

ABSTRACTS

DHEA

Failure of dehydroepiandrosterone to influence energy and protein metabolism in humans.

It was reported recently that 4 weeks of dehydroepiandrosterone (DHEA) treatment [5.55 mmol/day (1600 mg/day), orally] reduced body fat and increased lean body mass in healthy men. The present study was performed to examine whether these effects could be explained by increased energy expenditure and muscle protein synthesis. Eight healthy men were given placebo and DHEA (1600 mg/day) for 4 weeks each in a double blind cross-over study. DHEA treatment caused a 9-fold increase in mean plasma DHEA sulfate concentrations, but had no significant effect on body weight or on two indices of lean body mass (total body water and total body potassium). DHEA had no effect on any of the parameters of energy and protein metabolism, including resting metabolic rate, total energy expenditure (estimated by the 2H₂(18)O method during the final 2 weeks of each treatment period), leucine flux (an index of whole body proteolysis), the nonoxidized portion of leucine flux (an index of whole body protein synthesis), and the rate of incorporation of leucine into muscle protein. Circulating levels of cholesterol, T₃, and T₄ also were unaffected by DHEA. These data suggest that DHEA is not an important regulator of energy or protein metabolism in humans.

J Clin Endocrinol Metab. 1990 Nov;71(5):1259-64

Effects of DHEA replacement on bone mineral density and body composition in elderly women and men.

OBJECTIVE: Dehydroepiandrosterone (DHEA) is a precursor for both oestrogens and androgens. Its marked decline with ageing may influence age-related changes in tissues influenced by sex hormones. The aim of this study was to determine the effects of DHEA replacement on bone mineral density (BMD) and body composition in elderly women and men with low serum DHEA sulphate (DHEAS) levels. **DESIGN:** Prospective 6 month trial of oral DHEA replacement, 50 mg/day. **PATIENTS:** Experimental subjects were 10 women and eight men, aged 73 +/- 1 years. Control subjects were 10 women and eight men, aged 74 +/- 1 years. **MEASUREMENTS:** BMD, body composition, serum markers of bone turnover, serum lipids and lipoproteins, oral glucose tolerance, serum IGF-I, total serum oestrogens and testosterone. **RESULTS:** BMD of the total body and lumbar spine increased (mean +/- SEM; 1.6 +/- 0.6% and 2.5 +/- 0.8%, respectively; both P < or = 0.05), fat mass decreased (- 1.3 +/- 0.4 kg; P < 0.01) and fat-free mass increased (0.9 +/- 0.4 kg; P < or = 0.05) in response to DHEA replacement. DHEA replacement also resulted in increases in serum IGF-I (from 108 +/- 8 to 143 +/- 7 microg/l; P < 0.01) and total serum testosterone concentrations (from 10.7 +/- 1.2 to 15.6 +/- 1.8 nmol/l in the men and from 2.1 +/- 0.2 to 4.5 +/- 0.4 nmol/l in the women; both P < or = 0.05). **CONCLUSIONS:** The results provide preliminary evidence that DHEA replacement in those elderly women and men who have very low serum DHEAS levels can partially reverse age-related changes in fat mass, fat-free mass, and BMD, and raise the possibility that increases in IGF-I and/or testosterone play a role in mediating these effects of DHEA.

Clin Endocrinol (Oxf). 2000 Nov;53(5):561-8

Dehydroepiandrosterone supplementation improves endothelial function and insulin sensitivity in men.

