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ABSTRACTS

Sesame

USE OF FOLK REMEDIES AMONG PATIENTS IN KARACHI PAKISTAN.

BACKGROUND: The concept that food is medicine is being practiced in certain parts of the world, with positive outcomes on health of the population. We have such practice in Pakistan but it needs to be brought in line with the available scientific evidence. **METHODS:** The study was conducted on 270 patients, visiting the Family Practice Center, the Aga Khan University, Karachi. A questionnaire was used to collect information on the demographic profile, and the use of folk remedies for medicinal uses. **RESULTS:** Substantial use of folk remedies for different medical conditions has been documented. The remedies included cinnamon, ginger, cloves, cordimon, sesame oil, poppy seeds, honey, lemon, table salt, eggs and curd. The medical conditions in which folk remedies are used in respondents' view, include conditions such as common cold, cough and flu to more serious conditions such as asthma, jaundice and heat stroke. **CONCLUSIONS:** We have found a substantial use of folk remedies for treatment of medical conditions. There is a need to organize their use on scientific lines.

J Ayub Med Coll Abbottabad. 2003 Apr-Jun;15(2):31-3

NITRIC OXIDE NEUROTOXICITY IN NEURODEGENERATIVE DISEASES.

Nitric oxide (nitrogen monoxide; NO) is a simple molecule with diverse biological functions. NO and related reactive nitrogen oxide species (RNOS) mediate intricate physiological and pathophysiological effects in the central nervous system. Depending on environmental conditions, NO and RNOS can initiate and mediate neuroprotection or neurotoxicity either exclusively or synergistically with other effectors. The focus of this review is limited to the neuroprotectant/neurotoxic role of NO in Acquired Immune Deficiency Syndrome (AIDS) Dementia Complex (aka HIV--Associated Dementia; HAD) Amyotrophic Lateral Sclerosis (aka Lou Gehrig's Disease), Alzheimer's Disease, Huntington's Disease, Multiple Sclerosis and Parkinson's Disease. This review will shed light on the question: "How important is NO in neurodegenerative diseases?"

Front Biosci. 2004 Jan 01;9:763-76

THE EFFECT OF ALPHA- AND GAMMA-TOCOPHEROL AND THEIR CARBOXYETHYL HYDROXYCHROMAN METABOLITES ON PROSTATE CANCER CELL PROLIFERATION.

It is known that gamma-tocopherol inhibits human prostate cancer cell proliferation via down-regulation of cyclin-related signalling but tocopherol and tocotrienol metabolites with a shortened phytol chain, carboxyethyl hydroxychromans, were not previously investigated as anti-proliferative agents. In this study, the effect of the two main tocopherols, namely, alpha-tocopherol and gamma-tocopherol, and their corresponding metabolites (alpha- and gamma-carboxyethyl hydroxychromans) was studied on proliferation and cyclin D1 expression of the prostate cancer cell line PC-3. The hydrosoluble vitamin E analogues Trolox and alpha-tocopherol succinate were also tested. The most effective inhibitors of PC-3 proliferation were gamma-tocopherol and gamma-carboxyethyl hydroxychroman. Their effect was discernable at 1 microM and reached a plateau at concentrations \geq 10 microM with maximal inhibition values ranging between 70 and 82%. alpha-Tocopherol, alpha-carboxyethyl hydroxychroman, and the analogue Trolox were much less effective; a weak effect was observed for concentrations \leq 10 microM and a maximal inhibition of less than 45% was found at 50 microM concentration. PC-3 cells showed higher inhibition, particularly by the gamma derivatives, than HTB-82 and HECV cells. Tocopherols and carboxyethyl hydroxychromans exerted an inhibitory effect on cyclin D1 expression parallel to the retardation of cell growth. gamma-Carboxyethyl hydroxychroman and gamma-tocopherol showed effects also upstream of the cyclin modulation. Furthermore, the inhibition of cyclin D1 expression by gamma-carboxyethyl hydroxychroman was competed for by alpha-carboxyethyl hydroxychroman. In conclusion, this study shows that carboxyethyl hydroxychroman metabolites are as effective as their vitamin precursors to inhibit PC-3 growth by specific down-regulation of cyclin expression, with the gamma forms being the most effective ones. Although the inhibition of PC-3 cell growth and diminution of cyclin expression are clearly visible, more subtle mechanistic effects of tocopherols and their corresponding carboxyethyl hydroxychroman metabolites deserve further investigations.

