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Journal
ABSTRACTS**CoQ10****BIOCHEMICAL FUNCTIONS OF COENZYME Q10.**

Coenzyme Q is well defined as a crucial component of the oxidative phosphorylation process in mitochondria which converts the energy in carbohydrates and fatty acids into ATP to drive cellular machinery and synthesis. New roles for coenzyme Q in other cellular functions are only becoming recognized. The new aspects have developed from the recognition that coenzyme Q can undergo oxidation/reduction reactions in other cell membranes such as lysosomes. Golgi or plasma membranes. In mitochondria and lysosomes, coenzyme Q undergoes reduction/oxidation cycles during which it transfers protons across the membrane to form a proton gradient. The presence of high concentrations of quinol in all membranes provides a basis for antioxidant action either by direct reaction with radicals or by regeneration of tocopherol and ascorbate. Evidence for a function in redox control of cell signaling and gene expression is developing from studies on coenzyme Q stimulation of cell growth, inhibition of apoptosis, control of thiol groups, formation of hydrogen peroxide and control of membrane channels. Deficiency of coenzyme Q has been described based on failure of biosynthesis caused by gene mutation, inhibition of biosynthesis by HMG coA reductase inhibitors (statins) or for unknown reasons in ageing and cancer. Correction of deficiency requires supplementation with higher levels of coenzyme Q than are available in the diet.

J Am Coll Nutr. 2001 Dec;20(6):591-8

IMPROVEMENT OF VISUAL FUNCTIONS AND FUNDUS ALTERATIONS IN EARLY AGE-RELATED MACULAR DEGENERATION TREATED WITH A COMBINATION OF ACETYL-L-CARNITINE, N-3 FATTY ACIDS, AND COENZYME Q10.

The aim of this randomized, double-blind, placebo-controlled clinical trial was to determine the efficacy of a combination of acetyl-L-carnitine, n-3 fatty acids, and coenzyme Q10 (Phototrop) on the visual functions and fundus alterations in early age-related macular degeneration (AMD). One hundred and six patients with a clinical diagnosis of early AMD were randomized to the treated or control groups. The primary efficacy variable was the change in the visual field mean defect (VFMD) from baseline to 12 months of treatment, with secondary efficacy parameters: visual acuity (Snellen chart and ETDRS chart), foveal sensitivity as measured by perimetry, and fundus alterations as evaluated according to the criteria of the International Classification and Grading System for AMD. The mean change in all four parameters of visual functions showed significant improvement in the treated group by the end of the study period. In addition, in the treated group only 1 out of 48 cases (2%) while in the placebo group 9 out of 53 (17%) showed clinically significant (>2.0 dB) worsening in VFMD ($p = 0.006$, odds ratio: 10.93). Decrease in drusen-covered area of treated eyes was also statistically significant as compared to placebo when either the most affected eyes ($p = 0.045$) or the less affected eyes ($p = 0.017$) were considered. These findings strongly suggested that an appropriate combination of compounds which affect mitochondrial lipid metabolism, may improve and subsequently stabilize visual functions, and it may also improve fundus alterations in patients affected by early AMD.

Ophthalmologica. 2005 May-Jun;219(3):154-66

COENZYME Q10 FOR PREVENTION OF ANTHRACYCLINE-INDUCED CARDIOTOXICITY.

Preclinical and clinical studies suggest that anthracycline-induced cardiotoxicity can be prevented by administering coenzyme Q10 during cancer chemotherapy that includes drugs such as doxorubicin and daunorubicin. Studies further suggest that coenzyme Q10 does not interfere with the antineoplastic action of anthracyclines and might even enhance their anticancer effects. Preventing cardiotoxicity might allow for escalation of the anthracycline dose, which would further enhance the anticancer effects. Based on clinical investigation, although limited, a cumulative dose of doxorubicin of up to 900 mg/m², and possibly higher, can be administered safely during chemotherapy as long as coenzyme Q10 is administered concurrently. The etiology of the dose-limiting cardiomyopathy that is induced by anthracyclines can be explained by irreversible damage to heart cell mitochondria, which differ from mitochondria of other cells in that they possess a unique enzyme on the inner mitochondrial membrane. This enzyme reduces anthracyclines to their semiquinones, resulting in severe oxidative stress, disruption of mitochondrial energetics, and irreversible damage to mitochondrial DNA. Damage to mitochondrial DNA blocks the regenerative

capability of the organelle and ultimately leads to apoptosis or necrosis of myocytes. Coenzyme Q10, an essential component of the electron transport system and a potent intracellular antioxidant, appears to prevent damage to the mitochondria of the heart, thus preventing the development of anthracycline-induced cardiomyopathy.

Integr Cancer Ther. 2005 Jun;4(2):110-30

ROLE OF MITOCHONDRIA IN NEURONAL CELL DEATH INDUCED BY OXIDATIVE STRESS; NEUROPROTECTION BY COENZYME Q10.

Neuronal cells depend on mitochondrial oxidative phosphorylation for most of their energy needs and therefore are at a particular risk for oxidative stress. Mitochondria play an important role in energy production and oxidative stress-induced apoptosis. In the present study, we have demonstrated that external oxidative stress induces mitochondrial dysfunction leading to increased ROS generation and ultimately apoptotic cell death in neuronal cells. Furthermore, we have investigated the role of Coenzyme Q10 as a neuroprotective agent. Coenzyme Q10 is a component of the mitochondrial respiratory chain and a potent antioxidant. Our results indicate that total cellular ROS generation was inhibited by Coenzyme Q10. Further, pre-treatment with Coenzyme Q10 maintained mitochondrial membrane potential during oxidative stress and reduced the amount of mitochondrial ROS generation. Our study suggests that water-soluble Coenzyme Q10 acts by stabilizing the mitochondrial membrane when neuronal cells are subjected to oxidative stress. Therefore, Coenzyme Q10 has the potential to be used as a therapeutic intervention for neurodegenerative diseases.

Neurobiol Dis. 2005 Apr;18(3):618-27

Antioxidants

REDUCED RISK OF ALZHEIMER DISEASE IN USERS OF ANTIOXIDANT VITAMIN SUPPLEMENTS: THE CACHE COUNTY STUDY.

BACKGROUND: Antioxidants may protect the aging brain against oxidative damage associated with pathological changes of Alzheimer disease (AD). **OBJECTIVE:** To examine the relationship between antioxidant supplement use and risk of AD. **DESIGN:** Cross-sectional and prospective study of dementia. Elderly (65 years or older) county residents were assessed in 1995 to 1997 for prevalent dementia and AD, and again in 1998 to 2000 for incident illness. Supplement use was ascertained at the first contact. **SETTING:** Cache County, Utah. **PARTICIPANTS:** Among 4,740 respondents (93%) with data sufficient to determine cognitive status at the initial assessment, we identified 200 prevalent cases of AD. Among 3,227 survivors at risk, we identified 104 incident AD cases at follow-up. **MAIN OUTCOME MEASURE:** Diagnosis of AD by means of multistage assessment procedures. **RESULTS:** Analyses of prevalent and incident AD yielded similar results. Use of vitamin E and C (ascorbic acid) supplements in combination was associated with reduced AD prevalence (adjusted odds ratio, 0.22; 95% confidence interval, 0.05-0.60) and incidence (adjusted hazard ratio, 0.36; 95% confidence interval, 0.09-0.99). A trend toward lower AD risk was also evident in users of vitamin E and multivitamins containing vitamin C, but we saw no evidence of a protective effect with use of vitamin E or vitamin C supplements alone, with multivitamins alone, or with vitamin B-complex supplements. **CONCLUSIONS:** Use of vitamin E and vitamin C supplements in combination is associated with reduced prevalence and incidence of AD. Antioxidant supplements merit further study as agents for the primary prevention of AD.

