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## **Chemoprevention of rat prostate carcinogenesis by early and delayed administration of dehydroepiandrosterone.**

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Cancer Res 1999 Jul 1;59(13):3084-9

Two in vivo bioassays were conducted to evaluate the efficacy of dehydroepiandrosterone (DHEA) as an inhibitor of prostate carcinogenesis in rats. Prostate adenocarcinomas were induced in male Wistar-Unilever rats by a sequential regimen of cyproterone acetate and testosterone propionate, followed by a single i.v. injection of N-methyl-N-nitrosourea (MNU) and chronic androgen stimulation. In the first experiment, DHEA (1000 or 2000 mg/kg diet) was administered continuously to rats beginning 1 week before MNU exposure. In the second experiment, continuous administration of DHEA (2000 mg/kg diet) was begun either 1 week before, 20 weeks after, or 40 weeks after MNU exposure. Controls received basal diet without added DHEA. Studies were terminated at 13 months after MNU administration, and prostate cancer incidence was determined by histopathological evaluation of step sections of accessory sex glands. In the first study, continuous dietary administration of DHEA beginning 1 week before MNU resulted in a dose-related inhibition of prostate cancer induction. In the second experiment, comparable reductions in prostate cancer incidence were observed in groups exposed to DHEA beginning 1 week before, 20 weeks after, and 40 weeks after carcinogen exposure. These data demonstrate that nontoxic doses of DHEA confer significant protection against prostate carcinogenesis in rats. The efficacy of delayed administration of DHEA suggests that the compound

## **Endogenous sex hormones and prostate cancer: a quantitative review of prospective studies.**

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Br J Cancer 1999 Jun;80(7):930-4

This paper presents a quantitative review of the data from eight prospective epidemiological studies, comparing mean serum concentrations of sex hormones in men who subsequently developed prostate cancer with those in men who remained cancer free. The hormones reviewed have been postulated to be involved in the aetiology of prostate cancer: androgens and their metabolites testosterone (T), non-SHBG-bound testosterone (non-SHBG-bound T), di-hydrotestosterone (DHT), androstenediol glucuronide (A-diol-g), androstenedione (A-dione), dehydroepiandrosterone sulphate (DHEAS), sex hormone binding globulin (SHBG), the oestrogens, oestrone and oestradiol, luteinizing hormone (LH) and prolactin. The ratio of the mean hormone concentration in prostate cancer cases to that of controls (and its 95% confidence interval (CI)) was calculated for each study, and the results summarized by calculating the weighted average of the log ratios. No differences in the average concentrations of the hormones were found between prostate cancer cases and controls, with the possible exception of A-diol-g which exhibited a 5% higher mean serum concentration among cases relative to controls (ratio 1.05, 95% CI 1.00-1.11), based on 644 cases and 1048 controls. These data suggest that there are no large differences in circulating hormones between men who subsequently go on to develop prostate cancer and those who remain free of the disease. Further research is needed to substantiate the small difference found in A-diol-g concentrations between prostate cancer cases and controls.

## **Chemoprevention of hormone-dependent prostate cancer in the Wistar-Unilever rat.**

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Eur Urol 1999;35(5-6):464-7

The high incidence and long latent period of prostate cancer make it an ideal target for chemoprevention. We have evaluated a series of agents for chemopreventive efficacy using a model in which hormone-dependent prostate cancers are induced in the Wistar-Unilever (WU) rat by sequential treatment with antiandrogen (cyproterone acetate), androgen (testosterone propionate), and direct-acting chemical carcinogen (N-methyl-N-nitrosourea), followed by chronic androgen stimulation (testosterone). This regimen reproducibly induces prostate cancers in high incidence, with no gross toxicity and a low incidence of neoplasia in the seminal vesicle and other non-target tissues. Dehydroepiandrosterone (DHEA) and 9-cis-retinoic acid (9-cis-RA) are the most active agents identified to date. DHEA inhibits prostate cancer induction both when chronic administration is begun prior to carcinogen exposure, and when administration is delayed until preneoplastic prostate lesions are present. 9-cis-RA is the most potent inhibitor of prostate carcinogenesis identified; a study to determine the efficacy of delayed administration of 9-cis-RA is in progress. Liarozole fumarate confers modest protection against prostate carcinogenesis, while N-(4-hydroxyphenyl)retinamide (fenretinide), alpha-difluoromethylornithine, oltipraz, DL-alpha-tocopherol acetate (vitamin E), and L-selenomethionine are inactive. Chemoprevention efficacy evaluations in the WU rat will support the identification of agents that merit study for prostate cancer chemoprevention in humans.

