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JOURNAL ABSTRACTS

Tryptophan

CONVERSION RATIO OF TRYPTOPHAN TO NIACIN IN JAPANESE WOMEN FED A PURIFIED DIET CONFORMING TO THE JAPANESE DIETARY REFERENCE INTAKES.

In order to establish the human requirements of niacin, it is first important to know how much tryptophan is converted to niacin in the human body. In a general, 60 mg of tryptophan is equivalent to 1 mg of niacin, whereas the conversion ratio of tryptophan to niacin is yet to be confirmed. The aim of this study was to know the conversion ratio of tryptophan to niacin in Japanese females fed a purified diet, which followed the Japanese Dietary Reference Intakes. Ten young Japanese females were housed in the same facility and given the same daily living activity schedule for 7 d. The composition of their purified diet was conformed to the Dietary Reference Intakes in Japan. The diet was niacin free. In order to investigate the conversion ratio, daily urinary outputs were collected. Tryptophan-niacin metabolites in the urine were measured and the conversion ratio of tryptophan to niacin calculated. The conversion ratio was calculated by comparing the dietary intake of tryptophan and the sum of the niacin catabolites such as N1-methylnicotinamide, N1-methyl-2-pyridone-5-carboxamide, and N1-methyl-4-pyridone-3-carboxamide, which were derived only from the dietary intake of tryptophan. The ratio was calculated as 1.5 +/- 0.1 (mean +/- SE for 10 women; in molar basis) on the last day of the experiment. It was calculated that if the excretory percentage of niacin metabolites in the urine were 60%, of the tryptophan ingested, the conversion factor would be a value of 67, meaning that is 67 mg of tryptophan is equal to 1 mg of niacin.

J Nutr Sci Vitaminol (Tokyo). 2004 Dec;50(6):385-91

TRYPTOPHAN DEPLETION AND ITS IMPLICATIONS FOR PSYCHIATRY.

BACKGROUND: Over the past 10 years the technique of tryptophan depletion has been used increasingly as a tool for studying brain serotonergic systems. **AIMS:** To review the technique of tryptophan depletion and its current status as a tool for investigating psychiatric disorders. **METHOD:** Systematic review of preclinical and clinical studies. **RESULTS:** Tryptophan depletion produces a marked reduction in plasma tryptophan and consequently brain serotonin (5-HT) synthesis and release. In healthy volunteers the effects of tryptophan depletion are influenced by the characteristics of the subjects and include some mood lowering, some memory impairment and an increase in aggression. In patients with depression tryptophan depletion tends to result in no worsening of depression in untreated subjects but a relapse in those who have responded to antidepressants (particularly serotonergic agents). In panic disorder the results are similar. **CONCLUSIONS:** The findings that tryptophan depletion produces a relapse of symptoms in patients with depression and panic disorder who have responded to treatment with antidepressants suggests that enhanced 5-HT function is important in maintaining response in these conditions.

Br J Psychiatry. 2001 May;178:399-405

THE TRYPTOPHAN DEPLETION TEST: IMPACT ON SLEEP IN PRIMARY INSOMNIA—A PILOT STUDY.

The application of the tryptophan depletion test is based on the assumption that the decrease of plasma or serum tryptophan concentration following the ingestion of a tryptophan-free amino acid drink reflects a central nervous effect on serotonin metabolism. In the present study the impact of tryptophan depletion on polysomnographically recorded sleep in patients with primary insomnia was studied. Fifteen patients with primary insomnia slept for four nights in the sleep laboratory. Prior to the fourth night the tryptophan depletion test was applied. Sleep EEG variables served as outcome parameters. Patients with primary insomnia, compared to baseline values showed a highly significant decrease of serum tryptophan concentrations after the amino acid drink. Concerning sleep parameters, stage 1 (% sleep period time=SPT) was increased, whereas stage 2 (% SPT) was decreased. Indices of phasic activity of rapid eye movement (REM) sleep (REM density) were increased after the tryptophan depletion compared to baseline. The results suggest a negative impact of tryptophan depletion on sleep continuity and a stimulating effect on phasic measures of REM sleep in patients with primary insomnia.

Psychiatry Res. 2002 Mar 15;109(2):129-35

TREATMENT OF SEVERE CHRONIC INSOMNIA WITH L-TRYPTOPHAN: RESULTS OF A DOUBLE-BLIND CROSS-OVER STUDY.

Thirty-nine subjects with chronic insomnia were treated with L-tryptophan (L-TRP) in a double-blind, cross-over study. Instead of a placebo, a very low dose of 0.04 g L-TRP was used. The subjects suffered from a sleeping disorder classified as "psychophysiological, persistent". In the subgroup taking the full L-TRP (2 g) dose first, there was a significant difference between the treatment period with the full L-TRP dose and the ineffective dose (placebo). If the placebo was given first, however, there was no significant difference between the two treatment periods. It is suggested that psychological factors are responsible for the diverging results in the two subgroups of patients. On the basis of subjective ratings, it appears that L-TRP is effective in promoting sleep in cases of chronic insomnia.

Pharmacopsychiatry. 1987 Nov;20(6):242-4

CHRONIC INSOMNIA: EFFECTS OF TRYPTOPHAN, FLURAZEPAM, SECOBARBITAL, AND PLACEBO.

