

**ABSTRACTS****SOD****FREE RADICALS AND ANTIOXIDANTS IN PRIMARY FIBROMYALGIA: AN OXIDATIVE STRESS DISORDER?**

The role of free radicals in fibromyalgia is controversial. In this study, 85 female patients with primary fibromyalgia and 80 age-, height-, and weight-matched healthy women were evaluated for oxidant/antioxidant balance. Malondialdehyde is a toxic metabolite of lipid peroxidation used as a marker of free radical damage. Superoxide dismutase is an intracellular antioxidant enzyme and shows antioxidant capacity. Pain was assessed by visual analog scale. Tender points were assessed by palpation. Age, smoking, body mass index (BMI), and duration of disease were also recorded. Malondialdehyde levels were significantly higher and superoxide dismutase levels significantly lower in fibromyalgic patients than controls. Age, BMI, smoking, and duration of disease did not affect these parameters. We found no correlation between pain and number of tender points. In conclusion, oxidant/antioxidant balances were changed in fibromyalgia. Increased free radical levels may be responsible for the development of fibromyalgia. These findings may support the hypothesis of fibromyalgia as an oxidative disorder.

Rheumatol Int. 2005 Apr;25(3):188-90

**INHIBITION OF CELL GROWTH BY OVEREXPRESSION OF MANGANESE SUPEROXIDE DISMUTASE (MNSOD) IN HUMAN PANCREATIC CARCINOMA.**

Manganese superoxide dismutase (MnSOD) levels have been found to be low in human pancreatic cancer [Pancreas 26, (2003), 23] and human pancreatic cancer cell lines [Cancer Res. 63, (2003), 1297] when compared to normal human pancreas. We hypothesized that stable overexpression of pancreatic cancer cells with MnSOD cDNA would alter the malignant phenotype. MIA PaCa-2 cells were stably transfected with a pcDNA3 plasmid containing sense human MnSOD cDNA or containing no MnSOD insert by using the lipofectAMINE method. G418-resistant colonies were isolated, grown and maintained. Over expression of MnSOD was confirmed in two selected clones with a 2-4-fold increase in MnSOD immunoreactive protein. Compared with the parental and neo control cells, the MnSOD-over-expressing clones had decreased growth rates, growth in soft agar and plating efficiency in vitro, while in vivo, the MnSOD-over-expressing clones had slower growth in nude mice. These results suggest that MnSOD may be a tumor suppressor gene in human pancreatic cancer.

Free Radic Res. 2004 Nov;38(11):1223-33

**INFLUENCE OF AN ORALLY EFFECTIVE SOD ON HYPERBARIC OXYGEN-RELATED CELL DAMAGE.**

In a prospective, double-blind, randomised placebo-controlled study, we tested the hypothesis that a new formulation consisting of wheat gliadin chemically combined with a vegetal (thus orally effective) preparation of superoxide dismutase (SOD) allows to prevent hyperbaric oxygen (HBO)-induced oxidative cell stress. Twenty healthy volunteers were exposed to 100% oxygen breathing at 2.5 ATA for a total of 60 min. DNA strand breaks (tail moments) were determined using the alkaline version of the comet assay. Whole blood concentrations of reduced (GSH) and oxidised (GSSG) glutathione and F2-isoprostanes, SOD, glutathione peroxidase (GPx) and catalase (Cat) activities and red cell malondialdehyde (MDA) content were determined. After HBO exposure the tail moment ( $p = 0.03$ ) and isoprostane levels ( $p = 0.049$ ) were significantly lower in the group that received the vegetal formulation. Neither SOD and Cat nor GSH and GSSG were significantly affected by this preparation or HBO exposure. By contrast, blood GPx activity, which tended to be lower in the SOD-group already before the HBO exposure ( $p = 0.076$ ), was significantly lower afterwards ( $p = 0.045$ ). We conclude that an orally effective SOD-wheat gliadin mixture is able to protect against DNA damage, which coincided with reduced blood isoprostane levels, and may therefore be used as an antioxidant.

