

Autoimmune Diseases

ABSTRACTS

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antioxidant enzymes in autoimmune prone NZBxNZW F1 mice

Endotoxin induced production of interleukin-6 is enhanced by vitamin E deficiency and reduced by black tea extract

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Inflammation Research (Switzerland), 1995, 44/7 (301-305)

Studies were performed to investigate the effect of a polyphenol rich extract from black tea and vitamin E on bacterial lipopolysaccharide (endotoxin) induced IL-6 production, alterations in liver glutathione and antioxidant acute phase protein (caeruloplasmin) concentration, in rats fed on a synthetic diet for 21 days. In the vitamin E sufficient group a significantly lower IL-6 concentration than in vitamin E deficient animals was observed. Addition of tea extract to the diet produced a similar reduction in IL-6, but no synergism occurred in the presence of both vitamin E and tea extract. However, a significantly lower caeruloplasmin and a significantly higher liver glutathione concentration was observed in rats fed both substances. It is suggested that consideration of dietary components which alter antioxidant/oxidant status may contribute towards treatment of inflammatory/autoimmune diseases.

Modulation of immune dysfunction during murine leukaemia retrovirus infection of old mice by dehydroepiandrosterone sulphate (DHEAS).

Araghi-Niknam M, Liang B, Zhang Z, Ardestani SK, Watson RR Arizona Prevention Center, University of Arizona, Tucson 85724, USA. rwatson@ccit.arizona.edu

Immunology. 1997 Mar;90(3):344-9.

Ageing, leukaemia and acquired immune deficiency syndrome (AIDS) are conditions with dysregulated cytokine production. As dehydroepiandrosterone sulphate (DHEAS) restored normal cytokine production in old mice its effects on retrovirally infected old mice were investigated. Retrovirus infection and ageing-induced immune dysfunction. Murine retrovirus-infected old C57BL/6 female mice consumed 0.22 or 0.44 microgram of DHEAS/mouse/day beginning 2 weeks postinfection for 10 weeks. DHEAS largely prevented the retrovirus-induced reduction in T-cell and B-cell mitogenesis. DHEAS supplement prevented loss of cytokines [interleukin-2 (IL-2) and interferon-gamma] secretion by mitogen-stimulated splenocytes representing T helper 1 (Th1) cell phenotypes. It also suppressed the retrovirus-induced, excessive production of cytokines (IL-6 and IL-10) by Th2 cells. The highest dose of DHEAS reduced IL-6 production by splenocytes from uninfected old mice by 75% while increasing their IL-2 secretion by nearly 50%. Thus immune dysfunction induced by ageing, even when exacerbated by murine retrovirus infection, was largely prevented by DHEAS.

Depression of lymphocyte transformation following oral glucose ingestion

Bernstein J. ; Alpert S.; Nauss K.M.; Suskind R. Dept. Nutrit. Food Sci., MIT, Cambridge, Mass. United States

Clinical Research (CLIN. RES.) (United States) 1977 , 25/3 (534A)

No Abstracts Available

beta-Sitosterol and beta-sitosterol glucoside stimulate human peripheral blood lymphocyte proliferation: implications for their use as an immunomodulatory vitamin combination.

Bouic PJ, Etsebeth S, Liebenberg RW, Albrecht CF, Pegel K, Van Jaarsveld PP. Department of Medical Microbiology, Faculty of Medicine, University of Stellenbosch, Tygerberg, South Africa.

Int J Immunopharmacol 1996 Dec;18(12):693-700

The phytosterols, beta-sitosterol (BSS), and its glucoside (BSSG) enhance the in vitro proliferative response of T-cells stimulated by sub-optimal concentrations of phytohaemagglutinin (PHA) several fold at extremely low concentrations (femtogram level). A 100:1 (mass:mass) ratio of BSS:BSSG (termed essential sterolin formulation, ESF) showed higher stimulation than the individual sterols at the same concentration. In vivo activity of ESF was also demonstrated when volunteers ingested ESF for 4 weeks. Proliferation of their T-cells, stimulated maximally with PHA, was significantly enhanced (20-920%) when compared to baseline values. In vitro, ESF (1 microgram.ml) was able to significantly enhance the expression of CD25 and HLA-Dr activation antigens on T-cells and increased the secretion, into the medium, of IL-2 and gamma interferon. NK-cell activity was also increased by BSS and BSSG alone, but with EST a higher activity was always found at different effector:target ratios (100:1 12:1).

Unregulated inflammation shortens human functional longevity.

