

## DHEA Replacement Therapy

## ABSTRACTS

- Araghi-Niknam M., 1988. Dehydroepiandrosterone (DHEA) sulfate prevents reduction in tissue vitamin E and increased lipid peroxidation due to murine retrovirus infection of aged mice.
- Araneo BA., 1995. Dehydroepiandrosterone reduces progressive dermal ischemia caused by thermal injury.
- Arlt W., 1999. Dehydroepiandrosterone replacement in women with adrenal insufficiency.
- Barrett-Connor E., 1999. Endogenous levels of dehydroepiandrosterone sulfate, but not other sex hormones, are associated with depressed mood in older women: the Rancho Bernardo Study.
- Bellino FL., 1995. DHEA and aging.
- Bloch M., 1999. Dehydroepiandrosterone treatment of midlife dysthymia.
- Brincat M., 1983. Sex hormones and skin collagen content in postmenopausal women.
- Christeff N., 2000. Changes in cortisol/DHEA ratio in HIV-infected men are related to immunological and metabolic perturbations leading to malnutrition and lipodystrophy.
- Cutolo M., 2000. Sex hormone adjuvant therapy in rheumatoid arthritis.
- Danenberg HD., 1995. Dehydroepiandrosterone (DHEA) treatment reverses the impaired immune response of old mice to influenza vaccination and protects from influenza infection.
- Danenboerg HD., 1996. Dehydroepiandrosterone (DHEA) increases production and release of Alzheimer's amyloid precursor protein.
- Diallo K., 2000. Inhibition of human immunodeficiency virus type-1 (HIV-1) replication by immunor (IM28), a new analog of dehydroepiandrosterone.
- Du C., 2001. Administration of dehydroepiandrosterone suppresses experimental allergic encephalomyelitis in SJL/J mice.
- Ferraccioli G., 1996. Increase of bone mineral density and anabolic variables in patients with rheumatoid arthritis resistant to methotrexate after cyclosporin A therapy.
- Ferrucci L., 1999. Serum IL-6 level and the development of disability in older persons.
- Folsom AR., 2002. C-reactive protein and incident coronary heart disease in the Atherosclerosis Risk In Communities (ARIC) study.
- Friess E., 1995. DHEA administration increases rapid eye movement sleep and EEG power in the sigma frequency range.
- Futterman LG., 2002. High-sensitivity C-reactive protein is the most effective prognostic measurement of acute coronary events.
- Genazzani AD., 2001. Oral dehydroepiandrosterone supplementation modulates spontaneous and growth hormone-releasing hormone-induced growth hormone and insulin-like growth factor-1 secretion in early and late postmenopausal women.
- Glaser JL., 1992. Elevated serum dehydroepiandrosterone sulfate levels in practitioners of the Transcendental Meditation (TM) and TM-Sidhi programs.
- Goodyer IM., 1996. Adrenal secretion during major depression in 8- to 16-year-olds, I. Altered diurnal rhythms in salivary cortisol and dehydroepiandrosterone (DHEA) at presentation.
- Haden ST, 2000. Effects of age on serum dehydroepiandrosterone sulfate, IGF-I, and IL-6 levels in women.
- Hastings LA., 1988. Dehydroepiandrosterone and two structural analogs inhibit 12-O-tetradecanoylphorbol-13-acetate stimulation of prostaglandin E2 content in mouse skin.
- Heinz A., 1999. Severity of depression in abstinent alcoholics is associated with monoamine metabolites and dehydroepiandrosterone-sulfate concentrations.
- Herrington DM., 1995. Dehydroepiandrosterone and coronary atherosclerosis.
- Inagaki M., 1999. Effect of acute and chronic administration of dehydroepiandrosterone on (+/-)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane-induced wet dog shaking behavior in rats.
- Inserra P., 1998. Modulation of cytokine production by dehydroepiandrosterone (DHEA) plus melatonin (MLT) supplementation of old mice.
- James K., 1997. IL-6, DHEA and the ageing process.
- Jesse RL., 1995. Dehydroepiandrosterone inhibits human platelet aggregation in vitro and in vivo.
- Khorram O., 1997. Activation of immune function by dehydroepiandrosterone (DHEA) in age-advanced men.

Kim SH., 1999. Modulation of chemical carcinogen-induced unscheduled DNA synthesis by dehydroepiandrosterone (DHEA) in the primary rat hepatocytes.

Kipper-Galperin M., 1999. Dehydroepiandrosterone selectively inhibits production of tumor necrosis factor alpha and interleukin-6 [correction of interlukin-6] in astrocytes.

Labrie C., 1996. High bioavailability of dehydroepiandrosterone administered percutaneously in the rat.

Lavie CJ., 1999. Effects of cardiac rehabilitation and exercise training programs in women with depression.

Maurice T., 1997. Dehydroepiandrosterone sulfate attenuates dizocilpine-induced learning impairment in mice via sigma 1-receptors.

Metzger C., 1995. Sequential appearance and ultrastructure of amphophilic cell foci, adenomas, and carcinomas in the liver of male and female rats treated with dehydroepiandrosterone.

McCraty R., 1998. The impact of a new emotional self-management program on stress, emotions, heart rate variability, DHEA and cortisol.

Morales AJ., 1994. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age.

Morales AJ, 1998. The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women.

Murialdo G., 2000. Hippocampal perfusion and pituitary-adrenal axis in Alzheimer's disease.

Oberbeck R., 2001. Dehydroepiandrosterone decreases mortality rate and improves cellular immune function during polymicrobial sepsis.

Pashko LL., 1985. Inhibition of 7,12-dimethylbenz(a)anthracene-induced skin papillomas and carcinomas by dehydroepiandrosterone and 3-beta-methylandro-5-en-17-one in mice.

Rhodes ME., 1996. Enhancement of hippocampal acetylcholine release by the neurosteroid dehydroepiandrosterone sulfate: an in vivo microdialysis study.

Schwartz AG., 1986. Food restriction inhibits [3H] 7,12-dimethylbenz(a)anthracene binding to mouse skin DNA and tetradecanoylphorbol-13-acetate stimulation of epidermal [3H] thymidine incorporation.

Schwartz AG., 1995. Cancer prevention with dehydroepiandrosterone and non-androgenic structural analogs.

Simile M., 1995. Inhibition by dehydroepiandrosterone of growth and progression of persistent liver nodules in experimental rat liver carcinogenesis.

Straub RH., 1998. Serum dehydroepiandrosterone (DHEA) and DHEA sulfate are negatively correlated with serum interleukin 6 (IL 6), and DHEA inhibits IL 6 secretion from mononuclear cells in man in vitro: possible link between endocrinosenescence and immunosenescence.

Straub RH., 2000. Replacement therapy with DHEA plus corticosteroids in patients with chronic inflammatory diseases--substitutes of adrenal and sex hormones.

Swierczynski J., 1997. Dietary alpha-tocopherol prevents dehydroepiandrosterone-induced lipid peroxidation in rat liver microsomes and mitochondria.

Uozumi K., 1996. Serum dehydroepiandrosterone and DHEA-sulfate in patients with adult T-cell leukemia and human T-lymphotropic virus type I carriers.

van Vollenhoven RF., 1998. Treatment of systemic lupus erythematosus with dehydroepiandrosterone: 50 patients treated up to 12 months.

Watson RR., 1996. Dehydroepiandrosterone and diseases of aging.

Wellby ML., 2001. Serum interleukin-6 and thyroid hormones in rheumatoid arthritis.

Wolkowitz OM., 1997. Dehydroepiandrosterone (DHEA) treatment of depression.

**Dehydroepiandrosterone (DHEA) sulfate prevents reduction in tissue vitamin E and increased lipid peroxidation due to murine retrovirus infection of aged mice.**

Araghi-Niknam M, Ardestani SK, Molitor M, Inserra P, Eskelson CD, Watson RR. Arizona Prevention Center, University of Arizona, Tucson 85724, USA.

Proc Soc Exp Biol Med 1998 Jul;218(3):210-7

Dietary effects of dehydroepiandrosterone sulfate (DHEAS) supplementation on tissue antioxidants and lipids were investigated in retrovirus infected mice. DHEA is a powerful antioxidant and immunomodulator whose production declines with age. For this study, twenty-four female, 15-month-old C57BL/6 mice were left uninfected while twenty-four were infected with LP-BM5 murine leukemia virus, causing murine AIDS. The retroviral infection caused immune dysfunction and loss of hepatic and cardiac vitamins E and A, resulting in increased lipid peroxides. Treatment with DHEAS at 0.01 or 0.005% in drinking water for 10 weeks post-infection significantly ( $< 0.05$ ) lowered lipid peroxidation in both heart and liver tissues. Treatment with DHEAS also largely prevented loss of the antioxidants, such as vitamin E and A, and prevented loss of phospholipid in the hearts and livers of the old uninfected as well as infected mice. This study suggests that DHEAS supplementation reduces damage associated with elevated oxidation due to

aging and retrovirus infection.

### **Dehydroepiandrosterone reduces progressive dermal ischemia caused by thermal injury.**

Araneo BA, Ryu SY, Barton S, Daynes RA. Department of Pathology, University of Utah School of Medicine, Salt Lake City 84132, USA.

J Surg Res 1995 Aug;59(2):250-62

Progressive ischemia and necrosis of the skin following thermal injury are reduced by postburn administration of the steroid hormone dehydroepiandrosterone (DHEA). Thermally injured animals were provided with a subcutaneous injection of DHEA, or a related species of steroid hormone, at various times after burning. During the 96 hr following administration of the scald burn, tissue necrosis was closely monitored. Subcutaneous administration of DHEA at approximately 1 mg/kg/day achieved optimal protection against the development of progressive dermal ischemia. DHEA, 17 alpha-hydroxy-pregnenelone, 16 alpha-bromo-DHEA, and androstenediol each demonstrated, a similar level of protection. Other forms of steroids, including DHEA sulfate, androstenedione, 17 beta-estradiol, or dihydrotestosterone, exhibited no protective effect under the conditions tested. Additionally, intervention therapy with DHEA could be initiated up to 4 hr, but not 6 hr, after burn without a marked reduction in therapeutic benefit. Examination of the microvasculature of thermally injured dorsal skin suggested that postburn intervention with DHEA, either directly or indirectly, maintained a normal architecture in most of the dermal capillaries and venules within burn-exposed tissue. These findings suggest that systemic intervention therapy of burn patients with DHEA or a similar acting steroid hormone may be useful in preventing the progressive tissue destruction caused by progressive ischemia.

### **Dehydroepiandrosterone replacement in women with adrenal insufficiency.**

Arlt W, Callies F, van Vlijmen JC, Koehler I, Reincke M, Bidlingmaier M, Huebler D, Oettel M, Ernst M, Schulte HM, Allolio B. Department of Endocrinology, Medical University Hospital, Wuerzburg, Germany. w.arlt@medizin.uni-wuerzburg.de

N Engl J Med 1999 Sep 30;341(14):1013-20

**BACKGROUND:** The physiologic role of dehydroepiandrosterone in humans is still unclear. Adrenal insufficiency leads to a deficiency of dehydroepiandrosterone; we therefore, investigated the effects of dehydroepiandrosterone replacement, in patients with adrenal insufficiency. **METHODS:** In a double-blind study, 24 women with adrenal insufficiency received in random order 50 mg of dehydroepiandrosterone orally each morning for four months and placebo daily for four months, with a one-month washout period. We measured serum steroid hormones, insulin-like growth factor I, lipids, and sex hormone-binding globulin, and we evaluated well-being and sexuality with the use of validated psychological questionnaires and visual-analogue scales, respectively. The women were assessed before treatment, after one and four months of treatment with dehydroepiandrosterone, after one and four months of placebo, and one month after the end of the second treatment period. **RESULTS:** Treatment with dehydroepiandrosterone raised the initially low serum concentrations of dehydroepiandrosterone, dehydroepiandrosterone sulfate, androstenedione, and testosterone into the normal range; serum concentrations of sex hormone-binding globulin, total cholesterol, and high-density lipoprotein cholesterol decreased significantly. Dehydroepiandrosterone significantly improved overall well-being as well as scores for depression and anxiety. For the global severity index, the mean (+/-SD) change from base line was -0.18+/-0.29 after four months of dehydroepiandrosterone therapy, as compared with 0.03+/-0.29 after four months of placebo (P=0.02). As compared with placebo, dehydroepiandrosterone significantly increased the frequency of sexual thoughts (P=0.006), sexual interest (P=0.002), and satisfaction with both mental and physical aspects of sexuality (P=0.009 and P=0.02, respectively). **CONCLUSIONS:** Dehydroepiandrosterone improves well-being and sexuality in women with adrenal insufficiency.