This study compared the effects of L-tryptophan (1 g), secobarbital (100 mg), flurazepam (30 mg), and placebo on sleep in 96 serious insomniacs. Each treatment was given nightly for 7 nights in a separate-group design. Outcome measures were subjective estimates by subjects of a number of sleep parameters during the week of treatment and for 1 week after, and an overall evaluation made by subjects and investigators at the end of the 2 weeks. During the treatment week, flurazepam produced significant improvement on several sleep measures compared to placebo, while tryptophan and secobarbital did not. Flurazepam and secobarbital produced withdrawal symptoms during the post-treatment week, while tryptophan and placebo did not. Sleep latency was not significantly improved by tryptophan during the treatment week, but continued to improve during the post-treatment week, resulting in a significant difference between tryptophan and baseline in week 2.

Psychopharmacology (Berl). 1983;80(2):138-42

MEAL-INDUCED CHANGES IN TRYPTOPHAN:LNA A RATIO: EFFECTS ON CRAVING AND BINGE EATING.

This study investigated the effects of meals varying in macronutrient composition on plasma tryptophan/large neutral amino acid (tryp:LNA A) ratios and subsequent appetite and mood in women defined as "food cravers." Nine women consumed one of each of a high protein, high carbohydrate and mixed meal on three separate days. Blood samples and appetite and mood ratings were taken before and at intervals up to 150 min after meal consumption. The first subsequent ad libitum food intake was recorded in diaries. The tryp:LNA A ratio increased significantly after the carbohydrate meal compared to protein and mixed meals. No significant correlations between change in tryp:LNA A ratio and mood or macronutrient intake at the ad libitum eating episode were observed. There was a negative correlation between tryp:LNA A ratio and desire to binge eat ($p=0.03$) and a trend towards a negative correlation between tryp:LNA A ratio and craving for carbohydrate-rich foods ($p=0.07$). Participants whose ad libitum eating episode was categorized as a binge had a trend ($p=0.06$) toward lower plasma tryp:LNA A ratio than those who did not binge. Regression analysis showed that the effects of change in tryp:LNA A ratio on desire to binge eat was independent of meal type and changes in insulin and glucose concentrations. These findings suggest that reducing plasma tryp:LNA A ratio, via consumption of a protein-rich meal, may mediate the desire to binge eat in susceptible women.

Eat Behav. 2000 Sep;1(1):53-62

INTERVAL THERAPY WITH L-TRYPTOPHAN IN SEVERE CHRONIC INSOMNIACS. A PREDICTIVE LABORATORY STUDY.

Interval therapy is the concept of intermittent applications with drug-free intervals, based on the observation that in many cases L-tryptophan has the best effects on disturbed sleep during the drug-free interval after short-term application. This concept was formulated as an experimental hypothesis to be tested in the sleep laboratory in a predictive, double-blind design, comparing a 4-night placebo period following repetitive 3 X 2 g L-tryptophan application with baseline. All patients, severe chronic insomniacs, 5 males and 3 females (mean age 38.4 years) improved significantly at the predefined level of 0.05. Analyses of the polygraphic recordings proved highly significant sleep improvements in the parameters that are indicators of insomnia. No side effects were seen. It can be concluded that the interval therapy with L-tryptophan is a potent treatment for chronic primary insomnia.

Int Pharmacopsychiatry. 1981;16(3):162-73

SLEEP INDUCED BY L-TRYPTOPHAN. EFFECT OF DOSAGES WITHIN THE NORMAL DIETARY INTAKE.

Previous results have demonstrated sleep-inducing effects of L-tryptophan in doses of 1 to 15 g at bedtime. The present laboratory study extends the dose-response curve downward, comparing doses of 1/4 g, 1/2 g, and 1 g of L-tryptophan with placebo, in 15 mild insomniacs (subjects who reported sleep latencies of over 30 minutes). One gram of L-tryptophan

significantly reduced sleep latency: the lower doses produced a trend in the same direction. Stage IV sleep was significantly increased by 1/4 g of L-tryptophan. These results at low doses have interesting implications since the normal dietary intake of L-tryptophan is 1/2 g to 2 g per day.

J Nerv Ment Dis. 1979 Aug;167(8):497-9

Benfotiamine

INHIBITORS OF ADVANCED GLYCATION END PRODUCT FORMATION AND NEUROVASCULAR DYSFUNCTION IN EXPERIMENTAL DIABETES.

Advanced glycation and lipoxidation end products (AGEs/ALEs) have been implicated in the pathogenesis of the major microvascular complications of diabetes mellitus: nephropathy, neuropathy, and retinopathy. This article reviews the evidence regarding the peripheral nerve and its vascular supply. Most investigations done to assess the role of AGEs/ALEs in animal models of diabetic neuropathy have used aminoguanidine as a prototypic inhibitor. Preventive or intervention experiments have shown treatment benefits for motor and sensory nerve conduction velocity, autonomic nitrergic neurotransmission, nerve morphometry, and nerve blood flow. The latter depends on improvements in nitric oxide-mediated endothelium-dependent vasodilation and is responsible for conduction velocity improvements. A mechanistic interpretation of aminoguanidine's action in terms of AGE/ALE inhibition is made problematic by the relative lack of specificity. However, other unrelated compounds, such as pyridoxamine and pyridoxamine analogues, have recently been shown to have beneficial effects similar to aminoguanidine, as well as to improve pain-related measures of thermal hyperalgesia and tactile allodynia. These data also stress the importance of redox metal ion-catalyzed AGE/ALE formation. A further approach is to decrease substrate availability by reducing the elevated levels of hexose and triose phosphates found in diabetes. Benfotiamine is a transketolase activator that directs these substrates to the pentose phosphate pathway, thus reducing tissue AGEs. A similar spectrum of improvements in nerve and vascular function were noted when using benfotiamine in diabetic rats. Taken together, the data provide strong support for an important role for AGEs/ALEs in the etiology of diabetic neuropathy.

