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Alpha-Lipoic Acid: A 'New' Antioxidant Backed Up By Solid Scientific Research

Is there a need for another antioxidant?

If its essential role in health is any indication, alpha-lipoic acid may very well join the ranks of vitamins C and E as part of your first-line of defense against free radicals. Discovered in 1951, it serves as a coenzyme in the Krebs cycle and in the production of cellular energy. In the late 1980s, researchers realized that alpha-lipoic acid had been overlooked as a powerful antioxidant.

Over the past few years, the pace of research on lipoic acid has increased dramatically. Last year, Lester Packer, PhD, of the University of California, Berkeley, published a lengthy review article on alpha-lipoic acid in *Free Radical Biology & Medicine* (1995;19:227-50). In April 1996, he presented a short review of it in the same journal (*FRBM*;20:625-6).

Several qualities distinguish alpha-lipoic acid from other antioxidants, and Packer has described it at various times as the "universal," "ideal," and "metabolic" antioxidant. 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).

The body routinely converts some alpha-lipoic acid to dihydrolipoic acid, which appears to be an even more powerful antioxidant. Both forms of lipoic acid quench peroxynitrite radicals, an especially dangerous type consisting of both oxygen and nitrogen, according to a recent paper in *FEBS Letters* (Whiteman M, et al., *FEBS Letters*, 1996; 379:74-6). Peroxynitrite radicals play a role in the development of atherosclerosis, lung disease, chronic inflammation, and neurological disorders.

Alpha-lipoic acid also plays an important role in the synergism of antioxidants, what Packer prefers to call the body's "antioxidant network." It directly recycles and extends the metabolic lifespans of vitamin C, glutathione, and coenzyme Q10, and it indirectly renews vitamin E.

In Germany, alpha-lipoic acid is an approved medical treatment for peripheral neuropathy, a common complication of diabetes. It speeds the removal of glucose from the bloodstream, at least partly by enhancing insulin function, and it reduces insulin resistance, an underpinning of many cases of coronary heart disease and obesity. The therapeutic dose for lipoic acid is 600 mg/day. In the United States, it is sold as a dietary supplement, usually as 50 mg tablets. (The richest food source of alpha-lipoic acid is red meat.)

"From a therapeutic viewpoint, few natural antioxidants are ideal," Packer recently explained in *Free Radical Biology & Medicine*. "An ideal therapeutic antioxidant would fulfill several criteria. These include absorption from the diet, conversion in cells and tissues into usable form, a variety of antioxidant actions (including interactions with other antioxidants) in both membrane and aqueous phases, and low toxicity."

"Alpha-lipoic acid...is unique among natural antioxidants in its ability to fulfill all of these requirements," he continued, "making it a potentially highly efffective therapeutic agent in a number of conditions in which oxidative damage has been implicated."

Other research on alpha-lipoic acid has shown that it might:

- help people with genetic defects leading to muscle myopathies (Barbiroli B, et al., *Journal of Neurology*, 1995;242:472-7);
- reduce ischemia/reperfusion injury to the heart and brain. (Schonheit K, et al., *Biochimica et Biophysica Acta*, 1995;1271:335-42; and Cao X and Phillis JW, *Free Radical Research*, 1995;23:365-70); and
- inhibit the activation of "nuclear factor kappa-B," a protein complex involved in cancer and the progression of AIDS. (Suzuki YJ, et al., *Biochemical & Biophysical Research Communications*, 1992;189:1709-15).

"The therapeutic potential of alpha-lipoic acid is just beginning to be explored," observed Packer, "but this compound holds great promise." □

Vitamin E Deficiency Triggers Viral Mutations

Adequate intake of vitamin E prevents a dangerous mutation of the coxsackievirus, much the way sufficient dietary selenium prevents mutations in the same virus. That's the latest finding by Melinda Beck, PhD, of the University of North Carolina at Chapel Hill, and Orville Levander, PhD, of the U.S. Department of Agriculture.

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The coxsackievirus infects about 20 million Americans annually and usually causes no more than a sore throat or cold-like symptoms. However, about 10 percent of the cases lead to inflammatory heart disease.

Last year, Beck and Levander demonstrated that a selenium deficiency in mice consistently resulted in six distinct gene mutations in the coxsackievirus, which apparently increased its virulence. Now, in the *FASEB Journal* (March 1996;10:1101), Beck and Levander report that a deficiency of vitamin E during a coxsackievirus infection resulted in the same six gene mutations in mice.

