R-Form Alpha-Lipoic Acid

Monograph prepared by Rebecca Provorse ND, LAc

R-Isomer Lipoic Acid (thiotic acid)
*Optical rotation between +110 and +120 degrees*

100mg capsules
Recommended dosage: 1-6 caps daily

**A note on terminology:** There are many names for alpha-lipoic acid. In journal publications you will find all of the following used interchangeably: alpha-lipoic acid (ALA), α-lipoic acid, lipoic acid, alpha-dihydrolipoic acid (DHLA) and thiotic acid. In this monograph, we use “R-form alpha-lipoic acid” to differentiate the specific isomeric structure, which is the naturally occurring form.

**INDICATIONS**
- diabetes and related conditions (such as neuropathy, nephropathy, retinal damage)
- idiopathic neuropathy
- cerebral ischemia-reperfusion (i.e. post stroke)
- memory loss/cognitive dysfunction
- cardiac ischemia and/or age-related cardiac oxidative damage
- adjunctive chemotherapy treatment
- hepatitis

**INTRODUCTION**
The R-form of alpha-lipoic acid was first described in 1937 by researcher E.E. Snell and colleagues as a growth factor for bacteria. Later, in 1951 R.J. Reed isolated the growth factor and initially characterized it as a vitamin. He soon recognized its antioxidant properties and much research of the molecule and its reduced form has ensued. It is now commonly described as a cofactor to mitochondrial enzyme complexes.

**PHARMACOLOGY**
Alpha-lipoic acid is a lipophilic substance of low molecular weight that is rapidly absorbed from the diet and crosses the blood-brain barrier. Free alpha-lipoic acid is rapidly taken up by cells and reduced to alpha-dihydrolipoic acid (DHLA) by at least two enzymes. The structure of DHLA is depicted in diagram 1. Once in the reduced form, it influences many intracellular processes including scavenging of free radicals, redox cycling of other antioxidants (i.e. vitamins C and E), raising intracellular glutathione and modulating transcription factor activity. It is only DHLA that functions directly as an antioxidant, though R-form alpha-lipoic acid may have indirect antioxidant effects. Excretion is not believed to be via the kidney, rather perhaps degraded to smaller units in the catabolic process.

Conventional chemical synthesis of alpha-lipoic acid results in a 50/50 (racemic) mixture of its two optical isomers, R-alpha-lipoic acid (right optical isomer) and S-alpha-lipoic
acid (left optical isomer). Only the R-form of alpha-lipoic acid is naturally occurring. Research comparing the efficacy of the two forms has produced data in favor of the R-form as being superior with respect to mitochondrial ATP synthesis, as the mitochondria appear to be more sensitive to the naturally occurring form. This initial research suggests that R-form alpha-lipoic acid may be 10 times more potent than its mirror isomer. In addition, when measuring plasma concentrations after oral administration of the racemic mixture, plasma concentration of R-form alpha-lipoic acid has been measured at 40-50% higher than the S-form.

R-form alpha-lipoic acid is normally bound to proteins, by linkage of its carboxyl-group to a lysine residue in the protein. In its protein bound form, lipoamide, R-form alpha-lipoic acid is a required cofactor for critical energy metabolism reactions inside the mitochondria. It can be bound to enzyme complexes in the citric acid cycle and assists with synthesis of amino acids: leucine, isoleucine and valine. In addition, it is an important cofactor in nucleic acid production.

![Diagram 1: Structure of ALA](Adapted from the Linus Pauling Institute, Oregon State University)
RESEARCH TRIALS

Insulin Resistance/Diabetes

- Perhaps second to its antioxidant properties, alpha-lipoic acid has been studied for its antihyperglycemic effects. In a recently published study the mechanism was described as enhancing glucose uptake by enhancing receptor activity in adipose and muscle cells, mimicking insulin action.\textsuperscript{14}

- In a 4-week placebo-controlled pilot study done in 1999, patients previously diagnosed with type-2 diabetes mellitus were given the racemic mixture of alpha-lipoic acid and evaluated for improved insulin sensitivity. 600mg alpha-lipoic acid was administered orally in varying doses: once, twice and three times daily. Significant improvement in insulin resistance was seen in all three of the dose groups (as compared to placebo), though no difference was noted between the three dose groups.\textsuperscript{15} Two earlier studies performed by some of the same researchers provided groundwork for this clinical trial.\textsuperscript{16, 17}

- A second study done the same year provides additional support to the assertion that alpha-lipoic acid increases insulin sensitivity in diabetic subjects. In that study patients with type-2 diabetes were given oral alpha-lipoic acid twice daily. The dosing was 600mg each dose, for a total of 1200mg a day for 4 weeks. Markers of insulin sensitivity were measured prior to and after the treatment in both lean and obese subjects. Values were significantly lower in both groups after the 4-week protocol.\textsuperscript{18} The form of alpha-lipoic acid used is not indicated in the study and is, therefore, assumed to be the 50/50 racemic mixture.

