

ABSTRACTS

Sun damage

Recent trends in cutaneous melanoma incidence among whites in the United States.

BACKGROUND: It is not yet clear whether increasing melanoma incidence is real or whether recent incidence trends mainly reflect improved diagnosis. To address this question, we examined the most recent melanoma incidence patterns among the white population stratified by sex, age, tumor stage, and tumor thickness by use of data from the Surveillance, Epidemiology, and End Results Program. **METHODS:** We examined log-transformed age-specific rates for melanoma by 5-year age groups and time periods by year of diagnosis and birth cohort. Melanoma trends were further examined among broader age groups (<40 years, 40-59 years, and > or =60 years) by tumor stage and tumor thickness. Rates were age-adjusted to the 1970 U.S. standard population, and trends were tested by use of a two-sided Student's t test. **RESULTS:** Melanoma incidence increased in females born since the 1960s. From 1974-1975 through 1988-1989, upward trends for the incidence of localized tumors and downward trends for the incidence of distant-stage tumors occurred in the age group under 40 years. In the more recent time period, 1990-1991 through 1996-1997, age specific rates among females compared with males generally remained stable or declined more for distant-stage tumors and increased less for local-stage tumors. Thin tumors (<1 mm) increased statistically significantly in all age groups ($P < .05$ for all), except in men under age 40 years. In contrast, rates for thick tumors (> or =4 mm) increased statistically significantly ($P = .0003$) only in males aged 60 years and older. **CONCLUSION:** Melanoma incidence may well continue to rise in the United States, at least until the majority of the current population in the middle-age groups becomes the oldest population. The recent trends may reflect increased sunlight exposure.

J Natl Cancer Inst. 2001 May 2;93(9):678-83

Ultraviolet radiation: sun exposure, tanning beds, and vitamin D levels. What you need to know and how to decrease the risk of skin cancer.

This year, more than one million new cases of skin cancer will be diagnosed in the United States and an estimated 9800 individuals will die of the disease. Despite recent public education efforts and increased public awareness about the importance of the use of sunscreen and avoidance of ultraviolet radiation, the incidence of melanoma has more than tripled among white Americans from 1980 to 2001. This increase in cancer rates means that one person dies of melanoma in this country every hour of every day. The answer to this increasing problem is not a simple one, but public education seems to be a common starting point. The American Cancer Society and the American Academy of Dermatology have published recommendations with regard to sun exposure and sunscreen use. However, patients often ask questions that are not as easily answered. Questions such as, Which sunscreens are the safest? Are tanning beds safe? If I limit my sun exposure, do I need to take vitamin D supplements? If I tanned as a teenager, is the damage already done? How do I treat sunburn? This article provides a review of the current literature regarding these issues and provides the facts family physicians need to answer common patient questions. The author discusses the mechanisms of sun damage, the facts on tanning beds, and the importance of supplementing vitamin D.

Am Osteopath Assoc. 2003 Aug;103(8):371-5

Common skin disorders in the elderly.

Skin diseases commonly seen in the elderly are more often than not the effects of sun damage or vascular disease. The effects of a lifetime of even casual sun exposure can be dramatic. Chronically sun-exposed skin becomes thin, loses collagen, and has disrupted elastin and decreased glycosaminoglycans. The result is skin that breaks easily, bruises, sags, irritates easily, and itches. The spots and bumps that patients associate with age are all sun-induced. Consider how lesionless a 60-year-old's buttock is compared to the extensor forearm. The reason that bruising attributed to anticoagulation seems to occur exclusively on the extensor forearm and not the volar aspect of the arm is that sun-induced elastin degradation is greatest on the extensor forearm. Even trivial trauma will cause unsupported capillaries to shear and bleed whether the patient is anticoagulated or not. This article reviews the primary skin disorders associated with the elderly and some of the management approaches that the primary care physician can use.

Clin Cornerstone. 2001;4(1):39-44

Elderly and sun-affected skin. Distinguishing between changes caused by aging and changes caused by habitual exposure to sun.

OBJECTIVE: To review and distinguish between skin changes produced by aging and changes produced by habitual exposure to sun. **QUALITY OF EVIDENCE:** The literature was searched from 1969 to 1999 for articles on dermatoheliosis and sun-damaged

skin. Surprisingly few were found comparing the difference between elderly skin and sun-damaged skin. A few articles focused on certain small aspects of sun-damaged skin. Many excellent articles described particular changes (e.g., actinic keratosis), but few covered all the changes due to aging and to sun. MAIN MESSAGE: Skin changes due to aging can be distinguished from those due to sun damage. All changes due to sun exposure can be grouped under the term dermatoheliosis; five parts of the skin are involved: epidermis (actinic keratosis), dermis (solar elastosis), blood vessels (telangiectasia), sebaceous glands (solar comedones), and melanocytes (diffuse or mottled brown patches). Habitual exposure to sun and a white skin are prerequisites for developing these changes. Knowing the difference between changes caused by sun and by aging can help physicians predict which patients are most likely to get skin cancers. CONCLUSION: Knowledge of these common skin changes will help physicians diagnose and manage the skin abnormalities of elderly people and of people with dermatoheliosis.

Can Fam Physician. 2001 Jun;47:1236-43

Cutaneous photobiology. The melanocyte vs. the sun: who will win the final round?