Arch Biochem Biophys. 2004 Mar 1;423(1):97-102

INTERACTION OF DIETARY FAT TYPES AND SESAMIN ON HEPATIC FATTY ACID OXIDATION IN RATS.

The interaction of sesamin, one of the most abundant lignans in sesame seed, and types of dietary fats affecting hepatic fatty acid oxidation was examined in rats. Rats were fed purified experimental diets supplemented with 0% or 0.2% sesamin (1:1 mixture of sesamin and episesamin), and containing 8% of either palm, safflower or fish oil for 15 days. Among the groups fed sesamin-free diets, the activity of various fatty acid oxidation enzymes was higher in rats fed fish oil than in those fed palm and safflower oils. Dietary sesamin increased enzyme activities in all groups of rats given different fats. The extent of the increase depended on dietary fat type, and a diet containing sesamin and fish oil in combination appeared to increase many of these parameters synergistically. In particular, the peroxisomal palmitoyl-CoA oxidation rate and acyl-CoA oxidase activity levels were much higher in rats fed sesamin and fish oil in combination than in animals fed sesamin and palm or safflower oil in combination. Analyses of mRNA levels revealed that a diet containing sesamin and fish oil increased the gene expression of various peroxisomal fatty acid oxidation enzymes and PEX11alpha, a peroxisomal membrane protein, in a synergistic manner while it increased the gene expression of mitochondrial fatty acid oxidation enzymes and microsomal cytochrome P-450 IV A1 in an additive manner. It was concluded that a diet containing sesamin and fish oil in combination synergistically increased hepatic fatty acid oxidation primarily through up-regulation of the gene expression of peroxisomal fatty acid oxidation enzymes.

Biochim Biophys Acta. 2004 Jun 1;1682(1-3):80-91

IMPACT OF SESAME OIL ON NIFEDIPINE IN MODULATING OXIDATIVE STRESS AND ELECTROLYTES IN HYPERTENSIVE PATIENTS.

The aim of the study was to investigate the effect of sesame oil as sole edible oil in hypertensive patients who were on medication with nifedipine, a calcium channel blocker. A sample of 396 hypertensive patients (aged 58 +/- 3.8 years; 215 men and 181 women) participated in this study. Forty patients were treated only with nifedipine while three hundred and fifty six patients were treated with nifedipine and instructed to use sesame oil in place of other edible oils for 60 days. The consumption of sesame oil remarkably reduced the (systolic and diastolic blood pressure from 166 +/- 4.2 and 101 +/- 3.1 to 134.2 +/- 3.4 and 84.6 +/- 3.0 respectively) blood pressure. The dosage of the drug also reduced, as there was a fall in blood pressure during sesame oil consumption. Plasma levels of sodium decreased while potassium and chloride increased significantly. Lipid peroxidation (thiobarbituric acid reactive substances) level significantly decreased while activities of enzymic (superoxide dismutase, glutathione peroxidase and catalase) and concentrations of non-enzymic antioxidants (vitamin C, vitamin E, beta-carotene and reduced glutathione) increased in nifedipine - sesame oil group. Nifedipine group showed a significant reduction in blood pressure, lipid peroxidation and improvement in reduced glutathione, however, the values are significantly lower than nifedipine - sesame oil group. These results suggest that dietary substitution of sesame oil, in nifedipine-taking hypertensive patients, has an additive effect in the reduction of blood pressure and plays an important role in the modulation of electrolytes and in the reduction of lipid peroxidation and elevation of antioxidants.

