

Review article

Antioxidant activities of dithiol alpha-lipoic acid

Islam MT

Abstract

Alpha-lipoic acid, a dithiol compound derived from octanoic acid, which acts as a coenzyme for several redox reactions in almost all the tissue of the body. It retains its protective functions in both oxidized and reduced forms. Alpha-lipoic acid reduces oxidative stress by redox generation of other antioxidants such as vitamin C, E and increasing the intracellular glutathione. Exogenous alpha-lipoic acid has been shown to increase ATP production due to its role in the oxidation of pyruvate and alpha-ketoglutarate in the mitochondria. Alpha-lipoic acid administration has been shown to be effective in preventing pathology in various experimental models in which reactive oxygen species have been implicated.

Key words: Antioxidant, free radical, alpha-lipoic acid

Background information of alpha-lipoic acid

Alpha-lipoic acid first isolated in 1951 by Reed and coworkers as a catalytic agent associated with pyruvate dehydrogenase¹. Alpha-lipoic acid acts as a cofactor for several important enzymes in almost all the tissue of the body. It is also known as thiotic acid, 1,2-dithiolane-3-pentanoic acid, 1,2-dithiolane-3-valeric acid and 6,8-thiotic acid² (Figure 1). Alpha-lipoic acid is naturally occurring compound that is

synthesized by plants and animals, including humans³. Normally alpha-lipoic acid is present in very small amounts (5-25 nmol/g) in mammalian tissues, in bound form with enzyme. Alpha-lipoic acid is found in a wide variety of foods from plant and animal sources, but slightly more so in kidney, heart, liver and in vegetables like spinach, broccoli, carrots, beets and tomatoes⁴.

Bioavailability and metabolic fate of alpha-lipoic acid

Biological activity and bioavailability

Alpha-lipoic acid acts as an antioxidant in fat and water soluble tissue in both its oxidized and reduced forms⁶. Due to both the water and fat solubility, it is readily absorbed from an oral dose and converts to its reduced form dihydrolipoic acid (DHLA) in many tissue of the body. Dietary bioavailability studies show that an oral dose of alpha-lipoic acid is rapidly absorbed from the small intestine and distributed to the liver via the portal circulation and to various tissues in the

body via the systemic circulation and when given to cells *in vitro*, alpha-lipoic acid is readily taken up by the cells and reduced to DHLA which is released by the cell⁷. Free alpha-lipoic acid readily crosses the blood brain barrier. Both DHLA and alpha-lipoic acid are found intracellularly, intramitochondrially and extracellularly. The half life in plasma is approximately 30 min. After an oral dose in dogs the LD₅₀ is approximately 400-500mg/kg⁸.

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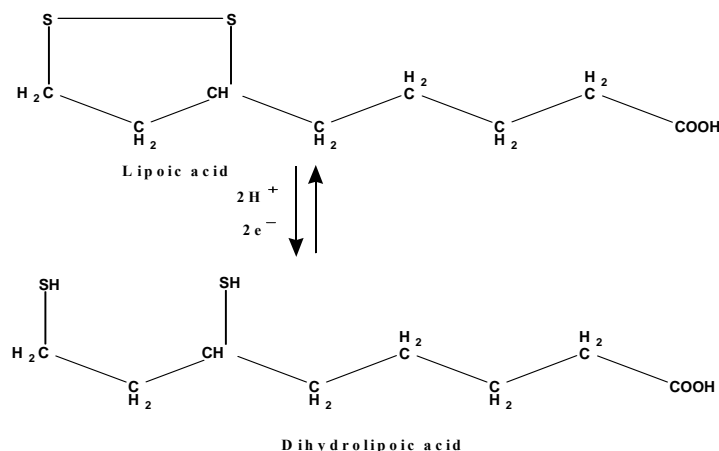


Figure 1: Structure of lipoic acid and dihydrolipoic acid⁵

The metabolism of alpha-lipoic acid

Alpha-lipoic acid taken up by the cells where it is converted to DHLA by glutathione reductase, thioredoxin reductase (TrxR) and lactate dehydrogenase (LDH) and extensively metabolized by β -oxidation, in tissue. The metabolites of alpha-lipoic acid and DHLA also suggested to play a significant role in the treatment of various pathological conditions⁹.

