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THERAPEUTIC PERSPECTIVES ON THE COMBINATION OF ALPHA-LIPOIC ACID AND VITAMIN E

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Abstract

Alpha-lipoic acid and vitamin E have synergistic effects, as determined in models of oxidant radical lesions. This review summarizes recent findings showing that the combination of alpha-lipoic acid plus vitamin E has beneficial effects in reducing oxidative damage in ischemic or other oxidation-related pathological events. Both antioxidants are common in the normal human diet and side effects are very rare. Therefore, alpha-lipoic acid and vitamin E can counteract oxidative processes and could have an important role in clinical medicine.

Keywords

Thioctic Acid; Lipoic Acid; Alpha-Lipoic Acid; Dihydrolipoic acid methyl ester; Reduced lipoic acid methyl ester; Lipoamide; Alpha-lipoic amide; Lipoic acid synthase; Vitamin E; Tocopherols; Tocotrienols; Antioxidants; Cryoprotective Agents; Radiation-Protective Agents; Oxidation-Reduction; Fatty acid beta-oxidation; Oxidative Stress; Oxygen Consumption; Oxygen Compounds; Lipid peroxidation; Oxides; Oxidative Phosphorylation; Free Radicals; Reactive Oxygen Species; Hydroxyl Radical; Nitric Oxide; Singlet Oxygen; Superoxides; Hypochlorous acid; Metabolism; Citric Acid Cycle; Decarboxylation; Electron Transport; Energy Metabolism; Enzyme Activation; Glycolysis; Hydrogenation; Lipolysis; Enzymatic pathways; Dihydrolipoamide Dehydrogenase; Lipoic Acid Dehydrogenase; Mitochondrial oxidative phosphorylation system); Glyceryl-ether monooxygenase; Alkylglycerol cleavage enzyme; Lactate 2-monooxygenase; Lactate oxidative

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decarboxylase; Magnesium protoporphyrin monomethyl ester oxidative cyclase; MPME-oxidative cyclase; Mitochondrial oxidative damage endonuclease

1. Introduction

Stroke is the third leading cause of death in North America, Europe, and Japan, and is a major cause of disability in people over 55 years of age [1,2]. Stroke can result from bleeding (haemorrhagic stroke) or vascular occlusion (ischemic stroke) in the brain. Approximately 80% of strokes occur by occlusion of cerebral arteries, which produces an infarction within the cerebral parenchyma [1,2]. The pathophysiology of ischaemia is a complex process arising from a deficiency in oxygen and glucose delivery to the cerebral parenchyma. During cerebral ischemia and subsequent reperfusion, there is an enhanced formation of oxygen free radicals in the damaged tissue [3,4]. These oxidant radicals produce post-ischemic neuronal death by oxidizing proteins, damaging DNA, and inducing lipid peroxidation of cellular membranes [4,5].

Despite dramatic advances in our understanding of stroke, 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. The aim of this review is to discuss recent evidence that strongly suggests that a combination of two antioxidants, alpha-lipoic acid (ALA) and vitamin E (VE), may be useful in reducing cellular damage in ischemia and other oxidation-related pathological events. Because both antioxidants are ingested in the normal human diet and side effects are uncommon, these compounds might have therapeutic or prophylactic potential in clinical medicine.

2. Antioxidants

Antioxidants are substances that react with oxygen free radicals and stop tissue oxidation by processes involving radical scavenging, sequestration of transition metals, enzymatic hydrolysis of ester bonds and enzyme-catalysed reduction of peroxides [6,7]. To be efficient, antioxidants must exhibit two basic properties. First, they should react rapidly with oxidant radicals to form a new radical; and, second, the subsequent radical should be less reactive than the preceding radical [7]. Two antioxidants, ALA and VE, have been widely studied because of their special chemical and nutritional properties.

3. Vitamin E

VE is an essential component in the normal mammalian diet. It is abundant in wheat germ and in sunflower, corn, and soybean oils, although cooking, congealment, and commercial processing of meal can rapidly destroy it. The most abundant natural form is alpha-tocopherol (Fig. 1), and this form possesses the highest biological activity in humans; in this form, VE is best absorbed by the gastrointestinal tract. For this reason, the term α -tocopherol is frequently referred to as vitamin E [7–10]. The antioxidant capacity of VE resides in transferring a phenolic H⁺ to oxidant radicals derived from oxidized polyunsaturated fatty acids; this antioxidant activity is independent of enzymatic processes [7,10,11]. Therefore, VE provides a “first line of defence” against DNA oxidative damage and lipid peroxidation of unsaturated fatty acids in the cell membrane [10,11]. After VE supplementation has been observed an increase in intracellular concentrations of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPX), but the mechanisms of this VE-mediated effects are still not fully understood [12,13]. In addition, administration of VE reduces lipid peroxidation level, malonaldehyde concentration, and mitochondrial activity, which are important cellular sources of oxidant radicals [14–16].

