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*Journal*  
**ABSTRACTS****Oral health****PERIODONTAL INFECTIONS AND CARDIOVASCULAR DISEASE: THE HEART OF THE MATTER.**

**BACKGROUND:** Oral infection models have emerged as useful tools to study the hypothesis that infection is a cardiovascular disease (CVD) risk factor. Periodontal infections are a leading culprit, with studies reporting associations between periodontal disease and CVD. The results, however, have varied, and it often is unclear what conclusions can be drawn from these data.

**SUMMARY:** An association exists between periodontal disease and CVD. It is unknown, however, whether this relationship is causal or coincidental. Early studies predominantly used nonspecific clinical and radiographic definitions of periodontal disease as surrogates for infectious exposure. While most studies demonstrated positive associations between periodontal disease and CVD, not all studies were positive, and substantial variations in results were evident. More recent studies have enhanced the specificity of infectious exposure definitions by measuring systemic antibodies to selected periodontal pathogens or by directly measuring and quantifying oral microbiota from subgingival dental plaque. Results from these studies have shown positive associations between periodontal disease and CVD. **CONCLUSIONS:** Evidence continues to support an association among periodontal infections, atherosclerosis and vascular disease. Ongoing observational and focused pilot intervention studies may inform the design of large-scale clinical intervention studies. Recommending periodontal treatment for the prevention of atherosclerotic CVD is not warranted based on scientific evidence. Periodontal treatment must be recommended on the basis of the value of its benefits for the oral health of patients, recognizing that patients are not healthy without good oral health. However, the emergence of periodontal infections as a potential risk factor for CVD is leading to a convergence in oral and medical care that can only benefit the patients and public health.

J Am Dent Assoc. 2006 Oct;137 Suppl:14S-20S

**BONE HEALTH AND ORAL HEALTH.**

**BACKGROUND:** Low bone mass in the skeleton, which increases the risk of osteoporotic fracture, also may be associated with periodontal bone loss and tooth loss. Osteoporosis and periodontal disease share several common risk factors, including older age, smoking and perhaps insufficient dietary intakes of calcium and vitamin D. **CONCLUSION:** Research supports the idea that osteoporosis independently influences alveolar bone height loss. Strategies for reducing osteoporosis risk also may help retard alveolar bone loss. Meeting dietary intake recommendations for calcium and vitamin D is one strategy that is appropriate for a broad segment of the population. **CLINICAL IMPLICATIONS:** A healthy lifestyle has multiple benefits for the mouth and throughout the body. Dental professionals can play a role in preventing osteoporosis by reinforcing this message.

J Am Dent Assoc. 2007 May;138(5):616-9

**PROFESSIONAL ORAL HEALTH CARE BY DENTAL HYGIENISTS REDUCED RESPIRATORY INFECTIONS IN ELDERLY PERSONS REQUIRING NURSING CARE.**

**OBJECTIVES:** Respiratory infection is a major cause of death in the elderly. We have evaluated the role of professional oral health care (POHC) by dental hygienists in reducing respiratory infections in elderly persons requiring nursing care. **METHODS:** Two populations of elderly persons, one receiving POHC and one not, were examined to determine numbers of microorganisms, potent pathogens of respiratory infection, enzymatic activity in saliva, fevers, prevalence of fatal aspiration pneumonia and prevalence of influenza. **RESULTS:** In the first population, we found a high prevalence of potent respiratory pathogens such as *Staphylococcus* species, *Pseudomonas aeruginosa* and *Candida albicans*. Patients who received POHC showed a lower prevalence for these pathogens than those who did not. The ratio of fatal aspiration pneumonia in POHC patients was significantly lower than that in patients without POHC (non-POHC) over a 24-month period ( $P < 0.05$ ). The prevalence of a fever of 37.8 degrees C or more in POHC patients was significantly lower than that in the non-POHC group ( $P < 0.05$ ). In the second study population, we investigated the effects of POHC on infection with influenza over a 6-month period. In the POHC group, neuraminidase and trypsin-like protease activities decreased, and one of 98 patients was diagnosed with influenza; whereas, in the non-POHC group, nine of 92 patients were diagnosed with influenza. The relative risk of developing influenza while under POHC was 0.1 (95% CI 0.01-0.81,  $P = 0.008$ ). **CONCLUSION:** These results suggest that POHC by dental hygienists is effective

