



Alpha-lipoic Acid

Introduction

Alpha-lipoic acid (ALA – also known as thioctic acid) was discovered in 1951 as a molecule that assists in acyl-group transfer and as a coenzyme in the Krebs cycle. In the 1980s, the scientific community realized alpha-lipoic acid is

a powerful antioxidant. Several qualities distinguish alpha-lipoic acid from other antioxidants: ALA can be synthesized by animals and humans;¹ it neutralizes free radicals in both the fatty and watery regions of cells, in contrast to vitamin C (water soluble) and vitamin E (fat soluble); and, ALA functions as an antioxidant in both its reduced and oxidized forms.²

Pharmacokinetics

ALA appears to be readily absorbed from an oral dose and converts easily to its reduced form, dihydrolipoic acid (DHLA), in many tissues of the body.³ The effects of ALA and DHLA are present both intra- and extracellularly.

ALA contains an asymmetrical carbon and thus has two possible optical isomers. These are designated as R-lipoic acid (R-ALA) and S-lipoic acid (S-ALA). Naturally occurring ALA is in the R configuration, bound to a protein where it functions as an essential cofactor for several mitochondrial enzyme complexes involved in energy production and the catabolism of alpha-keto acids and amino acids.⁴

Nutritional supplements of ALA are typically comprised either of R-ALA alone or a racemic mixture of R-ALA and S-ALA (RS-ALA). Human studies using oral racemic mixtures of ALA have observed plasma concentrations of R-ALA to be greater than that of S-ALA.^{5,6} One study found that, following oral administration of 50- or 600-mg racemic mixture of lipoic acid, maximum plasma concentrations (C_{max}) of R-ALA were double that of S-ALA (following 50-mg dose: 135.45 ng/mL and 67.83 ng/mL, respectively; following 600-mg dose: 1,812.32 ng/mL and 978.20 ng/mL, respectively).⁶

Mechanisms of Action

Alpha-lipoic acid is a potent antioxidant in both fat- and water-soluble mediums. Furthermore, its antioxidant activity extends to both its oxidized and reduced forms. DHLA is capable of directly regenerating ascorbic acid from dehydroascorbic acid and indirectly regenerating vitamin E.⁷ Researchers have also found ALA increases intracellular glutathione⁸ and coenzyme Q₁₀⁹ levels.

Alpha-lipoic acid appears capable of chelating certain metals. It forms stable complexes with copper, manganese, and zinc.¹⁰ In animal studies, it has been found to protect against arsenic poisoning,¹¹ and, in both animal and *in vitro* studies, ALA reduced cadmium-induced hepatotoxicity.¹² *In vitro*, ALA chelated mercury from renal slices.¹³

Mechanisms that may account for lipoic acid's benefit in preventing diabetic complications include prevention of protein glycosylation¹⁴ and inhibition of the enzyme aldose reductase, the latter of which subsequently inhibits conversion of glucose and galactose to sorbitol.^{15,16} Accumulation of sorbitol has been implicated in the pathogenesis of various diabetic complications, including "sugar cataracts" where sorbitol accumulates in the lens.

Clinical Indications

Diabetes

Lipoic acid has the potential to prevent diabetes (at least in animals), influence glucose control, and prevent chronic hyperglycemia-associated complications such as neuropathy.

Blood-sugar Management/Insulin Sensitivity

Acting as a potent antioxidant, DHLA protected rat pancreatic islet cells from destruction by reactive oxygen species.¹⁷ *In vitro*, lipoic acid stimulated glucose uptake by muscle cells in a manner similar to insulin.¹⁸

Type 2 diabetics given 1,000 mg lipoic acid intravenously (IV) experienced a 50-percent improvement in insulin-stimulated glucose uptake.¹⁹ In an uncontrolled pilot study, 20 type 2 diabetics were given 500 mg lipoic acid IV for 10 days. While there was an average 30-percent increased uptake of glucose, there were no changes in fasting blood sugar or insulin levels.²⁰

In a study examining the effect of lipoic acid as a co-factor of the pyruvate dehydrogenase complex on both lean and obese type 2 diabetics, insulin sensitivity, glucose effectiveness, serum lactate levels, and pyruvate levels were tested after oral glucose tolerance load. Treatment with 600 mg ALA twice daily for four weeks increased insulin sensitivity and prevented serum lactate/pyruvate-induced hyperglycemia.²¹

In a placebo-controlled, multi-center pilot study, 74 patients with type 2 diabetes were randomized to receive 600 mg ALA or placebo orally once, twice, or three times daily, for four weeks. Although no significant differences regarding the various doses of ALA were observed, at the end of the trial it was found that patients who received ALA experienced

significant improvement in insulin-stimulated glucose disposal compared to those on placebo (+27%; $p < 0.01$). This suggests oral administration of ALA can improve insulin sensitivity in type 2 diabetics.²²