### **Endogenous levels of dehydroepiandrosterone sulfate, but not other sex hormones, are associated with depressed mood in older women: the Rancho Bernardo Study.**

Barrett-Connor E, von Muhlen D, Laughlin GA, Kripke A. Department of Family and Preventive Medicine, University of California, San Diego, School of Medicine, La Jolla 92093-0607, USA.

J Am Geriatr Soc 1999 Jun;47(6):685-91

**OBJECTIVE:** The purpose of this study was to determine whether endogenous steroid hormone levels are associated with depressed mood in community-dwelling older women. **DESIGN:** A cross-sectional population-based study. **SETTING:** Rancho Bernardo, California **PARTICIPANTS:** A total of 699 non-estrogen using, community-dwelling, postmenopausal women (aged 50 to 90 years) from the Rancho Bernardo cohort who were screened for depressed mood and had plasma obtained for steroid hormone assays in 1984-1987. **MEASUREMENTS:** Plasma levels of total and bioavailable (non-SHBG-bound) estradiol and testosterone, estrone, androstenedione, cortisol, dehydroepiandrosterone, and (DHEA) and its sulfate (DHEAS) were measured by radioimmunoassay. Mood and depression were assessed using the Beck Depression Inventory. **RESULTS:** Only DHEAS levels were significantly and inversely associated with depressed mood, and the association was independent of age, physical activity,

and weight change ( $P = .0002$ ). Age, sedentary lifestyle, and weight loss were positively associated with depressed mood. Alcohol intake, cigarette smoking, marital status, type of menopause, and season of testing were unassociated with depressed mood. A subset of 31 women with categorically defined depression had lower DHEAS levels compared with 93 age-matched nondepressed women ( $1.17 \pm 1.08$  vs  $1.57 \pm .98$  micromol/L;  $P = .01$ ). **CONCLUSIONS:** These results add to the evidence that DHEA/S is a neuroactive steroid and point to the need for careful long-term clinical trials of DHEA therapy in older women with depressed mood.

### **DHEA and aging.**

Bellino, F.L., Daynes, R.A., Hornsby, P.J. et al.

Aging 1995 Dec 29; 774: 1-350.

No abstract available.

### **Dehydroepiandrosterone treatment of midlife dysthymia.**

Bloch M, Schmidt PJ, Danaceau MA, Adams LF, Rubinow DR. Behavioral Endocrinology Branch, National Institute of Mental Health, Bethesda, MD 20892-1276, USA.

Biol Psychiatry 1999 Jun 15;45(12):1533-41

**BACKGROUND:** This study evaluated the efficacy of the adrenal androgen, dehydroepiandrosterone, in the treatment of midlife-onset dysthymia. **METHODS:** A double-blind, randomized crossover treatment study was performed as follows: 3 weeks on 90 mg dehydroepiandrosterone, 3 weeks on 450 mg dehydroepiandrosterone, and 6 weeks on placebo. Outcome measures consisted of the following. Cross-sectional self-ratings included the Beck Depression Inventory, and visual analogue symptom scales. Cross-sectional objective ratings included the Hamilton Depression Rating Scale, the Cornell Dysthymia Scale and a cognitive test battery. Seventeen men and women aged 45 to 63 years with midlife-onset dysthymia participated in this study. Response to dehydroepiandrosterone or placebo was defined as a 50% reduction from baseline in either the Hamilton Depression Rating Scale or the Beck Depression Inventory. **RESULTS:** In 15 patients who completed the study, a robust effect of dehydroepiandrosterone on mood was observed compared with placebo. Sixty percent of the patients responded to dehydroepiandrosterone at the end of the 6-week treatment period compared with 20% on placebo. A significant response was seen after 3 weeks of treatment on 90 mg per day. The symptoms that improved most significantly were anhedonia, loss of energy, lack of motivation, emotional "numbness," sadness, inability to cope, and worry. Dehydroepiandrosterone showed no specific effects on cognitive function or sleep disturbance, although a type II error could not be ruled out. **CONCLUSIONS:** This pilot study suggests that dehydroepiandrosterone is an effective treatment for midlife-onset dysthymia.

### **Sex hormones and skin collagen content in postmenopausal women.**

Brincat M, Moniz CF, Studd JW, Darby AJ, Magos A, Cooper D.

Br Med J (Clin Res Ed) 1983 Nov 5;287(6402):1337-8

Skin biopsy specimens were taken from 29 postmenopausal women who had not been given hormone replacement therapy and from 26 women who had been treated with oestrogen and testosterone implants for two to 10 years. The mean hydroxyproline content and therefore the mean collagen content in the skin was found to be 48% greater in the treated than the untreated women, who were matched for age. This difference was significant ( $p$  less than 0.01). The implication of this finding is that oestrogen or testosterone, or both, prevents the decrease in skin collagen content that occurs with aging and protects skin in the same way as it protects bone in postmenopausal women.

### **Changes in cortisol/DHEA ratio in HIV-infected men are related to immunological and metabolic perturbations leading to malnutrition and lipodystrophy.**

Christeff N, Nunez EA, Gougeon ML. Viral Oncology Unit, CNRS URA 1930, AIDS and Retroviruses Department, Institut Pasteur, Paris, France.

Ann N Y Acad Sci 2000;917:962-70

HIV-1 infection is associated with immune deficiency and metabolic perturbations leading to malnutrition and lipodystrophy. Because immune response and metabolic perturbations (protein and lipid metabolism) are partly regulated by glucocorticoids and DHEA, we determined serum cortisol and DHEA concentrations, and the cortisol/DHEA ratio in HIV-positive men, either untreated or receiving various antiretroviral treatments (ART), including highly active antiretroviral therapy (HAART). Cortisol levels were found

increased in all patients, whatever the stage of the disease and independently of the ART treatment. In contrast, serum DHEA was elevated in the asymptomatic stage, and it was below normal values in AIDS patients, either untreated or mono-ART-treated. The DHEA level was low in HAART-treated patients with lipodystrophy (LD+) and highly increased in HAART-treated patients without lipodystrophy (LD-). Consequently, the cortisol/DHEA ratio was similar to controls in asymptomatic untreated or mono-ART-treated patients, but increased in AIDS patients. Interestingly, this ratio was increased in LD+ HAART-treated men, but normalized in LD-HAART-treated patients. Changes in the cortisol/DHEA ratio were negatively correlated with the in vivo CD4 T-cell counts, with the malnutrition markers, such as body-cell mass and fat mass, and with the increased circulating lipids (cholesterol, triglycerides, and apolipoprotein B) associated to the lipodystrophy syndrome. Our observations show that the cortisol/DHEA ratio is dramatically altered in HIV-infected men, particularly during the syndromes of malnutrition and lipodystrophy, and this ratio remains elevated whatever the antiretroviral treatment, including HAART. These findings have practical clinical implications, since manipulation of this ratio could prevent metabolic (protein and lipid) perturbations.

### **Sex hormone adjuvant therapy in rheumatoid arthritis.**

Cutolo M. Department of Internal Medicine, University of Genova, Italy. mcutolo@unige.it

Rheum Dis Clin North Am 2000 Nov;26(4):881-95

RA is an autoimmune rheumatic disorder resulting from the combination of several predisposing factors, including the relation between epitopes of possible triggering agents and histocompatibility epitopes, the status of the stress response system, and the sex hormone status. Estrogens are implicated as enhancers of humoral immunity, and androgens and progesterone are natural immune suppressors. Sex hormone concentrations have been evaluated in RA patients before glucocorticoid therapy and have frequently been found to be altered, especially in premenopausal women and male patients. In particular, low levels of gonadal and adrenal androgens (testosterone and DHT, DHEA and DHEAS) and a reduced androgen:estrogen ratio have been detected in body fluids (i.e., blood, synovial fluid, smears, saliva) of male and female RA patients. These observations support a possible pathogenic role for the decreased levels of the immune-suppressive androgens. Exposure to environmental estrogens (estrogenic xenobiotics), genetic polymorphisms of genes coding for hormone metabolic enzymes or receptors, and gonadal disturbances related to stress system activation (hypothalamic-pituitary-adrenocortical axis) and physiologic hormonal perturbations such as during aging, the menstrual cycle, pregnancy, the postpartum period, and menopause may interfere with the androgen:estrogen ratio. Sex hormones might exert their immune-modulating effects, at least in RA synovitis, because synovial macrophages, monocytes, and lymphocytes possess functional androgen and estrogen receptors and may metabolize gonadal hormones. The molecular basis for sex hormone adjuvant therapy in RA is thus experimentally substantiated. By considering the well-demonstrated immune-suppressive activities exerted by androgens, male hormones and their derivatives seem to be the most promising therapeutic approach. Recent studies have shown positive effects of androgen replacement therapy at least in male RA patients, particularly as adjuvant treatment. Interestingly, the increase in serum androgen metabolism induced by RA treatment with CSA should be regarded as a possible marker of androgen-mediated immune-suppressive activities exerted by CSA, at least in RA and at the level of sensitive target cells and tissues (i.e., synovial macrophages). The absence of altered serum levels of estrogens in RA patients and the reported immune-enhancing properties exerted by female hormones have represented a poor stimulus to test estrogen replacement therapy in RA. The different results obtained with OC use seem to depend on dose-related effects and the different type of response to estrogens in relation to the cytokine balance between Th1 cells (cellular immunity, i.e., RA) and Th2 cells (humoral immunity, i.e., SLE). The androgen replacement obtained directly (i.e., testosterone, DHT, DHEAS) or indirectly (i.e., antiestrogens) may represent a valuable concomitant or adjuvant treatment to be associated with other disease-modifying antirheumatic drugs (i.e., MTX, CSA) in the management of RA.

### **Dehydroepiandrosterone (DHEA) treatment reverses the impaired immune response of old mice to influenza vaccination and protects from influenza infection.**

Danenberg HD, Ben-Yehuda A, Zakay-Rones Z, Friedman G. Division of Medicine, Hadassah University Hospital, Jerusalem, Israel.

Vaccine 1995;13(15):1445-8

Dehydroepiandrosterone (DHEA) is a native steroid with an immunomodulating activity. Recently it was suggested that its age-associated decline is related with immunosenescence. To examine whether DHEA administration could effectively reverse the age-associated decline of immunity against influenza vaccine, aged mice were simultaneously vaccinated and treated with DHEA. Reversal of the age-associated decline and a significant constant increase of humoral response was observed in treated mice. Increased resistance to post-vaccination intranasal challenge with live influenza virus was observed in DHEA-treated aged mice. Thus, DHEA treatment overcame the age-related defect in the immunity of old mice against influenza.

### **Dehydroepiandrosterone (DHEA) increases production and release of Alzheimer's amyloid precursor protein.**

Danenboerg HD, Haring R, Fisher A, Pittel Z, Gurwitz D, Heldman E Department of Organic and Medicinal Chemistry, Israel Institute for Biological Research, Ness-Ziona, Israel.

Dehydroepiandrosterone (DHEA), the major secretory product of the human adrenal cortex, significantly declines with advanced age. We have previously demonstrated that DHEA prevents the reduction in non-amyloidogenic APP processing, following prolonged stimulation of the muscarinic receptor, in PC12 cells that express the ml acetylcholine-receptor. The present study examined whether this effect may be mediated via modulation of APP metabolism. It was found that DHEA treatment increases the content of membrane-associated APP holoprotein by 24%, and the accumulation of secreted APP in the medium by 63%. No increase in viable cell number nor in nonspecific protein production was observed in DHEA-treated cells. Thus, DHEA seems to increase specifically both APP synthesis and secretion. We propose that the age-associated decline in DHEA levels may be related to the pathological APP metabolism observed in Alzheimer's disease.

### **Inhibition of human immunodeficiency virus type-1 (HIV-1) replication by immunor (IM28), a new analog of dehydroepiandrosterone.**

Diallo K, Loemba H, Oliveira M, Mavoungou DD, Wainberg MA. McGill AIDS Centre, Jewish General Hospital, Montreal, Quebec, Canada.

Nucleosides Nucleotides Nucleic Acids 2000 Oct-Dec;19(10-12):2019-24

The inhibition of HIV-1 replication in vitro by Immunor 28 (IM28), an analog of dehydroepiandrosterone (DHEA), was monitored using the HIV-1 laboratory wild-type strain IIIB. Evaluation of the 50% inhibitory dose (IC50) revealed a decrease in HIV-1 replication giving an IC50 value around 22 microM. The toxicity of the drug has been determined also, in MT2 cells and PBMCs. 60 microM of IM28 provoked a 50% decrease in cell viability while DHEA caused the same decrease at 75 microM in MT2 cells. These values are 125 microM for IM28 in PBMCs and 135 microM for DHEA. Thus, DHEA is less toxic than IM28, but IM28 has a higher antiviral activity.