The dehydroepiandrosterone (DHEA) concentration decreases with age. There is evidence that DHEA has a protective effect against age-related disorders, including cardiovascular disease. Accordingly, we examined the effect of DHEA supplementation (25 mg/d) on endothelial function, insulin sensitivity, and fibrinolytic activity in 24 men with hypercholesterolemia (mean age, 54 +/- 1 yr). All subjects were enrolled in a randomized, double-blind study. Flow-mediated dilation of brachial artery after transient occlusion, which was expressed as the percent change from the baseline value of the diameter, increased significantly with DHEA supplementation [DHEA: baseline, 3.9 +/- 0.5%; 4 wk, 6.9 +/- 0.7%; 8 wk, 7.9 +/- 0.6%; 12 wk, 8.4 +/- 0.7% (P < 0.01 vs. baseline for all, by ANOVA); placebo: 4.1 +/- 0.6%, 4.5 +/- 0.5%, 3.9 +/- 0.5%, and 4.4 +/- 0.6% (P < 0.01 for all, by ANOVA)]. There was a significant concurrent reduction in the plasma levels of plasminogen activator inhibitor type 1 during DHEA supplementation [DHEA: 9.1 +/- 2.2, 6.4 +/- 2.3, 5.5 +/- 2.8, and 5.1 +/- 2.0 IU/ml (P < 0.01 vs. baseline, by ANOVA); placebo: 9.0 +/- 2.1, 10.4 +/- 2.2, 9.5 +/- 2.2, and 9.6 +/- 2.1 IU/ml (P < 0.01, by ANOVA)]. DHEA supplementation also decreased steady state plasma glucose [DHEA: baseline, 178.9 +/- 12.2; 12 wk, 132.0 +/- 12.8 mg/dl (P < 0.01, by ANOVA); placebo: 181.0 +/- 13.8 and 179.6 +/- 12.4 mg/dl (P < 0.01, by ANOVA)]. In contrast, steady state plasma insulin did not change during the study in either group. The low dose DHEA supplementation improves vascular endothelial function and insulin sensitivity and decreases the plasminogen activator inhibitor type 1 concentration. These beneficial changes have the potential to attenuate the development of age-related disorders such as cardiovascular disease.

Metabolic effects of 12-month percutaneous dehydroepiandrosterone replacement therapy in postmenopausal women.

We have evaluated the effect of dehydroepiandrosterone (DHEA) replacement therapy in 60- to 70-year-old women (n = 15) who received a single daily percutaneous application of a 10% DHEA cream for 12 months. While anthropometric measurements showed no change in body weight, we observed a 9.8% decrease in subcutaneous skinfold thickness at 12 months (P < 0.05). This was confirmed by measurements of midhigh fat and muscle areas by computed tomography where a 3.8% decrease (P < 0.05) in femoral fat and a 3.5% increase (P < 0.05) in femoral muscular areas were observed at 12 months. There was no significant change in abdominal fat measurements but the waist-to-hip ratio was only 0.83 at the onset of treatment. These changes in body fat and muscular mass were associated with an 11% decrease (P < 0.05) in fasting plasma glucose and a 17% decrease (P < 0.05) in fasting insulin levels. Treatment with DHEA had no adverse effect on the lipid or lipoprotein profile. In fact, an overall trend towards a decrease in total cholesterol and its lipoprotein fractions was observed. Plasma triglycerides were not affected. Plasma high-density lipoprotein (HDL) cholesterol decreased by 8% but the ratio HDL/cholesterol was unchanged by DHEA treatment because of a parallel decrease in total cholesterol. The index of sebum secretion showed a 73% increase (P < 0.05) during the 12 months of DHEA therapy followed by a return to pretreatment values 3 months after cessation of therapy. At the same time, sex hormone-binding globulin levels decreased (P < 0.05) during treatment and returned to pretreatment values 3 months after the end of therapy. Serum gonadotropins were not changed by DHEA treatment. Although not significant, we observed a tendency towards an elevation in serum GH levels. Values of serum IGF-I remained unchanged while plasma IGF-binding protein-3 levels significantly decreased (P < 0.05) during treatment and returned to pretreatment values after cessation of DHEA therapy. The present data clearly indicate the beneficial effects of DHEA therapy in postmenopausal women through its transformation into androgens and/or estrogens in specific intracrine tissues without any significant side effects.

J Endocrinol. 1996 Sep;150 Suppl:S43-50

Replacement of dehydroepiandrosterone enhances T-lymphocyte insulin binding in postmenopausal women.

