Your AntiOxiDense™ Product Science – Lipoic Acid Abstracts

{Note: the underlined sections within the text of the abstracts are highlighted for emphasis by us, not the authors}

(1)

Lipoic Acid Explored As Anti-Aging Compound

ScienceDaily (May 18, 2007) — Researchers announced they have identified the mechanism of action of lipoic acid, a remarkable compound that in animal experiments appears to slow down the process of aging, improve blood flow, enhance immune function and perform many other functions.

The findings, discussed at the "Diet and Optimum Health" conference sponsored by the Linus Pauling Institute at Oregon State University, shed light on how this micronutrient might perform such a wide range of beneficial functions.

"The evidence suggests that lipoic acid is actually a low-level stressor that turns on the basic cellular defenses of the body, including some of those that naturally decline with age," said Tory Hagen, an LPI researcher and associate professor of biochemistry and biophysics at OSU. "In particular, it tends to restore levels of glutathione, a protective antioxidant and detoxification compound, to those of a young animal. It also acts as a strong anti-inflammatory agent, which is relevant to many degenerative diseases."

Researchers at LPI are studying vitamins, dietary approaches and micronutrients that may be implicated in the aging or degenerative disease process, and say that lipoic acid appears to be one of those with the most compelling promise. It's normally found at low levels in green leafy vegetables, but can also be taken as a supplement.

According to Hagen, research on the natural processes of aging, and steps that could slow it or improve health until near the end of life, are of growing importance.

"We're coming into the middle of an aging epidemic in the country," he said. "In a short time more than 70 million Americans will be over 65. This is partly because of the Baby Boom, but also people are living longer, being saved with antibiotics and other medical treatments. In any case, it will be an unprecedented number of elderly people in this nation."

The goal of LPI research, Hagen said, is to address issues of "healthspan," not just lifespan -- meaning the ability to live a long life with comparatively good health and vigor, free of degenerative disease, until very near death. The best mechanisms to accomplish that, scientists say, have everything to do with diet, exercise, healthy lifestyle habits and micronutrient intake.

At the moment, Hagen said, that's not the way things appear to be headed -- diabetes is skyrocketing, about 50 percent of people over 65 have high blood pressure, heart disease often leads to permanent disability, and almost half of the elderly people in America have malnutrition that is easily preventable.

No single intervention can address all of these issues, Hagen said, but one that scientists keep coming back to is lipoic acid.

"Our studies have shown that mice supplemented with lipoic acid have a cognitive ability, behavior, and genetic expression of almost 100 detoxification and antioxidant genes that are comparable to that of young animals," Hagen said. "They aren't just living longer, they are living better -- and that's the goal we're after."

What the OSU researchers now believe is that the role of lipoic acid is not so much a direct one to benefit cells, but rather an indirect aid that "kick starts" declining function in cells and helps them recover the functions that came more easily and naturally in young animals.

In various effects, lipoic acid appears to help restore a cellular "signaling" process that tends to break down in older blood vessels. It reduces mitochondrial decay in cells, which is closely linked to the symptoms of aging. With age, glutathione levels naturally decline, making older animals more susceptible to both free radicals and other environmental toxins -- but lipoic acid can restore glutathione function to near normal. And the expression and function of other genes seems to come back to life.

"We never really expected such a surprising range of benefits from one compound," Hagen said. "This is really unprecedented, and we're pretty excited about it."

Many other presentations have been made at this conference on the role of diet, lifestyle and micronutrients in health and degenerative disease, including cancer, heart disease, neurological diseases and aging.

Oregon State U (2007, May 18). *Lipoic Acid Explored As Anti-aging Compound*. *ScienceDaily*.

(2)

IUBMB Life. 2008 Apr 11

Is alpha-lipoic acid a scavenger of reactive oxygen species in vivo? Evidence for its initiation of stress signaling pathways that promote endogenous antioxidant capacity.