### **Administration of dehydroepiandrosterone suppresses experimental allergic encephalomyelitis in SJL/J mice.**

Du C, Khalil MW, Sriram S. Department of Neurology, Multiple Sclerosis Research Center, Vanderbilt University Medical Center, Nashville, TN 37212, USA. caigan.du@mcm.vanderbilt.edu

J Immunol 2001 Dec 15;167(12):7094-101

Experimental allergic encephalomyelitis (EAE) is a Th1-mediated inflammatory demyelinating disease in the CNS, an animal model of multiple sclerosis. We have examined the effect of dehydroepiandrosterone (DHEA) on the development of EAE in mice. The addition of DHEA to cultures of myelin basic protein-primed splenocytes resulted in a significant decrease in T cell proliferation and secretion of (pro)inflammatory cytokines (IFN-gamma, IL-12 p40, and TNF-alpha) and NO in response to myelin basic protein. These effects were associated with a decrease in activation and translocation of NF-kappaB. In vivo administration of DHEA significantly reduced the severity and incidence of acute EAE, along with a decrease in demyelination/inflammation and expressions of (pro) inflammatory cytokines in the CNS. These studies suggest that DHEA has potent anti-inflammatory properties, which at least are in part mediated by its inhibition of NF-kappaB activation.

### **Increase of bone mineral density and anabolic variables in patients with rheumatoid arthritis resistant to methotrexate after cyclosporin A therapy.**

Ferraccioli G, Casatta L, Bartoli E. Department of Internal Medicine, School of Medicine, University of Udine, Italy.

J Rheumatol 1996 Sep;23(9):1539-42

**OBJECTIVE:** To determine the bone mineral density (BMD) and anabolic variables in a cohort of patients with severe, early rheumatoid arthritis (RA) resistant to weekly doses of methotrexate (MTX), after addition of cyclosporin A (CyA) therapy.  
**METHODS:** We studied 10 rheumatoid factor positive patients of 58 with early erosive, aggressive RA with poor response to a 6 month course of MTX (< 20% improvement in the American College of Rheumatology core set of criteria). BMD was assessed at entry, after 6 months of MTX, and after a further 6 months of combination therapy of MTX plus CyA. Bone Gla protein (BGP) dehydroepiandrosterone sulfate (DHEAS), and insulin-like growth factor-1 (IGF-1, somatomedin C) levels were determined along with clinical variables and acute phase reactants (C-reactive protein, erythrocyte sedimentation rate). **RESULTS:** An average BMD decline of 4.05 +/- 0.8% (mean, SD) occurred in the first 6 months of MTX treatment, along with a statistically significant decline of IGF-1 (-24.8%), DHEAS (-21.6%), and BGP (-19.7%) levels. After adding CyA 3 mg/kg daily for 6 months, BMD had increased by 3.9 +/- 0.97%, IGF-1 by 42.4%, DHEAS by 34.2%, BGP by +34.3%. These changes mirrored the clinical variables (Health Assessment Questionnaire, morning stiffness, joint count) and acute phase reactants, which improved in a statistically significant manner. **CONCLUSION:** Patients with active RA, even in the early phases, lose bone very rapidly. Effective control of systemic inflammation allowed a rapid rescue of BMD, at least in the short term. This happened with a simultaneous increase in some

anabolic variables such as IGF-1, BGP, and DHEAS.

### **Serum IL-6 level and the development of disability in older persons.**

Ferrucci L, Harris TB, Guralnik JM, Tracy RP, Corti MC, Cohen HJ, Penninx B, Pahor M, Wallace R, Havlik RJ. Geriatric Department, I Fraticini, National Research Institute (INRCA), Florence, Italy.

J Am Geriatr Soc 1999 Jun;47(6):639-46

**BACKGROUND:** The serum concentration of interleukin 6 (IL-6), a cytokine that plays a central role in inflammation, increases with age. Because inflammation is a component of many age-associated chronic diseases, which often cause disability, high circulating levels of IL-6 may contribute to functional decline in old age. We tested the hypothesis that high levels of IL-6 predict future disability in older persons who are not disabled. **METHODS:** Participants at the sixth annual follow-up of the Iowa site of the Established Populations for Epidemiologic Studies of the Elderly aged 71 years or older were considered eligible for this study if they had no disability in regard to mobility or in selected activities of daily living (ADL), and they were re-interviewed 4 years later. Incident cases of mobility-disability and of ADL-disability were identified based on responses at the follow-up interview. Measures of IL-6 were obtained from specimens collected at baseline from the 283 participants who developed any disability and from 350 participants selected randomly (46.9%) from those who continued to be non-disabled. **FINDINGS:** Participants in the highest IL-6 tertile were 1.76 (95% CI, 1.17-2.64) times more likely to develop at least mobility-disability and 1.62 (95% CI, 1.02-2.60) times more likely to develop mobility plus ADL-disability compared with to the lowest IL-6 tertile. The strength of this association was almost unchanged after adjusting for multiple confounders. The increased risk of mobility-disability over the full spectrum of IL-6 concentration was nonlinear, with the risk rising rapidly beyond plasma levels of 2.5 pg/mL. **INTERPRETATION:** Higher circulating levels of IL-6 predict disability onset in older persons. This may be attributable to a direct effect of IL-6 on muscle atrophy and/or to the pathophysiologic role played by IL-6 in specific diseases.

### **C-reactive protein and incident coronary heart disease in the Atherosclerosis Risk In Communities (ARIC) study.**

Folsom AR, Aleksic N, Catellier D, Juneja HS, Wu KK. Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis, Minn 55454-1015, USA. folsom@epi.umn.edu

Am Heart J 2002 Aug;144(2):233-8

**BACKGROUND:** Recent evidence implicates inflammation in the pathogenesis of coronary heart disease (CHD). C-reactive protein, a plasma marker of inflammation, is a marker of CHD risk but has been studied in few prospective investigations of the general population. **METHODS AND RESULTS:** We prospectively examined the association of CRP with incident CHD among middle-aged adults in the Atherosclerosis Risk In Communities (ARIC) study. With the use of a nested case-cohort approach, we measured CRP in stored, baseline blood samples of 2 groups of subjects in whom CHD developed during follow-up (242 incident cases from 1987 to 1993 and 373 from 1990 to 1995) and, for comparison, 2 stratified random samples of noncases. In analyses adjusted for demographic variables and traditional CHD risk factors, the relative risk of CHD across quintiles of CRP was 1.0, 0.8, 1.6, 1.9, and 1.5 for events from 1987 to 1995 (P for trend =.01). As expected, inclusion of fibrinogen, intracellular adhesion molecule-1, and white blood cell count (other potential markers of the inflammatory reaction) attenuated the association of CRP with CHD incidence. In a supplemental cross-sectional analysis, CRP was not associated with carotid intima-media thickness after adjustment for major risk factors. **CONCLUSIONS:** C-reactive protein is a moderately strong marker of risk of CHD in this cohort of middle-aged adults, consistent with the role of inflammation in the pathogenesis of CHD events. The association was not specific to CRP because other markers of inflammation could largely account for the finding.

### **DHEA administration increases rapid eye movement sleep and EEG power in the sigma frequency range.**

Friess E, Trachsel L, Guldner J, Schier T, Steiger A, Holsboer F. Max Planck Institute of Psychiatry, Department of Psychiatry, Munich, Germany.

Am J Physiol 1995 Jan;268(1 Pt 1):E107-13

Dehydroepi-androsterone (DHEA) exhibits various behavioral effects in mammals, at least one of which is enhancement of memory that appears to be mediated by an interaction with the gamma-aminobutyric acid (GABA) receptor complex. We investigated the effects of a single oral dose of DHEA (500 mg) on sleep stages, sleep stage-specific electroencephalogram (EEG) power spectra, and concurrent hormone secretion in 10 healthy young men. DHEA administration induced a significant (< 0.05) increase in rapid eye movement (REM) sleep, whereas all other sleep variables remained unchanged compared with the placebo condition. Spectral analysis of five selected EEG bands revealed significantly (< 0.05) enhanced EEG activity in the sigma frequency range during REM sleep in the first 2-h sleep period after DHEA administration. In contrast, the EEG power spectra of non-REM sleep were not affected, nor were the nocturnal time course curves of plasma cortisol, growth hormone, or testosterone concentration. The results suggest that DHEA administration has a mixed GABA-agonistic/antagonistic effect, exerted either directly or through DHEA-

induced changes in steroid metabolism. Because REM sleep has been implicated in memory storage, its augmentation in the present study suggests the potential clinical usefulness of DHEA in age-related dementia.

### **High-sensitivity C-reactive protein is the most effective prognostic measurement of acute coronary events.**

Futterman LG, Lemberg L. Department of Medicine, University of Miami School of Medicine, Fla 33101, USA.

Am J Crit Care 2002 Sep;11(5):482-6

Inflammation plays a major role in the pathogenesis of arterial atherosclerosis. The stages of atheroma development from early recruitment of leukocytes and fatty streaks to the unstable plaque and finally rupture are mediated by the inflammatory process. Several markers of vascular wall inflammation that can predict future risk of plaque rupture have been identified. However, these lack the specificity of CRP. Numerous large-scale prospective studies established hs-CRP as a strong biochemical marker for the prediction of future first or recurrent coronary events. A Food and Drug Administration-approved method for measuring hs-CRP is currently available.

### **Oral dehydroepiandrosterone supplementation modulates spontaneous and growth hormone-releasing hormone-induced growth hormone and insulin-like growth factor-1 secretion in early and late postmenopausal women.**

Genazzani AD, Stomati M, Strucchi C, Puccetti S, Luisi S, Genazzani AR. University of Pisa, Italy. algen@unimo.it

Fertil Steril 2001 Aug;76(2):241-8

**OBJECTIVE:** To evaluate the effects of dehydroepiandrosterone (DHEA) supplementation on the growth hormone-releasing hormone-growth hormone (GHRH-GH) axis in lean and obese postmenopausal women. **DESIGN:** Prospective study. **SETTING:** Postmenopausal women in a clinical research environment. **PATIENT(S):** Thirty-one postmenopausal women were divided in two groups by age (50 to 55 and 60 to 65 years). Within each group, lean and obese patients were considered. **INTERVENTION(S):** All patients underwent hormonal evaluations before and at the third and sixth month of therapy (50 mg of DHEA orally each day) and a GHRH test (1 microg/kg) before and at the sixth month of treatment. **Ultrasound and bone mass density (BMD) examinations were performed before and after the sixth month of therapy.** **MAIN OUTCOME MEASURE(S):** Plasma dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), E1, E2, androstenedione (A), testosterone (T), osteocalcin, GH, insulin-like growth factor 1 (IGF-1) concentrations. **RESULT(S):** The levels of all of the steroids that derived from DHEA metabolism (E1, E2, A, T, DHEAS) and osteocalcin were increased in plasma under DHEA supplementation. The supplementation protocol also increased the levels of GH and IGF-1. However, GHRH-induced GH and IGF-1 responses were not modified by DHEA supplementation. **CONCLUSION(S):** Administration of DHEA significantly affects several endocrine parameters in early and late postmenopausal women independently from body mass index. Our data support the hypothesis that DHEA treatment acts similarly to estrogen-progestin replacement therapy on the GHRH-GH-IGF-1 axis. This suggests that DHEA is more than a simple "diet supplement" or "antiaging product"; rather it should be considered an effective hormonal replacement treatment.

### **Elevated serum dehydroepiandrosterone sulfate levels in practitioners of the Transcendental Meditation (TM) and TM-Sidhi programs.**

Glaser JL, Brind JL, Vogelman JH, Eisner MJ, Dillbeck MC, Wallace RK, Chopra D, Orentreich N. Department of Physiological and Biological Sciences, Maharishi International University, Fairfield, Iowa 52556.

J Behav Med 1992 Aug;15(4):327-41

Serum dehydroepiandrosterone sulfate (DHEA-S) levels were measured in 270 men and 153 women who were experienced practitioners of the Transcendental Meditation (TM) and TM-Sidhi programs, mental techniques practiced twice daily, sitting quietly with the eyes closed. These were compared according to sex and 5-year age grouping to 799 male and 453 female nonmeditators. The mean DHEA-S levels in the TM group were higher in all 11 of the age groups measured in women and in 6 of 7 5-year age groups over 40 in men. There were no systematic differences in younger men. Simple regression using TM-group data revealed that this effect was independent of diet, body mass index, and exercise. The mean TM-group levels measured in all women and in the older men were generally comparable to those of nonmeditator groups 5 to 10 years younger. These findings suggest that some characteristics of TM practitioners are modifying the age-related deterioration in DHEA-S secretion by the adrenal cortex.

