

# $\alpha$ -Lipoic Acid: Biological Effects and Clinical Implications

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## Abstract

$\alpha$ -Lipoic acid is unique in its ability to act as an antioxidant in fat- and water-soluble tissues in both its oxidized and reduced forms. It is readily absorbed from an oral dose. Because of its myriad biological activities, including an ability to chelate metals and to scavenge a wide array of free radicals,  $\alpha$ -lipoic acid is considered by several experts to be an ideal antioxidant. Clinical applications for this nutrient include the following conditions: diabetic polyneuropathy, cataracts, glaucoma, ischemia-reperfusion injury, and Amanita mushroom poisoning. Because of its unique characteristics  $\alpha$ -lipoic acid is likely to have therapeutic application in a wide range of additional clinical conditions.

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## Introduction

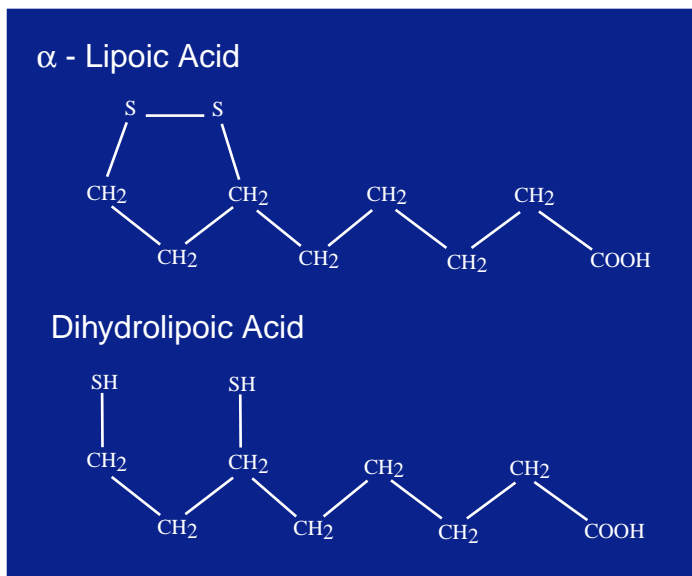
$\alpha$ -Lipoic acid, first isolated in 1951 by Reed and coworkers as a catalytic agent associated with pyruvate dehydrogenase, is known by a variety of names, including 2-dithiolane-3-pentanoic acid; 1,2-dithiolane-3-valeric acid; and thioctic acid.<sup>1</sup> It was originally classified as a vitamin; however, it subsequently was found to be synthesized by animals and humans.<sup>2</sup> Although the enzyme pathway for its de novo synthesis has not been fully elucidated, cysteine appears to be the source of sulfur, and octanoate serves as the intermediate precursor for the 8-carbon fatty acid.<sup>3</sup> It is readily converted to its reduced form, dihydrolipoic acid (DHLA), in many tissues of the body.

## Antioxidant Activity

$\alpha$ -Lipoic acid is unique in its ability to act as an antioxidant in fat- and water-soluble tissues in both its oxidized and reduced forms. It is also readily absorbed from an oral dose. Because of these advantages and its low toxicity,  $\alpha$ -lipoic acid is receiving increased attention as a potentially effective therapeutic agent in clinical conditions associated with free radical damage. Lester Packer, PhD, of the University of California at Berkeley, has suggested  $\alpha$ -lipoic acid is an ideal antioxidant candidate because of its role in the following: specificity of free radical quenching, metal chelating activity, interaction with other antioxidants, and effects on gene expression.<sup>4</sup>

An antioxidant function for  $\alpha$ -lipoic acid was discovered in 1959 by Rosenberg and Culik, who reported it prevented both scurvy symptoms in vitamin C-deficient guinea pigs and vitamin E deficiency in rats fed a diet lacking  $\alpha$ -tocopherol.<sup>5</sup> Podda et al reported  $\alpha$ -lipoic acid prevents symptoms of vitamin E deficiency in mice fed a vitamin E-deficient diet; however, it had no effect on sustaining vitamin E tissue concentrations.<sup>6</sup> Experimental evidence indicates

## Chemical Structure of Lipoic Acid



optimal reduction of dehydroascorbic to ascorbic acid is achieved in the presence of pyruvate,  $\alpha$ -lipoic acid, and ATP.<sup>7</sup>

$\alpha$ -Lipoic acid has a low redox potential, and through its reduced form, DHLA, very readily donates electrons to other compounds. Ascorbic acid, and indirectly vitamin E, are thought to be regenerated by DHLA.<sup>8</sup> Busse et al found  $\alpha$ -lipoic acid can cause an increase in intracellular glutathione.<sup>9</sup> DHLA can regenerate Coenzyme Q10, and NADPH or NADH via glutathione.<sup>10</sup>