Free Radic Res. 2004 Sep;38(9):927-32

**SUPPLEMENTATION WITH GLIADIN- COMBINED PLANT SUPEROXIDE DISMUTASE EXTRACT PROMOTES ANTIOXIDANT DEFENCES AND PROTECTS AGAINST OXIDATIVE STRESS.**

The potential benefits to health of antioxidant enzymes supplied either through dietary intake or supplementation is still a matter

of controversy. The development of dietary delivery systems using wheat gliadin biopolymers as a natural carrier represents a new alternative. Combination of antioxidant enzymes with this natural carrier not only delayed their degradation (i.e. the superoxide dismutase, SOD) during the gastrointestinal digestive process, but also promoted, in vivo, the cellular defences by strengthening the antioxidant status. The effects of supplementation for 28 days with a standardized melon SOD extract either combined (Glisodin) or not with gliadin, were evaluated on various oxidative-stress biomarkers. As already described there was no change either in superoxide dismutase, catalase or glutathione peroxidase activities in blood circulation or in the liver following non-protected SOD supplementation. However, animals supplemented with Glisodin showed a significant elevation in circulated antioxidant enzymes activities, correlated with an increased resistance of red blood cells to oxidative stress-induced hemolysis. In the presence of Sin-1, a chemical donor of peroxynitrites, mitochondria from hepatocytes regularly underwent membrane depolarization as the primary biological event of the apoptosis cascade. Hepatocytes isolated from animals supplemented with Glisodin presented a delayed depolarization response and an enhanced resistance to oxidative stress-induced apoptosis. It is concluded that supplementation with gliadin-combined standardized melon SOD extract (Glisodin) promoted the cellular antioxidant status and protected against oxidative stress-induced cell death.

Phytother Res. 2004 Dec;18(12):957-62

## Shark Liver Oil

### **IN VITRO CYTOPROTECTIVE ACTIVITY OF SQUALENE ON A BONE MARROW VERSUS NEUROBLASTOMA MODEL OF CISPLATIN-INDUCED TOXICITY. IMPLICATIONS IN CANCER CHEMOTHERAPY.**

The development of a non-toxic selective cytoprotective agent that preferentially protects normal tissues from chemotherapy toxicity, without protecting malignant tissues, is a major challenge in cancer chemotherapy research. The available cytoprotective agents are either toxic or lack selective cytoprotective activity. Here, we report the in vitro selective cytoprotective activity of squalene, an isoprenoid molecule with antioxidant properties. Normal human bone marrow (BM) derived colony-forming unit (CFU) growth was increased by squalene in a dose-dependent manner. Squalene (12.5-25 microM) treatment significantly protected the CFUs from cisplatin-induced toxicity; the protective effect was equivalent to reduced glutathione (GSH), a known cytoprotective agent. Squalene also increased the long-term survival of cisplatin-treated 4-week-old CFUs. Cisplatin-induced apoptosis of CFUs as measured by the TUNEL assay was reduced by squalene. To examine the squalene-induced protection of tumours, several neuroblastoma cell lines, including five MYCN-amplified cell lines, were grown in monolayers, as well as in anchorage-independent cultures, in the presence of squalene and cisplatin. Squalene did not protect the neuroblastoma (NBL) cell lines from cisplatin-induced toxicity. In addition, squalene did not protect the NBL cells from carboplatin, cyclophosphamide, etoposide and doxorubicin-induced toxicity. In conclusion, our results suggest that squalene has a selective in vitro cytoprotective effect on BM-derived haematopoietic stem cells that is equipotent to GSH.