OBJECTIVE: To demonstrate bioavailability of 3 weeks of oral micronized DHEA and to delineate changes induced on insulin sensitivity, morphometric indexes, and lipoprotein profiles. **DESIGN:** Oral micronized DHEA (50 mg/d) was administered in 3-week treatments to 11 postmenopausal women in a prospective, placebo-controlled, randomized, blinded, crossover trial with an interarm washout. After dose (23 hour) serum DHEA, DHEAS, testosterone(T), and cortisol levels were measured, as were fasting lipoproteins, oral glucose tolerance tests (OGTT), T-lymphocyte insulin binding and degradation, and urine collagen cross-links. Morphometric changes were determined by hydrostatic weighing. **RESULTS:** Dehydroepiandrosterone sulfate, DHEA, T, and free T increased up to two times premenopausal levels with treatment. Fasting triglycerides declined; no change in collagen cross-links or morphometric indexes was noted. Oral glucose tolerance test parameters did not change, but both T-lymphocyte insulin binding and degradation increased with DHEA. **CONCLUSION:** Fifty milligrams per day of oral DHEA gives supraphysiologic androgen levels; 25 mg/d may be more appropriate. Dehydroepiandrosterone enhanced tissue insulin sensitivity and lowered serum triglycerides. Rationale is provided for postmenopausal replacement therapy with this androgen.

Fertil Steril. 1995 May;63(5):1027-31

Dehydroepiandrosterone sulfate levels in women. Relationships with body mass index, insulin and glucose levels.

OBJECTIVE: Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S) are the most abundant steroids in human plasma. Previous studies have shown that administration of DHEA-S is more effective than DHEA in reducing adipose tissue mass and cellularity in rats. Another study suggested that maintaining high levels of DHEA-S might prevent the development of obesity. Therefore, this study aims to determine the relationship of plasma dehydroepiandrosterone sulfate (DHEA-S) levels with respect to obesity, fasting insulin and glucose levels in a cohort of obese and normal weight healthy Saudi women. **METHODS:** This study was carried out at King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia during the year 2001. A total of 65 healthy volunteers between 19-30 years of age with body mass index (BMI) of 15.35-38.30 kg/m² were grouped into 26 young obese females of BMI > 27 kg/m² and 39 young lean females of BMI < 27 kg/m². Weight, height, waist and hip circumference, fasting blood glucose, insulin and DHEA-S levels were measured. **RESULTS:** Dehydroepiandrosterone-S levels were found lower in the obese group than in the lean women. In all subjects, DHEA-S levels were related negatively with BMI (p=0.02, correlation co-efficient [r]=-0.25) and hip circumference (p=0.03, r=-0.27). In the obese group, DHEA-S levels showed a significant positive relationship with insulin (p=0.03, r=0.43). No significant relationship was found between DHEA-S and glucose levels in considering either the whole group or the obese women. **CONCLUSION:** Hip circumference, as a corollary for peripheral obesity, was better associated with DHEA-S than the waist circumference or waist-to-hip ratio. The data indicated that BMI and hip circumference are important factors in explaining DHEA-S variability. Insulin could have an independent regulatory effect on DHEA-S secretion, but glucose metabolism is not related.

Saudi Med J. 2003 Aug;24(8):837-41

Correlation of serum L-carnitine and dehydroepiandrosterone sulphate levels with age and sex in healthy adults.

OBJECTIVES: L-carnitine and dehydroepiandrosterone (DHEA) independently promote mitochondrial energy metabolism. We therefore wondered if an age-related deficiency of L-carnitine or DHEA may account for the declining energy metabolism associated with age. **METHODS:** we evaluated serum levels of L-carnitine and the sulphated derivative of DHEA (DHEAS) in cross-sectional study of 216 healthy adults, aged 20-95. **RESULTS:** serum DHEAS levels declined, while total carnitine levels increased with age ($P < 0.0001$). Total and free carnitine and DHEAS levels were lower in women than men ($P < 0.0001$). Esterified/free (E/F) carnitine (inversely related to carnitine availability) increased with age in both sexes ($P=0.012$). **CONCLUSION:** reduced carnitine availability correlates with the age-related decline of DHEAS levels. These results are consistent with the hypothesis that decreased energy metabolism with age relates to DHEAS levels and carnitine availability.

Age Ageing. 1999 Mar;28(2):211-6

Mental wellbeing and quality of sexual life in women with primary Sjogren's syndrome are related to circulating dehydroepiandrosterone sulphate.

