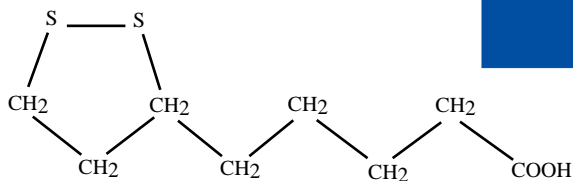
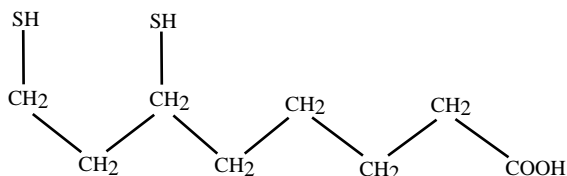


## $\alpha$ - Lipoic Acid



## Dihydrolipoic Acid



# Monograph

## $\alpha$ -Lipoic Acid

**Synonyms: Thioctic acid; 2-dithiolane-3 penatanoic acid; 1,2-dithiolane-3 valeric acid**

### Pharmacokinetics

$\alpha$ -Lipoic acid (ALA) can be synthesized by both animals and humans.<sup>1</sup> It seems to be readily absorbed from an oral dose and converts easily to its reduced

form, dihydrolipoic acid (DHLA), in many tissues of the body. An *in vitro* study<sup>2</sup> indicated that normal mammalian cells appear to be capable of taking up  $\alpha$ -lipoic acid and reducing it to DHLA. The effects of both ALA and DHLA are present both intra- and extracellularly when exposed to extracellular lipoic acid, e.g. in an oral dose.

### Mechanisms of Action

$\alpha$ -Lipoic acid is a potent antioxidant in both fat- and water-soluble mediums. Furthermore, its antioxidant activity extends to both the oxidized form and its reduced form. DHLA is capable of regenerating ascorbic acid from dehydroascorbic acid, directly regenerating vitamin C and indirectly regenerating vitamin E.<sup>3</sup> Researchers have found  $\alpha$ -lipoic acid to increase intracellular glutathione<sup>4</sup> and coenzyme Q10<sup>5</sup> levels.

$\alpha$ -Lipoic acid appears capable of chelating certain metals. It forms stable complexes with copper, manganese and zinc.<sup>6</sup> In animal studies, it has been found to protect from arsenic poisoning;<sup>7</sup> and, in both animal and *in vitro* studies, has been found to reduce cadmium-induced hepatotoxicity.<sup>8</sup> *In vitro*, it was found to chelate mercury from renal slices.<sup>9</sup>

### Clinical Indications

**Diabetes:** Acting as a potent antioxidant, DHLA was found to protect rat pancreatic islet cells from destruction by reactive oxygen species.<sup>10</sup> *In vitro*, lipoic acid was found to stimulate glucose uptake by muscle cells in a manner similar to insulin.<sup>11</sup> Type 2 diabetics, given 1000 mg intravenously (I.V.), experienced a 50 percent improvement in insulin-stimulated glucose uptake.<sup>12</sup> In an uncontrolled pilot study, 20 type 2 diabetics were given 500 mg lipoic acid I.V. for ten days. While there was an average of 30 percent increased uptake of glucose, there were no changes in either the fasting blood sugar or insulin levels.<sup>13</sup> Lipoic acid has been used extensively in Germany for the treatment of diabetic neuropathy.<sup>11</sup> Lipid peroxidation is believed to play a role in the development of neuropathy. In an *in vitro* study, lipoic acid was found to decrease lipid peroxidation of nerve tissue.<sup>14</sup> ALA was found to significantly reduce the symptoms of neuropathy in a group of 20 diabetics. It should be noted that two other groups of 20 each, one receiving vitamin E, the other selenium, also experienced significant improvement compared to the control group.<sup>15</sup> Other mechanisms to explain its potential to prevent complications of diabetes include prevention of protein glycosylation,<sup>16</sup> and inhibition of aldose reductase, which subsequently inhibits conversion of glucose and galactose to sorbitol.<sup>17</sup> Thus, it appears lipoic acid has the potential to prevent diabetes (at least in animals), influence glucose control, and prevent chronic hyperglycemia-associated complications such as neuropathy.

