

Chapter 124

The Dietary Antioxidants Alpha-Tocopherol and Alpha-Lipoic Acid and Their Synergy in Brain Disorders

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Abbreviations

HNE	4-Hydroxy-2-nonenal
5-HT	5-Hydroxytryptamine
ATPase	Adenosine triphosphatase
ALA	Alpha-lipoic acid
DNA	Deoxyribonucleic acid
GABA	Gamma-amino butyric acid
GPX	Glutathione peroxidase
GAP43	Growth-associated protein 43
NAD ⁺	Nicotinamide adenine dinucleotide oxidized
NADP ⁺	Nicotinamide adenine dinucleotide phosphate oxidized
NADHP	Nicotinamide adenine dinucleotide phosphate reduced
NADH	Nicotinamide adenine dinucleotide reduced
ROS	Reactive oxygen species
RNA	Ribonucleic acid
SOD	Superoxide dismutase
VE	Vitamin E

124.1 Introduction

The consumption of edible plants, fruits, and vegetables has shown to prevent the occurrence of a number of diseases and, under certain circumstances, to reduce the oxidative damage in humans. Vegetables, fruits, and seeds are rich sources of antioxidants, for instance lipoic acid, vitamins A, C, and E, flavonoids, polyphenols, lycopenes, proanthocyanidins, astaxanthins, and others. These compounds might protect the organism against free-radical-induced injuries and diseases. The utilization

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of antioxidants may be potentially useful for preventing lesion enlargement, and for treating pathological conditions that have an oxidative process as a major source of neurological damage, for instance brain ischemia, diabetic neuropathy, Parkinson's disease, multiple sclerosis, Huntington's disease, amyotrophic lateral sclerosis, or Alzheimer's disease. Despite dramatic advances in our understanding of these neurological diseases, at present there is no satisfactory treatment to reduce death and disability in patients. Antioxidant agents have been investigated as therapeutic alternatives to diminish cerebral damage, with varying results. In this chapter, we will discuss the role of oxidative stress in brain injury and the effects of two important antioxidants (vitamin E (VE) and lipoic acid) on the preservation of neural integrity after oxidative damage.

124.2 Reactive Oxygen Species and Oxidative Stress

Reactive oxygen species (ROS) play an important role in neuronal signaling and physiology; however, at higher levels, they can lead to neuronal dysfunction and cell death. There are two types of ROS: oxygen free radicals and nonradical oxygen derivatives (see Table 124.1).

ROS can arise from numerous sources including redox metal ion-catalyzed reactions, mitochondrial-resident electron transport chain function, glycation end products, and enzymatic reactions. Under physiological circumstances, ROS play important roles in body homeostasis by modulating and mediating vital processes, such as, glucose metabolism, cellular respiration, cerebral perfusion, vascular permeability, inflammation, immune response, physiological aging, and others. However, high levels of free radicals participate in tissue injury and disease progression in a number of pathologies: diabetes neuropathy, cancer, cardiac and brain ischemia, Alzheimer's disease, and others (Paravicini et al. 2004; Poon et al. 2004; Heo et al. 2005; Blomgren and Hagberg 2006; Butterfield 2006; Chrissobolis and Faraci 2008; Gonzalez-Perez et al. 2008).

Oxidative stress is manifested by excessive production of free radicals that, depending on the nature of the substrate attacked, produces different reactions including lipid peroxidation, protein oxidation, or deoxyribonucleic acid/ribonucleic acid (DNA/RNA) oxidation. These pathological processes have characteristic markers used to identify the targeted cell structure, for example:

1. Protein oxidation is characterized by overproduction of protein carbonyls, 3-nitrotyrosine or protein glutathionylation.
2. Lipid peroxidation is associated with production of free and protein-bound reactive alkenals as 2-propen-1-al (acrolein) and 4-hydroxy-2-nonenal (HNE); thiobarbituric acid reactive substances; and isoprostanes and neuroprostanes derived from peroxidation of arachidonic acid and docosahexanoic acid, respectively.