OBJECTIVES: To evaluate the possible effect of androgen status on sexuality and mental wellbeing in patients with primary Sjogren's syndrome (pSS). **METHODS:** Serum levels of dehydroepiandrosterone sulphate (DHEA-S), testosterone (T), androstenedione, sex hormone binding globulin (SHBG), and the SHBG/T ratio were measured in 21 women with pSS. Sexual life was assessed by a Swedish version of the McCoy scale, which covers sexual experience and responsiveness during the past 30 days. A standardised questionnaire, the Psychological General Well-Being Index (PGWB), was used to examine quality of life and psychological symptoms in patients with pSS. **RESULTS:** Positive correlations were found between DHEA-S serum levels and the total McCoy score ($r(s)=0.62$; $p<0.01$), as well as the subscales of this score reflecting arousal (0.59 ; $p<0.05$), desire ($r(s)=0.52$; $p<0.05$), and satisfaction ($r(s)=0.66$; $p<0.01$). Serum DHEA-S concentrations were also related to the total PGWB score ($r(s)=0.60$; $p<0.01$) and subscales of this score: depression ($r(s)=0.62$; $p<0.01$), wellbeing ($r(s)=0.64$; $p<0.01$), general health ($r(s)=0.67$; $p<0.01$), and self control ($r(s)=0.67$; $p<0.01$). Total McCoy and PGWB scores and their subscales were not related to the serum levels of testosterone and androstenedione or the T/SHBG ratio. **CONCLUSIONS:** Circulating levels of the weak androgen DHEA-S are positively related to the quality of sexual life and mental wellbeing in women with pSS.

Ann Rheum Dis. 2003 Sep;62(9):875-9

Comparison of immunological and endocrinological markers associated with major depression.

Natural-killer-(NK)-cell activity and blood levels of interleukin 2 (IL-2), dehydroepiandrosterone (DHEA), DHEA sulphate (DHEA-S), and cortisol were measured in 17 patients with major depression and 10 control subjects. Depression severity was evaluated using the Zung Self-rating Depression Scale. NK-cell activity and IL-2 levels were measured using a chromium-51 release test and an enzyme-linked immunosorbent assay, respectively. Radio-immunoassays were used to measure serum cortisol, DHEA and DHEA-S. As would be expected, patients with major depression had a higher score on the Zung Self-rating Depression Scale than healthy controls. Compared with controls, NK-cell activity and levels of cortisol and DHEA were reduced in patients with major depression, whereas IL-2 levels were increased. No difference was observed in DHEA-S levels between patients and controls. A reduction in NK-cell activity and DHEA levels, and an increase in IL-2 levels appear to be associated with major depression. Whether these changes are the cause or the consequence of the depression remains to be determined.

J Int Med Res. 2003 Jan-Feb;31(1):36-41

ABSTRACTS

Memory Assessment

Early detection of isolated memory deficits in the elderly: the need for more sensitive neuropsychological tests.

BACKGROUND: Early detection of cognitive decline in the elderly is important because this may precede progression to Alzheimer's disease. The aim of this study was to see whether sensitive neuropsychological tests could identify pre-clinical cognitive deficits and to characterize the cognitive profile of a subgroup with poor memory. **METHODS:** A neuropsychological test battery was administered to a community-dwelling sample of 155 elderly volunteers who were screened with CAMCOG at enrolment (mean age 74.7 years). The battery included tests of episodic memory, semantic and working memory, language and processing speed. **RESULTS:** Episodic memory test scores below 1 S.D. from the cohort mean identified 25 subjects with non-robust memory performance. This group was compared to the remaining 'robust memory' group with a General Linear Model controlling for age, IQ, education, and gender. Test performance was significantly different in all tests for episodic and semantic memory, but not in tests for working memory, processing speed, and language. CANTAB paired associates learning and spatial recognition tests identified the highest percentages of those in the 'non-robust memory' group. Processing speed partialled out the age effect on memory performance for the whole cohort, but the 'non-robust memory' group's performance was not associated with age or processing speed. **CONCLUSIONS:** Sensitive neuropsychological tests can detect performance below the norm in elderly people whose performance on MMSE and CAMCOG tests is well within the normal range. Age-related decline in memory performance in a cohort of the elderly may be largely due to inclusion within the cohort of individuals with undetected pre-clinical Alzheimer's disease or isolated memory impairment.

Psychol Med. 2002 Apr;32(3):483-91

Decline in learning ability best predicts future dementia type: the freedom house study.