Arch Neurol. 2004 Jan;61(1):82-8

FREE RADICALS AND AGING.

Aging is characterized by decrements in maximum function and accumulation of mitochondrial DNA mutations, which are best observed in organs such as the brain that contain post-mitotic cells. Oxygen radicals are increasingly considered responsible for part of these aging changes. Comparative studies of animals with different aging rates have shown that the rate of mitochondrial oxygen radical generation is directly related to the steady-state level of oxidative damage to mitochondrial DNA and is inversely correlated with maximum longevity in higher vertebrates. The degree of unsaturation of tissue fatty acids also correlates inversely with maximum longevity. These are the two known traits connecting oxidative stress with aging. Furthermore, caloric restriction, which decreases the rate of aging, proportionately decreases mitochondrial oxygen radical generation, especially at complex I. These findings are reviewed, highlighting the results obtained in the brain.

Trends Neurosci. 2004 Oct;27(10):595-600

AGING AND OXIDATIVE STRESS.

The scientific establishment has been discussing the relationship between aging and oxidative stress for quite some time now.

While we are still far from a general agreement about this subject, there is an impressive amount of data collected that can be used to draw a compelling picture of the events that take place during the human aging process and their correlation with the oxidant status of the organism. In this review, we bring forth the results of some key studies that can help to elucidate the aging-oxidative stress puzzle, as well as to explain which are the fundamental events in this interplay and why their causal relationships remain so elusive. We also put forward here data on the systemic oxidative stress status of a group of 503 healthy human subjects. The data consist of the plasma levels of TBARS and of the nutritional antioxidants, alpha-tocopherol, beta-carotene, and ascorbic acid, and of the activity of the antioxidant enzymes, Cu, Zn-superoxide dismutase, catalase and glutathione peroxidase, of red blood cells. The data indicate that a moderate situation of oxidative stress gradually develops during human aging.

Mol Aspects Med. 2004 Feb-Apr;25(1-2):5-16

MITOCHONDRIAL DNA REPAIR AND AGING.

The mitochondrial electron transport chain plays an important role in energy production in aerobic organisms and is also a significant source of reactive oxygen species that damage DNA, RNA and proteins in the cell. Oxidative damage to the mitochondrial DNA is implicated in various degenerative diseases, cancer and aging. The importance of mitochondrial ROS in age-related degenerative diseases is further strengthened by studies using animal models, *Caenorhabditis elegans*, *Drosophila* and yeast. Research in the last several years shows that mitochondrial DNA is more susceptible to various carcinogens and ROS when compared to nuclear DNA. DNA damage in mammalian mitochondria is repaired by base excision repair (BER). Studies have shown that mitochondria contain all the enzymes required for BER. Mitochondrial DNA damage, if not repaired, leads to disruption of electron transport chain and production of more ROS. This vicious cycle of ROS production and mtDNA damage ultimately leads to energy depletion in the cell and apoptosis.

Mutat Res. 2002 Nov 30;509(1-2):127-51

LUTEIN, BUT NOT ALPHA-TOCOPHEROL, SUPPLEMENTATION IMPROVES VISUAL FUNCTION IN PATIENTS WITH AGE-RELATED CATARACTS: A 2-Y DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT STUDY.

OBJECTIVE: We investigated the effect of long-term antioxidant supplementation (lutein and alpha-tocopherol) on serum levels and visual performance in patients with cataracts. **METHODS:** Seventeen patients clinically diagnosed with age-related cataracts were randomized in a double-blind study involving dietary supplementation with lutein (15 mg; n = 5), alpha-tocopherol (100 mg; n = 6), or placebo (n = 6), three times a week for up to 2 y. Serum carotenoid and tocopherol concentrations were determined with quality-controlled high-performance liquid chromatography, and visual performance (visual acuity and glare sensitivity) and biochemical and hematologic indexes were monitored every 3 mo throughout the study. Changes in these parameters were assessed by General Linear Model (GLM) repeated measures analysis. **RESULTS:** Serum concentrations of lutein and alpha-tocopherol increased with supplementation, although statistical significance was reached only in the lutein group. Visual performance (visual acuity and glare sensitivity) improved in the lutein group, whereas there was a trend toward the maintenance of and decrease in visual acuity with alpha-tocopherol and placebo supplementation, respectively. No significant side effects or changes in biochemical or hematologic profiles were observed in any of the subjects during the study. **CONCLUSIONS:** Visual function in patients with age-related cataracts who received the lutein supplements improved, suggesting that a higher intake of lutein, through lutein-rich fruit and vegetables or supplements, may have beneficial effects on the visual performance of people with age-related cataracts.

Nutrition. 2003 Jan;19(1):21-4

CAROTENOID AND VITAMIN E STATUS ARE ASSOCIATED WITH INDICATORS OF SARCOPENIA AMONG OLDER WOMEN LIVING IN THE COMMUNITY.

BACKGROUND AND AIMS: Oxidative stress may play a role in the pathogenesis of sarcopenia, and the relationship between dietary antioxidants and sarcopenia needs further elucidation. The aim was to determine whether dietary carotenoids and alpha-tocopherol are associated with sarcopenia, as indicated by low grip, hip, and knee strength. **METHODS:** Cross-sectional analyses were conducted on 669 non-disabled to severely disabled community-dwelling women aged 70 to 79 who participated in the Women's Health and Aging Studies. Plasma carotenoids and alpha-tocopherol were measured. Grip, hip, and knee strength were measured, and low strength was defined as the lowest tertile of each strength measure. **RESULTS:** Higher plasma concentrations of alpha-carotene, beta-carotene, beta-cryptoxanthin, and lutein/zeaxanthin were associated with reduced risk of low grip, hip, and knee strength. After adjusting for potential confounding factors such as age, race, smoking, cardiovascular disease, arthritis, and plasma interleukin-6 concentrations, there was an independent association for women in the highest compared with the lowest quartile of total carotenoids with low grip strength [Odds Ratios (OR) 0.34, 95% Confidence Interval (CI) 0.20-0.59], low hip strength (OR 0.28, 95% CI 0.16-0.48), and low knee strength (OR 0.45, 95% CI 0.27-0.75), and there was an independent association for women in the highest compared with the lowest quartile of alpha-tocopherol with low grip strength (OR 0.44, 95% CI 0.24-0.78) and low knee strength (OR 0.52, 95% CI 0.29-0.95). **CONCLUSIONS:** Higher carotenoid and alpha-

tocopherol status were associated with higher strength measures. These data support the hypothesis that oxidative stress is associated with sarcopenia in older adults, but further longitudinal and interventional studies are needed to establish causality.

Aging Clin Exp Res. 2003 Dec;15(6):482-7

DELAYING BRAIN MITOCHONDRIAL DECAY AND AGING WITH MITOCHONDRIAL ANTIOXIDANTS AND METABOLITES.