"Thus, both vitamin E as well as selenium deficiency drive identical changes in the viral genome," they wrote. "It is important to emphasize that the virus, once mutated, can then cause disease even in mice fed adequate diets."

Beck and Levander's experiments have direct relevance for people. A combination of coxsackievirus infection and a selenium deficiency is recognized as the cause of Keshan disease in China. The same combination of factors is suspected in the development of many cases of cardiomyopathy in the United States. □

Oxidized Glutathione Linked to Aging Process

Researchers increasingly believe that aging begins in the mitochondria of cells. These mitochondria—there may be hundreds in some cells—function as miniature organs with the primary purpose of producing energy.

Free radicals are a necessary part of the energy-production process and, under ideal circumstances, they are contained within the energy-producing chemical reactions. However, some free radicals inevitably leak out and damage the deoxyribonucleic acid (DNA) found in mitochondria. This damage deletes some of the instructions guiding energy production, resulting in an age-related increase in free radical production. As the number of free radicals increases, their damage spreads out farther, affecting nuclear DNA, which contains your genetic history, and other cell components.

Glutathione, a powerful antioxidant produced by the body, apparently plays a major role in protecting mitochondrial DNA from free radical damage. But to guard DNA, the glutathione must sacrifice itself, in the process becoming oxidized.

In a series of experiments conducted at the University of Valencia, Spain, researchers found that older mice and rats had significantly higher levels of oxidized glutathione, compared with reduced glutathione. Reduced glutathione contains electrons that can be used to quench free radicals, whereas oxidized glutathione has already donated its electrons.

José Viña, PhD, and his colleagues found that the liver cells of old animals contained 320 percent more oxidized glutathione than in young animals. The differences in brain and kidney cells were even more dramatic. Brain cells had 600 percent and kidney cells from old animals had 540 percent more oxidized glutathione than cells from young animals. The researchers also found that mitochondrial DNA damage was greater in the old mice and rats, and that this damage was directly related to the amount of oxidized glutathione, according to an article in the *FASEB Journal* (Feb 1996;10:333-8).

Much of the oxidation of glutathione was prevented when the mice were given extra amounts of dietary antioxidants. In one phase of the experiment, Viña gave the animals a precursor of cysteine, an amino acid and one of the primary building blocks of glutathione. The cysteine-fed mice had less oxidized glutathione and DNA damage, and they also had greater vitality and a longer lifespan.

In another phase of the experiment, Viña and his colleagues fed the mice extra vitamins C and E. Again, they had significantly less oxidized glutathione and DNA damage, probably because antioxidants tend to recycle each other. □

Calcium Lowers Blood Pressure...Some of the Time

Two new studies shed light on how and when dietary calcium reduces blood pressure. The mineral seems to work best when a person either has marginal intake of the mineral or has an exaggerated need for it—and those situations may be fairly common.

In an analysis of 14 studies published over the past 30 years, Heiner C. Bucher, MD, MPH, found that calcium supplements reduced the risk of preeclampsia by 62 percent. The condition, which can develop late in pregnancy, raises blood pressure and increases the risk of death to both mother and fetus.

Bucher found a "substantial reduction" in systolic and diastolic (the upper and lower numbers in blood pressure) among women consuming large amounts of calcium.

"Maternal blood pressure and maternal calcium intake may be related to blood pressure in infants and children," he wrote in the Jo*urnal of the American Medical Association* (April 10, 1996;275:1016-22). "Low birth weight, which may be a consequence of preeclampsia and early delivery, is associated with raised blood pressure and coronary artery disease in adult life."

In a more general analysis of 33 studies and 2,412 hypertensive patients, however, Bucher found a less dramatic effect. He and his colleagues reported in *JAMA* (April 3, 1996;275:1016-22) that 1,000 to 2,000 mg of calcium supplementation daily "may lead to a small

reduction in systolic but not diastolic blood pressure."

In fact, in the broader analysis, the effect of calcium was substantially less than that of drugs or other nutrients, such as potassium and the omega-3 fatty acids, Bucher wrote. But, he added, "it remains possible that calcium deficiency may raise blood pressure and that calcium supplementation in populations with inadequate intake may therefore prevent hypertension."