Petersen Shay K, **Moreau RF**, **Smith EJ**, **Hagen TM**.
Linus Pauling Institute, Oregon State University, Corvallis, OR, USA.

The chemical reduction and oxidation (redox) properties of alpha-lipoic acid (LA) suggest that it may have potent antioxidant potential. A significant number of studies now show that LA and its reduced form, dihydrolipoic acid (DHLA), directly scavenge reactive oxygen species (ROS) and reactive nitrogen species (RNS) species and protect cells against a host of insults where oxidative stress is part of the underlying etiology. However, owing to its limited and transient accumulation in tissues following oral intake, the efficacy of nonprotein-bound LA to function as a physiological antioxidant has been questioned. Herein, we review the evidence that the micronutrient functions of LA may be more as an effector of important cellular stress response pathways that ultimately influence endogenous cellular antioxidant levels and reduce proinflammatory mechanisms. This would promote a sustained improvement in cellular resistance to pathologies where oxidative stress is involved, which would not be forthcoming if LA solely acted as a transient ROS scavenger.

(3)

Rev Invest Clin. 2008 Jan-Feb;60(1):58-67.

[Alpha-tocopherol and alpha-lipoic acid. An antioxidant synergy with potential for preventive medicine]

González-Pérez O, **Moy-López NA**, **Guzmán-Muñiz J**.
Laboratorio de Neurociencias, Facultad de Psicología, Universidad de Colima. osglez@ucol.mx

Reactive oxygen species (ROS) have been involved in the induction and progression of damage of many human disorders, such as: heart infarction, cerebral ischemia, diabetic neuropathy, Alzheimer's disease,

etc. In several studies, the synergism between alpha-lipoic acid and vitamin E has been described and potent antioxidant effects can be obtained when both antioxidants are simultaneously used. This review highlights recent findings showing that the combination of alpha-lipoic acid plus vitamin E effectively reduces oxidative damage in brain and cardiac ischemia as well as in other pathological events related to ROS increasing. These antioxidants are present in a broad variety of foods, are also available in several dietary supplements and their side effects are very rare. Therefore, alpha-lipoic acid and vitamin E may play an important role in clinical preventive medicine and human nutrition.

(4)

Pharmacol Ther. 2007 Jan;113(1):154-64.

Lipoic acid as a novel treatment for Alzheimer's disease and related dementias.

Holmquist L, **Stuchbury G**, **Berbaum K**, **Muscat S**, **Young S**, **Hager K**, **Engel J**, **Münch G**.

Department of Biochemistry and Molecular Biology and Comparative Genomics Centre, School of Pharmacy and Molecular Sciences, James Cook University, Townsville, Australia.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that destroys patient memory and cognition, communication ability with the social environment and the ability to carry out daily activities. Despite extensive research into the pathogenesis of AD, a neuroprotective treatment - particularly for the early stages of disease - remains unavailable for clinical use. In this review, we advance the suggestion that lipoic acid (LA) may fulfil this therapeutic need. A naturally occurring precursor of an essential cofactor for mitochondrial enzymes, including pyruvate dehydrogenase (PDH) and alpha-ketoglutarate dehydrogenase (KGDH), LA has been shown to have a variety of properties which can interfere with pathogenic principles of AD. For example, LA increases acetylcholine (ACh) production by activation of choline acetyltransferase and increases glucose uptake, thus supplying more acetyl-CoA for the production of ACh. LA chelates redox-active transition metals, thus inhibiting the formation of hydroxyl radicals and also scavenges reactive oxygen species (ROS), thereby increasing the levels of reduced

glutathione. Via the same mechanisms, downregulation redox-sensitive inflammatory processes is also achieved. Furthermore, LA can scavenge lipid peroxidation products such as hydroxynonenal and acrolein. The reduced form of LA, dihydrolipoic acid (DHLA), is the active compound responsible for most of these beneficial effects. R-alpha-LA can be applied instead of DHLA, as it is reduced by mitochondrial lipoamide dehydrogenase, a part of the PDH complex. In this review, the properties of LA are explored with particular emphasis on how this agent, particularly the R-alpha-enantiomer, may be effective to treat AD and related dementias.