Inflamm Res 2000 Nov;49(11):561-70

Systemic inflammation, represented in large part by the production of pro-inflammatory cytokines, is the response of humans to the assault of the non-self on the organism. Three distinct types of human ailments - namely autoimmunity, presenile dementia (Alzheimer's disease), or atherosclerosis - are initiated or worsened by systemic inflammation. Autoimmunity is unregulated hyperimmunity to organ-specific proteins, inducing rapid turnover of antigen-specific T cells of the acquired immune system with ultimate exhaustion and loss of acquired immunity IL-2 and IFN-gamma production and proliferative decline, conforming to the limited capacity of clonal division (Hayflick phenomenon). In Alzheimer's disease (AD), the primary degenerative process of amyloid-beta (A β) protein precedes a cascade of events that ultimately leads to a local "brain inflammatory response". Unregulated systemic immune processes are secondary but important as a driving-force role in AD pathogenesis. Atherosclerosis, an underlying cause of myocardial infarction, stroke, and other cardiovascular diseases, consists of focal plaques characterized by cholesterol deposition, fibrosis, and inflammation. The presence of activated T lymphocytes and macrophages indicate a local immunologic activation in the atherosclerotic plaque that may be secondary to unregulated pro-inflammatory cytokines too. The premature hyperimmunity of autoimmunity, the local "brain inflammatory response" to A β protein in AD, and the immune response to fatty changes in vessels in atherosclerosis all signal the critical importance of unregulated systemic inflammation to common neurological and cardiovascular disease that shortens the nominal longevity of humans.

RAGE-mediated neutrophil dysfunction is evoked by advanced glycation end products (AGEs).

Collison KS, Parhar RS, Saleh SS, Meyer BF, Kwaasi AA, Hammami MM, Schmidt AM, Stern DM, Al-Mohanna FA. Biological & Medical Research, King Faisal Specialist Hospital and Research Centre, Riyadh 11211, Saudi Arabia.

J Leukoc Biol 2002 Mar;71(3):433-44

The accumulation of advanced glycation end products (AGEs) in the tissue and serum of subjects with diabetes has been linked to the pathogenesis of vascular complications. Because diabetes may be also complicated by increased susceptibility to recurrent infection, we investigated the effects of AGEs on human neutrophils, because their burst of activity immediately upon engagement of pathogens or other inflammatory triggers is critical to host response. We demonstrate the presence of receptor for advanced glycation end products (RAGE) at the message and protein levels. We also demonstrate that AGE albumin (but not control albumin) binds with high affinity to human neutrophils (K $_d$ of 3.7 \pm 0.4 nM). The binding was blocked almost completely by excess soluble RAGE, anti-RAGE antibodies, or antibodies to CML-modified albumin. AGE albumin induced a dose-dependent increase in intracellular-free calcium as well as actin polymerization. Further, AGE albumin inhibited transendothelial migration and Staphylococcus aureus-induced but not fMLP-induced production of reactive oxygen metabolite. Moreover, although AGE albumin enhanced neutrophil phagocytosis of S. aureus, it inhibited bacterial killing. We conclude that functional RAGE is present on the plasma membrane of human neutrophils and is linked to Ca $^{2+}$ and actin polymerization, and engagement of RAGE impairs neutrophil functions.

Serum concentrations of alpha tocopherol, beta carotene, and retinol preceding the diagnosis of rheumatoid arthritis and systemic lupus erythematosus.

Comstock GW, Burke AE, Hoffman SC, Helzlsouer KJ, Bendich A, Masi AT, Norkus EP, Malamet RL, Gershwin ME. Department of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Maryland, USA.

Ann Rheum Dis 1997 May;56(5):323-5

OBJECTIVES: Because oxidative damage has been implicated in the pathogenesis of rheumatoid arthritis and systemic lupus erythematosus, this study was designed to see if serum concentrations of alpha tocopherol, beta carotene, and retinol, substances believed to be involved in the prevention or repair of oxidative damage, might be lower among persons who develop rheumatoid arthritis or systemic lupus erythematosus than among those who do not.

METHODS: For this prospective case-control study, persons with rheumatoid arthritis and systemic lupus erythematosus that developed two to 15 years after donating blood for a serum bank in 1974 were designated as cases. For each case, four controls were selected from the serum bank donors, matched for race, sex, and age. Stored serum samples from cases and controls were assayed for alpha tocopherol, beta carotene, and retinol.

RESULTS: Cases of both diseases had lower serum concentrations of alpha tocopherol, beta carotene, and retinol in 1974 than their matched controls. For rheumatoid arthritis, the difference for beta carotene (-29%) was statistically significant.

CONCLUSIONS: These findings support those of a previous study that low antioxidant status is a risk factor for rheumatoid arthritis. They suggest a similar association for systemic lupus erythematosus.

Fatigue Study Group inquiry into asthenia in general practice.

Crocq, L., Bugard, P., Viaud, P.

Psychologie Medicale 1978; 10: 1943-53 (in French).

No Abstract available.

Reversibility by L-carnitine of immunosuppression induced by an emulsion of soya bean oil, glycerol and egg lecithin.