### **PUNICA GRANATUM (POMEGRANATE) EXTRACT IS ACTIVE AGAINST DENTAL PLAQUE.**

In the present work, we studied the effect of the hydroalcoholic extract (HAE) from *Punica granatum* (pomegranate) fruits on dental plaque microorganisms. The study was conducted on 60 healthy patients (33 females and 27 males, with age ranging from 9 to 25 years) using fixed orthodontic appliances, and randomly distributed into 3 groups of 20 patients each. The first group (control) used distilled water, while the second and third groups used chlorhexidine (standard) and HAE as mouth-rinses, respectively. The dental plaque material was collected from each patient, before and after a 1-min mouth-rinse with 15 ml of either distilled water, chlorhexidine or HAE. In both dental plaque collections, the material was removed from patients without oral hygiene, for 24 h (no tooth brushing). Dental plaque samples were diluted in phosphate buffered saline (PBS) plated on Mueller-Hinton agar, and incubated for 48 h, at 37 degrees C. Results, expressed as the number of colony forming units per milliliter (CFU/mL), show that the HAE was very effective against dental plaque microorganisms, decreasing the CFU/ml by 84% (CFU x 10<sup>5</sup>), before mouth-rinse: 154.0 +/- 41.18; after mouthrinse: 25.4 +/- 7.76). While similar values were observed with chlorhexidine, used as standard and positive control (79% inhibition), only an 11% inhibition of CFU/ml was demonstrated in the distilled water group, negative control (CFU x 10<sup>5</sup>), before mouth-rinse: chlorhexidine, 208.7 +/- 58.81 and distilled water, 81.1 +/- 10.12; after mouth-rinse: chlorhexidine, 44.0 +/- 15.85 and distilled water, 71.9 +/- 8.68). The HAE presented also an antibacterial activity against selected microorganisms, and may be a possible alternative for the treatment of dental plaque bacteria.

### **DENTAL PLAQUE FORMATION AND SALIVARY MUTANS STREPTOCOCCI IN SCHOOLCHILDREN AFTER USE OF XYLITOL-CONTAINING CHEWING GUM.**

**OBJECTIVE:** The aim of this study was to investigate the effect of a fixed daily dose of xylitol on mutans streptococci in saliva and the amount of visible dental plaque. A second aim was to explore if the possible effects differed between children with and without caries experience. **METHODS:** The study was designed as a double-blind randomized controlled trial with two parallel arms. All pupils (n=149) in grades 1-6 in a comprehensive school in northern Sweden were invited, and 128 children (mean age=12.7 years) consented to participate. The children were stratified as having caries experience (DMFS/dmfs>or=1) or not before the random allocation to a test or control group. The control group (A) was given two pellets containing sorbitol and maltitol three times daily for 4 weeks, and the test group (B) received corresponding pellets with xylitol as single sweetener (total dose=6.18 g day). Clinical scoring and saliva samples were collected at baseline and immediately after the test period. The outcome measures were visible plaque index, salivary mutans streptococci counts and salivary lactic acid production. **RESULTS:** The amount of visible plaque was significantly reduced in both groups after 4 weeks (P<0.05). Likewise, the sucrose-induced lactic acid formation in saliva diminished in both groups (P<0.05). The proportion of mutans streptococci decreased significantly in the test group compared to baseline, but not in the control group (P<0.05). The alterations in the test group seemed most prominent among children without previous caries experience. **CONCLUSIONS:** The results suggest that chewing gum with xylitol or sorbitol/maltitol can reduce the amount of dental plaque and acid production in saliva in schoolchildren, but only the xylitol-containing gum may also interfere with the microbial composition.

### **PERIODONTAL DISEASE—THE EMERGENCE OF A RISK FOR SYSTEMIC CONDITIONS: PRE-TERM LOW BIRTH WEIGHT.**

This paper addresses the problem of adverse pregnancy outcome in relation to periodontal disease. There is compelling evidence that a link exists between pre-term low birth weight (PLBW) and periodontitis. Although 25% to 50% of PLBW deliveries occur without any known aetiology, there is increasing evidence that infection may play a significant role in pre-term delivery. A model explaining the plausible relationship is proposed based upon the concept of infection leading to a cascade of inflammatory reactions associated with pre-term labour and periodontal disease. Current evidence has pointed to an interest in dental intervention studies to control periodontal disease as one of the potential strategies to reduce pre-term labour. This paper reviews the potential association between periodontal infection and adverse pregnancy outcomes.

