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Journal ABSTRACTS

Omega-3

SUPPLEMENTATION OF FISH OIL AND OLIVE OIL IN PATIENTS WITH RHEUMATOID ARTHRITIS.

OBJECTIVE: This study evaluated whether supplementation with olive oil could improve clinical and laboratory parameters of disease activity in patients who had rheumatoid arthritis and were using fish oil supplements. **METHODS:** Forty-three patients (34 female, 9 male; mean age = 49 +/- 19y) were investigated in a parallel randomized design. Patients were assigned to one of three groups. In addition to their usual medication, the first group (G1) received placebo (soy oil), the second group (G2) received fish oil omega-3 fatty acids (3 g/d), and the third group (G3) received fish oil omega-3 fatty acids (3 g/d) and 9.6 mL of olive oil. Disease activity was measured by clinical and laboratory indicators at the beginning of the study and after 12 and 24 wk. Patients' satisfaction in activities of daily living was also measured. **RESULTS:** There was a statistically significant improvement ($P < 0.05$) in G2 and G3 in relation to G1 with respect to joint pain intensity, right and left handgrip strength after 12 and 24 wk, duration of morning stiffness, onset of fatigue, Ritchie's articular index for pain joints after 24 wk, ability to bend down to pick up clothing from the floor, and getting in and out of a car after 24 wk. G3, but not G2, in relation to G1 showed additional improvements with respect to duration of morning stiffness after 12 wk, patient global assessment after 12 and 24 wk, ability to turn faucets on and off after 24 wk, and rheumatoid factor after 24 wk. In addition, G3 showed a significant improvement in patient global assessment in relation to G2 after 12 wk. **CONCLUSIONS:** Ingestion of fish oil omega-3 fatty acids relieved several clinical parameters used in the present study. However, patients showed a more precocious and accentuated improvement when fish oil supplements were used in combination with olive oil.

Nutrition. 2005 Feb;21(2):131-6

INTRAVENOUS APPLICATION OF OMEGA-3 FATTY ACIDS IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS. THE ORA-1 TRIAL. AN OPEN PILOT STUDY.

The objective of this work was to assess the therapeutic efficacy and tolerability of intravenously applied n-3-PUFA in patients with active rheumatoid arthritis (RA). Thirty-four patients with active RA [identified as having a DAS28 (disease activity score including a 28 joint count) > 4.0] were enrolled into this 5-wk open pilot study (one group design). From the time of screening (visit 0, or V0), background therapy had to remain unchanged. Patients received 2 mL/kg (= 0.1-0.2 g fish oil/kg) fish oil emulsion intravenously on 7 consecutive days (Visit 1-Visit 2, or V1-V2) in addition to their background therapy. A decrease of the DAS28 > 0.6 at day 8 (Visit 2) was the primary efficacy measure. Moreover, the DAS28 at day 35 (Visit 3, or V3), the modified Health Assessment Questionnaire, the American College of Rheumatology (ACR) response criteria (V2, V3) and the Short Form-36 (V3) were assessed. Thirty-three patients completed the trial. The mean DAS28 at V1 was 5.45; at V2, 4.51 ($P < .001$ V1-V2) and at V3, 4.73 ($P < .001$ V1-V3; V2-V3, not significantly different). Of the 34 patients, 56% achieved a reduction of the DAS28 > 0.6 at V2 (mean 1.52); 27% > 1.2 . At V3, 41% of the patients showed a DAS28 reduction > 0.6 (mean 1.06), and 36% > 1.2 . ACR 20 and 50% responses at V2 were seen in 29 and 12% of patients, respectively; at V3, the comparable values were 18 and 9%, respectively. Overall tolerability was excellent. Intravenous application of n-3-PUFA (as an add-on therapy) was considerably well tolerated and led to improvement of the disease activity status in a reasonable number of RA patients. Future trials are warranted to answer whether the intravenous application of n-3-PUFA constitutes a therapeutic option in RA patients.

Lipids. 2006 Jan;41(1):29-34

EFFICACY OF FISH OIL CONCENTRATE IN THE TREATMENT OF RHEUMATOID ARTHRITIS.

