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Journal
ABSTRACTS**DHEA****EFFECTS OF DEHYDROEPIANDROSTERONE ON GLUCONEOGENIC ENZYMES AND GLUCOSE UPTAKE IN HUMAN HEPATOMA CELL LINE, HEPG2.**

Dehydroepiandrosterone (DHEA), the most abundant human adrenal steroid, improves insulin sensitivity and obesity in human and model animals. In a previous study, we reported that orally administered DHEA suppresses the elevated activities of hepatic gluconeogenic enzymes like glucose-6-phosphatase (G6Pase) in C57BL/KsJ-db/db mice. However, the molecular mechanisms by which DHEA ameliorates insulin resistance are not clearly understood. In the present study, we cultured the human hepatoma cell line HepG2 with DHEA and measured the enzyme activity and protein expression of G6Pase to investigate the direct effect of DHEA on glucose metabolism in hepatocytes. DHEA significantly suppressed both the activity and protein expression of G6Pase. Moreover, DHEA decreased the gene expression of G6Pase and phosphoenolpyruvate carboxykinase, both of which were maximal at 1 microM DHEA, whereas the mRNA level of glucose-6-phosphate translocase was unchanged. Furthermore, DHEA enhanced 2-deoxyglucose uptake, although its effect was much smaller than that of insulin. These results suggest that DHEA may act at multiple steps in the regulation of glucose metabolism in the liver.

Endocr J. 2005 Dec;52(6):727-33

EFFECTS OF EARLY-LIFE STRESS ON BEHAVIOR AND NEUROSTEROID LEVELS IN THE RAT HYPOTHALAMUS AND ENTORHINAL CORTEX.

Recent evidence support the hypothesis that exposure to stress or trauma during early childhood may disturb the formation of functional brain pathways, in particular, of the limbic circuits. We examined the effects of exposure to early life trauma (juvenile stress) on emotional and cognitive aspects of behavior in adulthood as well as on dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) levels in relevant brain regions. Quantitative assessment of the effects of exposure to juvenile stress was made 1 month post-stress, and obtained by measuring: emotional (utilizing an open field and a startle response tests) and cognitive (Morris water-maze task) functions, as well as neurosteroids concentration (DHEA and its sulfate ester, DHEAS) in the hypothalamus and entorhinal cortex. We report here that an exposure to juvenile stress led to elevated levels of anxiety 1 month post-stress. Moreover, in a spatial learning task, the juvenile stress group performed poorer than the control group. Finally, an exposure to juvenile stress increased DHEAS but not DHEA concentrations both in the hypothalamus and the entorhinal cortex. These findings indicate that an exposure to juvenile stress has long-lasting effects on behavior and DHEAS levels in the hypothalamus and the entorhinal cortex. These effects may be of relevance to our understanding of early life stress-related disorders such as PTSD and major depression.

Brain Res Bull. 2006 Feb 15;68(6):419-24

PLACEBO-CONTROLLED TRIAL OF DEHYDROEPIANDROSTERONE (DHEA) FOR TREATMENT OF NONMAJOR DEPRESSION IN PATIENTS WITH HIV/AIDS.

OBJECTIVE: Subsyndromal major depressive disorder is common among HIV-positive adults. This study was designed to assess the efficacy of dehydroepiandrosterone (DHEA) as a potential treatment. **METHOD:** One hundred forty-five patients with subsyndromal depression or dysthymia were randomly assigned to receive either DHEA or placebo; 90% (69 of 77) of the DHEA patients and 94% (64 of 68) of the placebo patients completed the 8-week trial. The primary measure of efficacy was a Clinical Global Impression improvement rating of 1 or 2 (much or very much improved) plus a final Hamilton Depression Rating Scale score ≤ 8 . Outcome was assessed by using intent-to-treat analysis, followed by completer analysis. Safety was assessed by queries about side effects at every study visit plus measures of CD4 cell count and HIV RNA viral load at baseline and week 8. DHEA dosing was flexible (100-400 mg/day). **RESULTS:** On the basis of clinicians' ratings, DHEA was superior in the intent-to-treat analysis, where the response rate was 56% (43 of 77) for the DHEA group versus 31% (21 of 68) for the placebo group. In the completer analysis, the response rate was 62% (43 of 69) for the DHEA group, compared to 33% (21 of 64) for the placebo patients. The number needed to treat was 4 on the basis of intent-to-treat data and 3.4 on the basis of completer data. Few adverse events were reported in either treatment group, and no significant changes in CD4 cell count or HIV RNA viral load were

observed in either group. CONCLUSIONS: Nonmajor but persistent depression is common in patients with HIV/AIDS, and DHEA appears to be a useful treatment that is superior to placebo in reducing depressive symptoms. The low attrition rate in this group of physically ill patients, together with requests for extended open-label treatment, reflect high acceptance of this readily available intervention.

Am J Psychiatry. 2006 Jan;163(1):59-66

ANDROGEN THERAPY IN WOMEN.

Androgens in women either derive from direct ovarian production or from peripheral conversion of the adrenal sex steroid precursor, dehydroepiandrosterone, towards active androgens. Therefore, loss of adrenal or ovarian function, caused by Addison's disease or consequent to bilateral oophorectomy, results in severe androgen deficiency, clinically often associated with a loss of libido and energy. Importantly, physiological menopause does not necessarily lead to androgen deficiency, as androgen synthesis in the ovaries may persist despite the decline in estrogen production. However, the definition of female androgen deficiency, as recently provided by the Princeton consensus statement, is not precise enough and may lead to over-diagnosis due to the high prevalence of its diagnostic criteria: androgen levels below or within the lower quartile of the normal range and concurrent sexual dysfunction. Importantly, physiological menopause is not necessarily associated with androgen deficiency and therefore does not routinely require androgen therapy. Current replacement options include transdermal testosterone administration or dehydroepiandrosterone treatment, both of which have been shown to result in significant improvements, in particular in libido and mood, while effects on body composition and muscular function are not well documented. It is important to keep in mind that the number of randomized controlled trials is still limited and that currently none of the available preparations is officially approved for use in women. Currently, androgen replacement should be reserved for women with severe androgen deficiency due to an established cause and matching clinical signs and symptoms.

Eur J Endocrinol. 2006 Jan;154(1):1-11

RELATIONSHIP BETWEEN ANDROGENIC HORMONES AND ARTERIAL STIFFNESS, BASED ON LONGITUDINAL HORMONE MEASUREMENTS.

Circulating testosterone levels (T) decrease with age in men. Low T has been associated with coronary disease and with risk factors for atherosclerosis. This study examines the relationship in men between androgenic hormones and arterial stiffness, a major risk factor for cardiovascular events. T, sex hormone-binding globulin (SHBG), and dehydroepiandrosterone sulfate (DHEAS) were measured longitudinally over 33 yr (follow-up 11.8 +/- 8.3 yr) in 901 men from the Baltimore Longitudinal Study of Aging, of whom 206 (68.1 +/- 13.7 yr) underwent carotid duplex ultrasonography. The 901 men were used to characterize age-associated hormone levels by means of mixed-effects models. Hormone values were estimated for the 206 men at the time of ultrasonography. Free T index (FTI) was calculated by dividing T by SHBG. The arterial stiffness index was calculated from peak systolic and end diastolic diameters of the common carotid artery and simultaneous brachial artery blood pressure. T, FTI, and DHEAS were correlated negatively with age, pulse pressure (PP), and stiffness index (each $P < 0.01$), whereas SHBG was correlated positively with age and stiffness index ($P < 0.01$). However, T was the only hormone that predicted the stiffness index after adjustment for age, PP, fasting plasma glucose, body mass index, and total cholesterol. T values 5-10 yr before the carotid study also predicted the stiffness index ($P < 0.05$). Thus the adverse influence of low T on the cardiovascular system in men may be mediated in part via the effects of T on vascular structure and function.