Asia Pac J Clin Nutr. 2004;13(Suppl):S107

DIETARY MANIPULATIONS OF BODY FAT-REDUCING POTENTIAL OF CONJUGATED LINOLEIC ACID IN RATS.

To study whether the body fat-reducing potential of conjugated linoleic acid (CLA) could be increased through dietary manipulations, the effects of the combination of CLA with different proteins, fats, and sesamin were examined in rats. Male rats were fed diets containing 1% CLA or linoleic acid (LA) in combination with different proteins (20% of casein or soybean protein), fats (7% perilla oil or soybean oil) and 0.2% sesamin (SES) for 3 or 4 weeks. When the dietary fat source was soybean oil, CLA, as compared with LA, significantly reduced weights of epididymal and perirenal adipose tissues, irrespective of the dietary protein sources. However, the highest reducing effect was shown when soybean protein was given as a protein source. SES stimulated the reduction of epididymal and perirenal adipose tissue weights in both protein diets. In contrast, CLA increased the weight of brown adipose tissue, and SES further increased it in combination with soybean oil but not with perilla oil. No effect of dietary manipulation was observed on serum leptin and TNF-alpha levels. Thus, the body fat-reducing potential of CLA can be increased by an appropriate combination with food factors that may stimulate fatty acid beta-oxidation.

Biosci Biotechnol Biochem. 2001 Nov;65(11):2535-4

ABSTRACTS

Arrhythmia

ARE OMEGA-3 FATTY ACIDS THE MOST IMPORTANT NUTRITIONAL MODULATORS OF CORONARY HEART DISEASE RISK?

With each passing year, the evidence linking an increased risk for coronary heart disease (CHD) death with a chronic dietary deficiency in long-chain omega-3 (n-3) fatty acids (FAs) grows stronger. Recently, a federally mandated evidence-based review in the United States concluded that n-3 FAs, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have clear cardioprotective effects, and national and international expert panels and health organizations have begun to call for increased EPA and DHA intakes. Consumption of between 450 and 1000 mg/d is recommended for those without and with known CHD, respectively. Based on animal and isolated cell studies, these FAs were presumed to have antiarrhythmic effects. The first direct evidence for this in humans was recently published, as were new data linking low n-3 FA intakes with risk for developing atrial fibrillation. The strength of the n-3 story has now led to a proposal that blood levels of EPA plus DHA be considered a new, modifiable, and clinically relevant risk factor for death from CHD.

Curr Atheroscler Rep. 2004 Nov;6(6):447-52

ATORVASTATIN DECREASES THE COENZYME Q10 LEVEL IN THE BLOOD OF PATIENTS AT RISK FOR CARDIOVASCULAR DISEASE AND STROKE.

BACKGROUND: Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are widely used for the treatment of hypercholesterolemia and coronary heart disease and for the prevention of stroke. There have been various adverse effects, most commonly affecting muscle and ranging from myalgia to rhabdomyolysis. These adverse effects may be due to a coenzyme Q (10) (CoQ(10)) deficiency because inhibition of cholesterol biosynthesis also inhibits the synthesis of CoQ(10). **OBJECTIVE:** To measure CoQ(10) levels in blood from hypercholesterolemic subjects before and after exposure to atorvastatin calcium, 80 mg/d, for 14 and 30 days. **DESIGN:** Prospective blinded study of the effects of short-term exposure to atorvastatin on blood levels of CoQ(10). **SETTING:** Stroke center at an academic tertiary care hospital. **Patients** We examined a cohort of 34 subjects eligible for statin treatment according to National Cholesterol Education Program: Adult Treatment Panel III criteria. **RESULTS:** The mean +/- SD blood concentration of CoQ(10) was 1.26 +/- 0.47 micro g/mL at baseline, and decreased to 0.62 +/- 0.39 micro g/mL after 30 days of atorvastatin therapy (P<.001). A significant decrease was already detectable after 14 days of treatment (P<.001). **CONCLUSIONS:** Even brief exposure to atorvastatin causes a marked decrease in blood CoQ(10) concentration. Widespread inhibition of CoQ(10) synthesis could explain the most commonly reported adverse effects of statins, especially exercise intolerance, myalgia, and myoglobinuria.

