Smart Life Forum

David Carlson

A Critical Re-evaluation of the Supplemental Use of Alpha Lipoic Acid

Thursday, July 20, 2006
7:00 PM

Cubberly Community Center
4000 Middlefield Road, Room H1, Palo Alto, California

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Future Speakers:

• **August 17 -** David Stetzer and Martin Graham, PhD
Electrical Pollution; RF Frequencies and Your Health

- **September 21** - Bruce Ames, PhD
Increasing Longevity by Tuning up Metabolism

Meet David Carlson

David Carlson began his college career as a pre-med student but, under the inspirational instruction of Dr. Harry Walborsky at FSU, he became fascinated with the art and science of organic synthesis. He was selected "Outstanding Chemistry Undergraduate Student" in 1979, and worked under Dr. Walborsky in the development of "Super-reactive" and Chiral Gringard reagents.

In 1980, on completion of his undergraduate training, he moved to Brazil, and undertook studies in advanced chemistry with an emphasis on industrial process design, development and analysis. Over the next 14 years, he worked for three different Brazilian chemical and pharmaceutical companies in jobs ranging from analysis to large scale contract manufacturing.

In 1998, he returned to the U.S., began work as a private consultant in the nutritional supplement industry, and discovered the pioneering work of Dr. Bruce Ames on R-lipoic Acid. RLA was commercially unavailable at that time, so Mr. Carlson began to work out industrially feasible routes to produce RLA on a large scale. After much work, RLA became commercially available in 2001, which led to Mr. Carlson founding GeroNova Research, Inc., whose primary focus is the production, distribution and research of R-lipoic acid related products.

Main Presentation

Alpha-lipoic acid is a naturally occurring chemical produced by every cell of the body and is essential to the chemical reactions that allow our bodies to produce energy. As a supplement, it is rapidly absorbed into the blood and the cells where it can prevent free-radical damage. It is vital for the creation of energy in every organ of the body, but as we age, we don't produce enough of it for optimal health.

ALA has been shown to be beneficial in humans and animals as a preventive and/or treatment for many age-related diseases such as heart disease, ischemia-reperfusion injury, diabetes, cataract formation, HIV activation, multiple sclerosis, neurodegeneration, radiation injury, Parkinson's and Alzheimer's disease, as well as declines in energy, muscle strength, brain function and immunity.

ALA reverses the cellular redox status (from a more oxidized to a more reduced state) which prevents inflammation, associated with all of the chronic degenerative diseases of aging. In particular, ALA plays a crucial role in protecting the mitochondria, the energy-producing structures in cells and the genetic material, DNA. As we age, mitochondrial function is impaired, and it's theorized that this may be an important contributor to some of the adverse effects of aging.

ALA has been called the ideal antioxidant and is a key component in the antioxidant network. However, this compound acts as an antioxidant only when there is an excess of it and it is in the "free" state in the cells; but there is little free ALA circulating in your body, unless you take it as a supplement. Foods contain only tiny amounts of ALA.

What makes ALA special as an antioxidant is its versatility—it helps deactivate an unusually wide array of cell-damaging free radicals in many bodily systems. It has potent antioxidant actions in every cell of the body, protects membranes by boosting and recycling levels of other antioxidants (vitamin C, vitamin E, Coenzyme Q10 and glutathione), thus making them much more effective. It neutralizes free radicals in both the fatty and watery regions of cells, in contrast to vitamin C (which is water soluble) and vitamin E (which is fat soluble). ALA is actually much more than an anti-oxidant, even though it is most well-known for this use.

ALA is prescribed in Germany to treat diabetic and alcoholic neuropathies and alcoholic liver disease, thought to result in part from free-radical damage. There is also evidence that it can help decrease insulin resistance; it speeds the removal of glucose from the bloodstream by enhancing insulin function, and thus helps control blood sugar, underlying many cases of coronary heart disease and obesity.

ALA Occurs in 3 Different Forms

When molecules are produced by industrial synthesis they exist in a “racemic form”, which

is a 50/50 composition of the two enantiomers. Enantiomers are mirror image molecules which are chemically unique. In chemistry, a molecule is "chiral" if is not superimposable on its mirror image. Our hands are also chiral -- mirror images of one another and non-superimposable -- and chiral molecules are often described as being "left handed" or "right-handed."

"Racemic" ALA consists of 50/50 mixture of the "R" (natural) and "S" (unnatural) enantiomers called a "racemic mixture." It is the most widely available form of lipoic acid.

R-Lipoic Acid (the "R" enantiomer) is the only naturally-occurring form of ALA. RLA is responsible for the specific beneficial effects of alpha lipoic acid, including its ability to reduce inflammation.