Ann N Y Acad Sci. 2005 Jun;1043:784-92

PERIPHERAL NEUROPATHY: PATHOGENIC MECHANISMS AND ALTERNATIVE THERAPIES.

Peripheral neuropathy (PN), associated with diabetes, neurotoxic chemotherapy, human immunodeficiency virus (HIV)/antiretroviral drugs, alcoholism, nutrient deficiencies, heavy metal toxicity, and other etiologies, results in significant morbidity. Conventional pain medications primarily mask symptoms and have significant side effects and addiction profiles. However, a widening body of research indicates alternative medicine may offer significant benefit to this patient population. Alpha-lipoic acid, acetyl-L-carnitine, benfotiamine, methylcobalamin, and topical capsaicin are among the most well-researched alternative options for the treatment of PN. Other potential nutrient or botanical therapies include vitamin E, glutathione, folate, pyridoxine, biotin, myo-inositol, omega-3 and -6 fatty acids, L-arginine, L-glutamine, taurine, N-acetylcysteine, zinc, magnesium, chromium, and St. John's wort. In the realm of physical medicine, acupuncture, magnetic therapy, and yoga have been found to provide benefit. New cutting-edge conventional therapies, including dual-action peptides, may also hold promise.

Altern Med Rev. 2006 Dec;11(4):294-329

ADVANCED GLYCATION ENDPRODUCTS: WHAT IS THEIR RELEVANCE TO DIABETIC COMPLICATIONS?

Glycation is a major cause of spontaneous damage to proteins in physiological systems. This is exacerbated in diabetes as a consequence of the increase in glucose and other saccharides derivatives in plasma and at the sites of vascular complications. Protein damage by the formation of early glycation adducts is limited to lysine side chain and N-terminal amino groups whereas later stage adducts, advanced glycation endproducts (AGEs), modify these and also arginine and cysteine residues. Metabolic dysfunction in vascular cells leads to the increased formation of methylglyoxal which adds disproportionately to the glycation damage in hyperglycaemia. AGE-modified proteins undergo cellular proteolysis leading to the formation and urinary excretion of glycation free adducts. AGEs may potentiate the development of diabetic complications by activation of cell responses by AGE-modified proteins interacting with specific cell surface receptors, activation of cell responses by AGE free adducts, impairment of protein-protein and enzyme-substrate interactions by AGE residue formation, and increasing resistance to proteolysis of extracellular matrix proteins. The formation of AGEs is suppressed by intensive glycaemic control, and may in future be suppressed by thiamine and pyridoxamine supplementation, and several other pharmacological agents. Increasing expression of enzymes of the enzymatic defence against glycation provides a novel and potentially effective future therapeutic strategy to suppress protein glycation.

Diabetes Obes Metab. 2007 May;9(3):233-45

ROLE OF ADVANCED GLYCATION END PRODUCTS AND ATHEROSCLEROSIS: THERAPEUTIC IMPLICATIONS.

The vascular diseases, hypertension and atherosclerosis, affect millions of individuals worldwide, and account for a large number of deaths globally. A better understanding of the mechanism of these conditions will lead to more specific and effective therapies. Hypertension and atherosclerosis are both characterized by insulin resistance, and we suggest that this plays a major role in their etiology. The cause of insulin resistance is not known, but may be a result of a combination of genetic and lifestyle factors. In insulin resistance, alterations in glucose and lipid metabolism lead to the production of excess aldehydes including glyoxal and methylglyoxal. These aldehydes react non-enzymatically with free amino and sulfhydryl groups of amino acids of proteins to form stable conjugates called advanced glycation end products (AGEs). AGEs act directly, as well as via receptors to alter the function of many intra- and extracellular proteins including antioxidant and metabolic enzymes, calcium channels, lipoproteins, and transcriptional and structural proteins. This results in endothelial dysfunction, inflammation and oxidative stress. All these changes are

characteristic of hypertension and atherosclerosis. Human and animal studies have demonstrated that increased AGEs are also associated with these conditions. A pathological role for AGEs is substantiated by studies showing that therapies that attenuate insulin resistance and/or lower AGEs, are effective in decreasing oxidative stress, lowering blood pressure, and attenuating atherosclerotic vascular changes. These interventions include lipoic acid and other antioxidants, AGE breakers or soluble receptors of AGEs, and aldehyde-binding agents like cysteine. Such therapies may offer alternative specific means to treat hypertension and atherosclerosis. An adjunct therapy may be to implement lifestyle changes such as weight reduction, regular exercise, smoking cessation, and increasing dietary intake of fruits and vegetables that also decrease insulin resistance as well as oxidative stress.

Cell Biochem Biophys. 2007;49(1):48-63

DIABETIC NEUROPATHY: NEW STRATEGIES FOR TREATMENT.

Current therapeutic possibilities can be divided into two groups: the pathogenetically oriented and the symptomatic therapy. One of the most important component of etiology-based treatment is the stabilization of glycemic control. Based on efficacy and safety data benfotiamine and alpha-lipoic acid should be considered as first choices among pathogenetically oriented treatments of diabetic neuropathy. Promising data were published about the aldose reductase inhibitor ranirestat. The symptomatic effect of antiepileptic drugs in diabetic painful neuropathy (DPN) is originated from several possible pharmacological properties. Pregabalin and gabapentin have the highest efficacy and the lowest frequency of adverse events among these drugs. Antidepressants also extensively used for symptomatic treatment in DPN. In the last years several studies were published about the beneficial effect of duloxetine. Most likely combination therapy will be frequently applied in the future for the treatment of DPN, the optimal choice could be to combine pathogenetically oriented and symptomatic treatment.