Am J Physiol Endocrinol Metab. 2006 Feb;290(2):E234-42

SHORT-TERM DEHYDROEPIANDROSTERONE TREATMENT INCREASES PLATELET CGMP PRODUCTION IN ELDERLY MALE SUBJECTS.

OBJECTIVE: Several clinical and population-based studies suggest that dehydroepiandrosterone (DHEA) and its sulphate (DHEA-S) play a protective role against atherosclerosis and coronary artery disease in human. However, the mechanisms underlying this action are still unknown. It has recently been suggested that DHEA-S could delay atheroma formation through an increase in nitric oxide (NO) production. **STUDY DESIGN AND METHODS:** Twenty-four aged male subjects [age (mean +/- SEM): 65.4 +/- 0.7 year; range: 58.2-67.6 years] underwent a blinded placebo controlled study receiving DHEA (50 mg p.o. daily at bedtime) or placebo for 2 months. Platelet cyclic guanosine-monophosphate (cGMP) concentration (as marker of NO production) and serum levels of DHEA-S, DHEA, IGF-I, insulin, glucose, oestradiol (E(2)), testosterone, plasminogen activator inhibitor (PAI)-1 antigen (PAI-1 Ag), homocysteine and lipid profile were evaluated before and after the 2-month treatment with DHEA or placebo. **RESULTS:** At the baseline, all variables in the two groups were overlapping. All parameters were unchanged after treatment with placebo. Conversely, treatment with DHEA (a) increased ($P < 0.001$ vs. baseline) platelet cGMP (111.9 +/- 7.1 vs. 50.1 +/- 4.1 fmol/10(6) plts), DHEA-S (13.6 +/- 0.8 vs. 3.0 +/- 0.3 micromol/l), DHEA (23.6 +/- 1.7 vs. 15.3 +/- 1.4 nmol/l), testosterone (23.6 +/- 1.0 vs. 17.7 +/- 1.0 nmol/l) and E(2) (72.0 +/- 5.0 vs. 60.0 +/- 4.0 pmol/l); and (b) decreased ($P < 0.05$ vs. baseline) PAI-1 Ag (27.4 +/- 3.8 vs. 21.5 +/- 2.5 ng/ml) and low-density lipoprotein (LDL) cholesterol (3.4 +/- 0.2 vs. 3.0 +/- 0.2 mmol/l). IGF-I, insulin, glucose, triglycerides, total cholesterol, HDL cholesterol, HDL2 cholesterol, HDL3 cholesterol,

apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB) and homocysteine levels were not modified by DHEA treatment. CONCLUSIONS: This study shows that short-term treatment with DHEA increased platelet cGMP production, a marker of NO production, in healthy elderly subjects. This effect is coupled with a decrease in PAI-1 and LDL cholesterol levels as well as an increase in testosterone and E(2) levels. These findings, therefore, suggest that chronic DHEA supplementation would exert antiatherogenic effects, particularly in elderly subjects who display low circulating levels of this hormone.

Clin Endocrinol (Oxf). 2006 Mar;64(3):260-4

DEHYDROEPIANDROSTERONE INHIBITED THE BONE RESORPTION THROUGH THE UPREGULATION OF OPG/RANKL.

The plasma level of dehydroepiandrosterone (DHEA) decreases gradually along with aging. The beneficial effects of DHEA as an anti-aging steroid, such as the stimulatory effect on immune system, anti-diabetes mellitus, anti-atherosclerosis, anti-dementia, anti-obesity and anti-osteoporosis have been demonstrated in experiment both in vitro and in vivo. It is important to investigate the effective mechanism of DHEA in therapeutics for postmenopausal osteoporosis. Having isolated and cultured osteoblasts (OBs) and osteoclasts (OCs), we analysed the effect of DHEA on osteoblastic viability, regulation of DHEA on the expression of osteoprotegerin (OPG)/receptor activator of NF-kappaB ligand (RANKL) mRNA in OBs, and then observed the action of DHEA on bone resorption of OCs in the presence or absence of OBs. The results showed that DHEA improved viability of OBs within the concentration range of 0.01-1 microM, especially at the concentration of 0.1 microM. DHEA could apparently increase the ratio of OPG/RANKL mRNA in OBs. In the presence of OBs, DHEA could decrease the number and area of absorption lacuna of specula. We concluded, therefore, only in the presence of OBs, DHEA could inhibit the bone resorption of OCs, which may be mediated by OPG/RANKL of OBs.

Cell Mol Immunol. 2006 Feb;3(1):41-5

ROLE OF ANDROGENS AND DHEA IN BONE METABOLISM.

Androgens have a major role in the growth and the maintenance of both cancellous and cortical bone mass in men. Androgen receptor is expressed in osteoblasts, osteoclasts and bone marrow stromal cells. Androgens have been shown to regulate the expression and the activity of several cytokines and growth factors, and control the homeostasis in bones. Dehydroepiandrosterone (DHEA) has a protective effect against osteoporosis in women after menopause through the intracrine mechanism in osteoblasts, which DHEA is converted to estrogen through the aromatase activity.

Clin Calcium. 2006 Jan;16(1):61-6

DEHYDROEPIANDROSTERONE INCREASES BETA-CELL MASS AND IMPROVES THE GLUCOSE-INDUCED INSULIN SECRETION BY PANCREATIC ISLETS FROM AGED RATS.

The effect of dehydroepiandrosterone (DHEA) on pancreatic islet function of aged rats, an animal model with impaired glucose-induced insulin secretion, was investigated. The following parameters were examined: morphological analysis of endocrine pancreata by immunohistochemistry; protein levels of insulin receptor, IRS-1, IRS-2, PI 3-kinase, Akt-1, and Akt-2; and static insulin secretion in isolated pancreatic islets. Pancreatic islets from DHEA-treated rats showed an increased beta-cell mass accompanied by increased Akt-1 protein level but reduced IR, IRS-1, and IRS-2 protein levels and enhanced glucose-stimulated insulin secretion. The present results suggest that DHEA may be a promising drug to prevent diabetes during aging.

FEBS Lett. 2006 Jan 9;580(1):285-90

RELATIONSHIP BETWEEN SERUM SEX STEROIDS AND AGING MALE SYMPTOMS SCORE AND INTERNATIONAL INDEX OF ERECTILE FUNCTION.

OBJECTIVES: To determine the relationship between the total and subscale scores of the Aging Male Symptoms (AMS) and International Index of Erectile Function (IIEF) questionnaires, age, and serum sex steroids levels. METHODS: A total of 348 patients enrolled in the study answered the AMS and IIEF questionnaires. Hormonal analysis, including total testosterone, free testosterone (FT), estradiol (E2), and dehydroepiandrosterone-sulphate (DHEA-S) measurement, were performed. The patients with a total AMS score of 29 were considered to have aging male symptoms and the patients with an IIEF score of less than 26 were considered to have sexual dysfunction. RESULTS: Although DHEA-S levels were significantly lower and E2 levels were greater in the men with aging male symptoms according to the AMS, the DHEA-S and FT levels were significantly lower in the men with sexual dysfunction, as determined by the IIEF score. Serum DHEA-S and FT levels and age correlated significantly with the IIEF scores. The total AMS score correlated significantly only with age. Although serum total testosterone, FT, and DHEA-S levels correlated significantly with the andrologic symptoms of AMS, the serum E2 levels correlated with psychological symptoms of AMS. CONCLUSIONS: Although aging male symptoms and the effects of hormonal changes on these symptoms have been controversial, DHEA-S and E2 might play some important roles in the symptoms of aging men.