Arch Neurol. 2004 Jun;61(6):889-92

SYSTEMATIC REVIEW OF EFFECT OF COENZYME Q10 IN PHYSICAL EXERCISE, HYPERTENSION AND HEART FAILURE.

COENZYME Q10 IN PHYSICAL EXERCISE. We identified eleven studies in which CoQ10 was tested for an effect on exercise capacity, six showed a modest improvement in exercise capacity with CoQ10 supplementation but five showed no effect. **COENZYME Q10 IN HYPERTENSION.** We identified eight published trials of CoQ10 in hypertension. Altogether in the eight studies the mean decrease in systolic blood pressure was 16 mm Hg and in diastolic blood pressure, 10 mm Hg. Being devoid of significant side effects CoQ10 may have a role as an adjunct or alternative to conventional agents in the treatment of hypertension. **COENZYME Q10 IN HEART FAILURE.** We performed a randomised double blind placebo-controlled pilot trial of CoQ10 therapy in 35 patients with heart failure. Over 3 months, in the CoQ10 patients but not in the placebo patients there were significant improvements in symptom class and a trend towards improvements in exercise time. **META-ANALYSIS OF RANDOMISED TRIALS OF COENZYME Q10 IN HEART FAILURE.** In nine randomised trials of CoQ10 in heart failure published up to 2003 there were non-significant trends towards increased ejection fraction and reduced mortality. There were insufficient numbers of patients for meaningful results. To make more definitive conclusions regarding the effect of CoQ10 in cardiac failure we recommend a prospective, randomised trial with 200-300 patients per study group. Further trials of CoQ10 in physical exercise and in hypertension are recommended.

Biofactors. 2003;18(1-4):91-100

HAWTHORN EXTRACT FOR TREATING CHRONIC HEART FAILURE: META-ANALYSIS OF RANDOMIZED TRIALS.

The aim of this meta-analysis was to assess the evidence from rigorous clinical trials of the use of hawthorn extract to treat patients with chronic heart failure. We searched the literature using MEDLINE, EMBASE, the Cochrane Library, CINAHL, CISCOP, and AMED. Experts on and manufacturers of commercial preparations containing hawthorn extract were asked to contribute published and unpublished studies. There were no restrictions about the language of publication. Two reviewers independently performed the screening of studies, selection, validation, data extraction, and the assessment of methodological quality. To be included, studies were required to state that they were randomized, double-blind, and placebo controlled, and used hawthorn extract monoprparations. Thirteen trials met all inclusion criteria. In most of the studies, hawthorn was used as an adjunct to conventional treatment. Eight trials including 632 patients with chronic heart failure (New York Heart Association classes I to III) provided data that were suitable for meta-analysis. For the physiologic outcome of maximal workload, treatment with hawthorn extract was more beneficial than placebo (weighted mean difference, 7 Watt; 95% confidence interval [CI]: 3 to 11 Watt; $P < 0.01$; $n = 310$ patients). The pressure-heart rate product also showed a beneficial decrease (weighted mean difference, -20; 95% CI: -32 to -8 ; $n = 264$ patients) with hawthorn treatment. Symptoms such as dyspnea and fatigue improved significantly with hawthorn treatment as compared with placebo. Reported adverse events were infrequent, mild, and transient; they included nausea, dizziness, and cardiac and gastrointestinal complaints. In conclusion, these results suggest that there is a significant benefit from hawthorn extract as an adjunctive treatment for chronic heart failure.