Diabetes Obes Metab. 2008 Feb;10(2):99-108

CELLULAR AND MOLECULAR BASIS OF WOUND HEALING IN DIABETES.

Diabetic foot ulcers (DFUs), a leading cause of amputations, affect 15% of people with diabetes. A series of multiple mechanisms, including decreased cell and growth factor response, lead to diminished peripheral blood flow and decreased local angiogenesis, all of which can contribute to lack of healing in persons with DFUs. In this issue of the JCI, Gallagher and colleagues demonstrate that in diabetic mice, hyperoxia enhances the mobilization of circulating endothelial progenitor cells (EPCs) from the bone marrow to the peripheral circulation (see the related article beginning on page 1249). Local injection of the chemokine stromal cell-derived factor-1 α then recruits these EPCs to the cutaneous wound site, resulting in accelerated wound healing. Thus, Gallagher et al. have identified novel potential targets for therapeutic intervention in diabetic wound healing.

J Clin Invest. 2007 May;117(5):1219-22

SOLUBLE RAGE BLOCKS SCAVENGER RECEPTOR CD36-MEDIATED UPTAKE OF HYPOCHLORITE-MODIFIED LOW-DENSITY LIPOPROTEIN.

Engagement of the receptor for advanced glycation end products (RAGE) by its signal transduction ligands evokes inflammatory cell infiltration and activation of the vessel wall. However, soluble RAGE (sRAGE), the truncated form spanning the extracellular binding domain of RAGE, has potent anti-inflammatory properties by acting as a decoy for RAGE ligands. We now show that sRAGE binds with high affinity to atherogenic low-density lipoprotein (LDL) modified by hypochlorous acid (HOCl), the major oxidant generated by the myeloperoxidase-H₂O₂-chloride system of phagocytes activated during inflammation. We further demonstrate that sRAGE can be coprecipitated with HOCl-LDL from spiked serum. To determine the functional significance of sRAGE binding to HOCl-LDL, cell association studies with macrophages were performed. sRAGE effectively inhibited cellular uptake of HOCl-LDL and subsequent lipid accumulation. Using Chinese hamster ovary cells overexpressing class B scavenger

receptor CD36 or SR-BI, two preferential scavenger receptors for HOCl-LDL, we demonstrate that sRAGE only interferes with CD36-mediated uptake of HOCl-LDL. The present findings indicate that sRAGE acts as a sink for HOCl-LDL, which is abundantly present in human atherosclerotic lesions. We propose that sRAGE represents a physiological antagonist that interferes with scavenger receptor-mediated cholesterol accumulation and foam cell formation of macrophages.

FASEB J. 2007 Oct;21(12):3075-82

Serum level of advanced glycation end-products (AGEs) is an independent determinant of plasminogen activator inhibitor-1 (PAI-1) in nondiabetic general population.

Glucose can react nonenzymatically with amino groups of proteins to form senescent macroprotein derivatives termed advanced glycation end-products (AGEs). Recently, AGEs have been shown to play an important role in atherosclerosis even in nondiabetic subjects. However, the molecular mechanism underlying this is not fully understood. We have now investigated whether serum AGE level was an independent determinant of plasminogen activator inhibitor-1 (PAI-1), a major physiological inhibitor of fibrinolysis, in nondiabetic general population. One-hundred and eighty-six nondiabetic Japanese subjects underwent a complete history and physical examination, determination of blood chemistries, PAI-1, and AGEs. Uni- and multivariate analyses were applied for the determinants of PAI-1 levels. The average PAI-1 levels were 29.7±23.8 ng/ml in males and 21.8±17.1 ng/ml in females, respectively. Univariate regression analysis showed that PAI-1 levels were associated with age (inversely, $p=0.003$), male ($p=0.003$), body mass index (BMI) ($p<0.001$), HDL-cholesterol (inversely, $p<0.001$), triglycerides ($p<0.001$), fasting plasma glucose ($p<0.001$), insulin ($p<0.001$), uric acids ($p<0.001$), AGEs ($p=0.037$), and alcohol intake ($p<0.001$). By the use of multiple regression analyses, BMI ($p<0.001$), male ($p=0.003$), fasting plasma glucose ($p=0.005$), age (inversely, $p=0.017$), and AGEs ($p=0.034$) remained significant. The present study is the first demonstration that serum AGE level was one of the independent determinants of PAI-1 in nondiabetic general population. The AGE-associated thrombogenic abnormality may be involved in atherogenesis in nondiabetic subjects.

Horm Metab Res. 2007 Nov;39(11):845-8

CLINICAL AND PROGNOSTIC VALUE OF ADVANCED GLYCATION END-PRODUCTS IN CHRONIC HEART FAILURE.