(5)

Pharmacol Rep. 2005 Sep-Oct;57(5):570-7.

Lipoic acid - the drug of the future?

Bilska A, **Włodek L**.
Institute of Medical Biochemistry, Medical College, Jagiellonian University, Kopernika 7, PL 31-034 Kraków, Poland.

Numerous experimental and clinical studies proved efficiency of treatment with lipoic acid-containing drugs in diseases, in which pro- and antioxidant balance is disrupted (diabetes, neurodegenerative diseases, acquired immune deficiency syndrome (AIDS), tumors, etc.). Efficiency of lipoate has been attributed to unique antioxidant properties of lipoate/dihydrolipoate system, its reactive oxygen species (ROS) scavenging ability and significant effect on the tissue concentrations of reduced forms of other antioxidants, including one of the most powerful, glutathione (thus lipoate is called an antioxidant of antioxidants). Moreover, analysis of literature data suggests participation of lipoic acid in processes of cell growth and differentiation. This fact can be crucial to clinical practice, however, this problem requires further studies.

(6)

J Nutr. 2003 Nov;133(11):3327-30.

Alpha-lipoic acid and cardiovascular disease.

Wollin SD, **Jones PJ**.
School of Dietetics and Human Nutrition, McGill University, Ste-Anne-de-Bellevue, Québec, Canada.

Alpha-lipoic acid (ALA) has been identified as a powerful antioxidant found naturally in our diets, but appears to have increased functional capacity when given as a supplement in the form of a natural or synthetic isolate. ALA and its active reduced counterpart, dihydrolipoic acid (DHLA), have been shown to combat oxidative stress by quenching a variety of reactive oxygen species (ROS). Because this molecule is soluble in both aqueous and lipid portions of the cell, its biological functions are not limited solely to one environment. In addition to ROS scavenging, ALA has been shown to be involved in the recycling of other antioxidants in the body including vitamins C and E and glutathione. Not only have the antioxidant qualities of this molecule been studied, but there are also several reports pertaining to its blood lipid modulating characteristics, protection against LDL oxidation and modulation of hypertension. Therefore, ALA represents a possible protective agent against risk factors of cardiovascular disease (CVD). The objective of this review is to examine the literature pertaining to ALA in relation to CVD and describe the most powerful actions and potential uses of this naturally occurring antioxidant. Despite the numerous studies on ALA, many questions remain relating to the use of ALA as a supplement. There is no consensus on dosage, dose frequency, form of administration, and/or preferred form of ALA. However, collectively the literature increases our understanding of the potential uses for supplementation with ALA and identifies key areas for future research.

(7)

Arch Environ Health. 2003 Aug;58(8):528-32.

Lipoic acid as a potential first agent for protection from mycotoxins and treatment of mycotoxicosis.

Rogers SA.
Northeast Center for Environmental Medicine, Sarasota, Florida, USA.

Mycotoxins--toxic substances produced by fungi or molds--are ubiquitous in the environment and are capable of damaging

multiple biochemical mechanisms, resulting in a variety of human symptoms referred to collectively as "mycotoxicosis." In fact, mycotoxins mimic multiple xenobiotics, not only with respect to their ultimate damage, but also in their routes of detoxification. This suggests potential therapeutic options for the challenging treatment of mycotoxicosis. In this brief review, the author examines the use of lipoic acid as an example of an inexpensive and available nutrient that has been shown to protect against, or reverse, the adverse health effects of mycotoxins.

(8)

Toxicol Appl Pharmacol. 2002 Jul 1;182(1):84-90.

Antioxidant and prooxidant activities of alpha-lipoic acid and dihydrolipoic acid.