De Simone C, Ferrari M, Meli D, Midiri G, Sorice F

Arzneimittelforschung 1982;32(11):1485-8

Experimental and clinical data appear to indicate that Intralipid--an emulsion of soya bean oil, glycerol and egg lecithin--which is usually employed to improve caloric intake of parenteral nutrition regimens, may compromise human host defence mechanisms and therefore expose patients to an increased incidence of infectious diseases. Since from a biochemical point of view it has been suggested that a possible way whereby the somewhat poor reputation of Intralipid--attributable to the liver damage and the persistent lipaemia which attend its use--might be improved is to give supplementary carnitine which acts as a rate-limiting factor in the removal of the fat emulsion from blood, we hypothesized that the addition of carnitine to Intralipid could also result in an improvement of the immune responses both "in vitro" and "in vivo". Our results lend some support to the hypothesis in favour of a metabolic basis for some of the immunosuppressive properties of Intralipid and justify the inclusion of L-carnitine in parenteral nutrition regimens which, by abrogating some co-factor limitation, improves the immune responses of the host.

Milk thistle (Silybum marianum) for the therapy of liver disease.

Flora K, Hahn M, Rosen H, Benner K. Division of Gastroenterology, Oregon Health Sciences University, Portland 97201-3098, USA.

Am J Gastroenterol 1998 Feb;93(2):139-43

Silymarin, derived from the milk thistle plant, *Silybum marianum*, has been used for centuries as a natural remedy for diseases of the liver and biliary tract. As interest in alternative therapy has emerged in the United States, gastroenterologists have encountered increasing numbers of patients taking silymarin with little understanding of its purported properties. Silymarin and its active constituent, silybin, have been reported to work as antioxidants scavenging free radicals and inhibiting lipid peroxidation. Studies also suggest that they protect against genomic injury, increase hepatocyte protein synthesis, decrease the activity of tumor promoters, stabilize mast cells, chelate iron, and slow calcium metabolism. In this article we review silymarin's history, pharmacology, and properties, and the clinical trials pertaining to patients with acute and chronic liver disease.

Anti-inflammatory and antipyretic activities of beta-sitosterol.

Gupta MB, Nath R, Srivastava N, Shanker K, Kishor K, Bhargava KP.

Planta Med 1980 Jun;39(2):157-63

No Abstract Available

Prayer and healing. A case study.

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J Holist Nurs 1997 Sep;15(3):318-24; discussion 325-6

This article examines the relationship between prayer and healing and its relationship to holistic health. The apparent healing that results from prayer mystifies researchers. Numerous theories may be offered as to the mechanism by which this healing occurs. The belief of the praying person in the power of the prayer itself may stimulate healing, as the placebo effect suggests. The relaxation response and the sense of self-efficacy gained through the act of praying may enhance the immune system. Despite these explanations of the mechanisms through which prayer promotes healing, there some-times exists a facet of prayer and

healing that defies rational explanation and seems to suggest the existence of a higher power. A case is presented that explores assistance from a higher power as a potential explanation for the healing.

L-theanine-a unique amino acid of green tea and its relaxation effect in humans.

Juneja, L.R. et al.

Trends Food Sci. Tech. 1999; 10: 199-204.

No Abstract available.

Adverse reactions to food constituents: allergy, intolerance, and autoimmunity.

Kitts D, Yuan Y, Juneja J, Scott F, Szilagyi A, Amiot J, Zarkadas M. Department of Food Science, University of British Columbia, Vancouver, Canada.

Can J Physiol Pharmacol 1997 Apr;75(4):241-54

Food allergies and intolerance represent important health concerns to consumers who are predisposed to these illnesses. Unlike many current food safety issues, food sensitivities are complicated by both complex and multiple individual adverse reactions, which can vary from emotional to pathophysiological ailments. In some instances, the underlying mechanisms that result in the development of food allergies or intolerance have marked differences but produce common symptoms. The present-day diagnosis of these disorders can be impeded by intrinsic limitations in generating accurate information from patient history and biochemical, physicochemical, and immunochemical tests. Oral challenge tests represent effective methods for confirming and testing food allergens and food intolerance; however, these procedures are often restricted to clinical trials. It is important to be able to distinguish among food allergy, intolerance, and autoimmune disease in the management of these disorders. The role of food in the development of autoimmune disease may be exemplified by celiac disease, a food-induced enteropathy, requiring exposure to prolamins in wheat, rye, and barley. Various wheat and soy protein sources, including the soy protein isolates used to make infant formulas, have been related to juvenile or insulin-dependent diabetes mellitus (IDDM), a common chronic disease of childhood. Employing food process technologies to eliminate food constituents with potential for intolerance in some individuals is a potentially viable approach for reducing risk to food-related disorders. Finally, the development of food labelling regulations that require the identification of potential food allergens or agents for intolerance in the ingredient declaration on prepackaged food is a positive step toward the prevention of severe adverse reactions in hypersensitive individuals.

The effects of active and passive participation in musical activity on the immune system as measured by salivary immunoglobulin A (SIgA).