Potential therapeutic roles for alpha-lipoic acid

Alpha-lipoic acid, a dithiol compound derived from octanoic acid, which plays an essential role in mitochondrial dehydrogenase reactions. Alpha-lipoic acid acts by multiple mechanisms both physiologically and pharmacologically. Pharmacologically improves glycemic control, polyneuropathy. Physiologically as an antioxidant, alpha-lipoic acid directly terminates free radicals, chelates metal ions, increases cytosolic glutathione and vitamin C (Figure 2).

Enzyme cofactor

Alpha-lipoic acid acts as a cofactor in the multi-enzyme complexes that catalyze the oxidative decarboxylation of α -keto acids such as pyruvate, α -

ketoglutarate¹⁰. The pyruvate dehydrogenase complex catalyzes the conversion of pyruvate to acetyl-CoA, an important substrate for energy production via the citric acid cycle.

Antioxidants actions

Alpha-lipoic acid and its reduced form referred to as a universal antioxidant. Dietary supplementation of free unbound alpha-lipoic acid is able to function as an antioxidant⁴. Both the oxidized and reduced forms of alpha-lipoic acid are antioxidants. DHLA has more antioxidant properties than alpha-lipoic acid.

Increasing intracellular glutathione levels

Alpha-lipoic acid is able to increase intracellular glutathione levels. Glutathione is an important antioxidant that is synthesized from the sulfur-containing amino acid cysteine. Lipoic acid induces cysteine uptake thereby increasing synthesis of glutathione both *in vitro* and *in vivo*⁵. There is also indication that alpha-lipoic acid acts as a dose-dependent increase in GSH content of 30-70% in murine neuroblastoma and melanoma cell lines, compared to untreated controls.

Regulations of gene transcription

NF-kappa B (NF-κB) is a transcription factor which play important role in the regulation of number of genes which are related to inflammation and pathogenesis of number of diseases including atherosclerosis, cancer, diabetes and HIV¹¹. Physiologically concentrations of alpha-lipoic acid have been found to inhibit NF-κB induced activation of genes in cultured cells⁵.

Scavenger of free radicals

Alpha-lipoic acid and its metabolites can scavenge many other reactive oxygen species (ROS) and reactive nitrogen species (RNS) such as hypochlorous acid (HOCl), hydroxyl radicals, peroxy radicals, superoxide and peroxynitrire (Figure-2). During exposure to metal, administration of lipoate found to remarkably brings down the free radical production¹².

