ALPHA-LIPOIC ACID

by Dr. Van Beveren

"Age-associated deficit of mitochondrial oxidative phosphorylation in skeletal muscle: Role of carnitine and lipoic acid," Kumaran S, Panneerselvam KS, et al, Mol Cell Biochem, 2005; 280(1-2): 83-89. (Address: Department of Medical Biochemistry, Dr. AL Mudaliar Post Graduate Institute of Basic Medical Sciences, University of Madras, Chennai, India). Summary: In this study, administration of carnitine and alpha-lipoic acid to aged rats was found to increase skeletal muscle mitochondrial respiration, and in turn, increase the level of ATP. The study involved both young (3-4 months) and aged (over 24 months) rats. Measurements of mitochondrial membrane swelling and mitochondrial respiration (states 3 and 4) found that aged rats had an increased mitochondrial membrane swelling and state 4 respiration, whereas they had a decreased state 3 respiration, respiratory control ratio (RCR) and ADP:O ratio, compared with young rats. After administration of a combination of carnitine and alpha-lipoic acid for a period of 30 days, the condition of the aged rats improved. Specifically, mitochondrial membrane swelling and state 4 respiration returned to near normal levels, while the state 3 respiration and RCR increased. The results of this study suggest that the combination of carnitine and alpha-lipoic acid may have potential as a treatmen t for mitochondrial damage associated with aging.

the combination of ALA and exercise training brought about a greater improvement in insulin action on skeletal muscle glucose transport than either treatment alone. Oxidative stress is considered to be one potential factor in the multifactorial etiology of skeletal muscle insulin resistance, leading to impaired insulin signaling and eventually reduced glucose transport activity. Defects in IRS-1- dependent signaling are thought to be responsible for the impairment of insulin's ability to activate glucose transport in skeletal muscle. IRS-1-dependent insulin signaling in an animal model involving obesity-related insulin resistance. The studies reviewed in this article suggest that taking alpha-lipoic a cid while adhering to an endurance exercise program may offer significant benefits to people with insulin resistance ('prediabetes') and overt type 2 diabetes.

"dl-alpha-lipoic acid ameliorates cyclophosphamide induced cardiac mitochondrial injury," Mythili Y, Sudharsan PT, Varalakshmi P, Toxicology, 2005; 215(1-2): 108-114. (Address: Department of Medical Biochemistry, Dr. ALM. Post Graduate Institute of Basic Medical Sciences, University of Madras, Taramani Campus, Chennai 600113, India). Summary: In an animal study, supplementation with lipoic acid was found to ameliorate cardiac mitochondrial injury induced by the administration of cyclophosphamide (CP: an antineoplastic drug). 200 mg/kg-body-wt of CP were intraperitonealy administered to male albino rats of Wistar strain. In the CP treated rats, the activities of the TCA cycle enzymes and mitochondrial complexes of electron transport chain were found to decrease, thereby suggesting a loss in mitochondrial function and integrity. Additionally, the ultrastructural observations of the loss of myofilaments, and damage of mitochondria cristae demonstrated the cytotoxic effects of CP. Supplementation with 25 mg/kg-body-wt of lipoic acid was found to restore mitochondrial function to near normalcy in the CP treated rats. Thus, this study suggests that supplementation with lipoic acid may help amend cardiac mitochondrial injury caused by administration of CP.

In this longitudinal clinical intervention pilot study, children with severe kwashiorkor were found to benefit from treatment with the antioxidants, glutathione and alpha-lipoic acid. Subjects were randomly divided into one of four groups. Group 1 received the standard treatment (ST) recommended by the WHO; Group 2 received the ST + 2 x 600 mg reduced glutathione/day; Group 3 received the ST + 2 x 50 mg alpha-lipoic acid/day; and Group 4 received the ST + 2 x

100 mg N-acetylcysteine/day. Clinical and biochemical measurements were taken over the course of 20 days. Results found that survival improved among children receiving reduced glutathione supplementation (Group 2) and among those receiving alpha-lipoic acid supplementation (Group 3). In addition, blood tests revealed a positive correlation between levels of glutathione in the blood and survival rates. The results of this pilot study suggest that patients with kwashiorkor – which has often been associated with oxida tive stress – may significantly benefit from supplementation with glutathione and/or alpha-lipoic acid. Given the prevalence and lethality of kwashiorkor in several countries throughout Africa, further research into the effectiveness of these nutritional therapies is encouraged.