Moini H, **Packer L**, **Saris NE**.
Department of Applied Chemistry and Microbiology, PB 56 Viikki Biocenter, FIN-00014, University of Helsinki, Helsinki, Finland. hmoini@usc.edu

Reactive oxygen (ROS) and nitrogen oxide (RNOS) species are produced as by-products of oxidative metabolism. A major function for ROS and RNOS is immunological host defense. Recent evidence indicate that ROS and RNOS may also function as signaling molecules. However, high levels of ROS and RNOS have been considered to potentially damage cellular macromolecules and have been implicated in the pathogenesis and progression of various chronic diseases. alpha-Lipoic acid and dihydrolipoic acid exhibit direct free radical scavenging properties and as a redox couple, with a low redox potential of -0.32 V, is a strong reductant. Several studies provided evidence that alpha-lipoic acid supplementation decreases oxidative stress and restores reduced levels of other antioxidants in vivo. However, there is also evidence indicating that alpha-lipoic acid and dihydrolipoic acid may exert prooxidant properties in vitro. alpha-Lipoic acid and dihydrolipoic acid were shown to promote the mitochondrial permeability transition in permeabilized hepatocytes and isolated rat liver mitochondria. Dihydrolipoic acid also stimulated superoxide anion production in rat liver mitochondria and submitochondrial particles. alpha-Lipoic acid was recently shown to stimulate glucose uptake into 3T3-L1

adipocytes by increasing intracellular oxidant levels and/or facilitating insulin receptor autophosphorylation presumably by oxidation of critical thiol groups present in the insulin receptor beta-subunit. Whether alpha-lipoic acid and/or dihydrolipoic acid-induced oxidative protein modifications contribute to their versatile effects observed in vivo warrants further investigation.

(9)

Diabetologia. 1999 Aug;42(8):949-57.

Lipoic acid protects against oxidative stress induced impairment in insulin stimulation of protein kinase B and glucose transport in 3T3-L1 adipocytes.

Rudich A, **Tirosh A**, **Potashnik R**, **Khamaisi M**, **Bashan N**.
S. Daniel Abraham International Centre for Health and Nutrition, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

AIMS/HYPOTHESIS: Oxidative stress has been shown to impair insulin-stimulated glucose transporter 4 translocation in 3T3-L1 adipocytes. This study explores the potential of the antioxidant lipoic acid to protect the cells against the induction of insulin resistance when given before exposure to oxidative stress. METHODS: 3T3-L1 were exposed for 16 h to lipoic acid after which cells were exposed for 2 h to continuous production of H2O2 by adding glucose oxidase to the culture medium. RESULTS: These conditions resulted in a 50-70% reduction in insulin-stimulated glucose transport activity associated with a decrease in reduced glutathione content from 37.4 +/- 3.1 to 26.4 +/- 4.9 nmol/mg protein, ($p < 0.005$). Lipoic acid pretreatment increased insulin-stimulated glucose transport following oxidative stress, reaching 84.8 +/- 4.4% of the control, associated with an increase in reduced glutathione content. Oxidation impaired the 4.89 +/- 0.36-fold insulin-stimulated increase in glucose transporter 4 content in plasma membrane lawns of control cells. Lipoic acid pretreatment was, however, associated with preserved insulin-induced glucose transporter 4 translocation in cells exposed to oxidation, yielding 80% of its content in controls. Although tyrosine phosphorylation patterns were not affected by lipoic acid pretreatment, insulin-stimulated protein kinase B/Akt serine 473 phosphorylation and activity

were considerably impaired by oxidation but protected by lipoic acid pretreatment. A protective effect was not observed with either troglitazone, its isolated vitamin E moiety, or with vitamin C. CONCLUSION/INTERPRETATION: This study shows the ability of lipoic acid to provide partial protection against the impaired insulin-stimulated glucose transporter 4 translocation and protein kinase B/Akt activation induced by oxidative stress, potentially by its capacity to maintain intracellular redox state.

(10)

Gen Pharmacol. 1997 Sep;29(3):315-31.

The pharmacology of the antioxidant lipoic acid.

