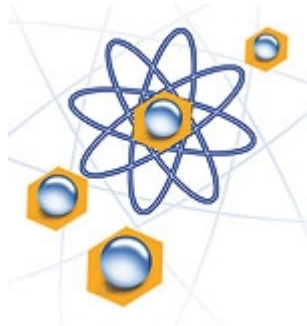


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REPORT**R-Dihydro-Lipoic Acid****The Optimal Form of Lipoic Acid**

By Jim English

**GROUNDBREAKING RESEARCH SHOWS THAT THE NATURAL, BIOLOGICALLY ACTIVE FORM OF LIPOIC ACID PROVIDES OPTIMAL ANTIOXIDANT PROTECTION**

Exciting new research links certain antioxidants to enhanced mitochondrial energy production. This finding is changing the way scientists view the interactions of damaging free radicals and beneficial antioxidants. Among the discoveries produced by this research are the disease-fighting properties of R-dihydro-lipoic acid (R-DHLA), a powerful antioxidant that is critically involved in cellular metabolism. Recent studies suggest that R-dihydro-lipoic acid may help prevent mitochondrial decay, diabetes, Alzheimer's disease, atherosclerosis, and other disorders associated with aging.

Antioxidants are known to play a vital role in preventing many of the health disorders associated with aging, including degenerative diseases such as diabetes, Alzheimer's disease, and cardiovascular disease.

Medical researchers continue to discover new antioxidant compounds as well as new applications for these protective nutrients. A vitamin-like substance known as alpha-lipoic acid is now at the forefront of antioxidant research. Alpha-lipoic acid was first introduced as a supplement in the late 1990s. Researchers are uncovering new applications to add to the already impressive list of therapeutic uses for alpha-lipoic acid.

A newly available version of alpha-lipoic acid, called R-dihydro-lipoic acid (R-DHLA), has been shown to offer substantially greater antioxidant and neuroprotective benefits than previous versions of alpha-lipoic acid.

ACTIONS OF ALPHA-LIPOIC ACID

Medical researchers initially classified alpha-lipoic acid, which was virtually unknown until the 1930s, as a new vitamin. Alpha-lipoic acid eventually was recognized as an essential coenzyme, following the discovery that it is naturally synthesized in tissues and plays a vital role in mitochondrial electron transport reactions required for metabolizing glucose into adenosine triphosphate (ATP) for cellular energy production.¹



By 1988, alpha-lipoic acid had been revealed as a powerful biological antioxidant, exhibiting a potential to quench free radicals equal to that of coenzyme Q10 (CoQ10) and vitamins C and E.² Researchers also discovered that alpha-lipoic acid is unique in being the only antioxidant known to work in both fat- and water-soluble tissues. By contrast, the actions of vitamin C (ascorbic acid) are restricted to watery (aqueous) tissues, while the actions of vitamin E, which is soluble only in fat, are restricted to fatty tissues and cellular membranes.

This dual-acting ability allows alpha-lipoic acid to be easily transported across cellular membranes to neutralize free radicals in both interior and exterior cellular structures, leading researchers to refer to alpha-lipoic acid as the "universal antioxidant." According to Lester Packer, PhD, professor of molecular biology at the University of California, Berkeley, alpha-lipoic acid "could have far-reaching consequences in the search for prevention and therapy of chronic degenerative diseases . . ."³

RECYCLING VITAMINS C AND E

To understand how alpha-lipoic acid and R-dihydro-lipoic acid work against various degenerative disorders, it is first necessary to understand how these compounds work in the body—specifically, how they interact chemically with other critical antioxidants such as glutathione and vitamins C and E to combat harmful reactive oxygen species.

Human aging is marked by a sharp decline in the concentration, synthesis, and recycling of central antioxidants such as vitamins C and E, CoQ10, and glutathione. This loss of antioxidant function reduces the body's ability to protect tissues from highly reactive free radicals. Left unchecked, free radical proliferation leads to increased oxidative damage to DNA strands, cell membranes, mitochondria, and organs. Over time, the cumulative effects of free radical damage can result in impaired immune function and increased incidence of cancers and degenerative diseases. In recent years, one of the leading breakthroughs in antioxidant research is an understanding of how alpha-lipoic acid recycles vitamins E and C to help control free radical damage.