In this study involving rats fed a high fructose diet (60% of total calories), daily intraperitoneal administration of lipoic acid (35 mg/kg b.w.) for a period of 20 days was found to significantly decrease plasma levels of glucose, fructosamine, glycated protein, and glycated hemoglobin, while preventing in vitro glycation and the accumulation of advanced glycation end products (AGE). In addition, glucose utilization in the rat diaphragm was found to be enhanced by lipoic acid administration, without interfering with the action of insulin. This animal study suggests that alpha-lipoic acid may be an important therapeutic agent in the treatment of people with diabetes and diabetes-related complications.

"Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis," Ziegler D, Nowak H, et al, Diabet Med., 2004; 21(2): 114-21. (Address: German Diabetes Research Institute, Leibriz Institute at the Heinrich Heine University, Dusseldorf, Germany. E-Mail: dan.ziegler@ddfi.uni-duesseldorf.de). Summary: In a meta-analysis to determine the efficacy and safety of 600 mg/day of alpha-lipoic acid given intravenously over 3 weeks in diabetic patients with symptomatic polyneuropathy, results showed that treatment with alpha-lipoic acid is safe and significantly improves both positive neuropathic symptoms and neuropathic deficits to a clinically meaningful degree in patients. The meta-analysis was conducted on 4 trials culled from searching the database of VIATRIS GmbH (based in Frankfurt, Germany), which met the eligibility criteria – randomized, double-masked, placebo-controlled, parallel- group trial using alpha-lipoic acid infusions of 600 mg/day for 3 weeks, except for weekends, in diabetic patients with positive sensory symptoms of polyneuropathy which were scored by the Total Symptom Score (TSS) in the feet on a daily basis. The trials in total comprised of 716 patients who received the alpha-lipoic acid treatment (active group), and 542 patients who received placebo (place bo group). Primary analysis results, comparing the measured difference in TSS from baseline to the end of treatment between the active and placebo groups, favored the active group over the placebo group by 24.1%. The measured difference in Neuropathy Impairment Score of the lower limbs (NIS-LL) from baseline to the end of treatment was also found to be in favor of the active group over the placebo group by 16%. The responder rates (greater than or equal to 50% improvement in TSS) were 52.7% in patients treated with alpha-lipoic acid and 36.9% in those treated with placebo. After the first 8 days of treatment, the active group consistently showed a greater improvement in TSS over the placebo group on a daily basis. Additionally, among the individual components of TSS, pain, burning, and numbness decreased in the active group, as compared with the placebo group, and among the NIS-LL components, pin- prick, touch-pressure sensation, and ankle reflexes improved in favor of t! he active group after 3 weeks. The rates of adverse events did not differ between the two groups. Thus, the results of this meta-analysis provide evidence that treatment with alpha- lipoic acid over 3 weeks is safe and significantly improves positive neuropathic symptoms and neuropathic deficits in diabetic patients with symptomatic polyneuropathy.

Acetyl-L-carnitine and alpha-lipoic acid enhance mitochondrial function and reduce oxidative stress in animal models. Oral administration of L-carnitine, which is a mitochondrial metabolite, has improved behavior in children with Rett syndrome.

Mercury removal:
Other helpful nutritional supplements include vitamin C and magnesium, which shorten the amount of time it takes for feces to pass through the bowel (this prevents excreted mercury from being reabsorbed by the body through the intestine); vitamin E; thioctic acid; and N–acetyl–cysteine.

High doses of alpha-lipoic acid are an efficient chelator of mercury and can penetrate the blood-brain barrier.