### **Adrenal secretion during major depression in 8- to 16-year-olds, I. Altered diurnal rhythms in salivary cortisol and dehydroepiandrosterone (DHEA) at presentation.**

Goodyer IM, Herbert J, Altham PM, Pearson J, Secher SM, Shiers HM. Department of Psychiatry, University of Cambridge.

The association between basal cortisol, dehydroepiandrosterone (DHEA), its sulphate (DHEAS) and major depression was investigated in 8- to 16-year-olds. Eighty-two subjects with major depression, 25 non-depressed psychiatric cases and 40 community controls were systematically assessed for current mental state and hormone levels at 08.00, 12.00 and 20.00 h, assayed from salivary samples collected over a 48 h period. The average mean of the two time points was compared between the three groups. Evening cortisol hypersecretion and morning DHEA hyposecretion were significantly, and independently, associated with major depression. High evening cortisol ( $< 0.594$  ng/mL) and low morning DHEA ( $< 0.200$  ng/mL) identified subgroups of depressives with different types of adrenal hormone dysregulation. The association between high evening cortisol or low morning DHEA and MDD was not affected by either age or gender.

#### **Effects of age on serum dehydroepiandrosterone sulfate, IGF-I, and IL-6 levels in women.**

Haden ST, Glowacki J, Hurwitz S, Rosen C, LeBoff MS. Endocrine-Hypertension Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, Boston, Massachusetts 02115, USA.

Calcif Tissue Int 2000 Jun;66(6):414-8

Data from animal and in vitro studies suggest that the growth-promoting effects of the adrenal androgen dehydroepiandrosterone sulfate (DHEAS) may be mediated by stimulation of insulin-like growth factor-I (IGF-I) and/or inhibition of interleukin 6 (IL-6), a cytokine mediator of bone resorption. This study tests the hypotheses that there are effects of age on serum DHEAS, IGF-I, and IL-6 levels, and that levels of IGF-I and IL-6 are related to DHEAS levels. The study included 102 women: 27 premenopausal and 75 postmenopausal, including 35 postmenopausal women with osteoporosis, as defined by bone mineral density scores by dual X-ray energy absorptiometry. DHEAS levels decreased significantly with age ( $r = -0.52$ ,  $< 0.0001$ ) and IGF-I levels decreased significantly with age ( $r = -0.49$ ,  $< 0.0001$ ). IL-6 levels increased significantly with age ( $r = 0.36$ ,  $P = 0.008$ ). IGF-I was positively correlated to DHEAS levels ( $r = 0.43$ ,  $< 0.0001$ ,  $n = 102$ ) and IL-6 levels were negatively correlated to DHEAS levels ( $r = -0.32$ ,  $P = 0.021$ ,  $n = 54$ ). Levels of DHEAS and IGF-I were correlated with T scores of the spine and some hip sites. In a multiple variable model to predict DHEAS, age was an important predictor ( $< 0.001$ ), but osteoporosis status, IGF-I, and IL-6 were not. The median DHEAS level was lower in the postmenopausal osteoporotic women (67 microg/dl,  $n = 35$ ) than in the nonosteoporotic postmenopausal women (106.3 microg/dl,  $n = 40$ ,  $P = 0.03$ ), but this was not significant after correction for age. Age accounted for 32% of the variance in DHEAS levels. In summary, DHEAS levels decreased with age and had a positive association with IGF-I levels and a negative association with IL-6 levels. DHEA deficiency may contribute to age-related bone loss through anabolic (IGF-I) and anti-osteolytic (IL-6) mechanisms.

#### **Dehydroepiandrosterone and two structural analogs inhibit 12-O-tetradecanoylphorbol-13-acetate stimulation of prostaglandin E2 content in mouse skin.**

Hastings LA, Pashko LL, Lewbart ML, Schwartz AG. Department of Microbiology, Temple University Medical School, Philadelphia, PA 19140.

Carcinogenesis 1988 Jun;9(6):1099-102

Dehydroepiandrosterone, a naturally occurring adrenal steroid, is a highly effective tumor chemopreventive agent in laboratory mice and rats, inhibiting spontaneous breast cancer and chemically induced tumors of the lung, colon, skin, liver and thyroid. Dehydroepiandrosterone blocks three processes that have been implicated in experimental tumorigenesis: (i) carcinogen activation through the mixed-function oxidases, (ii) 12-O-tetradecanoylphorbol-13-acetate stimulation of superoxide anion production in neutrophils, and (iii) 12-O-tetradecanoylphorbol-13-acetate stimulation of [3H]thymidine incorporation in mouse epidermis. All of these effects of dehydroepiandrosterone very likely result from glucose-6-phosphate dehydrogenase inhibition and a lowering of the NADPH cellular pool. It is now reported that oral administration of dehydroepiandrosterone (0.2% in the diet) for two weeks inhibits the stimulation in prostaglandin E2 content in mouse epidermis produced by topical application of 12-O-tetradecanoylphorbol-13-acetate. Two synthetic steroids, 16 alpha-fluoro-5-androsten-17-one and 16 alpha-fluoro-5 alpha-androstan-17-one, which are more potent inhibitors of the above three processes in tumorigenesis and are also more effective than dehydroepiandrosterone in inhibiting skin papilloma development in the mouse, are more active in suppressing prostaglandin E2 induction by 12-O-tetradecanoylphorbol-13-acetate. These two structural analogs, which also lack specific side-effects associated with dehydroepiandrosterone treatment, may find application as cancer chemopreventive drugs in humans.

#### **Severity of depression in abstinent alcoholics is associated with monoamine metabolites and dehydroepiandrosterone-sulfate concentrations.**

Heinz A, Weingartner H, George D, Hommer D, Wolkowitz OM, Linnoila M. National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD 20892, USA. heinza@as200.zi-mannheim.de

Depressed mood increases the relapse risk of abstinent alcoholics; its neurobiological correlates may include reduced serotonin and norepinephrine turnover rates and increased cortisol concentrations during detoxification stress. Neurosteroids such as dehydroepiandrosterone and its sulfate (DHEA and DHEA-S) may antagonize cortisol action and may have mood-elevating effects on their own. We measured severity of depression with Beck's Depression Inventory (BDI) and Hamilton's Depression Rating Scale (HDRS), plasma concentrations of cortisol, DHEA and DHEA-S, and CSF concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) and the dopamine metabolite homovanillic acid (HVA) in 21 abstinent alcoholics after 4 weeks of abstinence and in 11 age-matched healthy control subjects. Only CSF MHPG concentrations were reduced in alcoholics compared to control subjects (41.4 +/- 6.6 vs. 53.3 +/- 8.6 pmol/ml). Self-rated depression was significantly correlated with CSF MHPG (Spearman's  $R = +0.57, < 0.01$ ), CSF 5-HIAA ( $R = +0.51, < 0.05$ ) and plasma cortisol concentrations ( $R = +0.50, < 0.05$ ). Negative correlations were found between DHEA-S concentrations and both self-rated depression ( $R = -0.45, < 0.05$ ) and observer-rated depression ( $R = -0.55, < 0.05$ ). The ratio of DHEA-S to cortisol serum concentrations was also negatively correlated with depression (BDI:  $R = -0.55, < 0.01$ ; HDRS:  $R = -0.63, < 0.005$ ). Anxiety (Spielberger's State Anxiety Scale) was only associated with CSF MHPG concentrations ( $R = +0.58, < 0.01$ ). Our findings point to the importance of noradrenergic dysfunction in the pathogenesis of depression among abstinent alcoholics and indicate that their mood states may also be modulated by a low DHEA-S to cortisol ratio, hypothetically indicative of low stress protection capacities.

### **Dehydroepiandrosterone and coronary atherosclerosis.**

Herrington DM.

Section of Cardiology, Bowman Gray School of Medicine, Winston-Salem, North Carolina 27157, USA.

Ann N Y Acad Sci 1995 Dec 29;774:271-80

Tissue culture, animal model, and epidemiologic studies suggest that dehydroepiandrosterone (DHEA) may inhibit atherosclerosis through its potent antiproliferative effects. To examine the relation between DHEA and a direct measure of coronary atherosclerosis, plasma DHEA, and DHEA sulfate (DHEAS) levels were determined in 206 middle-aged patients undergoing coronary angiography. Plasma DHEAS levels were lower in subjects with at least one  $\leq 50\%$  stenosis than in those with no stenosis  $< 50\%$  ( $p = 0.05$ ) and was inversely associated with the number of diseased coronary vessels and the extent of coronary atherosclerosis ( $p = 0.05$  and  $0.01$ , respectively). Cardiac allograft vasculopathy is dominated by abnormal cellular proliferation and, therefore, may be uniquely influenced by DHEA. To study this, 61 cardiac allograft recipients with at least one annual follow-up cardiac catheterization were studied. Plasma levels of total and free DHEA were inversely related to the development of accelerated coronary allograft vasculopathy ( $p = 0.005$  and  $0.003$ , respectively). Furthermore, the time to development of accelerated allograft vasculopathy was shorter in subjects with low levels of total and free DHEA ( $p = 0.062$  and  $0.046$ , respectively). These data suggest that low plasma levels of DHEA may facilitate, and high levels may retard, the development of coronary atherosclerosis and coronary allograft vasculopathy.

### **Effect of acute and chronic administration of dehydroepiandrosterone on (+/-)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane-induced wet dog shaking behavior in rats.**

Inagaki M, Kagaya A, Takebayashi M, Horiguchi J, Yamawaki S. Department of Psychiatry and Neurosciences, Hiroshima University School of Medicine, Japan.

J Neural Transm 1999;106(1):23-33

It has been reported that dehydroepiandrosterone (DHEA) or dehydroepiandrosterone sulfate (DHEA-S) is associated with affective disorders and that pathology of affective disorders are related with dysfunction of serotonin(5-HT)-2A receptor-mediated responses. In this study, we investigated the effect of DHEA on (+/-)-1-(2,5-dimethoxy-4-iodophenyl)-2 aminopropane (DOI), 5-HT-2A receptor agonist, -induced wet dog shaking behavior (WDS) in rats. Acute treatment with DHEA inhibited the DOI-induced WDSs dose dependently. This inhibition was recovered by opioid receptor antagonist, naltrexone. 5-HT-2A receptor-mediated WDSs were desensitized after chronic treatment with DOI, however chronic treatment with DHEA had no effect on this desensitization. Chronic treatment with DHEA had no facilitating effect of chronic dexamethasone treatment on DOI-induced WDSs. These findings may lead the possibility that DHEA has the inhibitory effect of 5-HT-2A mediated signaling pathway via

### **Modulation of cytokine production by dehydroepiandrosterone (DHEA) plus melatonin (MLT) supplementation of old mice.**

Inserra P, Zhang Z, Ardestani SK, Araghi-Niknam M, Liang B, Jiang S, Shaw D, Molitor M, Elliott K, Watson RR. Arizona Prevention Center, University of Arizona, Tucson 87524, USA.

Tissue levels of the antioxidants melatonin (MLT) and dehydroepiandrosterone (DHEA) decline with age, and this decline is correlated with immune dysfunction. The aim of the current study is to determine whether hormone supplementation with MLT and DHEA together would synergize to reverse immune senescence. Old (16.5 months) female C57BL/6 mice were treated with DHEA, MLT, or DHEA + MLT. As expected, splenocytes were significantly ( $< 0.05$ ) higher in old mice as compared to young mice. DHEA, MLT, and DHEA + MLT significantly ( $< 0.005$ ) increased B cell proliferation in young mice. However, only MLT and DHEA + MLT significantly ( $< 0.05$ ) increased B cell proliferation in old mice. DHEA, MLT, and DHEA + MLT help to regulate immune function in aged female C57BL/6 mice by significantly ( $< 0.05$ ) increasing Th1 cytokines, IL-2, and IFN-gamma or significantly ( $< 0.05$ ) decreasing Th2 cytokines, IL-6, and IL-10, thus regulating cytokine production. DHEA and MLT effectively modulate suppressed Th1 cytokine and elevated Th2 cytokine production; however, their combined use produced only a limited additive effect.

#### **IL-6, DHEA and the ageing process.**

James K, Premchand N, Skibinska A, Skibinski G, Nicol M, Mason JI. Department of Surgery, University of Edinburgh Medical School, UK.

