

## ABSTRACTS

### Vitamin D

#### **BENEFITS AND REQUIREMENTS OF VITAMIN D FOR OPTIMAL HEALTH: A REVIEW.**

Vitamin D sufficiency is required for optimal health. The conditions with strong evidence for a protective effect of vitamin D include several bone diseases, muscle weakness, more than a dozen types of internal cancers, multiple sclerosis, and type 1 diabetes mellitus. There is also weaker evidence for several other diseases and conditions. There are good reasons that vitamin D sufficiency be maintained during all stages of life, from fetal development to old age. Adequate calcium intake is also recommended. The current vitamin D requirements in the United States are based on protection against bone diseases. These guidelines are being revised upward in light of new findings, especially for soft-tissue health. The consensus of scientific understanding appears to be that vitamin D deficiency is reached for serum 25-hydroxyvitamin D (25OHD) levels less than 20 ng/mL (50 nmol/L), insufficiency in the range from 20-32 ng/mL, and sufficiency in the range from 33-80 ng/mL, with normal in sunny countries 54-90 ng/mL, and excess greater than 100 ng/mL. Solar ultraviolet-B (UVB) irradiation is the primary source of vitamin D for most people. In general, the health benefits accruing from moderate UV irradiation, without erythema or excess tanning, greatly outweigh the health risks, with skin pigmentation (melanin) providing much of the protection. In the absence of adequate solar UVB irradiation due to season, latitude, or lifestyle, vitamin D can be obtained from fortified food, oily fish, vitamin D supplements, and artificial sources of UVB radiation.

*Altern Med Rev.* 2005 Jun;10(2):94-111

#### **VITAMIN D AND VITAMIN D ANALOGS IN CANCER TREATMENT.**

The secosteroid hormone 1,25-dihydroxyvitamin D<sub>3</sub> (1,25-(OH)<sub>2</sub>D<sub>3</sub>) is a key player in the regulation of bone mineralization and calcium homeostasis. In addition, 1,25-(OH)<sub>2</sub>D<sub>3</sub> has antiproliferative and prodifferentiation effects on various cells in vitro and in vivo. The growth-inhibitory properties of 1,25-(OH)<sub>2</sub>D<sub>3</sub> could be harnessed in the treatment of cancer. However, its use as an anti-cancer drug is limited because of the calcemic effects of pharmacological doses. In an attempt to dissociate the antiproliferative and calcemic effects, numerous vitamin D<sub>3</sub> analogs were developed. The mechanisms by which 1,25-(OH)<sub>2</sub>D<sub>3</sub> and 1,25-(OH)<sub>2</sub>D<sub>3</sub> analogs exert their growth-inhibitory effects are not clear but include effects on cell differentiation, apoptosis, cell cycle regulation, metastases, and angiogenesis. In the current review aspects involved in the tumor suppressive activity of 1,25-(OH)<sub>2</sub>D<sub>3</sub> and 1,25-(OH)<sub>2</sub>D<sub>3</sub> analogs will be addressed. The use of vitamin D<sub>3</sub> compounds, alone or in combination with other drugs, in cancer treatment and the potential drawbacks will also be discussed.

*Curr Drug Targets.* 2002 Feb;3(1):85-94

#### **VITAMIN D AND PREVENTION OF COLORECTAL CANCER.**

**BACKGROUND:** Inadequate photosynthesis or oral intake of vitamin D are associated with high incidence rates of colorectal cancer, but the dose-response relationship has not been adequately studied.

**METHODS:** Dose-response gradients from observational studies of vitamin D intake and serum 25-hydroxyvitamin D were plotted as trend lines. The point on each linear trend line corresponding to an odds ratio of 0.50 provided the prediagnostic vitamin D intake or 25-hydroxyvitamin D concentration associated with 50% lower risk compared to <100IU/day vitamin D or <13ng/ml serum 25-hydroxyvitamin D. Medians of these values were determined.

**RESULTS:** Overall, individuals with  $\geq 1000$  IU/day oral vitamin D ( $p < 0.0001$ ) or  $\geq 33$  ng/ml (82 nmol/l) serum 25-hydroxyvitamin D ( $p < 0.01$ ) had 50% lower incidence of colorectal cancer compared to reference values.

**CONCLUSIONS:** Intake of 1000 IU/day of vitamin D, half the safe upper intake established by the National Academy of Sciences, was associated with 50% lower risk. Serum 25-hydroxyvitamin D of 33 ng/ml, which is known to be safe, also was associated with 50% lower risk. Prompt public health action is needed to increase intake of vitamin D(3) to 1000 IU/day, and to raise 25-hydroxyvitamin D by encouraging a modest duration of sunlight exposure.

## **THE EPIDEMIOLOGY OF VITAMIN D AND COLORECTAL CANCER: RECENT FINDINGS.**

**PURPOSE OF REVIEW:** To highlight the human studies published over the past year examining the influence of vitamin D on risk of colorectal cancer.

**RECENT FINDINGS:** Studies over the past year have added more support to the idea that higher levels of vitamin D may decrease risk of colorectal cancer. Further, typical dietary intakes such as 200-400 IU/day may be too low to exert appreciable benefits, and protection may occur with higher levels of vitamin D associated with exposure to sunshine. Recent studies also suggest a potential benefit of vitamin D on other digestive-tract cancers, and that vitamin D status at the time of diagnosis and treatment may influence survival of cancer. However, the evidence for these latter findings is based on limited data and needs to be confirmed. Higher vitamin D levels may also be associated with a higher rate of apoptosis in colorectal mucosa.

**SUMMARY:** Recent studies add more support to a potential role of vitamin D on risk of colorectal cancer, but suggest that intakes higher than customary are required if solar ultraviolet-B exposure is low. More studies are required to determine the optimal levels and intakes of this vitamin to reduce cancer risk. Potential benefits of vitamin D on other digestive-tract cancers and on survival in patients with colorectal cancer have been suggested by recent studies, but require confirmation.

*Curr Opin Gastroenterol.* 2006 Jan;22(1):24-29

## **THE ASSOCIATION OF CALCIUM AND VITAMIN D WITH RISK OF COLORECTAL ADENOMAS.**

The Polyp Prevention Trial (PPT) was a multicenter randomized clinical trial designed to determine the effects of a high-fiber, high-fruit and vegetable, low-fat diet on the recurrence of adenomatous polyps in the large bowel. Detailed dietary intake and supplement use data were collected at baseline and at each of 4 annual study visits. Adenoma recurrence was ascertained by complete colonoscopy at baseline and after 1 and 4 y. Recurrence was found in 754 of the 1,905 trial participants. We evaluated the association between calcium and vitamin D intake and adenomatous polyp recurrence after adjusting for intervention group, age, gender, nonsteroidal anti-inflammatory drug use, total energy intake, and the interaction of gender and intervention group. Vitamin D models were also adjusted for the location of the clinic site. Dietary variables were adjusted for total energy intake via the residual method. There were no overall significant associations between adenoma recurrence and dietary calcium intake [odds ratio (OR) for the 5th compared with the lowest quintile = 0.91; 95% CI = 0.67-1.23; P-trend = 0.68], total calcium intake (OR = 0.86; 95% CI = 0.62-1.18; P-trend = 0.20), or dietary vitamin D intake (OR = 0.93; 95% CI = 0.69-1.25; P-trend = 0.43) averaged over follow-up. Total vitamin D intake was weakly inversely associated with adenoma recurrence (OR = 0.84; 95% CI = 0.62-1.13; P-trend = 0.03). Supplemental calcium and vitamin D use during follow-up also were inversely associated with adenoma recurrence (OR for any compared with no use = 0.82; 95% CI = 0.68-0.99; and OR = 0.82; 95% CI = 0.68-0.99; for calcium and vitamin D, respectively). Slightly stronger associations were noted for the prevention of multiple recurrences. Our analyses did not suggest a significant effect modification between total calcium and total vitamin D intake (P = 0.14) on risk for adenoma recurrence. This trial cohort provides some evidence that calcium and vitamin D may be inversely associated with adenoma recurrence.