Am J Med. 2003 Jun 1;114(8):665-74

MAGNESIUM DEFICIENCY AND SUDDEN DEATH.

A link between Mg deficiency and sudden death is suggested by a substantial number of studies published over the past three decades. Data come from epidemiologic, autopsy, clinical, and animal studies. They suggest that: (1) Sudden death is common in areas where community water supplies are Mg-deficient. (2) Myocardial Mg content is low in people who die of sudden death. (3) Cardiac arrhythmias and coronary artery vasospasm can be caused by Mg deficiency and (4) Intravenous Mg reduces the risk of arrhythmia and death immediately after acute myocardial infarction. Because of these data, Mg supplementation has been proposed as a possible method of reducing the risk of sudden death. Suggested ways of supplementing Mg include public education to change dietary habits, addition of Mg to community water supplies, fortification of foods, and oral supplementation. Despite the substantial number of studies linking Mg deficiency with sudden death, no prospective studies have yet investigated whether large-scale Mg supplementation is useful for the primary prevention of sudden death.

Am Heart J. 1992 Aug;124(2):544-9

EARLY PROTECTION AGAINST SUDDEN DEATH BY N-3 POLYUNSATURATED FATTY ACIDS AFTER MYOCARDIAL INFARCTION: TIME-COURSE ANALYSIS OF THE RESULTS OF THE GRUPPO ITALIANO PER LO STUDIO DELLA SOPRAVVIVENZA NELL'INFARTO MIOCARDICO (GISSI)-PREVENZIONE.

BACKGROUND: Our purpose was to assess the time course of the benefit of n-3 polyunsaturated fatty acids (PUFAs) on mortality documented by the GISSI-Prevenzione trial in patients surviving a recent (<3 months) myocardial infarction. **METHODS AND RESULTS:** In this study, 11 323 patients were randomly assigned to supplements of n-3 PUFAs, vitamin E (300 mg/d), both, or no treatment (control) on top of optimal pharmacological treatment and lifestyle advice. Intention-to-treat analysis adjusted for interaction between treatments was carried out. Early efficacy of n-3 PUFA treatment for total, cardiovascular, cardiac, coronary, and sudden death; nonfatal myocardial infarction; total coronary heart disease; and cerebrovascular events was assessed by right-censoring follow-up data 12 times from the first month after randomization up to 12 months. Survival curves for n-3 PUFA treatment diverged early after randomization, and total mortality was significantly lowered after 3 months of treatment (relative risk [RR] 0.59; 95% CI 0.36 to 0.97; $P=0.037$). The reduction in risk of sudden death was specifically relevant and statistically significant already at 4 months (RR 0.47; 95% CI 0.219 to 0.995; $P=0.048$). A similarly significant, although delayed, pattern after 6 to 8 months of treatment was observed for cardiovascular, cardiac, and coronary deaths. **CONCLUSIONS:** The early effect of low-dose (1 g/d) n-3 PUFAs on total mortality and sudden death supports the hypothesis of an antiarrhythmic effect of this drug. Such a result is consistent with the wealth of evidence coming from laboratory experiments on isolated myocytes, animal models, and epidemiological and clinical studies.

Circulation. 2002 Apr 23;105(16):1897-903

TERMINATION OF ASYNCHRONOUS CONTRACTILE ACTIVITY IN RAT ATRIAL MYOCYTES BY N-3 POLYUNSATURATED FATTY ACIDS.