ENDOGENOUS SEX HORMONES AND METABOLIC SYNDROME IN AGING MEN.

BACKGROUND: Sex hormone levels in men change during aging. These changes may be associated with insulin sensitivity and the metabolic syndrome. **METHODS:** We studied the association between endogenous sex hormones and characteristics of the metabolic syndrome in 400 independently living men between 40 and 80 yr of age in a cross-sectional study. Serum concentrations of lipids, glucose, insulin, total testosterone (TT), SHBG, estradiol (E2), and dehydroepiandrosterone sulfate (DHEA-S) were measured. Bioavailable testosterone (BT) was calculated using TT and SHBG. Body height, weight, waist-hip circumference, blood pressure, and physical activity were assessed. Smoking and alcohol consumption was estimated from self-report. The metabolic syndrome was defined according to the National Cholesterol Education Program definition, and insulin sensitivity was calculated by use of the quantitative insulin sensitivity check index. **RESULTS:** Multiple logistic regression analyses showed an inverse relationship according to 1 sd increase for circulating TT [odds ratio (OR) = 0.43; 95% confidence interval (CI), 0.32-0.59], BT (OR = 0.62; 95% CI, 0.46-0.83), SHBG (OR = 0.46; 95% CI, 0.33-0.64), and DHEA-S (OR = 0.76; 95% CI, 0.56-1.02) with the metabolic syndrome. Each sd increase in E2 levels was not significantly associated with the metabolic syndrome (OR = 1.16; 95% CI, 0.92-1.45). Linear regression analyses showed that higher TT, BT, and SHBG levels were related to higher insulin sensitivity; beta-coefficients (95% CI) were 0.011 (0.008-0.015), 0.005 (0.001-0.009), and 0.013 (0.010-0.017), respectively, whereas no effects were found for DHEA-S and E2. Estimates were adjusted for age, smoking, alcohol consumption, and physical activity score. Further adjustment for insulin levels and body composition measurements attenuated the estimates, and the associations were similar in the group free of cardiovascular disease and diabetes. **CONCLUSIONS:** Higher testosterone and SHBG levels in aging males are independently associated with a higher insulin sensitivity and a reduced risk of the metabolic syndrome, independent of insulin levels and body composition measurements, suggesting that these hormones may protect against the development of metabolic syndrome.

J Clin Endocrinol Metab. 2005 May;90(5):2618-23

EFFECT OF DHEA ON ABDOMINAL FAT AND INSULIN ACTION IN ELDERLY WOMEN AND MEN: A RANDOMIZED CONTROLLED TRIAL.

CONTEXT: Dehydroepiandrosterone (DHEA) administration has been shown to reduce accumulation of abdominal visceral fat and protect against insulin resistance in laboratory animals, but it is not known whether DHEA decreases abdominal obesity in humans. DHEA is widely available as a dietary supplement without a prescription. **OBJECTIVE:** To determine whether DHEA replacement therapy decreases abdominal fat and improves insulin action in elderly persons. **DESIGN AND SETTING:** Randomized, double-blind, placebo-controlled trial conducted in a US university-based research center from June 2001 to February 2004. **PARTICIPANTS:** Fifty-six elderly persons (28 women and 28 men aged 71 [range, 65-78] years) with age-related decrease in DHEA level. **INTERVENTION:** Participants were randomly assigned to receive 50 mg/d of DHEA or matching placebo for 6 months. **MAIN OUTCOME MEASURES:** The primary outcome measures were 6-month change in visceral and subcutaneous abdominal fat measured by magnetic resonance imaging and glucose and insulin responses to an oral glucose tolerance test (OGTT). **RESULTS:** Of the 56 men and women enrolled, 52 underwent follow-up evaluations. Compliance with the intervention was 97% in the DHEA group and 95% in the placebo group. Based on intention-to-treat analyses, DHEA therapy compared with placebo induced significant decreases in visceral fat area (-13 cm² vs +3 cm², respectively; P = .001) and subcutaneous fat (-13 cm² vs +2 cm², P = .003). The insulin area under the curve (AUC) during the OGTT was significantly reduced after 6 months of DHEA therapy compared with placebo (-1119 muU/mL per 2 hours vs +818 muU/mL per 2 hours, P = .007). Despite the lower insulin levels, the glucose AUC was unchanged, resulting in a significant increase in an insulin sensitivity index in response to DHEA compared with placebo (+1.4 vs -0.7, P = .005). **CONCLUSION:** DHEA replacement could play a role in prevention and treatment of the metabolic syndrome associated with abdominal obesity.

JAMA. 2004 Nov 10;292(18):2243-8

IS DEHYDROEPIANDROSTERONE A HORMONE?

Dehydroepiandrosterone (DHEA) is not a hormone but it is a very important prohormone secreted in large amounts by the adrenals in humans and other primates, but not in lower species. It is secreted in larger quantities than cortisol and is present in the blood at concentrations only second to cholesterol. All the enzymes required to transform DHEA into androgens and/or estrogens are expressed in a cell-specific manner in a large series of peripheral target tissues, thus permitting all androgen-sensitive and estrogen-sensitive tissues to make locally and control the intracellular levels of sex steroids according to local needs. This new field of endocrinology has been called intracrinology. In women, after menopause, all estrogens and almost all androgens are made locally in peripheral tissues from DHEA which indirectly exerts effects, among others, on bone formation, adiposity, muscle, insulin and glucose metabolism, skin, libido and well-being. In men, where the secretion of androgens by the testicles continues for life, the contribution of DHEA to androgens has been best evaluated in the prostate where about 50% of androgens are made locally from DHEA. Such knowledge has led to the development of combined androgen blockade (CAB), a

treatment which adds a pure anti-androgen to medical (GnRH agonist) or surgical castration in order to block the access of the androgens made locally to the androgen receptor. In fact, CAB has been the first treatment demonstrated to prolong life in advanced prostate cancer while recent data indicate that it can permit long-term control and probably cure in at least 90% of cases of localized prostate cancer. The new field of intracrinology or local formation of sex steroids from DHEA in target tissues has permitted major advances in the treatment of the two most frequent cancers, namely breast and prostate cancer, while its potential use as a physiological HRT could well provide a physiological balance of androgens and estrogens, thus offering exciting possibilities for women's health at menopause.

J Endocrinol. 2005 Nov;187(2):169-96

CORRELATIONS BETWEEN HORMONES, PHYSICAL, AND AFFECTIVE PARAMETERS IN AGING UROLOGIC OUTPATIENTS.

OBJECTIVE: To determine the relationship between sex hormones, physical complaints, depression, sexuality, and life satisfaction in aging men. **METHODS:** 263 outpatients aged 40 years and above (M=56.2; 40-84 years) were recruited from 6 andrological outpatient departments in Germany to evaluate "aging male" symptoms. Subjects were assessed by standardised self-report questionnaires, physical, and endocrinological examination. **RESULTS:** Total and free testosterone as well as DHEA-S (dehydroepiandrosterone-sulfate) levels decreased significantly with age. SHBG (sex hormone binding globulin) and LH (luteinizing hormone) increased; estradiol remained unchanged. Inactivity, lower urinary tract symptoms, erectile and orgasmic dysfunction also increased significantly with age. A low testosterone level was significantly associated with a reduced motivation and a lack of sexual desire. In addition to reduced testosterone levels, a reduced motivation was also predicted by depression and an impaired physical self-concept. Reduced activity, erectile dysfunction, and low testosterone levels contributed significantly to the lack of sexual desire. **CONCLUSIONS:** Aging men are frequently afflicted with a wide range of physical complaints (e.g. fatigue, prostate symptoms), erectile and orgasmic dysfunction, reflected in a reduced physical self-concept. Assessment and treatment of age-related physical and affective alterations must consider their close interplay with hormonal and lifestyle variables.