OBJECTIVE: To determine the efficacy of fish oil derived (n-3) fatty acid supplementation (3-6 capsules/day) in subjects with rheumatoid arthritis (RA) whose (n-6) fatty acid intake in the background diet was < 10 g/day, compared to olive/corn oil capsule supplement over a 15 week period. **METHODS:** A placebo controlled, double blind, randomized 15 week study to determine the effect of supplementation on clinical variables in 50 subjects with RA whose background diet was naturally low in (n-6) fatty acids. Fish oil containing 60% (n-3) fatty acids was supplemented at a rate of 40 mg/kg body weight. **RESULTS:** Analysis of 9 clinical variables indicated there was a significant difference ($p < 0.02$) between control and treatment groups. Five subjects in the treatment group and 3 in the control group met the American College of Rheumatology 20% improvement criteria. Dietary

supplementation resulted in a significant increase in eicosapentaenoic acid in plasma and monocyte lipids in the supplemented group. CONCLUSION: The findings suggest that fish oil supplementation that delivers (n-3) fatty acids at a dose of 40 mg/kg body weight/day, with dietary (n-6) fatty acid intake < 10 g/day in the background diet, results in substantial cellular incorporation of (n-3) fatty acids and improvements in clinical status in patients with RA.

J Rheumatol. 2000 Oct;27(10):2343-6

DIETARY N-3 FATS AS ADJUNCTIVE THERAPY IN A PROTOTYPIC INFLAMMATORY DISEASE: ISSUES AND OBSTACLES FOR USE IN RHEUMATOID ARTHRITIS.

Eicosanoids derived from the n-6 fatty acid, arachidonic acid, and the cytokines interleukin-1beta and tumour necrosis factor-alpha are involved in the signs and symptoms of inflammatory joint disease, as well as the cartilage degradation seen in established rheumatoid arthritis (RA). Then n-3 fatty acids in fish and fish oil can inhibit production of both eicosanoid and cytokine inflammatory mediators and therefore, have the potential to modify RA pathology. Epidemiological studies suggest that fish intake may be preventive for RA and double-blind placebo-controlled studies demonstrate that dietary fish oil can alleviate the signs and symptoms of RA. The implementation of these findings will require among other things, a range of n-3 fat enriched foods, as well as physician awareness of the possibilities for dietary n-3 fat increases to be used as adjunctive therapy in RA.

Prostaglandins Leukot Essent Fatty Acids. 2003 Jun;68(6):399-405

N-3 FATTY ACID SUPPLEMENTS IN RHEUMATOID ARTHRITIS.

Ingestion of dietary supplements of n-3 fatty acids has been consistently shown to reduce both the number of tender joints on physical examination and the amount of morning stiffness in patients with rheumatoid arthritis. In these cases, supplements were consumed daily in addition to background medications and the clinical benefits of the n-3 fatty acids were not apparent until they were consumed for > or =12 wk. It appears that a minimum daily dose of 3 g eicosapentaenoic and docosahexaenoic acids is necessary to derive the expected benefits. These doses of n-3 fatty acids are associated with significant reductions in the release of leukotriene B(4) from stimulated neutrophils and of interleukin 1 from monocytes. Both of these mediators of inflammation are thought to contribute to the inflammatory events that occur in the rheumatoid arthritis disease process. Several investigators have reported that rheumatoid arthritis patients consuming n-3 dietary supplements were able to lower or discontinue their background doses of nonsteroidal antiinflammatory drugs or disease-modifying antirheumatic drugs. Because the methods used to determine whether patients taking n-3 supplements can discontinue taking these agents are variable, confirmatory and definitive studies are needed to settle this issue. n-3 Fatty acids have virtually no reported serious toxicity in the dose range used in rheumatoid arthritis and are generally very well tolerated.

Am J Clin Nutr. 2000 Jan;71(1 Suppl):349S-51S

PATHOLOGIC INDICATORS OF DEGRADATION AND INFLAMMATION IN HUMAN OSTEOARTHROTIC CARTILAGE ARE ABROGATED BY EXPOSURE TO N-3 FATTY ACIDS.