AIMS: Advanced glycation end-products (AGEs) have been proposed as a novel factor involved in the development and progression of chronic heart failure (CHF). We aimed to determine whether plasma levels of N(epsilon)-(carboxymethyl)lysine (CML) and N(epsilon)-(carboxyethyl)lysine (CEL), two well-known AGEs, are related to the severity and prognosis of CHF. METHODS AND RESULTS: A total of 102 CHF patients, aged 58 ± 12 years, with an average left ventricular ejection fraction of 28 ± 9% were followed for 1.7 (1.2-1.9) years. NYHA functional class and NT-pro-BNP were used as estimates of the severity of CHF. CML and CEL were determined by LC-MS/MS. CML levels were associated with NYHA functional class ($P < 0.001$) and NT-pro-BNP levels ($P < 0.001$). Survival analysis for the combined end-point of death, heart transplantation, ischaemic cardiovascular event, and hospitalization for heart failure revealed that CML levels predicted outcome, even after adjustment for age, gender, aetiology of CHF, identified risk modifiers, and several known predictors of outcome in CHF. The predictive value of CML subsided after correction for renal function. CEL was not associated with the severity or prognosis of CHF. CONCLUSION: Plasma AGEs, in particular CML levels, are related to the severity and prognosis of CHF. The fact that the relation between CML and prognosis subsided after correction for renal function may suggest that AGE accumulation in renal failure explains part of the prognostic value of renal function in CHF. However, further investigation is warranted to exclude the possibility that CML is just an innocent marker of renal function.

Eur Heart J. 2007 Dec;28(23):2879-85

RAPID INCREASE IN HUMAN LIFE EXPECTANCY: WILL IT SOON BE LIMITED BY THE AGING OF ELASTIN?

The postponement of the most frequent age-related diseases stimulated speculations of the possibility of "dying of old age". The selective decline of individual physiological functions-aging in spare-parts-indicates however the potential limitation of the life-span by the rapid decline of some of the vital parameters. We explored a possibility of such a limitation of maximal life-span by the age-related alteration of elastin, consisting in Ca-accumulation, lipid deposition and elastolytic degradation. The quantitative evaluation of these processes suggests an approximative upper limit for the elastic properties of the cardio-respiratory system of about 100-120 years, at least, as far as elastin is involved. This process, age-related alterations of elastic fibers, is however not the only one limiting the functional value of the cardiovascular system. Crosslinking of collagen fibers by advanced glycation end-products certainly contributes also to the age-dependent rigidification of the cardiovascular system. Therefore the answer to the initial question, can age-dependent alterations of a single matrix macromolecule be limiting such vital functions as the cardio-respiratory system-is a cautious yes, with however the caveat that other, independent mechanisms, such as the Maillard reaction, can also interfere with and limit further the functional value of such vital physiological functions.

Biogerontology. 2008 Jan 4

THIAMINE PYROPHOSPHATE AND PYRIDOXAMINE INHIBIT THE FORMATION OF ANTIGENIC ADVANCED GLYCATION END-PRODUCTS: COMPARISON WITH AMINOGUANIDINE.

Nonenzymatic glycation of proteins by glucose leading to the formation of toxic and immunogenic advanced glycation end products (AGEs) may be a major contributor to the pathological manifestations of diabetes mellitus, aging, and, possibly, neurodegenerative diseases such as Alzheimer's. We tested the in vitro inhibition of antigenic AGE formation on bovine serum albumin, ribonuclease A, and human hemoglobin by various vitamin B1 and B6 derivatives. Among the inhibitors, pyridoxamine and thiamine pyrophosphate potently inhibited AGE formation and were more effective than aminoguanidine, suggesting that these two compounds may have novel therapeutic potential in preventing vascular complications of diabetes. An unexpected finding was that aminoguanidine inhibited the late kinetic stages of glycation much more weakly than the early phase.

Biochem Biophys Res Commun. 1996 Mar 7;220(1):113-9

IN VITRO KINETIC STUDIES OF FORMATION OF ANTIGENIC ADVANCED GLYCATION END PRODUCTS (AGES). NOVEL INHIBITION OF POST-AMADORI GLYCATION PATHWAYS.

Nonenzymatic protein glycation (Maillard reaction) leads to heterogeneous, toxic, and antigenic advanced glycation end products ("AGEs") and reactive precursors that have been implicated in the pathogenesis of diabetes, Alzheimer's disease, and normal aging. In vitro inhibition studies of AGE formation in the presence of high sugar concentrations are difficult to interpret, since AGE-forming intermediates may oxidatively arise from free sugar or from Schiff base condensation products with protein amino groups, rather than from just their classical Amadori rearrangement products. We recently succeeded in isolating an Amadori intermediate in the reaction of ribonuclease A (RNase) with ribose for rapid studies of post-Amadori AGE formation in absence of free sugar or reversibly formed Schiff base precursors to Amadori products. This provides a new bstrategy for a better understanding of the mechanism of AGE inhibition by established inhibitors, such as aminoguanidine, and for searching for novel inhibitors specifically acting on post-Amadori pathways of AGE formation. Aminoguanidine shows little inhibition of post-Amadori AGE formation in RNase and bovine serum albumin, in contrast to its apparently effective inhibition of initial (although not late) stages of glycation in the presence of high concentrations of sugar. Of several derivatives of vitamins B1 and B6 recently studied for possible AGE inhibition in the presence of glucose, pyridoxamine and, to a lesser extent, thiamine pyrophosphate proved to be novel and effective post-Amadori inhibitors that decrease the final levels of AGEs formed. Our mechanism-based approach to the study of AGE inhibition appears promising for the design and discovery of novel post-Amadori AGE inhibitors of therapeutic potential that may complement others, such as aminoguanidine, known to either prevent initial sugar attachment or to scavenge highly reactive dicarbonyl intermediates.

J Biol Chem. 1997 Feb 28;272(9):5430-7

DNA AND RNA AS NEW BINDING TARGETS OF GREEN TEA CATECHINS.