Mitochondria decay with age due to the oxidation of lipids, proteins, RNA, and DNA. Some of this decay can be reversed in aged animals by feeding them the mitochondrial metabolites acetylcarnitine and lipoic acid. In this review, we summarize our recent studies on the effects of these mitochondrial metabolites and mitochondrial antioxidants (alpha-phenyl-N-t-butyl nitron and N-t-butyl hydroxylamine) on the age-associated mitochondrial decay of the brain of old rats, neuronal cells, and human diploid fibroblast cells. In feeding studies in old rats, these mitochondrial metabolites and antioxidants improve the age-associated decline of ambulatory activity and memory, partially restore mitochondrial structure and function, inhibit the age-associated increase of oxidative damage to lipids, proteins, and nucleic acids, elevate the levels of antioxidants, and restore the activity and substrate binding affinity of a key mitochondrial enzyme, carnitine acetyltransferase. These mitochondrial metabolites and antioxidants protect neuronal cells from neurotoxin- and oxidant-induced toxicity and oxidative damage; delay the normal senescence of human diploid fibroblast cells, and inhibit oxidant-induced acceleration of senescence. These results suggest a plausible mechanism: with age, increased oxidative damage to proteins and lipid membranes, particularly in mitochondria, causes a deformation of structure of enzymes, with a consequent decrease of enzyme activity as well as substrate binding affinity for their substrates; an increased level of substrate restores the velocity of the reaction and restores mitochondrial function, thus delaying mitochondrial decay and aging. This loss of activity due to coenzyme or substrate binding appears to be true for a number of other enzymes as well, including mitochondrial complex III and IV.

Ann N Y Acad Sci. 2002 Apr;959:133-66

OXIDATIVE STRESS, MITOCHONDRIAL DNA MUTATION, AND IMPAIRMENT OF ANTIOXIDANT ENZYMES IN AGING.

Mitochondria do not only produce less ATP, but they also increase the production of reactive oxygen species (ROS) as by-products of aerobic metabolism in the aging tissues of the human and animals. It is now generally accepted that aging-associated respiratory function decline can result in enhanced production of ROS in mitochondria. Moreover, the activities of free radical-scavenging enzymes are altered in the aging process. The concurrent age-related changes of these two systems result in the elevation of oxidative stress in aging tissues. Within a certain concentration range, ROS may induce stress response of the cells by altering expression of respiratory genes to uphold the energy metabolism to rescue the cell. However, beyond the threshold, ROS may cause a wide spectrum of oxidative damage to various cellular components to result in cell death or elicit apoptosis by induction of mitochondrial membrane permeability transition and release of apoptogenic factors such as cytochrome c. Moreover, oxidative damage and large-scale deletion and duplication of mitochondrial DNA (mtDNA) have been found to increase with age in various tissues of the human. Mitochondria act like a biosensor of oxidative stress and they enable cell to undergo changes in aging and age-related diseases. On the other hand, it has recently been demonstrated that impairment in mitochondrial respiration and oxidative phosphorylation elicits an increase in oxidative stress and causes a host of mtDNA rearrangements and deletions. Here, we review work done in the past few years to support our view that oxidative stress and oxidative damage are a result of concurrent accumulation of mtDNA mutations and defective antioxidant enzymes in human aging.

Exp Biol Med (Maywood). 2002 Oct;227(9):671-82

MITOCHONDRIAL FREE RADICAL GENERATION, OXIDATIVE STRESS, AND AGING.

Mitochondria have been described as ³the powerhouses of the cell² because they link the energy-releasing activities of electron transport and proton pumping with the energy conserving process of oxidative phosphorylation, to harness the value of foods in the form of ATP. Such energetic processes are not without dangers, however, and the electron transport chain has proved to be somewhat ³leaky.² Such side reactions of the mitochondrial electron transport chain with molecular oxygen directly generate the superoxide anion radical (O₂⁻), which dismutates to form hydrogen peroxide (H₂O₂), which can further react to form the hydroxyl radical (HO^{*}). In addition to these toxic electron transport chain reactions of the inner mitochondrial membrane, the mitochondrial outer membrane enzyme monoamine oxidase catalyzes the oxidative deamination of biogenic amines and is a quantitatively large source of H₂O₂ that contributes to an increase in the steady state concentrations of reactive species within both the mitochondrial matrix and cytosol. In this article we review the mitochondrial rates of production and steady state levels of these reactive oxygen species. Reactive oxygen species generated by mitochondria, or from other sites within or outside the cell, cause damage to mitochondrial components and initiate degradative processes. Such toxic reactions contribute significantly to the aging process and form the central dogma of ³The Free Radical Theory of Aging.² In this article we review current

understandings of mitochondrial DNA, RNA, and protein modifications by oxidative stress and the enzymatic removal of oxidatively damaged products by nucleases and proteases. The possible contributions of mitochondrial oxidative polynucleotide and protein turnover to apoptosis and aging are explored.

Free Radic Biol Med. 2000 Aug;29(3-4):222-30

CAN ANTIOXIDANT DIET SUPPLEMENTATION PROTECT AGAINST AGE-RELATED MITOCHONDRIAL DAMAGE?

Harman's free radical theory of aging and our electron-microscopic finding of an age-related mitochondrial degeneration in the somatic tissues of the insect *Drosophila melanogaster* as well as in the fixed postmitotic Leydig and Sertoli cells of the mouse testis led us to propose a mitochondrial theory of aging, according to which metazoan senescence may be linked to oxygen stress-injury to the genome and membranes of the mitochondria of somatic differentiated cells. These concepts attract a great deal of attention, since, according to recent work, the mitochondrial damage caused by reactive oxygen species (ROS) and concomitant decline in ATP synthesis seem to play a key role not only in aging, but also in the fundamental cellular process of apoptosis. Although diet supplementation with antioxidants has not been able to increase consistently the species-characteristic maximum life span, it results in significant extension of the mean life span of laboratory animals. Moreover, diets containing high levels of antioxidants such as vitamins C and E seem able to reduce the risk of suffering age-related immune dysfunctions and arteriosclerosis. Presently, the focus of age-related antioxidant research is on compounds, such as deprenyl, coenzyme Q10, alpha-lipoic acid, and the glutathione-precursors thioprolin and N-acetylcysteine, which may be able to neutralize the ROS at their sites of production in the mitochondria. Diet supplementation with these antioxidants may protect the mitochondria against respiration-linked oxygen stress, with preservation of the genomic and structural integrity of these energy-producing organelles and concomitant increase in functional life span.

Ann N Y Acad Sci. 2002 Apr;959:508-16

ANTIOXIDANT PROPERTIES OF PREPARED BLUEBERRY (VACCINIUM MYRTILLUS) EXTRACTS.