### **PERIODONTAL DISEASE AND MORTALITY IN TYPE 2 DIABETES.**

**OBJECTIVE:** Periodontal disease may contribute to the increased mortality associated with diabetes. **RESEARCH DESIGN AND METHODS:** In a prospective longitudinal study of 628 subjects aged > or =35 years, we examined the effect of periodontal

disease on overall and cardiovascular disease mortality in Pima Indians with type 2 diabetes. Periodontal abnormality was classified as no or mild, moderate, and severe, based on panoramic radiographs and clinical dental examinations. RESULTS: During a median follow-up of 11 years (range 0.3-16), 204 subjects died. The age- and sex-adjusted death rates for all natural causes expressed as the number of deaths per 1,000 person-years of follow-up were 3.7 (95% CI 0.7-6.6) for no or mild periodontal disease, 19.6 (10.7-28.5) for moderate periodontal disease, and 28.4 (22.3-34.6) for severe periodontal disease. Periodontal disease predicted deaths from ischemic heart disease (IHD) (P trend = 0.04) and diabetic nephropathy (P trend < 0.01). Death rates from other causes were not associated with periodontal disease. After adjustment for age, sex, duration of diabetes, HbA1c, macroalbuminuria, BMI, serum cholesterol concentration, hypertension, electrocardiographic abnormalities, and current smoking in a proportional hazards model, subjects with severe periodontal disease had 3.2 times the risk (95% CI 1.1-9.3) of cardiorenal mortality (IHD and diabetic nephropathy combined) compared with the reference group (no or mild periodontal disease and moderate periodontal disease combined). CONCLUSIONS: Periodontal disease is a strong predictor of mortality from IHD and diabetic nephropathy in Pima Indians with type 2 diabetes. The effect of periodontal disease is in addition to the effects of traditional risk factors for these diseases.

Diabetes Care. 2005 Jan;28(1):27-32

### **THE PREVALENCE OF INFLAMMATORY PERIODONTITIS IS NEGATIVELY ASSOCIATED WITH SERUM ANTIOXIDANT CONCENTRATIONS.**

Chronic periodontitis is an inflammatory disease that affects the supporting tissues of the teeth. It is initiated by specific bacteria within the plaque biofilm and progresses due to an abnormal inflammatory-immune response to those bacteria. Periodontitis is the major cause of tooth loss and is also significantly associated with an increased risk of stroke, type-2 diabetes and atheromatous heart disease. Oxidative stress is reported in periodontitis both locally and peripherally (serum), providing potential mechanistic links between periodontitis and systemic inflammatory diseases. It is therefore important to examine serum antioxidant concentrations in periodontal health/disease, both at an individual species and total antioxidant (TAOC) level. To determine whether serum antioxidant concentrations were associated with altered relative risk for periodontitis, we used multiple logistic regression for dual case definitions (both mild and severe disease) of periodontitis in an analysis of 11,480 NHANES III adult participants (>20 y of age). Serum concentrations of vitamin C, bilirubin, and TAOC were inversely associated with periodontitis, the association being stronger in severe disease. Vitamin C and TAOC remained protective in never-smokers. Higher serum antioxidant concentrations were associated with lower odds ratios for severe periodontitis of 0.53 (CI, 0.42,0.68) for vitamin C, 0.65 (0.49,0.93) for bilirubin, and 0.63 (0.47,0.85) for TAOC. In the subpopulation of never-smokers, the protective effect was more pronounced: 0.38 (0.26,0.63, vitamin C) and 0.55 (0.33,0.93, TAOC). Increased serum antioxidant concentrations are associated with a reduced relative risk of periodontitis even in never-smokers.

J Nutr. 2007 Mar;137(3):657-64

### **RESOLUTION OF INFLAMMATION: A NEW PARADIGM FOR THE PATHOGENESIS OF PERIODONTAL DISEASES.**

The periodontal diseases are infectious diseases caused by predominantly Gram-negative bacteria. However, as our understanding of the pathogenesis of the periodontal diseases grows, it is becoming clear that most of the tissue damage that characterizes periodontal disease is caused by the host response to infection, not by the infectious agent directly. Investigation into the mechanism of action of host-mediated tissue injury has revealed that the neutrophil plays an important role in destruction of host tissues. In this paper, we review the biochemical pathways and molecular mediators that are responsible for regulation of the inflammatory response in diseases such as periodontitis, with a focus on lipid mediators of inflammation. Pro-inflammatory mediators, such as prostaglandins and leukotrienes, are balanced by counter-regulatory signals provided by a class of molecules called lipoxins. The role of lipoxins in the control and resolution of inflammation is discussed, as is the possibility of the development of new therapeutic strategies for the control and prevention of neutrophil-mediated tissue injury in inflammatory diseases like periodontitis.