The authors studied longitudinal change in learning efficiency as a predictor of future dementia type among healthy, well-educated, noninstitutionalized elderly retirees. Serial assessments of memory were obtained using the California Verbal Learning Test (CVLT). Latent growth (LG) models were developed from the slopes of the subjects' performance over the first five CVLT learning trials at each of three serial administrations (e.g., cohort inception [i.e., baseline] [CVLT1], 18 months [CVLT2] and 36 months [CVLT3]). The resulting growth curves were incorporated into a higher order LG model representing the dynamic change in learning efficiency over time (DeltaCVLT). DeltaCVLT was used to predict each subject's "dementia type" (i.e., clinical state) at 36 months (e.g., no dementia, Type 1 [Alzheimer type] dementia or Type 2 [non-Alzheimer type] dementia), after adjusting for CVLT1, baseline age, and baseline dementia type. Nonlinear (logarithmic) LG models of CVLT1-CVLT3 and DeltaCVLT best fit the data. There was significant variability about both CVLT1 and DeltaCVLT, suggesting subgroups in the sample with significantly different baseline memory function, and different rates of deterioration in learning efficiency. Age, baseline dementia type, and DeltaCVLT made significant independent contributions to final dementia type. CVLT1 did not predict final dementia type independently of the other covariates. These data suggest that baseline memory performance in noninstitutionalized elderly retirees does not predict future dementia type independently of the dynamic rate of change in memory measures. Serial administrations of memory tests may help identify nondemented persons at greater or lesser risk for conversion to frank dementia in the near-term.

Exp Aging Res. 2003 Oct-Dec;29(4):385-406

P300 (latency) event-related potential: an accurate predictor of memory impairment.

To determine if P300 latency changes precede and correlate with memory and mental status, patients (N=1506 aged 20-100 years) who received medical and psychiatric diagnoses (from 1997 to 2002), were assessed for P300 (N=1496), WMS-III (N=694), and MMSE (N=456). Patient and control groups included, a) normal WMS-III on all 4 subscales (N=36), b) normal WMS-III and MMSE (N=189) with subjective memory/mental status complaints, and c) medical patients with normal WMS-III and no memory complaints (N=205), and d) P300 control group without medical, psychiatric or memory problems for ROC. Patients with impaired/borderline memory had a prolonged P300 latency ($P < 0.02$) compared to age matched non-impaired controls; in patients with normal WMS-III/MMSE, with subjective mild memory/mental status impairment, P300 latency was prolonged compared to controls ($P = 0.0004$). The P300 latency increased by 0.72ms per year ($P = 7.9 \times 10^{-65}$) and voltage decreased by 0.03dV per year ($P = 6.7 \times 10^{-10}$), and both parameters were linearly correlated with the age of the subjects. Male subjects had an average voltage of 6.1dV and female 6.8dV ($P = 0.00009$). Statistically, prolonged latency began at age range 41-50 ($P = 0.0002$); reduced P300 voltage began at age range 51-60 ($P = 0.003$). WMS-III memory decline for all measures began in females at age range 61-70 (P value at least=0.02) and for males at age range 61-80 ($P = 0.02$). Prolonged P300 latency ($P < 0.0001$) and memory impairment (at least < 0.02) were greater for females than males. MMSE memory decline, male and female, began at age range 81-90 (P value of at least 0.00007). In our logistic regression model P300 latency was more predictive of WMS-III impairment than MMSE > 24 . In patients whose WMS-III score is impaired $< \text{or} = 69$, or borderline $< \text{or} = 79$ (P at least=0.004), a P300 latency more prolonged than the norm ($> \text{or} = 300 + 30 + \text{Age}$) identifies these patients, whereas a MMSE

> 24 failed. With the ROC curve, we confirmed that P300 latency could accurately identify borderline/impaired memory.

Clin Electroencephalogr. 2003 Jul;34(3):124-39

P300 latency and age: a quadratic regression explains their relationship from age 5 to 85.