Eur J Cancer. 2003 Nov;39(17):2556-65

### **SQUALENE: POTENTIAL CHEMOPREVENTIVE AGENT.**

Squalene is a triterpene that is an intermediate of the cholesterol biosynthesis pathway and it can be obtained from the diet. Olive oil contains 0.2-0.7% squalene. The average intake of squalene is 30 mg/day in the United States, however, when consumption of olive oil is high, the intake of squalene can reach 200-400 mg/day as observed in Mediterranean countries. The decreased risk for various cancers associated with high olive oil consumption may be due to the presence of squalene. Experimental studies have shown that squalene can effectively inhibit chemically-induced colon, lung and skin tumourigenesis in rodents. The protective effect is observed when squalene is given before and/or during carcinogen treatment. The mechanisms involved for the chemopreventive activity of squalene may include inhibition of Ras farnesylation, modulation of carcinogen activation and anti-oxidative activities. However, several factors must be taken into consideration when the evidence for the inhibition of carcinogenesis by squalene is examined, these include the effective dose used and the time of exposure. The information obtained is from animal bioassays and the long-term effects from consuming increased levels of squalene are not known. Although animal studies have enhanced our understanding of the possible action of squalene in decreasing carcinogenesis, one must apply caution in extrapolating the information obtained in animal studies to humans, because of possible species differences. In order to evaluate the overall implications of squalene to human cancer prevention, further studies are needed to fully identify its protective effects, as well as possible detrimental effects.

Expert Opin Investig Drugs. 2000 Aug;9(8):1841-8

### **1-O-ALKYLGLYCEROLS IMPROVE BOAR SPERM MOTILITY AND FERTILITY.**

1-O-alkylglycerols are naturally occurring ether lipids with potent biological activities. They may interfere with lipidic signaling, and they amplify platelet-activating factor (PAF) biosynthesis in a monocyte cell line. The PAF is produced by mammalian sperm

and is an important activator of sperm motility. The aim of this study was to evaluate the effect of in vitro treatment of boar spermatozoa with natural 1-O-alkylglycerols (10 microM) on 1) boar sperm motility; 2) production of PAF and its metabolite, lyso-PAF, by spermatozoa; and 3) fertility in artificial inseminations of breeding sows. Using a computer-assisted spermatozoa analyzer, we found that 1-O-alkylglycerols increased percentage motility as well as velocity parameters after 24 h. These effects were partially or totally reversed by the PAF receptor-antagonist SR 27417. After [3H]-1-O-alkylglycerol incubation with boar spermatozoa, we identified [3H]lyso-PAF by high-performance liquid chromatography. Production of PAF and lyso-PAF was measured with a biological assay using [3H] serotonin release from rabbit platelets. 1-O-alkylglycerols significantly increased lyso-PAF production but had no effect on PAF production. The effect of 1-O-alkylglycerols on fertilization was also evaluated in industrial breedings: 1-O-alkylglycerol-treated or untreated semen dilutions were alternately used for artificial inseminations of sows on 12 farms. 1-O-alkylglycerol treatment increased the number of farrows but had no effect on the mean size of the litters. This study demonstrates that 1-O-alkylglycerol treatment of boar spermatozoa in vitro improves their motility and fertility, and it suggests that this effect is related to PAF metabolism and function in boar spermatozoa.

Biol Reprod. 2002 Feb;66(2):421-8

## ABSTRACTS

### Women and heart disease

#### **PREVENTION OF CORONARY HEART DISEASE: A NONHORMONAL APPROACH.**

Coronary heart disease (CHD) is a common and serious health problem facing women as they move beyond the reproductive years. Until recently, many postmenopausal women and their physicians relied heavily on hormone therapy to prevent cardiovascular disease, neglecting the well-recognized nonhormonal aspects of cardiovascular health. Simple lifestyle changes—exercise, diet, weight control, and avoidance of tobacco—can significantly reduce the chance of heart disease and its major risk factors, which are essentially the same for men and women. As with men, obesity, hypertension, hyperlipidemia, and diabetes are the major risk factors for heart disease in women. This review discusses the epidemiologic studies linking these risk factors to CHD in women, the guidelines for screening, and a brief overview of treatment recommendations.