*J Nutr.* 2005 Feb;135(2):252-9

## **CLINICAL TRIALS INVOLVING VITAMIN D ANALOGS IN PROSTATE CANCER.**

Vitamin D shows significant potential as a therapy for prostate cancer. However, its use in clinical trials has been hampered by its induction of hypercalcemia at serum concentrations required to suppress cancer cell proliferation. This has spurred the development of less calcemic analogs of vitamin D. In this article, we review the clinical trials and consider the future directions of the use of vitamin D and its analogs in the treatment or chemoprevention of prostate cancer. First, we summarize the epidemiological evidence leading to the hypothesis that vitamin D has anticancer activity. We then review the clinical trials using vitamin D analogs that involve patients with prostate cancer and conclude with a brief overview of our planned study with vitamin D<sub>5</sub>, [1 $\alpha$ (OH)D<sub>5</sub>], which will begin shortly. Data for this review were identified by searches of PubMed, the Cochrane Library, Biosis, and references from relevant articles, using the search terms "vitamin D," "prostate cancer," "chemoprevention" and "vitamin D analog." Abstracts from recent international meetings were also reviewed but were only included when they were the only known reference to the clinical trial or the research mentioned.

*Cancer J.* 2005 Sep-Oct;11(5):362-73

## **SUN EXPOSURE, VITAMIN D RECEPTOR GENE POLYMORPHISMS, AND RISK OF ADVANCED PROSTATE CANCER.**

Substantial experimental evidence indicates that the hormonal form of vitamin D promotes the differentiation and inhibits the proliferation, invasiveness, and metastasis of human prostatic cancer cells. Results from epidemiologic studies of vitamin D status and/or vitamin D receptor (VDR) polymorphisms and prostate cancer risk have been mixed. We conducted a population-based, case-control study of advanced prostate cancer among men ages 40 to 79 years from the San Francisco Bay area. Interview data on lifetime sun exposure and other risk factors were collected for 905 non-Hispanic White men (450 cases and 455 controls). Using a reflectometer, we measured constitutive skin pigmentation on the upper underarm (a sun-protected site) and facultative pigmentation on the forehead (a sun-exposed site) and calculated a sun exposure index from these measurements. Biospecimens were collected for 426 cases and 440 controls. Genotyping was done for VDR polymorphisms in the 5' regulatory region (Cdx-2), exon 2 (FokI), and the 3' region (TaqI and BglI). Reduced risk of advanced prostate cancer was associated with high sun exposure determined by reflectometry [odds ratio (OR), 0.51; 95% confidence interval (95% CI), 0.33-0.80] and high occupational outdoor activity (OR, 0.73; 95% CI, 0.48-1.11). Significant risk reductions with the high-activity alleles FokI FF or Ff, TaqI tt, and BglI BB genotypes and a nonsignificant reduction with Cdx-2 AG or AA genotype were observed in the presence of high sun exposure, with ORs ranging from 0.46 to 0.67. Our findings support the hypothesis that sun exposure and VDR polymorphisms together play important roles in the etiology of prostate cancer.

*Cancer Res.* 2005 Jun 15;65(12):5470-9

### **PILOT STUDY: POTENTIAL ROLE OF VITAMIN D (CHOLECALCIFEROL) IN PATIENTS WITH PSA RELAPSE AFTER DEFINITIVE THERAPY.**

When local treatments for prostate cancer have failed, and prostate-specific antigen (PSA) rises in the absence of symptoms, there is little consensus as to the best management strategy. Calcitriol has been shown to prolong the doubling time of PSA in this context, but near-toxic doses are required. We investigated the effect of the nutrient vitamin D (cholecalciferol), a biochemical precursor of calcitriol, on PSA levels and the rate of rise of PSA in these patients. Fifteen patients were given 2,000 IU (50 microg) of cholecalciferol daily and monitored prospectively every 2-3 mo. In 9 patients, PSA levels decreased or remained unchanged after the commencement of cholecalciferol. This was sustained for as long as 21 mo. Also, there was a statistically significant decrease in the rate of PSA rise after administration of cholecalciferol ( $P = 0.005$ ) compared with that before cholecalciferol. The median PSA doubling time increased from 14.3 mo prior to commencing cholecalciferol to 25 mo after commencing cholecalciferol. Fourteen of 15 patients had a prolongation of PSA doubling time after commencing cholecalciferol. There were no side effects reported by any patient. Further study is needed to confirm this finding and to explore the potential therapeutic benefit of nutrient vitamin D in prostate cancer.

*Nutr Cancer.* 2005;51(1):32-6

### **PRENATAL AND PERINATAL CORRELATES OF ADULT MAMMOGRAPHIC BREAST DENSITY.**

**BACKGROUND:** Adult mammographic percent density is one of the strongest known risk factors for breast cancer. In utero exposure to high levels of endogenous estrogens (or other pregnancy hormones) has been hypothesized to increase breast cancer risk in later life. We examined the hypothesis that those factors associated with higher levels of estrogen during pregnancy or shortly after birth are associated with higher mammographic breast density in adulthood.

**METHODS:** We analyzed data on 1,893 women from 360 families in the Minnesota Breast Cancer Family Study who had screening mammograms, risk factor data, over age 40, and no history of breast cancer. Prenatal and perinatal risk factor data were ascertained using a mailed questionnaire. Mammographic percent density and dense area were estimated from the mediolateral oblique view using Cumulus, a computer-assisted thresholding program. Linear mixed effects models incorporating familial correlation were used to assess the association of risk factors with percent density, adjusting for age, weight, and other breast cancer risk factors, all at time of mammography.