Solar ultraviolet radiation (UV) is a major environmental factor that dramatically alters the homeostasis of the skin as an organ by affecting the survival, proliferation and differentiation of various cutaneous cell types. The effects of UV on the skin include direct damage to DNA, apoptosis, growth arrest, and stimulation of melanogenesis. Long-term effects of UV include photoaging and photocarcinogenesis. Epidermal melanocytes synthesize two main types of melanin: eumelanin and pheomelanin. Melanin, particularly eumelanin, represents the major photoprotective mechanism in the skin. Melanin limits the extent of UV penetration through the epidermal layers, and scavenges reactive oxygen radicals that may lead to oxidative DNA damage. The extent of UV-induced DNA damage and the incidence of skin cancer are inversely correlated with total melanin content of the skin. Given the importance of the melanocyte in guarding against the adverse effects of UV and the fact that the melanocyte has a low self-renewal capacity, it is critical to maintain its survival and genomic integrity in order to prevent malignant transformation to melanoma, the most fatal form of skin cancer. Melanocyte transformation to melanoma involves the activation of certain oncogenes and the inactivation of specific tumor suppressor genes. This review summarizes the current state of knowledge about the role of melanin and the melanocyte in photoprotection, the responses of melanocytes to UV, the signaling pathways that mediate the biological effects of UV on melanocytes, and the most common genetic alterations that lead to melanoma.

Pigment Cell Res. 2003 Oct;16(5):434-47

Determinants of melanocyte density in adult human skin.

The distribution of melanocytes in human skin has been observed to vary within and among individuals, yet little is known of the factors that determine the density of these pigment cells. These factors were explored in a molecular epidemiological study conducted among a population-based sample of 97 male subjects aged over 50 years in Queensland, Australia. Information relating to environmental and phenotypic factors was collected through face-to-face interviews and physical examination of all participants. In addition, 2-mm biopsies of representative skin were taken from the dorsum of the hand and another anatomical site. Melanocytes were identified by cytoplasmic staining with the B8G3 (anti-TRP1) monoclonal antibody using standard immunohistochemical techniques. Melanocyte counts were performed blind by two observers. On crude analysis, melanocyte density decreased with advancing age ($P = 0.0002$), and increased with increasing number of naevi ($P = 0.01$). Other pigmentary characteristics (such as hair and eye colour and depth of tan) were not associated with epidermal melanocyte density. Melanocyte density varied significantly by anatomical site ($P = 0.02$), with highest densities observed on the back/shoulders ($n = 50$, 17.1 ± 8.8 cells/mm, mean \pm SD) followed by the upper limbs ($n = 11$, 12.6 ± 8.8 cells/mm) and lower limbs ($n = 14$, 14.4 ± 5.9 cells/mm). Lowest melanocyte densities were recorded on the anterior trunk ($n = 3$, 3.2 ± 2.4 cells/mm). These findings confirm the results of earlier studies in which site-specific differences in melanocyte density have been found. We speculate that the unequal distribution of melanocytes may partially explain the site-specific incidence of melanoma, offering fresh perspectives on the aetiology of this cancer.

Arch Dermatol Res. 1999 Sep;291(9):511-6

Epidemiology of ultraviolet-DNA repair capacity and human cancer.

The following conclusions are derived from an epidemiological study. Reduced repair of ultraviolet (UV)-induced DNA damage contributes directly to basal cell carcinoma (BCC) in individuals with prior sunlight overexposure. A family history of BCC is a predictor of low DNA repair. Repair of UV-damaged DNA declines at a fixed rate of approximately 1% per annum in noncancerous controls. The DNA repair differences between young BCC cases and their controls disappear as they age. Hence, BCC, in terms of DNA repair, is a premature aging disease. The persistence of photochemical damage because of reduced repair results in point mutations in the p53 gene and allelic loss of the nevoid BCC gene (Gorlin's syndrome) located on chromosome 9q. The fact that environmental vulnerability is gender oriented implicates hormones in regulating DNA repair. Xeroderma pigmentosum appears to be a valid paradigm for the role of DNA repair in BCC in the general population.

Environ Health Perspect. 1997 Jun;105 Suppl 4:927-30

Repair of UV light-induced DNA damage and risk of cutaneous malignant melanoma.

BACKGROUND: The mechanism underlying the role of UV light exposure from sunlight in the etiology of cutaneous malignant

melanoma (CMM) is unclear. Patients with xeroderma pigmentosum, a disease characterized by severe sensitivity to UV radiation and a defect in nucleotide excision repair, have a high incidence of CMM, which suggests that DNA repair capacity (DRC) plays a role in sunlight-induced CMM in the general population as well. METHODS: We conducted a hospital-based case-control study of DRC and CMM among 312 non-Hispanic white CMM patients who had no prior chemotherapy or radiation therapy, and 324 cancer-free control subjects who were frequency-matched to case patients on age, sex, and ethnicity. Information on demographic variables, risk factors, and tumor characteristics was obtained from questionnaires and medical records. We used the host-cell reactivation assay to measure the DRC in study subjects' lymphocytes. All statistical tests were two sided. RESULTS: Case patients had a 19% lower mean (\pm standard deviation [SD]) DRC (8.5 \pm 3.4%) than control subjects (10.5 \pm 5.1%), a statistically significant difference ($P < .001$). DRC that was at or below the median value (i.e., 9.4%) in control subjects was associated with increased risk for CMM after adjustment for age, sex, and other covariates (odds ratio [OR] = 2.02, 95% confidence interval [CI] = 1.45 to 2.82). We observed a dose-response relationship between decreased DRC and increased risk of CMM ($P(\text{trend}) < .001$). Patients with tumors on sun-exposed skin had statistically significantly lower DRC than patients with tumors on unexposed skin (8.2 \pm 3.3% versus 9.5 \pm 3.5%; $P = .004$). CONCLUSIONS: Reduced DRC is an independent risk factor for CMM and may contribute to susceptibility to sunlight-induced CMM among the general population.

J Natl Cancer Inst. 2003 Feb 19;95(4):308-15

ABSTRACTS

Diabetes

Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase.