Semin Reprod Med. 2005 May;23(2):157-66

#### **RISK FACTORS FOR CORONARY HEART DISEASE AMONG INPATIENTS WHO HAVE MILD INTELLECTUAL DISABILITY AND MENTAL ILLNESS.**

**BACKGROUND:** Coronary heart disease (CHD) is a major cause of morbidity and mortality in the UK. The aim of this study was to screen inpatients with mild or borderline intellectual disability, many of whom also have mental illness, for risk factors for CHD. **METHODS:** Cross sectional survey. Participants were interviewed, measured and had blood samples taken. **RESULTS:** Of the 53 participants, 20 (37.7%) were overweight and 18 (34.0%) obese. The mean body mass index (BMI) of those participants prescribed regular antipsychotics was higher than those who were not. Nine (20.9%) had waist circumference measurements placing them at increased risk of CHD and 21 (48.8%) were at substantially increased risk. Twenty-eight (52.8%) were current smokers. Of the 49 participants who had their blood pressure measured, 3 (6.1%) had readings above the reference range. Of the 19 participants who had random blood tests, one (5.3%) had an elevated cholesterol level. **CONCLUSIONS:** In this population there was a high prevalence of two risk factors for CHD (obesity and smoking), requiring ongoing monitoring and long-term measures to reduce risk.

J Intellect Disabil Res. 2005 May;49(Pt 5):309-16

#### **STREPTOKINASE—A CLINICALLY USEFUL THROMBOLYTIC AGENT.**

A failure of hemostasis and consequent formation of blood clots in the circulatory system can produce severe outcomes such as stroke and myocardial infarction. Pathological development of blood clots requires clinical intervention with fibrinolytic agents such as urokinase, tissue plasminogen activator and streptokinase. This review deals with streptokinase as a clinically important and cost-effective plasminogen activator. The aspects discussed include: the mode of action; the structure and structure-function relationships; the structural modifications for improving functionality; recombinant streptokinase; microbial production; and recovery of this protein from crude broths.

Biotechnol Adv. 2004 Feb;22(4):287-307

### Antioxidants

#### **INTAKE OF ALPHA-TOCOPHEROL IS LIMITED AMONG US ADULTS.**

**OBJECTIVE:** To examine alpha-tocopherol intake and food sources of alpha-tocopherol in the US population relative to current Dietary Reference Intakes for vitamin E. **DESIGN:** We analyzed food source and intake data from the 1994 to 1996 Continuing Survey of Food Intakes by Individuals (CSFII) with added values for alpha-tocopherol from the US Department of Agriculture National Nutrient Database for Standard Reference Release 15. **SUBJECTS:** Data from 5,056 men and 4,703 women aged 20 years and older were obtained from the 1994 to 1996 CSFII. **STATISTICAL ANALYSES PERFORMED:** The complex design and sampling weights of the CSFII survey were taken into account to calculate the mean alpha-tocopherol intake from diet, the SEM, and the percent of the Estimated Average Requirements (EARs) for alpha-tocopherol intake by age group and region. **RESULTS:** Only 8.0% of men and 2.4% of women in the United States met the new EARs for vitamin E intake from foods alone. Regionally, only 5.8% of men and 2.1% of women in the South met these EARs, relative to 9.0% and 2.6%, respectively, in the Northeast.

Top contributors of alpha-tocopherol for men and women included ready-to-eat cereal, sweet baked products, white bread, beef, oils, and salad dressing. APPLICATIONS/CONCLUSIONS: The majority of men and women in the United States fail to meet the current recommendations for vitamin E intake. Many of the top contributors are not particularly high sources of alpha-tocopherol but are consumed frequently. Greater inclusion of sources such as nuts, seeds, and vitamin E-rich oils, could improve intake of alpha-tocopherol.