**RESULTS:** The mean age at mammography was 60.4 years (range, 40-91 years), and 76% were postmenopausal. Among postmenopausal women, there was a positive association of birthweight with percent density ( $P$  trend  $< 0.01$ ), with an adjusted mean percent density of 17.1% for  $< 2.95$  kg versus 21.0% for  $\geq 3.75$  kg. There were suggestive positive associations with gestational age (mean percent density of 16.7% for preterm birth, 20.2% for term birth, and 23.0% for late birth;  $P$  trend = 0.07), maternal eclampsia/preeclampsia (mean percent density of 19.9% for no and 14.6% for yes;  $P = 0.16$ ), and being breast-fed as an infant (mean percent density of 18.2% for never and 20.0% for ever;  $P = 0.08$ ). There was no association of percent density with maternal age, birth order, maternal use of alcohol or cigarettes, or neonatal jaundice. Except for being breast-fed, these associations showed similar but attenuated trends among premenopausal women, although none were statistically significant. The results for dense area paralleled the percent density results. The associations of gestational age and being breast-fed as an infant with percent density attenuated when included in the same model as birthweight.

**CONCLUSIONS:** Birthweight was positively associated with mammographic breast density and dense area among postmenopausal women and more weakly among premenopausal women, suggesting that it may be a marker of this early life exposure. These results offer some support to the hypothesis that pregnancy estrogens or other pregnancy changes may play a

role in breast cancer etiology, and suggest that these factors may act in part through long-term effects on breast density.

*Cancer Epidemiol Biomarkers Prev.* 2005 Jun;14(6):1502-8

### **VITAMIN D IS ASSOCIATED WITH IMPROVED SURVIVAL IN EARLY-STAGE NON-SMALL CELL LUNG CANCER PATIENTS.**

Vitamin D may inhibit the development and progression of a wide spectrum of cancers. We investigated the associations of surgery season and vitamin D intake with recurrence-free survival (RFS) and overall survival in 456 early-stage non-small cell lung cancer patients. The data were analyzed using logrank test and Cox proportional hazards models. The median (range) follow-up time was 71 (0.1-140) months, with 161 recurrence and 231 deaths. Patients who had surgery in summer had a better RFS than those who had surgery in winter (adjusted hazard ratio, 0.75; 95% confidence interval, 0.56-1.01), with 5-year RFS rates of 53% (45-61%) and 40% (32-49%), respectively ( $P = 0.10$ , log-rank test). Similar association between surgery season and RFS was found among the 321 patients with dietary information ( $P = 0.33$ , log-rank test). There was no statistically significant association between vitamin D intake and RFS. Because both season and vitamin D intake are important predictors for vitamin D levels, we investigated the joint effects of surgery season and vitamin D intake. Patients who had surgery during summer with the highest vitamin D intake had better RFS (adjusted hazard ratio, 0.33; 95% confidence interval, 0.15-0.74) than patients who had surgery during winter with the lowest vitamin D intake, with the 5-year RFS rates of 56% (34-78%) and 23% (4-42%), respectively. Similar associations of surgery season and vitamin D intake with overall survival were also observed. In conclusion, the joint effects of surgery season and recent vitamin D intake seem to be associated with the survival of early-stage non-small cell lung cancer patients.

*Cancer Epidemiol Biomarkers Prev.* 2005 Oct;14(10):2303-9

## ABSTRACTS

### Cherries

#### **TART CHERRY ANTHOCYANINS SUPPRESS INFLAMMATION-INDUCED PAIN BEHAVIOR IN RATS.**

The use of complementary and alternative medicine (CAM) has increased in the United States and more patients are seeking CAM therapies for control of pain. The present investigation tested the efficacy of orally administered anthocyanins extracted from tart cherries on inflammation-induced pain behavior in rats. Paw withdrawal latency to radiant heat and paw withdrawal threshold to von Frey probes were measured. The first set of experiments examined the effects of tart cherry anthocyanins (400 mg/kg) on the nociceptive behaviors and edema associated with inflammation induced by intraplantar injection of 1% carrageenan. These studies also included tests of motor coordination. The second set of experiments determined if tart cherry anthocyanins (15, 85, and 400 mg/kg) dose-dependently affected the inflammation induced by intraplantar injection of 25% complete Freund's adjuvant. We found that tart cherry extracts reduce inflammation-induced thermal hyperalgesia, mechanical hyperalgesia and paw edema. The suppression of thermal hyperalgesia was dose-dependent and the efficacy of highest dose (400 mg/kg) was similar to indomethacin (5 mg/kg). The highest dose anthocyanin (400 mg/kg) had no effects on motor function. These data suggest that tart cherry anthocyanins may have a beneficial role in the treatment of inflammatory pain. The antihyperalgesic effects may be related to the anti-inflammatory and antioxidant properties of anthocyanins. A better understanding of the modulatory role of dietary constituents and phytonutrients on pain will offer further therapeutic options for treating patients with persistent and chronic pain conditions.

*Behav Brain Res.* 2004 Aug 12;153(1):181-8

#### **STRUCTURAL AND FUNCTIONAL CHARACTERIZATION OF POLYPHENOLS ISOLATED FROM ACEROLA (MALPIGHIA EMARGINATA DC.) FRUIT.**

Two anthocyanins, cyanidin-3-alpha-O-rhamnoside (C3R) and pelargonidin-3-alpha-O-rhamnoside (P3R), and quercitrin (quercetin-3-alpha-O-rhamnoside), were isolated from acerola (*Malpighia emarginata* DC.) fruit. These polyphenols were evaluated based on the functional properties associated with diabetes mellitus or its complications, that is, on the radical scavenging activity and the inhibitory effect on both alpha-glucosidase and advanced glycation end product (AGE) formation. C3R and quercitrin revealed strong radical scavenging activity. While the inhibitory profiles of isolated polyphenols except quercitrin towards alpha-glucosidase activity were low, all polyphenols strongly inhibited AGE formation.

*Biosci Biotechnol Biochem.* 2005 Feb;69(2):280-6

#### **ANTHOCYANIDINS INHIBIT CYCLOOXYGENASE-2 EXPRESSION IN LPS-EVOKED MACROPHAGES: STRUCTURE-ACTIVITY RELATIONSHIP AND MOLECULAR MECHANISMS INVOLVED.**

The effects of anthocyanidins, the aglycon nucleuses of anthocyanins widely occurring in reddish fruits and vegetables, on the expression of cyclooxygenase-2 (COX-2) were investigated in lipopolysaccharide (LPS)-activated murine macrophage RAW264 cells. Of five anthocyanidins, delphinidin and cyanidin inhibited LPS-induced COX-2 expression, but pelargonidin, peonidin and malvidin did not. The structure-activity relationship suggest that the ortho-dihydroxyphenyl structure of anthocyanidins on the B-ring appears to be related with the inhibitory actions. Delphinidin, the most potent inhibitor, caused a dose-dependent inhibition of COX-2 expression at both mRNA and protein levels. Western blotting analysis indicated that delphinidin inhibited the degradation of I $\kappa$ B-alpha, nuclear translocation of p65 and CCAAT/enhancer-binding protein (C/EBP) $\delta$  and phosphorylation of c-Jun, but not CRE-binding protein (CREB). Moreover, delphinidin suppressed the activations of mitogen-activated protein kinase (MAPK) including c-Jun N-terminal kinase (JNK), extracellular signalregulated kinase (ERK) and p38 kinase. MAPK inhibitors (U0126 for MEK1/2, SB203580 for p38 kinase and SP600125 for JNK) specifically blocked LPS-induced COX-2 expression. Thus, our results demonstrated that LPS-induced COX-2 expression by activating MAPK pathways and delphinidin suppressed COX-2 by blocking MAPK-mediated pathways with the attendant activation of nuclear factor-kappaB (NF-kappaB), activator protein-1 (AP-1) and C/EBP $\delta$ . These findings provide the first molecular basis that anthocyanidins with orthodihydroxyphenyl structure may have anti-inflammatory properties through the inhibition of MAPK-mediated COX-2 expression.