## **The relationship of serum dehydroepiandrosterone and its sulfate to subsequent cancer of the prostate.**

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Cancer Epidemiol Biomarkers Prev 1993 May-Jun;2(3):219-21

Levels of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) in sera collected and frozen in 1974 were studied among 81 prostate cancer cases diagnosed in the following 12 years and 81 age- and race-matched controls. Although mean levels of DHEA were 11% lower among cases than controls and DHEA-S levels were 12% lower than among controls, no dose-response association was noted for either DHEA or DHEA-S. It seems unlikely that serum levels of DHEA or DHEA-S are important risk factors for prostate cancer.

## **Dehydroepiandrosterone in the treatment of erectile dysfunction: a prospective, double-blind, randomized, placebo-controlled study.**

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Urology 1999 Mar;53(3):590-4; discussion 594-5

**OBJECTIVES:** In 1994, the Massachusetts Male Aging Study presented an inverse correlation of the serum levels of dehydroepiandrosterone (DHEA) and the incidence of erectile dysfunction (ED). We evaluated the efficacy of DHEA replacement in the treatment of ED in a prospective, double-blind, randomized, placebo-controlled study.

**METHODS:** The inclusion criteria included ED, normal physical and neurologic examinations, serum levels of testosterone, dihydrotestosterone, prolactin, and prostate-specific antigen (PSA) within the normal range, and a serum DHEA sulfate level below 1.5 micromol/L. Also all patients had a full erection after a pharmacologic erection test with 100 microg prostaglandin E1; pharmacocavernosography showed no visualization in corporeal venous structures. Forty patients from our impotence clinic were recruited and randomly divided into two groups of 20 patients each. Group 1 was treated with an oral dose of 50 mg DHEA and group 2 with a placebo one time a day for 6 months. The International Index of Erectile Function (IIEF), a 15-item questionnaire, was used to rate the success of this therapy.

**RESULTS:** Therapy response was defined as the ability to achieve or maintain an erection sufficient for satisfactory sexual performance according to the National Institutes of Health Consensus Development Panel on Impotence. DHEA treatment was associated with higher mean scores for all five domains of the IIEF. There was no impact of DHEA treatment on the mean serum levels of PSA, prolactin, testosterone, the mean prostate volume, and the mean postvoid residual urine volume.

**CONCLUSIONS:** Our results suggest that oral DHEA treatment may be of benefit in the treatment of ED. Although our patient data base is too small to do relevant statistical analysis, we believe that our data show a biologically obvious trend that justifies further extended studies.

## **Androgens in patients with benign prostatic hyperplasia before and after prostatectomy.**

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J Clin Endocrinol Metab 1976 Dec;43(6):1250-4

Plasma androgens [testosterone (T), 17beta-hydroxy-5alpha-androstan-3-one (DHT), androst-4-en-3,17 dione(A), and dehydroepiandrosterone (DHEA)] as well as 17 hydroxyprogesterone were measured in a group of patients (age 60-80 yrs.) with benign prostatic hyperplasia (BPH) just before prostatectomy and compared to values obtained in subjects of similar age without signs of BPH. The most important difference was observed in the mean DHT level which was significantly (P less than 0.025) higher than in the control group; mean T and free testosterone levels in BPH patients were slightly higher (P less than 0.05) in the age group 70-80 yrs; whereas in age group 60-70 mean values were similar to those observed in normal controls. Mean A, DHEA and 17 OHP and E2 levels were not significantly different in BPH patients when compared to age matched controls. 2-5 months after prostatectomy, T and DHT levels were significantly higher than immediately preoperatively. The preoperative stress may have influenced the preprostatectomy values.