Mech Ageing Dev 1997 Feb;93(1-3):15-24

The age-related increase in circulating IL-6 levels in humans which has been attributed to a decline in DHEA production by the adrenal gland is currently attracting attention because of its possible relevance to the aetiology and management of a number of age-related clinical disorders. The potential importance of these observations and suggestions has prompted us to perform more detailed studies on the relationship between IL-6 and DHEA. Using immunoassay techniques we have found in normal healthy individuals over the age of 40 an inverse relationship between plasma DHEA levels and the presence of detectable levels of IL-6 (more than 1 pg/ml). In vitro, studies also revealed that low dose ( $10^{-6}$ - $10^{-8}$  M) of DHEA and DHEAS inhibited the production of IL-6 in unstimulated human spleen cell suspension cultures whilst enhancing its release by explant cultures of the same tissue. In contrast they had no effect on immunoglobulin production. These studies suggest that there is a real, but complex relationship between IL-6 production and DHEA levels which warrants further investigation.

#### **Dehydroepiandrosterone inhibits human platelet aggregation in vitro and in vivo.**

Jesse RL, Loesser K, Eich DM, Qian YZ, Hess ML, Nestler JE. Department of Medicine, Medical College of Virginia/Virginia Commonwealth University, Richmond 23298, USA.

Ann N Y Acad Sci 1995 Dec 29;774:281-90

The hypothesis has been advanced that the adrenal steroids dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) exert antiatherogenic and cardioprotective actions. Platelet activation has also been implicated in atherogenesis. To determine if DHEA and DHEAS affect platelet activation, the effects of these steroids on platelet aggregation were assessed both in vitro and in vivo. When DHEAS was added to pooled platelet-rich plasma before the addition of the agonist arachidonate, either the rate of platelet aggregation was slowed or aggregation was completely inhibited. Inhibition of platelet aggregation by DHEA was both dose- and time-dependent. Inhibition of platelet aggregation by DHEA was accompanied by reduced platelet thromboxane B2 (TxB2) production. Inhibition of platelet aggregation by DHEA was also demonstrated in vivo. In a randomized, double-blind trial, 10 normal men received either DHEA 300 mg ( $n = 5$ ) or placebo capsule ( $n = 5$ ) orally three times daily for 14 days. In one man in the DHEA group arachidonate-stimulated platelet aggregation was inhibited completely during DHEA administration, whereas in three other men in the DHEA group the rate of platelet aggregation was prolonged, and the sensitivity and responsiveness to agonist were reduced. None of the men in the placebo group manifested any change in platelet activity. These findings suggest that DHEA retards platelet aggregation in humans. Inhibition of platelet activity by DHEA may contribute to the putative antiatherogenic and cardioprotective effects of DHEA.

#### **Activation of immune function by dehydroepiandrosterone (DHEA) in age-advanced men.**

Khorram O, Vu L, Yen SS. Department of Reproductive Medicine, University of California, San Diego School of Medicine, USA.

J Gerontol A Biol Sci Med Sci 1997 Jan;52(1):M1-7

**BACKGROUND:** Substantial data from animal studies have demonstrated a stimulatory effect of dehydroepiandrosterone (DHEA) on immune function. However, little is known about the effects of DHEA on the human immune system. Since aging is associated with a decline in immune function and in DHEA production, we proposed that oral administration of DHEA to elderly men would result in activation of their immune system.

**METHODS:** Nine healthy age-advanced men (mean age of 63 years) with low DHEA-sulfate levels participated in this study. They were treated nightly with an oral placebo for 2 weeks followed by DHEA (50 mg) for 20 weeks. Fasting (0800h-0900h) blood samples were obtained at 4- to 8-week intervals for immune function studies and hormone determinations. Freshly isolated peripheral lymphocytes were used for flow cytometric identification of lymphocyte subsets, cells expressing the IL-2 receptor (IL-2R), mitogen stimulation studies, and for determining natural killer (NK) cell number and cytotoxicity. Levels of interleukin-2 (IL-2) and IL-6 secreted from cultured lymphocytes were determined under basal and mitogen stimulated conditions. Sera were analyzed for soluble IL-2 Receptor (sIL-2R) levels, insulin-like growth factor-I (IGF-I) and IGF binding protein-I (IGFBP-I) concentrations.

**RESULTS:** Baseline levels of serum DHEA sulfate (DHEAS), a stable marker of circulating DHEA levels, were 2 standard deviations below young adult values and increased 3-4 fold within 2 weeks. These levels were sustained throughout the duration of DHEA administration. When compared with placebo, DHEA administration resulted in a 20% increase ( $< .01$ ) in serum IGF-I, a decreasing trend in IGFBP-I, and a 32% increase in the ratio of IGF-I/IGFBP-I ( $< .01$ ). Activation of immune function occurred within 2-20 weeks of DHEA treatment. The number of monocytes increased significantly ( $< .01$ ) after 2 (45%) and 20 (35%) weeks of treatment. The population of B cells fluctuated with increases ( $< .05$ ) at 2 (35%) and 10 (29%) weeks of treatment. B cell mitogenic response increased 62% ( $< .05$ ) by 12 weeks unaccompanied by changes in serum IgG, IgA, and IgM levels. Total T cells and T cell subsets were unaltered. However, a 40% increase ( $< .05$ ) in T cell mitogenic response, 39% increase in cells expressing the IL-2R (CD25+) ( $< .05$ ), and 20% increase in serum sIL-2R levels ( $< .01$ ) were found at 12-20 weeks of DHEA treatment, suggesting a functional activation of T lymphocytes occurred. In vitro mitogen stimulated release of IL-2 and IL-6 was enhanced 50% ( $< .05$ ) and 30% ( $< .01$ ) respectively by 20 weeks of treatment without basal secretion being affected. NK cell number showed a 22-37% increase ( $< .01$ ) by 18-20 weeks of treatment with a concomitant 45% increase ( $< .01$ ) in cytotoxicity. There were no adverse effects noted with DHEA administration.

**CONCLUSION:** Administration of oral DHEA at a daily dose of 50 mg to age-advanced men with low serum DHEAS levels significantly activated immune function. The mechanism(s) to account for the immunoenhancing properties of DHEA are unclear. Consideration is given to the potential role of an increase in bioavailable IGF-I, which by virtue of its mitogenic effects on immune cell function, may mediate the DHEA effects. While extended studies are required, our findings suggest potential therapeutic benefits of DHEA in immunodeficient states.

### **Modulation of chemical carcinogen-induced unscheduled DNA synthesis by dehydroepiandrosterone (DHEA) in the primary rat hepatocytes.**

Kim SH, Han HM, Kang SY, Jung KK, Kim TG, Oh HY, Lee YK, Rhee HM. Department of Pharmacology, Korea Food and Drug Administration, Eunpyunggu, Seoul. [biolam@kfda.go.kr](mailto:biolam@kfda.go.kr)

Arch Pharm Res 1999 Oct;22(5):474-8

Modulation of unscheduled DNA synthesis by dehydroepiandrosterone (DHEA) after exposure to various chemical carcinogens was investigated in the primary rat hepatocytes. Unscheduled DNA synthesis was induced by treatment of such direct acting carcinogens as methyl methanesulfonate (MMS) and ethyl methanesulfonate (EMS) or procarcinogens including benzo(a)pyrene (BaP) and 7,12-dimethylbenz(a)anthracene (DMBA). Unscheduled DNA synthesis was determined by measuring [methyl-3H] thymidine radioactivity incorporated into nuclear DNA of hepatocytes treated with carcinogens in the presence or absence of DHEA. Hydroxyurea ( $5 \times 10^{-3}$  M) was added to growth medium to selectively suppress normal replication. DHEA at concentrations ranging from  $1 \times 10^{-6}$  M to  $5 \times 10^{-4}$  M did not significantly inhibit unscheduled DNA synthesis induced by either MMS ( $1 \times 10^{-4}$  M) or EMS ( $1 \times 10^{-2}$  M). In contrast, DHEA significantly inhibited unscheduled DNA synthesis induced by BaP ( $6.5 \times 10^{-5}$  M) and DMBA ( $2 \times 10^{-5}$  M). DHEA-induced hepatotoxicity in rats was examined using lactate dehydrogenase (LDH) release as an indicator of cytotoxicity. DHEA exhibit no significant increase in LDH release compared with the solvent control at 18 h. These data suggest that nontoxic concentration of DHEA does not affect the DNA excision repair process, but it probably influence the enzymatic system responsible for the metabolic activation of procarcinogens and thereby decreases the amount of the effective DNA adducts formed by the ultimate reactive carcinogenic species.

### **Dehydroepiandrosterone selectively inhibits production of tumor necrosis factor alpha and interleukin-6 [correction of interlukin-6] in astrocytes.**

Kipper-Galperin M, Galilly R, Danenberg HD, Brenner T. Laboratory of Neuroimmunology, Hadassah University Hospital, Jerusalem, Israel.

Int J Dev Neurosci 1999 Dec;17(8):765-75

Dehydroepiandrosterone (DHEA) is a native neurosteroid with immunomodulating activity. DHEA effectively protects animals from several viral, bacterial and parasitic infections and it was suggested that its age-associated decline is related with immunosenescence. In the present study we examined the ability of DHEA to inhibit the production of inflammatory mediators by

mycoplasma-stimulated glial cells and to change the course of acute central nervous system (CNS) inflammatory disease in vivo. Addition of DHEA (10 microg/ml) markedly inhibited tumor necrosis factor alpha (TNFalpha) and interleukin-6 (IL-6) production (98 and 95%, respectively), whereas nitric oxide (NO) and prostaglandin E2 (PGE2) production was not affected. However, daily administration of 0.5 mg DHEA to mice or 5 mg to rats did not change the clinical outcome of experimental autoimmune encephalomyelitis (EAE).

### **High bioavailability of dehydroepiandrosterone administered percutaneously in the rat.**

Labrie C, Flamand M, Belanger A, Labrie F. Laboratory of Molecular Endocrinology CHUL Research Center, Quebec, Canada.

J Endocrinol 1996 Sep;150 Suppl:S107-18

Dehydroepiandrosterone (DHEA) administered percutaneously by twice daily application for 7 days to the dorsal skin of the rat stimulates an increase in ventral prostate weight with approximately one third the potency of the compound given by subcutaneous injection. The doses required to achieve a 50% reversal of the inhibitory effect of orchietomy are approximately 3 and 1 mg respectively. By the oral route, on the other hand, DHEA has only 10-15% of the activity of the compound given percutaneously. Taking the bioavailability obtained by the subcutaneous route as 100%, it is estimated that the potencies of DHEA by the percutaneous and oral routes are approximately 33 and 3% respectively. Similar ratios of activity were obtained when dorsal prostate and seminal vesicle weight were used as parameters of androgenic activity. When examined on an estrogen-sensitive parameter, namely uterine weight in ovariectomized rats, the stimulatory effect of DHEA was much less potent than its androgenic activity measured in the male animal, a 50% reversal of the inhibitory effect of ovariectomy on uterine weight being observed at the 3 and 30 mg doses of DHEA administered by the subcutaneous and percutaneous routes respectively. When measured on uterine weight, percutaneous DHEA thus shows a 10% potency compared with the subcutaneous route. The sulfate of DHEA (DHEA-S), on the other hand, was approximately 50% as potent as DHEA at increasing ventral prostate weight after subcutaneous or percutaneous administration. When the effect was measured on dorsal prostate and seminal vesicle weight, percutaneous DHEA-S had 10-25% of the activity of DHEA. DHEA decreased serum LH levels in ovariectomized animals, an effect which was completely reversed by treatment with the antiandrogen flutamide. On the other hand, flutamide had no significant effect on the increase in uterine weight caused by DHEA, thus suggesting a predominant estrogenic effect of DHEA at the level of the uterus and an estrogenic effect on the feedback control of LH secretion. The present data show a relatively high bioavailability of percutaneous DHEA as measured by its androgenic and/or estrogenic biological activity in well-characterized peripheral target intracrine tissues in the rat.

### **Effects of cardiac rehabilitation and exercise training programs in women with depression.**

Lavie CJ, Milani RV, Cassidy MM, Gilliland YE. Cardiovascular Health Center and the Ochsner Heart and Vascular Institute, New Orleans, Louisiana, USA. clavie@ohvi.ochsner.org

Am J Cardiol 1999 May 15;83(10):1480-3, A7

Depression is prevalent in women with coronary artery disease, and increases morbidity and mortality following major coronary events. We demonstrated that women with depression had markedly abnormal overall cardiovascular risk profiles and have marked benefits in exercise capacity, obesity indexes, behavioral characteristics (including depression), and quality of life following formal, outpatient phase II cardiac rehabilitation and exercise training programs.