Leptin is a hormone secreted by adipocytes that plays a pivotal role in regulating food intake, energy expenditure and neuroendocrine function. Leptin stimulates the oxidation of fatty acids and the uptake of glucose, and prevents the accumulation of lipids in nonadipose tissues, which can lead to functional impairments known as "lipotoxicity". The signalling pathways that mediate the metabolic effects of leptin remain undefined. The 5'-AMP-activated protein kinase (AMPK) potently stimulates fatty-acid oxidation in muscle by inhibiting the activity of acetyl coenzyme A carboxylase (ACC). AMPK is a heterotrimeric enzyme that is conserved from yeast to humans and functions as a 'fuel gauge' to monitor the status of cellular energy. Here we show that leptin selectively stimulates phosphorylation and activation of the alpha2 catalytic subunit of AMPK (alpha2 AMPK) in skeletal muscle, thus establishing a previously unknown signalling pathway for leptin. Early activation of AMPK occurs by leptin acting directly on muscle, whereas later activation depends on leptin functioning through the hypothalamic-sympathetic nervous system axis. In parallel with its activation of AMPK, leptin suppresses the activity of ACC, thereby stimulating the oxidation of fatty acids in muscle. Blocking AMPK activation inhibits the phosphorylation of ACC stimulated by leptin. Our data identify AMPK as a principal mediator of the effects of leptin on fatty-acid metabolism in muscle.

Nature. 2002 Jan 17;415(6869):339-43

Can correction of sub-optimal coenzyme Q status improve beta-cell function in type II diabetics?

A stimulus to mitochondrial respiratory activity is a crucial component of the signal transduction mechanism whereby increased plasma glucose evokes insulin secretion by beta-cells. Efficient function of the glycerol-3-phosphate shuttle is important in this regard, and the rate-limiting enzyme in this shuttle--the mitochondrial glycerol-3-phosphate dehydrogenase (G3PD)--is underexpressed in the beta cells of human type II diabetics as well of rodents that are models for this disorder. Suboptimal tissue levels of coenzyme Q10 (CoQ) could be expected to further impair G3PD activity. Clinical reports from Japan suggest that supplemental CoQ may often improve beta-cell function and glycemic control in type II diabetics. Thus, it is proposed that correction of suboptimal CoQ status, by aiding the efficiency of G3PD and of respiratory chain function, will improve the glucose-stimulated insulin secretion of diabetic beta-cells.

Med Hypotheses. 1999 May;52(5):397-400

Beneficial effects of antioxidants in diabetes: possible protection of pancreatic beta-cells against glucose toxicity.

Oxidative stress is produced under diabetic conditions and possibly causes various forms of tissue damage in patients with diabetes. The aim of this study was to examine the involvement of oxidative stress in the progression of pancreatic beta-cell dysfunction in type 2 diabetes and to evaluate the potential usefulness of antioxidants in the treatment of type 2 diabetes. We used diabetic C57BL/KsJ-db/db mice, in whom antioxidant treatment (N-acetyl-L-cysteine [NAC], vitamins C plus E, or both) was started at 6 weeks of age; its effects were evaluated at 10 and 16 weeks of age. According to an intraperitoneal glucose tolerance test, the treatment with NAC retained glucose-stimulated insulin secretion and moderately decreased blood glucose levels. Vitamins C and E were not effective when used alone but slightly effective when used in combination with NAC. No effect on insulin secretion was observed when the same set of antioxidants was given to nondiabetic control mice. Histologic analyses of the pancreases revealed that the beta-cell mass was significantly larger in the diabetic mice treated with the antioxidants than in the untreated mice. As a possible cause, the antioxidant treatment suppressed apoptosis in beta-cells without changing the rate of beta-cell proliferation, supporting the hypothesis that in chronic hyperglycemia, apoptosis induced by oxidative stress causes reduction of beta-cell mass. The antioxidant treatment also preserved the amounts of insulin content and insulin mRNA, making the extent of insulin degranulation less evident. Furthermore, expression of pancreatic and duodenal homeobox factor-1 (PDX-1), a beta-cell-specific transcription factor, was more clearly visible in the nuclei of islet cells after the antioxidant treatment. In conclusion, our observations indicate that antioxidant treatment can exert beneficial effects in diabetes, with preservation of in vivo beta-cell function. This finding suggests a potential usefulness of antioxidants for treating diabetes and provides further support for the implication of oxidative stress in beta-cell dysfunction in diabetes.

Diabetes. 1999 Dec;48(12):2398-406

A prospective study of exercise and incidence of diabetes among US male physicians.

OBJECTIVE--To examine prospectively the association between regular exercise and the subsequent development of non-insulin-dependent diabetes mellitus (NIDDM). **DESIGN**--Prospective cohort study including 5 years of follow-up. **PARTICIPANTS**--21,271 US male physicians participating in the Physicians' Health Study, aged 40 to 84 years and free of diagnosed diabetes mellitus, myocardial infarction, cerebrovascular disease, and cancer at baseline. Morbidity follow-up was 99.7% complete. **MAIN OUTCOME MEASURE**--Incidence of NIDDM. **RESULTS**--At baseline, information was obtained about frequency of vigorous

exercise and other risk indicators. During 105,141 person-years of follow-up, 285 new cases of NIDDM were reported. The age-adjusted incidence of NIDDM ranged from 369 cases per 100,000 person-years in men who engaged in vigorous exercise less than once weekly to 214 cases per 100,000 person-years in those exercising at least five times per week (P, trend, less than .001). Men who exercised at least once per week had an age-adjusted relative risk (RR) of NIDDM of 0.64 (95% CI, 0.51 to 0.82; P = .0003) compared with those who exercised less frequently. The age-adjusted RR of NIDDM decreased with increasing frequency of exercise: 0.77 for once weekly, 0.62 for two to four times per week, and 0.58 for five or more times per week (P, trend, .0002). A significant reduction in risk of NIDDM persisted after adjustment for both age and body-mass index: RR, 0.71 (95% CI, 0.56 to 0.91; P = .006) for at least once per week compared with less than once weekly, and P, trend, .009, for increasing frequency of exercise. Further control for smoking, hypertension, and other coronary risk factors did not materially alter these associations. The inverse relation of exercise to risk of NIDDM was particularly pronounced among overweight men. CONCLUSIONS--Exercise appears to reduce the development of NIDDM even after adjusting for body-mass index. Increased physical activity may be a promising approach to the primary prevention of NIDDM.