Vitamin E is a potent biological antioxidant and a central component of the antioxidant cycle. Vitamin E protects fatty tissues, primarily cellular membranes, by quenching free radicals such as lipid peroxy and lipid alkoxy radicals. By donating an electron to pair up unpaired electrons present in lipid radicals, vitamin E is transformed into its oxidized form. The oxidized vitamin E then interacts with vitamin C by accepting one of vitamin C's electrons. The process continues as vitamin C, in its oxidized form as dehydroascorbic acid, accepts an electron from glutathione. Glutathione is in turn recycled by reduced nicotinamide adenine dinucleotide phosphate (NADPH). It is at this point in the cycle, however, that the body's antioxidant complex runs into a limiting factor determined by the availability of glutathione.

THE MISSING LINK: ALPHA-LIPOIC ACID

Glutathione is one of the body's most important intracellular antioxidants. In addition to playing a central role in quenching free radicals, glutathione protects against cataract formation, enhances immune function, prevents liver damage, slows the initiation of cancers, and aids in the elimination of heavy metals. Glutathione levels can quickly be depleted when the body is exposed to high levels of oxidative stress during times of illness, infection, trauma, or surgery. Glutathione deficiency is also seen in cases of low protein intake, diabetes, liver disease, cataracts, HIV infection, respiratory distress syndrome, cancer, and idiopathic pulmonary fibrosis, along with other conditions that produce oxidative stress.

When researchers sought ways to increase cellular glutathione levels, they encountered a problem. Normally, cellular glutathione is produced only in the body. When taken orally, glutathione is largely broken down in the stomach, resulting in modest serum increases in glutathione but almost no change in intracellular levels of glutathione.

Dr. Packer and other researchers at UC-Berkeley have spent almost four decades studying glutathione and antioxidant recycling. Despite a detailed understanding of the antioxidant regeneration cycle, Dr. Packer ran into the same problem that had stymied other researchers when attempting to increase cellular glutathione levels. This problem was finally solved when he began working with alpha-lipoic acid, which, according to Dr. Packer, proved to be the missing link.³ (*Editor's note: The real problem was found to be that the amino acid building blocks of glutathione could not be transported across age-damaged cell membranes, and intracellular glutathione levels decline with age.*)

Packer and his team discovered that, in addition to being a powerful biological antioxidant, alpha-lipoic acid, when administered orally, quickly crosses cellular membranes to enter cells where it is rapidly converted into its reduced form, R-dihydro-lipoic acid (R-DHLA).

It was later discovered that it makes more sense to take R-dihydro-lipoic acid directly because it is immediately usable, as the body does not have to convert it from alpha-lipoic acid. In addition, the synthetic form of alpha-lipoic acid used in the older studies is a mixture of right-handed and left-handed molecules. Only the right-handed R- portion of alpha-lipoic acid is biologically active.

Alpha-lipoic acid, and especially R-dihydro-lipoic acid, is effective against hydroxyl radicals, peroxynitrite hydrogen peroxide, and hypochlorite. In addition, alpha-lipoic acid has been shown to regenerate and elevate intracellular glutathione levels, thereby participating in the recycling of the antioxidant complex.^{4,5}

Initial research revealed that, in addition to conferring general health benefits like other antioxidant supplements, alpha-lipoic acid possesses properties that can be helpful in managing a wide range of diseases. According to Dr. Packer, "Alpha-lipoic acid could have far-reaching consequences in the search for prevention and therapy of chronic degenerative diseases such as diabetes and cardiovascular disease, and because it's the only antioxidant that can easily get into the brain, it could be useful in preventing damage from a stroke."³

ALPHA-LIPOIC ACID'S EFFECTS ON DIABETES

Alpha-lipoic acid has been shown to be particularly helpful for conditions arising from diabetes, and has been used in Europe for over 30 years for diabetic complications caused by overproduction of reactive oxygen species and nitrogen radicals.⁶ Alpha-lipoic acid has also been shown to aid in increasing glucose uptake in skeletal muscles, as well as in enhancing insulin-stimulated glucose disposal.^{7,8}

Alpha-lipoic acid has proven especially effective in treating diabetes-related neuropathy, the functional or pathological changes in the peripheral nervous system that can include pain, tingling, or sensory abnormalities. In one study, German scientists tested a group of 80 diabetic patients who were randomly assigned to four groups of 20 patients each. Each group received alpha-lipoic acid, selenium, vitamin E, or placebo. After three months, the researchers found that treatment with 600 mg of alpha-lipoic acid daily resulted in significant improvements in two markers of diabetes (thiobarbituric acid reactive substances and urinary albumin excretion rates). The researchers also noted significant improvements in neuropathy, leading them to conclude that alpha-lipoic acid was effective in reducing late diabetic complications.⁹