OBJECTIVE: To determine if n-3 polyunsaturated fatty acid (PUFA) supplementation (versus treatment with n-6 polyunsaturated or other fatty acid supplements) affects the metabolism of osteoarthrotic (OA) cartilage. METHODS: The metabolic profile of human OA cartilage was determined at the time of harvest and after 24-hour exposure to n-3 PUFAs or other classes of fatty acids, followed by explant culture for 4 days in the presence or absence of interleukin-1 (IL-1). Parameters measured were glycosaminoglycan release, aggrecanase and matrix metalloproteinase (MMP) activity, and the levels of expression of messenger RNA (mRNA) for mediators of inflammation, aggrecanases, MMPs, and their natural tissue inhibitors (tissue inhibitors of metalloproteinases [TIMPs]). RESULTS: Supplementation with n-3 PUFA (but not other fatty acids) reduced, in a dose-dependent manner, the endogenous and IL-1-induced release of proteoglycan metabolites from articular cartilage explants and specifically abolished endogenous aggrecanase and collagenase proteolytic activity. Similarly, expression of mRNA for ADAMTS-4, MMP-13, and MMP-3 (but not TIMP-1, -2, or -3) was also specifically abolished with n-3 PUFA supplementation. In addition, n-3 PUFA supplementation abolished the expression of mRNA for mediators of inflammation (cyclooxygenase 2, 5-lipoxygenase, 5-lipoxygenase-activating protein, tumor necrosis factor alpha, IL-1alpha, and IL-1beta) without affecting the expression of message for several other proteins involved in normal tissue homeostasis. CONCLUSION: These studies show that the pathologic indicators manifested in human OA cartilage can be significantly altered by exposure of the cartilage to n-3 PUFA, but not to other classes of fatty acids.

Arthritis Rheum. 2002 Jun;46(6):1544-53

FAT INTAKE AND COMPOSITION OF FATTY ACIDS IN SERUM PHOSPHOLIPIDS IN A RANDOMIZED, CONTROLLED, MEDITERRANEAN DIETARY INTERVENTION STUDY ON PATIENTS WITH RHEUMATOID ARTHRITIS.

BACKGROUND: We have previously reported that rheumatoid arthritis patients, who adopted a modified Cretan Mediterranean diet, obtained a reduction in disease activity and an improvement in physical function and vitality. This shift in diet is likely to result in an altered intake of fatty acids. Therefore, the objective of the present study was to examine the dietary intake of fatty acids, as well as the fatty acid profile in serum phospholipids, during the dietary intervention study presented earlier. **RESULTS:** From baseline to the end of the study, changes in the reported consumption of various food groups were observed in the Mediterranean diet group. The change in diet resulted in a number of differences between the Mediterranean diet group and the control diet group regarding the fatty acid intake. For instance, a lower ratio of n-6 to n-3 fatty acids was observed in the Mediterranean diet group, both assessed by diet history interviews (dietary intake) and measured in serum phospholipids. Moreover, the patients in the Mediterranean diet group that showed a moderate or better clinical improvement during the study (diet responders), had a higher reported intake of n-3 fatty acids and a lower ratio of n-6 to n-3 fatty acids compared to the patients with minor or no improvement. Also the fatty acid profile in serum phospholipids differed in part between the diet responders and the diet non-responders. **CONCLUSION:** The changes in the fatty acid profile, indicated both by dietary assessments and through fatty acids in s-phospholipids may, at least in part, explain the beneficial effects of the Cretan Mediterranean diet that we have presented earlier.

Nutr Metab (Lond). 2005 Oct 10;2:26

FISH OIL INTERACTION WITH WARFARIN.

OBJECTIVE: To report a case of elevated international normalized ratio (INR) in a patient taking fish oil and warfarin. **CASE SUMMARY:** A 67-year-old white woman had been taking warfarin for 1(1/2) years due to recurrent transient ischemic attacks. Her medical history included hypothyroidism, hyperlipidemia, osteopenia, hypertension, and coronary artery disease. She also experienced an inferior myocardial infarction in 1995 requiring angioplasty, surgical repair of her femoral artery in 1995, and hernia repair in 1996. This patient has her INR checked in the anticoagulation clinic and is followed monthly by the clinical pharmacist. Prior to the interaction, her INR was therapeutic for 5 months while she was taking warfarin 1.5 mg/d. The patient admitted to doubling her fish oil dose from 1000 to 2000 mg/d. Without dietary, lifestyle, or medication changes, the INR increased from 2.8 to 4.3 within 1 month. The INR decreased to 1.6 one week after subsequent fish oil reduction, necessitating a return to the original warfarin dosing regimen. **DISCUSSION:** Fish oil supplementation could have provided additional anticoagulation with warfarin therapy. Fish oil, an omega-3 polyunsaturated fatty acid, consists of eicosapentaenoic acid and docosahexaenoic acid. This fatty acid may affect platelet aggregation and/or vitamin K-dependent coagulation factors. Omega-3 fatty acids may lower thromboxane A(2) supplies within the platelet as well as decrease factor VII levels. Although controversial, this case report illustrates that fish oil can provide additive anticoagulant effects when given with warfarin. **CONCLUSIONS:** This case reveals a significant rise in INR after the dose of concomitant fish oil was doubled. Patients undergoing anticoagulation therapy with warfarin should be educated about and monitored for possible drug-herb interactions. Pharmacists can play a crucial role in identifying possible drug interactions by asking patients taking warfarin about herbal and other alternative medicine product use.