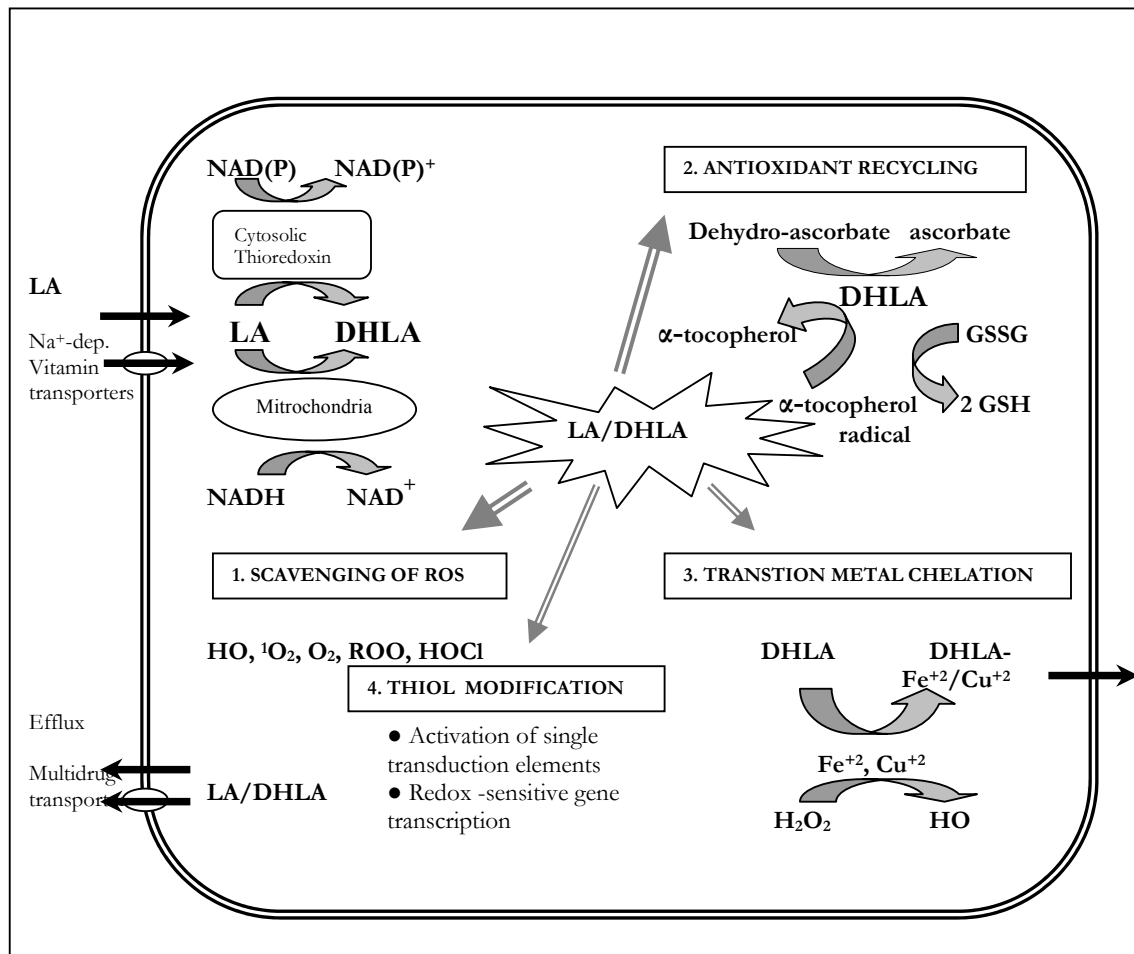


Figure 2: Mechanism of action of lipoic acid. LA and/or DHLA may acts as a metal chelators, antioxidants or intracellular thiol modifying agents. LA is reduced intracellularly either by mitochondrial lipoamide dehydrogenase or by the thioredoxin/thioredoxin reductase system, using NAD(P)H as the reducing source. Non protein-bound LA, acts as an antioxidant by directly scavenging ROS/RNS, by reducing the oxidized forms of other endogenous antioxidants, and by chelating transition metals, rendering such metals either redox inactive or facilitating their removal from the cell. Moreover, LA appears to stimulate certain signal transduction pathways and redox-sensitive gene expression⁵.

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Regenerating other endogenous antioxidants

Alpha-lipoic acid is a potent reducing agent, and has the capacity to regenerate a number of oxidized antioxidants to their active antioxidant forms. A number

of studies suggest that alpha-lipoic acid is able to recycle other natural antioxidants specially is capable of reducing the oxidized forms of vitamin C, glutathione and coenzyme-Q, α -tocopherol^{4,5,9}.

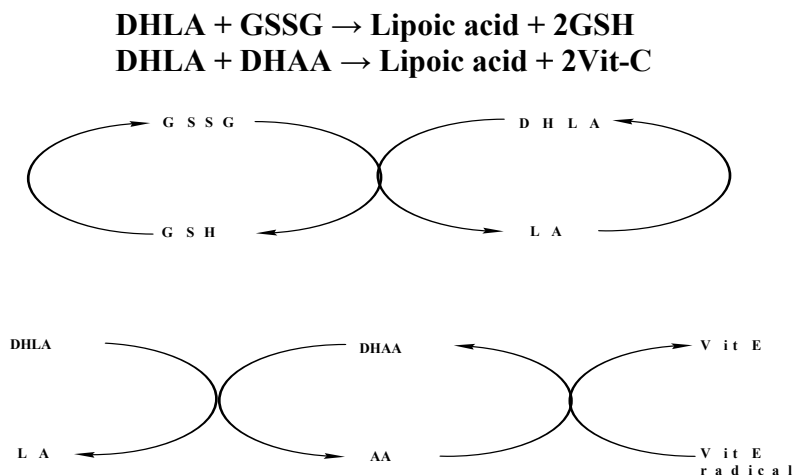


Figure 3: Antioxidant recycling. LA reduced to DHLA and regenerates glutathione from oxidized glutathione. DHLA also recycles vitamin C from oxidized ascorbate, consequently restoring vitamin E¹³.