A protective effect of the n-3 polyunsaturated fatty acids (PUFAs) in preventing ventricular fibrillation in experimental animals and cultured cardiomyocytes has been demonstrated in a number of studies. In this study, a possible role for the n-3 PUFAs in the treatment of atrial fibrillation (AF) was investigated at the cellular level using atrial myocytes isolated from young adult rats as the experimental model. Electrically-stimulated, synchronously-contracting myocytes were induced to contract asynchronously by the addition of 10 microM isoproterenol. Asynchronous contractile activity was reduced following acute addition of the n-3 PUFAs docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) at 10 microM, compared with no fatty acid addition (from 99.0+/-

1.0% to 30.7 \pm 5.2% ($p < 0.05$) for DHA and 23.8 \pm 2.8% ($p < 0.01$) for EPA), while the saturated fatty acid, docosanoic acid (DA) and the methyl ester of DHA (DHA m.e.) did not exert a significant effect on asynchronous contractile activity. Asynchronous contractile activity was also reduced to 1.7 \pm 1.7% in the presence of the membrane fluidising agent, benzyl alcohol ($p < 0.001$ vs no fatty acid addition). Cell membrane fluidity was determined by steady state fluorescence anisotropy using the fluorescent probe, TMAP-DPH. Addition of DHA, EPA or benzyl alcohol significantly increased sarcolemmal membrane fluidity (decreased anisotropy, $r(ss)$) of atrial myocytes compared with no addition of fatty acid (control) (from $r(ss) = 0.203 \pm 0.004$ to 0.159 \pm 0.004 ($p < 0.01$) for DHA, 0.166 \pm 0.001 ($p < 0.01$) for EPA and 0.186 \pm 0.003 ($p < 0.05$) for benzyl alcohol, while DA and DHA m.e. were without effect. It is concluded that the n-3 PUFAs exert anti-asynchronous effects in rat atrial myocytes by a mechanism which may involve changes in membrane fluidity.

Mol Cell Biochem. 2000 Mar;206(1-2):33-41

CONCISE REVIEW OF ATRIAL FIBRILLATION: TREATMENT UPDATE CONSIDERATIONS IN LIGHT OF AFFIRM AND RACE.

Atrial fibrillation (AF) is the most common clinically significant arrhythmia seen by clinicians. Prevalence is as high as 9.0% in patients aged ≥ 80 years, and incidence is projected to be more than 5.6 million patients in the U.S. by 2050. Recently, new trials have challenged the traditional belief that rhythm control is inherently superior to rate control in these patients. This article reviews the basic tenets of treatment for AF and discusses how new trial data integrate into these protocols. A concise treatment algorithm is provided and new and upcoming more aggressive interventional treatment options are discussed. This review is designed to help the general practitioner decide how to treat patients in the outpatient setting, evaluate which patients should be hospitalized for management, and which patients should be referred to a cardiologist.

Clin Cardiol. 2004 Sep;27(9):495-500

ABSTRACTS**Alpha Lipoic****DIHYDROLIPOIC ACID INHIBITS 15-LIPOXYGENASE-DEPENDENT LIPID PEROXIDATION.**

The potential antioxidant effects of the hydrophobic therapeutic agent lipoic acid (LA) and of its reduced form dihydrolipoic acid (DHLA) on the peroxidation of either linoleic acid or human non-HDL fraction catalyzed by soybean 15-lipoxygenase (SLO) and rabbit reticulocyte 15-lipoxygenase (RR15-LOX) were investigated. DHLA, but not LA, did inhibit SLO-dependent lipid peroxidation, showing an IC(50) of 15 microM with linoleic acid and 5 microM with the non-HDL fraction. In specific experiments performed with linoleic acid, inhibition of SLO activity by DHLA was irreversible and of a complete, noncompetitive type. In comparison with DHLA, the well-known lipoxygenase inhibitor nordihydroguaiaretic acid and the nonspecific iron reductant sodium dithionite inhibited SLO-dependent linoleic acid peroxidation with an IC(50) of 4 and 100 microM, respectively, while the hydrophilic thiol N-acetylcysteine, albeit possessing iron-reducing and radical-scavenging properties, was ineffective. Remarkably, DHLA, but not LA, was also able to inhibit the peroxidation of linoleic acid and of the non-HDL fraction catalyzed by RR15-LOX with an IC(50) of, respectively, 10 and 5 microM. Finally, DHLA, but once again not LA, could readily reduce simple ferric ions and scavenge efficiently the stable free radical 1,1-diphenyl-2-picrylhydrazyl in ethanol; DHLA was considerably less effective against 2,2'-azobis(2-amidinopropane) dihydrochloride-mediated, peroxy radical-induced non-HDL peroxidation, showing an IC(50) of 850 microM. Thus, DHLA, at therapeutically relevant concentrations, can counteract 15-lipoxygenase-dependent lipid peroxidation; this antioxidant effect may stem primarily from reduction of the active ferric 15-lipoxygenase form to the inactive ferrous state after DHLA-enzyme hydrophobic interaction and, possibly, from scavenging of fatty acid peroxy radicals formed during lipoperoxidative processes. Inhibition of 15-lipoxygenase oxidative activity by DHLA could occur in the clinical setting, eventually resulting in specific antioxidant and antiatherogenic effects.