Ann Pharmacother. 2004 Jan;38(1):50-2

TEMPORAL RELATIONSHIP BETWEEN USE OF NSAIDS, INCLUDING SELECTIVE COX-2 INHIBITORS, AND CARDIOVASCULAR RISK.

BACKGROUND AND OBJECTIVE: The search for NSAIDs with less gastrointestinal toxicity led to the introduction of the selective cyclo-oxygenase-2 (COX-2) inhibitors. However, following their introduction into the market, concerns have developed regarding their safety, particularly their cardiovascular safety. The purpose of this study was to assess the cardiovascular risk (events included were myocardial infarction, stroke and myocardial infarction-related deaths) associated with long-term (>180 days of exposure) and short-term (<=180 days of exposure) use of non-selective NSAIDs, including 'preferential COX-2 inhibitors' (i.e. etodolac, nabumetone and salsalate), and selective COX-2 inhibitors. **METHODS:** A retrospective analysis of the Veterans Integrated Service Network 17 Veterans Affairs (VA) database was conducted. Medicare data and Texas Department of Health mortality data were incorporated to capture events occurring outside the VA healthcare network. Patients >=35 years of age who received celecoxib, rofecoxib, ibuprofen, etodolac and naproxen from 1 January 1999 through 31 December 2001, were included. Multivariate Cox proportional hazard models were used to analyse the relationship between cardiovascular risk and NSAID use, including selective COX-2 inhibitor use, while adjusting for various risk factors. **RESULTS:** We identified 12 188 exposure periods (11,930 persons) and 146 cardiovascular events over the entire study period. Compared with long-term ibuprofen use, long-term use of celecoxib (adjusted hazard ratio [HR] 3.64; 95% CI 1.36, 9.70) and rofecoxib (adjusted HR 6.64; 95% CI 2.17, 20.28) was associated with a significant increase in cardiovascular risk. When restricted to patients >=65 years of age, the cardiovascular risks associated with long-term celecoxib (adjusted HR 7.36; 95% CI 1.62, 33.48) and rofecoxib (adjusted HR 13.24; 95% CI 2.59, 67.68) use increased. Short-term use of celecoxib (adjusted HR 0.75; 95% CI 0.42, 1.35) and rofecoxib (adjusted HR 0.85; 95% CI 0.39, 1.86) was not associated with any significant change in cardiovascular risk when compared with short-term ibuprofen use. Neither long- nor short-term exposure to naproxen and etodolac was associated with cardioneutral or cardioprotective effects when compared with ibuprofen use. **CONCLUSIONS:** The findings of this observational study, along with recent clinical trial results, suggest that prolonged exposure to selective COX-2 inhibitors may be associated with an increased risk of adverse cardiovascular outcomes.

DIFFERENTIAL EFFECTS OF BLUEBERRY PROANTHOCYANIDINS ON ANDROGEN SENSITIVE AND INSENSITIVE HUMAN PROSTATE CANCER CELL LINES.

Blueberries are rich in health-promoting polyphenolic compounds including proanthocyanidins. The purpose of this study was to determine if proanthocyanidin-rich fractions from both wild and cultivated blueberry fruit have the same inhibitory effects on the proliferation of LNCaP, an androgen-sensitive prostate cancer cell line, and DU145, a more aggressive androgen insensitive prostate cancer cell line. When 20 microg/ml of a wild blueberry proanthocyanidin fraction (fraction 5) was added to LNCaP media, growth was inhibited to 11% of control with an IC50 of 13.3 microg/ml. Two similar proanthocyanidin-rich fractions from cultivated blueberries (fractions 4 and 5) at the same concentration inhibited LNCaP growth to 57 and 26% of control with an IC50 of 22.7 and 5.8 microg/ml, respectively. In DU145 cells, the only fraction that significantly reduced growth compared to control was fraction 4 from cultivated blueberries with an IC50 value of 74.4 microg/ml, indicating only minor inhibitory activity. Differences in cell growth inhibition of LNCaP and DU145 cell lines by blueberry fractions rich in proanthocyanidins indicate that blueberry proanthocyanidins have an effect primarily on androgen-dependant growth of prostate cancer cells. Possible molecular mechanisms for growth inhibition are reviewed.

Cancer Lett. 2006 Jan 18;231(2):240-6

SUPPLEMENTATION WITH EVELLE IMPROVES SKIN SMOOTHNESS AND ELASTICITY IN A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY WITH 62 WOMEN.