Eur Urol. 2005 Jun;47(6):749-55

STEROID SULFATASE INHIBITORS AS NOVEL ADDITIONS TO THE ANTIPSORIATIC ARMAMENTARIUM.

Psoriasis is a clinical conundrum that affects an estimated 1-3% of the world's population. The psoriatic disease process, characterized by a type 1 cytokine pattern, is supposed to be maintained by a continuing immune response in a "peripheral lymphoid tissue" that forms in lesional skin and is composed of T cells, dendritic cells, and vessels arranged like a T-dependent zone in lymph nodes. Dehydroepiandrosterone (DHEA), produced from dehydroepiandrosterone sulfate (DHEAS) through the enzymatic activity of DHEA-sulfatase, plays a pivotal role in the development of the type 1 immune response generated in peripheral lymphoid organs. Taken together, it could be reasoned that DHEA-sulfatase inhibitors may have utility in the treatment of psoriasis. Furthermore, the addition of DHEA-sulfatase inhibitors to calcipotriol, which encourages type 2 immune response, may provide an additive or synergistic inhibition of the type 1 immune response underlying psoriasis. It has been shown that topical application of cholesterol sulfate in the hairless mouse causes epidermal hyperkeratosis, which can be prevented by co-application of topical cholesterol. Therefore, as the inhibition of conversion of cholesterol sulfate to cholesterol can induce epidermal hyperkeratosis and may thus abbreviate the benefit obtained by inhibition of DHEAS to DHEA conversion, topical sulfatase inhibitors should preferably be co-applied with topical cholesterol, though it is also possible that the beneficial immunological effects of steroid sulfatase inhibitors outweigh their possible hyperkeratosis stimulation. Alternatively, the production of specific DHEA-sulfatase inhibitors can resolve the above concern. DHEA-sulfatase inhibitors may prove invaluable in the treatment of psoriasis.

Med Sci Monit. 2005 Mar;11(3):HY7-9

TREATMENT OF ADHD WITH FRENCH MARITIME PINE BARK EXTRACT, PYCNOGENOL((R)).

Attention Deficit/Hyperactivity Disorder (ADHD) is the most common psychiatric disorder in children. Pycnogenol((R)), an extract from the bark of the French maritime pine, consisting of phenolic acids, catechin, taxifolin and procyanidins, has shown improvement of ADHD in case reports and in an open study. Aim of the present study was to evaluate the effect of Pycnogenol ((R)) on ADHD symptoms. Sixty-one children were supplemented with 1 mg/kg/day Pycnogenol((R)) or placebo over a period of 4 weeks in a randomised, placebo-controlled, doubleblind study. Patients were examined at start of trial, 1 month after treatment and 1 month after end of treatment period by standard questionnaires: CAP (Child Attention Problems) teacher rating scale, Conner's Teacher Rating Scale (CTRS), the Conner's Parent Rating Scale (CPRS) and a modified Wechsler Intelligence Scale for children. Results show that 1-month Pycnogenol((R)) administration caused a significant reduction of hyperactivity, improves attention and visual-motoric coordination and concentration of children with ADHD. In the placebo group no positive effects were found. One month after termination of Pycnogenol((R)) administration a relapse of symptoms was noted. Our results point to an option to use Pycnogenol as a natural supplement to relieve ADHD symptoms of children.

Eur Child Adolesc Psychiatry. 2006 May 13

SLEEP HYGIENE AND MELATONIN TREATMENT FOR CHILDREN AND ADOLESCENTS WITH ADHD AND INITIAL INSOMNIA.

OBJECTIVE: To evaluate the efficacy of sleep hygiene and melatonin treatment for initial insomnia in children with attention-deficit/hyperactivity disorder (ADHD). **METHOD:** Twenty-seven stimulant-treated children (6-14 years of age) with ADHD and initial insomnia (>60 minutes) received sleep hygiene intervention. Nonresponders were randomized to a 30-day double-blind, placebo-controlled, crossover trial of 5-mg pharmaceutical-grade melatonin provided by the study's sponsor. **RESULTS:** Sleep hygiene reduced initial insomnia to <60 minutes in 5 cases, with an overall effect size in the group as a whole of 0.67. Analysis of the trial data able to be evaluated showed a significant reduction in initial insomnia of 16 minutes with melatonin relative to placebo, with an effect size of 0.6. Adverse events were generally mild and not different from those recorded with placebo treatment. The effect size of the combined sleep hygiene and melatonin intervention from baseline to 90 days' posttrial was 1.7, with a mean decrease in initial insomnia of 60 minutes. Improved sleep had no demonstrable effect on ADHD symptoms. **CONCLUSION:** Combined sleep hygiene and melatonin was a safe and effective treatment for initial insomnia in children with ADHD taking stimulant medication.

J Am Acad Child Adolesc Psychiatry. 2006 May;45(5):512-9

MAGNESIUM VITB6 INTAKE REDUCES CENTRAL NERVOUS SYSTEM HYPEREXCITABILITY IN CHILDREN.

OBJECTIVE: Ionic magnesium (Mg(2+)) depletion has long been known to cause hyperexcitability with convulsive seizures in rodents, effects that have been reversed by treatment with magnesium (Mg). Metabolic disorders and genetic alterations are suspected in this pathology, in which Mg(2+) transport and intracellular distribution may be reduced without change in serum Mg (2+) concentrations. We evaluated the effects of Mg(2+)/vitamin B6 regimen on the behavior of 52 hyperexcitable children (under 15 years of age) and their families. **METHODS:** To assess intracellular Mg(2+), we measured intra-erythrocyte Mg(2+) levels (ERC-Mg). Our reference values for normal subjects were 2.46 to 2.72 mmol/L. In 30 of the 52 hyperactive children, there were low ERC-Mg values: 2.041 +/- 0.279 mmol/L. Combined Mg(2+)/vitamin B6 intake (100 mg/day) for 3 to 24 weeks restored normal ERC-Mg values (2.329 +/- 0.386 mmol/L). **RESULTS:** In all patients, symptoms of hyperexcitability (physical aggressivity, instability, scholar attention, hypertony, spasm, myoclony) were reduced after 1 to 6 months treatment. Other family members shared similar symptoms, had low ERC-Mg values, and also responded clinically to increased Mg(2+)/vitamin B6 intakes. Two typical families are described. **CONCLUSION:** This open study indicates that hyperexcitable children have low ERC-Mg with normal serum Mg(2+) values, and that Mg(2+)/vitamin B6 supplementation can restore normal ERC-Mg levels and improve their abnormal behavior.

J Am Coll Nutr. 2004 Oct;23(5):545S-548S

EFFECT OF MAGNE-B6 ON THE CLINICAL AND BIOCHEMICAL MANIFESTATIONS OF THE SYNDROME OF ATTENTION DEFICIT AND HYPERACTIVITY IN CHILDREN.

MAGNE-B6 was used for the therapy of a group of 31 children aged from 6 to 12 with attention deficiency and hyperactivity syndrome. The control group included 20 children with similar manifestations of the same pathology, which received a polyvitamin complex. The efficacy of therapy was assessed in the 30th day with the aid of a complex clinical-neuropsychological and biochemical investigations. It was established that the administration of MAGNE-B6 led to improvements in the behavior, decreased the level of anxiety and aggression, improved both large- and small-scale mobility, decreased the level of synkinesis, increased the characteristics of attention, corrected the magnesium homeostasis, and favored normalization of the blood electrolytes. Reliable differences ($p < 0.01$ or 0.001) between the test and control groups in the degree of expression of the indicated disorders were observed.