J Am Diet Assoc. 2004 Apr;104(4):567-75

### **OXIDATIVE STRESS AND NEUROINFLAMMATION IN ALZHEIMER'S DISEASE AND AMYOTROPHIC LATERAL SCLEROSIS: COMMON LINKS AND POTENTIAL THERAPEUTIC TARGETS.**

Many neurological diseases, including Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS), are now recognized to share atypical inflammatory reactions as a major pathological feature. Neuroinflammation can both be a cause, and a consequence, of chronic oxidative stress. Cytokine-stimulated microglia generate copious amounts of reactive oxygen and reactive nitrogen species, creating a stress upon ambient neurons. Conversely, oxidants can stimulate pro-inflammatory gene transcription in glia, leading to various inflammatory reactions. This review compares literature regarding neuroinflammation in AD and ALS, with special emphasis on roles played by tumor necrosis factor alpha (TNFalpha) and aberrant arachidonic acid metabolism in the genesis of chronic oxidative conditions. Based on our observations made in the G93A-SOD1 mouse model of ALS, and a body of Alzheimer's disease findings, we hypothesize a prominent pathological role for the TNFalpha-signaling axis and neuroinflammation in the pathogenesis of both diseases. A discussion is made regarding the relevance of neuroinflammation to potential therapeutic implications for both ALS and AD.

J Alzheimers Dis. 2004 Apr;6(2):147-57

### **THE COMBINED EFFECT OF TRANSFERRIN SATURATION AND LOW DENSITY LIPOPROTEIN ON MORTALITY.**

BACKGROUND AND OBJECTIVES: Evidence suggests that cardiovascular disease (CVD) is accelerated by the oxidation of low-density lipoprotein (LDL) in the presence of iron. This study examined whether adults with elevated iron, as measured by transferrin saturation (TS), and elevated LDL are at an increased risk for mortality. METHODS: This is a cohort study of the adult US population using the National Health and Nutrition Examination Survey 1976-1980 (NHANES II) merged with the NHANES II Mortality Study in 1992. Multivariate Cox regression was performed to determine hazard ratios (HR) for CVD and all-cause mortality for high (>55%) or low (<55%) levels of TS and high (>160 mg/dl) or low (<160 mg/dl) levels of LDL. RESULTS: An elevated LDL alone did not significantly increase CVD mortality or all-cause mortality in the adjusted model. Individuals with elevated LDL and elevated TS had a statistically significant increase in both CVD mortality and all-cause mortality (HR=5.74 and 3.53, respectively) compared to the low LDL and low TS group. CONCLUSIONS: The results of this study indicate an increased risk associated with the combination of elevated LDL and elevated TS, which suggests that iron-mediated oxidation of LDL may be a significant factor in the progression of CVD.

Fam Med. 2004 May;36(5):324-9

### **COPPER MEDIATES DITYROSINE CROSS-LINKING OF ALZHEIMER'S AMYLOID-BETA.**

We have previously reported that amyloid Abeta, the major component of senile plaques in Alzheimer's disease (AD), binds Cu with high affinity via histidine and tyrosine residues and produces H<sub>2</sub>O<sub>2</sub> by catalyzing the reduction of Cu(II) or Fe(III). Incubation with Cu induces the SDS-resistant oligomerization of Abeta, a feature characteristic of neurotoxic soluble Abeta extracted from the AD brain. Since residues coordinating Cu are most vulnerable to oxidation, we investigated whether modifications of these residues were responsible for Abeta cross-linking. SDS-resistant oligomerization of Abeta caused by incubation with Cu was found to induce a fluorescence signal characteristic of tyrosine cross-linking. Using ESI-MS and a dityrosine specific antibody, we confirmed that Cu(II) (at concentrations lower than that associated with amyloid plaques) induces the generation of dityrosine-cross-linked, SDS-resistant oligomers of human, but not rat, Abeta peptides. The addition of H<sub>2</sub>O<sub>2</sub> strongly promoted Cu-induced dityrosine cross-linking of Abeta1-28, Abeta1-40, and Abeta1-42, suggesting that the oxidative coupling is initiated by interaction of H<sub>2</sub>O<sub>2</sub> with a Cu(II) tyrosinate. The dityrosine modification is significant since it is highly resistant to proteolysis and is known to play a role in increasing structural strength. Given the elevated concentration of Cu in senile plaques, our results suggest that Cu interactions with Abeta could be responsible for causing the covalent cross-linking of Abeta in these structures.