- In a 1996 study, glucose metabolism was observed in skeletal muscle tissue of known insulin-resistant rats. Short-term (100 mg/kg body wt for 1 h) and long-term supplementation (5-100 mg/kg for 10 days) of racemic alpha-lipoic acid was given to the rats. Results were positive: short-term supplementation improved insulin-mediated glucose uptake in muscles from the obese rats by 62 and 64%. Long-term racemic alpha-lipoic acid treatment increased both insulin-stimulated glucose oxidation (33%) and glycogen synthesis (38%) and was associated with a significantly greater (21%) in vivo muscle glycogen concentration. The adaptive responses after long-term racemic alpha-lipoic acid administration was also associated with significantly lower (15-17%) plasma levels of insulin and free fatty acids.\textsuperscript{19}

Neuropathy, Nephropathy, Retinopathy (idiopathic &/or diabetes-related)

- In a double blind controlled study, 60 patients diagnosed with Burning Mouth Syndrome (BMS) were given the racemic alpha-lipoic acid for 2 months. Patients were prescreened for nutrient deficiencies and none were found. Comparing racemic alpha-lipoic acid with placebo at the end of
the treatment phase, there was a significant symptomatic improvement in the alpha-lipoic acid group. This improvement was maintained in over 70% of patients at the 1-year follow-up.20

- In an open, controlled, clinical trial of patients with idiopathic dysguesia, patients were administered racemic alpha-lipoic acid for two months. Compared to the control group, the subjects receiving the alpha-lipoic acid treatment reported significant improvement of symptoms.21

- In a recent randomized, double blind controlled Australian clinical trial patients with diabetic neuropathy had 600mg racemic alpha-lipoic acid infused daily (IV) for five days/week for 14 treatments. Symptoms, objective exam and nerve conduction test results were compared with those patients who’d received placebo treatment. Statistically significant improvement was noted for all symptoms, neuropathy signs and one nerve conduction test.22

- In a 1999 clinical trial of 26 patients with type-2 diabetes, subjects were given 600mg racemic alpha-lipoic acid per day for three months. After the treatment period, nerve conduction studies were done to assess peripheral neuropathy status. Improvements to subjective symptoms and objective measurements were noted. Women appeared to respond better than men. There was no control group in this trial.23

- In another clinical trial, lipid peroxidation was evaluated in patients with diabetic neuropathy. The results showed no significant change in ceruloplasmin(Cp) after treatment with 600mg racemic alpha-lipoic acid a day for 70 days. However, lipid peroxide (Lp) levels were significantly reduced. As oxidative stress is the primary cause of nerve ischemia, it is fair to conclude that alpha-lipoic acid supplementation will reduce (if not prevent) peripheral neuropathy.24

- In a 2002 animal study, rats were given racemic alpha-lipoic acid for two weeks prior to induced ischemic events. Compared to the control group, the rats given alpha-lipoic acid were protected against damage of the ganglion cells in the retina.25

**Cerebral Ischemia/ Cognitive Dysfunction**

- In a small 2001 open study, nine geriatric patients with Alzheimer’s disease were given 600mg of racemic alpha-lipoic acid over 10-12 months. The treatments lead to stabilized cognitive function, as measured by mental state examinations. Though tiny and unrandomized, the results were promising and suggested possible neuro-protective effects of alpha-lipoic acid.26
• A small randomized, double blind, placebo-controlled trial comparing deprenyl and alpha lipoic acid (assumed to be racemic) revealed alpha-lipoic acid had no positive effect on HIV-related dementia.  

• In a 2002 rat study at the Linus Pauling Institute at Oregon State University, elderly rats were given dietary supplementation of R-form alpha-lipoic acid and tested for improved memory (both spatial and temporal). R-form alpha-lipoic acid significantly improved memory (given alone and in conjunction with L-acetyl carnitine). Improvement was believed to be due to repair of mitochondria oxidative damage and was measured to be significant.  

• A more recent animal study on Wistar rats confirmed the cytoprotective effects of alpha-lipoic acid on brain cells. The rats were fasted on water for 24 hours prior to the experiment. The internal carotids were occluded to produce an ischemic event to the brain. Following, racemic alpha-lipoic acid was infused in to carotids at different doses and for varying duration. Brain tissue was subsequently evaluated. There was a statistically significant increase of brain GSH levels after the racemic alpha-lipoic infusion. In addition, EEG studies revealed cytoprotective effects from the infusions, as measured by increased theta waves. Interestingly, lower dose infusions demonstrated both pro-oxidative and anti-oxidative effects, while moderate doses produced anti-oxidant effects only. At high doses, the effects were primarily pro-oxidative. These findings suggest dose may be very important. A human study using R-form alpha-lipoic acid in correlative doses is warranted.  