The use of P300 latency to demonstrate cognitive dysfunction is important. P300 latency decreases with age in children and then increases with age in adults. It has been debated whether the relationship between age and P300 latency is linear or quadratic. If the relationship is linear, then at least two regression equations in opposite directions are required for children and for adults, and perhaps a third for the elderly. This is a report of data from an age-stratified sample of 97 normal individuals ages 5 through 85. The best regression equation is quadratic, using log transformed age, with accurate projection of 95% confidence limits for P300 latency by age. This quadratic regression simplifies the application of P300 latency across the lifespan in the management of disorders affecting cognition, such as Traumatic Brain Injury, Attention Deficit-Hyperactivity Disorder, and Obstructive Sleep Apnea.

Clin Electroencephalogr. 1998 Jan;29(1):1-6

A critical discussion of the role of neuroimaging in mild cognitive impairment.

OBJECTIVE: In this paper, the current neuroimaging literature is reviewed with regard to characteristic findings in mild cognitive impairment (MCI). Particular attention is drawn to the possible value of neuroimaging modalities in the prediction and early diagnosis of Alzheimer's disease (AD). **METHODS:** First, the potential contribution of neuroimaging to an early, preclinical diagnosis of degenerative disorders is discussed at the background of our knowledge about the pathogenesis of AD. Second, relevant neuroimaging studies focusing on MCI are explored and summarized. Neuroimaging studies were found through Medline search and by systematically checking through the bibliographies of relevant articles. **RESULTS:** Structural volumetric magnetic resonance imaging (MRI) and positron emission tomography (PET)/single photon emission tomography (SPECT) are currently the most commonly used neuroimaging modalities in studies focusing on MCI. There were considerable variations in demographical and clinical characteristics across studies. However, significant hippocampal and entorhinal cortex volume reductions were consistently found in subjects with MCI as compared with cognitively unimpaired controls. While hippocampal and entorhinal cortex atrophy in subjects with MCI are also well-established risk factors for the development of AD, these measures cannot be regarded as being of high predictive value in an individual case. Evidence for other typical neuroimaging changes in MCI is still scarce. In PET and SPECT studies, reduced blood flow and/or glucose metabolism in temporoparietal association areas, posterior cingulate and hippocampus were associated with a higher risk of progressive cognitive decline in MCI. In quantitative electroencephalogram (QEEG), low beta, high theta, low alpha and slowed mean frequency were associated with development of dementia. **CONCLUSIONS:** Existing studies suggest that neuroimaging measures have the potential to become valuable tools in the early diagnosis of AD. To establish their value in routine use, larger studies, preferably with long prospective follow-up are needed.

Acta Neurol Scand Suppl. 2003;179:52-76

Effects of alcoholism, anxiety and depression on P300 in women: a pilot study.

OBJECTIVE: The present investigation was designed for the purpose of revealing functional brain impairments associated with alcoholism, anxiety and depression. **METHOD:** The subjects were 56 women, with an average (SD) age of 34.8 (7.3) years. None reported a history of neurological or major medical disorders, or drug abuse. Twenty-nine of the women met DSM-IV lifetime criteria for a diagnosis of alcohol abuse or dependence. Twenty-five women reported mild or higher levels of anxiety, as indexed by a Beck Anxiety Inventory (BAI) score greater than 7. Electroencephalographic activity was recorded while subjects performed a visual ("oddball") selective attention task comprised of rare target, rare nontarget and frequent nontarget stimuli. P300 event-related potentials elicited by the rare target and rare nontarget stimuli were analyzed. **RESULTS:** The initial analysis was structured as a 2 (alcoholism) by 2 (anxiety) factorial. Analyses revealed no significant effects of alcoholism on P300. However, women reporting a BAI score greater than 7 exhibited significantly smaller P300 amplitudes than their nonanxious counterparts. The P300 decrement remained significant when depression level (Beck Depression Inventory [BDI-II]) and age were entered as covariates. A separate analysis was conducted in which the 56 subjects were classified by alcoholism and depression level (BDI-II score < or =13 vs >13). The analysis revealed no significant P300 differences associated with these factors. **CONCLUSIONS:** It is hypothesized that anxiety might play a role in mediating or amplifying the P300 decrements that have been attributed to alcoholism and depression in women. Additional and more comprehensive studies are needed to discern the validity of this hypothesis.

J Stud Alcohol. 2001 Sep;62(5):571-9

The P300 brain potential is reduced in smokers.