### **Dehydroepiandrosterone sulfate attenuates dizocilpine-induced learning impairment in mice via sigma 1-receptors.**

Maurice T, Junien JL, Privat A. INSERM U 336, Developpement, Plasticite et Vieillessement du Systeme Nerveux, Ecole Nationale Supérieure de Chimie, Montpellier, France. maurice@cit.enscm.fr

Behav Brain Res 1997 Feb;83(1-2):159-64

We previously reported that high-affinity sigma type 1 (sigma 1) ligands attenuate the learning impairment induced in mice by dizocilpine, a non-competitive N-methyl-D-aspartate (NMDA) antagonist. Neurosteroids, such as pregnenolone sulfate, progesterone and dehydroepiandrosterone sulfate (DHEAS), modulate NMDA-evoked responses in the central nervous system. Furthermore, some of them were reported to interact with sigma-receptors. This study was carried out to investigate whether DHEAS, a neurosteroid with memory-enhancing effects, attenuates the dizocilpine-induced learning impairment in mice, and, if so, by a mechanism involving sigma 1-receptors. Learning was evaluated using spontaneous alternation in the Y-maze for spatial working memory and step-down type of passive avoidance for long-term memory. At doses about 10-20 mg/kg s.c., DHEAS significantly attenuated dizocilpine (0.15 mg/kg i.p.)-induced impairment of learning on both tests. The enhancing effect of DHEAS (20 mg/kg s.c.) was antagonized by co-administration of the sigma-antagonist BMY-14802 (5 mg/kg i.p.) and suppressed by a subchronic treatment with haloperidol (4 mg/kg/day s.c. for 7 days). These results indicate that DHEAS attenuates dizocilpine-induced learning impairment via an interaction with sigma 1-receptors.

## **Sequential appearance and ultrastructure of amphophilic cell foci, adenomas, and carcinomas in the liver of male and female rats treated with dehydroepiandrosterone.**

Metzger C, Mayer D, Hoffmann H, Bocker T, Hobe G, Benner A, Bannasch P. Deutsches Krebsforschungszentrum, Abteilung Cytopathologie, Heidelberg, Germany.

Toxicol Pathol 1995 Sep-Oct;23(5):591-605

Dehydroepiandrosterone (DHEA), a hormone of the adrenal cortex, acts as a peroxisome proliferator and hepatocarcinogen in rats upon long-term treatment with high doses in the diet. The aim of the present study was to identify the site of origin of hepatocellular neoplasms and the sequence of preneoplastic lesions. Twenty-five female and 25 male rats were given 0.6% DHEA in the diet; 25 animals of each sex were controls. Groups of 5 treated and untreated animals were sacrificed after 4, 20, 32, 70, and 84 wk. Amphophilic cell foci were detected after 32 wk of treatment; they developed from the liver parenchyma almost exclusively in the vicinity of portal tracts. Adenomas of the amphophilic or amphophilic/tigroid cell phenotype were observed at 70 wk of treatment. Highly differentiated hepatocellular carcinomas presenting a similar cellular phenotype occurred after 70-84 wk. The incidence of hepatocellular carcinomas was 44% in female and 11% in male rats. Ultrastructural studies of the amphophilic cell foci and tumors revealed a marked proliferation of mitochondria and a moderate proliferation of peroxisomes in all lesions. In addition, a very strong peroxisome proliferation was observed in perivenular hepatocytes in the liver of female rats. Peroxisomes usually lacked core and showed flocculent matrices. In male rats, weak peroxisomal proliferation was observed. Typical morphological abnormalities of these peroxisomes were paracrystalline inclusions of striated appearance. Although the most prominent peroxisome proliferation was observed in perivenular hepatocytes, these cells did not seem to be involved in tumor development. In contrast, the morphological similarity of the amphophilic cell foci and the amphophilic/tigroid cell adenomas and carcinomas, their coincident localization near portal tracts, and the sequential appearance of these lesions suggest that the amphophilic cell foci represent an early stage in DHEA-induced hepatocellular neoplasia. Mitochondrial proliferation as the most prominent feature in all stages of this model of hepatocarcinogenesis may offer a new approach for analysis of hepatocarcinogenesis induced by DHEA and possibly other peroxisomal proliferators.

## **The impact of a new emotional self-management program on stress, emotions, heart rate variability, DHEA and cortisol.**

McCarty R, Barrios-Choplin B, Rozman D, Atkinson M, Watkins AD. Institute of HeartMath, Boulder Creek, California 95006, USA. rollin@heartmath.org

Integr Physiol Behav Sci 1998 Apr-Jun;33(2):151-70

This study examined the effects on healthy adults of a new emotional self-management program, consisting of two key techniques, "Cut-Thru" and the "Heart Lock-In." These techniques are designed to eliminate negative thought loops and promote sustained positive emotional states. The hypotheses were that training and practice in these techniques would yield lowered levels of stress and negative emotion and cortisol, while resulting in increased positive emotion and DHEA levels over a one-month period. In addition, we hypothesized that increased coherence in heart rate variability patterns would be observed during the practice of the techniques. Forty-five healthy adults participated in the study, fifteen of whom acted as a comparison group for the psychological measures. Salivary DHEA/DHEAS and cortisol levels were measured, autonomic nervous system function was assessed by heart rate variability analysis, and emotions were measured using a psychological questionnaire. Individuals in the experimental group were assessed before and four weeks after receiving training in the self-management techniques. The experimental group experienced significant increases in the positive affect scales of Caring and Vigor and significant decreases in the negative affect scales of Guilt, Hostility, Burnout, Anxiety and Stress Effects, while no significant changes were seen in the comparison group. There was a mean 23 percent reduction in cortisol and a 100 percent increase in DHEA/DHEAS in the experimental group. DHEA was significantly and positively related to the affective state Warmheartedness, whereas cortisol was significantly and positively related to Stress Effects. Increased coherence in heart rate variability patterns was measured in 80 percent of the experimental group during the use of the techniques. The results suggest that techniques designed to eliminate negative thought loops can have important positive effects on stress, emotions and key physiological systems. The implications are that relatively inexpensive interventions may dramatically and positively impact individuals' health and well-being. Thus, individuals may have greater control over their minds, bodies and health than previously suspected.

## **Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age.**

Morales AJ, Nolan JJ, Nelson JC, Yen SS. Department of Reproductive Medicine, University of California School of Medicine, La Jolla 92093-0802.

J Clin Endocrinol Metab 1994 Jun;78(6):1360-7

Aging in humans is accompanied by a progressive decline in the secretion of the adrenal androgens dehydroepiandrosterone

(DHEA) and DHEA sulfate (DS), paralleling that of the GH-insulin-like growth factor-I (GH-IGF-I) axis. Although the functional relationship of the decline of the GH-IGF-I system and catabolism is recognized, the biological role of DHEA in human aging remains undefined. To test the hypothesis that the decline in DHEA may contribute to the shift from anabolism to catabolism associated with aging, we studied the effect of a replacement dose of DHEA in 13 men and 17 women, 40-70 yr of age. A randomized placebo-controlled cross-over trial of nightly oral DHEA administration (50 mg) of 6-month duration was conducted. During each treatment period, concentrations of androgens, lipids, apolipoproteins, IGF-I, IGF-binding protein-1 (IGFBP-1), IGFBP-3, insulin sensitivity, percent body fat, libido, and sense of well-being were measured. A subgroup of men (n = 8) and women (n = 5) underwent 24-h sampling at 20-min intervals for GH determinations. DHEA and DS serum levels were restored to those found in young adults within 2 weeks of DHEA replacement and were sustained throughout the 3 months of the study. A 2-fold increase in serum levels of androgens (androstenedione, testosterone, and dihydrotestosterone) was observed in women, with only a small rise in androstenedione in men. There was no change in circulating levels of sex hormone-binding globulin, estrone, or estradiol in either gender. High density lipoprotein levels declined slightly in women, with no other lipid changes noted for either gender. Insulin sensitivity and percent body fat were unaltered. Although mean 24-h GH and IGFBP-3 levels were unchanged, serum IGF-I levels increased significantly, and IGFBP-1 decreased significantly for both genders, suggesting an increased bioavailability of IGF-I to target tissues. This was associated with a remarkable increase in perceived physical and psychological well-being for both men (67%) and women (84%) and no change in libido. In conclusion, restoring DHEA and DS to young adult levels in men and women of advancing age induced an increase in the bioavailability of IGF-I, as reflected by an increase in IGF-I and a decrease in IGFBP-1 levels. These observations together with improvement of physical and psychological well-being in both genders and the absence of side-effects constitute the first demonstration of novel effects of DHEA replacement in age-advanced men and women.

### **The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women.**

Morales AJ, Haubrich RH, Hwang JY, Asakura H, Yen SS. Department of Reproductive Medicine, School of Medicine, University of California San Diego, La Jolla, USA.

Clin Endocrinol (Oxf) 1998 Oct;49(4):421-32

**OBJECTIVE:** The biological role of the adrenal sex steroid precursors--DHEA and DHEA sulphate (DS) and their decline with ageing remains undefined. We observed previously that administration of a 50 daily dose of DHEA for 3 months to age-advanced men and women resulted in an elevation (10%) of serum levels of insulin-like growth factor-I (IGF-I) accompanied by improvement of self-reported physical and psychological well-being. These findings led us to assess the effect of a larger dose (100 mg) of DHEA for a longer duration (6 months) on circulating sex steroids, body composition (DEXA) and muscle strength (MedX). **SUBJECTS AND DESIGN:** Healthy non-obese age-advanced (50-65 yrs of age) men (n = 9) and women (n = 10) were randomized into a double-blind placebo-controlled cross-over trial. Sixteen subjects completed the one-year study of six months of placebo and six months of 100 mg oral DHEA daily. **MEASUREMENTS:** Fasting early morning blood samples were obtained. Serum DHEA, DS, sex steroids, IGF-I, IGFBP-1, IGFBP-3, growth hormone binding protein (GHBP) levels and lipid profiles as well as body composition (by DEXA) and muscle strength (by MedX testing) were measured at baseline and after each treatment. **RESULTS:** Basal serum levels of DHEA, DS, androstenedione (A), testosterone (T) and dihydrotestosterone (DHT) were at or below the lower range of young adult levels. In both sexes, a 100 mg daily dose of DHEA restored serum DHEA levels to those of young adults and serum DS to levels at or slightly above the young adult range. Serum cortisol levels were unaltered, consequently the DS/cortisol ratio was increased to pubertal (10:1) levels. In women, but not in men, serum A, T and DHT were increased to levels above gender-specific young adult ranges. Basal SHBG levels were in the normal range for men and elevated in women, of whom 7 of 8 were on oestrogen replacement therapy. While on DHEA, serum SHBG levels declined with a greater (< 0.02) response in women (-40 +/- 8%; P = 0.002) than in men (-5 +/- 4%; P = 0.02). Relative to baseline, DHEA administration resulted in an elevation of serum IGF-I levels in men (16 +/- 6%, P = 0.04) and in women (31 +/- 12%, P = 0.02). Serum levels of IGFBP-1 and IGFBP-3 were unaltered but GHBP levels declined in women (28 +/- 6%; P = 0.02) not in men. In men, but not in women, fat body mass decreased 1.0 +/- 0.4 kg (6.1 +/- 2.6%, P = 0.02) and knee muscle strength 15.0 +/- 3.3% (P = 0.02) as well as lumbar back strength 13.9 +/- 5.4% (P = 0.01) increased. In women, but not in men, an increase in total body mass of 1.4 +/- 0.4 kg (2.1 +/- 0.7%; P = 0.02) was noted. Neither gender had changes in basal metabolic rate, bone mineral density, urinary pyridinoline cross-links, fasting insulin, glucose, cortisol levels or lipid profiles. No significant adverse effects were observed. **CONCLUSIONS:** A daily oral 100 mg dose of DHEA for 6 months resulted in elevation of circulating DHEA and DS concentrations and the DS/cortisol ratio. Biotransformation to potent androgens near and slightly above the range of their younger counterparts occurred in women with no detectable change in men. Given this hormonal milieu, an increase in serum IGF-I levels was observed in both genders but dimorphic responses were evident in fat body mass and muscle strength in favour of men. These differences in response to DHEA administration may reflect a gender specific response to DHEA and/or the presence of confounding factor(s) in women such as oestrogen replacement therapy.