*Biochem Pharmacol.* 2005 Aug 1;70(3):417-25

#### **THE HUMAN PINEAL GLAND AND MELATONIN IN AGING AND ALZHEIMER'S DISEASE.**

The pineal gland is a central structure in the circadian system which produces melatonin under the control of the central clock,

the suprachiasmatic nucleus (SCN). The SCN and the output of the pineal gland, i.e. melatonin, are synchronized to the 24-hr day by environmental light, received by the retina and transmitted to the SCN via the retinohypothalamic tract. Melatonin not only plays an important role in the regulation of circadian rhythms, but also acts as antioxidant and neuroprotector that may be of importance in aging and Alzheimer's disease (AD). Circadian disorders, such as sleep-wake cycle disturbances, are associated with aging, and even more pronounced in AD. Many studies have reported disrupted melatonin production and rhythms in aging and in AD that, as we showed, are taking place as early as in the very first preclinical AD stages (neuropathological Braak stage I-II). Degeneration of the retina-SCN-pineal axis may underlie these changes. Our recent studies indicate that a dysfunction of the sympathetic regulation of pineal melatonin synthesis by the SCN is responsible for melatonin changes during the early AD stages. Reactivation of the circadian system (retina-SCN-pineal pathway) by means of light therapy and melatonin supplementation, to restore the circadian rhythm and to relieve the clinical circadian disturbances, has shown promising positive results.

*J Pineal Res.* 2005 Apr;38(3):145-52

### **ANTI-INFLAMMATORY ACTIONS OF MELATONIN AND ITS METABOLITES, N1-ACETYL-N2-FORMYL-5-METHOXYKYNURAMINE (AFMK) AND N1-ACETYL-5-METHOXYKYNURAMINE (AMK), IN MACROPHAGES.**

Inflammation is a complex phenomenon involving multiple cellular and molecular interactions which must be tightly regulated. Cyclooxygenase-2 (COX) is the key enzyme that catalyzes the two sequential steps in the biosynthesis of PGs from arachidonic acid. The inducible isoform of COX, namely COX-2, plays a critical role in the inflammatory response and its overexpression has been associated with several pathologies including neurodegenerative diseases and cancer. Melatonin is the main product of the pineal gland with well documented antioxidant and immuno-modulatory effects. Since the action of the indole on COX-2 has not been previously described, the goal of the present report was to test the effect of melatonin on the activities of COX-2 and inducible nitric oxide synthase (iNOS), using lipopolysaccharide (LPS)-activated RAW 264.7 macrophages as a model. Melatonin and its metabolites, N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK), prevented COX-2 activation induced by LPS, without affecting COX-1 protein levels. The structurally related compound 6-methoxymelatonin only partially prevented the increase in COX-2 protein levels induced by the toxin. Likewise melatonin prevented iNOS activation and reduced the concentration of products from both enzymes, PGE(2) and nitric oxide. Another endogenous antioxidant like N-acetyl-cysteine (NAC) did not reduced COX-2 significantly. The current finding corroborates a role of melatonin as an anti-inflammatory agent and, for the first time, COX-2 and iNOS as molecular targets for either melatonin or its metabolites AFMK and AMK. These anti-inflammatory actions seem not to be exclusively mediated by the free radical scavenging properties of melatonin. As a consequence, the present work suggests these substances as a new class of potential anti-inflammatory agents without the classical side effects due to COX-1 inhibition.

*J Neuroimmunol.* 2005 Aug;165(1-2):139-49

### **FAST ACCESS OF SOME GRAPE PIGMENTS TO THE BRAIN.**

Anthocyanins represent the main flavonoid pigments in red grape and wine, in red berries, and in many other fruits and vegetables and are widespread in the human diet. After ingestion, these complex, hydrophilic compounds quickly appear as intact molecules in the plasma. This study investigated their presence in the brain of anesthetized rats that received 8 mg/kg of body weight of a pure anthocyanin mixture extracted from *Vitis vinifera* grapes. The mixture was maintained in the stomach for 10 min. After this time, intact anthocyanins were detected by HPLC-DAD-MS not only in the plasma (176.4 +/- 50.5 ng/mL, mean +/- SEM) but also in the brain (192.2 +/- 57.5 ng/g). These results demonstrate for the first time that grape pigments can reach the mammalian brain within minutes from their introduction into the stomach.

*J Agric Food Chem.* 2005 Sep 7;53(18):7029-34

### **EFFECT OF MURAGLITAZAR ON DEATH AND MAJOR ADVERSE CARDIOVASCULAR EVENTS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS.**

**CONTEXT:** Peroxisome proliferator-activated receptors (PPARs) are nuclear transcription factors that modulate gene expression. Therapeutic agents targeting 2 distinct families of PPARs (alpha and gamma) have been introduced in the United States. The first dual-PPAR agonist, muraglitazar, was reviewed by a US Food and Drug Administration (FDA) advisory committee on September 9, 2005, resulting in a vote of 8:1 recommending approval for its use in controlling blood glucose levels in patients with type 2 diabetes.

**OBJECTIVE:** To evaluate the incidence of death, myocardial infarction (MI), stroke, congestive heart failure (CHF), and transient ischemic attack (TIA) in diabetic patients treated with muraglitazar compared with controls.

**DESIGN, SETTING, AND PARTICIPANTS:** The source material for this analysis consisted of documents about phase 2 and 3 clinical trials released under public disclosure laws for the FDA advisory committee meeting. All reviewed trials were prospective,

randomized, doubleblind, multicenter studies enrolling patients with type 2 diabetes and hemoglobin A(1c) levels between 7% and 10%. Patients (N = 3725) were randomized to receive differing doses of muraglitazar, pioglitazone, or placebo as monotherapy or in combination with metformin or glyburide in trials ranging from 24 to 104 weeks.

**MAIN OUTCOME MEASURES:** The primary outcome was the incidence of death, nonfatal MI, or nonfatal stroke. A more comprehensive composite outcome included these events plus the incidence of CHF and TIA.

**RESULTS:** In the muraglitazar-treated patients, death, MI, or stroke occurred in 35 of 2374 (1.47%) patients compared with 9 of 1351 (0.67%) patients in the combined placebo and pioglitazone treatment groups (controls) (relative risk [RR], 2.23; 95% confidence interval [CI], 1.07-4.66; P = .03). For the more comprehensive outcome measure that included TIA and CHF, the incidence was 50 of 2374 (2.11%) for muraglitazar compared with 11 of 1351 (0.81%) for controls (RR, 2.62; 95% CI, 1.36-5.05; P = .004). Relative risks for each of the individual components of the composite end point exceeded 2.1 but were not statistically significant. Incidence of adjudicated CHF was 13 of 2374 (0.55%) muraglitazar-treated patients and 1 of 1351 controls (0.07%) (RR, 7.43; 95% CI, 0.97-56.8; P = .053).