Biochemistry. 2004 Jan 20;43(2):560-8

### **CURCUMIN INTERACTION WITH COPPER AND IRON SUGGESTS ONE POSSIBLE MECHANISM OF ACTION IN ALZHEIMER'S DISEASE ANIMAL MODELS.**

Curcumin is a polyphenolic diketone from turmeric. Because of its anti-oxidant and anti-inflammatory effects, it was tested in

animal models of Alzheimer's disease, reducing levels of amyloid and oxidized proteins and preventing cognitive deficits. An alternative mechanism of these effects is metal chelation, which may reduce amyloid aggregation or oxidative neurotoxicity. Metals can induce Abeta aggregation and toxicity, and are concentrated in AD brain. Chelators desferrioxamine and clioquinol have exhibited anti-AD effects. Using spectrophotometry, we quantified curcumin affinity for copper, zinc, and iron ions. Zn<sup>2+</sup> showed little binding, but each Cu<sup>2+</sup> or Fe<sup>2+</sup> ion appeared to bind at least two curcumin molecules. The interaction of curcumin with copper reached half-maximum at approximately 3-12 microM copper and exhibited positive cooperativity, with Kd1 approximately 10-60 microM and Kd2 approximately 1.3 microM (for binding of the first and second curcumin molecules, respectively). Curcumin-iron interaction reached half-maximum at approximately 2.5-5 microM iron and exhibited negative cooperativity, with Kd1 approximately 0.5-1.6 microM and Kd2 approximately 50-100 microM. Curcumin and its metabolites can attain these levels in vivo, suggesting physiological relevance. Since curcumin more readily binds the redox-active metals iron and copper than redox-inactive zinc, curcumin might exert a net protective effect against Abeta toxicity or might suppress inflammatory damage by preventing metal induction of NF-kappaB.

Alzheimers Dis. 2004 Aug;6(4):367-77

### **ALPHA-LIPOIC ACID PREVENTS DIABETES MELLITUS IN DIABETES-PRONE OBESE RATS.**

Several lines of evidence have suggested that triglyceride accumulation in skeletal muscle and pancreatic islets is causally related to type 2 diabetes mellitus. We recently showed that alpha-lipoic acid (ALA), a potent antioxidant and cofactor of mitochondrial respiratory enzymes, reduces body weight of rodents by suppressing food intake and increasing energy expenditure. We sought to determine if ALA can prevent the development of diabetes mellitus in obese Otsuka Long-Evans Tokushima Fatty (OLETF) rats. Most (78%) untreated OLETF rats showed glycosuria at 40 weeks of age, but this was completely prevented by ALA. Compared with untreated OLETF rats, ALA reduced body weight and protected pancreatic beta-cells from destruction. ALA also reduced triglyceride accumulation in skeletal muscle and pancreatic islets. These results indicate that ALA prevents diabetes mellitus in obese diabetes-prone rats by reducing lipid accumulation in non-adipose tissue as well as in adipose tissue.

Biochem Biophys Res Commun. 2005 Jan 7;326(1):197-2

## ABSTRACTS

### Theanine

#### **ANTI-OBESITY EFFECTS OF THREE MAJOR COMPONENTS OF GREEN TEA, CATECHINS, CAFFEINE AND THEANINE, IN MICE.**

To elucidate the anti-obesity effects of three major components of green tea, catechins, caffeine and theanine, female ICR mice were fed on diets containing 2% green tea powder and diets containing 0.3% catechins, 0.05% caffeine and 0.03% theanine, which correspond, respectively, to their concentrations in a 2% green tea powder diet, singly and in combination for 16 weeks. Body weight and food intake were determined monthly during this period, kidneys, adrenals, liver, spleen, brain, pituitary and intraperitoneal adipose tissues (IPAT) were weighed and lipid levels in the serum and liver were measured at the end of this period. The body weight increase and weight of IPAT were significantly reduced by the diets containing green tea, caffeine, theanine, caffeine + catechins, caffeine + theanine and caffeine + catechins + theanine. Noticeably, the IPAT weight decreased by 76.8% in the caffeine + catechins compared to the control group. Serum concentrations of triglycerides (TG) and non-esterified fatty acids (NEFA) were decreased by green tea, catechins and theanine. Moreover, caffeine + catechins, caffeine + theanine and caffeine + catechins + theanine also decreased NEFA in the serum. The TG level in the liver was significantly reduced by catechins and catechins + theanine in comparison with the control. These results indicated that at least caffeine and theanine were responsible for the suppressive effect of green tea powder (GTP) on body weight increase and fat accumulation. Moreover, it was shown that catechins and caffeine were synergistic in anti-obesity activities.