A blueberry extract (A) and two anthocyanin-derived extracts (B and C) were prepared. The contents of polyphenols, flavonoids, anthocyanins, and anthocyanin-derived pigments of the extracts were determined for the first time. The pigment profile of blueberry extract A corresponded to 15 anthocyanins, whereas extract B was mainly composed of anthocyanin-pyruvic acid adducts of the blueberry original anthocyanins and extract C was mainly composed of the respective vinylpyranoanthocyanin-catechins (portisins). The extracts¹ abilities to inhibit lipid peroxidation, induced by 2,2'-azobis(2-methyl-propanimidamide) dihydrochloride in a liposomal membrane system were examined. The antioxidant capacities of the extracts were evaluated through monitoring oxygen consumption and by measuring the formation of conjugated dienes. All of the extracts provided protection of membranes against peroxy radicals by increasing the induction time of oxidation. This effect increased with the polyphenol content and with the structural complexity of the anthocyanin-derived pigments of the extracts. The pigments present in extract C seemed to induce a higher protection of the liposome membranes toward oxidation. In addition, the antiradical properties and the reducing power of the extracts were determined by using DPPH and FRAP methods, respectively. The results from these assays were in agreement with those obtained with the liposome membranes.

J Agric Food Chem. 2005 Aug 24;53(17):6896-902

PHENOLIC COMPOUNDS FROM BLUEBERRIES CAN INHIBIT COLON CANCER CELL PROLIFERATION AND INDUCE APOPTOSIS.

Research has shown that diets rich in phenolic compounds may be associated with lower risks of several chronic diseases including cancer. This study systematically evaluated the bioactivities of phenolic compounds in rabbiteye blueberries and assessed their potential antiproliferation and apoptosis induction effects using two colon cancer cell lines, HT-29 and Caco-2. Polyphenols in three blueberry cultivars, Briteblue, Tifblue, and Powderblue, were extracted and freeze-dried. The extracts were further separated into phenolic acids, tannins, flavonols, and anthocyanins using an HLB cartridge and LH20 column. Some individual phenolic acids and flavonoids were identified by HPLC with >90% purity in anthocyanin fractions. The dried extracts and fractions were added to the cell culture medium to test for antiproliferation activities and induction of apoptosis. Flavonol and tannin fractions resulted in 50% inhibition of cell proliferation at concentrations of 70-100 and 50-100 microg/mL in HT-29 and Caco-2 cells, respectively. The phenolic acid fraction showed relatively lower bioactivities with 50% inhibition at approximately 1000 microg/mL. The greatest antiproliferation effect among all four fractions was from the anthocyanin fractions. Both HT-29 and Caco-2 cell growth was significantly inhibited by >50% by the anthocyanin fractions at concentrations of 15-50 microg/mL. Anthocyanin fractions also resulted in 2-7 times increases in DNA fragmentation, indicating the induction of apoptosis. The effective dosage levels are close to the reported range of anthocyanin concentrations in rat plasma. These findings suggest that blueberry intake may reduce colon cancer risk.

J Agric Food Chem. 2005 Sep 7;53(18):7320-9

BLUEBERRY SUPPLEMENTED DIET REVERSES AGE-RELATED DECLINE IN HIPPOCAMPAL HSP70 NEUROPROTECTION.

Dietary supplementation with antioxidant rich foods can decrease the level of oxidative stress in brain regions and can ameliorate age-related deficits in neuronal and behavioral functions. We examined whether short-term supplementation with blueberries might enhance the brain's ability to generate a heat shock protein 70 (HSP70) mediated neuroprotective response to stress. Hippocampal (HC) regions from young and old rats fed either a control or a supplemented diet for 10 weeks were subjected to an *in vitro* inflammatory challenge (LPS) and then examined for levels of HSP70 at various times post LPS (30, 90, and 240 min). While baseline levels of HSP70 did not differ among the various groups compared to young control diet rats, increases in HSP70 protein levels in response to an *in vitro* LPS challenge were significantly less in old as compared to young control diet rats at the 30, 90, and 240 min time points. However, it appeared that the blueberry diet completely restored the HSP70 response to LPS in the old rats at the 90 and 240 min times. This suggests that a short-term blueberry (BB) intervention may result in improved HSP70-mediated protection against a number of neurodegenerative processes in the brain. Results are discussed in terms of the multiplicity of the effects of the BB supplementation which appear to range from antioxidant/anti-inflammatory activity to signaling.

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. LC-MS 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

DIETARY SUPPLEMENTATION WITH BLUEBERRIES, SPINACH, OR SPIRULINA REDUCES ISCHEMIC BRAIN DAMAGE.

Free radicals are involved in neurodegenerative disorders, such as ischemia and aging. We have previously demonstrated that treatment with diets enriched with blueberry, spinach, or spirulina have been shown to reduce neurodegenerative changes in aged animals. The purpose of this study was to determine if these diets have neuroprotective effects in focal ischemic brain. Adult male Sprague-Dawley rats were fed with equal amounts of diets (blueberry, spinach, and spirulina) or with control diet. After 4 weeks of feeding, all animals were anesthetized with chloral hydrate. The right middle cerebral artery was ligated with a 10-0 suture for 60 min. The ligature was later removed to allow reperfusion injury. Animals were sacrificed and brains were removed for caspase-3 enzymatic assays and triphenyltetrazolium chloride staining at 8 and 48 h after the onset of reperfusion. A subgroup of animals was used for locomotor behavior and biochemical assays. We found that animals which received blueberry, spinach, or spirulina enriched diets had a significant reduction in the volume of infarction in the cerebral cortex and an increase in post-stroke locomotor activity. There was no difference in blood biochemistry, blood CO₂, and electrolyte levels among all groups, suggesting that the protection was not indirectly mediated through the changes in physiological functions. Animals treated with blueberry, spinach, or spirulina had significantly lower caspase-3 activity in the ischemic hemisphere. In conclusion, our data suggest that chronic treatment with blueberry, spinach, or spirulina reduces ischemia/reperfusion-induced apoptosis and cerebral infarction.

Exp Neurol. 2005 May;193(1):75-84

BLUEBERRY EXTRACT ENHANCES SURVIVAL OF INTRAOCULAR HIPPOCAMPAL TRANSPLANTS.

Transplantation of neural tissue has been explored as a potential therapy to replace dead or dying cells in the brain, such as after brain injury or neurodegenerative disease. However, survival of transplanted tissue is poor, especially when the transplant recipient is of advanced age. Recent studies have demonstrated improvement of neuronal deficits in aged animals given a diet supplemented with blueberry extract. The present study focuses on the survival of fetal hippocampal transplants to young (4 months) or middle-aged (16 months) animals with or without dietary supplementation with blueberry extract. Results indicate that fetal hippocampus transplanted to middle-aged host animals exhibits poor survival characterized by reduced growth and compromised tissue organization. However, when middle-aged animals were maintained on a diet supplemented with 2% blueberry extract, hippocampal graft growth was significantly improved and cellular organization of grafts was comparable to that seen in tissue grafted to young host animals. Thus, the data suggest that factor(s) in blueberries may have significant effects on development and organization of this important brain region.

Cell Transplant. 2005;14(4):213-23

FATTY ACID COMPOSITION AND ANTIOXIDANT PROPERTIES OF COLD-PRESSED MARIONBERRY, BOYSENBERRY, RED RASPBERRY, AND BLUEBERRY SEED OILS.