Experts are in general agreement that  $\alpha$ -lipoic acid is capable of scavenging hydroxyl radicals, hypochlorous acid, and singlet oxygen, but not hydrogen peroxide, peroxy, and superoxide.<sup>4,11-13</sup> DHLA is both an antioxidant and prooxidant in studies where hydroxyl radicals were generated. It protects against single strand DNA breaks induced by singlet oxygen, although it does not do so directly and several steps might be involved in the process.<sup>13</sup> Sandhya et al indicate  $\alpha$ -lipoic acid acts in a dose-dependent manner as a nephroprotective agent against experimentally induced gentamicin toxicity.<sup>14</sup>

### Metal Chelation

$\alpha$ -Lipoic acid appears capable of chelating transition metals in biological

systems. It forms stable complexes with copper, manganese and zinc ions.<sup>15</sup> Its ability to chelate iron remains equivocal.<sup>16,17</sup>

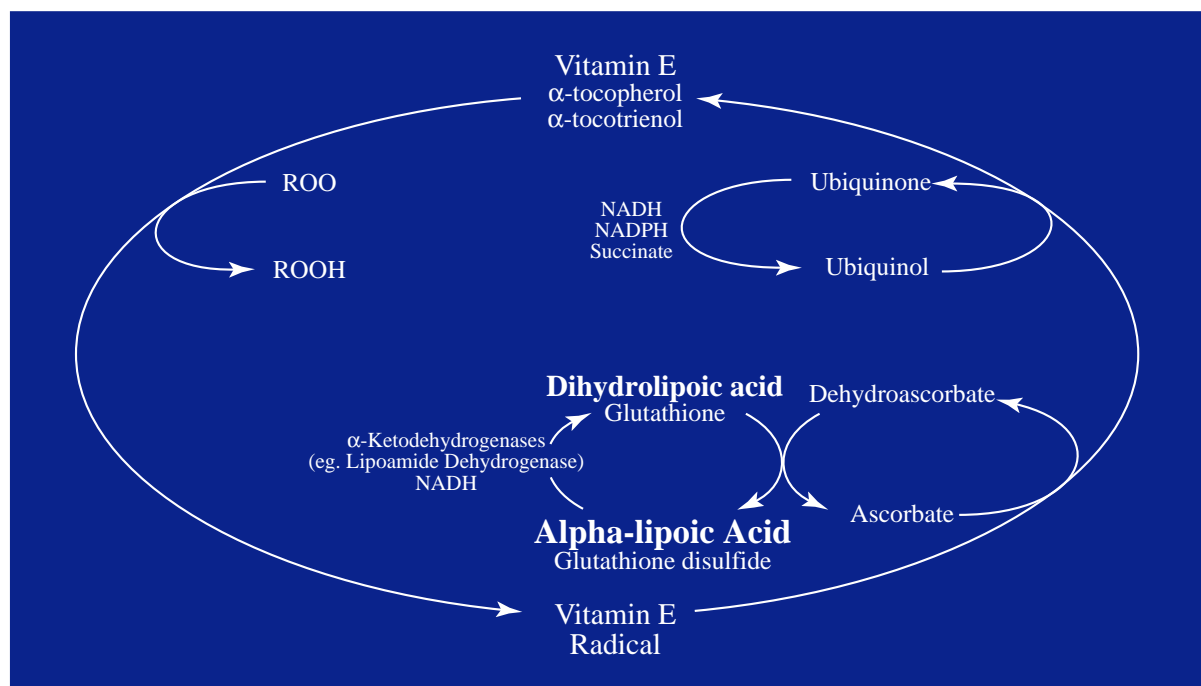
Mice were protected from arsenite poisoning with  $\alpha$ -lipoic acid administration when the ratio of  $\alpha$ -lipoic acid to arsenite was at least 8:1. Protection occurred even if the administration was after severe symptoms of poisoning were present.<sup>18</sup> Evidence suggests  $\alpha$ -lipoic acid might chelate copper. Ou et al report the R-enantiomer and racemic mixture of  $\alpha$ -lipoic acid seemed more effective than the S-enantiomer in their assays of metal chelation.<sup>19</sup> In isolated hepatocytes,  $\alpha$ -lipoic acid has been found to reduce cadmium-induced toxicity, although DHLA was much more effective.<sup>20</sup> Sumathi et al also reported  $\alpha$ -lipoic acid offers significant hepatoprotection against cadmium toxicity, even under glutathione-depleted experimental conditions.<sup>21</sup> In a rat model, a dose of 30 mg of  $\alpha$ -lipoic acid completely prevented cadmium-induced lipid peroxidation in the brain, heart, and testicles.<sup>22</sup> In vitro experiments have indicated  $\alpha$ -lipoic acid, while not the most effective chelating agent, will remove mercury from renal slices.<sup>23</sup>  $\alpha$ -Lipoic acid administration to rats increased biliary excretion of injected mercury 12-37 fold but decreased the excretion of cadmium, zinc, copper, and methylmercury.<sup>24</sup>