Table 124.1 Reactive oxygen species

Oxygen free radicals		Nonradical oxygen derivatives	
Name	Formula	Name	Formula
Hydroxyl radical	$\cdot\text{OH}$	Hydrogen peroxide	H_2O_2
Hypochlorite ion	$\text{ClO}\cdot$	Singlet oxygen	$^1\text{O}_2$
Superoxide anion	$\cdot\text{O}_2^-$	Ozone or trioxygen	O_3
Hydroperoxyl	$\text{HO}_2\cdot$	Peroxynitrite or peroxonitrite	$\text{ONOO}-$
Alkoxy	$\text{RO}\cdot$	Hypochlorous acid	HOCl
Peroxy	$\text{ROO}\cdot$		

Condensed formulas and chemical names of the two types of reactive oxygen species: oxygen free radicals and nonradical oxygen derivatives

3. DNA oxidation can be identified by quantifying the levels of 8-hydroxy-2-deoxyguanosine and advanced glycation end products (reaction products of reducing sugars with amines).

Regardless of the targeted cell structure, the oxidation of proteins, lipids, or DNA leads to structural changes, biochemical dysfunction, and cell death.

124.3 Brain Injury and Oxidative Stress

The brain consumes about one-third of the inspired oxygen, has the second highest concentration of fatty acids (exceeded only by adipose tissue), and has a high abundance of redox-capable transition metal ions coupled. In addition, this organ has very little glycogen deposits and a relatively low abundance of antioxidant defense systems. These characteristics make the brain the most vulnerable organ to *lipid peroxidation*. Recently, reactive nitrogen species are considered novel sources of oxidative stress in brain, which has been associated with protein deposits in several neurodegenerative disorders. This pathological process is called *nitrosative stress* and is also considered critical in brain dysfunction. The elevated production of reactive oxygen or nitrogen species, their production in inappropriate relative amounts, or deficiencies in antioxidant defenses may result in pathological stress to neurons and cerebral tissue. In summary, if oxidative or nitrosative stress is excessive or if defense and repair responses are inadequate, neuronal injury is caused. Therefore, antioxidant therapies appear to be a feasible approach to reduce brain damage and disease progression.

124.4 Dietary Antioxidants Against Oxidative Stress

There is considerable evidence for a role of antioxidant nutrients in the maintenance of health in contributing to the decreased incidence of free radical-induced diseases. Specifically, alpha-lipoic acid (ALA) and VE have been broadly studied under experimental and clinical conditions because of their unique chemical and nutritional properties. Moreover, these antioxidants are present in the normal human diet, their side effects are infrequent and the combinations of both substances appear to have synergistic effects for reducing cellular damage in oxidation-related pathological events. Therefore, this chapter will be focused on discussing the role of ALA and VE to neutralize oxidative processes in the brain.

124.4.1 Alpha-Lipoic Acid (ALA)

ALA, also known as lipoate, was discovered in 1951 as a molecule essential for aerobic life, participates in various transfer reactions within the pyruvate dehydrogenase complex by assisting in acyl-group transfer and as a coenzyme in the Krebs cycle. ALA helps preserve the homeostasis of cellular and mitochondrial membranes by modifying the metabolism of ketoacids and modulating mitochondrial ratios of nicotinamide adenine dinucleotide reduced/nicotinamide adenine dinucleotide oxidized (NADH/NAD⁺) and nicotinamide adenine dinucleotide phosphate reduced/nicotinamide adenine dinucleotide phosphate oxidized (NADHP/NADP⁺) (Packer et al. 1995, 1997). Lipoic acid is synthesized in the body in very small amounts and is covalently bound to the E2 enzyme subunit