RATIONALE: Tobacco smoking is the most prevalent type of substance abuse, yet its biobehavioral etiology is little understood. Identification of differences between smokers and non-smokers on basic characteristics of neurocognitive functioning may help to elucidate the mechanisms of tobacco dependence. **OBJECTIVES:** This study assessed the relationship between smoking status and the P300 component of event-related potential (ERP) while controlling for potential confounders such as alcoholism, drug

abuse, and psychopathology. METHODS: The ERP responses elicited by a visual oddball task were measured at the mid-parietal site in 905 current smokers, 463 ex-smokers, and 979 never smokers. RESULTS: P300 amplitude was significantly lower in current cigarette smokers compared to never-smokers. Ex-smokers did not differ significantly from never-smokers. P300 reduction was also associated with alcoholism, drug dependence, and family density of alcoholism. However, after controlling for smoking, only family density of alcoholism remained a significant predictor of P300 amplitude. CONCLUSIONS: The results indicate a significant effect of smoking status on P300 amplitude, which is additive to family history of alcoholism and suggest that either (1) long-term tobacco smoking may produce a reversible change in brain function, or (2) reduced P300 may be a marker of risk for nicotine dependence.

Psychopharmacology (Berl). 2000 May;149(4):409-13

Pectin

Endogenous galactoside-binding lectins: a new class of functional tumor cell surface molecules related to metastasis.

The formation of secondary tumors by circulating cancer cells (blood-borne metastasis) correlates with an increased tendency of the cells to form emboli by aggregation with other tumor cells or with host cells. Although it is evident that cell-cell recognition and adhesion are mediated by cell surface components, the identity of these molecules is only now being unraveled. Over the last decade an increasing number of studies have demonstrated the presence of endogenous carbohydrate-binding proteins on the surface of various normal cells, and it has been proposed that such lectin-like molecules might be involved in intercellular adhesion. We have shown that various tumor cell lines contain endogenous galactose-specific lectins. Lectin activity was detected at the cell surface by the binding of asialofetuin. This glycoprotein also enhanced the aggregation of the tumor cells. After purification by affinity chromatography on immobilized asialofetuin the lectin activity was associated with two proteins of Mr 14,500 and 34,000. By using polyclonal and monoclonal antilectin antibodies in conjunction with various immunologic techniques we have demonstrated that the endogenous lectins are present on the surface of different tumor cells. Quantitation of cell surface lectins by flow cytometric analyses of antilectin antibody binding revealed that among related tumor cells those exhibiting a higher metastatic potential expressed more lectin on their surface. The binding of monoclonal antilectin antibodies to metastatic cells decreased asialofetuin-induced homotypic aggregation in vitro and suppressed the ability of the cells to form lung metastases after intravenous injection in the tail vein of syngeneic mice. These results strongly implicate the tumor cell surface lectins in cell adhesion and metastasis. We propose that such lectins can increase the ability of tumor cells that enter the blood stream to form aggregates with other tumor cells, or to adhere to host cells or the extracellular matrix and thereby increase their metastatic potential. Other contributing components to tumor cell-host cell interactions are cell surface carbohydrate-binding proteins that have been detected on lymphocytes, platelets, macrophages, hepatocytes, and endothelial cells. These lectin-like molecules might recognize and bind carbohydrates expressed on the surface of tumor cells and enhance emboli formation and organ colonization.

Cancer Metastasis Rev. 1987;6(3):433-52

Expression of the endogenous galactose-binding protein galectin-3 correlates with the malignant potential of tumors in the central nervous system.

BACKGROUND: The 31-kilodalton beta-galactoside-binding protein galectin-3 has been associated with cellular transformation and metastasis. Because neural tissues contain large amounts of glycoconjugates, and endogenous carbohydrate-binding proteins have been described in the human brain, the authors examined the expression of galectin-3 in human brain tumors and metastases to the central nervous system. METHODS: Brain tumors were categorized by the World Health Organization system and galectin-3 expression by immunoperoxidase staining using a quantitative staining score. RESULTS: Glioblastomas (Grade 4 astrocytomas) all stained strongly for galectin-3, whereas low grade astrocytomas (Grade 2) did not express the endogenous lectin. Anaplastic astrocytomas (Grade 3) exhibited intermediate expression. The staining score was significantly associated with tumor grade ($P < 0.001$). Normal brain tissue and benign tumors did not express galectin-3, whereas metastases to the brain were all positive for galectin-3 expression. Metastases expressed significantly more galectin-3 than the primary tumors from which they were derived ($P = 0.003$). CONCLUSIONS: Galectin-3 expression correlates with the malignant potential of tumors in the central nervous system.