JAMA. 1992 Jul 1;268(1):63-7

Physical activity and incidence of non-insulin-dependent diabetes mellitus in women.

The potential role of physical activity in the primary prevention of non-insulin-dependent diabetes mellitus (NIDDM) is largely unknown. We examined the association between regular vigorous exercise and the subsequent incidence of NIDDM in a prospective cohort of 87,253 US women aged 34-59 years and free of diagnosed diabetes, cardiovascular disease, and cancer in 1980. During 8 years of follow-up, we confirmed 1303 cases of NIDDM. Women who engaged in vigorous exercise at least once per week had an age-adjusted relative risk (RR) of NIDDM of 0.67 (p less than 0.0001) compared with women who did not exercise weekly. After adjustment for body-mass index, the reduction in risk was attenuated but remained statistically significant (RR = 0.84, p = 0.005). When analysis was restricted to the first 2 years after ascertainment of physical activity level and to symptomatic NIDDM as the outcome, age-adjusted RR of those who exercised was 0.5, and age and body-mass index adjusted RR was 0.69. Among women who exercised at least once per week, there was no clear dose-response gradient according to frequency of exercise. Family history of diabetes did not modify the effect of exercise, and risk reduction with exercise was evident among both obese and nonobese women. Multivariate adjustments for age, body-mass index, family history of diabetes, and other variables did not alter the reduced risk found with exercise. Our results indicate that physical activity may be a promising approach to the primary prevention of NIDDM.

Lancet. 1991 Sep 28;338(8770):774-8

Relationship between acute insulin response and vitamin K intake in healthy young male volunteers.

To evaluate the effects of vitamin K (VK) on pancreatic function, especially on acute insulin response, 25 healthy young male volunteers were given an oral load of 75 g of glucose, and their mean daily VK intake was estimated by a one-week food check list. After excluding low (<20) and high (> or =25) body mass index (BMI) subjects, the remaining 16 participants were divided into three semi-equal groups according to VK intake. Blood VK status of the low VK intake group tended to be poorer than that of the high intake group (median of 5 samples: prothrombin time; 12.5 vs 12.2s and protein-induced VK absence-factor-II; 23 vs 15 mAU/ml), but fasting plasma glucose status was not markedly different between both groups: [plasma glucose (PG); 87 vs 86 mg/dl, immunoreactive insulin (IRI); 6.7 vs 5.3 microU/ml, HbA1c; 4.8 vs 4.9%]. However, at 30 min after glucose loading, PG of the low VK intake group tended to be higher than those of the high intake group (160 vs 145 mg/dl) and IRI was lower (36.1 vs 52.3 microU/ml). Insulinogenic index (incremental IRI/incremental PG, 0-30 min) of the low VK intake group was significantly lower than that of the high intake group (0.4 vs 0.9). These results suggested that VK may play an important role on the acute insulin response in glucose tolerance.

Diabetes Nutr Metab. 1999 Feb;12(1):37-41

Salmon calcitonin - a potent inhibitor of food intake in states of impaired leptin signalling in laboratory rodents.

To compare the anorectic effectiveness of leptin and the amylin analogue salmon calcitonin (sCT), rodents were treated on 1 day with subcutaneous injections. In chow-fed C57Bl/6J mice, leptin and sCT reduced energy intake and acted additively. After C57Bl/6J mice had become leptin-resistant on being fed chocolate as a palatable high-caloric supplement to chow, their sCT-induced decrease in energy intake was more pronounced than in chow-fed mice with differential changes in the intake of chocolate (strong reduction) and chow (slight increase). Dose-response relationships for sCT-induced reductions in energy intake were analysed in chow-fed C57Bl/6J mice and two obese strains, ob/ob mice and melanocortin-4 receptor knockout (MC4-r-KO) mice, as well as in wild-type and fatty (fa/fa) rats. Compared to C57Bl/6J mice, reduction in food intake induced by sCT was attenuated in MC4-r-KO mice, and nearly absent in ob/ob mice, over the dose range investigated. Compared to C57Bl/6J mice, wild-type rats responded more sensitively to sCT and its efficiency was only slightly reduced in fatty (fa/fa) rats. Thus, while genetically induced failures of leptin signalling reduce the action of sCT, it effectively inhibits the intake of a palatable, high fat-high sugar diet even in states of diet-induced obesity with functional leptin resistance.

J Physiol. 2002 Jun 15;541(Pt 3):1041-8

ABSTRACTS

Parkinson's Disease

A population-based investigation of Parkinson's disease with and without dementia. Relationship to age and gender.

Because the prevalence of idiopathic Parkinson's disease (PD) with or without dementia remains controversial, we initiated a population-based investigation in the Washington Heights-Inwood section of New York, NY, so that nearly complete case ascertainment could be achieved. A "registry" was developed for the study, and we advertised in periodicals and on radio and television. Subjects, or their records, were examined by experienced neurologists, and most underwent a battery of neuropsychological tests specifically designed for assessment in this community. All data were reviewed by a team of clinicians to achieve a consensus diagnosis. The crude prevalence of idiopathic PD, with and without dementia, was 99.4 per 100,000, increasing from 2.3 per 100,000 for those younger than 50 years to 1144.9 per 100,000 for those aged 80 years and older. The crude prevalence for PD with dementia alone was 41.1 per 100,000 and also increased with age from zero for those younger than 50 years to 787.1 per 100,000 for those aged 80 years and older. Prevalence ratios were comparable with those of other published population-based studies in similar settings. After standardization, men had PD with and without dementia more frequently than did women. The major difference between patients with and without dementia was a later estimated age at onset of motor manifestations. We conclude that PD is a frequent disorder in the elderly population that affects men and whites more frequently than women and nonwhites. Moreover, dementia in patients with PD is more frequent than previously recognized and is strongly related to the age at onset of motor manifestations.

Arch Neurol. 1992 May;49(5):492-7

Worldwide occurrence of Parkinson's disease: an updated review.