OBJECTIVE: To investigate whether nutritional intervention with a proprietary formulation and other micronutrients may favourably alter skin roughness and elasticity. **METHODS:** Sixty-two women aged 45-73 years participated in a double-blind, placebo-controlled trial testing the efficacy of a proprietary oral supplement for skin nutrition (Evelle), for improvement of skin elasticity and roughness. The active ingredients were vitamins C and E, carotenoids, selenium, zinc, amino acids and glycosaminoglycans, blueberry extract and Pycnogenol. **RESULTS:** Skin elasticity, measured using an optical cutometer, was found to be statistically significantly increased by 9% after 6 weeks of treatment compared with placebo ($p=0.0351$). Skin roughness, as evaluated by three-dimensional microtopography imaging, was found to be statistically significantly lowered by 6% compared with the control group after 12 weeks treatment ($p=0.0157$). **CONCLUSION:** Evelle can potentially improve visible signs of cutaneous ageing.

J Dermatolog Treat. 2004 Jul;15(4):222-6

THE BENEFICIAL EFFECTS OF FRUIT POLYPHENOLS ON BRAIN AGING.

Brain aging is characterized by the continual concession to battle against insults accumulated over the years. One of the major insults is oxidative stress, which is the inability to balance and to defend against the cellular generation of reactive oxygen species (ROS). These ROS cause oxidative damage to nucleic acid, carbohydrate, protein, and lipids. Oxidative damage is particularly detrimental to the brain, where the neuronal cells are largely post-mitotic. Therefore, damaged neurons cannot be replaced readily via mitosis. During normal aging, the brain undergoes morphological and functional modifications resulting in the observed behavioral declines such as decrements in motor and cognitive performance. These declines are augmented by neurodegenerative diseases including amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), and Parkinson's disease (PD). Research from our laboratory has shown that nutritional antioxidants, such as the polyphenols found in blueberries, can reverse age-related declines in neuronal signal transduction as well as cognitive and motor deficits. Furthermore, we have shown that short-term blueberry (BB) supplementation increases hippocampal plasticity. These findings are briefly reviewed in this paper.

Neurobiol Aging. 2005 Dec;26 Suppl 1:128-32

BLUEBERRY- AND SPIRULINA-ENRICHED DIETS ENHANCE STRIATAL DOPAMINE RECOVERY AND INDUCE A RAPID, TRANSIENT MICROGLIA ACTIVATION AFTER INJURY OF THE RAT NIGROSTRIATAL DOPAMINE SYSTEM.

Neuroinflammation plays a critical role in loss of dopamine neurons during brain injury and in neurodegenerative diseases. Diets enriched in foods with antioxidant and anti-inflammatory actions may modulate this neuroinflammation. The model of 6-

hydroxydopamine (6-OHDA) injected into the dorsal striatum of normal rats, causes a progressive loss of dopamine neurons in the ventral mesencephalon. In this study, we have investigated the inflammatory response following 6-OHDA injected into the striatum of adult rats treated with diet enriched in blueberry or spirulina. One week after the dopamine lesion, a similar size of dopamine degeneration was found in the striatum and in the globus pallidus in all lesioned animals. At 1 week, a significant increase in OX-6- (MHC class II) positive microglia was found in animals fed with blueberry- and spirulina-enriched diets in both the striatum and the globus pallidus. These OX-6-positive cells were located within the area of tyrosine hydroxylase (TH) - negativity. At 1 month after the lesion, the number of OX-6-positive cells was reduced in diet-treated animals while a significant increase beyond that observed at 1 week was now present in lesioned control animals. Dopamine recovery as revealed by TH-immunohistochemistry was significantly enhanced at 4 weeks postlesion in the striatum while in the globus pallidus the density of TH-positive nerve fibers was not different from control-fed lesioned animals. In conclusion, enhanced striatal dopamine recovery appeared in animals treated with diet enriched in antioxidants and anti-inflammatory phytochemicals and coincided with an early, transient increase in OX-6-positive microglia.

Exp Neurol. 2005 Dec;196(2):298-307

REVERSING THE DELETERIOUS EFFECTS OF AGING ON NEURONAL COMMUNICATION AND BEHAVIOR: BENEFICIAL PROPERTIES OF FRUIT POLYPHENOLIC COMPOUNDS.