4. Alpha-lipoic acid (Lipoate)

Monosulfurated octanoic acids are substrates for *in vivo* synthesis of lipoic acid [17]. ALA is found in wheat germ, beer yeast, and red meat. Lipoate is absorbed into the circulation from the intestine, and crosses the blood brain barrier where can be reduced within cerebral cells to be exported to interstitial space as dihydrolipoate (Fig. 2). Thus, antioxidant effects of ALA or its derivatives occur both in the hydrophilic phase and in the hydrophobic membrane portion [18–20]. Lipoic acid is synthesized in the body in very small amounts and is covalently bound to the E2 enzyme subunit of the four different alpha-keto acid dehydrogenase complexes in mitochondria. However, supplementation or exogenous administration leads to transient free lipoate that can chelate transition metals [21]. The antioxidant capacity of ALA is located in the thiol group, which reacts directly with oxidant radicals. Lipoate also contributes in other antioxidant systems by enhancing the effects of SOD [22], coenzyme Q10 and glutathione [11,23], and by regenerating other antioxidants such as vitamins C and E [18]. Furthermore, ALA plays an important role in cellular and mitochondrial membranes by modifying the metabolism of ketoacids and modulating mitochondrial ratios of NADH/NAD⁺ and NADHP/NADP⁺ [19,20]. Therefore, ALA is considered an important antioxidant that may be of therapeutic value in some pathological conditions related to the overproduction of oxidant radicals [19].

5. Lipoate and tocopherol in oxidative processes

Both antioxidants VE and ALA are essential components found in the normal mammalian diet, and oral supplementation with these compounds is well tolerated. They are inexpensive and their chronic administration is very safe. Variable results have been reported when ALA or VE are used alone or without other antioxidants. For instance, intraperitoneal administration of alpha-tocopherol diminishes the effects of oxidative damage caused by alteration of the antioxidant defence system in rats [24]. Stoffel et al. [25] reported that alpha-tocopherol does not reduce post-traumatic cerebral oedema induced in a model of focal cold injury. In contrast, using a model of permanent occlusion of the middle cerebral artery (MCA) in rats, van der Worp et al. [8] found that deprivation of dietary VE is associated with larger cerebral infarcts. Similar VE beneficial effects were reported in acute myocardial infarction [26]. Thus, the data are inconsistent and, unfortunately, these studies did not explore the possibility of combining VE with other antioxidants that regenerate and increase alpha-tocopherol tissue concentrations, such as ALA or vitamin C (Fig. 3). Some attempts to combine VE and vitamin C have been developed, but the pro-oxidant activity of ascorbate is important [27,28]. Ascorbate recycles alpha-tocopherol, after this process semidehydroascorbyl radicals are regenerated by ALA. In addition, lipoate can reduce glutathione disulfide, ubiquinone, dehydroascorbate radical that contribute to VE regeneration. ALA is also capable of reducing thioredoxin, thus the antioxidant properties of ALA are more complete than vitamin C [20].

New evidence is emerging about the efficacy of ALA in reducing oxidative damage. Several reports suggest a neuroprotective effect against oxidant radical damage in models of focal and global cerebral ischemia [29,30], and in degenerative processes affecting the peripheral nervous system (e.g., neuropathies) [23]. In contrast, it has been reported that intraperitoneal or intracranial administration of lipoate did not have a significant neuroprotective effect in brain ischemia [31]. Thus, the data are inconsistent. Therefore, to establish if synergistic beneficial effects of antioxidants become more evident, the combination of antioxidants has recently been investigated.

6. Synergism between lipoate and tocopherol

Several reports regarding the possible therapeutic applications of alpha-tocopherol and ALA have been published during the past two decades. These studies suggest that the combination

of both antioxidants can be beneficial in limiting pathological processes in which excessive production of oxidant radicals may be involved in the initiation and progression of damage (e.g., diabetic neuropathy, Alzheimer's disease, rheumatic arthritis, cardiac and cerebral ischemia), and in the aging process [19,23]. ALA markedly modifies *in situ* concentrations of VE [32,33], which suggests a possible synergistic effect of the two compounds.