Eksp Klin Farmakol. 2006 Jan-Feb;69(1):74-7

SUPPLEMENTATION WITH FLAX OIL AND VITAMIN C IMPROVES THE OUTCOME OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD).

Considerable clinical and experimental evidence now supports the idea that deficiencies or imbalances in certain highly unsaturated fatty acids may contribute to a range of common developmental disorders including Attention Deficit Hyperactivity Disorder (ADHD). Few intervention studies with LCPUFA supplementation have reported inconsistent and marginal results. This pilot study evaluates the effect of alpha linolenic acid (ALA)-rich nutritional supplementation in the form of flax oil and antioxidant emulsion on blood fatty acids composition and behavior in children with ADHD. Post-supplementation levels of RBC membrane fatty acids were significantly higher than pretreatment levels as well as the levels in control. There was significant improvement in the symptoms of ADHD reflected by reduction in total hyperactivity scores of ADHD children derived from ADHD rating scale.

Prostaglandins Leukot Essent Fatty Acids. 2006 Jan;74(1):17-21

EFFECT OF THE HERBAL EXTRACT COMBINATION PANAX QUINQUEFOLIUM AND GINKGO BILOBA ON ATTENTION-DEFICIT HYPERACTIVITY DISORDER: A PILOT STUDY.

OBJECTIVE: A combination herbal product containing American ginseng extract, Panax quinquefolium, (200 mg) and Ginkgo biloba extract (50 mg) (AD-FX; CV Technologies, Edmonton, Alta.) was tested for its ability to improve the symptoms of attention-deficit hyperactivity disorder (ADHD). **DESIGN:** Open study. **PATIENTS:** 36 children ranging in age from 3 to 17 years who fit the diagnostic criteria for ADHD. **INTERVENTIONS:** AD-FX capsules were taken twice a day on an empty stomach for 4 weeks. Patients were instructed not to change any other medications during the study. **OUTCOME MEASURES:** At the beginning of the study, after 2 weeks, and then at the end of the 4-week trial, parents completed the Conners' Parent Rating Scale--revised, long version, a questionnaire that assesses a broad range of problem behaviours (and was used as an indication of ADHD symptom severity). **RESULTS:** After 2 weeks of treatment, the proportion of the subjects exhibiting improvement (i.e., decrease in T-score of at least 5 points) ranged from 31% for the anxious-shy attribute to 67% for the psychosomatic attribute. After 4 weeks of treatment, the proportion of subjects exhibiting improvement ranged from 44% for the social problems attribute to 74% for the Conners' ADHD index and the DSM-IV hyperactive-impulsive attribute. Five (14%) of 36 subjects reported adverse events, only 2 of which were considered related to the study medication. **CONCLUSIONS:** These preliminary results suggest AD-FX treatment may improve symptoms of ADHD and should encourage further research on the use of ginseng and ginkgo biloba extracts to treat ADHD symptoms.

J Psychiatry Neurosci. 2001 May;26(3):221-8

DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ZINC SULFATE IN THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER.

BACKGROUND: The most commonly used medications for attention deficit hyperactivity disorder (ADHD) are the psychostimulants. There is, however, considerable awareness in alternative, nonstimulant therapies, because some patients respond poorly to stimulants or are unable to tolerate them. Some studies suggest that deficiency of zinc play a substantial role in the aetiopathogenesis of ADHD. Therefore, to assess the efficacy of zinc sulfate we conducted treatment trial. **METHODS:** Patients with a primary DSM-IV diagnosis of ADHD (N=400; 72 girls, 328 boys, mean age=9.61+/-1.7) were randomly assigned in a 1:1 ratio to 12 weeks of double-blind treatment with zinc sulfate (n=202) (150 mg/day) or placebo (n=198). Efficacy was assessed with the Attention Deficit Hyperactivity Disorder Scale (ADHDS), Conners Teacher Questionnaire, and DuPaul Parent Ratings of ADHD. Primary efficacy variables were differences from baseline to endpoint (last observation carried forward) in mean ADHDS and Conners Teacher Questionnaire scores between the zinc sulfate and the placebo groups. Safety evaluations included monitoring of adverse events, vital signs and clinical laboratory values. **RESULTS:** Zinc sulfate was statistically superior to placebo in reducing both hyperactive, impulsive and impaired socialization symptoms, but not in reducing attention deficiency symptoms, as assessed by ADHDS. However, full therapeutic response rates of the zinc and placebo groups remained 28.7% and 20%, respectively. It was determined that the hyperactivity, impulsivity and socialization scores displayed significant decrease in patients of older age and high BMI score with low zinc and free fatty acids (FFA) levels. Zinc sulfate was well

tolerated and associated with a low rate of side effect. CONCLUSIONS: Zinc monotherapy was significantly superior to placebo in reducing symptoms of hyperactivity, impulsivity and impaired socialization in patients with ADHD. Although by themselves, these findings may not be sufficient, it may well be considered that zinc treatment appears to be an efficacious treatment for ADHD patients having older age and high BMI score with low zinc and FFA levels.

Prog Neuropsychopharmacol Biol Psychiatry. 2004 Jan;28(1):181-90

EFFECT OF RANDOMIZED SUPPLEMENTATION WITH HIGH DOSE OLIVE, FLAX OR FISH OIL ON SERUM PHOSPHOLIPID FATTY ACID LEVELS IN ADULTS WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Dietary intake of omega-3 fatty acids has been positively correlated with cardiovascular and neuropsychiatric health in several studies. The high seafood intake by the Japanese and Greenland Inuit has resulted in low ratios of the omega-6 fatty acid arachidonic acid (AA, 20:4n-6) to eicosapentaenoic acid (EPA, 20:5n-3), with the Japanese showing AA:EPA ratios of approximately 1.7 and the Greenland Eskimos showing ratios of approximately 0.14. It was the objective of this study to determine the effect of supplementation with high doses (60 g) of flax and fish oils on the blood phospholipid (PL) fatty acid status, and AA/EPA ratio of individuals with Attention Deficit Hyperactivity Disorder (ADHD), commonly associated with decreased blood omega-3 fatty acid levels. Thirty adults with ADHD were randomized to 12 weeks of supplementation with olive oil (< 1% omega-3 fatty acids), flax oil (source of alpha-linolenic acid; 18:3n-3; alpha-LNA) or fish oil (source of EPA and docosahexaenoic acid; 22:6n-3; DHA). Serum PL fatty acid levels were determined at baseline and at 12 weeks. Flax oil supplementation resulted in an increase in alpha-LNA and a slight decrease in the ratio of AA/EPA, while fish oil supplementation resulted in increases in EPA, DHA and total omega-3 fatty acids and a decrease in the AA/EPA ratio to values seen in the Japanese population. These data suggest that in order to increase levels of EPA and DHA in adults with ADHD, and decrease the AA/EPA ratio to levels seen in high fish consuming populations, high dose fish oil may be preferable to high dose flax oil. Future study is warranted to determine whether correction of low levels of long-chain omega-3 fatty acids is of therapeutic benefit in this population.

Reprod Nutr Dev. 2005 Sep-Oct;45(5):549-58

THE OXFORD-DURHAM STUDY: A RANDOMIZED, CONTROLLED TRIAL OF DIETARY SUPPLEMENTATION WITH FATTY ACIDS IN CHILDREN WITH DEVELOPMENTAL COORDINATION DISORDER.