Comparison of Parkinson's disease (PD) prevalence and incidence in various parts of the world is difficult because methods of case ascertainment, diagnostic criteria, classification, medical facilities, and age distribution of the populations vary broadly in different studies. We minimized these differences by adjusting available data to a single standard population. Using this we calculated age-adjusted rates for 27 regional populations and analyzed PD frequency from 45 communities. We conclude: (1) with the exception of China, Japan and Africa, which have the lowest prevalence ratios, the actual prevalence variation for PD is probably lower than previously reported in geographically diverse populations; (2) geographic variation is unlikely to be due exclusively to racial factors, and (3) environmental risk factors for PD might differ regionally.

Neuroepidemiology. 1993;12(4):195-208

Twin study of Parkinson disease.

Zero concordance for Parkinson disease was found in the first 12 monozygotic twin pairs examined in an ongoing twin study. One co-twin (subject without Parkinson disease) had essential tremor, another had cerebral vascular disease, and a third was an alcoholic. Cigarette smoking appeared to be less frequent in the probands than in the co-twins (11.9 versus 16.1 pack-years). There was also evidence of premorbid personality differences between probands and co-twins dating back to late adolescence or early adult years. These preliminary findings suggest that genetic factors do not play a major role in the etiology of Parkinson disease and point to a prodromal onset of the disease as early as late adolescence or early adult life.

Neurology. 1981 Jan;31(1):77-80

Effect of deprenyl on the progression of disability in early Parkinson's disease. The Parkinson Study Group.

In a clinical trial that is still in progress, we studied the ability of deprenyl and tocopherol, antioxidative agents that act through complementary mechanisms, to delay the onset of disability necessitating levodopa therapy (the primary end point) in patients with early, untreated Parkinson's disease. Eight hundred subjects were randomly assigned in a two-by-two factorial design to receive deprenyl, tocopherol, a combination of both drugs, or placebo, and were followed up to determine the frequency of development of the end point. The interim results of independent monitoring prompted a preliminary comparison of the 401 subjects assigned to tocopherol or placebo with the 399 subjects assigned to deprenyl, alone or with tocopherol. Only 97 subjects who received deprenyl reached the end point during an average 12 months of follow-up, as compared with 176 subjects who did not receive deprenyl (P less than 10^{-8}). The risk of reaching the end point was reduced by 57% for the subjects who received deprenyl (Cox hazard ratio, 0.43; 95% confidence limits, 0.33 and 0.55; P less than 10^{-10}). The subjects who received deprenyl also had a significant reduction in their risk of having to give up full-time employment ($P = 0.01$). We conclude from these preliminary results that the use of deprenyl (10 mg per day) delays the onset of disability associated with early, otherwise untreated cases of Parkinson's disease.

N Engl J Med. 1989 Nov 16;321(20):1364-71

Ropinirole for the treatment of early Parkinson's disease. The Ropinirole Study Group.

A prospective, randomized, placebo-controlled, double-blind, parallel-group, 6-month study assessed the efficacy and safety of ropinirole, a nonergoline D2-dopamine agonist, in patients with early Parkinson's disease (n = 241; Hoehn & Yahr stages I to III) with limited or no prior dopaminergic therapy. Patients (mean age, 62.8 years), stratified by concomitant use of selegiline, were randomized to ropinirole (n = 116) or placebo (n = 125). The starting dose of ropinirole was 0.25 mg tid with titration to at least 1.5 mg tid (maximum dose, 8 mg tid). Primary efficacy endpoint was the percentage improvement in Unified Parkinson's Disease Rating Scale (UPDRS) motor score. Ropinirole-treated patients had a significantly greater percentage improvement in UPDRS motor score than patients who received placebo (+24% vs -3%; p < 0.001). Ropinirole was well tolerated and patient withdrawals were infrequent. Most adverse experiences were related to peripheral dopaminergic activity. Ropinirole monotherapy is an effective and well-tolerated therapeutic option for treatment of early Parkinson's disease.

Neurology . 1997 Aug;49(2):393-9

Smoking, alcohol, and coffee consumption preceding Parkinson's disease: a case-control study.

OBJECTIVE: To study the association of PD with preceding smoking, alcohol, and coffee consumption using a case-control design. **METHODS:** The authors used the medical records linkage system of the Rochester Epidemiology Project to identify 196 subjects who developed PD in Olmsted County, MN, during the years 1976 to 1995. Each incident case was matched by age (± 1 year) and sex to a general population control subject. The authors reviewed the complete medical records of cases and control subjects to abstract exposure information. **RESULTS:** For coffee consumption, the authors found an OR of 0.35 (95% CI = 0.16 to 0.78, p = 0.01), a dose-effect trend (p = 0.003), and a later age at PD onset in cases who drank coffee compared with those who never did (median 72 versus 64 years; p = 0.0002). The inverse association with coffee remained significant after adjustment for education, smoking, and alcohol drinking and was restricted to PD cases with onset at age <72 years and to men. The OR for cigarette smoking was 0.69 (95% CI = 0.45 to 1.08, p = 0.1). The authors found no association between PD and alcohol consumption. Extreme or unusual behaviors such as tobacco chewing or snuff use and a diagnosis of alcoholism were significantly more common in control subjects than cases. **CONCLUSIONS:** These findings suggest an inverse association between coffee drinking and PD; however, this association does not imply that coffee has a direct protective effect against PD. Alternative explanations for the association should be considered.

Neurology. 2000 Nov 14;55(9):1350-8

Diet and Parkinson's disease. II: A possible role for the past intake of specific nutrients. Results from a self-administered food-frequency questionnaire in a case-control study.