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J Music Ther 2002 Spring;39(1):30-9

The purposes of this study were (a) to determine if musical activity would produce a significant change in the immune system as measured by Salivary Immunoglobulin A (SIgA), and (b) to determine if active participation in musical activity had a significantly different effect on the immune system than passive participation. Thirty-three participants (28 women and 5 men) were randomly assigned to one of 3 groups, 2 experimental and 1 control. Active group participants participated in a 30-minute session where they played various percussive instruments and sang. Passive group participants listened to 30 minutes worth of live music. Saliva samples were taken before and after sessions and SIgA concentrations were determined using radial immunodiffusion technique. All groups were found to be significantly different from each other. SIgA levels of the active group showed a significantly greater increase than those of the passive group and the control group, suggesting that active participation in musical activity produces a greater effect on the immune system than passive participation.

Psychological aspects of asthma.

Lehrer P, Feldman J, Giardino N, Song HS, Schmaling K. Department of Psychiatry, Robert Wood Johnson Medical School, Piscataway, New Jersey 08854, USA. lehrer@umdnj.edu

J Consult Clin Psychol 2002 Jun;70(3):691-711

Asthma can be affected by stress, anxiety, sadness, and suggestion, as well as by environmental irritants or allergens, exercise, and infection. It also is associated with an elevated prevalence of anxiety and depressive disorders. Asthma and these psychological states and traits may mutually potentiate each other through direct psychophysiological mediation, nonadherence to

medical regimen, exposure to asthma triggers, and inaccuracy of asthma symptom perception. Defensiveness is associated with inaccurate perception of airway resistance and stress-related bronchoconstriction. Asthma education programs that teach about the nature of the disease, medications, and trigger avoidance tend to reduce asthma morbidity. Other promising psychological interventions as adjuncts to medical treatment include training in symptom perception, stress management, hypnosis, yoga, and several biofeedback procedures.

Which complementary and alternative therapies benefit which conditions? A survey of the opinions of 223 professional organizations.

Long L, Huntley A, Ernst E. Department of Complementary Medicine, School of Postgraduate Medicine and Health Sciences, University of Exeter, UK.

Complement Ther Med 2001 Sep;9(3):178-85

With the increasing demand and usage of complementary/alternative medicine (CAM) by the general public, it is vital that healthcare professionals can make informed decisions when advising or referring their patients who wish to use CAM. Therefore they might benefit from advice by CAM-providers as to which treatment can be recommended for which condition. AIM: The primary aim of this survey was to determine which complementary therapies are believed by their respective representing professional organizations to be suited for which medical conditions.

METHOD: 223 questionnaires were sent out to CAM organizations representing a single CAM therapy. The respondents were asked to list the 15 conditions they felt benefited most from their CAM therapy, the 15 most important contra-indications, the typical costs of initial and any subsequent treatments and the average length of training required to become a fully qualified practitioner. The conditions and contra-indications quoted by responding CAM organizations were recorded and the top five of each were determined. Treatment costs and hours of training were expressed as ranges.

RESULTS: Of the 223 questionnaires sent out, 66 were completed and returned. Taking undelivered questionnaires into account, the response rate was 34%. Two or more responses were received from CAM organizations representing twelve therapies: aromatherapy, Bach flower remedies, Bowen technique, chiropractic, homoeopathy, hypnotherapy, magnet therapy, massage, nutrition, reflexology, Reiki and yoga. The top seven common conditions deemed to benefit by all twelve therapies, in order of frequency, were: stress/anxiety, headaches/migraine, back pain, respiratory problems (including asthma), insomnia, cardiovascular problems and musculoskeletal problems. Aromatherapy, Bach flower remedies, hypnotherapy, massage, nutrition, reflexology, Reiki and yoga were all recommended as suitable treatments for stress/anxiety. Aromatherapy, Bowen technique, chiropractic, hypnotherapy, massage, nutrition, reflexology, Reiki and yoga were all recommended for headache/migraine. Bowen technique, chiropractic, magnet therapy, massage, reflexology and yoga were recommended for back pain. None of the therapies cost more than £60 for an initial consultation and treatment. No obvious correlation between length of training and treatment cost was apparent.

CONCLUSION: The recommendations by CAM organizations responding to this survey may provide guidance to health care professionals wishing to advise or refer patients interested in using CAM.

A review of plants used in the treatment of liver disease: part 1.

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Altern Med Rev 1998 Dec;3(6):410-21

Botanicals have been used traditionally by herbalists and indigenous healers worldwide for the prevention and treatment of liver disease. Clinical research in this century has confirmed the efficacy of several plants in the treatment of liver disease. Basic scientific research has uncovered the mechanisms by which some plants afford their therapeutic effects. *Silybum marianum* (milk thistle) has been shown to have clinical applications in the treatment of toxic hepatitis, fatty liver, cirrhosis, ischemic injury, radiation toxicity, and viral hepatitis via its antioxidative, anti-lipid peroxidative, antifibrotic, anti-inflammatory, immunomodulating, and liver regenerating effects. *Picrorhiza kurroa*, though less well researched than *Silybum*, appears to have similar applications and mechanisms of action. When compared with *Silybum*, the hepatoprotective effect of *Picrorhiza* was found to be similar, or in many cases, superior to the effect of *Silybum*.