### Clinical Implications

**Diabetes:** Because many of the systemic complications of diabetes mellitus, such as polyneuropathy and cataract formation, appear to be secondary to free radical damage,  $\alpha$ -lipoic acid and DHLA have been proposed as possible therapeutic agents in these conditions.

In heart tissue of diabetic rats, high doses of  $\alpha$ -lipoic acid first normalized glucose uptake and utilization, and consequently normalized oxygen uptake, myocardial ATP levels, and cardiac output, while a low dose

**Figure 1. α - Lipoic Acid: Antioxidant Regeneration**



of α-lipoic acid normalized lactate and pyruvate production.<sup>25</sup> In cell cultures, α-lipoic acid stimulated basal glucose transport and had a positive effect on insulin-stimulated glucose uptake.<sup>26</sup> α-Lipoic acid administration prevented diabetes in 70% of diabetes induced animals. This effect was thought to be secondary to DHLA suppression of nitric oxide release from macrophages involved in islet cell inflammation.<sup>27</sup> In a type II diabetic model using insulin-resistant obese Zucker rats, α-lipoic acid increased the uptake of glucose in the absence of insulin.<sup>28</sup>

Glycation of protein caused by elevated blood and tissue glucose is believed to contribute to many of the complications seen in diabetes. These sugar-damaged proteins are referred to as advanced glycosylation end products (AGEs). AGEs increase with the length of hyperglycemia and are thought to be responsible for the kidney damage and advanced atherosclerosis seen in diabetes.<sup>4</sup> Packer and Kawabata found noncovalent binding of α-lipoic acid to albumin protected proteins against glycation.<sup>29</sup>

Type II diabetic humans given an acute dose of α-lipoic acid (1000 mg intravenously) experienced 50% improvement in insulin-stimulated glucose disposal.<sup>30</sup> In an uncontrolled pilot study 20 patients with type II diabetes received daily α-lipoic acid (500 mg/500 ml NaCl, 0.9%) parenterally for ten days. An increase of insulin-stimulated glucose disposal of approximately 30% was reported; however, no changes in fasting plasma levels for glucose or insulin were found during the short period of treatment and observation.<sup>31</sup>

Diabetic polyneuropathy has been treated clinically in Germany with α-lipoic acid for over 20 years. Findings indicate α-lipoic acid can correct neuropeptide deficits in diabetic rats.<sup>32</sup> A model of streptozotocin-induced diabetic neuropathy was evaluated using α-lipoic acid and measuring improved nerve blood flow (NBF) after one month in age controlled rats. The α-lipoic acid-supplemented rats exhibited normal NBF.<sup>33</sup> A three-week multicenter double-blind, placebo-controlled trial of α-lipoic acid administered intravenously at 1200, 600, or 100 mg was conducted in patients with diabetic

neuropathy. Symptom scoring including pain, burning, paresthesia, and numbness was conducted at baseline and at each visit. Intravenous treatment with 600 mg/day for three weeks was superior to placebo in reducing symptoms of neuropathy and caused no significant adverse reactions.<sup>34</sup> In a non-blinded study of diabetic patients with both type I and II diabetes, 600 mg/day of  $\alpha$ -lipoic acid was given for two weeks, followed by 300 mg/day for 10 weeks. Albuminuria decreased 50% as compared to placebo controls. A clinical improvement in neurological symptoms was found in the  $\alpha$ -lipoic acid group but not in the control group.<sup>35</sup>

**Cataracts:** High levels of activity of the enzyme aldose reductase have been associated with diabetic cataracts. Aldose reductase is inhibited by  $\alpha$ -lipoic acid in rat lenses.<sup>36</sup>

Dietary supplementation of  $\alpha$ -lipoic acid has been shown to prevent cataract formation caused by buthionine sulfoximine-induced (BSO) inhibition of glutathione synthesis in newborn rats.<sup>37</sup> The protective effects of  $\alpha$ -lipoic acid against BSO-induced cataract appear to be stereospecific. Both a racemic mixture and R-alpha-lipoic acid were able to decrease cataract formation, while S-alpha-lipoic acid had no effect. Maitra et al suggest  $\alpha$ -lipoic acid's protective effect for BSO-induced cataract formation is probably due to its protective effects on lens antioxidants. The lens antioxidants glutathione, ascorbate, and vitamin E were depleted to 45, 62, and 23% of control levels, respectively, by BSO treatment, but were maintained at 84-97% of control levels when either racemic or R-alpha-lipoic acid were administered. S-alpha-lipoic acid administration was unable to prevent the depletion of lens antioxidant levels.<sup>38</sup>

**Glaucoma:** Forty-five patients with stage I and II open-angle glaucoma (OAG) were administered either 75 mg of  $\alpha$ -lipoic acid for 2 months or 150 mg for 1 month. A control group of 31 patients with OAG were administered only local hypotensive therapy.