S-Lipoic Acid (The "S" enantiomer) is not found in nature. SLA is a by-product from chemical synthesis of racemic ALA and may inhibit the most essential properties of the "R" form, including interactions with proteins, enzymes and genes.

Much of the research over the past 30 years has been done with racemic alpha lipoic acid because the "R" form was not commercially available, due to its instability and the challenges of delivering the "R" form to the body in bio-available dosages compared to racemic ALA.

R-Lipoic Acid (RLA) and R-Dihydrolipoic Acid (R-DHLA)

Within the mitochondria, R-lipoic acid is reduced to R-dihydrolipoic acid (R-DHLA), the more potent antioxidant, 28 times faster than S-lipoic acid. Researchers at ASTA Medica claim that R-lipoic acid is 10 times stronger than racemic alpha-lipoic acid for reducing inflammation.

The "S" form can oppose the action of the " R" form. In the aging rat heart, R-lipoic acid stimulated ATP production, whereas S-lipoic acid inhibited it.

Pro-oxidant Effects

It is now clear that many of the positive benefits and dangerous side effects of alpha-

lipoic acid are the result of pro-oxidant effects. Since lipoic acid can interchange between a reduced form and an oxidized form, it displays reducing (antioxidant) and pro-oxidant properties related to dosage, half-life, and metabolism.

It is suggested that pro-oxidants produced by alpha-lipoic acid are involved in activation of insulin receptors and in elevated glucose uptake in muscle and fat cells. On the other hand, alpha-lipoic acid appears to protect the insulin-signaling cascade from oxidative stress-induced insulin resistance through its reducing capacities.

ALA and R-DHLA can effectively induce apoptosis in human colon cancer cells by a pro-oxidant mechanism that is initiated by an increased uptake of oxidizable substrates into mitochondria. The ability of ALA and/or R-DHLA to function as either anti- or pro-oxidants, at least in part, is determined by the type of oxidative stress and the physiological circumstances.

The Benefits of R-Lipoic Acid (RLA)

- RLA significantly reduces inflammation, an underlying cause of the degenerative diseases of aging and is more potent by a factor of 10 over commercial ALA.

- RLA was found to reach higher plasma levels than S-lipoic acid (1.6:1) when given orally as the racemic mixture in a human study.

- RLA was more effective than the SLA in a battery of metal chelation tests. One hypothesis of the cause of diabetic complications involves overloading by transition metals which could explain the stereospecific effect of RLA.

- RLA is the only form of lipoic acid found in nature and, therefore, the only form recognized by the critical mitochondrial enzymes.

- RLA was more effective than SLA in enhancing insulin-stimulated glucose transport and metabolism in insulin-resistant rat skeletal muscle.

- RLA was more effective than racemic ALA and SLA in preventing cataracts in rats.

- RLA increases cellular and mitochondrial antioxidant activity and prevents mitochondrial

decay. This effectively attenuates the reported increase in oxidative stress with aging.

- RLA improves memory, reverses cognitive dysfunction, and protects the brain from neurodegeneration associated with aging.

- RLA protects body fats against oxidative damage and reverses stress damage in the heart.

- RLA supplementation improves metabolic activity and lowers oxidative stress and damage evidentin aging.

- RLA significantly increase insulin sensitivity, enhances glucose transport, increases metabolic rate and reduces the gain in body fat from aging. RLA has insulin-mimetic effects in glucose uptake in insulin resistant cells and may have therapeutic implications in restoring glucose availability in tissues such as the skeletal muscle.

- RLA significantly increases or maintain levels of other antioxidants including Coenzyme Q10, vitamin C, vitamin E and glutathione.

- RLA prevents depletion of the glutathione pool within the cytoplasm and mitochondria. Pre-treatment of PC12 cells with RLA leads to the preservation of mitochondrial complex I activity lost due to glutathione depletion.

- RLA is much more effective than SLA at enhancing insulin-stimulated glucose transport and non-oxidative and oxidative glucose metabolism.

- RLA, through its positive effects on cellular energy metabolism, attenuates metabolic dysfunction associated with advanced glycation endproducts (AGEs). AGEs accumulate on long-lived proteins, including beta-amyloid plaques in Alzheimer's disease and contributes to neuronal dysfunction and cell death.

- RLA , a membrane permeable antioxidant, prevents the up-regulation of the AGE-induced gene expression responsible for regulating nitric oxide (NO) production. NO oxidizes and nitrates proteins which are markers of a chronic neuroinflammatory condition. This mechanism is relevant for Alzheimer's disease and for many chronic inflammatory conditions.