Thyroid and other organ-specific autoantibodies in healthy centenarians.

Mariotti S, Sansoni P, Barbesino G, Caturegli P, Monti D, Cossarizza A, Giacomelli T, Passeri G, Fagiolo U, Pinchera A, et al. Institute of Endocrinology, University of Pisa, Italy.

Lancet 1992 Jun 20;339(8808):1506-8

To investigate the prevalence of thyroid autoantibodies in very old subjects, we assayed sera from 34 healthy centenarians (7 men, 27 women; age range 100-108 years) for these antibodies. There was a clear age-dependent increase in prevalence of thyroid autoantibodies in sera from 549 control subjects aged 7-85 years, prevalence in 40 subjects aged 70-85 being significantly greater (p less than 0.001, χ^2) than that in 436 subjects aged less than 50. By contrast, prevalence of thyroid autoantibodies in centenarians was not significantly different from that in controls aged less than 50. Cytofluorimetric analysis of peripheral blood lymphocytes showed a striking age-dependent decrease in total and CD5+B cells (without changes in their ratio), which reached its nadir in centenarians. The age-dependent increase in prevalence of thyroid autoantibodies in the elderly is not seen after the ninth decade of life. What relation this characteristic has to derangement of circulating B cells is unknown.

Proteolysis, caloric restriction and aging.

Merker K, Stolzing A, Grune T. Neuroscience Research Center, Medical Faculty (Charite), Humboldt University Berlin, Schumannstr. 20/21, D-10098, Berlin, Germany.

Mech Ageing Dev 2001 May 31;122(7):595-615

The nature of the aging process has been the subject of considerable speculation. It is believed that free radical damage to cellular components is one of the main contributors to the aging process. Studies on proteins have shown age-related decline in enzyme activities, age-related accumulation of oxidized proteins and a decline of the proteolytic machinery of the cell. The proteasome, a highly regulated intracellular proteolytic system, is the major enzymatic system responsible for the degradation of damaged proteins. The current knowledge on regulation and of the properties of this unique proteolytic system with special emphasis to the aging process are discussed in this review. Since it is known that caloric restriction (CR) is the only method to delay the aging process and extend the maximal lifespan the effects of CR on the age-related decline in protein degradation is highlighted.

In vitro glycooxidation alters the interactions between collagens and human polymorphonuclear leucocytes.

Monboisse JC, Rittie L, Lamfarraj H, Garnotel R, Gillery P. Laboratoire de Biochimie Medicale et Biologie Moleculaire, CNRS UPRESA 6021, IFR-53 Biomolecules, Faculte de Medecine, University of Reims Champagne-Ardenne, 51095 Reims cedex, France. jc.monboisse@univ-reims.fr

Biochem J 2000 Sep 15;350 Pt 3:777-83

Glycation and glycooxidation processes, which are increased in diabetes mellitus, are generally considered causative mechanisms of long-term complications. With reference to our previous studies, type-I and -IV collagens could induce differentially the adhesion and stimulation of polymorphonuclear leucocytes (PMNs). As PMNs play a role in sustained diabetic oxidative stress, the present study was designed to determine whether in vitro glycooxidation of these macromolecules could alter PMN adhesion, activation and migration. The adhesion of PMNs to in vitro-glycooxidized collagens was significantly increased when compared with control collagens: +37% (< 0.05) and +99% (< 0.01) for collagens I and IV, respectively. Glycooxidized type-I collagen increased the chemotactic properties of PMNs without significant stimulatory effect on respiratory burst, whereas pre-incubation of PMNs with glycooxidized type-I collagen induced a priming on subsequent stimulation by N-formyl-methionyl-leucyl-phenylalanine. Glycooxidation of type-IV collagen suppressed its inhibitory effect on further PMN stimulation or migration. Collectively, these results indicate that glycooxidation of two major extracellular-matrix collagens considerably alters their ability to modulate PMN migration and production of reactive oxygen species. This imbalance in PMN metabolism may be a major event in the increased oxidative status that characterizes diabetes mellitus.

Some biological actions of alkylglycerols from shark liver oil.

Pugliese PT, Jordan K, Cederberg H, Brohult J. Karolinska Institute (Soderjukhuset), Stockholm, Sweden.

J Altern Complement Med 1998 Spring;4(1):87-99

Shark liver oil has been used for over 40 years as both a therapeutic and preventive agent. The active ingredients in shark liver oil have been found to be a group of ether-linked glycerols known as alkylglycerols. Initial clinical use was for treating leukemias, and later to prevent radiation sickness from cancer x-ray therapy. Studies over the last 30 years have shown that alkylglycerols are multifunctional. The level of natural alkylglycerols rises within tumor cells, apparently in an effort to control cell growth. Recent studies indicate that the activation of protein kinase C, an essential step in cell proliferation, can be inhibited by alkylglycerols. This action suggests a competitive inhibition of 1,2-diacylglycerol by alkylglycerols. Further studies on the immunostimulatory action of alkylglycerols suggest a primary action on the macrophage. The process of macrophage activation has been demonstrated with both synthetic and natural alkylglycerols. While the exact mechanism has not been found, both an autocrine and paracrine system have been suggested. Shark liver is a major natural source of alkylglycerols, which have no known side effects in dosages of 100 mg three times a day. The information presented in this article suggests that alkylglycerols may be used both as an adjunct

therapy in the treatment of neoplastic disorders and as an immune booster in infectious diseases.