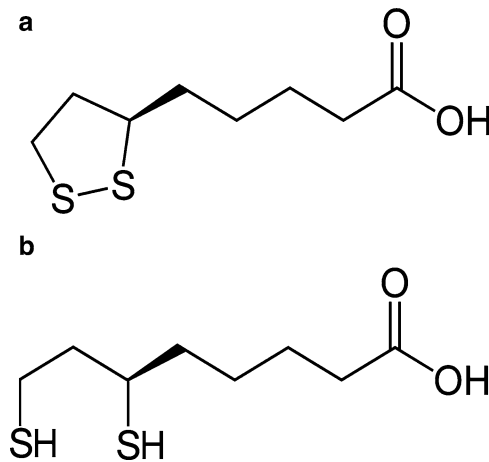


Fig. 124.1 Chemical structure of alpha-lipoic acid (ALA). Structural formulas of ALA (a) and dihydrolipoic acid (the reduced form of lipoate) (b)

of the four different alpha-keto acid dehydrogenase complexes in mitochondria. Under physiological conditions, the normal serum level of lipoate is 0.1 mg/mL, but this level can be rapidly modified by variety of foods where ALA is abundantly found, such as liver, heart, kidney, and red meat, as well as wheat germ, spinach, broccoli, potatoes, and beer yeast.

After dietary intake, lipoate is absorbed into the circulation from the intestine and within cells is reduced and exported to interstitial space as dihydrolipoate (Fig. 124.1). Due to its amphiphilic properties, the ALA neutralizes free radicals in both the fatty and watery regions of cells (Packer, et al. 1995, 1997). These antioxidant properties are mainly located in its thiol group, which reacts directly with ROS and provides strong chelating activity on transition metals. Lipoate also contributes in other antioxidant systems by enhancing the effects of superoxide dismutase (SOD) (Seaton et al. 1996), coenzyme Q10, and glutathione (Murphy et al. 1992; Roy et al. 1997), and by regenerating other antioxidants such as ascorbate (vitamin C) and alpha-tocopherol (Packer et al. 1995, 1997). Lipoic acid is thought to function as a neuroprotective agent and an anti-inflammatory compound, providing effective treatment for Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Additionally, lipoic acid has been tested to treat mercury intoxication. The administration of ALA at dose of 600–1,200 mg/day is sufficient to reach therapeutic serum levels of 4–8 mg/mL at 3rd to 5th day. Taken together, this evidence indicates that ALA is an important antioxidant that may be clinically useful to control neurological conditions related to the overproduction of oxidant radicals (Packer et al. 1995).

124.4.2 Vitamin E (VE)

Alpha-tocopherol is the most abundant natural isoform of VE (Fig. 124.2) and the one with the highest bioavailability. For this reason, the term alpha-tocopherol is frequently referred as synonymous of VE. VE is abundant in wheat germ, almonds, hazelnuts, peanuts, spinaches, broccoli, kiwi, and mango, and in several oils including soybean, sunflower, corn, and safflower. In humans, the normal serum levels of VE oscillate between 11.6 and 46.4 mmol/L. The antioxidant capacity of VE is independent of enzymatic reactions and resides in transferring a phenolic H⁺ to oxidant radicals derived from oxidized

and Krieglstein 1995), *x*-irradiation-induced oxidative stress (Manda et al. 2007), mitochondrial aging, and peripheral neuropathy (Roy et al. 1997). ALA prevents the development of clinical signs and preserves the integrity of brain–blood barrier in acute experimental allergic encephalomyelitis, a rodent model for multiple sclerosis (Schreibelt et al. 2006) and in human patients (Yadav et al. 2005). Lipoate has important anti-inflammatory effects as shown by reducing glial reactivity and by modulating the levels of nuclear factor kappa B p65 in brain (NFkappaB) (Jesudason et al. 2008). When administered to pregnant rats, ALA decreases DNA damage and oxidative stress induced by alcohol in the developing hippocampus and cerebellum (Shirpoor et al. 2008). Dietary supplementation of ALA delays the progression of age-related cognitive decline (Arivazhagan et al. 2002; Suchy et al. 2009) and reduces ischemic cerebral damage when complicated with diabetes (Piotrowski et al. 2001). ALA is also effective in protecting neural cells against glutamate-induced cytotoxicity. This protective effect of ALA plus appears to be independent of its stereochemistry and is synergistically enhanced by selenium (Tirosch et al. 1999).