Cold-pressed marionberry, boysenberry, red raspberry, and blueberry seed oils were evaluated for their fatty acid composition, carotenoid content, tocopherol profile, total phenolic content (TPC), oxidative stability index (OSI), peroxide value, and antioxidant

properties. All tested seed oils contained significant levels of alpha-linolenic acid ranging from 19.6 to 32.4 g per 100 g of oil, along with a low ratio of n-6/n-3 fatty acids (1.64-3.99). The total carotenoid content ranged from 12.5 to 30.0 micromoles per kg oil. Zeaxanthin was the major carotenoid compound in all tested berry seed oils, along with beta-carotene, lutein, and cryptoxanthin. Total tocopherol was 260.6-2276.9 micromoles per kg oil, including alpha-, gamma-, and delta-tocopherols. OSI values were 20.07, 20.30, and 44.76 h for the marionberry, red raspberry, and boysenberry seed oils, respectively. The highest TPC of 2.0 mg gallic acid equivalents per gram of oil was observed in the red raspberry seed oil, while the strongest oxygen radical absorbance capacity was in boysenberry seed oil extract (77.9 micromol trolox equivalents per g oil). All tested berry seed oils directly reacted with and quenched DPPH radicals in a dose- and time-dependent manner. These data suggest that the cold-pressed berry seed oils may serve as potential dietary sources of tocopherols, carotenoids, and natural antioxidants.

J Agric Food Chem. 2005 Feb 9;53(3):566-73

WILD BLUEBERRY-RICH DIETS AFFECT THE CONTRACTILE MACHINERY OF THE VASCULAR SMOOTH MUSCLE IN THE SPRAGUE-DAWLEY RAT.

Weanling male Sprague-Dawley rats were randomly fed a control diet (AIN-93) (C) or a blueberry diet (B) for 13 weeks, or a reverse diet (R) (C diet for 13 weeks, switched to the B diet for 8 weeks). Aortas were excised, and two intact and two endothelium-denuded rings were immersed in tissue baths containing physiological salt solution at 37 degrees C and aerated with 95% O₂ and 5% CO₂ (pH 7.4). Following equilibration and preconditioning under 1.5-g preload, cumulative dose-response curves were generated with six doses of the alpha1-adrenergic receptor-selective agonist L-phenylephrine (L-Phe, 10⁽⁸⁾-3 x 10⁽⁻⁶⁾ M) and relaxed with one dose of acetylcholine (3 x 10⁽⁻⁶⁾ M) to assess intact endothelium. The maximum force of contraction (F_{max}) and vessel sensitivity (pD₂) were determined in intact and endothelium-denuded rings. A two-way analysis of variance test revealed that blueberry-fed animals (B and R diets) developed a significantly lower F (max) (0.873 +/- 0.0463 and 0.9266 +/- 0.0463 g, respectively) when contracted with L-Phe, compared with the animals on the C diet (1.109 +/- 0.0463 g) (P < .05). The pD₂ of the intact rings was not significantly different among diet groups. Additionally, diet did not significantly affect the mean F (max) or pD₂ of endothelium-denuded rings. Our results indicate for the first time that wild blueberries incorporated into the diet affect the vascular smooth muscle contractile machinery by suppressing the alpha1-adrenergic receptor agonist-mediated contraction while having no effect on membrane sensitivity of the endothelial or vascular smooth muscle cell layer. Furthermore, their mechanism of action seems to be accomplished through an endothelium-dependent pathway.

J Med Food. 2005 Spring;8(1):8-13

Rhodiola

ACUTE RHODIOLA ROSEA INTAKE CAN IMPROVE ENDURANCE EXERCISE PERFORMANCE.

PURPOSE: The purpose of this study was to investigate the effect of acute and 4-week *Rhodiola rosea* intake on physical capacity, muscle strength, speed of limb movement, reaction time, and attention. **METHODS:** PHASE I: A double blind placebo-controlled randomized study (n= 24) was performed, consisting of 2 sessions (2 days per session). Day 1: One hour after acute *Rhodiola rosea* intake (R, 200-mg *Rhodiola rosea* extract containing 3% rosavin + 1% salidroside plus 500 mg starch) or placebo (P, 700 mg starch) speed of limb movement (plate tapping test), aural and visual reaction time, and the ability to sustain attention (Fepsy Vigilance test) were assessed. Day 2: Following the same intake procedure as on day 1, maximal isometric knee-extension torque and endurance exercise capacity were tested. Following a 5-day washout period, the experimental procedure was repeated, with the treatment regimens being switched between groups (session 2). PHASE II: A double blind placebo-controlled study (n = 12) was performed. Subjects underwent sessions 3 and 4, identical to Phase I, separated by a 4-week R/P intake, during which subjects ingested 200 mg R/P per day. **RESULTS:** PHASE I: Compared with P, acute R intake in Phase I increased (p < .05) time to exhaustion from 16.8 +/- 0.7 min to 17.2 +/- 0.8 min. Accordingly, VO_{2peak} (p < .05) and VCO_{2peak} (p < .05) increased during R compared to P from 50.9 +/- 1.8 ml x min⁽⁻¹⁾ x kg⁽⁻¹⁾ to 52.9 +/- 2.7 ml x min⁽⁻¹⁾ x kg⁽⁻¹⁾ (VO_{2peak}) and from 60.0 +/- 2.3 ml x min⁽⁻¹⁾ x kg⁽⁻¹⁾ to 63.5 +/- 2.7 ml x min⁽⁻¹⁾ x kg⁽⁻¹⁾ (VCO_{2peak}). Pulmonary ventilation (p = .07) tended to increase more during R than during P (P: 115.9 +/- 7.7 L/min; R: 124.8 +/- 7.7 L/min). All other parameters remained unchanged. PHASE II: Four-week R intake did not alter any of the variables measured. **CONCLUSION:** Acute *Rhodiola rosea* intake can improve endurance exercise capacity in young healthy volunteers. This response was not altered by prior daily 4-week *Rhodiola* intake.

Int J Sport Nutr Exerc Metab. 2004 Jun;14(3):298-307

EXPERIMENTAL ANALYSIS OF THERAPEUTIC PROPERTIES OF RHODIOLA ROSEA L. AND ITS POSSIBLE APPLICATION IN MEDICINE.

The paper presents a review of the scientific publications on *Rhodiola rosea* L. known for its adaptogenic characteristics.

Biologically active substances salidroside, rosin, rosavin, rosarin, and tyrosol, which are mainly found in plant rhizomes, demonstrate therapeutic effect. These active components effect the central nervous system by increasing the ability to concentrate, the mental and physical power; they are efficient in the asthenic states and improve general resistance of the cells and the organism against the harmful outer influence. They also prevent the heart system from stress and arrhythmias, and posses some antioxidant activity. Some data confirm that the *Rhodiola rosea* L. preparations stop the growth of the malignant tumors and metastases in the liver. Some preclinical and clinical data of the golden root preparations are discussed in the survey. The interaction of the herb with other medicines, its usage and effect, recommended doses, and its side effects are also reviewed in the paper.

Medicina (Kaunas). 2004;40(7):614-9

RHODIOLA ROSEA IN STRESS INDUCED FATIGUE--A DOUBLE BLIND CROSS-OVER STUDY OF A STANDARDIZED EXTRACT SHR-5 WITH A REPEATED LOW-DOSE REGIMEN ON THE MENTAL PERFORMANCE OF HEALTHY PHYSICIANS DURING NIGHT DUTY.