In a second study, 328 non-insulin-dependent diabetic patients diagnosed with symptomatic peripheral neuropathy (causing pain, burning, or numbness) were treated either with alpha-lipoic acid or placebo. At the study's end, pain scores had declined significantly in the group treated with alpha-lipoic acid, leading researchers to conclude that alpha-lipoic acid was effective in reducing symptoms of diabetic peripheral neuropathy, without side effects.¹⁰



ACTIONS AGAINST HIV/AIDS

Acquired immunodeficiency syndrome (AIDS) results from infection with the human immunodeficiency virus (HIV-1). Certain regions of HIV-1 DNA contain binding sites for nuclear factor-kappa beta, a transcriptional activator with a major role in the regulation of HIV-1 gene expression. Research has shown that alpha-lipoic acid inhibits the replication of HIV-1 and other viruses by blocking reactive oxygen species used in signal transduction pathways that lead to activation of nuclear factor-kappa beta. Dr. Packer and his colleagues theorized that alpha-lipoic acid, by eliminating reactive oxygen species, may prevent activation of nuclear factor-kappa beta and subsequently halt HIV transcription.¹¹ When Dr. Packer and his team tested their theory by exposing cells to alpha-lipoic acid, they discovered that alpha-lipoic acid was able to completely inhibit nuclear factor-kappa beta to block activation of the gene sequence that allows the AIDS virus to reproduce. These results, the authors suggested, "indicate that alpha-lipoic acid may be effective in AIDS therapeutics."

In a related finding, when Japanese researchers exposed cells infected with HIV-1 to alpha-lipoic acid, "initiation of HIV-1 induction by [tumor necrosis factor-alpha] was completely abolished." The scientists concluded that their findings confirm "the efficacy of alpha-lipoic acid as a therapeutic regimen for HIV infection and [AIDS]."¹²

SYNTHETIC VS. NATURAL LIPOIC ACID

Natural alpha-lipoic acid, or R-lipoic acid, is present in exceedingly tiny amounts in, and tightly bound to, mitochondrial complexes in animal and plant tissues. Because of the extreme difficulty and high cost of isolating natural R-lipoic acid, early studies were conducted with synthetic alpha-lipoic acid. Unlike R-lipoic acid, synthetic lipoic acid comprises a fifty-fifty mixture of two forms of alpha-lipoic acid: R-lipoic acid and S-lipoic acid. The R- and S- forms of alpha-lipoic acid are isomers—identical chemical structures, with the three-dimensional atomic arrangements reversed to form mirror images of each other.

Initial studies with synthetic alpha-lipoic acid helped scientists to understand its antioxidant-recycling and energy-production properties. When pure samples of the natural R- form of lipoic acid version became available, however, researchers quickly discovered that the body has a strong preference for R-lipoic acid. German researchers reported that, unlike the natural R-lipoic acid, synthetic lipoic acid does not improve ATP synthesis in isolated cells. Furthermore, whereas the natural R- form was shown to increase membrane fluidity and transport, the synthetic form was far less effective in doing so.¹³

Continuing experimentation revealed that R-lipoic acid is more biologically active and offers greater antioxidant and neuroprotective benefits at substantially lower doses than the synthetic forms of lipoic acid. This became apparent when researchers compared the effects of natural and synthetic lipoic acid in the prevention of cataracts. Half of all healthy adults over 65 will eventually develop cataracts, an opacity of the eye lens that can cause vision impairment or blindness. For those with diabetes, the odds of developing cataracts are substantially higher, as eye lenses are especially susceptible to damage from elevated glucose levels. Researchers have found that R-lipoic acid may aid in preventing cataracts and their complications by increasing levels of glutathione, ascorbate, vitamin E, and certain protective enzymes in lens tissues.

In one study, researchers induced cataracts by incubating rat lenses in glucose to mimic the damaging processes seen in diabetes. R-lipoic acid was shown to be highly effective in preventing cataract formation, while synthetic lipoic acid was only half

as effective at protecting lens cells.¹⁴ In a follow-up study, when eye lenses were exposed to either R-lipoic or synthetic lipoic acid, glutathione concentrations in the lenses incubated with the natural form were significantly higher than those incubated with the synthetic form. These data showed that R-lipoic acid was more effective in maintaining glutathione levels and protecting the lens from damage.¹⁵

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memory.¹⁷**R-LIPOIC ACID MAY BOOST BRAIN FUNCTION**