Despite elegant research involving molecular biology studies and determination of the genetic mechanisms of aging, practical information on how to forestall or reverse the deleterious effects of aging may be years away. If this is the case, then it is prudent to try to establish other methods that can be used now to alter the course of aging. Numerous epidemiologic studies have indicated that individuals who consume diets containing large amounts of fruits and vegetables may reduce their risk for developing age-related diseases such as Alzheimer disease. Research from our laboratory suggested that dietary supplementation with fruit or vegetable extracts high in antioxidants (eg, blueberry or spinach extracts) might decrease the enhanced vulnerability to oxidative stress that occurs in aging. These reductions might be expressed as improvements in motor and cognitive behavior. Additional research suggested that mechanisms in addition to antioxidant and antiinflammatory activities might be involved in the beneficial effects of these extracts; the most important of these might be their ability to increase cellular signaling and neuronal communication.

Am J Clin Nutr. 2005 Jan;81(1 Suppl):313S-316S

INHIBITION OF CANCER CELL PROLIFERATION IN VITRO BY FRUIT AND BERRY EXTRACTS AND CORRELATIONS WITH ANTIOXIDANT LEVELS.

The effects of 10 different extracts of fruits and berries on cell proliferation of colon cancer cells HT29 and breast cancer cells MCF-7 were investigated. The fruits and berries used were rosehips, blueberries, black currant, black chokeberries, apple, sea buckthorn, plum, lingonberries, cherries, and raspberries. The extracts decreased the proliferation of both colon cancer cells HT29 and breast cancer cells MCF-7, and the effect was concentration dependent. The inhibition effect for the highest concentration of the extracts varied 2-3-fold among the species, and it was in the ranges of 46-74% (average = 62%) for the HT29 cells and 24-68% (average = 52%) for the MCF-7 cells. There were great differences in the content of the analyzed antioxidants in the extracts. The level of the vitamin C content varied almost 100-fold, and the content of total carotenoids varied almost 150-fold among the species. Also in the composition and content of flavonols, hydroxycinnamic acids, anthocyanins, and phenolics were found great differences among the 10 species. The inhibition of cancer cell proliferation seen in these experiments correlated with levels of some carotenoids and with vitamin C levels, present at levels that can be found in human tissues. The same inhibition of cell proliferation could not be found by ascorbate standard alone. This correlation might indicate a synergistic effect of vitamin C and other substances. In MCF-7 cells, the anthocyanins may contribute to the inhibition of proliferation.

J Agric Food Chem. 2004 Dec 1;52(24):7264-71

BLUEBERRY SUPPLEMENTED DIET REVERSES AGE-RELATED DECLINE IN HIPPOCAMPAL HSP70 NEUROPROTECTION.

Dietary supplementation with antioxidant rich foods can decrease the level of oxidative stress in brain regions and can ameliorate age-related deficits in neuronal and behavioral functions. We examined whether short-term supplementation with blueberries might enhance the brain's ability to generate a heat shock protein 70 (HSP70) mediated neuroprotective response to stress. Hippocampal (HC) regions from young and old rats fed either a control or a supplemented diet for 10 weeks were subjected to an in vitro inflammatory challenge (LPS) and then examined for levels of HSP70 at various times post LPS (30, 90 and 240 min). While baseline levels of HSP70 did not differ among the various groups compared to young control diet rats, increases in HSP70 protein levels in response to an in vitro LPS challenge were significantly less in old as compared to young control diet rats at the 30, 90 and 240 min time points. However, it appeared that the blueberry diet completely restored the HSP70 response to LPS in the old rats at the 90 and 240 min times. This suggests that a short-term blueberry (BB) intervention may result in improved HSP70-mediated protection against a number of neurodegenerative processes in the brain. Results are discussed in terms of the

multiplicity of the effects of the BB supplementation which appear to range from antioxidant/anti-inflammatory activity to signaling.

Neurobiol Aging. 2006 Feb;27(2):344-50

PARKINSON'S DISEASE AND PARKINSONIAN SYNDROMES.

The parkinsonian syndrome rests on the clinical tripod: akinesia, rigidity, tremor. Akinesia is the key symptom, broadly defined as a difficulty in initiating and performing movements in proportion to their complexity (sophisticated, simultaneous movements) and their duration (repetitive movements). The most frequent cause of the syndrome is Parkinson's disease. Although this diagnosis needs to be confirmed in pathological terms by the loss of neurons and the presence of Lewy's bodies in the substantia nigra, some clinical data enable it to be envisaged with a minimum of errors; these are pure parkinsonian triad, good response to dopatherapy and asymmetrical symptoms. The other causes of parkinsonian syndrome are usually related to the administration of neuroleptic drugs and to degenerative diseases with lesions that are more diffuse than those of Parkinson's disease. In Steele-Richardson-Olzewski disease a parkinsonian syndrome is associated with supranuclear ophthalmoplegia. Multiple systematized atrophy presents under three different clinical aspects: a parkinsonian syndrome without tremor and resistant to L-dopa, suggesting atrophy of the strionigral tract; a parkinsonian syndrome associated with a cerebellar syndrome, suggesting olivo-cerebellar-pontine atrophy, and Shy-Drager disease which includes primary dysautonomy and other neurological syndromes.