However, ALA and VE are not always effective in diminishing oxidative damage in the brain, especially when these compounds are used alone or without combination of antioxidants. For instance, alpha-tocopherol does not reduce post-traumatic cerebral edema induced by cold injury (Stoffel et al. 1997) and has limited clinical benefits in Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease (Parkinson 1993; Sano et al. 1997; Gaedicke et al. 2009). Other reports indicate that ALA does not have clinical relevance to treat trigeminal trophic syndrome (Fruhauf et al. 2008) and does not have a significant neuroprotective effect in brain ischemia after intraperitoneal or intracranial administration (Wolz and Krieglstein 1996). Therefore, researchers are now interested in establishing whether beneficial effects of antioxidants become more evident when these substances are administered together. On this regard, recent evidence indicates that antioxidant combinations are more effective than the use of a single antioxidant. One of the combinations with reproducible and promising results is the combination of ALA plus VE. ALA markedly modifies in situ concentrations of VE (Packer et al. 1995, 1997). This process is mediated by ascorbate recycling, glutathione disulfide reduction, and involves ubiquinone and dehydroascorbate radicals (Fig. 124.3). The combination of VE and vitamin C has been studied, but the pro-oxidant activity of ascorbate is important and its benefits are not quite evident. In addition, ALA is also capable of reducing thioredoxin; thus the antioxidant properties of ALA are more complete than that of vitamin C (Packer et al. 1997).

124.4.4 Synergism Between Lipoate and Tocopherol

During the past 2 decades, an increasing number of reports regarding the therapeutic applications of the combination of VE plus ALA have been published (see Table 124.2). These investigations indicate that the combination of both antioxidants is effective in reducing oxidative damage in several pathological conditions, such as diabetic neuropathy, Alzheimer's disease, rheumatic arthritis, cardiac and cerebral ischemia, cataract degeneration, and in the aging process (Haramaki et al. 1993, 1995; Maitra et al. 1995; Stoyanovsky et al. 1995; Coombes et al. 2000a, b, 2001; Gonzalez-Perez and Gonzalez-Castaneda 2006). One of the first studies that revealed the synergistic effect between alpha-tocopherol and lipoate was done in microsomal fractions obtained from normal and VE-deficient animals (Scholich et al. 1989). In that study, the controls showed a prolonged lag phase before the onset of low-level chemiluminescence in microsomes that were not found in the VE-deficient fractions. Oral supplementation of ALA–VE significantly reduces lymphocyte apoptosis in a global cerebral ischemia model. Favorable effects of an ALA–VE mixture were found in