Free Radic Biol Med . 2003 Nov 15;35(10):1203-9

PROTECTION AGAINST AMYLOID BETA PEPTIDE AND IRON/HYDROGEN PEROXIDE TOXICITY BY ALPHA LIPOIC ACID.

Current evidence supports the role of oxidative stress in the pathogenesis of neuron degeneration in Alzheimer's disease (AD). alpha-Lipoic acid (LA), an essential cofactor in mitochondrial dehydrogenase reactions, functions as an antioxidant and reduces oxidative stress in aged animals. Here, we describe the effects of LA and its reduced form, dihydrolipoic acid (DHLA), in neuron cultures treated with amyloid beta-peptide (A β 25-35) and iron/hydrogen peroxide (Fe/H₂O₂). Pretreatment of dissociated primary hippocampal cultures with LA significantly protected against A β and Fe/H₂O₂ toxicity. In contrast, concomitant treatment of cultures with LA and Fe/H₂O₂ significantly potentiated the toxicity. Decreased cell survival in cultures treated concomitantly with LA and Fe/H₂O₂ correlated with increased free radical production measured by dichlorofluorescein fluorescence. Treatment of cortical neurons with DHLA significantly protected glucose-transport against Fe/H₂O₂ or beta-mediated decreases although treatment with LA did not provide protection. These data suggest that DHLA, the reduced form of LA, significantly protects against both A β and Fe/H₂O₂ mediated toxicity. The data also suggest that concomitant exposure to LA and Fe/H₂O₂ significantly potentiates the oxidative stress. Overall, these data suggest that the oxidation state of LA is critical to its function and that in the absence of studies of LA/DHLA equilibria in human brain the use of LA as an antioxidant in disorders where there is increased Fe such as AD is of questionable efficacy.

J Alzheimers Dis . 2003 Jun;5(3):229-39

DELAYING BRAIN MITOCHONDRIAL DECAY AND AGING WITH MITOCHONDRIAL ANTIOXIDANTS AND METABOLITES.

Mitochondria decay with age due to the oxidation of lipids, proteins, RNA, and DNA. Some of this decay can be reversed in aged animals by feeding them the mitochondrial metabolites acetylcarnitine and lipoic acid. In this review, we summarize our recent studies on the effects of these mitochondrial metabolites and mitochondrial antioxidants (alpha-phenyl-N-t-butyl nitron and N-t-butyl hydroxylamine) on the age-associated mitochondrial decay of the brain of old rats, neuronal cells, and human diploid fibroblast cells. In feeding studies in old rats, these mitochondrial metabolites and antioxidants improve the age-associated decline of ambulatory activity and memory, partially restore mitochondrial structure and function, inhibit the age-associated increase of oxidative damage to lipids, proteins, and nucleic acids, elevate the levels of antioxidants, and restore the activity and substrate binding affinity of a key mitochondrial enzyme, carnitine acetyltransferase. These mitochondrial metabolites and antioxidants protect neuronal cells from neurotoxin- and oxidant-induced toxicity and oxidative damage; delay the normal senescence of human diploid fibroblast cells, and inhibit oxidant-induced acceleration of senescence. These results suggest a plausible mechanism: with age, increased oxidative damage to proteins and lipid membranes, particularly in mitochondria,