**CONCLUSIONS:** Compared with placebo or pioglitazone, muraglitazar was associated with an excess incidence of the composite end point of death, major adverse cardiovascular events (MI, stroke, TIA), and CHF. This agent should not be approved to treat diabetes based on laboratory end points until safety is documented in a dedicated cardiovascular events trial.

*JAMA.* 2005 Nov 23;294(20):2581-6

### **ANTHOCYANINS IN AGED BLUEBERRY-FED RATS ARE FOUND CENTRALLY AND MAY ENHANCE MEMORY.**

Research has shown that fruits and vegetables containing high levels of polyphenolics (flavonoids) display high total antioxidant activity. Our laboratory found that various fruit and vegetable extracts, particularly blueberry (BB), were effective in reversing age-related deficits in neuronal signaling and behavioral parameters following 8 weeks of feeding, possibly due to their polyphenolic content. However, it was unclear if these phytonutrients were able to directly access the brain from dietary BB supplementation (BBS). The present study examined whether different classes of polyphenols could be found in brain areas associated with cognitive performance following BBS. Thus, 19 month old F344 rats were fed a control or 2% BB diet for 8-10 weeks and tested in the Morris water maze (MWM), a measure of spatial learning and memory. LCMS analyses of anthocyanins in the diet and subsequently in different brain regions of BBS and control rats were carried out. Several anthocyanins (cyanidin-3-O-beta-galactoside, cyanidin-3-O-beta-glucoside, cyanidin-3-O-beta-arabinose, malvidin-3-O-beta-galactoside, malvidin-3-O-beta-glucoside, malvidin-3-O-beta-arabinose, peonidin-3-O-beta-arabinose and delphinidin-3-O-beta-galactoside) were found in the cerebellum, cortex, hippocampus or striatum of the BBS rats, but not the controls. These findings are the first to suggest that polyphenolic compounds are able to cross the blood brain barrier and localize in various brain regions important for learning and memory. Correlational analyses revealed a relationship between MWM performance in BBS rats and the total number of anthocyanin compounds found in the cortex. These findings suggest that these compounds may deliver their antioxidant and signaling modifying capabilities centrally.

*Nutr Neurosci.* 2005 Apr;8(2):111-20

### **RISK OF DEMENTIA AND ALCOHOL AND WINE CONSUMPTION: A REVIEW OF RECENT RESULTS.**

The term dementia refers to a clinical syndrome of acquired intellectual disturbances produced by brain dysfunction. Dementia may result from a wide variety of disorders, including degenerative (e.g. Alzheimer's disease, AD), vascular (e.g. multi-infarct dementia), and traumatic (e.g. head injury). Long-term abuse of alcohol is related to the development of the Wernicke-Korsakoff's syndrome or alcohol dementia. However, light to moderate alcohol intake might also reduce the risk of dementia and AD. In Bordeaux (France), a populationbased prospective study found that subjects drinking 3 to 4 standard glasses of wine per day (> 250 and up to 500 ml), categorized as moderate drinkers, the crude odds ratio (OR) was 0.18 for incident dementia (p < 0.01) and 0.25 for Alzheimer's disease (p < 0.03), as compared to the non-drinkers. After adjusting for age, sex, education, occupation, baseline cognitive performances and other possible confounders, the ORs were respectively 0.19 (p < 0.01) and 0.28 (p < 0.05). In the 922 mild drinkers (< 1 to 2 glasses per day) there was a negative association only with AD. after adjustment (OR = 0.55; p < 0.05). The inverse relationship between moderate wine drinking and incident dementia was explained neither by known predictors of dementia nor by medical, psychological or socio-familial factors. These results were confirmed from data of the Rotterdam study. Light-to-moderate drinking (one to three drinks per day) was significantly associated with a lower risk of any dementia (hazard ratio 0.58 [95% CI 0.38-0.90]) and vascular dementia (hazard ratio 0.29 [0.09-0.93]). No evidence that the relation between alcohol and dementia varied by type of alcoholic beverage was found. Stroke constitutes one of the most common causes of serious functional impairment in developed countries. Ischaemic strokes represent about 80% of all strokes. Several studies have been published and the overall conclusion is that heavy drinking is a risk factor for most stroke subtypes. Regular light to moderate drinking seemed to be associated with a decreased risk for ischaemic stroke.

*Biol Res.* 2004;37(2):189-93

## **MELATONIN INHIBITS NEURAL APOPTOSIS INDUCED BY HOMOCYSTEINE IN HIPPOCAMPUS OF RATS VIA INHIBITION OF CYTOCHROME C TRANSLOCATION AND CASPASE-3 ACTIVATION AND BY REGULATING PRO- AND ANTI-APOPTOTIC PROTEIN LEVELS.**

In the present study, we examined the molecular mechanism by which homocysteine causes neuronal cell apoptosis. We further investigated the mechanisms of melatonin's ability to reduce homocysteine-induced apoptosis. Consistent with its antioxidant properties, melatonin reduced homocysteine-induced lipid peroxidation and stimulated glutathione peroxidase enzyme activity in hippocampus of rats with hyperhomocysteinemia. Furthermore, melatonin treatment diminished cytochrome c release from mitochondria and reduced caspase 3 and caspase 9 activation induced by hyperhomocysteinemia. Chronic hyperhomocysteinemia also led to poly(ADP-ribose) polymerase cleavage and subsequently DNA fragmentation. Treatment with melatonin markedly inhibited poly(ADP-ribose) polymerase cleavage and reduced DNA damage. Hyperhomocysteinemia caused an elevation of pro-apoptotic Bax levels while reducing anti-apoptotic protein, Bcl-2, levels. Daily administration of melatonin up-regulated Bcl-2 and down-regulated Bax levels. We propose that, in addition to its antioxidant properties, melatonin has the ability to protect neuronal cells against apoptosis mediated homocysteine neurotoxicity by modulating apoptosis-regulatory proteins in the hippocampus of rats.

*Neuroscience*. 2005;135(3):879-86

## **PROTECTIVE ACTIVITY OF TOMATO PRODUCTS ON IN VIVO MARKERS OF LIPID OXIDATION.**

**BACKGROUND:** It has been suggested that regular consumption of tomato products improves antioxidant defenses due to their endogenous antioxidant compounds, notably lycopene.

**AIM OF THE STUDY:** We evaluated the effects of tomato consumption on parameters of lipid oxidation in healthy human volunteers.

**METHODS:** Twelve females (enrolled at T-7), after a one-week of carotenoid-poor diet (T0), were instructed to supplement the same diet with different tomato products (raw, sauce, and paste), thereby providing approximately eight mg lycopene/day for three weeks (T21). Blood samples were periodically collected in order to evaluate plasma carotenoid concentrations, plasma antioxidant capacity, and susceptibility of LDL to metal ion-induced oxidation. Furthermore, 8-iso-PGF(2 $\alpha$ ), a marker of in vivo oxidative stress, was analyzed in the 24-hour urine.