In a case-control study, we compared the past dietary habits of 342 Parkinson's disease (PD) patients recruited from nine German clinics with those of 342 controls from the same neighborhood or region. Data were gathered with a structured interview and a self-administered food-frequency questionnaire. Nutrient intakes were calculated from the reported food intakes through linkage with the German Federal Food Code and analyzed using multivariate conditional logistic regression to control for total energy intake, educational status, and cigarette smoking. At the macronutrient level, patients reported higher carbohydrate intake than controls after adjustment for total energy intake, smoking, and educational status (OR = 2.74, 95% confidence interval [CI]: 1.30-6.07, for the highest versus lowest quartile, p trend = 0.02). This was reflected in higher monosaccharide and disaccharide intakes at the nutrient level. There was no difference between patients and controls in protein and fat intake after adjustment for energy intake. We found an inverse association between the intakes of beta-carotene (OR = 0.67, 95% CI: 0.37-1.19, p trend = 0.06) and ascorbic acid (OR = 0.60, 95% CI: 0.33-1.09, p trend = 0.04) by patients, although only the trend for ascorbic acid intake reached statistical significance. There was no difference between groups for alpha-tocopherol intake after adjustment for energy intake. We also found that patients reported a significantly lower intake of niacin than controls (OR = 0.15, 95% CI: 0.07-0.33, p trend < 0.00005). Our results suggest that if antioxidants play a protective role in this disease, the amounts provided by diet alone are insufficient. Although the interpretation of the inverse association between niacin intake and PD is complicated by the high niacin content in coffee and alcoholic beverages, which were also inversely associated with PD in this study, the strength of this association and its biologic plausibility warrant further investigation.

Neurology . 1996 Sep;47(3):644-50

ABSTRACTS

Pregnenolone

Sex-and age-related changes in epitestosterone in relation to pregnenolone sulfate and testosterone in normal subjects.

Epitestosterone has been demonstrated to act at various levels as a weak antiandrogen. So far, its serum levels have been followed up only in males. Epitestosterone and its major circulating precursor pregnenolone sulfate and T were measured in serum from 211 healthy women and 386 men to find out whether serum concentrations of epitestosterone are sufficient to exert its antiandrogenic actions. In women, epitestosterone exhibited a maximum around 20 yr of age, followed by a continuous decline up to menopause and by a further increase in the postmenopause. In men, maximum epitestosterone levels were detected at around 35 yr of age, followed by a continuous decrease. Pregnenolone sulfate levels in women reached their maximum at about age 32 yr and then declined continuously, and in males the maximum was reached about 5 yr earlier and then remained nearly constant. Epitestosterone correlated with pregnenolone sulfate only in males. In both sexes a sharp decrease of the epitestosterone/T ratio around puberty occurred. In conclusion, concentrations of epitestosterone and pregnenolone sulfate are age dependent and, at least in prepubertal boys and girls, epitestosterone reaches or even exceeds the concentrations of T, thus supporting its role as an endogenous antiandrogen. The dissimilarities in the course of epitestosterone levels through the lifespan of men and women and its relation to pregnenolone sulfate concentrations raise the question of the contribution of the adrenals and gonads to the production of both steroids and even to the uniformity of the mechanism of epitestosterone formation.

J Clin Endocrinol Metab . 2002 May;87(5):2225-31

Sex steroids and 5-en-3 beta-hydroxysteroids in specific regions of the human brain and cranial nerves.

Sex steroids and 5-en-3 beta-hydroxysteroids were determined by radioimmunoassay in specific regions of the human brain, in the anterior and posterior pituitary, in one sensory organ, the retina and in the cranial nerves. Progesterone, androstenedione, testosterone and estrone were found in all areas of the brain and in all the cranial nerves but not in all cases. There was no sex difference except in the case of androstenedione where values were higher in women in some brain areas. Estrone values were always higher than those of estradiol in both men and women. No 5 alpha-dihydrotestosterone was detected in any of the samples studied. The values for pregnenolone, dehydroepiandrosterone and their sulfates were much higher than those of the sex steroids in all areas of the brain and in all the cranial nerves. Values for pregnenolone were greater than those of its sulfate while those of dehydroepiandrosterone were in general equal to or higher than those of its sulfate. The values for pregnenolone were greater than those of dehydroepiandrosterone. There were no obvious regional differences in the concentrations of the 5-en-3 beta-hydroxysteroids either in specific areas of the brain or in the cranial nerves. But there was a definite trend for the free dehydroepiandrosterone values to be higher in women. The possible significance of these observations is discussed.

J Steroid Biochem . 1986 Sep;25(3):445-9

Individual differences in cognitive aging: implication of pregnenolone sulfate.

In humans and animals, individual differences in aging of cognitive functions are classically reported. Some old individuals exhibit performances similar to those of young subjects while others are severely impaired. In senescent animals, we have previously demonstrated a significant correlation between the cognitive performance and the cerebral concentration of a neurosteroid, the pregnenolone sulfate (PREG-S). Neurotransmitter systems modulated by this neurosteroid were unknown until our recent report of an enhancement of acetylcholine (ACh) release in basolateral amygdala, cortex and hippocampus induced by intracerebroventricular (i.c.v.) or intracerebral administrations of PREG-S. Central ACh neurotransmission is known to be involved in the regulation of memory processes and is affected in normal aging and severely altered in human neurodegenerative pathologies like Alzheimer's disease. In the central nervous system, ACh neurotransmission is also involved in the modulation of sleep-wakefulness cycle, and particularly the paradoxical sleep (PS). Relationships between paradoxical sleep and memory are documented in the literature in old animals in which the spatial memory performance positively correlates with the basal amounts of paradoxical sleep. PREG-S infused at the level of ACh cell bodies (nucleus basalis magnocellularis, NBM, or pedunculopontine nucleus, PPT) increases paradoxical sleep in young animals. Finally, aging related cognitive dysfunctions, particularly those observed in Alzheimer's disease, have also been related to alterations of mechanisms underlying cerebral plasticity. Amongst these mechanisms, neurogenesis has been extensively studied recently. Our data demonstrate that PREG-S central infusions dramatically increase neurogenesis, this effect could be related to the negative modulator properties of this steroid at the GABA(A) receptor level. Taken together these data suggest that neurosteroids can influence cognitive processes, particularly in senescent subjects, through a modulation of ACh neurotransmission associated with paradoxical sleep modifications; furthermore, our recent data suggest a critical role for neurosteroids in the modulation of cerebral plasticity, mainly on hippocampal neurogenesis.