• Since the above rat study, another study was recently performed specifically using R-form alpha-lipoic acid. Heart and brain tissue of young rats and old rats was compared with respect to the glutathione levels before and after R-form alpha-lipoic acid supplementation. Treating old rats with R-form alpha-lipoic acid (40 mg/kg body wt.), markedly increased tissue cysteine levels by 54% 12 hours following treatment and subsequently restored the cerebral glutathione levels to the levels of the young rats. R-form alpha-lipoic acid also improved the age-related glutathione changes in the heart.  

Cardiac Ischemia  
• In a 4-month randomized controlled multicenter trial, patients with non-insulin dependent diabetes mellitus (NIDDM) and cardiac autonomic neuropathy (CAN) were given 800mg racemic alpha lipoic acid daily. Heart rate variability (HRV) was measured and compared with placebo. The results were a positive trend toward favorable results with the alpha lipoic acid supplementation. Further study is warranted.
In a 2001 rat study at the Linus Pauling Institute at Oregon State University, old rats were given dietary supplementation of R-alpha-lipoic acid to determine if myocardial damage could be reversed. The findings were promising. Cardiac myocytes from the old, lipoic acid-supplemented rats exhibited a markedly lower rate of oxidant production that, after the treatment, was no longer significantly different from that in cells from non-supplemented, young rats. In addition, R-form alpha-lipoic acid supplementation restored myocardial ascorbic acid levels and reduced oxidative DNA damage.32

Chemotherapy Adjunct

In an open, non-randomized clinical trial, 42 cancer patients were treated with an identical chemotherapy regimen plus antioxidants or control. Antioxidant agents included alpha-lipoic acid at 300 mg/day and N-acetyl cysteine at 1800 mg/day. The treatment was administered for 1 year, unless progression of the disease occurred. Results were significant for improvement of cognitive function. Absolute lymphocyte count, interleukin(IL)-2 and glutathione peroxidase increased; Whereas IL-6, IL-1 beta, tumor necrosis factor-alpha, CRP, fibrinogen and reactive oxygen species decreased significantly. No toxicity was reported.33

Another open, non-randomized study was performed on 28 patients with advance-stage cancers. The patients were divided into five groups and each administered a different anti-oxidant. One group was given alpha-lipoic acid (presumed to be racemic) orally at 200mg daily for 10 consecutive days. Comparing the anti-oxidants as a group, there was a significant decrease of blood levels of reactive oxygen species after treatment and a significant increase of glutathione peroxidase. Also the levels of proinflammatory cytokines decreased significantly.34

Hepatitis/Liver Damage

Case studies presented at the Integrative Medical Center of New Mexico, described three patients with chronic Hepatitis C, who were awaiting liver transplantation. The subjects were treated with a triple antioxidant therapy (racemic alpha-lipoic acid, silymarin and selenium). Following the treatment, the patients’ lab values and symptoms improved to such an extent that liver transplantation was avoided for all three subjects.35

Promising new studies that warrant more research:

In a randomized, placebo-controlled, double blind study on 33 female patients (mean age 54), 5% racemic alpha-lipoic acid face cream was applied to half of the face of the subjects. The other half of the face was a control cream. The treatment was administered twice daily for 12 weeks. Treatment efficacy (with respect to photo-damage) was assessed clinically, photographically and with laser profilometric measurements.
Results supported the alpha-lipoic acid treatment as having reduced age-related changes due to photo-damage.\textsuperscript{36}

- Preliminary research done on mice indicates alpha-lipoic acid treatment may reduce (and even prevent) autoimmune encephalomyelitis, a marker condition for Multiple Sclerosis. Further research in this area is needed.\textsuperscript{37}

- In vitro, alpha lipoic acid has been shown to block NF-KappaB gene expression, resulting in decreased cellular toxicity. The authors of this study believe alpha lipoic acid will be effective as a therapeutic agent within a treatment regimen for HIV infection and acquired immunodeficiency syndrome (AIDS).\textsuperscript{38}

**TOXICOLOGY**
There is no known side-effect profile. Insufficient data is available to determine safety during pregnancy or lactation.

**DRUG INTERACTIONS**
Levothyroxine (T4): one study demonstrated that racemic alpha-lipoic acid taken with T4 could reduce conversion of T4 to T3.\textsuperscript{39} It is unknown if these effects are applicable to pure R-form alpha-lipoic acid.

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