al.*, 1998; Karg *et al.*, 1999). Patients with MS in acute exacerbation exhibit significantly higher levels of pentane and exane, products of lipid peroxidation, in expired breath compared to either MS patients in remission or control subjects (Toshniwal and Zarling, 1992). White matter has a low concentration of antioxidant enzymatic activities and therefore is particularly vulnerable to damage from exposure to ROS species (Zhang *et al.*, 2001).

This hypothesis was supported by the finding that individuals with MS have lower concentration of glutathione and alpha-tocopherol and increased uric acid in plaques compared with surrounding white matter. In addition, MS patients have lower average serum uric acid than controls, and an inverse relationship exists between MS and gout. Moreover, recent clinical and animal studies suggest that NO and its reactive derivative peroxynitrite are implicated in the pathogenesis of MS (Bo *et al.*, 1994). Patients dying with MS demonstrate increased astrocytic inducible nitric oxide synthase (iNOS) activity as well as increased levels of iNOS mRNA and nitrotyrosine residues (Bo *et al.*, 1994). In EAE both astrocytes and microglia express iNOS (Hooper *et al.*, 1997). Formation of free radicals is influenced by antioxidants that can thus modify the intensity of inflammatory reaction and immune response. In view of recent evidence indicating that antioxidants and peroxynitrite inhibitor uric acid suppresses the MS animal model, EAE (Constantinescu *et al.*, 2000), it is conceivable that substances with antioxidant capabilities, such as vitamin E, might protect against the development of MS. Vitamin E levels have been reported to be decreased in demyelinating plaques of MS brains (Langemann *et al.*, 1992).

Epidemiological data relating intakes of dietary carotenoids, vitamin C and vitamin E to risk of MS are sparse. A case-control study reported a lower risk with vitamin C intake, whereas no association with dietary intakes of vitamin C and vitamin E was observed (Ghadirian *et al.*, 1998). Also, intakes of fruit and vegetables, which are rich in carotenoids, vitamin C and vitamin E were not associated with a decreased incidence of MS (Gusev *et al.*, 1996). A prospective investigation was conducted in two large cohorts of women to examine the association between dietary antioxidants and risk of MS (Zhang *et al.*, 2001). Although no associations were found between intakes of fruits and vegetables

and risk of MS as well as between multivitamin supplements and reduced MS incidence, the authors concluded that additional large prospective investigations will be necessary to determine whether or not antioxidants may benefit women with MS. Studies of vitamin E supplementation of people with multiple sclerosis need to be performed to determine the efficacy of megadose vitamin E supplementation in the treatment of this demyelinating disorder.

CONCLUSION

Vitamin E is a prototype of phenolic-based, chain-breaking antioxidants. Other such molecules, some of which occur in food sources, may be better suited for use as neuroprotectants against oxidative stress due to faster kinetics of blood-brain barrier penetration than vitamin E. Nevertheless, vitamin E, or synthetic variants of vitamin E that penetrate the blood-brain barrier more rapidly, show promise in some neurodegenerative disorders in which oxidative stress is implicated. For example, in AD high dose vitamin E is the only reported intervention to slow the progress of the disease (Sano *et al.*, 1997). A large number of human studies involving vitamin E have not been undertaken with multiple sclerosis and HD; however, the promising results of vitamin E supplementation in some neurodegenerative disorders warrants the exploration of vitamin E supplementation in the therapeutic intervention of these diseases as well. In the absence of other brain-accessible highly efficient free radical scavengers, vitamin E will continue to be one therapeutic strategy in neurodegenerative disorders associated with oxidative stress.

Acknowledgements

This work was supported in part by NIH grants to D.A.B. [AG-05119; AG-10836].

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