Mitochondrial disorder: carnitine, coenzyme q10, creatine, lipoic acid, vitamin b1, vitamin b3, vitamin c, vitamin e, vitamin k - mitochondrial diseases are degenerative diseases which result in a reduction in the ability of mitochondria to supply cellular energy requirements. In the mitochondrial respiratory chain, protons (H+) are pumped from the mitochondrial matrix to the intermembrane space through complexes I, III, and IV. Complex V utilizes the proton gradient as an energy source to produce ATP. Coenzyme Q10 moves electrons from complexes I and II to complex III. Vitamin B2 is a precursor of flavin mononucleotide and flavin adenine dinucleotide and is important in the conversion of succinate to fumarate in complex II. Vitamin B2 is also important in flavin mononucleotide as a precursor for nicotinamide adenine nucleotide conversion to FeS in complex I. The amine form of niacin, nicotinamide, is a precursor for nicotinamide adenine dinucleotide, which is involved in complex I. Vitamin K3 and Vitamin C are electron receptors which can bypass a deficiency in complex III. Carnitine transfers long- chain fatty acids across the mitochondrial membrane. Dose ranges of vitamin C used in mitochondrial disorders are 250-4,000 mg/day; vitamin E, 400-1,200 IU/day; lipoic acid, 600 mg/day; vitamin B2, 9-300 mg/day; vitamin B1, 25-300 mg/day; vitamin B3, 3 g/day, although side effects such as flushing and nausea can be noted at 1,500 mg/day; vitamin K3, 40-80 mg/day; creatine, 10 g/d up to 330 g/day; and carnitine, 100-200 mg/kg/day. Some combination therapies include coenzyme Q10 between 30-120 mg/day, vitamin K3 at 20-60 mg/day, vitamin C at 2 g/day and methylprednisolone at 2-16 mg every other day, or coenzyme Q10 at 300 mg/day, vitamin K3 at 60 mg/day, vitamin C at 2 g/day, vitamin B1 at 100 mg/day, vitamin B2 at 25 mg/day and vitamin B3 at 200 mg/day. "Nutritional Cofactor Treatment in Mitochondrial Disorders," Marriage B, Clandinin MT, et al, J Am Diet Assoc, August 2003;103(8):1029-1038. (Address: Barbara Marriage, PhD, RD, E-mail: Barbara.Marriage@abbott.com)

Cardiovascular Support: coenzyme Q10 in the 200-400 mg range taken with a fatty meal, L-carnitine at 2-4 g/day, taurine at 2-4 g/day, L-arginine at 3-6 g/day, along with a high dose of B-complex nutrients, vitamin C at 1-2 g/day, selenium at 200-400 mcg/day, magnesium at 400-600 mg/d and alpha-lipoic acid at 100-300 mg/day.

Alzheimer's disease: alpha-lipoic acid, dementia - eight men and 1 woman who were between 52 and 81 years of age (mean age of 67 years, mean duration of dementia of 2.9 years) were evaluated in an open clinical trial of subjects with a primary degenerative form of dementia (alzheimer's disease). Subjects were given 600 mg of alpha-lipoic acid per day in addition to an acetylcholinesterase inhibitor (Aricept , Exelon) for an average period of 337 days. There was stabilization of cognitive function shown by constant scores in the Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale (ADAScog). This study came from an observation of a 74-year-old female patient with documented deficits in cognitive function and early Alzheimer's disease who took 600 mg/day of alpha-lipoic acid for polyneuropathy. When