The greatest improvement of biochemical parameters (gamma-glutamyl transpeptidase and non-protein SH-groups), visual function, and the coefficient of efficacy of liquid discharge was observed in the patients administered the higher dose of  $\alpha$ -lipoic acid.<sup>39</sup>

**Ischemia-Reperfusion Injury:** Ischemia-reperfusion injury occurs when free radicals are produced in a burst during reperfusion of the tissue. This is important in cardiac tissue following thrombus-dissolving treatment and in brain tissue following stroke. Scheer et al demonstrated DHLA prevents ischemia-reperfusion injury in rat mitochondria.<sup>40</sup> Assadnazar et al found DHLA accelerated the recovery of the aortic flow during reperfusion and increased ATP synthesis in the rat heart.<sup>41</sup> In middle cerebral artery occlusion in mice, treatment with DHLA, but not  $\alpha$ -lipoic acid, reduced the size of the infarct.<sup>42</sup> Based upon their findings, Wolz et al suggest  $\alpha$ -lipoic acid must be reduced to DHLA, which is then responsible for the neuroprotection.<sup>43</sup>

The effect of  $\alpha$ -lipoic acid was examined on the morbidity and mortality of rats subjected to reperfusion following cerebral ischemia induced by bilateral carotid artery occlusion and hypotension.  $\alpha$ -Lipoic acid reduced the mortality rate from 78% to 26% during 24 hours of reperfusion.<sup>44</sup> Gerbils were protected against cerebral ischemia-reperfusion injury with  $\alpha$ -lipoic acid in a study conducted by Cao et al.<sup>45</sup> The combination of vitamin E supplementation with DHLA perfusion synergistically improves cardiac functional recovery during post-ischemic reperfusion or post-hypoxic reoxygenation of the rat heart. Cardiac tissue glutathione status shows significant elevation of reduced glutathione in vitamin E supplemented rat hearts, while elevation of oxidized glutathione was observed in DHLA perfused heart.<sup>46</sup>

**Amanita mushroom poisoning:**  $\alpha$ -Lipoic acid infusions were used to treat Amanita mushroom poisoning from 1974 to

1978 in 75 patients. Sixty-seven patients recovered, compared with an expected rate of between 10-50%.<sup>47</sup> Nagy et al and Sabeel et al both report comprehensive protocols, including the administration of α-lipoic acid, to be effective in the treatment of individuals with Amanita poisoning.<sup>48,49</sup>

### Safety and future implications

α-Lipoic acid is considered to be extremely safe in the amounts utilized clinically; however, because of lack of available data, it is recommended that it be avoided during pregnancy. During more than three decades of scientific research and clinical usage no serious adverse effects have been reported as a consequence of α-lipoic acid supplementation. The LD50 is approximately 400-500 mg/kg after oral dosing in dogs.<sup>4</sup>

α-Lipoic acid should not be given in high doses to patients suspected of having a thiamine deficiency unless the thiamine deficiency is also corrected. High doses of α-lipoic acid (20 mg/kg) administered intraperitoneally to rats is reported to cause fatal complications. The prior administration of thiamine prevents these adverse effects.<sup>50</sup> In humans, reported side effects include allergic skin conditions and possible hypoglycemia in diabetic patients as a consequence of improved glucose utilization.<sup>4</sup> Gregus et al have expressed concern regarding α-lipoic acid's impact on glycine conjugation of benzoic acid. They report α-lipoic acid inhibited glycine conjugation of benzoic acid in a dose-dependent manner in experimental animals.<sup>51</sup>

Potential areas of therapeutic intervention with α-lipoic acid might include Alzheimer's disease, Parkinson's disease, mitochondrial dysfunctions, and other neurological disorders. The author has seen improvement following high-dose therapy, in combination with Coenzyme Q10 and DMSO, in several patients with fascioscapulohumeral dystrophy and Krabbe's disease. Controlled

clinical intervention trials are needed in these areas. Finally, the role of α-lipoic acid and other antioxidants on the aging process and in the prevention of cancer should keep scientists and clinicians busy well into the next millennium.

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