**RESULTS:** Carotenoid concentrations decreased significantly during the carotenoid-poor diet ( $P < 0.05$ ), while lycopene concentrations increased significantly after tomato consumption ( $P < 0.001$ ). The antioxidant capacity of plasma did not vary during the study. Conversely, LDL oxidizability decreased after tomato consumption, as demonstrated by a shortening of the lag phase ( $P < 0.001$ ). This parameter was significantly correlated with lycopene concentration ( $r = 0.36$ ,  $P < 0.05$ ). The excretion of 8-iso-PGF(2 $\alpha$ ) in urine was also significantly lower (-53%,  $P < 0.05$  compared with T0) after tomato supplementation.

**CONCLUSIONS:** These results further support a role for tomato products in the prevention of lipid peroxidation, a risk factor of atherosclerosis and cardiovascular disease.

*Eur J Nutr*. 2003 Aug;42(4):201-6

## ABSTRACTS

### Tissue Regeneration

#### **EMBRYONIC AND EXTRAEMBRYONIC STEM CELL LINES DERIVED FROM SINGLE MOUSE BLASTOMERES.**

The most basic objection to human embryonic stem (ES) cell research is rooted in the fact that ES cell derivation deprives embryos of any further potential to develop into a complete human being. ES cell lines are conventionally isolated from the inner cell mass of blastocysts and, in a few instances, from cleavage stage embryos. So far, there have been no reports in the literature of stem cell lines derived using an approach that does not require embryo destruction. Here we report an alternative method of establishing ES cell lines-using a technique of single-cell embryo biopsy similar to that used in preimplantation genetic diagnosis of genetic defects-that does not interfere with the developmental potential of embryos. Five putative ES and seven trophoblast stem (TS) cell lines were produced from single blastomeres, which maintained normal karyotype and markers of pluripotency or TS cells for up to more than 50 passages. The ES cells differentiated into derivatives of all three germ layers in vitro and in teratomas, and showed germ line transmission. Single-blastomerebiopsied embryos developed to term without a reduction in their developmental capacity. The ability to generate human ES cells without the destruction of ex utero embryos would reduce or eliminate the ethical concerns of many. *Nature*. 2005 Oct 16 Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury. Demyelination contributes to loss of function after spinal cord injury, and thus a potential therapeutic strategy involves replacing myelin-forming cells. Here, we show that transplantation of human embryonic stem cell (hESC)-derived oligodendrocyte progenitor cells (OPCs) into adult rat spinal cord injuries enhances remyelination and promotes improvement of motor function. OPCs were injected 7 d or 10 months after injury. In both cases, transplanted cells survived, redistributed over short distances, and differentiated into oligodendrocytes. Animals that received OPCs 7 d after injury exhibited enhanced remyelination and substantially improved locomotor ability. In contrast, when OPCs were transplanted 10 months after injury, there was no enhanced remyelination or locomotor recovery. These studies document the feasibility of predifferentiating hESCs into functional OPCs and demonstrate their therapeutic potential at early time points after spinal cord injury.

*J Neurosci*. 2005 May 11;25(19):4694-705

#### **ALTERED CNS RESPONSE TO INJURY IN THE MRL/MPJ MOUSE.**

The MRL/MpJ mouse has a greatly enhanced healing response and an absence of scarring compared with other mouse strains. Following lesions to the CNS mammals show a scarring response known as reactive gliosis, and this CNS scar tissue blocks regeneration of cut axons. We have therefore compared reactive gliosis in the MRL/MpJ mouse and the Swiss Webster mouse, which exhibits normal scarring in the periphery. The lesion model was a stab lesion to the cortex, in which reactive gliosis has previously been quantified. Axon regeneration was examined following a cut lesion to the dopaminergic projection from the substantia nigra to the striatum used in previous regeneration experiments. In the MRL/MpJ following the lesion compared with Swiss Webster mice there was greater cell loss around the lesion followed by greater and more widespread and more prolonged cellular proliferation. Early after the lesion there was a greater loss of glial fibrillary acidic protein (GFAP)-positive astrocytes around the injury site in the MRL/MpJ, and an enhancement and prolongation of the microglial inflammatory response. This was accompanied by greater and more widespread blood-brain barrier leakage following injury. RNA levels for the matrix metalloproteinases (MMP)-2 and MMP-9 as well as for the thrombin receptors PAR-1 and PAR-4 were also greater at the MRL/MpJ injury site. All of these differences were transient and by 14 days post-injury there were no differences observed between MRL/MpJ and control mice. No axonal regeneration was observed following axotomy to the nigrostriatal pathway of the MRL/MpJ or the Swiss Webster mice at any time point.

*Neuroscience*. 2004;127(4):821-32

#### **HEART VALVE TISSUE ENGINEERING.**

Tissue-engineered heart valves have been proposed by physicians and scientists alike to be the ultimate solution for treating valvular heart disease. Rather than replacing a diseased or defective native valve with a mechanical or animal tissue-derived artificial valve, a tissue-engineered valve would be a living organ, able to respond to growth and physiological forces in the same way that the native aortic valve does. Two main approaches have been attempted over the past 10 to 15 years: regeneration and repopulation. Regeneration involves the implantation of a resorbable matrix that is expected to remodel in vivo and yield a functional valve composed of the cells and connective tissue proteins of the patient. Repopulation involves implanting a whole porcine aortic valve that has been previously cleaned of all pig cells, leaving an intact, mechanically sound connective tissue matrix. The cells of the patients are expected to repopulate and revitalize the acellular matrix, creating living tissue that already has the complex microstructure necessary for proper function and durability. Regrettably, neither of the 2 approaches has fared

well in animal experiments, and the only clinical experience with tissue-engineered valves resulted in a number of early failures and patient death. This article reviews the technological details of the 2 main approaches, their rationale, their strengths and weaknesses, and the likely mechanisms for their failure. Alternative approaches to valvular tissue engineering, as well as the role of industry in shaping this field in the future, are also reviewed.

*Circ Res.* 2005 Oct 14;97(8):743-55

### **THE MRL MOUSE HEART HEALING RESPONSE SHOWS DONOR DOMINANCE IN ALLOGENEIC FETAL LIVER CHIMERIC MICE.**

We previously demonstrated that after a severe cryoinjury to the right ventricle of the heart, adult MRL mice display structural and functional recovery with myocardial tissue replacement resembling that seen in amphibians. The control non-regenerating adult C57BL/6 (B6) mouse shows a predominant scar response. In the present study, radiation chimeras reconstituted with fetal liver cells from either healer MRL or nonhealer B6 mice were generated to test for a transfer of phenotype. Allogeneic MRL fetal liver cells were injected into x-irradiated (9 Gy) B6 mice and B6 fetal liver cells were injected into x-irradiated MRL mice. In these allogeneic chimeras, the healing response to cardiac cryoinjury was predominantly of the donor phenotype. Thus, MRL fetal liver cells transferred the healing phenotype to the B6 nonhealer with the appearance of Y-chromosome positive, donor-derived cardiomyocytes in the injury site and MRL-like healing with little scar. Similarly, B6 fetal liver cells transferred the nonhealing phenotype to the MRL with little cardiomyocyte growth and an acellular B6-like scar. These results are in contrast to the ear hole closure response which was of the recipient phenotype. We conclude that, in the case of the heart, fetal liver-derived stem cells regulate regenerative healing.