## **Neuropsychiatric function and dehydroepiandrosterone sulfate in elderly women: a prospective study.**

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Biol Psychiatry 1998 May 1;43(9):694-700

**BACKGROUND:** Though among the most abundant human steroid hormones, the physiologic role of dehydroepiandrosterone and its sulfate (DHEAS) is not known. Our goal was to determine if DHEAS is associated with cognition and mood in older women, and if baseline DHEAS levels are predictive of cognitive decline.

**METHODS:** In a prospective cohort, we studied 394 randomly selected community-dwelling women, aged 65 years or older,

currently enrolled in the Study of Osteoporotic Fractures. Subjects were administered a modified Mini-Mental State Exam, Trails B, Digit Symbol, and the Geriatric Depression Scale-Shortened (GDSS), at study onset and 4-6 years later. Serum was obtained at study initiation for DHEAS analysis.

**RESULTS:** DHEAS levels declined with age, as expected. There was no consistent association of DHEAS quartile or log DHEAS with any of the four outcomes, even after multivariate adjustment. Change in cognitive performance overtime was not associated with DHEAS levels. Analysis of the 32 women without any detectable DHEAS compared to those with detectable levels revealed higher measures on the GDSS (mean score 3.4 +/- 3.6 compared with 1.6 +/- 2.3,  $p = .028$ ) and a higher percentage with depression (21.7% compared with 4.6%,  $p = .001$ ).

**CONCLUSIONS:** Serum DHEAS is not a sensitive predictor of cognitive performance or decline on a selected neuropsychological battery in elderly community women; however, nondetectable levels may be associated with depression.

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

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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 non-genomic action.

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

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Psychol Med 1996 Mar;26(2):245-56

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

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J Clin Endocrinol Metab 1994 Jun;78(6):1360-7  
Published erratum appears in J Clin Endocrinol Metab 1995 Sep;80(9):2799

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.

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

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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.

### **Antidepressant and cognition-enhancing effects of DHEA in major depression.**

Wolkowitz OM, et al.

Ann N Y Acad Sci 1995 Dec 29;774:337-9

No abstract.

## **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.

## **Double-blind treatment of major depression with dehydroepiandrosterone.**

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Am J Psychiatry 1999 Apr;156(4):646-9

**OBJECTIVE:** This study was designed to assess possible antidepressant effects of dehydroepiandrosterone (DHEA), an abundant adrenocortical hormone in humans.

**METHOD:** Twenty-two patients with major depression, either medication-free or on stabilized antidepressant regimens, received either DHEA (maximum dose = 90 mg/day) or placebo for 6 weeks in a double-blind manner and were rated at baseline and at the end of the 6 weeks with the Hamilton Depression Rating Scale. Patients previously stabilized with antidepressants had the study medication added to that regimen; others received DHEA or placebo alone.

**RESULTS:** DHEA was associated with a significantly greater decrease in Hamilton depression scale ratings than was placebo. Five of the 11 patients treated with DHEA, compared with none of the 11 given placebo, showed a 50% decrease or greater in depressive symptoms.

**CONCLUSIONS:** These results suggest that DHEA treatment may have significant antidepressant effects in some patients with major depression. Further, larger-scale trials are warranted.

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

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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.

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

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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 estrogen replacement therapy on dehydroepiandrosterone, dehydroepiandrosterone sulfate, and cortisol responses to exercise in postmenopausal women.**

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Fertil Steril 1997 Nov;68(5):836-43  
Published erratum appears in Fertil Steril 1998 Mar;69(3):606

**OBJECTIVE:** To determine the effects of hormone replacement therapy (HRT) on dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), and cortisol (F) responses to treadmill exercise.