About S-Lipoic Acid (SLA)

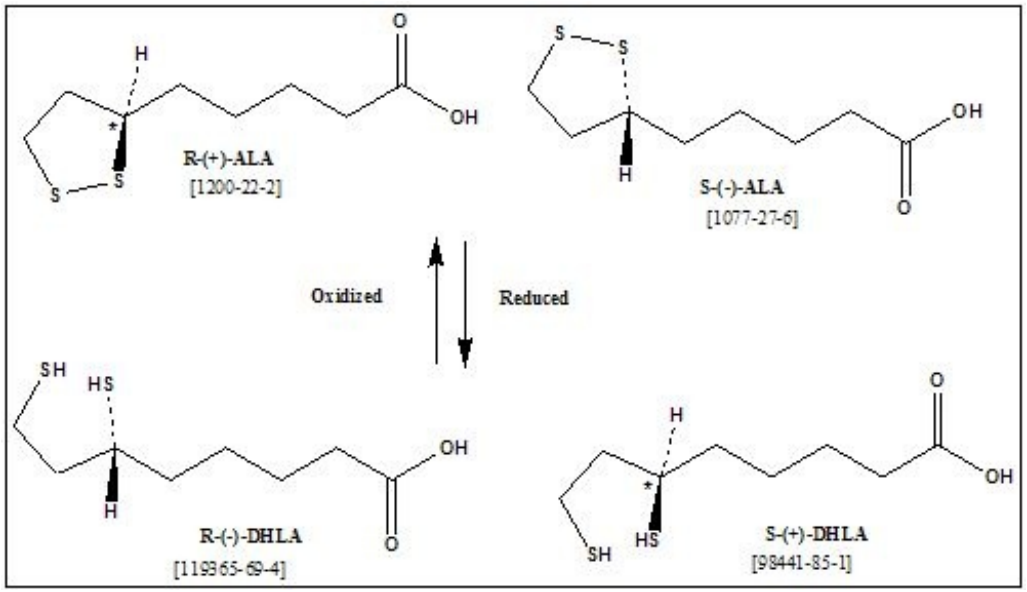
Until recently it was believed that S-lipoic acid (SLA) was physiologically inactive. Now there are a few reports from the patent literature suggesting this is not the case. There have been no human clinical trials to date that directly compare RLA, SLA and racemic ALA , although this will be forthcoming in the near future. In the meantime, we believe that enough evidence has been reported from in vitro and animal studies to warrant the use of pure RLA over the racemic ALA, when there is a choice.

SLA produces different biological actions than RLA, actions that may be undesirable.

SLA is metabolized in the outer cell membrane or cytoplasm. This may interfere with RLA's Sability to penetrate the inner mitochondrial membrane, thus limiting energy production. At high concentrations, SLA inhibits mitochondria metabolism. SLA cannot bind with critical mitochondrial enzymes and inhibits ATP production.

SLA is reported to be less effective than RLA as an antioxidant. However, Geronova's recent evaluation of the literature and its own laboratory and clinical measurements indicate that the 3 forms of alpha lipoic acid are approximately equal in antioxidant potency. The differences in activity are primarily due to stereospecific binding and competitive inhibition at the active sites of signalling proteins, transcription factors and enzymes.

R-(+)-alpha lipoic acid (RLA) and its redox (reduction/oxidation) partner R-(-)-dihydrolipoic acid are medium chain fatty acids with two sulfur atoms. The couple interconvert and have been utilized by evolution for at least 500,000,000 years as co-factors of several mitochondrial enzyme complexes involved in carbohydrate and fat metabolism and energy production. Alpha Lipoic acid (ALA , rac-ALA, R/S-ALA) has a chiral carbon and therefore exists as two mirror image forms called enantiomers. Only the R forms are found in cells and thus the food supply. Every living organism, from the simple prokaryotes (bacteria and cyanobacteria), up through more complex life forms, including humans either make or require and utilize RLA/R-DHLA.



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Brief History:

Thirty milligrams of the pure crystalline RLA was isolated in 1951 from ten tons of beef liver and was identified and characterized shortly after. Racemic lipoic acid (rac-ALA, R/S-ALA), contains S-(-)-alpha lipoic acid (SLA) as a 50% by-product, was synthesized a year later and is not found in nature. Within ten years there were dozens of processes reported in the peer reviewed and patent literature for synthesizing rac-ALA, so the extraction from natural sources was therefore never repeated.

Due to the endogenous roles of RLA/R-DHLA in cellular energy production there was immediate enthusiasm by the pharmaceutical industry and significant research efforts to test the efficacy of the pair in “energy-deficit” disorders. In addition, the Free Radical Theory of Aging had just been proposed by Harman who observed structural similarities between aged tissues and tissues damaged by radiation. Lipoic Acid was shown to block radiation damage in animal models and had a structural similarity to anti-Lewisite (the antidote for Lewisite, a chemical warfare agent). The cold-war was escalating and there was tremendous urgency in developing antidotes and radioprotectants in the event of a chemical or nuclear war. The Japanese pharmaceutical industry was actively researching and developing processes for making lipoic acid and derivatives in the hopes of treating the survivors of Hiroshima and Nagasaki.