The significance of catechins, the main constituent of green tea, is being increasingly recognized with regard to cancer prevention. Catechins have been studied for interactions with various proteins, but the mechanisms of the various catechins are not yet elucidated. Based on our previous observation that nucleic acids extracted from catechin-treated cells are colored, we studied whether catechins directly interact with nucleic acids using surface plasmon resonance assay (Biacore) and cold spray ionization-mass spectrometry. These two methods clearly showed that (-)-epigallocatechin gallate (EGCG) binds to both DNA and RNA molecules: the Biacore assay indicated that four catechins bound to DNA oligomers, and cold spray ionization-mass spectrometry analysis showed one to three EGCG molecules bound to single strand 18 mers of DNA and RNA. Moreover, one or two molecules of EGCG bound to double-stranded (AG-CT) oligomers of various nucleotide lengths. These results suggest that multiple binding sites of EGCG are present in DNA and RNA oligomers. Double-stranded DNA (dsDNA) oligomers were detected only as EGCG-bound forms at high temperature, whereas at low temperature both the free and bound forms were detected, suggesting that EGCG protects dsDNA oligomers from dsDNA melting to single-stranded DNA. Because both galloyl and catechol groups of EGCG are essential for DNA binding, both groups seem to hold strands of DNA via their branching structure. These findings reveal for the first time the link between catechins and polynucleotides and will intensify our understanding of the effects of catechins on DNA in terms of cancer prevention.

J Biol Chem. 2006 Jun 23;281(25):17446-56

GREEN TEA CATECHIN AS A CHEMICAL CHAPERONE IN CANCER PREVENTION.

Green tea catechins have recently gained significant acceptance as a cancer preventive, and one of the important features of catechins is their interactions with various target molecules. We recently found a functional and structural similarity between catechins and chaperones: Stochastic conformational analysis *in silico* revealed numerous conformations of (-)-epigallocatechin gallate, (-)-epicatechin gallate and (-)-epigallocatechin, showing a unique flexibility and mobility of the catechin molecules and suggesting the significance of a galloyl group in conformational variation. Since these conformations result in interaction with various types of molecules, we think that green tea catechin induces cancer preventive activity mediated through a chaperone-like property.

Cancer Lett. 2007 Dec 7

Biotransformation of green tea polyphenols and the biological activities of polyphenol constituents, the catechins, have been reported to have many health benefits including the prevention of cancer and heart disease. Many mechanisms of action have been proposed based on *in vitro* models; however, the importance of most of these mechanisms remains to be determined *in vivo*. The bioavailability and biotransformation of tea catechins play a key role in determining the importance of various mechanisms *in vivo*. Likewise, the biological activity and bioavailability of tea catechin metabolites, an understudied area, are important in understanding the potential beneficial effects of tea. In this article, we review the data available on the biotransformation of the tea catechins and the limited data set available on the biological activities of the catechin metabolites. Careful interpretation of available data, carefully designed animal experiments, and integration of bioavailability and biological activity data are needed if the disease preventive activity of tea is to be understood. We hope this article will spark research efforts on some of the important questions regarding tea polyphenol bioavailability, biotransformation, and the biological activities of tea catechin metabolites.

Mol Pharm. 2007 Nov-Dec;4(6):819-25

ANTI-OBESITY EFFECTS OF GREEN TEA: FROM BEDSIDE TO BENCH.

During the last decade, the traditional notion that green tea consumption benefits health has received significant scientific attention and, particularly, the areas of cardiovascular disease and cancer were subject to numerous studies. Due to the ever-growing obesity pandemic, the anti-obesity effects of green tea are being increasingly investigated in cell, animal, and human studies. Green tea, green tea catechins, and epigallocatechin gallate (EGCG) have been demonstrated in cell culture and animal models of obesity to reduce adipocyte differentiation and proliferation, lipogenesis, fat mass, body weight, fat absorption, plasma levels of triglycerides, free fatty acids, cholesterol, glucose, insulin and leptin, as well as to increase beta-oxidation and

thermogenesis. Adipose tissue, liver, intestine, and skeletal muscle are target organs of green tea, mediating its anti-obesity effects. Studies conducted with human subjects report reduced body weight and body fat, as well as increased fat oxidation and thermogenesis and thereby confirm findings in cell culture systems and animal models of obesity. There is still a need for well-designed and controlled clinical studies to validate the existing and encouraging human studies. Since EGCG is regarded as the most active component of green tea, its specific effects on obesity should also be investigated in human trials.

Mol Nutr Food Res. 2006 Feb;50(2):176-87

NEUROLOGICAL MECHANISMS OF GREEN TEA POLYPHENOLS IN ALZHEIMER'S AND PARKINSON'S DISEASES.

Tea consumption is varying its status from a mere ancient beverage and a lifestyle habit, to a nutrient endowed with possible prospective neurobiological-pharmacological actions beneficial to human health. Accumulating evidence suggest that oxidative stress resulting in reactive oxygen species generation and inflammation play a pivotal role in neurodegenerative diseases, supporting the implementation of radical scavengers, transition metal (e.g., iron and copper) chelators, and nonvitamin natural antioxidant polyphenols in the clinic. These observations are in line with the current view that polyphenolic dietary supplementation may have an impact on cognitive deficits in individuals of advanced age. As a consequence, green tea polyphenols are now being considered as therapeutic agents in well controlled epidemiological studies, aimed to alter brain aging processes and to serve as possible neuroprotective agents in progressive neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. In particular, literature on the putative novel neuroprotective mechanism of the major green tea polyphenol, (-)-epigallocatechin-3-gallate, are examined and discussed in this review.

