

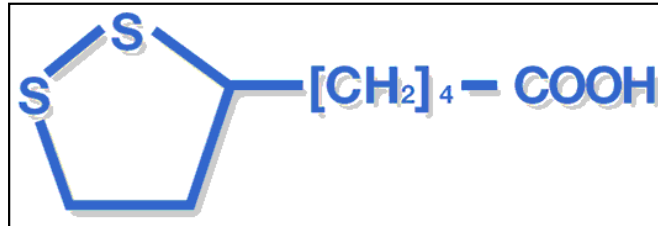
α -Lipoic Acid for Aging and Diabetes: The Benefits of Extending Plasma Half-Life

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α -Lipoic Acid: Role in Mitochondrial Metabolism

In 1937, a component of potato extract, named “potato growth factor”, was discovered to be necessary for the growth of *Lactobacillus* (1). Subsequent work by a number of laboratories led to the isolation and purification of the active compound in 1951 (2). The compound was identified as α -lipoic acid (LA; formerly referred to as thioctic acid), an eight-carbon dithiol containing a single chiral center (Figure 1).

Figure 1. Chemical structure of α -lipoic acid



LA is synthesized in organisms from bacteria to man. In humans, it is synthesized in liver and other tissues, where it functions as a natural cofactor in multienzyme dehydrogenase complexes, such as pyruvate dehydrogenase. Pyruvate dehydrogenase is localized in mitochondria where it catalyzes the oxidative decarboxylation of pyruvate to acetyl CoA, a critical step in oxidative glucose metabolism. Thus, LA plays an essential role in mitochondrial-specific pathways that generate energy from glucose.

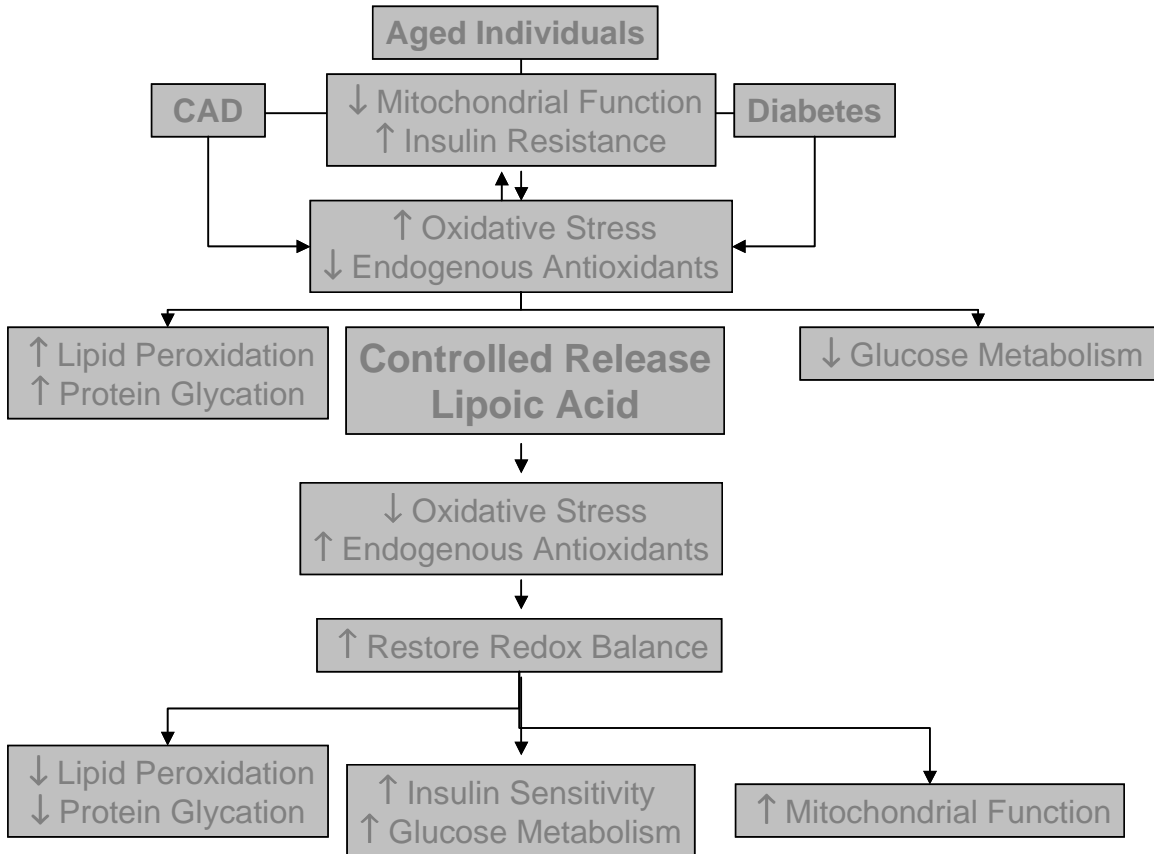
Free Radical Damage to Mitochondria

Mitochondria are the cellular sites of electron transport, which is the process of passing electrons through the respiratory chain of proteins located in the inner membrane. This creates a transmembrane pH gradient that drives the production of ATP. There is an inherent inefficiency in the process of transferring electrons through the chain, and that inefficiency increases with age. This occasionally results in an electron bonding to an oxygen molecule outside the respiratory chain. This single reduction, or transfer of a single electron, creates a molecule with unpaired electrons, or a free radical.