Beginning in 1954 and extending into the mid 1960's, rac-ALA was tested in a variety of experimental disease models and used clinically. Early studies revealed patients suffering liver and skin diseases had lower tissues concentrations of enzyme bound RLA but higher plasma levels. In humans, rac-ALA has been used to treat various toxicities, diabetes, radiation poisoning and several liver diseases. A recent meta-analysis of 4 human clinical trials demonstrated that rac-ALA is effective in the treatment of diabetic neuropathy at doses of 600 mg (IV). Other trials have shown benefits from oral administration at 600-1200 mg/day.

After a 40 year history of safe usage in Europe, Rac-ALA became available as a dietary supplement in the US in the early 1990's and became an overnight sensation. Rac-ALA was branded as an “antioxidant” when ABC News featured the research of Dr Lester Packer in 1999. Dr Packer recommended 50-100 mg/ day rac-ALA/day (although he favored RLA) and suggested that it might strengthen the anti-oxidant defense network and mitigate age-related increases in oxidative stress. As of 6/24/06 Pub Med has 1843 citations under the search terms “lipoic acid, antioxidant” and this “branding” has limited research into other and maybe more important mechanisms with physiological significance.

As opposed to rac-ALA, Pure RLA is difficult to manufacture, isolate, purify and convert into dosage forms. Until recently RLA was not available in sufficient quantities, so most research was done on the cheap and widely available rac-ALA. From the early 1950's through the 1990's, in vitro and animal models demonstrated physiological differences in the ways living tissues process and utilize the natural and unnatural forms of lipoic acid.

RLA and R-DHLA became available in kilogram quantities and were provided to the

research communities and the nutritional supplement industries in 2001 and 2003. The sudden availability was based on the results of numerous in vitro and animal models that revealed biological differences between the pure enantiomers and the racemic mixtures. The differences reported in the literature prompted numerous use patents and attempts to develop RLA as a drug in Europe.

To date there have been no double blind placebo controlled studies in humans comparing the efficacy of RLA versus rac-ALA as a drug or a supplement. There have been no published reports attempting to systematize the experimental findings or proposals indicating clinically useful markers helping to differentiate the enantiomers or supplemental doses from therapeutic doses.

Dosage, Concentration Relationships:

Evidence supporting the efficacy of 50-100 mg/day of either racemic or RLA as an antioxidant is weak, and several studies have been unable to show any measurable benefits at these doses. Free radicals are continuously produced as a by product of metabolism but the plasma and tissue profiles of ALA and RLA show that levels peak very quickly following oral supplementation and return to baseline just as fast. How could rac-ALA or RLA limited by short ½ lives have any effect on free radical levels? Interestingly, research at GeroNova has revealed that supplemental doses of 300mg/ day of RLA/R-DHLA mixtures can improve the antioxidant and thiol status of plasma, and reduce CRP and IL-6; two markers of inflammation.

The mechanisms of action of ALA and RLA are complex and poorly understood. Recent reports and our own findings indicate clinically relevant differences between RLA and rac-ALA and new light is being shed on how RLA functions as a modulator of cell signaling, enzymatic activity, gene transcription, gene expression and cellular proliferation by regulating the cellular redox status and critical energy systems.

This talk will address the most frequently asked questions and re-evaluate the current paradigm from the reported literature, the last five years of research at GeroNova. Recommendations for clinical and supplemental uses will be proposed, as well as standardization of protocols for future studies.

Frequently Asked Questions:

1-Is there any evidence that the natural form is superior to the less expensive rac-ALA in humans or is it all marketing hype to sell a high priced product?

2-How much RLA should I take if I've been taking 100 mg of rac-ALA/day?

3-Is naturally occurring RLA isolated from potatoes or other natural sources?

4- Is ALA or RLA really an antioxidant, pro-oxidant or redox modulator in vivo?

5- What are the mechanisms of action of rac-ALA and how do they differ from RLA?

6- What is the difference between the usual quick release rac-ALA products and sustained release rac-ALA or RLA products?

7-Don't some studies show that SLA or rac-ALA might be superior to the natural form?

8-What other supplements should be used with ALA/RLA and what affect do they have on the metabolism and biological effects of ALA/RLA?

9-Are there any advantages or disadvantages to using DHLA or R-DHLA?

10-What is the advantage of using RLA and R-DHLA mixtures in dosage forms?

11- What is the relationship between the dose and in vivo concentrations of rac-ALA and RLA?

12-How, can I get my blood tested for RLA levels, antioxidant status, thiol status?

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