Role of sugars in human neutrophilic phagocytosis.

Sanchez A, Reeser JL, Lau HS, Yahiku PY, Willard RE, McMillan PJ, Cho SY, Magie AR, Register UD

Am J Clin Nutr 1973 Nov;26(11):1180-4

No abstract.

Immunohistochemical distribution of the receptor for advanced glycation end products in neurons and astrocytes in Alzheimer's disease.

Sasaki N, Toki S, Chowei H, Saito T, Nakano N, Hayashi Y, Takeuchi M, Makita Z. Department of Neuropsychiatry, Sapporo Medical University, South 1, West 16, Chuo-ku, 060-8543, Sapporo, Japan. nsasaki@sapmed.ac.jp

Brain Res 2001 Jan 12;888(2):256-262

Advanced glycation end products (AGE) and the receptor for AGE (RAGE) have been implicated in the chronic complications of diabetes mellitus (DM), and have been reported to play an important role in the pathogenesis of Alzheimer's disease (AD). In this study, we established a polyclonal anti-RAGE antibody, and examined the immunohistochemical localization of amyloid beta protein (Abeta), AGE, and RAGE in neurons and astrocytes from patients with AD and DM. Our anti-RAGE antibody recognized full-length RAGE (50 kd) and N-terminal RAGE (35 kd) in human brain tissue. Abeta-, AGE-, and RAGE-positive granules were identified in the perikaryon of hippocampal neurons (especially from CA3 and CA4) in all subjects. The distribution and staining pattern of these immunopositive granules showed good concordance with each antibody. In AD, most astrocytes contained both AGE- and RAGE-positive granules and their distribution was almost the same. Abeta-positive granules were less common, but Abeta-, AGE-, and RAGE-positive granules were colocalized in one part of a single astrocyte. In DM patients and control cases, AGE- and RAGE-positive astrocytes were very rare. These findings support the hypothesis that glycated Abeta is taken up via RAGE and is degraded through the lysosomal pathway in astrocytes. In addition to the presence of AGE, the process of AGE degradation and receptor-mediated reactions may contribute to neuronal dysfunction and promote the progression of AD.

Protein oxidation and degradation during cellular senescence of human BJ fibroblasts: part II--aging of nondividing cells.

Sitte N, Merker K, Von Zglinicki T, Davies KJ, Grune T. Clinics of Physical Medicine and Rehabilitation, Humboldt University Berlin, Germany.

FASEB J 2000 Dec;14(15):2503-10

Oxidized/cross-linked intracellular protein materials, known as ceroid pigment, age pigment, or lipofuscin, accumulate in postmitotic tissues. It is unclear, however, whether diminishing proteolytic capacities play a role in the accumulation of such oxidized intracellular proteins. Previous studies revealed that the proteasome is responsible for the degradation of most oxidized soluble cytoplasmic and nuclear proteins and, we propose, for the prevention of such damage accumulations. The present investigation was undertaken to test the changes in protein turnover, proteasome activity, lysosome activity, and protein oxidation status during the aging of nondividing cells. Since the companion paper shows that both proteasome activity and the overall protein turnover decline during proliferative senescence whereas the accumulation of oxidized proteins increases significantly, we decided to use the same human BJ fibroblasts, this time at confluency, at different PD levels (including those that are essentially postmitotic) to investigate the same parameters under conditions where cells do not divide. We find that the activity of the cytosolic proteasome declines dramatically during senescence of nondividing BJ fibroblasts. The peptidyl-glutamyl-hydrolyzing activity was particularly affected. This decline in proteasome activity was accompanied by a decrease in the overall turnover of short-lived (radiolabeled) proteins in the nondividing BJ fibroblasts. On the other hand, no decrease in the actual cellular proteasome content, as judged by immunoblots, was found. The decline in the activity of the proteasome was also accompanied by an increased accumulation of oxidized proteins, especially of oxidized and cross-linked material. Unlike the loss of lysosomal function seen in our accompanying studies of proliferative senescence (1), however, the present study of hyperoxic senescence in nondividing cells actually revealed marked increases in lysosomal cathepsin activity in all but the very 'oldest' postmitotic cells. Our comparative studies of proliferating (1) and nonproliferating (this paper) human BJ fibroblasts reveal a good correlation between the accumulation of oxidized/cross-linked proteins and the decline in proteasome activity and overall cellular protein turnover during in vitro senescence, which may predict a causal relationship during actual cellular aging.