Free radicals are highly reactive molecular by-products produced in all cells as a result of normal metabolism, disease, and aging. Excessive production of free radicals, or their inadequate neutralization by antioxidants, leads to the damage of proteins, lipids, and DNA. Due to their essential role in cellular metabolism, mitochondria are the chief sources of free radical production inside the cell. According to Professor Bruce Ames (University of California, Berkeley), an individual produces approximately 1 kilogram of

oxygen radicals per year, the consequence of which is approximately 100,000 oxidative 'attacks' on mitochondrial DNA per cell each day. The cumulative effect of these attacks on mitochondrial DNA leads to an even further impairment of function.

Figure 2. Association of increased oxidative stress and mitochondrial dysfunction with aging, diabetes, and coronary artery disease (CAD).



The degree of free radical damage is a function of age (3). This is evidenced by observations that young rats have approximately 25,000 oxidative DNA adducts (damaged), while aged rats have well over 75,000 oxidative DNA adducts. The free radicals produced by mitochondria are the same type as those produced in ionizing radiation, prompting Professor Ames to refer to mitochondria as 'mini-Chernobyls'.

The cell has a wide array of endogenous antioxidants to call upon for protection against free radical assault. However, the ranking of an antioxidant is actually dependent on its redox potential, or its ability to be oxidized and reduced. According to Professor Lester Packer (University of California, Berkeley), LA has a redox potential of approximately negative 325 millivolts, while the value for vitamin C is approximately 290 millivolts. Glutathione, the other major endogenous antioxidant, is even lower at about negative 250 millivolts. Because it is one that can be oxidized and reduced most readily, LA is regarded as the most potent antioxidant.

LA is both water and fat-soluble. Because LA is fat soluble (similar to vitamin E), it is highly effective at reducing free radicals, including lipid peroxides, in cell

membranes. Because LA is also water soluble (similar to vitamin C), it is able to gain access to the cytosol (watery compartment in cells), where it effectively scavenges free radicals at their mitochondrial source (4). The solubility of LA in both water and lipid provides a distinct advantage over either vitamin C or E. Furthermore, studies have shown that LA regenerates tissue levels of vitamins E and C, and dramatically elevates glutathione, thereby strengthening the entire antioxidant network (5).

α -Lipoic Acid and Aging

Aging is an inevitable biological event that is associated with a progressive decline in mitochondrial function (3;6;7). Work from several laboratories has revealed that mitochondrial membrane potential, respiratory control ratios, cellular oxygen consumption, cardiolipin content, and membrane fluidity decline with age, while proton leakage and oxidant production rise. The etiology of mitochondrial deterioration is primarily linked to increased oxidant formation resulting from aerobic metabolism, coupled with a general decline in endogenous antioxidant defenses. Increased oxidant formation imparts damage to mitochondrial DNA, protein, and lipids ultimately leading to impaired and even loss of function. Increased oxidant formation is not restricted to aging, but is also evident in many age-associated pathologies such as diabetes, cardiovascular disease, neurodegenerative disease, cancer, and immune dysfunction. Therapeutic agents that reduce oxidative stress have the potential to improve mitochondrial function, combat disease, delay the aging process, and improve the quality of life.

LA has recently emerged as an attractive and effective therapeutic candidate to increase energy metabolism and decrease oxidative stress. LA can partially reverse the decline in mitochondrial function and increase in oxidative stress associated with aging. Lykkesfeldt, Hagen, Ames and colleagues have reported that dietary supplementation of aged rats for two weeks with LA (0.5%) reversed the age-associated impairment of hepatocyte ascorbate (Vitamin C) content and biosynthesis (8). More recently, this group has demonstrated that LA reversed the age-associated decline in hepatocyte mitochondrial O₂ consumption and increased mitochondrial membrane potential in rats (9). LA treatment also reversed the age-associated decline in glutathione content, and attenuated the age-associated rise in lipid peroxidation. The improvement in mitochondrial metabolism and antioxidant status of aged rats mediated by LA supplementation was reflected by a significant improvement in their motor activity. Although the plasma level of LA was not reported in these studies, it is likely that the normal feeding cycle of rodents resulted in a higher steady state plasma of LA compared to what can be achieved by oral administration of 'non-controlled release' dosage forms. Taken together, these data support the belief that LA supplementation provides multiple beneficial effects to counteract the decline in mitochondrial function, energy metabolism, and oxidative stress associated with aging, and that appropriate plasma levels need to be achieved to ensure maximum therapeutic benefit.