The aim of this study was to investigate the effect of repeated low-dose treatment with a standardized extract SHR/5 of rhizome *Rhodiola rosea* L, (RRE) on fatigue during night duty among a group of 56 young, healthy physicians. The effect was measured as total mental performance calculated as Fatigue Index. The tests chosen reflect an overall level of mental fatigue, involving complex perceptive and cognitive cerebral functions, such as associative thinking, short-term memory, calculation and ability of concentration, and speed of audio-visual perception. These parameters were tested before and after night duty during three periods of two weeks each: a) a test period of one RRE/placebo tablet daily, b) a washout period and c) a third period of one placebo/RRE tablet daily, in a double-blind cross-over trial. The perceptive and cognitive cerebral functions mentioned above were investigated using 5 different tests. A statistically significant improvement in these tests was observed in the treatment group (RRE) during the first two weeks period. No side-effects were reported for either treatment noted. These results suggest that RRE can reduce general fatigue under certain stressful conditions.

Phytomedicine. 2000 Oct;7(5):365-71

A DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT STUDY OF THE STIMULATING AND ADAPTOGENIC EFFECT OF RHODIOLA ROSEA SHR-5 EXTRACT ON THE FATIGUE OF STUDENTS CAUSED BY STRESS DURING AN EXAMINATION PERIOD WITH A REPEATED LOW-DOSE REGIMEN.

The objective was to investigate the stimulating and normalizing effect of the adaptogen *Rhodiola rosea* extract SHR-5 in foreign students during a stressful examination period. The study was performed as a double-blind, randomized and placebo-controlled with low repeated dose regime. The study drug and the placebo were taken for 20 days by the students during an examination period. The physical and mental performance were assessed before and after the period, based on objective as well as on subjective evaluation. The most significant improvement in the SHR-5 group was seen in physical fitness, mental fatigue and neuro-motoric tests ($p < 0.01$). The self-assessment of the general well-being was also significantly ($p < 0.05$) better in the verum group. No significance was seen in the correction of text tests or a neuro-muscular tapping test. The overall conclusion is that the study drug gave significant results compared to the placebo group but that the dose level probably was suboptimal.

Phytomedicine. 2000 Apr;7(2):85-9

A RANDOMIZED TRIAL OF TWO DIFFERENT DOSES OF A SHR-5 RHODIOLA ROSEA EXTRACT VERSUS PLACEBO AND CONTROL OF CAPACITY FOR MENTAL WORK.

A randomized, double-blind, placebo-controlled, parallel-group clinical study with an extra non-treatment group was performed to measure the effect of a single dose of standardized SHR-5 *Rhodiola rosea* extract on capacity for mental work against a background of fatigue and stress. An additional objective was to investigate a possible difference between two doses, one dose being chosen as the standard mean dose in accordance with well-established medicinal use as a psychostimulant/adaptogen, the other dose being 50% higher. Some physiological parameters, e.g. pulse rate, systolic and diastolic blood pressure, were also measured. The study was carried out on a highly uniform population comprising 161 cadets aged from 19 to 21 years. All groups were found to have very similar initial data, with no significant difference with regard to any parameter. The study showed a pronounced antifatigue effect reflected in an antifatigue index defined as a ratio called AFI. The verum groups had AFI mean values of 1.0385 and 1.0195, 2 and 3 capsules respectively, whilst the figure for the placebo group was 0.9046. This was statistically highly significant ($p < 0.001$) for both doses (verum groups), whilst no significant difference between the two dosage groups was observed. There was a possible trend in favour of the lower dose in the psychometric tests. No such trend was found in the physiological tests.

Phytomedicine. 2003 Mar;10(2-3):95-105

REDUCTION OF NOISE-STRESS-INDUCED PHYSIOLOGICAL DAMAGE BY RADICES OF ASTRAGALI AND

RHODIOLAE: GLYCOGEN, LACTIC ACID AND CHOLESTEROL CONTENTS IN LIVER OF THE RAT.

Noise is one of the factors that induces critical stress in animals. The contents of glycogen, lactic acid and cholesterol in the liver of noise-stressed rats were analyzed in order to investigate the alleviation of noise-stress-induced physiological damages by traditional medicine using Astragali and Rhodiola radices. More than 95 dB noise ranging from 2 to 4 kHz reduced the contents of these compounds in the liver of rats not injected with the extract of Astragali or Rhodiola, but did not change the contents in the liver of rats injected with the Astragali or Rhodiola extract. These results show that noise induced stress in the rats via a decrease in contents of these compounds in the liver and that Astragali or Rhodiola maintained the contents of these compounds in the liver of the noise-stressed rats. The results indicate that Astragali or Rhodiola improved the ability for rats to resist noise stress.

Biosci Biotechnol Biochem. 2003 Sep;67(9):1930-6

EFFECTS OF ALCOHOL AQUEOUS EXTRACT FROM RHODIOLA ROSEA L. ROOTS ON LEARNING AND MEMORY.

The effect of alcohol-aqueous extract (1:1) from *Rhodiola rosea* L. roots on the processes of learning and memory is studied on rats. Several methods of active avoidance with negative and positive reinforcements are used, as well as of passive avoidance. Using the maze-method with negative (punitive) reinforcement, it has been found that *Rhodiola* extract in a single dose of 0.10 ml per rat essentially improves learning and retention after 24 hours. Significant improvement of the long-term memory is also established in memory tests after 10-day treatment with the same dose of the extract. In the other two doses tested (0.02 and 1.0 ml per rat) the extract has no substantial effect on learning and memory. In a dose of 0.10 ml per rat the *Rhodiola* extract had a favourable effect on the training process using the ³staircase² method with positive (food) reinforcement as well. With the other methods used (active avoidance method with negative reinforcement ³shuttle-box² and passive avoidance methods ³step down² and ³step through²) *Rhodiola* extract in the dose used (0.10 ml per rat) had no substantial effect on learning and memory (a certain deterioration of the training process was even observed using the ³shuttle-box² method, while the ³step-down² method resulted in deterioration of the memory). The great significance of the method used for studying the effects of the pharmacological agents on learning and memory for the results obtained is evident.

Acta Physiol Pharmacol Bulg. 1986;12(1):3-16

EXTRACT OF RHODIOLA ROSEA RADIX REDUCES THE LEVEL OF C-REACTIVE PROTEIN AND CREATININE KINASE IN THE BLOOD.

The effects of extracts of *Rhodiola rosea* radix on blood levels of inflammatory C-reactive protein and creatinine kinase were studied in healthy untrained volunteers before and after exhausting exercise. *Rhodiola rosea* extract exhibited an antiinflammatory effect and protected muscle tissue during exercise.

Bull Exp Biol Med. 2004 Jul;138(1):63-4

EFFECT OF RHODIOLA ROSEA ON THE YIELD OF MUTATION ALTERATIONS AND DNA REPAIR IN BONE MARROW CELLS.

The study was made of the influence of the *Rhodiola rosea* extracts administration on chromosome aberrations, production of cells with micronuclei and unscheduled DNA synthesis in bone marrow cells of mice under action of mutagens cyclophosphamide and N-nitroso-N-methylurea (NMU). It was found that *Rhodiola rosea* extracts reduce significantly the yield of cells with the chromosome aberrations and micronuclei induced by cyclophosphamide in vivo, inhibit unscheduled DNA synthesis induced by NMU in vitro. It is emphasized that *Rhodiola rosea* extracts are antimutagens due to ability to raise the efficiency of the intracell DNA repair mechanisms.