Protein oxidation and degradation during cellular senescence of human BJ fibroblasts: part I--effects of proliferative senescence.

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Oxidized and cross-linked proteins tend to accumulate in aging cells. Declining activity of proteolytic enzymes, particularly the proteasome, has been proposed as a possible explanation for this phenomenon, and direct inhibition of the proteasome by oxidized and cross-linked proteins has been demonstrated in vitro. We have further examined this hypothesis during both proliferative senescence (this paper) and postmitotic senescence (see the accompanying paper, ref 1) of human BJ fibroblasts. During proliferative senescence, we found a marked decline in all proteasome activities (trypsin-like activity, chymotrypsin-like activity, and peptidyl-glutamyl-hydrolyzing activity) and in lysosomal cathepsin activity. Despite the loss of proteasome activity, there was no concomitant change in cellular levels of actual proteasome protein (immunoassays) or in the steady-state levels of mRNAs for essential proteasome subunits. The decline in proteasome activities and lysosomal cathepsin activities was accompanied by dramatic increases in the accumulation of oxidized and cross-linked proteins. Furthermore, as proliferation stage increased, cells exhibited a decreasing ability to degrade the oxidatively damaged proteins generated by an acute, experimentally applied oxidative stress. Thus, oxidized and cross-linked proteins accumulated rapidly in cells of higher proliferation stages. Our data are consistent with the hypothesis that proteasome is progressively inhibited by small accumulations of oxidized and cross-linked proteins during proliferative senescence until late proliferation stages, when so much proteasome activity has been lost that oxidized proteins accumulate at ever-increasing rates. Lysosomes attempt to deal with the accumulating oxidized and cross-linked proteins, but declining lysosomal cathepsin activity apparently limits their effectiveness. This hypothesis, which may explain the progressive intracellular accumulation of oxidized and cross-linked proteins in aging, is further explored during postmitotic senescence in the accompanying paper (1).

Protein oxidation and degradation during proliferative senescence of human MRC-5 fibroblasts.

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One of the highlights of age-related changes of cellular metabolism is the accumulation of oxidized proteins. The aging process on a cellular level can be treated either as the ongoing proliferation until a certain number of cell divisions is reached (the Hayflick limit) or as the aging of nondividing cells, that is, the age-related changes in cells without proliferation. The present investigation was undertaken to reveal the changes in protein turnover, proteasome activity, and protein oxidation status during proliferative senescence. We were able to demonstrate that the activity of the cytosolic proteasomal system declines dramatically during the proliferative senescence of human MRC-5 fibroblasts. Regardless of the loss in activity, it could be demonstrated that there are no changes in the transcription and translation of proteasomal subunits. This decline in proteasome activity was accompanied by an increased concentration of oxidized proteins. Cells at higher proliferation stages were no longer able to respond with increased degradation of endogenous [(35)S]-Met-radiolabeled proteins after hydrogen peroxide- or quinone-induced oxidative stress. It could be demonstrated that oxidized proteins in senescent human MRC-5 fibroblasts are not as quickly removed as they are in young cells. Therefore, our study demonstrates that the accumulation of oxidized proteins and decline in protein turnover and activity of the proteasomal system are not only a process of postmitotic aging but also occur during proliferative senescence and result in an increased half-life of oxidized proteins.

Dysregulation of IL-10 production with aging: possible linkage to the age-associated decline in DHEA and its sulfated derivative.

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Peripheral lymphoid cells isolated from the spleens and peritoneal cavities of aged mice were found to constitutively secrete the multifunctional cytokine interleukin (IL)-10 when cultured in vitro. B-Lymphocytes were implicated as the cell type responsible. Abnormal expression of this cytokine was also detected in vivo because high levels of mRNA for IL-10 were present in splenocytes freshly isolated from aged animals. In addition to the spontaneous secretion of IL-10, lymphoid cells from aged donors were hyperresponsive to exogenous stimulation with endotoxin, producing exaggerated quantities of both IL-10 and IL-6 in culture. Treatment of aged animals with dehydroepiandrosterone sulfate (DHEAS), a natural steroid, reversed the age-associated alterations in cytokine production, rendering the treated mice quite similar to mature adult controls. DHEAS treatment of aged mice also resulted in a lowering in the number of B1 cells present in the peritoneal cavity and also reduced the titers of circulating autoantibodies specific for phosphatidylcholine (PtC). Based on its wide range of biologic activities, a dysregulation in the mechanisms that control IL-10 production could be a major contributor to immunosenescence. The ability of DHEAS treatment to

restore normal control over the expression of IL-10 may explain how this steroid enhances immunocompetence in aged animals.

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

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

Carnosine and anserine as modulators of neutrophil function.

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Clin Lab Haematol 1998 Aug;20(4):239-44

Carnosine and anserine, the bioactive peptides found in most meats and fish, were tested for their ability to modulate neutrophil and U937 cell function, specifically with respect to respiratory burst, interleukin-1 beta production and apoptosis. Both peptides increased the respiratory burst and interleukin-1 beta production of human neutrophils but not of U937 cells. They suppressed apoptosis of human neutrophils but enhanced apoptosis of U937 cells as assessed by DNA strand breaks. These results suggest that carnosine and anserine have the capacity to modulate the immune response at least in human neutrophils.