J Nutr Biochem. 2004 Sep;15(9):506-16

USE OF TEA EXTRACTS (CAMELIA SINENSIS) IN JELLY CANDIES AS POLYPHENOLS SOURCES IN HUMAN DIET.

Diet rich in polyphenols may be important factor in preventing cardiovascular, neoplastic diseases and slowing down the aging processes. Because tea (*Camellia sinensis*) is most popular beverage containing relatively large amounts of polyphenols, it could be tremendously important source of polyphenolic constituents in human diet. However, there has been no data on the tea extracts use in particular everyday snacks. Objective of the study was to investigate potential use of tea polyphenol extracts in jelly candies, its taste, colour, consistency and general consumer's acceptance. Sensory analyses were conducted on two kinds of sweet jellies, with gelatin and agar used as thickening agents. As polyphenol source green and black tea extracts (*Camellia sinensis*) were used at concentration of 1.0% and 1.5%. Total polyphenol content in jellies ranged between 245.9-1256.5 mg/100g of candies and EGCG (epigallocatechin gallate) strong antioxidant content ranged between 3.2-170.1 mg/100g of candies. Sensory analyses included evaluation of overall appearance, colour, taste, aroma, consistence (homogeneity, clot presence) and clarity of jellies. Comparison of two thickening agents resulted in better properties of gelatin jellies according to its quality: colour, clarity, consistence, taste and aroma ($p < 0.05$). It was found that agar containing jellies were not so clear and aromatic as compared with gelatin ($p < 0.05$). Colour and overall appearance was also much more acceptable by the consumers in gelatin jellies. According to tea extract used it was found that ethanol extracts resulted in lower acceptance for overall acceptance and consistency ($p < 0.05$). Present study indicated that tea polyphenols extracts were accepted by consumers as food product constituents, and might be an interest of wider usage as food components.

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GREEN TEA CONSUMPTION AND PROSTATE CANCER RISK IN JAPANESE MEN: A PROSPECTIVE STUDY.

The incidence of prostate cancer is much lower in Asian than Western populations. Given that environmental factors such as dietary habits may play a major role in the causation of prostate cancer and the high consumption of green tea in Asian populations, this low incidence may be partly due to the effects of green tea. The JPHC Study (Japan Public Health Center-based Prospective Study) was established in 1990 for cohort I and in 1993 for cohort II. The subjects were 49,920 men aged 40-69 years who completed a questionnaire that included their green tea consumption habit at baseline and were followed until the end of 2004. During this time, 404 men were newly diagnosed with prostate cancer, of whom 114 had advanced cases, 271 were localized, and 19 were of an undetermined stage. Green tea was not associated with localized prostate cancer. However, consumption was associated with a dose-dependent decrease in the risk of advanced prostate cancer. The multivariate relative risk was 0.52 (95% confidence interval: 0.28, 0.96) for men drinking 5 or more cups/day compared with less than 1 cup/day (p (trend) = 0.01). Green tea may be associated with a decreased risk of advanced prostate cancer.

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GREEN TEA CONSUMPTION AND MORTALITY DUE TO CARDIOVASCULAR DISEASE, CANCER, AND ALL CAUSES IN JAPAN: THE OHSAKI STUDY.

CONTEXT: Green tea polyphenols have been extensively studied as cardiovascular disease and cancer chemopreventive agents in vitro and in animal studies. However, the effects of green tea consumption in humans remain unclear. **OBJECTIVE:** To investigate the associations between green tea consumption and all-cause and cause-specific mortality. **DESIGN, SETTING, AND PARTICIPANTS:** The Ohsaki National Health Insurance Cohort Study, a population-based, prospective cohort study initiated in 1994 among 40,530 Japanese adults aged 40 to 79 years without history of stroke, coronary heart disease, or cancer at baseline. Participants were followed up for up to 11 years (1995-2005) for all-cause mortality and for up to 7 years (1995-2001) for cause-specific mortality. **MAIN OUTCOME MEASURES:** Mortality due to cardiovascular disease, cancer, and all causes. **RESULTS:** Over 11 years of follow-up (follow-up rate, 86.1%), 4,209 participants died, and over 7 years of follow-up (follow-up rate, 89.6%), 892 participants died of cardiovascular disease and 1,134 participants died of cancer. Green tea consumption was inversely associated with mortality due to all causes and due to cardiovascular disease. The inverse association with all-cause mortality was stronger in women ($P = .03$ for interaction with sex). In men, the multivariate hazard ratios of mortality due to all causes associated with different green tea consumption frequencies were 1.00 (reference) for less than 1 cup/d, 0.93 (95% confidence interval [CI], 0.83-1.05) for 1 to 2 cups/d, 0.95 (95% CI, 0.85-1.06) for 3 to 4 cups/d, and 0.88 (95% CI, 0.79-0.98) for 5 or more cups/d, respectively ($P = .03$ for trend). The corresponding data for women were 1.00, 0.98 (95% CI, 0.84-1.15), 0.82 (95% CI, 0.70-0.95), and 0.77 (95% CI, 0.67-0.89), respectively ($P < .001$ for trend). The inverse association with cardiovascular disease mortality was stronger than that with all-cause mortality. This inverse association was also stronger in women ($P = .08$ for interaction with sex). In women, the multivariate hazard ratios of cardiovascular disease mortality across increasing green tea consumption categories were 1.00, 0.84 (95% CI, 0.63-1.12), 0.69 (95% CI, 0.52-0.93), and 0.69 (95% CI, 0.53-0.90), respectively ($P = .004$ for trend). Among the types of cardiovascular disease mortality, the strongest inverse association was observed for stroke mortality. In contrast, the hazard ratios of cancer mortality were not significantly different from 1.00 in all green tea categories compared with the lowest-consumption category. **CONCLUSION:** Green tea consumption is associated with reduced mortality due to all causes and due to cardiovascular disease but not with reduced mortality due to cancer.