One of the first studies to reveal the synergistic effect between alpha-tocopherol and lipoate was performed using microsomal fractions obtained from normal and alpha-tocopherol-deficient animals [34]. Those findings showed that there was a prolonged lag phase before the onset of low-level chemiluminescence in microsomes obtained from normal rats but not in VE-deficient fractions. In a later study, Haramaki et al. [35] used an *in vitro* cardiac model of ischemia-reperfusion to show that a high concentration of myocardial VE plus exogenous dihydrolipoate had synergistic effects on the recovery after ischemia-reperfusion; this effect was not achieved when both antioxidants were administered separately. The mechanism by which both antioxidants exert these effects is their capacity to modulate glutathione tissue levels in the hypoxic heart [36]. In retinal membranes that underwent oxidation by UV-irradiation, ascorbate and dihydrolipoate exerted synergistic effects in regenerating VE [37]. By combining lipoate and alpha-tocopherol, Coombes et al. [38] found a favourable effect on lipid peroxidation levels after *in vivo* cardiac ischemia-reperfusion; levels of malondialdehyde and hydroperoxides (lipid peroxidation markers) were also reduced by the ALA-VE mixture. Later, they showed that a similar combination of lipoate and alpha-tocopherol improved lipid peroxidation levels, enhanced heart performance, reduced post-ischemia ventricular dysrhythmias, and preserved cardiac contractility [39]. These authors also found that a similar combination modified skeletal muscle contractile properties [40].

Oral supplementation of ALA-VE significantly reduces lymphocyte apoptosis in a global cerebral ischemia model [41]. Furthermore, the beneficial effects of an ALA-VE mixture have been demonstrated using a thromboembolic stroke model; this study established the potential utility of both prophylactic and intensive treatment after ischemia. The research showed that ALA-VE mixtures reduce glial scar and increase the expression of remodelling proteins when both antioxidants were administered pre- and post-ischemia. In addition, the authors reported important functional recovery as a consequence of the prophylactic administration of these antioxidants [42]. Additional findings indicate that a prophylactic treatment with an ALA-VE mixture can reduce infarct volume and lipid peroxidation after cerebral ischemia [43]. Most recent findings indicate that an ALA-VE combination increased endothelial levels of the anti-apoptotic protein Bcl-2 with no significant changes in the levels of the pro-apoptotic protein Bax [44]. However, these beneficial effects seem to be dose-dependent [45]. Taken together, this evidence strongly suggests that combining ALA and VE is better than monotherapy. In parallel, the ALA-VE mixture has been combined with other dietary antioxidants, such as vitamin C, beta-carotene, and selenium, and evaluated under several conditions of exercise, experimental diabetes, cold, age and cancer, and promising results have also been obtained [46–51].

To explain the synergy between ALA and VE, it has been proposed that alpha-tocopherol is regenerated via lipoate [32,33,37]. Nevertheless, this phenomenon, by itself, cannot explain the magnitude of findings. ALA requires at least two metabolic intermediate steps (via ubiquinol and ascorbate) to regenerate alpha-tocopherol (Fig. 3). Therefore, it is likely that other processes are involved in the ALA-VE synergism. Other mechanisms involving a higher GPX activity [12,35,38] and increasing SOD, specifically the manganese SOD form (MnSOD), have been associated with the ALA-VE synergism [39]. Due to microsomal selenium uptake is dependent on the presence of VE in the diet [52], some author have suggested that VE increases GPX activity by influencing selenium utilization [39,53]. On the other hand, the enhancement of MnSOD activity is not well explained. Modulation in the balance of Bcl-2/

Bax, anti- and pro-apoptotic proteins, seems to be also an important pathway to preserve antioxidant homeostasis [44,45].

As investigated in the retina, heart and brain ischemia models, the synergistic mechanism of ALA-VE combination is not entirely known, but it is clear that the best *in vitro* and *in vivo* antioxidant effects are achieved when both ALA and VE are used simultaneously.

7. Conclusions

In summary, oxidative stress is involved in the pathogenesis of a wide spectrum of conditions. Therefore, the ALA-VE combination may be potentially useful for preventing lesion enlargement and for treating pathological conditions that have an oxidative process as a major source of damage, such as: heart and brain ischemia, diabetic neuropathy, aging process or Alzheimer's disease. In consequence, strategies directed at counteracting oxidative processes will certainly be important in clinical medicine.

Although administration of an ALA-VE mixture cannot prevent an ischemic or another oxidation-related pathological event, findings from brain ischemia, diabetes or aging experimental models strongly suggest that an ALA-VE combination may be valuable for reducing oxidative damage or improving hearth performance after infarction. Lipoate and alpha-tocopherol are contained in many foods that are often part of the human diet, they are inexpensive, and side affects by chronic or elevated supplementation with these antioxidants are very rare. Therefore, diets or commercial supplements enriched with these two specific antioxidants may be mandatory on people suffering from diabetes, hypertension, cardiac arrhythmias or hearth ischemia, which have a significant risk to develop devastating complications related to over-production of oxygen free radicals. However, further studies and clinical trails are necessary to establish the therapeutic potential of the ALA-VE combination in humans.

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A **B**

Fig. 1. Chemical structure of alpha-tocopherol (A) and alpha-tocopheroxyl radical an oxidised form of VE (B).

Fig. 2.
Chemical structures of lipoate (A) and dihydrolipoate (B).

Figure 3. Vitamin E recycling mediated by alpha-lipoic acid is dependent on Vitamin C (ascorbate) and Ubiquinol.