Prog Neurobiol . 2003 Sep;71(1):43-8

GABA--the quintessential neurotransmitter: electroneutrality, fidelity, specificity, and a model for the ligand binding site of GABAA receptors.

Alone of the known neurotransmitters, GABA is an electroneutral zwitterion ($pI = 7.3$) at physiological pH. This confers the highest probability of successfully traversing densely packed synaptic gaps without interacting electrostatically with charged entities enroute, making GABA a high fidelity neurotransmitter. Inhibitory tone in the nervous system is coordinately coupled with physiological activity by means of the GABA system, acidification increasing GABA formation and its Cl^- channel-opening efficacy, while decreasing its removal by transport and metabolic degradation. The above, together with diminution upon acidification of the postsynaptic efficacy of glutamate on excitatory NMDA receptors constitutes a sensitively responsive mechanism by which protons control levels of neural activity, locally and globally. A model made of the GABA binding site of GABAA receptors based on H-bond and hydrophobic interactions makes it seem unlikely that any other substance known to occur in nerve tissue would give rise to a high noise level at GABAA receptors.

Neurochem Res . 1993 Apr;18(4):365-76

The neurosteroid pregnenolone sulfate increases cortical acetylcholine release: a microdialysis study in freely moving rats.

The effects of pregnenolone sulfate (Preg-S) administrations (0, 12, 48, 96, and 192 nmol intracerebroventricularly) on acetylcholine (ACh) release in the frontal cortex and dorsal striatum were investigated by on-line microdialysis in freely moving rats. Following Preg-S administration, extracellular ACh levels in the frontal cortex increased in a dose-dependent manner, whereas no change was observed in the striatum. The highest doses (96 and 192 nmol) induced a threefold increase above control values of ACh release, the intermediate dose of 48 nmol led to a twofold increase, whereas after the dose of 12 nmol, the levels of ACh were not different from those observed after vehicle injection. The increase in cortical ACh reached a maximum 30 min after administration for all the active doses. Taken together, these results suggest that Preg-S interacts with the cortical cholinergic system, which may account, at least in part, for the promnesic and/or anti-amnesic properties of this neurosteroid.

J Neurochem . 1998 Nov;71(5):2018-22

Neurosteroids: deficient cognitive performance in aged rats depends on low pregnenolone sulfate levels in the hippocampus.

Pregnenolone sulfate (PREG S) is synthesized in the nervous system and is a major neurosteroid in the rat brain. Its concentrations were measured in the hippocampus and other brain areas of single adult and aged (22-24 month-old) male Sprague-Dawley rats. Significantly lower levels were found in aged rats, although the values were widely scattered and reached, in about half the animals, the same range as those of young ones. The spatial memory performances of aged rats were investigated in two different spatial memory tasks, the Morris water maze and Y-maze. Performances in both tests were significantly correlated and, accompanied by appropriate controls, likely evaluated genuine memory function. Importantly, individual hippocampal PREG S and distance to reach the platform in the water maze were linked by a significant correlation, i.e., those rats with lower memory deficit had the highest PREG S levels, whereas no relationship was found with the PREG S content in other brain areas (amygdala, prefrontal cortex, parietal cortex, striatum). Moreover, the memory deficit of cognitively impaired aged rats was transiently corrected after either intraperitoneal or bilateral intrahippocampal injection of PREG S. PREG S is both a gamma-aminobutyric acid antagonist and a positive allosteric modulator at the N-methyl-D-aspartate receptor, and may reinforce neurotransmitter system(s) that decline with age. Indeed, intracerebroventricular injection of PREG S was shown to stimulate acetylcholine release in the adult rat hippocampus. In conclusion, it is proposed that the hippocampal content of PREG S plays a physiological role in preserving and/or enhancing cognitive abilities in old animals, possibly via an interaction with central cholinergic systems. Thus, neurosteroids should be further studied in the context of prevention and/or treatment of age-related memory disorders.

Proc Natl Acad Sci U S A. 1997 Dec 23;94(26):14865-70

Role of pregnenolone, dehydroepiandrosterone and their sulfate esters on learning and memory in cognitive aging.

Aging is a general process of functional decline which involves in particular a decline of cognitive abilities. However, the severity of this decline differs from one subject to another and inter-individual differences have been reported in humans and animals. These differences are of great interest especially as concerns investigation of the neurobiological factors involved in cognitive aging. Intensive pharmacological studies suggest that neurosteroids, which are steroids synthesized in the brain in an independent manner from peripheral steroid sources, could be involved in learning and memory processes. This review summarizes data in animals and humans in favor of a role of neurosteroids in cognitive aging. Studies in animals demonstrated that the neurosteroids pregnenolone (PREG) and dehydroepiandrosterone (DHEA), as sulfate derivatives (PREGS and DHEAS, respectively), display memory-enhancing properties in aged rodents. Moreover, it was recently shown that memory performance was correlated with PREGS levels in the hippocampus of 24-month-old rats. Human studies, however, have reported contradictory results. First, improvement of learning and memory dysfunction was found after DHEA administration to individuals with low DHEAS levels, but other studies failed to detect significant cognitive effects after DHEA administration. Second, cognitive dysfunctions have been associated with low DHEAS levels, high DHEAS levels, or high DHEA levels; while in other studies, no relationship was found.

As future research perspectives, we propose the use of new methods of quantification of neurosteroids as a useful tool for understanding their respective role in improving learning and memory impairments associated with normal aging and/or with pathological aging, such as Alzheimer's disease.

Brain Res Brain Res Rev . 2001 Nov;37(1-3):301-12

The neurosteroid pregnenolone sulfate infused into the medial septum nucleus increases hippocampal acetylcholine and spatial memory in rats.