*Cloning Stem Cells.* 2004;6(4):352-63

### **THE SCARLESS HEART AND THE MRL MOUSE.**

The ability to regenerate tissues and limbs in its most robust form is seen in many non-mammalian species. The serendipitous discovery that the MRL mouse has a profound capacity for regeneration in some ways rivalling the classic newt and axolotl species raises the possibility that humans, too, may have an innate regenerative ability. The adult MRL mouse regrows cartilage, skin, hair follicles and myocardium with near perfect fidelity and without scarring. This is seen in the ability to close through-and-through ear holes, which are generally used for lifelong identification of mice, and the anatomic and functional recovery of myocardium after a severe cryo-injury. We present histological, biochemical and genetic data indicating that the enhanced breakdown of scar-like tissue may be an underlying factor in the MRL regenerative response. Studies as to the source of the cells in the regenerating MRL tissue are discussed. Such studies appear to support multiple mechanisms for cell replacement.

*Philos Trans R Soc Lond B Biol Sci.* 2004 May 29;359(1445):785-93

### **A NEW MURINE MODEL FOR MAMMALIAN WOUND REPAIR AND REGENERATION.**

Regeneration is generally considered to be a phenomenon restricted to amphibians in which amputated limbs reform and regrow. We have recently noted a strain of mouse, the MRL, which displays a remarkable capacity for cartilagenous wound closure and provides an example of a phenomenon previously considered to be a form of regeneration. Specifically, through-and-through ear punches rapidly attain full closure with normal tissue architecture reminiscent of regeneration seen in amphibians as opposed to scarring, as usually seen in mammals. Histologically, we have demonstrated normal cell growth and microanatomy, including angiogenesis and chondrogenesis, as opposed to control C57BL/6 mice which have ear holes that contract minimally but do not close. Finally, this phenomenon is a genetically definable quantitative trait.

*Clin Immunol Immunopathol.* 1998 Jul;88(1):35-45

### **ANGIOGENESIS IN ISCHAEMIC MYOCARDIUM BY INTRAMYOCARDIAL AUTOLOGOUS BONE MARROW MONONUCLEAR CELL IMPLANTATION.**

Results of experimental studies have shown that intramyocardial implantation of bone marrow cells induces neovascularisation and improves heart function after myocardial infarction. Our aim was to test this notion in people. We implanted autologous mononuclear bone marrow cells into the ischaemic myocardium of eight patients with severe ischaemic heart disease as guided by electromechanical mapping with a percutaneous catheter procedure. After 3 months of follow-up, there was improvement in symptoms, myocardial perfusion, and function at the ischaemic region on MRI. Future randomised, controlled studies are required to validate this initial encouraging result.

*Lancet.* 2003 Jan 4;361(9351):47-9

## **INTRACORONARY AUTOLOGOUS BONE-MARROW CELL TRANSFER AFTER MYOCARDIAL INFARCTION: THE BOOST RANDOMIZED CONTROLLED CLINICAL TRIAL.**

**BACKGROUND:** Emerging evidence suggests that stem cells and progenitor cells derived from bone marrow can be used to improve cardiac function in patients after acute myocardial infarction. In this randomised trial, we aimed to assess whether intracoronary transfer of autologous bone-marrow cells could improve global leftventricular ejection fraction (LVEF) at 6 months' follow-up.

**METHODS:** After successful percutaneous coronary intervention (PCI) for acute ST-segment elevation myocardial infarction, 60 patients were randomly assigned to either a control group (n=30) that received optimum postinfarction medical treatment, or a bone-marrow-cell group (n=30) that received optimum medical treatment and intracoronary transfer of autologous bone-marrow cells 4.8 days (SD 1.3) after PCI. Primary endpoint was global leftventricular ejection fraction (LVEF) change from baseline to 6 months' follow-up, as determined by cardiac MRI. Image analyses were done by two investigators blinded for treatment assignment. Analysis was per protocol.

**FINDINGS:** Global LVEF at baseline (determined 3.5 days [SD 1.5] after PCI) was 51.3 (9.3%) in controls and 50.0 (10.0%) in the bone-marrow cell group (p=0.59). After 6 months, mean global LVEF had increased by 0.7 percentage points in the control group and 6.7 percentage points in the bone-marrow-cell group (p=0.0026). Transfer of bone-marrow cells enhanced left-ventricular systolic function primarily in myocardial segments adjacent to the infarcted area. Cell transfer did not increase the risk of adverse clinical events, in-stent restenosis, or proarrhythmic effects.

**INTERPRETATION:** Intracoronary transfer of autologous bone-marrow-cells promotes improvement of left-ventricular systolic function in patients after acute myocardial infarction.

*Lancet.* 2004 Jul 10-16;364(9429):141-8

## ABSTRACTS

### Whey Protein

#### **CASEIN AND WHEY EXERT DIFFERENT EFFECTS ON PLASMA AMINO ACID PROFILES, GASTROINTESTINAL HORMONE SECRETION AND APPETITE.**

Protein, generally agreed to be the most satiating macronutrient, may differ in its effects on appetite depending on the protein source and variation in digestion and absorption. We investigated the effects of two milk protein types, casein and whey, on food intake and subjective ratings of hunger and fullness, and on postprandial metabolite and gastrointestinal hormone responses. Two studies were undertaken. The first study showed that energy intake from a buffet meal ad libitum was significantly less 90 min after a 1700 kJ liquid preload containing 48 g whey, compared with an equivalent casein preload ( $P < 0.05$ ). In the second study, the same whey preload led to a 28 % increase in postprandial plasma amino acid concentrations over 3 h compared with casein (incremental area under the curve (iAUC),  $P < 0.05$ ). Plasma cholecystikinin (CCK) was increased by 60% (iAUC,  $P < 0.005$ ), glucagon-like peptide (GLP)-1 by 65% (iAUC,  $P < 0.05$ ) and glucose-dependent insulinotropic polypeptide by 36% (iAUC,  $P < 0.01$ ) following the whey preload compared with the casein. Gastric emptying was influenced by protein type as evidenced by differing plasma paracetamol profiles with the two preloads. Greater subjective satiety followed the whey test meal ( $P < 0.05$ ). These results implicate post-absorptive increases in plasma amino acids together with both CCK and GLP-1 as potential mediators of the increased satiety response to whey and emphasise the importance of considering the impact of protein type on the appetite response to a mixed meal.