Patol Fiziol Eksp Ter. 1997 Oct-Dec;(4):22-4

THE ROLE OF HUMORAL FACTORS OF REGENERATING LIVER IN THE DEVELOPMENT OF EXPERIMENTAL TUMORS AND THE EFFECT OF RHODIOLA ROSEA EXTRACT ON THIS PROCESS.

In experiment on rats with Pliss lymphosarcoma (PLS) it was shown that partial hepatectomy (PHE), a course application of *Rhodiola rosea* extract (RRE) or combined effects inhibit the growth of tumors by 37, 39, and 59%, respectively, and that of metastases by 42, 50, and 75%. In combined treatment the process of hepatic regeneration was completed in earlier terms versus the animals which underwent PHE, and proliferative activity of the tumor and metastases decreased by 15 and 59%, respectively, judging by the degree of 3H-thymidine incorporation into DNA of these tissues. The assessment of clonogenic activity of PLS cells taken in the animals of this group, using the method of diffusion chambers, revealed a significant decrease in

this index versus the rats which underwent PHE or which were given RRE (number of colonies per chamber being 4.8 +/- 0.5; 8.6 +/- 0.9; 5.7 +/- 0.6, respectively; in control 13.8 +/- 1.5). The assumption that these effects are determined by factors originating from the regenerating liver was confirmed in experiments with double-layer agar systems. Inhibition of colony-forming activity of PLS cells was the maximum in application of the hepatocytes of the rats which underwent a complex of effects, as a feeder, versus the hepatocytes taken in intact or hepatectomized animals, or the rats which were given RRE (number of colonies per plate well being 4.6 +/- 0.3; 15.7 +/- 1.6; 7.4 +/- 0.8; 8.7 +/- 0.9, respectively; in the control 25.6 +/- 6.5). In experiments on mice with Ehrlich adenocarcinoma, the factors isolated from the liver of animals subjected to PHE against a background of RRE administration and from the liver of mice which were given RRE only, as well as operated or intact ones, inhibited the tumor growth to 63, 38, 35, and 21%, respectively.

Neoplasma. 1991;38(3):323-31

Vinpocetine

LATE-ONSET DEMENTIA: STRUCTURAL BRAIN DAMAGE AND TOTAL CEREBRAL BLOOD FLOW.

PURPOSE: To prospectively compare indicators of structural brain damage and total cerebral blood flow in patients with late-onset dementia, subjects of the same age with optimal cognitive function, and young subjects. **MATERIALS AND METHODS:** The institutional ethics committee approved the studies, and all participants (or their guardians) gave informed consent. The test group included 17 patients older than 75 years (four men, 13 women; median age, 83 years) and with a diagnosis of dementia according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. The control group included 16 subjects (four men, 12 women; median age, 87 years) with optimal cognitive function, who were selected from among 599 elderly subjects enrolled in a population-based follow-up study, and 15 young healthy subjects (seven men, eight women; median age, 29 years). Measurements of intracranial and total brain volumes, structural brain damage, and cerebral blood flow were obtained with magnetic resonance imaging. Mean values were compared with the t test; medians, with the Mann-Whitney U test. **RESULTS:** Values for total brain volume were significantly smaller in elderly subjects ($P < .001$) but did not differ significantly between patients with dementia and subjects of the same age with optimal cognitive function ($P = .69$). Among the elderly, significantly higher scores for number and extent of white matter areas of signal hyperintensity ($P = .028$) and lower magnetization transfer ratios ($P = .016$) indicated greater structural brain damage in those with dementia. Cerebral blood flow was 246 mL/min lower ($P < .001$) in elderly subjects than in young subjects. In patients with dementia, cerebral blood flow was 108 mL/min lower than that in subjects of the same age with optimal cognitive function (551 vs 443 mL/min, $P < .001$). **CONCLUSION:** The combined observations of more structural brain damage and lower cerebral blood flow in demented elderly individuals than in subjects of the same age with optimal cognitive function support the hypothesis that vascular factors contribute to dementia in old age.

Radiology. 2005 Sep;236(3):990-5.

EFFECTS OF VINPOCETINE ON THE REDISTRIBUTION OF CEREBRAL BLOOD FLOW AND GLUCOSE METABOLISM IN CHRONIC ISCHEMIC STROKE PATIENTS: A PET STUDY.

The pharmacological effects of the neuroprotective drug vinpocetine, administered intravenously in a 14-day long treatment regime, on the cerebral blood flow and cerebral glucose metabolism in chronic ischemic stroke patients ($n=13$) were studied with positron emission tomography in a double-blind design. The regional and global cerebral metabolic rates of glucose (CMRglc) and cerebral blood flow (CBF) as well as vital physiological parameters, clinical performance scales, and transcranial Doppler parameters were measured before and after the treatment period in patient groups treated with daily intravenous infusion with or without vinpocetine. While the global CMRglc values did not change markedly as a result of the infusion treatment with ($n=6$) or without ($n=7$) vinpocetine, the global CBF increased and regional CMRglc and CBF values showed marked changes in several brain structures in both cases, with more accentuated changes when the infusion contained vinpocetine. In the latter case the highest rCBF changes were observed in those structures in which the highest regional uptake of labelled vinpocetine was measured in other PET studies (thalamus and caudate nucleus: increases amounting to 36% and 37%, respectively). The findings indicate that a 2-week long intravenous vinpocetine treatment can contribute effectively to the redistribution of rCBF in chronic ischemic stroke patients. The effects are most pronounced in those brain regions with the highest uptake of the drug.

J Neurol Sci. 2005 Mar 15;229-230:275-84

ACUTE AND CHRONIC EFFECTS OF VINPOCETINE ON CEREBRAL HEMODYNAMICS AND NEUROPSYCHOLOGICAL PERFORMANCE IN MULTI-INFARCT PATIENTS.

A double-blind, prospective, randomized, placebo-controlled clinical trial was carried out to test the acute and long-term hemodynamical and beneficial cognitive effects of the vasoactive agent vinpocetine on patients suffering from multiple cerebral

infarcts by means of functional transcranial Doppler examinations and by neuropsychological tests. Twenty-six patients (17 men, 9 women) with multiple cerebral infarctions, aged between 50 and 83 years (mean age \pm SD=63.4 \pm 9.39 years) were examined, 14 of whom received vinpocetine and 12 placebo. The functional transcranial Doppler included breath-holding tests, finger movement, word fluency, and picture-discrimination tasks. Twenty-five patients were assessed by neuropsychological battery. No serious side effect was found in the vinpocetine group. The flow velocities were significantly lower in the acute phase after breath holding in the vinpocetine group than in the placebo group. Three months later, the vinpocetine patients did not show any significant worsening in digit span backward test, while the placebo group did. No other significant differences in the neuropsychological test could be detected between the treatment and the placebo groups. Longer lasting and higher dosage of vinpocetine therapy is suggested to prove its potential effect.

J Clin Pharmacol. 2005 Sep;45(9):1048-54

VINPOCETINE FOR COGNITIVE IMPAIRMENT AND DEMENTIA.