In an editorial in *JAMA* (April 10, 1996;275:1128-9), David A. McCarron, MD, and Daniel Hatton, PhD, of Oregon Health Sciences University, wrote that calcium deficiency may affect more than half of all Americans, with the consequences being elevated blood pressure and an increased risk of osteoporosis. The two studies, they observed, support the idea that increased calcium can benefit people with normal and high blood pressure.

McCarron and Hatton, who have conducted extensive research on the relationship between calcium intake and blood pressure wrote, "Calcium requirements vary across the life span. When calcium needs are increased, the relationship between calcium intake and biological responses may be amplified...[For example,] gestation is a transient period of increased risk of elevated arterial pressure. It is also a period in which the metabolic demand for calcium increases dramatically....Younger pregnant women must provide calcium for the fetus as well as their own continued skeletal growth, thus multiplying their daily requirement. While the current calcium recommendation for pregnant women and adolescent females is 1200 to 1500 mg/day, their reported median intake is 600 to 700 mg/day." □

Vitamin C Needs Increase with Blood Infections

Hospitalized patients with sepsis, an infection of the blood usually caused by either *Staphylococcus aureus* or *Escherichia coli*, have lower than normal blood levels of antioxidant nutrients and higher levels of free radical byproducts.

Recently, doctors at the universities of Aberdeen and York, in the United Kingdom, gave eight sepsis patients 1 gram of intravenous vitamin C. These patients, who had been fed a standard hospital diet with 100 mg of vitamin C daily, had low blood levels of the vitamin and high levels of "free" iron, which can generate free radicals.

"The low levels of total vitamin C, found in this study, suggest that in patients with sepsis, there is inadequate regeneration and ultimate destruction of dehydroascorbic acid [the oxidized form of vitamin C]," the researchers wrote in *Free Radical Biology & Medicine* (Jan 1996;20;139-43). "The data prove that in the presence of high concentrations of 'free' iron, total levels of vitamin C are depleted...the overall effect, however, is that vitamin C is depleted and is thus unavailable to act as an antioxidant and prevent further tissue damage." □

Lutein and Lycopene Are Powerful Antioxidants

Of all the carotenoids, beta-carotene has probably been the most thoroughly researched, in large part because scientists focused on its role as a vitamin A precursor. However, recent research on two related carotenoids, lutein and lycopene, suggest that these nutrients may have been inadvertently overlooked. As antioxidants, both appear to be far more potent than beta-carotene.

In the *Journal of Cellular Biochemistry* (1995;suppl 22:236-46), Frederick Khachik, PhD, and two colleagues at the U.S. Department of Agriculture noted that 40-50 carotenoids are found in the American diet, but only 14 are actually absorbed and found in the bloodstream. And contrary to popular opinion, lutein and lycopene (not beta-carotene) are the most common carotenoids in the diet and human blood plasma. Kale, spinach, peaches, and oranges are rich in lutein, and tomatoes are the primary dietary source of lycopene.

The implications could mean that many beta-carotene studies were really studies of lutein and lycopene, or mixed carotenoids in general. Observed Khachik: "since the dietary intake of lutein and lycopene is usually higher than that of beta-carotene for most people, the results from epidemiological and human studies can be better interpreted if bioavailability, metabolism, and potential cancer preventive effects of these major dietary carotenoids are also studied."

In an approved experiment, Khachik and his colleagues deprived themselves of lutein-containing vegetables for several weeks, then began consuming lutein capsules (10 mg/day). Their lutein levels rose dramatically—to about 5 times the typical blood levels of this nutrient. Blood levels of lutein oxidation products also increased, a sign that the body was using lutein to neutralize free radicals.

"Lutein and lycopene possess exceptionally high antioxidant activity compared to other carotenoids and may therefore be useful in chemoprevention of cancer," Khachik wrote. □

Vitamin E Protects Blood Fats

In a recent experiment, Sushil K Jain, MD, of Louisiana State University Medical Center gave 35 insulin-dependent diabetics 100 IU of vitamin E or a placebo daily for three months. According to an article in *Lipids* (1996;31:S87-S90) the vitamin E lowered levels of blood fats and lipid peroxidation, a sign of free radical damage to essential cellular fats. □

Quick Reviews of Recent Research

• **N-acetyl-L-cysteine and rheumatoid arthritis**

Rheumatoid arthritis is characterized by inflamed joints. During the inflammatory process, lymphocytes and macrophages (types of white blood cells) infiltrate the joints and release a number of compounds, including "tumor necrosis factor alpha," or TNF-a, a key promoter of the inflammatory process. In an experiment at Nagoya University, Japan, Motoyoshi Sato, MD, found that N-acetyl-L-cysteine, a form of the amino acid L-cysteine, suppressed TNF-a.