In Vivo. 2004 Jan-Feb;18(1):55-62

#### **POSSIBLE INVOLVEMENT OF GROUP I MGLURS IN NEUROPROTECTIVE EFFECT OF THEANINE.**

We investigated the molecular mechanism underlying the neuroprotective effect of theanine, a green tea component, using primary cultured rat cortical neurons, focusing on group I metabotropic glutamate receptors (mGluRs). Theanine and a group I mGluR agonist, DHPG, inhibited the delayed death of neurons caused by brief exposure to glutamate, and this effect of theanine was abolished by group I mGluR antagonists. Although the administration of glutamate alone decreased the neuronal expression of phospholipase C (PLC)-beta1 and -gamma1, which are linked to group I mGluRs, their expression was equal to the control levels on cotreatment with theanine. Treatment with theanine or DHPG alone for 5-7 days resulted in increased expression of PLC-beta1 and -gamma1, and the action of theanine was completely abolished by group I mGluR antagonists. These findings indicate that group I mGluRs might be involved in neuroprotective effect of theanine by increasing the expression levels of PLC-beta1 and -gamma1.

Biochem Biophys Res Commun. 2004 Jul 16;320(1):116-22

#### **ENHANCEMENT OF THE ACTIVITY OF DOXORUBICIN BY INHIBITION OF GLUTAMATE TRANSPORTER.**

Theanine enhanced doxorubicin (DOX) induced antitumor activity by increasing the concentration of DOX in the tumor through the inhibition of efflux of DOX from tumor cells. As theanine reduced the level of glutamate via suppression of the glutamate transporter in tumor cells, we studied the change in the intracellular concentration of glutathione (GSH) and the correlation with the GSH S-conjugate export (GS-X) pump. The reduction in the concentration of glutamate in tumor cells caused by theanine, induced decreases in the intracellular GSH and GS-DOX levels. The expression of MRP5 in M5076 cells, was confirmed. We concluded that the GS-DOX conjugate was transported extracellularly via the MRP5/GS-X pump in M5076 cells and that theanine affected this route. Namely, theanine increases the concentration of DOX in a tumor in vivo through inhibition of the glutamate transporter via the GS-X pump.

Toxicol Lett. 2001 Sep 15;123(2-3):159-67

#### **THEANINE, A SPECIFIC GLUTAMATE DERIVATIVE IN GREEN TEA, REDUCES THE ADVERSE REACTIONS OF DOXORUBICIN BY CHANGING THE GLUTATHIONE LEVEL.**

We previously showed that theanine, a specific glutamate derivative in green tea, decreased doxorubicin (DOX)-induced adverse reactions such as the induction of the lipid peroxide level and the reduction of glutathione peroxidase activity in normal tissues. In order to clarify how theanine attenuates the adverse reactions of DOX, we have focused on the effects of theanine on glutamate and glutathione (GSH) levels in normal tissues. The administration of theanine to mice increased the glutamate concentration in the liver and heart, and not in tumors. In vitro examinations indicated that theanine was metabolized to glutamate mainly in the

liver. Moreover, theanine inhibited GSH reduction induced by DOX in the liver and heart. Therefore, these results suggested that theanine attenuated the DOX-induced adverse reactions involved in oxidative damage, due to increase in glutamate and the recovery of GSH levels in normal tissues.

Cancer Lett. 2004 Aug 30;212(2):177-84

All Contents Copyright © 1995-2009 Life Extension Foundation All rights reserved.

**LifeExtension®**

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.