**DESIGN:** Controlled clinical study.

**SETTING:** Female volunteers in an academic research environment.

**PATIENT(S):** Sixteen healthy, postmenopausal women (7 were receiving HRT, 9 were not). **INTERVENTION(S):** Blood samples were taken from an intravenous catheter before, during, and after 30 minutes of treadmill exercise following an overnight fast. A second session was conducted one month later for the same subjects using the same blood sampling protocol without exercise.

**MAIN OUTCOME MEASURE(S):** Serum DHEA, DHEAS, and F concentrations.

**RESULT(S):** The HRT and untreated DHEA area under the curve (AUC) for the exercise trials was significantly greater than that for the control trials. The untreated, but not the HRT, DHEAS AUC for the exercise trials was significantly greater than that for the control trials. The HRT and untreated F AUC for the exercise trials was significantly greater than that for the control trials. The AUC for the HRT exercise trials was significantly higher than the untreated exercise trials for DHEA and F, but not DHEAS.

**CONCLUSION(S):** Data suggest that treadmill exercise elevates DHEA, DHEAS, and F levels in postmenopausal women and that HRT enhances the DHEA and F responses.

## **Inhibition of migration and proliferation of vascular smooth muscle cells by dehydroepiandrosterone sulfate.**

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Biochim Biophys Acta 1998 Feb 27;1406(1):107-14

Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) are the most abundant steroids in humans, and their serum concentrations progressively decrease with age. Although relationships between DHEA(-S) and many age-related illnesses have been postulated, the mechanisms for their effects remain unknown, and specific receptors for these molecules have not been identified. In this paper, to investigate the role of DHEA(-S) in atherogenesis, we studied the proliferation and migration of a rabbit vascular smooth muscle cell line, SM-3, in the presence of DHEA(-S). Cellular proliferation was inhibited by DHEA-S, and to a lesser extent by DHEA. Modified Boyden's chamber assays revealed that DHEA-S inhibited the migration of SM-3 cells toward PDGF-BB. In cell attachment assays, DHEA-S inhibited the attachment of SM3 cells to fibronectin. It was suggested that the inhibitory effect of DHEA-S for SM-3 proliferation and migration was due to the decreased interaction with fibronectin. Scatchard analysis revealed the presence of two populations of DHEA-S binding sites in the nuclear fraction, and a smaller number in the cytosolic fraction. Since the dissociation constant of the higher affinity site was similar to the serum DHEA-S concentration in humans ( $K_d = 5.8 \text{ } \mu\text{M}$ ), this binding site could be functional under physiologic conditions. These findings suggest that there may be receptor-mediated anti-atherogenic actions of DHEA-S.

## **Endogenous androgens and carotid intimal-medial thickness in women.**

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J Clin Endocrinol Metab 1999 Jun;84(6):2008-12

The influence of endogenous androgens on atherosclerotic disease in women is unknown. In this study involving 101 pre- and post-menopausal females, we evaluated the relationship between serum androgen levels and both carotid artery intimal-medial thickness (IMT) and major cardiovascular risk factors. In addition to evaluation of blood pressure, body mass index, and waist-to-hip ratio, serum dehydroepiandrosterone sulfate (DHEA-S), androstenedione (A), total testosterone (TTS), free testosterone (FTS), insulin, cholesterol (total and high density lipoproteins), triglycerides, and glucose were measured. All women underwent carotid ultrasonography. Spearman correlation coefficients showed that serum DHEA-S and A levels were negatively related ( $P < 0.03-0.0004$ ) to several IMT measures. Higher tertiles of DHEA-S, A, and FTS corresponded to significantly lower measures of carotid thickness. DHEA-S, and all androgens were inversely related to age ( $P < 0.03$  or less), showing no unfavorable association with major cardiovascular risk factors. In contrast, serum DHEA-S was negatively associated with WHR ( $P < 0.02$ ), while A was negatively associated with body mass index ( $P < 0.02$ ). Stepwise multiple regression analysis indicated that A and FTS showed an inverse association with IMT measures ( $P < 0.05-0.001$ ). In conclusion, our data indicate that in women serum DHEA-S and androgens decline with age and that normal hormonal levels are not associated with major cardiovascular risk factors. They also show that higher DHEA-S and androgen concentrations are related to lower carotid wall thickness; for A this association is independent of cardiovascular risk factors. Our results suggest that, in the physiological range, DHEA-S and androgens in women are correlated with lower risk of carotid artery atherosclerosis.