Sato M, et al., *Journal of Rheumatology*, 1996;23:432-8.

• **Diabetes, free radicals, and antioxidants**

Researchers at the University of Madras, India, reported non-insulin-dependent diabetics have lower than normal antioxidant defenses, which result in higher levels of free radicals and free radical damage. In analyzing red blood cells, the researchers found lipid peroxidation to be 125 percent above normal in diabetics' cells—and more than 300 percent higher in the blood cells of diabetics with complications. Lipid peroxidation in the cell membrane was even greater—four fold higher in diabetics and five fold higher in diabetics with complications. The free radical damage to red blood cell membranes can reduce the cell's life span and make it more likely to deform when passing through small blood vessels.

Parthiban A, et al., *Cell Biology International*, Dec 1995, 19:987-93.

• **Reperfusion injury and vitamin E**

During a heart attack, stroke, and bypass surgery, the flow of blood is interrupted. When it resumes, or reperfuses, oxygen-carrying blood generates large numbers of free radicals, which injure cells. In an experiment, researchers focused on how this process affected endothelial cells from the aorta and saphenous vein. The saphenous vein is routinely used as a replacement for arteries in bypass surgery. Supplemental vitamin E substantially increased cellular concentrations of the vitamin, but after reperfusion, vitamin levels decreased by 18 percent in the aortic cells and by 62 percent in the saphenous cells. The researchers wrote, "This suggests that saphenous grafts used in bypass surgery are highly vulnerable to oxidative stress following reperfusion." They recommended using vitamin E supplements pre-surgically to prevent damage to saphenous vein grafts.

Martin A, et al., *Free Radical Biology & Medicine*, 1996;20:99-105.

• **Tempeh as an antioxidant**

Tempeh, a traditional Indonesian food now common in American health food stores, contains a number of powerful antioxidants. These antioxidants probably account for the use of dried tempeh as a food preservative. Recently, researchers at Sugiyama Jogakuen and Nagoya universities, Japan, isolated a new antioxidant in tempeh. Identified as 3-hydroxyanthranilic acid, the antioxidant is a result of the fermentation process that produces tempeh. Levels of the antioxidant peaked after two days of fermentation.

Esaki H, et al., *Journal of Agricultural and Food Chemistry*," 1996;44:696-700.

• **Beta-carotene and immune enhancement**

In a study of healthy young men, Japanese researchers found that beta-carotene supplements (30 mg/day) substantially increased the proliferation of lymphocytes, an important type of immune cell, compared with a placebo. Blood levels of beta-carotene increased 20-fold after supplementation, and lymphocyte activity was 1.4 to 1.9 times higher.

Moriguchi S, et al., *Nutrition Research*, 1996;16:211-8.

• **Oxidized low-density lipoprotein**

Researchers increasingly believe that the low-density lipoprotein (LDL) may pose the greatest risk of coronary heart disease and that oxidized LDL (in which the blood fat is damaged by free radicals) may pose the greatest danger. "The oxidation of LDL has been shown to be reduced by antioxidants, and in animal models, these antioxidants decrease atherosclerotic lesion formation."

Jialal I and Devaraj D, *Journal of Nutrition*, 1996;126:1053S-7S.

• **Cigarette smoke and antioxidant destruction**

Cigarette smoke contains numerous free radicals, including peroxyl radicals, superoxide anions, and nitrogen dioxide, which destroy antioxidants. When blood plasma containing antioxidants was exposed to cigarette smoke, the antioxidants were rapidly destroyed. For example, 20 percent of the plasma vitamin E was destroyed after three hours and 70 percent after nine hours. In contrast, exposure to normal room air resulted in negligible changes. Antioxidants were destroyed in the following order: lycopene, vitamin E, beta-carotene, lutein and zeaxanthin, cryptoxanthin, and gamma tocopherol.

Handelman GJ, *American Journal of Clinical Nutrition*, April 1996;63:559-65.

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