Experimental research indicates R-ALA may be more effective than S-ALA in improving insulin sensitivity. In an animal model of non-diabetic insulin resistance, R-ALA for 10 days increased glucose uptake by skeletal muscle of obese rats by 65 percent, compared to 29 percent with S-ALA. In addition, R-ALA significantly reduced plasma insulin by 17 percent; whereas, S-ALA increased insulin levels by 15 percent. This seems to indicate an increase in insulin resistance with S-ALA.²³

Diabetic Nephropathy

One animal study suggested that ALA may be effective in the prevention of early diabetic glomerular injury and may provide more protection than high doses of vitamin C or vitamin E.²⁴ The study observed ALA (30 mg/kg body weight daily for two months) given to diabetic rats either prevented or significantly attenuated increases in urinary albumin excretion, fractional albumin clearance, glomerular volume, and glomerular content of immunoreactive transforming growth factor- β and collagen $\alpha 1$ to levels no different from non-diabetic controls. In addition, it was found that ALA, but not vitamins C or E, significantly increased renal-cortical glutathione content.

Diabetic Neuropathy

Alpha-lipoic acid has been studied extensively in Europe for the treatment of diabetic neuropathy.²⁵⁻²⁷ Three large-scale, double-blind, placebo-controlled trials have been conducted on the effect of ALA for neuropathy – the Alpha-Lipoic Acid in Diabetic Neuropathy (ALADIN) studies. The first ALADIN study (n=328 type 2 diabetics) found three weeks of IV ALA at 600 mg daily was superior to placebo for reducing symptoms of neuropathy.²⁵ ALADIN II examined nerve conduction parameters in a two-year trial and found improvement in some nerve conduction parameters with ALA compared to placebo.²⁶ In the seven-month ALADIN III trial, 509 subjects received either 600 mg IV ALA for three weeks, followed by 600 mg orally three times daily for six

months; 600 mg IV ALA daily for three weeks, followed by placebo three times daily for six months; or double placebo. While no significant differences were noted in subjective symptom evaluation among the groups, treatment with ALA was associated with improvement in nerve function.²⁷

In one randomized, double-blind, placebo-controlled study, known as the SYDNEY trial, 60 type 2 diabetic patients with diabetic sensorimotor polyneuropathy (DSPN) were administered 600 mg IV ALA daily, five days/week for a total of 14 treatments, while an equivalent number of DSPN patients were given placebo for the same duration. At the end of the trial, the ALA group reported significant improvement in overall symptoms (e.g., lancinating and burning pain, numbness, and tingling) compared to the placebo group (average decrease in total symptom score (TSS): 5.7 versus 1.8) ($p < 0.001$).²⁸

Another smaller study demonstrated similar results using oral ALA. In this trial, 24 type 2 diabetic patients with symptomatic polyneuropathy were randomly assigned to 600 mg ALA three times daily or placebo for three weeks. Neuropathic symptoms (pain, burning, paresthesia, and numbness) in the feet were scored regularly and summarized as a TSS. At the end of the trial the ALA group reported significant improvements in TSS compared to placebo (TSS decreases: 3.8 versus 1.9) ($p = 0.021$).²⁹

Lipid peroxidation is believed to play a role in the development of neuropathy. In an *in vitro* study, lipoic acid decreased lipid peroxidation of nerve tissue.³⁰ ALA significantly reduced neuropathy symptoms in a group of 20 diabetics taking 600 mg daily for three months. It should be noted that two other groups of 20 each, receiving vitamin E or selenium, also experienced significant improvement compared to the control group.³¹

ALA may be beneficial for diabetic cardiac autonomic neuropathy (CAN). A four-month trial of oral ALA at a dose of 800 mg daily ($n = 39$) or placebo ($n = 34$) demonstrated a trend toward improvement in measurements of CAN in the treatment group.³²

Cataracts

The enzyme aldose reductase plays an important role in the development of cataracts in diabetes. Lipoic acid inhibited aldose reductase activity in the rat lens.¹⁵ In another animal study, ALA inhibited

cataract formation experimentally induced by buthionine sulfoximine, an inhibitor of glutathione synthesis. ALA administration maintained levels of glutathione, ascorbic acid, and alpha-tocopherol in the lens.³³ These same researchers found that R-ALA reached concentrations in rat lens two- to seven-fold higher than S-ALA, with the racemic mixture reaching levels between the two.³⁴