retests were performed, she had no substantial decline of cognitive function. The diagnosis of mild Alzheimer's disease was reevaluated on several occasions, but the diagnostic features did not change and the neuropsychological tests kept showing no further cognitive impairment. The authors believe that alpha-lipoic acid may be a "neuroprotective" agent and that placebo-controlled, double-blind trials are warranted. "Alpha-Lipoic Acid as a New Treatment Option for Alzheimer Type Dementia," Hager K, Marahrens A, Kenklies M, et al, Arch Gerontol Geriatr, 2001;32:275-282. (Address: Klaus Hager, Dept Med Rehabil Geriatr, Henriettenstiftung, Schwemannstrasse 19, D-30559 Hannover, Germany, +49-511-2893222, (FAX) +49-511-2893004, E-mail: geriatre.hannover@t-online.de) 38165
Clinical Pearls: I call these types of studies landmark, and sometimes they give me chills. When one sees a condition that is so relentless as Alzheimer's disease, and one reads an article like this, one begins to see how molecular medicine in the near future should be able to deal with these difficult illnesses, and hopefully we can find ways to start treating these conditions earlier rather than later. We have some evidence that NADH can be of benefit in Alzheimer's disease, as well as intravenous glutathione, acetylcarnitine, hydrothiamin and now alpha-lipoic acid. What I really like about this article is that it was based on a clinical observation of an individual with polyneuropathy who also had early Alzheimer's disease. That is where the concept of using alpha-lipoic acid in the Alzheimer's study developed. Without clinical observation, medical science won't move forward.

Nutrients with **natural calcium channel blocker activity** include: alpha-lipoic acid (ALA), vitamin C, vitamin B6, N- acetylcysteine (NAC), magnesium, vitamin E, hawthorn, celery, omega-3 fatty acids, calcium and garlic.

Vitamins and minerals involved in **cellular energy production** include: magnesium, vitamin B1, vitamin B2, niacinamide, menadione, tocopherols, folate, vitamin C, acetyl-L-carnitine, and alpha-lipoic acid.

Treatments that may help with energy production in the mitochondria may also help in a wide variety of conditions that result in fatigue. Nutrients that may be important, along with L-carnitine, include NADH, alpha-lipoic acid, magnesium, coenzyme Q10 and B-complex vitamins.

Chronic fatigue syndrome: carnitine - in evaluating 27 female and 8 male patients suffering from chronic fatigue syndrome, there was found significantly lower serum total carnitine, free carnitine and acylcarnitine levels. Previously, only lower acylcarnitine levels were noted. There was a correlation between serum levels of total and free carnitine and clinical symptoms of chronic fatigue. Higher serum carnitine levels correlated with better functional capacity in these chronic fatigue syndrome patients. These data suggest there may be mitochondrial dysfunction in chronic fatigue syndrome patients. "Serum Levels of Carnitine in Chronic Fatigue Syndrome: Clinical Correlates," Plioplys AV, Plioplys S, Neuropsychobiology, 1995;32:132-138.

Exercise: thiol, alpha-lipoic acid, n-acetylcysteine - physical activity may result in oxidative stress. A consistent marker of exercise-induced oxidative stress is blood glutathione oxidation. N-acetyl-L-cysteine and alpha-lipoic acid are thiol compounds that may have antioxidant effects at the biochemical level and are also known to influence redox-sensitive cell signaling. In one human study, 1 g of glutathione and 2 g of vitamin C daily for 7 days showed in all 5 male subjects studied a 34% to 320% increase in blood glutathione disulfide. This antioxidant supplementation protected against blood glutathione oxidation induced by exercise. "Thiol Homeostasis and Supplements in Physical Exercise," Sen CK, Packer L, Am J Clin Nutr, 2000;72(Suppl):653S-669S. (Address: C. K. Sen, E-mail: sen-1@medctr.osu.edu)

This is truly a "clinical pearl." Although these are just 3 **Hepatitis** case reports, thiamine supplementation is such a simple therapy and so safe that it is worth trying. One hundred mg of thiamine orally is virtually without side effects. This is something I will add to my armamentarium of vitamin C, selenium, alpha lipoic acid, silymarin, N-acetylcysteine and coenzyme Q10 in approaching chronic hepatitis.