**Cataracts:** The enzyme, aldose reductase, plays an important role in the development of cataracts in diabetes.  $\alpha$ -Lipoic acid was found to inhibit aldose reductase activity in the rat lens;<sup>17</sup> and, in further animal studies, was found to inhibit cataract formation experimentally induced by buthionine sulfoxamine.<sup>18</sup>

**Glaucoma:** Lipoic acid, at dosages of either 75 mg daily for two months or 150 mg daily for one month, was administered to 75 subjects with open-angle glaucoma. Thirty-one others served as controls and were given only local hypotensive therapy. The greatest improvements in both biochemical parameters of glaucoma and visual function were seen in the group receiving 150 mg lipoic acid.<sup>19</sup>

**Ischemia-Reperfusion Injury:** After an area has been deprived of blood for a period of time, such as occurs in the brain after a stroke or in cardiac tissue 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.<sup>20-24</sup>

**Amanita mushroom poisoning:**  $\alpha$ -Lipoic acid infusions were used in the treatment of amanita mushroom poisoning in 75 patients between 1974 and 1978. While 10-50 percent of patients recover without intervention, 89 percent (67 of 75) recovered after lipoic acid infusion.<sup>25</sup>

**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.<sup>26</sup>

**Other possible effects:** Other potential therapeutic uses for ALA or DHLA include: protection from radiation injury, prevention of neurological disorders by preventing oxidative damage of the central nervous system,<sup>27</sup> prevention of HIV viral replication by inhibition of reverse transcriptase,<sup>28</sup> protection from the effects of cigarette smoke, and treatment of heavy metal toxicity.<sup>27</sup> These are interesting theoretical considerations requiring further research.

## Dosage

Recommended therapeutic dosage of  $\alpha$ -lipoic acid is in the range of 300-600 mg/day taken orally.

## Safety, Toxicity and Side Effects

$\alpha$ -Lipoic acid appears to be safe in the dosages generally prescribed clinically. The LD<sub>50</sub> was 400-500 mg/kg after an oral dosage in dogs.<sup>27</sup> However, lower dosages (20 mg/kg) given intraperitoneally to severely thiamin-deficient rats proved fatal. These adverse effects were prevented when thiamin was administered with the lipoic acid.<sup>29</sup> There have not been sufficient studies to guarantee safety for its use in pregnancy. Allergic skin conditions are among the few reported side effects of lipoic acid administration in humans.

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### **Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial.**

Heinonen OP, Albanes D, Virtamo J, et al. *J Natl Cancer Inst* 1998;90:440-446.

**BACKGROUND:** Epidemiologic studies have suggested that vitamin E and beta-carotene may each influence the development of prostate cancer. In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, a controlled trial, we studied the effect of alpha-tocopherol (a form of vitamin E) and beta-carotene supplementation, separately or together, on prostate cancer in male smokers. **METHODS:** A total of 29133 male smokers aged 50-69 years from southwestern Finland were randomly assigned to receive alpha-tocopherol (50 mg), beta-carotene (20 mg), both agents, or placebo daily for 5-8 years (median, 6.1 years). The supplementation effects were estimated by a proportional hazards model, and two-sided P values were calculated. **RESULTS:** We found 246 new cases of and 62 deaths from prostate cancer during the follow-up period. A 32% decrease (95% confidence interval [CI] = -47% to -12%) in the incidence of prostate cancer was observed among the subjects receiving alpha-tocopherol (n = 14564) compared with those not receiving it (n = 14569). The reduction was evident in clinical prostate cancer but not in latent cancer. Mortality from prostate cancer was 41% lower (95% CI = -65% to -1%) among men receiving alpha-tocopherol. Among subjects receiving beta-carotene (n = 14560), prostate cancer incidence was 23% higher (95% CI = -4%-59%) and mortality was 15% higher (95% CI = -30%-89%) compared with those not receiving it (n = 14573). Neither agent had any effect on the time interval between diagnosis and death. **CONCLUSIONS:** Long-term supplementation with alpha-tocopherol substantially reduced prostate cancer incidence and mortality in male smokers. Other controlled trials are required to confirm the findings.