Rev Prat. 1989 Mar 9;39(8):647-51

Carnitine

ACETYL-L-CARNITINE-INDUCED UP-REGULATION OF HEAT SHOCK PROTEINS PROTECTS CORTICAL NEURONS AGAINST AMYLOID-BETA PEPTIDE 1-42-MEDIATED OXIDATIVE STRESS AND NEUROTOXICITY: IMPLICATIONS FOR ALZHEIMER'S DISEASE.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by loss of memory and cognition and by senile plaques and neurofibrillary tangles in brain. Amyloid-beta peptide, particularly the 42-amino-acid peptide (Abeta(1-42)), is a principal component of senile plaques and is thought to be central to the pathogenesis of the disease. The AD brain is under significant oxidative stress, and Abeta(1-42) peptide is known to cause oxidative stress in vitro and in vivo. Acetyl-L-carnitine (ALCAR) is an endogenous mitochondrial membrane compound that helps to maintain mitochondrial bioenergetics and lowers the increased oxidative stress associated with aging. Glutathione (GSH) is an important endogenous antioxidant, and its levels have been shown to decrease with aging. Administration of ALCAR increases cellular levels of GSH in rat astrocytes. In the current study, we investigated whether ALCAR plays a protective role in cortical neuronal cells against Abeta(1-42)-mediated oxidative stress and neurotoxicity. Decreased cell survival in neuronal cultures treated with Abeta(1-42) correlated with an increase in protein oxidation (protein carbonyl, 3-nitrotyrosine) and lipid peroxidation (4-hydroxy-2-nonenal) formation. Pretreatment of primary cortical neuronal cultures with ALCAR significantly attenuated Abeta(1-42)-induced cytotoxicity, protein oxidation, lipid peroxidation, and apoptosis in a dose-dependent manner. Addition of ALCAR to neurons also led to an elevated cellular GSH and heat shock proteins (HSPs) levels compared with untreated control cells. Our results suggest that ALCAR exerts protective effects against Abeta(1-42) toxicity and oxidative stress in part by up-regulating the levels of GSH and HSPs. This evidence supports the pharmacological potential of acetyl carnitine in the management of Abeta(1-42)-induced oxidative stress and neurotoxicity. Therefore, ALCAR may be useful as a possible therapeutic strategy for patients with AD.

J Neurosci Res. 2006 Apr 21

ANTIOXIDANT ACTIVITY OF PROPIONYL-L-CARNITINE IN LIVER AND HEART OF SPONTANEOUSLY HYPERTENSIVE RATS.

Oxidative stress plays an important role in arterial hypertension and propionyl-L-carnitine (PLC) has been found to protect cells from toxic reactive oxygen species. In this work, we have evaluated the antioxidant capacity of chronic PLC treatment in spontaneously hypertensive rats (SHR) by measuring the activity of antioxidant enzymes and the lipid peroxidation in liver and cardiac tissues. The activity of glutathione peroxidase was decreased in liver and cardiac tissues of SHR when compared with their normotensive controls, Wistar-Kyoto (WKY) rats, this alteration being prevented by PLC treatment. Glutathione reductase activity was increased in hypertensive rats and no effect was observed after the treatment. No significant changes in superoxide dismutase activity were observed among all experimental groups. Liver of hypertensive rats showed higher catalase activity than that of normotensive rats, and PLC enhanced this activity in both rat strains. Thiobarbituric acid reactive substances, determined as a measure of lipid peroxidation, were increased in SHR compared with WKY rats, and PLC treatment decreased these values not only in hypertensive rats but also in normotensive ones. The content of carnitine in serum, liver and heart was higher in PLC-treated rats, but PLC did not prevent the hypertension development in young SHR. In addition, triglyceride levels, which were lower in SHR than WKY rats, were reduced by chronic PLC treatment in both rat strains. These results demonstrate: i) the hypotriglyceridemic effect of PLC and ii) the antioxidant capacity of PLC in SHR and its beneficial use protecting tissues from hypertension-accompanying oxidative damage.