Cancer. 1997 Aug 15;80(4):776-87

Inhibition of spontaneous metastasis in a rat prostate cancer model by oral administration of modified citrus pectin.

BACKGROUND: Prostate cancer is the most common cancer diagnosed in U.S. men and remains incurable once it has metastasized. Many stages of the metastatic cascade involve cellular interactions mediated by cell surface components, such as carbohydrate-binding proteins, including galactoside-binding lectins (galectins). Modified citrus pectin (pH-modified), a soluble component of plant fiber derived from citrus fruit, has been shown to interfere with cell-cell interactions mediated by cell surface carbohydrate-binding galectin-3 molecules. PURPOSE: The aim of this study was to determine whether modified citrus pectin, a

complex polysaccharide rich in galactosyl residues, could inhibit spontaneous metastasis of prostate adenocarcinoma cells in the rat. **METHODS:** The ability of modified citrus pectin to inhibit the adhesion of Dunning rat prostate cancer MAT-LyLu cells to rat endothelial cells was measured by ⁵¹Cr-labeling. Modified citrus pectin inhibition of MAT-LyLu cell anchorage-independent growth was measured by colony formation in agarose. The presence of galectin-3 in rat MAT-LyLu cells and human prostate carcinoma was demonstrated by immunoblotting and immunohistochemistry. One million MAT-LyLu cells were injected subcutaneously into the hind limb of male Copenhagen rats on day 0. Rats were given 0.0%, 0.01%, 0.1%, or 1.0% (wt/vol) modified citrus pectin continuously in their drinking water (from day 4 until necropsy on day 30). The number of MAT-LyLu tumor colonies in the lungs were counted. **RESULTS:** Compared with 15 or 16 control rats that had lung metastases on day 30, seven of 14 rats in the 0.1% and nine of 16 rats in the 1.0% modified citrus-pectin group had statistically significant (two-sided; $P < .03$ and $P < .001$, respectively) reductions in lung metastases. The lungs of the 1.0% modified citrus pectin-treated rats had significantly (two-sided; $P < .05$) fewer metastatic colonies than control groups (9 colonies \pm 4 [mean \pm SE] in the control group compared with 1 colony \pm 1 in the treated group). Modified citrus pectin had no effect on the growth of the primary tumors. In vitro, modified citrus pectin inhibited MAT-LyLu cell adhesion to rat endothelial cells in a time- and dose-dependent manner as well as their colony formation in semisolid medium. **CONCLUSIONS:** We present a novel therapy in which oral intake of modified citrus pectin acts as a potent inhibitor of spontaneous prostate carcinoma metastasis in the Copenhagen rat. **IMPLICATIONS:** Further investigations are warranted to determine the following: 1) the role of galectin-3 in normal and cancerous prostate tissues and 2) the ability of modified citrus pectin to inhibit human prostate metastasis in nude mice.

J Natl Cancer Inst. 1995 Mar 1;87(5):348-53

Modified citrus pectin (MCP) increases the prostate-specific antigen doubling time in men with prostate cancer: a phase II pilot study.

This trial investigated the tolerability and effect of modified citrus pectin (Pecta-Sol®) in 13 men with prostate cancer and biochemical prostate-specific antigen (PSA) failure after localized treatment, that is, radical prostatectomy, radiation, or cryosurgery. A total of 13 men were evaluated for tolerability and 10 for efficacy. Changes in the prostate-specific antigen doubling time (PSADT) of the 10 men were the primary end point in the study. We found that the PSADT increased (P -value <0.05) in seven (70%) of 10 men after taking MCP for 12 months compared to before taking MCP. This study suggests that MCP may lengthen the PSADT in men with recurrent prostate cancer.

Prostate Cancer Prostatic Dis. 2003;6(4):301-4

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