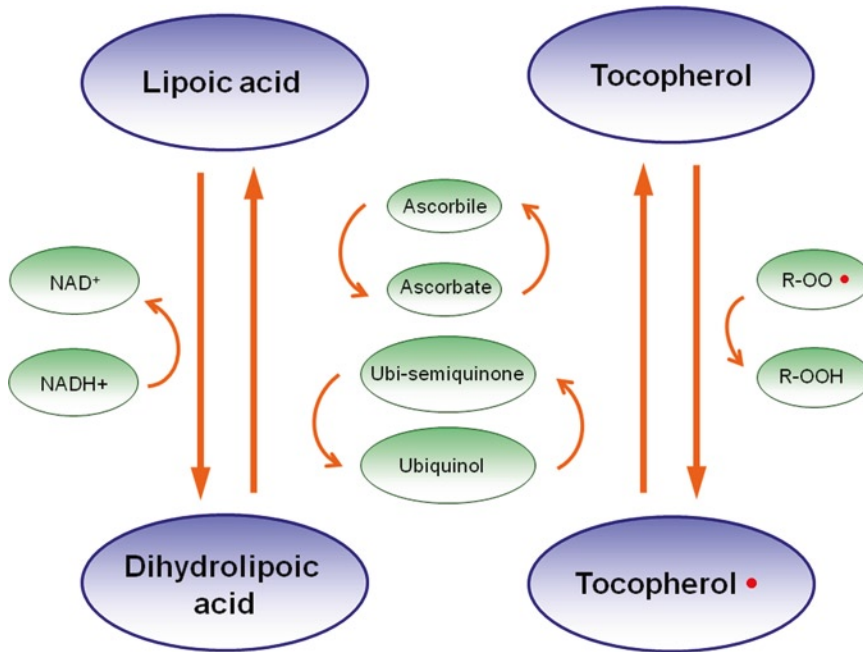


Fig. 124.3 Biochemical recycling of VE. Vitamin E is recycled via intracellular alpha-lipoic acid. In this complex mechanism, the main metabolic intermediaries are vitamin C (ascorbate) and ubiquinol. R-OO•: Oxidant radical; R-OOH: Neutralized radical

a thromboembolic stroke model; this study analyzed the efficacy of the prophylactic administration of ALA plus VE upon ischemia. ALA-VE mixtures efficiently reduced glial scar, improved the recovery after brain ischemia, and increased the tissue levels of synaptophysin and growth-associated protein 43 (GAP43), a couple of synaptic remodeling proteins (Gonzalez-Perez et al. 2002). This prophylactic treatment also reduces infarct volume and lipid peroxidation after cerebral ischemia (Garcia-Estrada et al. 2003). Additional findings indicated that the ALA-VE combination decreases the age-associated Na(+),K(+)-adenosine triphosphatase (ATPase) activity. Because of the critical importance of Na(+),K(+)-ATPase in neuronal functions, the results of this study may have important implications in controlling age-related functional deficits of the brain (Bagh et al. 2008). In a model of acute intoxication with lindane, ALA and VE were neuroprotective as shown by preservation of the neurotransmitters gamma-amino butyric acid (GABA) and serotonin (5-hydroxytryptamine, or 5-HT) in olfactory lobe, cerebrum, hippocampus-hypothalamus, cerebellum, and pons-medulla (Bist and Bhatt 2009). Interestingly, a treatment with a triple combination of VE, LA, and vitamin C protects the arachidonic acid level in the brains of diabetic and nondiabetic rats (Ozkan et al. 2005). Arachidonic acid is crucial to the optimal development of the brain and eyes and to preserve cognitive abilities.

Other findings indicate that the combination of ALA and VE increases endothelial levels of the antiapoptotic protein Bcl-2 without significant changes in the levels of the proapoptotic protein Bax (Marsh et al. 2005). In parallel, the ALA/VE mixture has been combined with other dietary antioxidants, such as vitamin C, beta-carotene, and selenium, and then evaluated under several conditions of exercise, experimental diabetes, cold, age, and cancer, and promising results have also been obtained (Bailey and Davies 2001; Sharman and Bondy 2001; Mosca et al. 2002; Schmidt et al. 2002; Mantovani et al. 2003; Ozkan, et al. 2005). Taken together, this evidence strongly suggests that the combination of ALA and VE is better than the antioxidant monotherapy.