Biewenga GP, **Haenen GR**, **Bast A**.
Leiden/Amsterdam Center for Drug Research, Vrije Universiteit, Department of Pharmacochemistry, The Netherlands.

1. Lipoic acid is an example of an existing drug whose therapeutic effect has been related to its antioxidant activity. 2. Antioxidant activity is a relative concept: it depends on the kind of oxidative stress and the kind of oxidizable substrate (e.g., DNA, lipid, protein). 3. In vitro, the final antioxidant activity of lipoic acid is determined by its concentration and by its antioxidant properties. Four antioxidant properties of lipoic acid have been studied: its metal chelating capacity, its ability to scavenge reactive oxygen species (ROS), its ability to regenerate endogenous antioxidants and its ability to repair oxidative damage. 4. Dihydrolipoic acid (DHLA), formed by reduction of lipoic acid, has more antioxidant properties than does lipoic acid. Both DHLA and lipoic acid have metal-chelating capacity and scavenge ROS, whereas only DHLA is able to regenerate endogenous antioxidants and to repair oxidative damage. 5. As a metal chelator, lipoic acid was shown to provide antioxidant activity by chelating Fe2+ and Cu2+; DHLA can do so by chelating Cd2+. 6. As scavengers of ROS, lipoic acid and DHLA display antioxidant activity in most experiments, whereas, in particular cases, pro-oxidant activity has been observed. However, lipoic acid can act as an antioxidant against the pro-oxidant activity produced by DHLA. 7. DHLA has the capacity to regenerate the endogenous antioxidants vitamin E, vitamin C and

glutathione. 8. DHLA can provide peptide methionine sulfoxide reductase with reducing equivalents. This enhances the repair of oxidatively damaged proteins such as alpha-1 antiprotease. 9. Through the lipoamide dehydrogenase-dependent reduction of lipoic acid, the cell can draw on its NADH pool for antioxidant activity additionally to its NADPH pool, which is usually consumed during oxidative stress. 10. Within drug-related antioxidant pharmacology, lipoic acid is a model compound that enhances understanding of the mode of action of antioxidants in drug therapy.

(11)

Free Radic Biol Med. 1995 Aug;19(2):227-50.

alpha-Lipoic acid as a biological antioxidant.

Packer L, **Witt EH**, **Tritschler HJ**.
Department of Molecular & Cell Biology, University of California, Berkeley 94720, USA.

alpha-Lipoic acid, which plays an essential role in mitochondrial dehydrogenase reactions, has recently gained considerable attention as an antioxidant. Lipoate, or its reduced form, dihydrolipoate, reacts with reactive oxygen species such as superoxide radicals, hydroxyl radicals, hypochlorous acid, peroxyl radicals, and singlet oxygen. It also protects membranes by interacting with vitamin C and glutathione, which may in turn recycle vitamin E. In addition to its antioxidant activities, dihydrolipoate may exert prooxidant actions through reduction of iron. alpha-Lipoic acid administration has been shown to be beneficial in a number of oxidative stress models such as ischemia-reperfusion injury, diabetes (both alpha-lipoic acid and dihydrolipoic acid exhibit hydrophobic binding to proteins such as albumin, which can prevent glycation reactions), cataract formation, HIV activation, neurodegeneration, and radiation injury. Furthermore, lipoate can function as a redox regulator of proteins such as myoglobin, prolactin, thioredoxin and NF-kappa B transcription factor. We review the properties of lipoate in terms of (1) reactions with reactive oxygen species; (2) interactions with other antioxidants; (3) beneficial effects in oxidative stress models or clinical conditions.

**CAUTION-DISCLAIMER: This information is for informational and educational purposes only. It has not been reviewed or approved by the Food & Drug Administration. It does not constitute competent, qualified professional advice for the diagnosis, treatment, cure, or prevention of any human disease or disorder. Consult your family healthcare professional before taking any products or other actions, based on this information, especially if you are currently taking prescription medication or you have been or are currently being treated for a serious illness, disease, or medical condition.*