*Br J Nutr.* 2003 Feb;89(2):239-48

#### **A HIGH-WHEY-PROTEIN DIET REDUCES BODY WEIGHT GAIN AND ALTERS INSULIN SENSITIVITY RELATIVE TO RED MEAT IN WISTAR RATS.**

A high-protein diet can reduce body weight and increase insulin sensitivity, but whether the type of dietary protein affects these outcomes is unknown. We hypothesized that feeding insulin-resistant rats a high-protein diet (32%) containing whey protein concentrate (WPC) would reduce body weight and tissue lipid levels and increase insulin sensitivity more than a diet containing red meat (RM). Rats were fed a high-fat diet (300 g fat/kg diet) for 9 wk, then switched to a diet containing either 80 or 320 g protein/kg diet, provided by either WPC or RM, for 6 wk ( $n = 8$ ). The rats were then killed after overnight food deprivation. High dietary protein reduced energy intake ( $P < 0.001$ ) and visceral ( $P < 0.001$ ), subcutaneous ( $P < 0.001$ ), and carcass fat ( $P < 0.05$ ). Increasing the dietary density of WPC, but not of RM, reduced body weight gain by 4% ( $P < 0.001$ ). Dietary WPC also reduced plasma insulin concentration by 40% ( $P < 0.05$ ) and increased insulin sensitivity, compared to RM ( $P < 0.05$ ). These findings support the conclusions that a high-protein diet reduces energy intake and adiposity and that whey protein is more effective than red meat in reducing body weight gain and increasing insulin sensitivity.

*J Nutr.* 2004 Jun;134(6):1454-8

#### **A PREEXERCISE ALPHALACTALBUMIN-ENRICHED WHEY PROTEIN MEAL PRESERVES LIPID OXIDATION AND DECREASES ADIPOSITY IN RATS.**

The composition of the preexercise food intake is known to affect substrate utilization during exercise and thus can affect long-term changes in body weight and composition. These parameters were measured in male rats exercised 2 h daily over 5 wk, either in the fasting state or 1 h after they ingested a meal enriched with glucose (Glc), whole milk protein (WMP), or alpha-lactalbumin-enriched whey protein (CPalphaL). Compared with fasting, the Glc meal increased glucose oxidation and decreased lipid oxidation during and after exercise. In contrast, the WMP and CPalphaL meals preserved lipid oxidation and increased protein oxidation, the CPalphaL meal increasing protein oxidation more than the WMP meal. At the end of the study, body weight was larger in the WMP-, Glc, and CPalphaL-fed rats than in the fasted ones. This resulted from an increased fat mass in the WMP and Glc rats and to an increased lean body mass, particularly muscles, in the CPalphaL rats. We conclude that the potential of the CPalphaL meal to preserve lipid oxidation and to rapidly deliver amino acids for use during exercise improved the efficiency of exercise training to decrease adiposity.

*Am J Physiol Endocrinol Metab.* 2002 Sep;283(3):E565-72

#### **THE BOVINE PROTEIN ALPHALACTALBUMIN INCREASES THE PLASMA RATIO OF TRYPTOPHAN TO THE OTHER LARGE NEUTRAL AMINO ACIDS, AND IN VULNERABLE SUBJECTS RAISES BRAIN SEROTONIN ACTIVITY, REDUCES CORTISOL CONCENTRATION, AND IMPROVES MOOD UNDER STRESS.**

**BACKGROUND:** Increased brain serotonin may improve the ability to cope with stress, whereas a decline in serotonin activity is involved in depressive mood. The uptake of the serotonin precursor, tryptophan, into the brain is dependent on nutrients that influence the cerebral availability of tryptophan via a change in the ratio of plasma tryptophan to the sum of the other large neutral amino acids (Trp-LNAA ratio). Therefore, a diet-induced increase in tryptophan availability may increase brain serotonin synthesis and improve coping and mood, particularly in stress-vulnerable subjects.

**OBJECTIVE:** We tested whether alpha-lactalbumin, a whey protein with a high tryptophan content, may increase the plasma Trp-LNAA ratio and reduce depressive mood and cortisol concentrations in stress-vulnerable subjects under acute stress. **DESIGN:** Twenty-nine highly stress-vulnerable subjects and 29 relatively stress-invulnerable subjects participated in a double-blind, placebo-controlled study. Subjects were exposed to experimental stress after the intake of a diet enriched with either alpha-lactalbumin or sodium-caseinate. Diet-induced changes in the plasma Trp-LNAA ratio and prolactin were measured. Changes in mood, pulse rate, skin conductance, and cortisol concentrations were assessed before and after the stressor.

**RESULTS:** The plasma Trp-LNAA ratio was 48% higher after the alpha-lactalbumin diet than after the casein diet ( $P = 0.0001$ ). In stress-vulnerable subjects this was accompanied by higher prolactin concentrations ( $P = 0.001$ ), a decrease in cortisol ( $P = 0.036$ ), and reduced depressive feelings ( $P = 0.007$ ) under stress.

**CONCLUSIONS:** Consumption of a dietary protein enriched in tryptophan increased the plasma Trp-LNAA ratio and, in stress-vulnerable subjects, improved coping ability, probably through alterations in brain serotonin.

*Am J Clin Nutr.* 2000 Jun;71(6):1536-44

## **ROLE OF CALCIUM AND DAIRY PRODUCTS IN ENERGY PARTITIONING AND WEIGHT MANAGEMENT.**

Dietary calcium plays a pivotal role in the regulation of energy metabolism because high-calcium diets attenuate adipocyte lipid accretion and weight gain during the overconsumption of an energy-dense diet and increase lipolysis and preserve thermogenesis during caloric restriction, which thereby markedly accelerates weight loss. Intracellular  $\text{Ca}(2+)$  plays a key regulatory role in adipocyte lipid metabolism and triacylglycerol storage; increased intracellular  $\text{Ca}(2+)$  results in the stimulation of lipogenic gene expression and lipogenesis and the suppression of lipolysis, which results in increased lipid filling and increased adiposity. Moreover, the increased calcitriol produced in response to low-calcium diets stimulates adipocyte  $\text{Ca}(2+)$  influx and, consequently, promotes adiposity, whereas higher calcium diets inhibit lipogenesis, inhibit diet-induced obesity in mice, and promote lipolysis, lipid oxidation, and thermogenesis. Notably, dairy sources of calcium markedly attenuate weight and fat gain and accelerate fat loss to a greater degree than do supplemental sources of calcium. This augmented effect of dairy products relative to supplemental calcium is likely due to additional bioactive compounds, including the angiotensin-converting enzyme inhibitors and the rich concentration of branched-chain amino acids in whey, which act synergistically with calcium to attenuate adiposity. These concepts are confirmed by epidemiologic data and recent clinical trials, which indicate that diets that include  $>$  or  $=3$  daily servings of dairy products result in significant reductions in adipose tissue mass in obese humans in the absence of caloric restriction and markedly accelerate weight and body fat loss secondary to caloric restriction compared with diets low in dairy products. These data indicate an important role for dairy products in both the prevention and treatment of obesity.

*Am J Clin Nutr.* 2004 May;79(5):907S-912S

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