Age-related declines in physical activity and mental function are partly the result of a drop in mitochondrial energy production. Mitochondria are known to lose efficiency with age due to the oxidation of proteins, lipids, DNA, and RNA.¹⁶ Researchers led by Bruce Ames, PhD, professor of biochemistry and molecular biology at the University of California, Berkeley, have shown that the age-related decay of mitochondrial function can be partially reversed in older animals following treatment with R-lipoic acid or a combination of R-lipoic acid and acetyl-L-carnitine. In their study, older rats receiving either R-lipoic acid or a combination of R-lipoic acid and acetyl-L-carnitine showed signs of reduced lipid peroxidation and improved

Over time, oxidative stress in brain cells damages mitochondria, proteins, and nucleic acids, particularly in the region of the hippocampus. Left unchecked, these changes can contribute to impaired memory and loss of cognitive functions. In a groundbreaking study designed to mimic age-related loss of cognitive function and memory in humans, Dr. Ames and his colleagues treated older rats with either R-lipoic acid or a combination of R-lipoic acid and acetyl-L-carnitine. Dietary supplementation with R-lipoic acid and/or acetyl-L-carnitine was shown to significantly improve both spatial and temporal memory performance. Additionally, both R-lipoic acid and R-lipoic acid/acetyl-L-carnitine were found to significantly reduce the extent of oxidized RNA. Follow-up electron microscopic studies in the hippocampus showed that R-lipoic acid and R-lipoic acid/acetyl-L-carnitine reversed age-associated mitochondrial structural decay. The study results suggest that R-lipoic acid, either alone or in combination with acetyl-L-carnitine, may aid in lowering oxidative damage and improving mitochondrial function, thus improving memory and cognitive functions in aging humans.¹⁸

A BETTER FORM OF R-LIPOIC ACID

In the body, alpha-lipoic acid occurs in two forms: R-lipoic acid and R-dihydro-lipoic acid (R-DHLA). The two make up a “redox couple.” Oxidation reduction (redox reactions) involves the transfer of an electron from a donor to an acceptor. When the donor loses an electron, it is transformed from its reduced form to its oxidized form; conversely, when an acceptor gains an electron, it changes from its oxidized form to its reduced form. Together, the oxidized and reduced forms of a redox component are said to form a redox couple.

In the case of R-lipoic acid, when it donates an electron to R-dihydro-lipoic acid, the R-dihydro-lipoic acid is oxidized back into R-lipoic acid, and the R-lipoic acid is then reduced back into R-dihydro-lipoic acid. As the two forms swap electrons, they rapidly convert. Many of the properties of lipoic acid depend on this ability to rapidly swap electrons, and most health benefits are observed regardless of which form is used. As always, however, there are important exceptions.

R-DIHYDRO-LIPOIC ACID'S UNIQUE EFFECTS

As researchers continued to study lipoic acid, they discovered that R-dihydro-lipoic acid exerts a number of antioxidant and neuroprotective actions that are not seen with alpha-lipoic acid. One important difference is that while both alpha-lipoic acid and R-dihydro-lipoic acid effectively scavenge a number of radical species (hydroxyl radicals, nitric oxide radicals, peroxynitrite, hydrogen peroxide, and hypochlorite), only R-dihydro-lipoic acid has been shown effective against superoxide and peroxyl reactive oxygen species.¹⁹

Moreover, whereas alpha-lipoic acid and R-dihydro-lipoic acid both regenerate endogenous antioxidants and prevent oxidative stress, only R-dihydro-lipoic acid has been shown capable of actually repairing oxidative damage. Alpha-1 antiprotease (alpha 1-AP) is a physiologically essential macromolecule that helps lung tissue remain elastic. Oxidized alpha 1-AP has been implicated in the etiology of certain lung diseases, such as cystic fibrosis. German researchers discovered that R-dihydro-lipoic acid was effective in reversing the oxidative damage to alpha 1-AP, leading them to conclude, “[R-]dihydro-lipoic acid may exert a curative effect in diseases accompanied by oxidative stress.”²⁰

R-dihydro-lipoic acid has also been shown to interact with and enhance the antioxidant effects of CoQ10. By donating an electron

to oxidized CoQ10, R-dihydro-lipoic acid has been demonstrated to prevent the formation of damaging pro-oxidants, while maintaining CoQ10 in its active antioxidant form to prevent peroxidation of susceptible biomembranes.²¹