Chelation of metal ions

Alpha-lipoic acid is considered as a potential therapeutic agent for heavy metal toxicity. Both alpha-lipoic acid and DHLA may chelate or bind metal ions that prevent them from generating free radicals⁸. Due to its chelating

capability, alpha-lipoic acid is beneficial against cadmium¹⁴ and mercury poisoning¹⁵. Earlier Gregus et al (1992) observed that administration of alpha-lipoic acid lowered Cu^{2+} levels in liver, which accumulates metal to a great extent¹⁶.

Experimental and clinical therapeutic studies

Alpha-lipoic acid administration has been shown to be effective in preventing or at least delaying pathological processes in various experimental models in which ROS have been implicated.

- Administration of alpha-lipoic acid has found to have beneficial effects in diabetic neuropathy. A smaller randomized controlled trial examined the effect of long-term oral alpha-lipoic acid supplementation on the results of electrophysiologic nerve conduction studies in 65 diabetic

patients with symptomatic peripheral neuropathy. After two years of follow up, study groups taking 600 mg/day or 1,200 mg/day of alpha-lipoic acid orally showed significant improvements in 3 out of 4 nerve conduction assessments compared to the placebo group¹⁷. Currently it is used in Europe to treat diabetic peripheral neuropathy¹⁷.

- Study has suggested a possible role of alpha-lipoic acid in controlling blood sugar. Intravenous infusions of 600 mg and 1,000 mg of alpha-lipoic

acid to type 2 diabetics, improved insulin sensitivity by 27% and 51%, respectively compared to a placebo group¹⁸.

- It has been shown to inhibit glycation which is responsible for accelerated tissues damage¹⁸ and suggested to slow aging of the brain and act an anti-aging substance, in general¹⁹. Since alpha-lipoic is postulated to prevent the oxidation of LDL-cholesterol and thus suggested to be protective against atherosclerosis⁷.
- Alpha-lipoic found to chelates heavy metals and postulated its use reducing the oxidants from blood system^{1,5,8,14}.
- Use of alpha-lipoic acid suggested to be useful in relieving symptoms of stomatopyrosis, or Burning Mouth Syndrome (BMS)²⁰.
- Since lipoic acid also found to be a potential agent for protection from mycotoxins and suggested to be used in the treatment of mycotoxicosis¹⁷.
- Alpha-lipoic acid dietary supplementation has been shown to prevent cataract formation. Researchers at the University of California investigated the effect of alpha-lipoic acid on cataract formation in specially treated newborn rats and found that a dose

of 25 mg/kg body weight protected 60% of animals from cataract formation⁴. It has also been suggested to improve of glaucoma⁵.

- Use of alpha-lipoic acid has also been thought to be a useful as adjunctive therapy for asthmatic patients²¹.

Concluding Remarks

ROS and RNOS are produced as by-products of oxidative metabolism. However, high levels of ROS and RNOS have been considered to potentially damage cellular macromolecules and have been implicated in the pathogenesis and progression of various chronic diseases. Several lines of evidence indicate that alpha-lipoic acid exerts potent antioxidant activity *in vitro* and *in vivo*¹⁷. Some observations obtained from *in vitro* model systems support the idea that alpha-lipoic acid may directly or indirectly cause oxidation of cellular proteins and thereby modulate biological processes. Future studies of the antioxidant effects of alpha-lipoic acid should be targeted to patient groups at high risk of oxidant damage and should be designed with attention to the pharmacokinetics of orally administered alpha-lipoic acid.

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