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GREEN TEA CONSUMPTION AND COGNITIVE FUNCTION: A CROSS-SECTIONAL STUDY FROM THE TSURUGAYA PROJECT 1.

BACKGROUND: Although considerable experimental and animal evidence shows that green tea may possess potent activities of neuroprotection, neurorescue, and amyloid precursor protein processing that may lead to cognitive enhancement, no human data are available. **OBJECTIVE:** The objective was to examine the association between green tea consumption and cognitive function in humans. **DESIGN:** We analyzed cross-sectional data from a community-based Comprehensive Geriatric Assessment (CGA) conducted in 2002. The subjects were 1,003 Japanese subjects aged ≥ 70 y. They completed a self-administered questionnaire that included questions about the frequency of green tea consumption. We evaluated cognitive function by using the Mini-Mental State Examination with cutoffs of <28 , <26 , and <24 and calculated multivariate-adjusted odds ratios (ORs) of cognitive impairment. **RESULTS:** Higher consumption of green tea was associated with a lower prevalence of cognitive impairment. At the <26 cutoff, after adjustment for potential confounders, the ORs for the cognitive impairment associated with different frequencies of green tea consumption were 1.00 (reference) for < 3 cups/wk, 0.62 (95% CI: 0.33, 1.19) for 4-6 cups/wk or 1 cup/d, and 0.46 (95% CI: 0.30, 0.72) for ≥ 2 cups/d (P for trend = 0.0006). Corresponding ORs were 1.00 (reference), 0.60 (95% CI: 0.35, 1.02), and 0.87 (95% CI: 0.55, 1.38) (P for trend = 0.33) for black or oolong tea and 1.00 (reference), 1.16 (95% CI: 0.78, 1.73), and 1.03 (95% CI: 0.59, 1.80) (P for trend = 0.70) for coffee. The results were essentially the same at cutoffs of <28 and <24 . **CONCLUSION:** A higher consumption of green tea is associated with a lower prevalence of cognitive impairment in humans.

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A GREEN TEA EXTRACT HIGH IN CATECHINS REDUCES BODY FAT AND CARDIOVASCULAR RISKS IN HUMANS.

OBJECTIVE: The body fat reducing effect and reduction of risks for cardiovascular disease by a green tea extract (GTE) high in catechins was investigated in humans with typical lifestyles. **RESEARCH METHODS AND PROCEDURES:** Japanese women and men with visceral fat-type obesity were recruited for the trial. After a 2-week diet run-in period, a 12-week double-blind parallel multicenter trial was performed, in which the subjects ingested green tea containing 583 mg of catechins (catechin group) or 96 mg of catechins (control group) per day. Randomization was stratified by gender and body mass index at each medical institution. The subjects were instructed to maintain their usual dietary intake and normal physical activity. **RESULTS:** Data were analyzed using per-protocol samples of 240 subjects (catechin group; $n = 123$, control group; $n = 117$). Decreases in body weight, body mass index, body fat ratio, body fat mass, waist circumference, hip circumference, visceral fat area, and subcutaneous fat area were found to be greater in the catechin group than in the control group. A greater decrease in systolic blood pressure (SBP) was found in the catechin group compared with the control group for subjects whose initial SBP was 130 mm Hg or higher. Low-density lipoprotein (LDL) cholesterol was also decreased to a greater extent in the catechin group. No adverse effect was found. **DISCUSSION:** The continuous ingestion of a GTE high in catechins led to a reduction in body fat, SBP, and LDL cholesterol, suggesting that the ingestion of such an extract contributes to a decrease in obesity and cardiovascular disease risks.

SPECIFIC FORMULATION OF CAMELLIA SINENSIS PREVENTS COLD AND FLU SYMPTOMS AND ENHANCES GAMMA,DELTA T CELL FUNCTION: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY.

OBJECTIVE: Determine if a specific formulation of Camellia sinensis (CSF) can prevent illness and symptoms due to cold and flu, and enhance gammadelta T cell function **METHODS:** Design: Randomized, double-blind, placebo-controlled study. Subjects: Healthy adults 18-70 years old. Intervention: Proprietary formulation of Camellia sinensis (green tea) capsules, or a placebo, twice a day, for 3 months. Measures of Outcome: As assessed by daily symptom logs, percentage of subjects experiencing cold and flu symptoms, number of days subjects experienced symptoms, and percentage of subjects seeking medical treatment. Mean in vivo and ex vivo proliferative and interferon gamma responses of subjects' peripheral blood mononuclear cells to gammadelta T cell antigen stimulation. **RESULTS:** Among subjects taking CSF there were 32.1% fewer subjects with symptoms ($P = 0.035$), 22.9% fewer overall illnesses of at least 2 days duration ($P = 0.092$), and 35.6% fewer symptom days ($P < 0.002$), compared to subjects taking placebo. gammadelta T cells from subjects taking CSF proliferated 28% more ($P = 0.017$) and secreted 26% more IFN-gamma ($P = 0.046$) in response to gammadelta T cell antigens, as compared to gammadelta T cells from subjects taking placebo. CSF was well-tolerated. **CONCLUSIONS:** This proprietary formulation of CSF is a safe and effective dietary supplement for preventing cold and flu symptoms, and for enhancing gammadelta T cell function.

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