α -Lipoic Acid and Diabetes

The role of increased oxidative stress in the processes leading to atherosclerosis is relatively well-established (10-12). Several lines of evidence strongly suggest that insulin resistance and diabetes mellitus are also associated with increased oxidative stress and free radical production (13-15). Increased production of reactive oxygen species, as well as reduced antioxidant defense mechanisms have been suggested to occur in Type 1 and Type 2 diabetic patients (16-18). There is accumulating evidence

that the generation of reactive oxygen species (oxidative stress) plays an important role in the etiology of diabetic complications (19). Many of the biochemical pathways (e.g. protein glycation, polyol pathway, glucose autoxidation) associated with hyperglycemia can result in increased free radical production. In Germany, non-controlled release LA has been prescribed for over a decade for complications associated with diabetes (20;21).

A role for oxidative stress in the occurrence of insulin resistance has been suggested by several small trials demonstrating improved insulin sensitivity in diabetic patients treated with either LA or Vitamin E (22;23). In addition, a prospective study of 4,000 Finnish men demonstrated that reduced plasma levels of Vitamin E were associated with an increased risk of developing Type 2 diabetes (24). The significance of the role oxidative stress in the etiology of diabetes and associated complications is recognized by both the American Diabetes Association and the Juvenile Diabetes Foundation. Each organization sponsors an increasing number of research projects aimed at deciphering the role of oxidative stress in diabetes in hope of uncovering new therapeutic strategies.

A newly emerging concept suggests that the role of oxidative stress in diabetes mellitus is not strictly limited to the later stages of the disease, but that it negatively impacts the early stages (e.g. impaired insulin signaling), perhaps even linked to its etiology. Agents that induce oxidative stress impair insulin-stimulated glucose transport and GLUT4 translocation *in vitro* (25;26). The inhibitory effects of oxidative stress apparently target the early molecular events in the insulin signaling cascade, including the ability to suppress the activation of the insulin receptor (27;28). Importantly, LA is able to provide substantial protection against the damages of oxidative stress, (29). This means that glucose transport in cells exposed to LA and then subjected to oxidative stress was far more sensitive to insulin compared to cells that were not treated with LA. Although the mechanism of action leading to this protective effect is not completely understood, it presumably involves the ability of LA to restore the intracellular redox balance.

The clinical significance of this result is provided by the ability of orally administered LA to improve insulin sensitivity in individuals with type 2 diabetes (30). Unfortunately, this same non-controlled release LA was ineffective at reducing blood glucose levels. This limitation might stem from the abbreviated half-life of LA in plasma (approximately 30 minutes) (31). While the molecular basis for oxidative stress-mediated insulin resistance is still unclear, it is likely that the pharmacological reduction of free radicals responsible for the oxidative damage holds great promise for improving the overall health status of individuals with insulin resistance and diabetes mellitus.

Treatment with Lipoic Acid and The Pharmacological Benefits of Extending Plasma Half-Life

Until now, LA has been commercially available only in non-controlled release forms. The major limitation of non-controlled release LA is that it has a very short half-life in plasma (approximately 30 minutes) (31). Thus, the rapid clearance of non-controlled release LA severely limits its ability to effectively reduce oxidative stress in individuals with diabetes, coronary artery disease, and in aged individuals. It is likely that that this is a principal reason why non-controlled release LA has little impact at reducing plasma glucose or lipid levels.

A controlled release formulation of LA has been developed recently and is commercially available. This formulation delivers micromolar concentrations of LA in the plasma. This plasma level of LA level persists for an extended period, significantly reducing oxidative stress and improving insulin sensitivity. In Type 2 diabetics, preliminary data collected by Medical Research Institute (San Francisco, CA) indicate that controlled release LA decreases blood glucose levels in as little as ten days, when administered in combination with other antihyperglycemic agents. In some cases, a clinically significant reduction in glycohemoglobin (Hb_{A1c}) over a period of twelve to sixteen weeks was also observed.

Conclusions and Future Prospects

LA is a multifunctional cofactor that plays a critical role as a key component of several mitochondrial enzyme complexes responsible for oxidative glucose metabolism and cellular energy production. In its natural role, LA is a mitochondrial-specific molecule that directly impacts energy production. When used in pharmacological concentrations, LA functions as a powerful antioxidant, recycling vitamins C and E and elevating tissue glutathione. The abbreviated plasma half-life of non-controlled release LA limits its efficacy *in vivo*. The recent work of Ames, Hagen and colleagues reveals the remarkable ability of LA to improve mitochondrial function in aged rodents. As judged by a number of criteria, animals provided with a diet fortified with LA functioned as if they were younger. There is a growing body of evidence suggesting that controlled release LA will be a welcome addition to current antidiabetic treatments. It is well tolerated, has an excellent safety record, and possesses a different mode of action (*i.e.* a modulator of redox balance) compared to existing treatments. Thus, it can be used in a complimentary fashion to enhance the therapeutic effect of other available treatments. In light of the association of increased oxidative stress and decreased mitochondrial function with a variety of other diseases (especially those affecting aged individuals), the possibility of identifying additional beneficial effects of controlled release LA merits further investigation.

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