N-acetylcysteine has chelating activities against heavy metals, especially when given intravenously, and has a positive effect on cell survival after lead exposure. Alpha-lipoic acid may work by scavenging reactive oxygen species, regenerating other antioxidants, such as vitamins E and C and glutathione, and chelating heavy metals. Alpha-lipoic acid can enhance cell survival.
Lipoic acid - dermatology - thioctic acid, or lipoic acid, is an essential cofactor in mitochondrial dehydrogenases. The metabolic activity of lipoic acid is probably due to its byproduct, dihydrolipoic acid. Dihydrolipoic acid is very unstable and oxidizes quickly in skin within minutes of application. Lipoic acid is absorbed in a stable form and after entering the cells it immediately is converted to dihydrolipoic acid. Lipoic acid is unique in that it is both water soluble and lipid soluble. Lipoic acid can chelate metals, scavenge reactive oxygen species, regenerate the antioxidant vitamins C and E, and it can repair oxidative damage. In human skin, topical 3% lipoic acid in a lecithin base has been shown to reduce UVB-induced erythema twice as quickly as lecithin alone. Lipoic acid is well absorbed into the skin. Lipoic acid is beneficial for the treatment of pigment disorders. Lipoic acid enhances desquamation by reducing keratinocyte cohesiveness, which allows superficial melanin- containing cells to slough off. Recommended concentrations of lipoic acid range from 1-4% for treating the skin and 5-7% for treating scars. Lipoic acid is useful in a dermatologic practice because it can be used as a superficial peel to resurface the skin in a way similar to glycolic acid. When a patient applies lipoic acid it should be done on an every-other-day schedule, and if there are no side effects it can be increased to twice a day by week 3. Tingling may be felt with the application of lipoic acid but this will disappear within a few minutes. Lipoic acid can cause a significant amount of inflammation, so patients should be followed closely. Make-up can be applied immediately over lipoic acid without altering its antioxidant effect. "Cosmeceutical Critique: Lipoic Acid," Baumann L, Skin and Allergy News, April 2001;13

Thioctic acid, also known as alpha-lipoic acid, is found to be active in various biochemical systems in mammals. Chemists and biologists have known of its involvement as a coenzyme in the tricarboxylic acid cycle for many years. As a coenzyme it is essential for and involved in, ATP production and cell efficiency. As an antioxidant, thioctic acid works alone and interacts with glutathione to protect the cell. I have found thioctic acid to be an antitoxin and research demonstrates that it has radioprotectant properties. Some European scientists have reported neuroregenerative effects with thioctic acid and I have personally observed liver regeneration using thioctic acid.

"Alpha-Lipoic Acid Protects Against Hemolysis of Human Erythrocytes Induced by Peroxyl Radicals", Constantinescu, Anastasia, et al, Biochemistry and Molecular Biology International, July 1994;33(4):669-679. (Address: Anastasia Constantinescu, Department of Molecular and Cell Biology, 251 LSA, University of California at Berkeley, Berkeley, CA 94720,

Cerebral ischemia: à-lipoic acid - ischemic-reperfusion injury occurs in conditions such as stroke, cardiac arrest, subarachnoid hemorrhage or head trauma. Oxygen free radicals are the main cause of tissue injury. In these conditions, cellular glutathione is depleted, leading to oxidation of protein thiols to disulfide and loss of activity of critical enzymes which have thiol groups. In rats, cerebral ischemia was induced by bilateral coronary artery occlusion and

hypotension. While it was found that the isopropyl ester of glutathione had no significant protective effect, after pretreatment of rats with à-lipoic acid there was a dramatic reduction in mortality rate from 78% to 26% during 24 hours of reperfusion. The natural thiol antioxidant, à-lipoic acid, is effective in improving survival and protecting the rat brain against reperfusion injury following cerebral ischemia. "à-Lipoic Acid Protects Against Reperfusion Injury Following Cerebral Ischemia in Rats," Panigrahi, Manas, et al, Brain Research, 1996;717:184-188. (Address: Vijayalakshmi Ravindranath, Department of Neurochemistry, NIMHANS, Hosur Road, Bangalore, 560 029, India / 91 80 663-1830 (Fax))

Zinc, vitamin E and ALA are involved in gene expression of NFKB. Potassium modulates baroceptor sensitivity. Potassium, magnesium, calcium, fiber, garlic, vitamin C, flavonoids, coenzyme Q10, ALA, L-arginine, taurine, celery, monounsaturated fatty acids, soy, omega-3 fatty acids and vitamin E result in direct vasodilation.

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