Table 124.2 Key facts of the synergy alpha-tocopherol/alpha-lipoic acid

Findings	Antioxidant isoforms (dose)	Model (specie)	Reference
Reduction in the lipid peroxidation induced by UV-light on microsomal fractions	α -Tocopherol (62.7 mg/kg diet)/dihydrolipoic acid (50 μ M)	In vitro (rat)	Scholich et al. (1989)
Less retinal degeneration induced by UV light	α -Tocopherol (50–100 μ M)/dihydrolipoic acid (25–100 μ M)	In vitro (rat)	Stoyanovsky et al. (1995)
Restoration of the activities of glutathione peroxidase, catalase, and ascorbate free-radical reductase in lenses that prevents cataract formation	α -Tocopherol (62.7 mg/kg diet)/lipoic acid (25 mg/kg body weight)	In vivo (rat)	Maitra et al. (1995)
Improvement of cardiac recovery, less arrhythmias incidence and lipid peroxide levels, and strong myocardial contractility during postschemic reperfusion and posthypoxic reoxygenation of heart	α -Tocopherol (100 μ M)/ dihydrolipoic acid (50 μ M) (Haramaki et al. 1993, 1995 α -Tocopherol (1,000 IU VE/kg diet)/lipoic acid (1.65 g/kg diet) (Coombes et al. 2000a, b, 2001; Ko and Yu 2001)	In vitro e in vivo (rat)	Haramaki et al. (1993, 1995); Coombes et al. (2000a, b); Ko et al. (2001)
Reduction in maximal twitch tension and tetanic force production in unfatigued skeletal muscle	α -Tocopherol (1,000 IU VE/kg diet)/lipoic acid (1.65 g/kg diet)	In vivo (rat)	Coombes et al. (2001)
Attenuation of acute mountain sickness and improvement of the physiological profile of mountaineers at high altitude	α -Tocopherol (100 UI/day)/lipoic acid (150 mg/day)	In vivo (human)	Bailey and Davies (2001)
Modulation of apoptosis in CD4 and CD8 lymphocytes	α -Tocopherol (10 mg/day)/lipoic acid (100 mg/day)	In vivo (human)	Mosca et al. (2002)
Increase in remodeling proteins (GAP43 and synaptophysin) in the ischemic penumbra area and smaller brain infarction volume	α -Tocopherol (50 mg/kg body weight)/lipoic acid (20 mg/kg body weight)	In vivo (rat)	Gonzalez-Perez et al. (2002); García-Estrada et al. (2003)
Reduction in serum levels of IL-6 and TNF α	α -Tocopherol (70 mg/day)/lipoic acid (200 mg/day)	In vivo (human)	Mantovani et al. (2003)
Apoptosis protection by increasing the levels of endothelial cell Bel-2	α -Tocopherol (50 μ M)/lipoic acid (1 mM)	In vitro (bovine)	Marsh et al. (2005)
Attenuation of the cyclosporine-induced decrease in erythrocyte superoxide dismutase activity and cyclosporine-induced vascular dysfunction	α -Tocopherol (1,000 IU VE/kg diet)/lipoic acid (1.6 g/kg diet)	In vivo (rat)	Lexis et al. (2006)
Less antioxidant enzyme activity of GPX and catalase under exercise training conditions	α -tocopherol (1,000 UI/kg diet)/lipoic acid (1.6 g/kg diet)	In vivo (rat)	Marsh et al. (2006)
Less accumulation of high-molecular-weight amyloid beta-proteins	α -Tocopherol (50 μ M)/lipoic acid (1 mM)	In vitro (human)	Woltjer et al. (2007)
Reduction in the age-associated Na(+),K(+)-ATPase neuronal activity	α -Tocopherol (1.5 mg/100 g body weight)/lipoic acid (3 mg/100 g body weight) and N-acetylcysteine (500 mg/kg body weight)	In vivo (rat)	Bagh et al. (2008)
Neuroprotection in GABA and 5-HT levels in the brain of mice acutely intoxicated with lindane	α -Tocopherol (50 mg/kg body weight)/lipoic acid (20 mg/kg body weight)	In vivo (mouse)	Bist and Bhatt (2009)

This table summarizes the experimental and clinical evidence regarding on the synergy between ALA and VE analyzed under different oxidative processes

The mechanism by which ALA and VE have synergic effects are not well understood; as mentioned above it has been proposed that alpha-tocopherol is regenerated via lipoate (Maitra et al. 1995; Stoyanovsky et al. 1995; Ko and Yiu 2001). Yet, the VE recycling alone requires at least two metabolic intermediate steps and cannot explain the magnitude of findings described above. Therefore, it is possible that other processes are involved in this synergism. Other possible mechanisms include:

1. The increase of SOD levels, specifically the manganese SOD form (MnSOD) (Coombes et al. 2000b).
2. The increase of activity levels of GPX mediated by selenium (Scott et al. 1976; Conti et al. 1993; Haramaki et al. 1993; Coombes et al. 2000a, b).
3. The modulation of the balance between the anti- and proapoptotic proteins Bcl-2/Bax (Marsh et al. 2005).