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

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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.

### **Enhanced plasma DHEAS, brain acetylcholine and memory mediated by steroid sulfatase inhibition.**

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Brain Res 1997 Oct 31;773(1-2):28-32

Steroid sulfatase inhibitors can alter the metabolism of neurosteroids which modulate brain function. Administration of the non-steroidal steroid sulfatase inhibitor (p-O-sulfamoyl)-N-tetradecanoyl tyramine (DU-14) to rats for 15 days increased plasma dehydroepiandrosterone sulfate (DHEAS) concentrations by 88.2%, decreased plasma dehydroepiandrosterone (DHEA) concentrations by 84.6%, increased hippocampal acetylcholine (ACh) release determined via in vivo microdialysis by almost 3-fold, and produced a significant blockade of scopolamine-induced amnesia as measured by a passive avoidance test. These results suggest DHEAS rather than DHEA enhances brain cholinergic function and that steroid sulfatase inhibition may become an important tool for enhancing neuronal functions, such as memory, mediated by excitatory neurosteroids.

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

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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.

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

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Department of Organic and Medicinal Chemistry, Israel Institute for Biological Research, Ness-Ziona, Israel.

Life Sci 1996;59(19):1651-7

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.

## **DHEAS inhibits TNF production in monocytes, astrocytes and microglial cells.**

Di Santo E, Foddi MC, Ricciardi-Castagnoli P, Mennini T, Ghezzi P  
Istituto di Ricerche Farmacologiche, Mario Negri, Milan, Italy.  
Neuroimmunomodulation 1996 Sep-Oct;3(5):285-8

We previously reported that neurosteroids, including dehydroepiandrosterone sulfate (DHEAS), inhibit the production of TNF in vitro and in vivo. In this paper we evaluated the effect of DHEAS on TNF production by cultured rat astrocytes and murine glial cell clones, and compared it with the effect on monocytic THP-1 cells. We found that DHEAS at a concentration of  $10^{-4}$ - $10^{-7}$  M inhibits TNF production induced by lipopolysaccharide (LPS, 1 microgram/ml) in these cells. Since the inhibitory effect of DHEAS is not mediated by the glucocorticoid (GC) receptor and DHEAS is an allosteric antagonist of the GABAA receptor, we investigated the possible role of GABAA receptors in this effect. The results showed that the inhibitory effect of DHEAS ( $10^{-6}$  M) on TNF production by THP-1 cells was completely reversed by addition of  $10^{-6}$  M GABA. However, a GABAA receptor antagonist (bicuculline) did not mimic the action of DHEAS. In conclusion, DHEAS can inhibit TNF production in astrocytic and microglial cells suggesting it could be an endogenous regulator of TNF production in the

## **Use of dehydroepiandrosterone in psychiatric practice.**

Strauss EB, et al.  
J Neurol Neurosurg Psychiatry 18:137-44. 1955.

No abstract.

## **Treatment of inadequate personality in juveniles by dehydroisoandrosterone: preliminary report.**

Sands DE, et al.  
BMJ 2:66-68. 1952.

No abstract.

## **DHEA and Aging, Annals of the New York Academy of Science**

Bellino, F.L., Daynes. R.A., Hornsby, P.J., et al., eds  
Aging (Dec. 29, 1995, 774:1-350).

No abstract.

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