BACKGROUND: Developmental coordination disorder (DCD) affects approximately 5% of school-aged children. In addition to the core deficits in motor function, this condition is associated commonly with difficulties in learning, behavior, and psychosocial adjustment that persist into adulthood. Mounting evidence suggests that a relative lack of certain polyunsaturated fatty acids may contribute to related neurodevelopmental and psychiatric disorders such as dyslexia and attention-deficit/hyperactivity disorder. Given the current lack of effective, evidence-based treatment options for DCD, the use of fatty acid supplements merits investigation. METHODS: A randomized, controlled trial of dietary supplementation with omega-3 and omega-6 fatty acids, compared with placebo, was conducted with 117 children with DCD (5-12 years of age). Treatment for 3 months in parallel groups was followed by a 1-way crossover from placebo to active treatment for an additional 3 months. RESULTS: No effect of treatment on motor skills was apparent, but significant improvements for active treatment versus placebo were found in reading, spelling, and behavior over 3 months of treatment in parallel groups. After the crossover, similar changes were seen in the placebo-active group, whereas children continuing with active treatment maintained or improved their progress. CONCLUSIONS: Fatty acid supplementation may offer a safe efficacious treatment option for educational and behavioral problems among children with DCD. Additional work is needed to investigate whether our inability to detect any improvement in motor skills reflects the measures used and to assess the durability of treatment effects on behavior and academic progress.

Pediatrics. 2005 May;115(5):1360-6

INCREASED LEVELS OF ETHANE, A NON-INVASIVE MARKER OF N-3 FATTY ACID OXIDATION, IN BREATH OF CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER.

Attention deficit hyperactivity disorder (ADHD) comprises a range of behavioural problems including inattention, hyperactivity and impulsivity. Diagnosis and treatment of the disorder is made difficult due to its unknown biological basis. Several studies have identified abnormalities in membrane fatty acids in some subjects with ADHD, and some success has been reported using lipid therapies. We have measured exhalant ethane levels, a non-invasive measure of oxidative damage to n-3 fatty acids, to probe biochemical alterations in ADHD. Patients with ADHD (N = 10) had higher levels of ethane in exhalant than in healthy volunteers (N = 12) with approximately 50% of ADHD cases being above the control range. In contrast, levels of butane, a marker of protein oxidation, were unaltered. Our data, although preliminary, suggests that some patients with ADHD have higher rates of oxidative breakdown of n-3 polyunsaturated fatty acids (PUFAs). Such a biochemical abnormality may underlie the previously observed fatty acid deficiencies, as well as providing further rationale for the use of anti-oxidant and/or lipid supplementation therapy in the treatment of ADHD. Larger studies of ADHD using this non-invasive assessment of oxidative stress appear warranted.

PREVALENCE AND CORRELATES OF ILLICIT METHYLPHENIDATE USE AMONG 8TH, 10TH, AND 12TH GRADE STUDENTS IN THE UNITED STATES, 2001.

The prevalence and correlates of illicit methylphenidate use were examined within a nationally representative U.S. sample of 8th, 10th, and 12th graders. The annual prevalence of illicit methylphenidate use was 4%. Race, grade level, geographical region, grade point average, and substance use were all significantly associated with illicit methylphenidate use.

J Adolesc Health. 2004 Dec;35(6):501-4

METHYLPHENIDATE AND DEXTROAMPHETAMINE ABUSE IN SUBSTANCE-ABUSING ADOLESCENTS.

The prevalence of methylphenidate and dextroamphetamine misuse and abuse was examined in 450 adolescents referred for substance abuse treatment. Twenty three percent reported nonmedical use of these substances and six percent were diagnosed as methylphenidate or dextroamphetamine abusers. Abuse was more common in individuals who were out of school and had an eating disorder. Methylphenidate and dextroamphetamine abuse appears to be much less common than abuse of most other substances. It does occur, however, and parents and schools need to exert greater control over the dispensing of these medications. Physicians are advised to prescribe non-stimulant medications (eg, bupropion) when treating attention deficit hyperactivity disorder in substance-abusing individuals.

Am J Addict. 2004 Jul-Sep;13(4):381-9

Selenium

ROLE OF SE-DEPENDENT GLUTATHIONE PEROXIDASES IN GASTROINTESTINAL INFLAMMATION AND CANCER.

Increase in reactive oxygen species plays an integral part in the inflammatory response, and chronic inflammation increases cancer risk. Selenium-dependent glutathione peroxidase (GPX) is well recognized for its antioxidant, and thus anti-inflammatory, activity. However, due to the multiple antioxidant families present in the gastrointestinal tract, it has been difficult to demonstrate the importance of individual antioxidant enzymes. Using genetically altered mice deficient in individual Gpx genes has provided insight into the physiological functions of these genes. Insufficient GPX activity in the mucosal epithelium can trigger acute and chronic inflammation. The presence of certain microflora, such as *Helicobacter* species, may affect cancer risk significantly. However, when damaged cells have progressed into a precancerous status, increased GPX activity may become procarcinogenic, presumably due to inhibition of hydroperoxide-mediated apoptosis. This review summarizes the current view of GPX in inflammation and cancer with emphasis on the GI tract.

Free Radic Biol Med. 2004 Jun 15;36(12):1481-95

CANCER CHEMOPREVENTION BY GARLIC AND GARLIC-CONTAINING SULFUR AND SELENIUM COMPOUNDS.

As early as 1550 B.C., Egyptians realized the benefits of garlic as a remedy for a variety of diseases. Many epidemiological studies support the protective role of garlic and related allium foods against the development of certain human cancers. Natural garlic and garlic cultivated with selenium fertilization have been shown in laboratory animals to have protective roles in cancer prevention. Certain organoselenium compounds and their sulfur analogs have been identified in plants. Organoselenium compounds synthesized in our laboratory were compared with their sulfur analogs for chemopreventive efficacy. Diallyl selenide was at least 300-fold more effective than diallyl sulfide in protecting against 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary adenocarcinomas in rats. In addition, benzyl selenocyanate inhibited the development of DMBA-induced mammary adenocarcinomas and azoxymethane-induced colon cancer in rats and benzo[a]pyrene-induced forestomach tumors in mice. The sulfur analog, benzyl thiocyanate, had no effect under the same experimental conditions. Furthermore, we showed that 1,4-phenylenebis(methylene)selenocyanate, but not its sulfur analog, significantly inhibited DMBA-DNA adduct formation and suppressed DMBA-induced mammary carcinogenesis. Collectively, these results indicate that structurally distinctive organoselenium compounds are superior to their corresponding sulfur analogs in cancer chemoprevention. Additionally, synthetic aromatic selenocyanates are more effective cancer chemopreventive agents than the naturally occurring selenoamino acids. Because plants are capable of utilizing selenium in a manner similar to that in sulfur assimilation pathways, future studies should aim at determining whether, under appropriate conditions, these potent cancer chemopreventive synthetic selenium compounds can be synthesized by garlic and related allium foods.

J Nutr. 2006 Mar;136(3 Suppl):864S-869S

BIOAVAILABILITY OF SELENIUM FROM FOODS.

Selenium (Se), an essential nutrient, is needed for activity of several important proteins. Additionally, the consumption of Se in amounts that exceed the Recommended Dietary Allowance (RDA) may protect against prostate and colorectal cancer. Supplemental Se may be acquired through the diet, but Se bioavailability depends on the source. Therefore, dietary advice concerning improvement of Se intake depends on characterization of Se bioavailability from Se-containing food sources.

Nutr Rev. 2006 Mar;64(3):146-51

COMPARATIVE EFFECTS OF 2 ANTIOXIDANTS, SELENOMETHIONINE AND EPIGALLOCATECHIN-GALLATE, ON CATABOLIC AND ANABOLIC GENE EXPRESSION OF ARTICULAR CHONDROCYTES.