### **Hippocampal perfusion and pituitary-adrenal axis in Alzheimer's disease.**

Murialdo G, Nobili F, Rollero A, Gianelli MV, Copello F, Rodriguez G, Polleri A. Department of Endocrinological and Metabolic Sciences, Epidemiology Service, University of Genova, Italy. disem@unige.it

The hippocampus is involved in Alzheimer's disease (AD) and regulates the hypothalamus-pituitary-adrenal axis (HPAA). Enhanced cortisol secretion has been reported in AD. Increased cortisol levels affect hippocampal neuron survival and potentiate beta-amyloid toxicity. Conversely, dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are believed to antagonize noxious glucocorticoid effects and exert a neuroprotective activity. The present study was aimed at investigating possible correlations between hippocampus perfusion - evaluated by SPECT - and HPAA function in AD. Fourteen patients with AD and 12 healthy age-matched controls were studied by (99m)Tc-HMPAO high-resolution brain SPECT. Plasma adrenocorticotropin, cortisol, and DHEAS levels were determined at 2.00, 8.00, 14.00, 20.00 h in all subjects and their mean values were computed. Cortisol/DHEAS ratios (C/Dr) were also calculated. Bilateral impairment of SPECT hippocampal perfusion was observed in AD patients as compared to controls. Mean cortisol levels were significantly increased and DHEAS titers were lowered in patients with AD, as compared with controls. C/Dr was also significantly higher in patients. Using a stepwise procedure for dependent SPECT variables, the variance of hippocampal perfusional data was accounted for by mean basal DHEAS levels. Moreover, hippocampal SPECT data correlated directly with mean DHEAS levels, and inversely with C/Dr. These data show a relationship between hippocampal perfusion and HPAA function in AD. Decreased DHEAS, rather than enhanced cortisol levels, appears to be correlated with changes of hippocampal perfusion in dementia. Copyright 2000 S. Karger AG, Basel.

### **Dehydroepiandrosterone decreases mortality rate and improves cellular immune function during polymicrobial sepsis.**

Oberbeck R, Dahlweid M, Koch R, van Griensven M, Emmendorfer A, Tscherne H, Pape HC. Department of Trauma Surgery, University Hospital of Essen, Essen, Germany.

Crit Care Med 2001 Feb;29(2):380-4

**OBJECTIVE:** Sepsis is associated with a marked depression of cellular immune function. The steroid hormone dehydroepiandrosterone (DHEA) is proposed to have immunoenhancing activities. We, therefore, investigated the effect of DHEA on the mortality rate and cellular immune functions in an experimental model of sepsis. **DESIGN:** Randomized animal study. **SETTING:** Level I trauma center, university research laboratory. **SUBJECTS:** Male NMRI mice. **INTERVENTIONS:** Mice were subjected to laparotomy (sham) or cecal ligation and puncture (CLP). Mice were treated with (sham/DHEA; CLP/DHEA) or without (sham; CLP) the steroid hormone DHEA (30 mg/kg sc). Animals were killed 48 hrs after the onset of sepsis. **MEASUREMENTS AND MAIN RESULTS:** The survival rate of septic mice was determined 24 and 48 hrs after onset of sepsis. Forty-eight hours after the septic challenge, a white blood cell count was performed and serum tumor necrosis factor (TNF)-alpha and interleukin (IL)-1beta concentrations were monitored using ELISA. Furthermore, the delayed type of hypersensitivity (DTH) reaction was evaluated on the basis of ear pinna swelling after dinitrofluorobenzene (DNFB) administration, and clinical variables (body weight, temperature, heart rate, fluid input/output, food intake) were monitored using metabolic cages. DHEA administration improved the survival rate (87% vs. 53% after 48 hrs; <001). This was accompanied by a restoration of the depressed DTH reaction and a reduction in TNF-alpha serum concentrations (20.7 +/- 1.4 pg/mL vs. 32.4 +/- 6.6 pg/mL). **CONCLUSIONS:** These results demonstrate that DHEA administration leads to an increased survival following a septic challenge. The immunoenhancing effect of DHEA is accompanied by a reduction of TNF-alpha release and an improved activity of T-cellular immunity. DHEA administration may, therefore, be beneficial in systemic inflammation.

### **Inhibition of 7,12-dimethylbenz(a)anthracene-induced skin papillomas and carcinomas by dehydroepiandrosterone and 3-beta-methylandrosterone in mice.**

Pashko LL, Hard GC, Rovito RJ, Williams JR, Sobel EL, Schwartz AG.

Cancer Res 1985 Jan;45(1):164-6

Topical application of the adrenal steroid, dehydroepiandrosterone, or the synthetic steroid, 3-beta-methylandrosterone, which unlike dehydroepiandrosterone is not demonstrably uterotrophic, inhibits 7,12-dimethylbenz(a)anthracene-induced skin papillomas and carcinomas in the CD-1 mouse.

### **Enhancement of hippocampal acetylcholine release by the neurosteroid dehydroepiandrosterone sulfate: an in vivo microdialysis study.**

Rhodes ME, Li PK, Flood JF, Johnson DA Division of Pharmacology-Toxicology, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, PA 15282, USA.

Brain Res 1996 Sep 16;733(2):284-6

The effect of dehydroepiandrosterone sulfate (DHEAS) administered i.p. on the release of acetylcholine (ACh) from the hippocampus

of anesthetized rats was examined using in vivo microdialysis. DHEAS significantly increased ACh release above the pre-treatment levels for all doses tested. The administration of 100 mg/kg significantly enhanced ACh release greater than 4-fold when compared to the saline-treated group 80 min following drug administration. This study is the first to demonstrate that the neurosteroid DHEAS, a negative allosteric modulator of the GABAA receptor, can enhance the release of ACh from neurons in the hippocampus.

### **Food restriction inhibits [3H] 7,12-dimethylbenz(a)anthracene binding to mouse skin DNA and tetradecanoylphorbol-13-acetate stimulation of epidermal [3H] thymidine incorporation.**

Schwartz AG, Pashko LL.

Anticancer Res 1986 Nov-Dec;6(6):1279-82

It has been known for many years that reducing the food intake of laboratory mice and rats inhibits the development of a broad spectrum of chemically induced and spontaneous tumors, but the mechanism of this effect is poorly understood. Food restriction of A/J mice for two weeks is now shown to inhibit the binding of topically applied [3H]7,12-dimethylbenz(a)anthracene (DMBA) to skin DNA by 50% and to abolish the stimulation of [3H]-thymidine incorporation in the epidermis produced by topical application of the tumor promoter tetradecanoylphorbol-13-acetate (TPA). Similar effects on the actions of DMBA and TPA are observed following topical application of the adrenal steroid, dehydroepiandrosterone (DHEA), a potent glucose-6-phosphate dehydrogenase (G6PDH) inhibitor, while food restriction for two weeks depresses epidermal G6PDH activity by 60%. It is suggested that both the inhibition of [3H]DMBA binding to skin DNA and the TPA stimulation in epidermal [3H]thymidine incorporation result from a reduction in the NADPH cellular pool as a result of G6PDH inhibition.

### **Cancer prevention with dehydroepiandrosterone and non-androgenic structural analogs.**

Schwartz AG, Pashko LL.

Fels Institute for Cancer Research and Molecular Biology, Temple University School of Medicine, Philadelphia, PA 19140, USA.

J Cell Biochem Suppl 1995;22:210-7

There is increasing evidence that the adrenocortical steroid, dehydroepiandrosterone (DHEA), is an important mammalian hormone. Administration of DHEA to laboratory mice and rats inhibits development of experimental tumors of the breast, lung, colon, liver, skin and lymphatic tissue. In the two-stage skin tumorigenesis model in mice, DHEA treatment inhibits tumor initiation, as well as tumor promoter-induced epidermal hyperplasia and promotion of papillomas. There is much evidence that DHEA produces its antiproliferative and tumor preventive effects by inhibiting glucose-6-phosphate dehydrogenase and the pentose phosphate pathway. This pathway is an important source of NADPH, a critical reductant for many biochemical reactions that generate oxygen free radicals, which may act as second messengers in stimulating hyperplasia. The therapeutic use of DHEA in humans may be limited by its sex hormonal side effects. DHEA is metabolized in vivo to both testosterone and estrone, producing both androgenic and estrogenic effects in laboratory animals. We have developed a synthetic steroid, 16 alpha-fluoro-5-androsten-17-one, which does not demonstrate the androgenic or estrogenic activity of DHEA, yet retains the antiproliferative and cancer preventive activity of the native steroid.

### **Inhibition by dehydroepiandrosterone of growth and progression of persistent liver nodules in experimental rat liver carcinogenesis.**

Simile M, Pascale RM, De Miglio MR, Nuftris A, Daino L, Seddaiu MA, Muroli MR, Rao KN, Feo F. Istituto di Patologia Generale, Università di Sassari, Italy.

Int J Cancer 1995 Jul 17;62(2):210-5

Dehydroepiandrosterone (DHEA) inhibits the development of early pre-neoplastic lesions and prevents tumor development in various tissues when given to animals during the initiation/promotion stages of carcinogenesis. Our purpose was to evaluate whether DHEA can also arrest the growth and progression of late lesions, such as persistent nodules (PNs) of rat liver. Male F344 rats were subjected to initiation by diethylnitrosamine followed by selection according to the "resistant hepatocyte" (RH) protocol. Fifteen weeks after initiation, when PNs were present in the liver, the rats were fed a diet with/without 0.6% DHEA for a maximum of 15 weeks. Glucose-6-phosphate dehydrogenase (G6PD) activity was 17- to 20-fold higher in PNs than in normal liver 15-30 weeks after initiation. It significantly decreased, in both liver and PNs, 16 hr after starting DHEA feeding. Further DHEA feeding for 3-15 weeks decreased G6PD activity by 55-58% in both tissues. Eight weeks after starting DHEA, a fall in the proportion of labeled cells, after continuous contact with 3H thymidine for 7 days, was found in nodules. Treatment for 15 weeks with DHEA caused a marked decrease in the number of nodules per liver, as well as in the incidence of PNs with diameters of 3-6 and < 6 mm, respectively, while it did not affect PNs with diameters < 3 mm. Nodules showing patterns of malignant transformation were present in 40% of

rats not treated with DHEA, but not in DHEA-treated rats. All of 8 surviving rats not treated with DHEA had carcinomas at the 56th week, while only 1 out of 4 surviving rats treated with DHEA had carcinoma. These data indicate that DHEA inhibits G6PD activity in rat liver and in PNs in vivo. This is associated with growth restraint of PNs and results in inhibition of their progression to malignancy.

### **Serum dehydroepiandrosterone (DHEA) and DHEA sulfate are negatively correlated with serum interleukin 6 (IL 6), and DHEA inhibits IL 6 secretion from mononuclear cells in man in vitro: possible link between endocrinosenescence and immunosenescence.**

Straub RH, Konecna L, Hrach S, Rothe G, Kreutz M, Scholmerich J, Falk W, Lang B Department of Internal Medicine I, University Medical Center, Regensburg, Germany. rainer.straub@klinik.uni-regensburg.de

J Clin Endocrinol Metab 1998 Jun;83(6):2012-7

Interleukin 6 (IL 6) is one of the pathogenetic elements in inflammatory and age related diseases such as rheumatoid arthritis, osteoporosis, atherosclerosis, and late onset B cell neoplasia. In these diseases or during aging, the decrease in production of sex hormones such as dehydroepiandrosterone (DHEA) is thought to play an important role in IL 6 mediated pathogenetic effects in mice. In humans, we investigated the correlation of serum levels of DHEA, DHEA sulfate (DHEAS), or androstenedione (ASD) and IL 6, tumor necrosis factor alpha, or IL 2 with age in 120 female and male healthy subjects (15-75 yr of age). Serum DHEA, DHEAS, and ASD levels significantly decreased with age (all  $< 0.001$ ), whereas serum IL 6 levels significantly increased with age ( $< 0.001$ ). DHEA/DHEAS and IL 6 (but not tumor necrosis factor alpha or IL 2) were inversely correlated (all patients:  $r = 0.242/0.312$ ;  $P = 0.010/0.001$ ). In female and male subjects, DHEA and ASD concentration dependently inhibited IL 6 production from peripheral blood mononuclear cells ( $P = 0.001$ ). The concentration response curve for DHEA was U shaped (maximal effective concentration,  $1.5 \times 10^{-8}$  mol/L), which may be the optimal range for immunomodulation. In summary, the data indicate a functional link between DHEA or ASD and IL 6. It is concluded that the increase in IL 6 production during the process of aging might be due to diminished DHEA and ASD secretion. Immunosenescence may be directly related to endocrinosenescence, which, in turn, may be a significant cofactor for the manifestation of inflammatory and age related diseases.