causes a deformation of structure of enzymes, with a consequent decrease of enzyme activity as well as substrate binding affinity for their substrates; an increased level of substrate restores the velocity of the reaction and restores mitochondrial function, thus delaying mitochondrial decay and aging. This loss of activity due to coenzyme or substrate binding appears to be true for a number of other enzymes as well, including mitochondrial complex III and IV.

Ann N Y Acad Sci . 2002 Apr;959:133-66

ALPHA-LIPOIC ACID AS A NEW TREATMENT OPTION FOR AZHEIMER TYPE DEMENTIA.

Oxidative stress and energy depletion are characteristic biochemical hallmarks of Alzheimer's disease (AD), thus antioxidants with positive effects on glucose metabolism such as thioctic (alpha-lipoic) acid should exert positive effects in these patients. Therefore, 600 mg alpha-lipoic acid was given daily to nine patients with AD and related dementias (receiving a standard treatment with acetylcholinesterase inhibitors) in an open study over an observation period of, on average, 337+/-80 days. The treatment led to a stabilization of cognitive functions in the study group, demonstrated by constant scores in two neuropsychological tests (mini-mental state examination: MMSE and AD assessment scale, cognitive subscale: ADAScog). Despite the fact that this study was small and not randomized, this is the first indication that treatment with alpha-lipoic acid might be a successful 'neuroprotective' therapy option for AD and related dementias.

Arch Gerontol Geriatr . 2001 Jun;32(3):275-282

AGE-ASSOCIATED MITOCHONDRIAL OXIDATIVE DECAY: IMPROVEMENT OF CARNITINE ACETYLTRANSFERASE SUBSTRATE-BINDING AFFINITY AND ACTIVITY IN BRAIN BY FEEDING OLD RATS ACETYL-L- CARNITINE AND/OR R-ALPHA -LIPOIC ACID.

We test whether the dysfunction with age of carnitine acetyltransferase (CAT), a key mitochondrial enzyme for fuel utilization, is due to decreased binding affinity for substrate and whether this substrate, fed to old rats, restores CAT activity. The kinetics of CAT were analyzed by using the brains of young and old rats and of old rats supplemented for 7 weeks with the CAT substrate acetyl-L-carnitine (ALCAR) and/or the mitochondrial antioxidant precursor R-alpha-lipoic acid (LA). Old rats, compared with young rats, showed a decrease in CAT activity and in CAT-binding affinity for both substrates, ALCAR and CoA. Feeding ALCAR or ALCAR plus LA to old rats significantly restored CAT-binding affinity for ALCAR and CoA, and CAT activity. To explore the underlying mechanism, lipid peroxidation and total iron and copper levels were assayed; all increased in old rats. Feeding old rats LA or LA plus ALCAR inhibited lipid peroxidation but did not decrease iron and copper levels. Ex vivo oxidation of young-rat brain with Fe(II) caused loss of CAT activity and binding affinity. In vitro oxidation of purified CAT with Fe(II) inactivated the enzyme but did not alter binding affinity. However, in vitro treatment of CAT with the lipid peroxidation products malondialdehyde or 4-hydroxy-nonenal caused a decrease in CAT-binding affinity and activity, thus mimicking age-related change. Preincubation of CAT with ALCAR or CoA prevented malondialdehyde-induced dysfunction. Thus, feeding old rats high levels of key mitochondrial metabolites can ameliorate oxidative damage, enzyme activity, substrate-binding affinity, and mitochondrial dysfunction.

Proc Natl Acad Sci U S A. 2002 Feb 19;99(4):1876-81

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