OBJECTIVE: To determine the effects of selenomethionine (Se-met) and epigallocatechin-gallate (EGCg) on gene expression, activation of mitogen-activating kinases, and DNA binding of nuclear factor-kappaB (NF-kappaB) and apolipoprotein-1 (AP-1) in articular chondrocytes. **METHODS:** Chondrocytes, cultured in low-oxygen tension, were pretreated with L-selenomethionine or EGCg for 24 h, followed by interleukin 1 (IL-1beta) for 1 h (nuclear and cytoplasmic extracts) or 24 h (RNA extraction). Reverse transcription-polymerase chain reaction was performed to determine mRNA levels of matrix metalloproteinases (MMP-1, -3, -13),

aggrecanases (-1, -2), IL-1beta, inducible nitric oxide synthase, cyclooxygenases (-1, -2), type II collagen and aggrecan, and transforming growth factor-beta (TGF-beta1, -2, -3) and their receptors I and II. Activity of mitogen-activating protein kinases (MAPK) was assayed by Western blot and AP-1/NF-kB DNA binding by electrophoretic mobility shift assay. RESULTS: Pretreatment with 0.5 microM Se-met prevented IL-1beta-induced MMP-1 and aggrecanase-1 expression, and reduced the cytokine inhibitory effect on type II collagen, aggrecan core protein, and TGF-beta receptor II (TGF-betaRII) mRNA levels. EGCg was more efficient in modulating the effects of IL-1beta on the genes studied. Whereas EGCg inhibited the IL-1beta-activated MAPK, NF-kappaB, and AP-1, Se-met stimulated that signaling pathway. This could account for the differential effects exerted by these antioxidants on chondrocytes. CONCLUSION: Our data provide insights into the mechanisms whereby EGCg and selenium modulate chondrocyte metabolism. Despite their differential mechanisms of action, the 2 compounds may exert global beneficial effects on articular cartilage.

J Rheumatol. 2005 Oct;32(10):1958-67

THE INFLAMMATORY CONSEQUENCES OF PSYCHOLOGIC STRESS: RELATIONSHIP TO INSULIN RESISTANCE, OBESITY, ATHEROSCLEROSIS AND DIABETES MELLITUS, TYPE II.

Inflammation is frequently present in the visceral fat and vasculature in certain patients with cardiovascular disease (CVD) and/or adult onset Diabetes Mellitus Type II (NIDDM). An hypothesis is presented which argues that repeated acute or chronic psychologically stressful states may cause this inflammatory process. The mediators are the major stress hormones norepinephrine (NE) and epinephrine (E) and cortisol together with components of the renin-angiotensin system (RAS), the proinflammatory cytokines (PIC), as well as free fatty acids (ffa), the latter as a result of lipolysis of neutral fat. NE/E commence this process by activation of NF(kappa)B in macrophages, visceral fat, and endothelial cells which induces the production of toll-like receptors which, when engaged, produce a cascade of inflammatory reactions comprising the acute phase response (APR) of the innate immune system (IIS). The inflammatory process is most marked in the visceral fat depot as well as the vasculature, and is involved in the metabolic events which culminate in the insulin resistance/metabolic syndromes (IRS/MS), the components of which precede and comprise the major risk factors for CVD and NIDDM. The visceral fat has both the proclivity and capacity to undergo inflammation. It contains a rich blood and nerve supply as well as proinflammatory molecules such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNFalpha), leptin, and resistin, the adipocytokines, and acute phase proteins (APP) which are activated from adipocytes and/or macrophages by sympathetic signaling. The inflammation is linked to fat accumulation. Cortisol, IL-6, angiotensin II (angio II), the enzyme 11(beta) hydroxysteroid dehydrogenase-1 and positive energy balance, the latter due to increased appetite induced by the major stress hormones, are factors which promote fat accumulation and are linked to obesity. There is also the capacity of the host to limit fat expansion. Sympathetic signaling induces TNF which stimulates the production of IL-6 and leptin from adipocytes; these molecules promote lipolysis and ffa fluxes from adipocytes. Moreover, catecholamines and certain PIC inhibit lipoprotein lipase, a fat synthesizing enzyme. The brain also participates in the regulation of fat cell mass; it is informed of fat depot mass by molecules such as leptin and ffa. Leptin stimulates corticotrophin releasing hormone in the brain which stimulates the SNS and HPA axes, i.e. the stress response. Also, ffa through portal signaling from the liver evoke a similar stress response which, like the response to psychologic stress, evokes an innate immune response (IIR), tending to limit fat expansion, which culminates in inflammatory cascades, the IRS-MS, obesity and disease if prolonged. Thus, the brain also has the capacity to limit fat expansion. A competition apparently exists between fat expansion and fat loss. In "western" cultures, with excessive food ingestion, obesity frequently results. The linkage of inflammation to fat metabolism is apparent since weight loss diminishes the concentration of inflammatory mediators. The linkage of stress to inflammation is all the more apparent since the efferent pathways from the brain in response to fat signals, which results in inflammation to decrease and limit fat cell mass, is the same as the response to psychologic stress, which strengthens the hypothesis presented herein.

Med Hypotheses. 2006;67(4):879-91. Epub 2006 Jun 15

CHEMICAL FORMS OF SELENIUM FOR CANCER PREVENTION.

Cancer is becoming an increasingly significant disease worldwide. Currently, more than 7 million people die each year from cancer. With the existing knowledge, at least one-third of worldwide cancer cases could be prevented. Searching for naturally occurring agents in routinely consumed foods that may inhibit cancer development, although challenging, constitutes a valuable and plausible approach to the control and prevention of cancer. To date, the use of the micronutrient selenium (Se) in human clinical trials is limited, but the outcome indicates that Se is among the most promising agents. Although it is convenient to describe the effects of Se in terms of the element, it must always be kept in mind that the chemical form of Se and the dose are determinants of its biological activities. Hyphenated techniques based on coupling chromatographic separation with inductively coupled plasma mass spectrometric (ICP-MS) detection are now established as the most realistic and potent analytical tools available for real-life speciation analysis. These speciation investigations provide evidence that the Se compounds, which can generate monomethylated Se (e.g., Se-methylselenocysteine and methylseleninic acid), are more efficacious than other Se compounds because of their chemoprevention activity.

J Trace Elem Med Biol. 2005;19(2-3):141-50. Epub 2005 Oct 24

THE EFFECT OF ANTIOXIDANT SUPPLEMENTATION ON SUPEROXIDE DISMUTASE ACTIVITY, CU AND ZN LEVELS, AND TOTAL ANTIOXIDANT STATUS IN ERYTHROCYTES OF PATIENTS WITH GRAVES' DISEASE.

The effects of supplementation with a fixed combination of antioxidants (vitamins C and E, beta-carotene and selenium) on superoxide dismutase activity, copper and zinc concentrations, and total antioxidant status were monitored in erythrocytes derived from a group of patients with Graves' disease treated with methimazole, with respect to the rate of achieving euthyroidism. Thyroid-stimulating hormone (TSH), thyroid hormones and the above-mentioned parameters were measured before therapy, and on days 30 and 60 after therapy initiation. The patients receiving antioxidant supplementation along with methimazole therapy (group A, n = 27) achieved euthyroidism at a faster rate than those treated with methimazole alone (group B, n = 28). The activity of superoxide dismutase decreased significantly in both patient groups during the treatment; however, there was no significant difference between the groups. There was no significant change in the erythrocyte concentration of copper, whereas the zinc concentration and total antioxidant status showed significant between-group differences. The study results clearly show that antioxidant supplementation in the treatment of Graves' disease is justified, while zinc and total antioxidant status in erythrocytes seem to be sensitive indicators of the efficacy of supplemental therapy.