R-DIHYDRO-LIPOIC ACID AND ALZHEIMER'S DISEASE

Alzheimer's disease is a progressive neurodegenerative disorder that typically develops in people aged 50 or older. Its hallmarks include oxidative stress and energy depletion. German researchers theorized that alpha-lipoic acid's positive effects on glucose metabolism might assist in treating Alzheimer's. They administered 600 mg of alpha-lipoic acid daily to nine Alzheimer's patients in an open study for periods lasting close to a year. Alpha-lipoic acid treatment led to a stabilization of cognitive functions in the study group, determined by constant scores in two neuropsychological tests. Despite the limited sample size, the research team reported that treatment with alpha-lipoic acid might be a successful neuroprotective therapy for Alzheimer's disease and related dementias.²²

In a second study, researchers at the Sanders-Brown Center on Aging at the University of Kentucky Chandler Medical Center have shown that R-dihydro-lipoic acid protects cortical neurons from the toxic effects of two oxidative substances implicated in Alzheimer's disease. The researchers found that cortical neurons were significantly protected by R-dihydro-lipoic acid following exposure to iron/hydrogen peroxide and amyloid beta-peptide. Interestingly, whereas pretreatment with alpha-lipoic acid protected cells subsequently exposed to iron/hydrogen peroxide, there was no protection noticed in cells exposed to alpha-lipoic acid and iron/hydrogen peroxide at the same time. Reviewing the results of the study, the authors concluded, "Treatment of cortical neurons with [R-]dihydro-lipoic acid significantly protected glucose transport against [iron/hydrogen peroxide] or beta-mediated decreases, although treatment with alpha-lipoic acid did not provide protection. These data suggest that R-dihydro-lipoic acid, the reduced form of R-lipoic acid, significantly protects against both [amyloid beta] and [iron/hydrogen peroxide] mediated toxicity."²³

R-DIHYDRO-LIPOIC ACID AND ATHEROSCLEROSIS

Atherosclerosis is theorized to begin when low-density lipoprotein (LDL) particles circulating in the blood are damaged by lipid peroxidation. When the oxidatively modified LDL particles become implanted beneath the endothelial layers lining arterial walls, they are recognized as foreign invaders. This triggers apoptosis, or the cellular suicide of artery cells. A build-up of foam cells later causes bulges in the artery wall and atherosclerotic plaque develops. In-vitro experiments have shown that R-dihydro-lipoic acid—but not alpha-lipoic acid—can counteract lipid peroxidation of LDL particles, demonstrating a potential therapeutic effect for the early prevention of atherosclerosis. In the same study, R-dihydro-lipoic acid—but not alpha-lipoic acid—was shown to readily reduce iron and scavenge free radicals in a model of atherosclerosis, demonstrating a potential therapeutic effect for the early prevention of inflammatory processes implicated in cardiovascular disease.²⁴

R-DIHYDRO-LIPOIC ACID IMPROVES THE HEART'S ENERGY PRODUCTION

Heart attack and stroke are significant causes of mortality and disability. Therapeutics that can optimize healing from these events thus may be valuable aids in restoring health and function. When blood flow is restored following a heart attack or stroke, cells previously deprived of oxygen generate a flood of free radicals that inflict damage to surrounding tissues that is more severe than that caused by the original trauma. When researchers treated isolated rat hearts with lipoic acid (given in the form of R-dihydro-lipoic acid), mitochondrial function significantly improved. This resulted in significantly higher ATP levels in the heart tissue compared to untreated hearts.²⁵

In one study, a combination of R-dihydro-lipoic acid and vitamin E was shown to synergistically improve cardiac functional recovery during post-ischemic reperfusion or post-hypoxic reoxygenation of working rat hearts. After 30 minutes of oxygen deprivation (hypoxia), hearts treated with R-dihydro-lipoic acid showed significantly higher levels of ATP following reoxygenation than did untreated hearts.²⁶ R-dihydro-lipoic acid combined with vitamin E may therefore help guard against damage to heart tissue inflicted by cardiac events.

CONCLUSION

According to Dr. Packer, "Just 10 years ago, scientists had a simplistic view of free radicals and antioxidants. Today, knowledge of a global antioxidant network has emerged which is linked to the metabolic energy-producing process—a new perspective that is leading to an explosion of basic research and therapeutic studies."³

R-dihydro-lipoic acid is a powerful new supplement that sits at the forefront of this new wave of antioxidant research. As a powerful biological antioxidant involved in cellular metabolism and the recycling of endogenous antioxidants, R-dihydro-lipoic acid has been shown to aid in the prevention of numerous disorders associated with aging and oxidative stress, including diabetes, Alzheimer's disease, and atherosclerosis.



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