Low serum dehydroepiandrosterone sulfate in women with primary Sjogren's syndrome as an isolated sign of impaired HPA axis function.

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OBJECTIVE: To assess the hypothalamic-pituitary-adrenal (HPA) and thyroid axes in women with primary Sjogren's syndrome (pSS).

METHODS: In 10 women with pSS and 10 age matched female controls, we evaluated serum dehydroepiandrosterone sulfate (DHEA-S), testosterone, androstenedione, follicle stimulating hormone, luteinizing hormone, thyroid stimulating hormone, prolactin, growth hormone, sex hormone binding globulin, cortisol, and adrenocorticotropin hormone (ACTH), in both basal condition and after stimulation with corticotropin releasing hormone, thyrotropin releasing hormone, and luteinizing hormone releasing hormone intravenously. Patients had not previously been treated with glucocorticoids.

RESULTS: Patients with pSS had significantly lower basal mean DHEA-S values compared with healthy controls (2.4 ± 0.4 vs 3.9 ± 0.3 $\mu\text{mol/L}$; < 0.05) and significantly lower DHEA-S values after stimulation. The cortisol/DHEA-S ratio in the patient group was higher than in controls (171 ± 39 vs 76 ± 5 ; < 0.05). A correlation was found between basal ACTH and DHEA-S values in the patients ($r = 0.650$; $p = 0.05$). No correlation was seen between disease activity or age and the serum concentration of DHEA-S. The levels of other hormones both at baseline and after stimulation were similar in patients and controls.

CONCLUSION: The results show that women with pSS have intact cortisol synthesis but decreased serum concentrations of

DHEA-S and increased cortisol/DHEA-S ratio compared with healthy controls. The findings may reflect a constitutional or disease mediated influence on adrenal steroid synthesis. The thyroid axis and gonadotropin secretion were similar in patients and controls.

Yoga-based guided relaxation reduces sympathetic activity judged from baseline levels.

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35 male volunteers whose ages ranged from 20 to 46 years were studied in two sessions of yoga-based guided relaxation and supine rest. Assessments of autonomic variables were made for 15 subjects, before, during, and after the practices, whereas oxygen consumption and breath volume were recorded for 25 subjects before and after both types of relaxation. A significant decrease in oxygen consumption and increase in breath volume were recorded after guided relaxation (paired t test). There were comparable reductions in heart rate and skin conductance during both types of relaxation. During guided relaxation the power of the low frequency component of the heart-rate variability spectrum reduced, whereas the power of the high frequency component increased, suggesting reduced sympathetic activity. Also, subjects with a baseline ratio of LF/HF < 0.5 showed a significant decrease in the ratio after guided relaxation, while subjects with a ratio < or = 0.5 at baseline showed no such change. The results suggest that sympathetic activity decreased after guided relaxation based on yoga, depending on the baseline levels.

Effects of n 3 and n 6 fatty acids on the activities and expression of hepatic antioxidant enzymes in autoimmune prone NZBxNZW F1 mice

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Menhaden fish oil (FO) containing n 3 fatty acids dramatically extends the life span and delays the onset and progression of autoimmune disease in (NZBxNZW)F1 (B/W) female mice as compared to those fed corn oil (CO) rich in n 6 lipids. As an inefficient antioxidant defense system has been linked to autoimmune diseases, the present study was undertaken to determine whether the protective action of n 3 lipids is mediated through their antioxidant defense system. Weanling B/W mice were fed a nutritionally adequate, semipurified diet containing CO or krill oil (KO) or FO at 10% level (w/w) ad libitum until the mice were 6.5 months old. All diets contained the same level of vitamin E (21.5 mg/100 g diet). We compared the effects of feeding D 6 and n 3 lipids on survival, kidney disease, hepatic microsomal lipid composition, peroxidation, and on the activity and mRNA expression of the antioxidant enzymes catalase, glutathione peroxidase (GSH Px) and superoxide dismutase (SOD) in 6.5 month old B/W mice. The results showed that when compared to livers from CO fed mice, livers from KO and FO fed mice showed: (i) significantly higher (< 0.001) activities and expression of CAT, GSH Px and SOD; (ii) significantly lower (< 0.001) arachidonic acid (20:4n 6) and linoleic acid (18:2n 6) and higher (< 0.001) eicosapentaenoic acid (20:5n 3) and docosahexaenoic acid (22:6n 3) levels in hepatic microsomes; and (iii) significantly lower (< 0.001) estimated peroxidation indices and thiobarbituric acid reactive substances generation. The data indicate that one of the mechanisms through which the n 3 lipids delay the onset of autoimmune diseases in B/W mice may be through maintenance of higher activities and expression of hepatic antioxidant enzymes.

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