Clin Chem Lab Med. 2005;43(4):383-8

PLASMA SELENIUM CONCENTRATION, GLUTATHIONE PEROXIDASE AND GLUTATHIONE S-TRANSFERASE ACTIVITIES IN PATIENTS WITH CHRONIC LIVER DISEASES.

The effects exerted on hepatocytes by alcohol metabolites, drugs or other toxins and also hepatotropic viruses lead to chronic liver diseases. Reactive oxygen species (ROS) have been implicated in a number of pathologies, including different types of liver diseases. Organism has developed several mechanisms to counteract or prevent reactive oxygen species effects. These include enzymes such as: glutathione peroxidase (GSH-Px) with selenium (Se) in the active site and glutathione S-transferase (GST). Measurement of GST, compared with alanine aminotransferase (AIAT), has been advocated as a superior marker of hepatocellular damage. The aim of this study was to assess selenium concentration, glutathione peroxidase and glutathione S-transferase activities in plasma of patients with various types of liver diseases. The study population consisted of 54 patients and 25 healthy volunteers. The patients were divided into two groups according to etiology of the disease. Plasma selenium concentration was reduced in patients with cirrhosis, as compared to controls, irrespective of etiology and activity of AIAT. Plasma GSH-Px activity was significantly lower in both groups of patients with normal AIAT activity, whereas it was higher in both groups with activity of AIAT higher than 40 U/l. GST activity was higher only in post-viral group in patients with high AIAT activity. Impaired intestinal absorption and distribution of selenium among plasma proteins have been suggested as possible mechanism of reduced selenium concentration. Changes in the activities of glutathione-dependent enzymes in plasma may arise from increased formation of reactive oxygen species or from release of these enzymes from injured hepatocytes to plasma.

Pol Merkuriusz Lek. 2002 Oct;13(76):312-5

SELENIUM, GLUTATHIONE AND GLUTATHIONE PEROXIDASES IN BLOOD OF PATIENTS WITH CHRONIC LIVER DISEASES.

Disturbances in the antioxidant system could play a role in pathogenesis of chronic liver disease. The aim of our study was to evaluate the levels/activities of antioxidants in blood of patients with chronic liver disease. We estimated selenium and glutathione concentrations and glutathione peroxidase activities in blood of 59 patients with chronic hepatitis B or C virus infection (group 1) and 64 patients with alcoholic, autoimmune or cryptogenic chronic liver disease (group 2). The results were compared with 50 healthy controls. Whole blood and plasma selenium and red cell glutathione concentrations were significantly lower in the patients compared with the controls. Red cell glutathione peroxidase activity was slightly reduced in both subgroups of group 1 and in group 2 with normal alanine aminotransferase values. Plasma glutathione peroxidase activity was slightly but significantly higher in patients with elevated aminotransferase values. The findings suggest that disturbances in antioxidant parameters in blood of patients with chronic liver disease may be the cause of the peroxidative damage of cells.

Acta Biochim Pol. 2003;50(4):1147-54

SELENIUM IN THE TREATMENT OF AUTOIMMUNE THYROIDITIS.

We recently conducted a prospective, placebo-controlled clinical study, where we could demonstrate, that a substitution of 200 microg sodium selenite for three months in patients with autoimmune thyroiditis reduced thyroid peroxidase antibody (TPO-Ab) concentrations significantly. Forty-seven patients from the initially 70 patients agreed to participate in a follow-up cross-over study for further six months. One group (n = 13), which initially received selenium continued to take 200 microg sodium selenite (Se-Se), one group stopped taking selenium (Se-0) (n = 9), another group which received placebo started to take 200 microg selenium (n = 14) (Plac-Se) and the last group was without selenium substitution (Plac-0) (n = 11). TPO-Ab concentrations were measured at beginning and the end of the study. In the Se-Se group, the TPO-Ab concentrations further significantly (p = 0.004) decreased from 625 +/- 470 U/ml to 354 +/- 321 U/ml, in the Se-0 group the TPO-Ab concentrations increased significantly (p =

0.017) from 450 +/- 335 to 708 +/- 313 U/ml. In the placebo group, the TPO-Ab concentrations in those patients who were followed without selenium substitution were unchanged (1351 +/- 940 vs. 1724 +/- 1112 U/ml, $p = 0.555$). In contrast, the patients who received 200 microg sodium selenite after placebo, the TPO-Ab concentrations decreased significantly ($p = 0.029$) from 1182 +/- 723 to 643 +/- 477 U/ml.

Biofactors. 2003;19(3-4):165-70

SUPPLEMENTATION WITH ANTIOXIDANTS IN THE TREATMENT OF GRAVES' DISEASE; THE EFFECT ON GLUTATHIONE PEROXIDASE ACTIVITY AND CONCENTRATION OF SELENIUM.

BACKGROUND: The effect of supplementation with a fixed combination of antioxidants (vitamins C and E, beta-carotene and selenium) was monitored on the speed of attaining euthyroidism in a group of patients with Graves' disease, treated with methimazole. **METHODS:** The activity of glutathione peroxidase in whole blood and the concentrations of selenium, pituitary and thyroid hormones in serum were measured, prior to commencement of therapy and after 30 and 60 days. **RESULTS** Patients who received supplementation with antioxidants in addition to therapy with methimazole (Group A, $n=29$) attained euthyroidism faster than the patients treated with only methimazole (Group B, $n=28$). The concentration of selenium in the serum of patients in Group A increased significantly during treatment ($p<0.001$), while there was no statistically significant change in the patients in Group B. The concentration of selenium in the serum between the groups differed statistically significantly 30 days ($p<0.05$) and 60 days ($p<0.01$) after the commencement of therapy. Activity of glutathione peroxidase in whole blood increased during treatment in both groups of patients. However, a statistically more significant increase occurred in Group A compared to Group B, 30 days after the commencement of therapy ($p<0.01$). **CONCLUSION:** The results of the study clearly indicate that supplementation with antioxidants in the treatment of Graves' disease is justified, particularly those containing selenium.

Clin Chim Acta. 2004 Mar;341(1-2):55-63

SELENIUM AND ENDOCRINE SYSTEMS.

The trace element selenium (Se) is capable of exerting multiple actions on endocrine systems by modifying the expression of at least 30 selenoproteins, many of which have clearly defined functions. Well-characterized selenoenzymes are the families of glutathione peroxidases (GPXs), thioredoxin reductases (TRs) and iodothyronine deiodinases (Ds). These selenoenzymes are capable of modifying cell function by acting as antioxidants and modifying redox status and thyroid hormone metabolism. Se is also involved in cell growth, apoptosis and modifying the action of cell signalling systems and transcription factors. During thyroid hormone synthesis GPX1, GPX3 and TR1 are up-regulated, providing the thyrocytes with considerable protection from peroxidative damage. Thyroidal D1 in rats and both D1 and D2 in humans are also up-regulated to increase the production of bioactive 3,5,3'-tri-iodothyronine (T3). In the basal state, GPX3 is secreted into the follicular lumen where it may down-regulate thyroid hormone synthesis by decreasing hydrogen peroxide concentrations. The deiodinases are present in most tissues and provide a mechanism whereby individual tissues may control their exposure to T3. Se is also able to modify the immune response in patients with autoimmune thyroiditis. Low sperm production and poor sperm quality are consistent features of Se-deficient animals. The pivotal link between Se, sperm quality and male fertility is GPX4 since the enzyme is essential to allow the production of the correct architecture of the midpiece of spermatozoa. Se also has insulin-mimetic properties, an effect that is probably brought about by stimulating the tyrosine kinases involved in the insulin signalling cascade. Furthermore, in the diabetic rat, Se not only restores glycaemic control but it also prevents or alleviates the adverse effects that diabetes has on cardiac, renal and platelet function.

J Endocrinol. 2005 Mar;184(3):455-65

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