Glaucoma

Lipoic acid was administered to 75 subjects with open-angle glaucoma at dosages of either 75 mg daily for two months or 150 mg daily for one month. Thirty-one others served as controls and were given only local hypotensive therapy. The greatest improvements in the biochemical parameters of glaucoma and visual function were observed in the group receiving 150 mg lipoic acid.³⁵

Ischemia-Reperfusion Injury

After an area of tissue has been deprived of blood for a period of time, such as occurs in the brain after a stroke or in the heart after clot dissolution, reperfusion of the tissues causes a burst of free radical formation. Several animal studies have demonstrated the effectiveness of DHLA in the prevention of reperfusion injury.³⁶⁻⁴⁰

Animal studies support the efficacy of ALA as a neuroprotectant after ischemia.^{41,42} One week after ischemia injury and reperfusion in rats, the amplitude of sensory action potential and sensory conduction velocity was significantly improved with ALA.⁴¹

Amanita Mushroom Poisoning

Alpha-lipoic acid infusions were used in the treatment of amanita mushroom poisoning in 75 patients between 1974 and 1978. Normally, up to 50 percent of patients recover without intervention; however, 89 percent (67 of 75) recovered after lipoic acid infusion.⁴³

Alcoholic Liver Disease

Although preliminary studies have indicated possible benefit of lipoic acid in the treatment of alcoholic liver disease, the only controlled, double-blind study found ALA had no significant influence on the course of the disease.⁴⁴

Cognitive Function

Alpha-lipoic acid may have a positive effect on patients with Alzheimer's disease and other types of memory dysfunction secondary to trauma or cerebral vascular accident. By decreasing oxidative damage in the central nervous system, ALA may decrease the severity of central nervous system disorders.²

An animal study has shown supplementation with lipoic acid improves long-term memory in aged mice; however, no effect in young mice was shown.⁴⁵ This lack of treatment effect in young mice suggests ALA does not improve memory from a general standpoint; instead, it appears ALA compensates for age-related memory deficits.

Alpha-lipoic acid also appears to protect brain cells from the damaging effects of some hazardous chemicals. Researchers at the University of Rochester reported neuron damage from excess N-methyl-D-aspartate was prevented by lipoic acid.⁴⁶ Another study found buthionine sulfoximine-stimulated neurotoxicity in rat brain was partially prevented by R-ALA, but not RS-ALA, S-ALA, or RS-DHLA.⁴⁷

Heavy Metal Toxicity

In vitro and animal studies suggest lipoic acid supplementation might be a beneficial component in the treatment of heavy metal toxicity, particularly toxicity involving lead, cadmium, mercury, or copper.^{2,48-53} In one study an intraperitoneal injection of 25 mg/kg ALA given to rats for seven days was able to significantly alter the oxidative stress induced by lead toxicity.⁴⁸ Another study demonstrated ALA, at concentrations of 5 mM, was able to protect rat hepatocytes from cadmium toxicity (200 μ M) by preventing decreases in total glutathione and increases in lipid peroxidation.⁴⁹ Furthermore, a study on mercury intoxication revealed an injection of 10 mg/kg/day ALA in rats inoculated with 1 mg/kg/day mercuric chloride prevented damage to nerve tissue caused by lipid peroxidation.⁵² Long-Evans Cinnamon rats have a genetic defect that causes them to accumulate copper in the liver – in a manner similar to patients with Wilson's disease – and spontaneously develop acute hepatitis. ALA has been shown to protect these rats from developing hepatitis.⁵³ ALA appears to improve tissue redox status in metal toxicity and during chelation with dithiol compounds, including

dimercaptosuccinic acid (DMSA).⁵⁴ Anecdotal reports note the use of lipoic acid may improve the clearance of toxic metals.

Other Indications

Other therapeutic uses for ALA or DHLA include protection from radiation injury and prevention of HIV viral replication by inhibition of reverse transcriptase and nuclear factor kappa-B (a protein that functions as a nuclear transcription factor and appears to play a role in inflammation).^{55,56}

Side Effects and Toxicity

Alpha-lipoic acid appears to be safe in dosages generally prescribed clinically. The LD₅₀ was 400-500 mg/kg after an oral dosage in dogs;² however, lower dosages (20 mg/kg) given intraperitoneally to severely thiamine-deficient rats proved fatal. These adverse effects were prevented when thiamine was administered with lipoic acid.⁵⁷ Anecdotal evidence suggests ALA may be hepatotoxic to cats at doses greater than 20 mg daily. There have not been sufficient studies to guarantee safe use in pregnancy. Allergic skin conditions are among the few reported side effects of lipoic acid administration in humans.

Dosage

Recommended oral therapeutic dosages of alpha-lipoic acid range from 600-1800 mg daily. Because R-lipoic acid is more efficiently absorbed and utilized by the body, R-ALA may be equally effective at lower doses.

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