Life Sci. 2006 Mar 20;78(17):1945-52

A DOUBLE-BLIND, RANDOMISED, CONTROLLED CLINICAL TRIAL OF ACETYL-L-CARNITINE VS. AMISULPRIDE IN THE TREATMENT OF DYSTHYMIA.

AIM: Evaluation of the effect of acetyl-L-carnitine (ALCAR) vs. amisulpride measured by total Hamilton Depression Rating Scale score (HAM-D(21)) in patients with pure dysthymia (DSM IV). Two hundred and four patients were randomised and treated with ALCAR 500 mg b.i.d. or amisulpride 50 mg u.i.d. in a double-blind study, for 12 weeks. RESULTS: A solid improvement of HAM-D(21) was observed in both treatment groups throughout the study. The results did not disclose statistically significant differences between treatments, although the confidence interval for the non-inferiority of the primary end-point exceeded the pre-established limit of 2 by 0.46 points. According to a non-inferiority margin of 3 (considered acceptable by recent published data) the primary end-point could have been fully satisfied. CDRS, MADRS and CGI, employed to further measure the clinical

outcome, reported similar results in both treatment groups. The greater tolerability of ALCAR is of clinical relevance considering the chronicity of dysthymia, which often requires prolonged treatment.

Eur Neuropsychopharmacol. 2006 May;16(4):281-7

ACETYL-L-CARNITINE IN THE TREATMENT OF PAINFUL ANTIRETROVIRAL TOXIC NEUROPATHY IN HUMAN IMMUNODEFICIENCY VIRUS PATIENTS: AN OPEN LABEL STUDY.

Antiretroviral toxic neuropathy causes morbidity in human immunodeficiency virus (HIV) patients under dideoxynucleoside therapy, benefits only partially from medical therapy, and often leads to drug discontinuation. Proposed pathogeneses include a disorder of mitochondrial oxidative metabolism, eventually related to a reduction of mitochondrial DNA content, and interference with nerve growth factor activity. Carnitine is a substrate of energy production reactions in mitochondria and is involved in many anabolic reactions. Acetyl carnitine treatment promotes peripheral nerve regeneration and has neuroprotective properties and a direct analgesic role related to glutamatergic and cholinergic modulation. The aim of this study was to evaluate acetyl-l-carnitine in the treatment of painful antiretroviral toxic neuropathy in HIV patients. Twenty subjects affected by painful antiretroviral toxic neuropathy were treated with oral acetyl-l-carnitine at a dose of 2,000 mg/day for a 4-week period. Efficacy was evaluated by means of the modified Short Form McGill Pain Questionnaire with each item rated on an 11-point intensity scale at weekly intervals and by electromyography at baseline and final visit. Mean pain intensity score was significantly reduced during the study, changing from 7.35 +/- 1.98 (mean +/- SD) at baseline to 5.80 +/- 2.63 at week 4 ($p = 0.0001$). Electrophysiological parameters did not significantly change between baseline and week 4. In this study, acetyl-l-carnitine was effective and well tolerated in symptomatic treatment of painful neuropathy associated with antiretroviral toxicity. On the contrary, no effect was noted on neurophysiological parameters.

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SYMPTOMATIC AND NEUROPHYSIOLOGICAL RESPONSES OF PACLITAXEL- OR CISPLATIN-INDUCED NEUROPATHY TO ORAL ACETYL-L-CARNITINE.

Acetyl-L-carnitine (ALC) improves non-oncological neuropathies. We tested oral ALC (1 g tid) for 8 weeks in 25 patients with neuropathy grade 3 (common toxicity criteria--CTC) during paclitaxel or cisplatin therapy, or grade 2 persisting for at least three months after discontinuing the drugs. An independent neurologist assessed patients before and after ALC. All patients except one reported symptomatic relief, and only two described grade 1 nausea. The sensory neuropathy grade improved in 15 of 25 (60%), and motor neuropathy in 11 of 14 patients (79%). Total neuropathy score (TNS) that included neurophysiological measures improved in 23 (92%). Amelioration of sensory amplitude and conduction velocity (sural and peroneal nerves) was measured in 22 and 21 patients, respectively. Symptomatic improvement persisted in 12 of 13 evaluable patients at median 13 months after ALC. In view of its effect in improving established paclitaxel- and cisplatin-neuropathy, we recommend ALC testing in preventing progression or revert symptoms during neurotoxic chemotherapy.

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