BACKGROUND: Vinpocetine is a synthetic ethyl ester of apovincamine, a vinca alkaloid obtained from the leaves of the Lesser Periwinkle (*Vinca minor*) and discovered in the late 1960s. Although used in human treatment for over twenty years, it has not been approved by any regulatory body for the treatment of cognitive impairment. Basic sciences studies have been used to claim a variety of potentially important effects in the brain. However, despite these many proposed mechanisms and targets, the relevance of this basic science to clinical studies is unclear. **OBJECTIVES:** To assess the efficacy and safety of vinpocetine in the treatment of patients with cognitive impairment due to vascular disease, Alzheimer's disease, mixed (vascular and Alzheimer's disease) and other dementias. **SEARCH STRATEGY:** The Cochrane Dementia & Cognitive Improvement Group's Specialized Register was searched using the terms vinpocetin, cavinton, kavinton, Rgh-4405, Tcv-3B, ³ethyl apovincamate², vinRx, periwinkle, ³myrtle vincapervinc² and cezayirmeneksesi. The manufacturers of vinpocetine were asked for information on trials of vinpocetine for dementia. In addition we tried to collect articles not listed in MEDLINE or other sources on the Internet (e.g. articles in Hungarian and Romanian). **SELECTION CRITERIA:** All human, unconfounded, double-blind, randomized trials in which treatment with vinpocetine was administered for more than a day and compared to control in patients with vascular dementia, Alzheimer's dementia or mixed Alzheimer's and vascular dementia and other dementias. Non-randomized trials were excluded. **DATA COLLECTION AND ANALYSIS:** Data were independently extracted by the two reviewers (SzSz and PW) and cross-checked. Data from ³washout² periods were not used for the analysis. For continuous or ordinal variables, such as cognitive test results, the main outcomes of interest were the change in score from baseline. The categorical outcome of global impression was transformed to binary data (improved or not improved) as was the occurrence of adverse effects; here the endpoint itself was of interest the Peto method of the ³typical odds ratio² was used. A test for heterogeneity of treatment effects between the trials was made if appropriate. Data synthesis and analysis were performed using the Cochrane Review Manager software (RevMan version 4.1). **MAIN RESULTS:** All identified studies were performed before the 1990s and used various terms and criteria for cognitive decline and dementia. The three studies included in the review involved a total of 583 people with dementia treated with vinpocetine or placebo. The reports of these studies did not make possible any differentiation of effects for degenerative or vascular dementia. The results show benefit associated with treatment with vinpocetine 30mg/day and 60 mg/day compared with placebo, but the number of patients treated for 6 months or more was small. Only one study extended treatment to one year. Adverse effects were inconsistently reported and without regard for relationship to dose. The available data do not demonstrate many problems of adverse effects but intention-to-treat data were not available for any of the trials. **REVIEWER'S CONCLUSIONS:** Although the basic science is interesting, the evidence for beneficial effect of vinpocetine on patients with dementia is inconclusive and does not support clinical use. The drug seems to have few adverse effects at the doses used in the studies. Large studies evaluating the use of vinpocetine for people suffering from well defined types of cognitive impairment are needed to explore possible efficacy of this treatment.

Cochrane Database Syst Rev. 2003;(1) CD003119

CLINICAL AND NON-CLINICAL INVESTIGATIONS USING POSITRON EMISSION TOMOGRAPHY, NEAR INFRARED SPECTROSCOPY AND TRANSCRANIAL DOPPLER METHODS ON THE NEUROPROTECTIVE DRUG VINPOCETINE: A SUMMARY OF EVIDENCES.

Vinpocetine is widely used as a neuroprotective drug in the prevention and treatment of cerebrovascular diseases. Vinpocetine is a potent inhibitor of the voltage-dependent Na⁽⁺⁾ channels and a selective inhibitor of the Ca⁽²⁺⁾/calmoduline-dependent phosphodiesterase 1. The clinical efficacy has been supported by several previous studies. Positron emission tomography (PET) is a powerful method to evaluate the fate, the site of action, the pharmacological and physiological effects of a drug in the brain and other organs. We have demonstrated in monkey that the [¹¹C]-labelled vinpocetine rapidly enters the brain after intravenous (i.v.) injection, the maximal uptake being approximately 5% of the total injected radioactivity. The distribution pattern of vinpocetine in the brain was heterogenous, with the highest uptake in the thalamus, basal ganglia and visual cortex. These findings were confirmed in healthy humans, where the i.v. administered [¹¹C]-labelled vinpocetine had a similar distribution pattern. The highest uptake in the brain was 3.71% of the total administered radioactivity. Quite recently, we have shown that [¹¹C]-labelled vinpocetine administered orally to healthy human volunteers also rapidly appears in the brain and shows a similar distribution pattern, the highest uptake being 0.71% of the total administered radioactivity. In two separate sets of clinical studies where chronic ischaemic post-stroke patients were either treated with a single infusion (Study 1) or with daily vinpocetine infusion

for 2 weeks (Study 2), we have shown that vinpocetine increases the regional cerebral glucose uptake and to a certain extent glucose metabolism in the so-called peri-stroke region as well as in the relatively intact brain tissue. The 2-week-long treatment also increased the regional cerebral blood flow (CBF) especially in the thalamus, basal ganglia and visual cortex of the nonsymptomatic hemisphere. We have demonstrated the cerebral perfusion-enhancing and parenchymal oxygen extraction-increasing effects of vinpocetine in subacute ischaemic stroke patients by near infrared spectroscopy (NIRS) and transcranial Doppler (TCD) methods.

J Neurol Sci. 2002 Nov 15;203-204:259-62

EFFECT OF VINPOCETINE ON THE HEMORHEOLOGIC PARAMETERS IN PATIENTS WITH CHRONIC CEREBROVASCULAR DISEASE.

INTRODUCTION: Data collected from large number of multicenter, randomized trials in acute and chronic stroke patients provide evidence, that incidence and high mortality of cerebrovascular disorders can be decreased mainly by prevention and that the effectiveness of acute stroke treatment is limited. The terminology of ³chronic cerebrovascular diseases² involves many pathologic entities and often atypical clinical symptoms refer to the focal or global hypoperfusion of the brain. However, hemorheological disturbances seem to be important factors of the complex pathomechanism. Vinpocetine has successfully been used in the treatment of cerebrovascular diseases, the part of the mechanism of action are the favourable rheological effects demonstrated after oral administration in more previous studies. **AIMS AND METHODS:** In this study the hemorheological changes after administration of small (30 mg/day) and high dose (increased to 70 mg/day) intravenous vinpocetine for 7 days in 30 patients in chronic phase of ischemic cerebrovascular disease were investigated. **RESULTS:** High dose parenteral vinpocetine treatment significantly ($p < 0.05-0.005$) decreased the hematocrit, the whole blood and plasma viscosity and red blood cell aggregation compared to the values before the treatment. Only red blood cell aggregation was improved significantly ($p < 0.05$) by small dose treatment. **CONCLUSION:** This study and other hemorheological studies in cerebrovascular patients demonstrated persistent rheological abnormalities despite the preventive therapy. The beneficial rheological effect of high dose parenteral vinpocetine indicates the use of this drug in the treatment of chronic cerebrovascular diseases. Orv Hetil. 2003 May 18;144(20):973-8

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