The effects of an infusion of the neurosteroid pregnenolone sulfate into the medial septum on acetylcholine release in the hippocampus and on spatial memory were evaluated in two experiments. Results show that pregnenolone sulfate enhanced acetylcholine release by more than 50% of baseline and improved recognition memory of a familiar environment. Therefore, our results suggest that the septo-hippocampal pathway could be involved in the promnesic properties of this neurosteroid.

Brain Res . 2002 Oct 4;951(2):237-42

Pregnenolone sulfate and aging of cognitive functions: behavioral, neurochemical, and morphological investigations.

Neurosteroids are a subclass of steroids that can be synthesized in the central nervous system independently of peripheral sources. Several neurosteroids influence cognitive functions. Indeed, in senescent animals we have previously demonstrated a significant correlation between the cerebral concentration of pregnenolone sulfate (PREG-S) and cognitive performance. Indeed, rats with memory impairments exhibited low PREG-S concentrations compared to animals with correct memory performance. Furthermore, these memory deficits can be reversed by intracerebral infusions of PREG-S. Neurotransmitter systems modulated by this neurosteroid were unknown until our recent report of an enhancement of acetylcholine (ACh) release in basolateral amygdala, cortex, and hippocampus induced by central administrations of PREG-S. Central ACh neurotransmission is involved in the regulation of memory processes and is affected in normal aging and in human neurodegenerative pathologies like Alzheimer's disease. ACh neurotransmission is also involved in the modulation of sleep-wakefulness cycle and relationships between paradoxical sleep and memory are well documented in the literature. PREG-S infused at the level of ACh cell bodies induces a dramatic increase of paradoxical sleep in young animals. Cognitive dysfunctions, particularly those observed in Alzheimer's disease, have also been related to alterations of cerebral plasticity. Among these mechanisms, neurogenesis has been recently studied. Preliminary data suggest that PREG-S central infusions dramatically increase neurogenesis. Taken together these data suggest that PREG-S can influence cognitive processes, particularly in senescent subjects, through a modulation of ACh neurotransmission associated with paradoxical sleep modifications; furthermore our recent data suggest a role for neurosteroids in the modulation of hippocampal neurogenesis.

Horm Behav . 2001 Sep;40(2):215-7

CSF neuroactive steroids in affective disorders: pregnenolone, progesterone, and DBI.

Recently several steroid compounds have been discovered to act as neuromodulators in diverse central nervous system (CNS) functions. We wondered if neuroactive steroids might be involved in affective illness or in the mode of action of mood-regulating medications such as carbamazepine. Levels of the neuroactive steroids pregnenolone and progesterone, as well as the neuropeptide diazepam binding inhibitor (DBI) (known to promote steroidogenesis), were analyzed from cerebrospinal fluid (CSF) obtained by lumbar puncture (LP) from 27 medication-free subjects with affective illness and 10 healthy volunteers. Mood-disordered subjects who were clinically depressed at the time of the LP had lower CSF pregnenolone ($n = 9$, 0.16 ng/ml) compared with euthymic volunteers ($n = 10$, 0.35 ng/ml; $p < 0.01$). In addition, pregnenolone was lower in all affectively ill subjects ($n = 26$, 0.21 ng/ml), regardless of mood state on the LP day, than healthy volunteers ($p < 0.05$). No differences were found for progesterone or DBI levels by mood state or diagnosis. Progesterone, pregnenolone, and DBI did not change significantly or consistently in affectively ill subjects after treatment with carbamazepine. CSF pregnenolone is decreased in subjects with affective illness, particularly during episodes of active depression. Further research into the role of neuroactive steroids in mood regulation is warranted.

Biol Psychiatry . 1994 May 15;35(10):775-80

Low pregnenolone sulphate plasma concentrations in patients with generalized social phobia.

BACKGROUND: Animal studies have shown that neuroactive steroids modulate the activity of the gamma-aminobutyric acid type A/benzodiazepine receptor complex and that these steroids display anxiolytic or anxiogenic activity depending on their positive (e.g. allopregnanolone) or negative allosteric modulation (e.g. dehydroepiandrosterone sulphate) of this receptor. This study compared plasma levels of allopregnanolone, dehydroepiandrosterone sulphate and pregnenolone sulphate in healthy controls and in patients with generalized social phobia, as assessed with the Mini-International Neuropsychiatric Interview. **METHODS:** Plasma concentrations of allopregnanolone, pregnenolone sulphate, and dehydroepiandrosterone sulphate were measured in 12 unmedicated male patients with generalized social phobia and 12 matched healthy male volunteers. **RESULTS:** Concentrations of pregnenolone sulphate were significantly lower in patients with generalized social phobia than in healthy controls. No statistically significant differences were found for the concentrations of allopregnanolone and dehydroepiandrosterone sulphate in

plasma. CONCLUSIONS: These results are particularly interesting since we also observed lower pregnenolone sulphate concentrations in male patients suffering from generalized anxiety disorder. Their relevance to the pathophysiology of social anxiety disorder remains to be determined.

Psychol Med . 2002 Jul;32(5):929-33

Key role for pregnenolone in combination therapy that promotes recovery after spinal cord injury.

Controlled compressive injury to rat spinal cord was chosen to test therapies that might attenuate the progression of tissue destruction and locomotor deficits that characteristically occur after spinal injury. A highly significant reduction of damage was achieved by immediate postinjury treatment with a combination of the following: an antiinflammatory substance, indomethacin; a stimulator of cytokine secretion, bacterial lipopolysaccharide; and the parent steroid, from which all other steroids arise, pregnenolone. This treatment reduced histopathological changes, spared tissue from secondary injury, and increased restoration of motor function. Remarkably, 11 of 16 of the animals treated with the above combination were able to stand and walk at 21 days after injury, 4 of them almost normally. The results were far superior to those obtained in controls or in animals to which the substances were given separately or in combination of two. This approach may prove to be applicable to nervous system injury, in general, and to injury in other tissues.

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