### **Replacement therapy with DHEA plus corticosteroids in patients with chronic inflammatory diseases--substitutes of adrenal and sex hormones.**

Straub RH, Scholmerich J, Zietz B. Laboratory of Neuroendocrinology, Department of Internal Medicine I, University Hospital, Franz-Josef-Strauss-Allee 11, D-93042 Regensburg, Germany. Rainer.Straub@klinik.uni-regensburg.de

Z Rheumatol 2000;59 Suppl 2:II/108-18

A dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis was found in animal models of chronic inflammatory diseases, and the defect was located in more central portions of the HPA axis. This defect of neuroendocrine regulatory mechanisms contributes to the onset of the model disease. Since these first observations in animal models were made, evidence has accumulated that the possible defect in the HPA axis in humans is more distal to the hypothalamus or pituitary gland: In chronic inflammatory diseases, such as rheumatoid arthritis, an alteration of the HPA stress response results in inappropriately low cortisol secretion in relation to adrenocorticotropic hormone (ACTH) secretion. Furthermore, it has recently been shown that the serum levels of another adrenal hormone, dehydroepiandrosterone (DHEA), were significantly lower after ACTH stimulation in patients with rheumatoid arthritis without prior corticosteroids than in healthy controls. These studies clearly indicate that chronic inflammation alters, particularly, the adrenal response. However, at this point, the reason for the specific alteration of adrenal function in relation to pituitary function remains to be determined. Since one of the down-regulated adrenal hormones, DHEA, is an inhibitor of cytokines due to an inhibition of nuclear factor-kappa B (NF-kappa B) activation, low levels of this hormone may be deleterious in chronic inflammatory diseases. We have recently demonstrated that DHEA is a potent inhibitor of IL-6, which confirmed an earlier study in mice. Since IL-6 is an important factor for B lymphocyte differentiation, the missing down-regulation of this cytokine, and others such as TNF, may be a significant risk factor in rheumatic diseases. Since in these patients, administration of prednisolone or the chronic inflammatory process itself alters adrenal function, endogenous adrenal hormones in relation to proinflammatory cytokines change. Furthermore, these mechanisms may also lead to shifts in steroidogenesis which have been demonstrated in chronic inflammatory diseases. It was repeatedly demonstrated that the serum level of the sulphated form of DHEA (DHEAS) was significantly lower in patients with chronic inflammatory diseases. Since DHEAS is the pool for peripheral sex steroids, such as testosterone and 17 beta-estradiol, lack of this hormone leads to a significant sex hormone deficiency in the periphery. This overview will demonstrate mechanisms why DHEAS is reduced in chronic inflammatory diseases. The importance of DHEAS deficiency will be demonstrated with respect to osteoporosis. As a consequence, we suggest a combined therapy with corticosteroids plus DHEA in chronic inflammatory diseases.

### **Dietary alpha-tocopherol prevents dehydroepiandrosterone-induced lipid peroxidation in rat liver microsomes and mitochondria.**

Toxicol Lett 1997 Apr 28;91(2):129-36

Dehydroepiandrosterone (DHEA), an adrenal steroid, causes lipid peroxidation in rat liver microsomes and mitochondria and induces hepatocarcinogenesis. It was investigated whether alpha-tocopherol, a naturally occurring free radical chain terminator, could decrease lipid peroxidation. When DHEA-free diet supplemented with increasing concentrations of alpha-tocopherol (25, 50, 100, 200, 400 and 1000 mg/kg diet) was fed to rats for 7 days, a marked lipid peroxidation (measured as thiobarbituric acid reactive substances formation) was observed at concentrations 25 and 50 mg/kg in liver microsomes and mitochondria isolated from these animals. Lipid peroxidation was significantly reduced at concentrations  $\leq 100$  mg/kg. When DHEA (500 mg/kg diet) was fed to rats simultaneously with increasing concentrations of alpha-tocopherol, strong lipid peroxidation was observed at alpha-tocopherol concentrations  $\leq 200$  mg/kg diet. However, microsomes and mitochondria isolated from livers of rats fed alpha-tocopherol at doses of 400 and 1000 mg/kg diet produced only negligible amounts of thiobarbituric acid reactive substances. The data show that high concentrations of alpha-tocopherol in the diet decrease DHEA-induced microsomal and mitochondrial lipid peroxidation. Our results support the concept that alpha-tocopherol can protect against DHEA-induced lipid peroxidation and consequently against steroid-induced liver cell damage and, perhaps, also tumour development.

### **Serum dehydroepiandrosterone and DHEA-sulfate in patients with adult T-cell leukemia and human T-lymphotropic virus type I carriers.**

Uozumi K, Uematsu T, Otsuka M, Nakano S, Takatsuka Y, Iwahashi M, Hanada S, Arima T. Second Department of Internal Medicine, Faculty of Medicine, Kagoshima University, Japan.

Am J Hematol 1996 Nov;53(3):165-8

The serum levels of dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S) were determined by radioimmunoassay in 38 patients with adult T-cell leukemia (ATL). Levels of serum DHEA and DHEA-S were also measured in 60 human T-lymphotropic virus type I (HTLV-I) carriers, and did not differ from those in 60 healthy control subjects. Serum levels in patients with ATL were lower than those in the age- and sex-matched healthy controls and in HTLV-I carriers with statistical significance. Serum DHEA and DHEA-S in male patients with acute and lymphoma-type ATL were  $1.06 \pm 0.77$  ng/ml and  $245.8 \pm 192.9$  ng/ml, respectively. Levels in male patients with chronic and smoldering-type ATL were  $1.69 \pm 0.68$  ng/ml and  $477.6 \pm 251.5$  ng/ml, respectively. Serum levels of DHEA and DHEA-S in patients with acute and lymphoma-type ATL were significantly lower than those in patients with chronic and smoldering-type ATL ( $< 0.05$ ). These data suggest that a decrease in serum levels of DHEA and DHEA-S may be associated with patients who have some clinical subtypes of ATL. Moreover, androgens may have a therapeutic role in patients with ATL, as administered in patients with hairy-cell leukemia. Because there is at present no curative chemotherapy for ATL, a trial combination of androgens and standard chemotherapy may be a reasonable therapeutic option in such patients.

### **Treatment of systemic lupus erythematosus with dehydroepiandrosterone: 50 patients treated up to 12 months.**

van Vollenhoven RF, Morabito LM, Engleman EG, McGuire JL. Division of Immunology and Rheumatology, Stanford University Medical Center, CA 94305-5111, USA.

J Rheumatol 1998 Feb;25(2):285-9

**OBJECTIVE:** To determine whether longterm therapy (up to 1 year) with the weakly androgenic adrenal steroid dehydroepiandrosterone (DHEA) is feasible and beneficial in patients with mild to moderate systemic lupus erythematosus (SLE). **METHODS:** In a prospective, open label, uncontrolled longitudinal study 50 female patients (37 premenopausal, 13 postmenopausal) with mild to moderate SLE were treated with oral DHEA 50-200 mg/day. **RESULTS:** DHEA therapy was associated with increases in the serum levels of DHEA, DHEA sulfate, and testosterone and, for those patients who continued DHEA, with decreasing disease activity measured by SLE Disease Activity Index score ( $< 0.01$ ), patient global assessment ( $< 0.01$ ), and physician global assessment ( $< 0.05$ ), compared to baseline. Concurrent prednisone doses were reduced ( $< 0.05$ ). These improvements were sustained over the entire treatment period. Thirty-four patients (68%) completed 6 months of treatment and 21 patients (42%) completed 12 months. Mild acneiform dermatitis was the most common adverse event (54%). Pre and postmenopausal women experienced similar efficacy and adverse effects from DHEA. **CONCLUSION:** DHEA was well tolerated and appeared clinically beneficial, with the benefits sustained for at least one year in those patients who maintained therapy.

### **Dehydroepiandrosterone and diseases of aging.**

Watson RR, Huls A, Araghinikam M, Chung S. Arizona Prevention Center, University of Arizona, School of Medicine, Tucson, USA. rwatson@ccit.arizona.edu

Dehydroepiandrosterone (DHEA; prasterone) is a major adrenal hormone with no well accepted function. In both animals and humans, low DHEA levels occur with the development of a number of the problems of aging: immunosenescence, increased mortality, increased incidence of several cancers, loss of sleep, decreased feelings of well-being, osteoporosis and atherosclerosis. DHEA replacement in aged mice significantly normalised immunosenescence, suggesting that this hormone plays a key role in aging and immune regulation in mice. Similarly, osteoclasts and lymphoid cells were stimulated by DHEA replacement, an effect that may delay osteoporosis. Recent studies do not support the original suggestion that low serum DHEA levels are associated with Alzheimer's disease and other forms of cognitive dysfunction in the elderly. As DHEA modulates energy metabolism, low levels should affect lipogenesis and gluconeogenesis, increasing the risk of diabetes mellitus and heart disease. Most of the effects of DHEA replacement have been extrapolated from epidemiological or animal model studies, and need to be tested in human trials. Studies that have been conducted in humans show essentially no toxicity of DHEA treatment at dosages that restore serum levels, with evidence of normalisation in some aging physiological systems. Thus, DHEA deficiency may expedite the development of some diseases that are common in the elderly.

### **Serum interleukin-6 and thyroid hormones in rheumatoid arthritis.**

Wellby ML, Kennedy JA, Pile K, True BS, Barreau P. Departments of Clinical Chemistry and Rheumatology, The Queen Elizabeth Hospital Campus, North Western Adelaide Health Service, Woodville South, South Australia.

Metabolism 2001 Apr;50(4):463-7

Using rheumatoid arthritis (RA) as a model, we have investigated whether the activation of the cytokine system, in particular, activation of interleukin (IL)-6 production, is a major cause of the depressed serum T(3) seen frequently in the nonthyroidal illness syndrome (NTIS). RA was chosen because it is a chronic autoimmune disease leading to increased serum IL-6 concentrations. We studied 16 untreated RA and 35 treated RA patients. Twenty-seven treated and 27 untreated patients with noninflammatory musculoskeletal symptoms served as controls. The patient groups displayed similar age distribution and nutritional status. Untreated RA patients displayed elevations of serum IL-6 (mean, 37.5 pg/mL) and C-reactive protein (CRP; mean, 41.3 mg/L), consistent with the inflammatory nature of their disease. Treated RA patients had significantly reduced serum IL-6 (mean, 9.9 pg/mL) and CRP (mean, 13.3 mg/L) compared with untreated RA patients, while untreated and treated patients with noninflammatory musculoskeletal symptoms had near normal serum IL-6 (mean, 2.5, 6.6 pg/mL, respectively) and CRP levels (mean, 5.8, 8.1 mg/L, respectively). However, there were no significant differences in serum concentrations of free T(3) (FT(3)) and free T(4) (FT(4)) between groups, and thyroid indices were in the normal range in RA patients. Moreover, no significant correlations between serum concentration of IL-6 and any of the thyroid hormones were demonstrated for any of the patient groups. In conclusion, we have been unable to confirm in RA that IL-6 activation leads to the low T(3) state of NTIS. Copyright 2001 by W.B. Saunders Company

### **Dehydroepiandrosterone (DHEA) treatment of depression.**

Wolkowitz OM, Reus VI, Roberts E, Manfredi F, Chan T, Raum WJ, Ormiston S, Johnson R, Canick J, Brizendine L, Weingartner H. Department of Psychiatry, University of California, San Francisco, School of Medicine 94143-0984, USA.

Biol Psychiatry 1997 Feb 1;41(3):311-8

Dehydroepiandrosterone (DHEA) and its sulfate, DHEA-S, are plentiful adrenal steroid hormones that decrease with aging and may have significant neuropsychiatric effects. In this study, six middle-aged and elderly patients with major depression and low basal plasma DHEA f1p4or DHEA-S levels were openly administered DHEA (30-90 mg/d x 4 weeks) in doses sufficient to achieve circulating plasma levels observed in younger healthy individuals. Depression ratings, as well as aspects of memory performance significantly improved. One treatment-resistant patient received extended treatment with DHEA for 6 months: her depression ratings improved 48-72% and her semantic memory performance improved 63%. These measures returned to baseline after treatment ended. In both studies, improvements in depression ratings and memory performance were directly related to increases in plasma levels of DHEA and DHEA-S and to increases in their ratios with plasma cortisol levels. These preliminary data suggest DHEA may have antidepressant and promemory effects and should encourage double-blind trials in depressed patients.

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.