In summary, the synergistic mechanism of ALA–VE combination is not entirely understood, but it is clear that potent antioxidant effects are achieved when both ALA and VE are administered simultaneously. Because both antioxidants are essential components in our diet and the oral supplementation is well tolerated, inexpensive, and very safe, the combination of ALA and VE can be a feasible prophylactic/therapeutic alternative for oxidative processes in the brain. Therefore, diets or commercial supplements enriched with these two specific antioxidants are a promising alternative for people suffering from neurological conditions associated with overproduction of oxygen free radicals.

124.5 Applications to Other Areas of Health and Disease

Oxidative stress is involved in the pathogenesis of a wide spectrum of systemic conditions. Therefore, the ALA–VE combination might be useful for preventing initiation and progression of damage of many pathological conditions that have an oxidative process as the major source of injury, such as cancer, rheumatoid arthritis, chemotherapy, exercise, cataracts, heart failure, myocardial infarction, diabetic neuropathy, atherosclerosis, chronic fatigue syndrome, aging process, and others. In consequence, strategies directed at counteracting oxidative processes will certainly be important in clinical medicine. However, further experimental studies and clinical trials are needed to establish the therapeutic potential of the ALA–VE combination in humans.

Summary Points

- The central nervous system consumes about one-third of the inspired oxygen and has the second highest concentration of fatty acids. Therefore is the most vulnerable tissue to oxidative damage.
- The main mechanism of cerebral injury is called lipid peroxidation, which occurs when unsaturated fatty acids are oxidized by oxygen free radicals.
- Overproduction of oxidant radicals and/or a deficit in antioxidant defenses can give rise to a pathological condition or contribute to disease progression in the brain.
- VE and lipoic acid are dietary antioxidants that cross the brain–blood barrier and react rapidly with ROS and neutralize oxidative damage, but when they are administered as monotherapy their benefits are limited. Hence, the combination of antioxidants appears to be more effective to control oxidative brain damage.
- Besides its antioxidant capabilities, the ALA plays an important role in VE recycling. As consequence, the combination of tocopherol/lipoate has potent synergistic effects to efficiently reduce the magnitude of cerebral damage.

Definitions

Reactive oxygen species (ROS): Family of highly reactive ions or molecules that have at least one unpaired electron at their last orbital.

Oxidative stress: Biochemical process that arises when the production of free radicals is not equivalently balanced by their scavenging or conversion to non-free-radical products.

Lipid peroxidation: Mechanism of oxidative damage that occurs when a saturated fatty acid is oxidized by oxygen free radicals and a hydroperoxide is generated in the brain.

Antioxidant: Substances that react with ROS and inhibit initiation and propagation of oxidative damage by radical scavenging, sequestering transition metals, and reducing peroxides by enzymatic hydrolysis of ester bonds. The efficiency of antioxidants is determined by their ability of rapidly reacting with oxidant radicals to form new radicals less reactive.

Alpha-lipoic acid (C₈H₁₄O₂S₂): Organic sulfur-containing fatty acid that consists of a cyclic disulfide and a carboxylic acid with a molar mass of 206.33 g/mol. It is also known as lipoate, thioctic acid, or 6,8-dithiooctanoic acid.

Vitamin E (C₂₉H₅₀O₂): It is the collective name for a set of eight fat-soluble vitamins (molar mass is 430.69 g/mol): α -, β -, γ -, and δ - tocopherols, and α -, β -, γ -, and δ - tocotrienols.

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