J Dent Res. 2003 Feb;82(2):82-90

### **THE EFFECT OF INFECTIONS AND VACCINATIONS ON STROKE RISK.**

There is increasing evidence that, in addition to conventional risk factors, acute and chronic infectious diseases increase the risk of stroke. Acute infection, mainly respiratory, and both bacterial and viral infection, represent temporarily active trigger factors for cerebral ischemia. Chronic infectious diseases that may increase the risk of stroke include periodontitis, chronic bronchitis and infections with microbial antigens, such as *Helicobacter pylori* and *Chlamydia pneumoniae*. From observational studies, there is evidence that vaccination against influenza is associated with a reduced risk of stroke, myocardial infarction and all-cause mortality. This report provides an overview on the influence of infection on stroke risk and potential anti-infective strategies that may play a future role in stroke prevention.

Expert Rev Neurother. 2006 Feb;6(2):175-83



### **PSYCHIATRIC CO-MORBIDITY & DIABETES.**

Diabetes mellitus as well as psychiatric disorders are common. These may occur with one another and/or one may worsen the other. Psychological stress may follow screening for diabetes, as well as when diabetes is first identified. Acting through the hypothalamo-pituitary-adrenal axis, stress may initiate or worsen hyperglycaemia. Depression may be a risk factor for the development of diabetes; it also commonly occurs in subjects with diabetes. Identification and management are both important in preventing the disability. A variety of antipsychotic medications, especially the newer agents can induce weight gain, dyslipidaemia, insulin resistance and diabetes. Therefore in choosing a drug, one must consider the risk factors and screen for metabolic syndrome. Subjects with type 1 diabetes can have cognitive dysfunction, eating disorders and developmental disturbances. Physicians caring for people with diabetes must be trained to recognize and manage co-morbid psychiatric conditions that commonly occur. A biopsychosocial disease model for both conditions can leverage the social strengths and medical knowledge in developing countries.

Indian J Med Res. 2007 Mar;125(3):311-20

### **ATTENUATION OF LABORATORY-INDUCED STRESS IN HUMANS AFTER ACUTE ADMINISTRATION OF MELISSA OFFICINALIS (LEMON BALM).**

**OBJECTIVE:** Melissa officinalis (lemon balm) is contemporaneously used as a mild sedative and/or calming agent. Although recent research has demonstrated modulation of mood in keeping with these roles, no studies to date have directly investigated the effects of this herbal medication on laboratory-induced psychological stress. **METHODS:** In this double-blind, placebo-controlled, randomized, balanced crossover experiment, 18 healthy volunteers received two separate single doses of a standardized M. officinalis extract (300 mg, 600 mg) and a placebo, on separate days separated by a 7-day washout period. Modulation of mood was assessed during predose and 1-hour postdose completions of a 20-minute version of the Defined Intensity Stressor Simulation (DISS) battery. Cognitive performance on the four concurrent tasks of the battery was also assessed. **RESULTS:** The results showed that the 600-mg dose of Melissa ameliorated the negative mood effects of the DISS, with significantly increased self-ratings of calmness and reduced self-ratings of alertness. In addition, a significant increase in the speed of mathematical processing, with no reduction in accuracy, was observed after ingestion of the 300-mg dose. **CONCLUSION:** These results suggest that the potential for M. officinalis to mitigate the effects of stress deserves further investigation.

Psychosom Med. 2004 Jul-Aug;66(4):607-13.

### **ANXIETY AS AN INDEPENDENT CARDIOVASCULAR RISK.**

Anxiety itself, and anxiety disorders in particular, seem to represent an independent risk factor for cardiovascular diseases as important as obesity, hypertension, sedentary lifestyle or hyperlipidemia. Anxiety-related noradrenaline and HPA overactivity, excessive sympathetic nervous system activation, and the permanently elevated level of several neuropeptides and cytokines result in hypertension and arrhythmias, endothel lesions, detrimental hemodynamic changes and platelet overactivation facilitating thrombosis. Patients with severe and sustained anxiety usually have additional adverse health behaviors which further aggravate the hazards. Epidemiological studies agree in finding markedly increased incidence of myocardial infarct, coronary heart disease or other cardiovascular conditions, often with earlier age of onset, faster progression and higher lethality, in anxiety disorder patients. Better recognition and adequate treatment of anxiety disorders may therefore contribute to curbing the excessive—and typically early-onset—cardiovascular morbidity and mortality in Hungary.

Neuropsychopharmacol Hung. 2006 Mar;8(1):5-11

### **L-THEANINE REDUCES PSYCHOLOGICAL AND PHYSIOLOGICAL STRESS RESPONSES.**

L-Theanine is an amino acid contained in green tea leaves which is known to block the binding of L-glutamic acid to glutamate receptors in the brain. Because the characteristics of L-Theanine suggest that it may influence psychological and physiological states under stress, the present study examined these possible effects in a laboratory setting using a mental arithmetic task as an acute stressor. Twelve participants underwent four separate trials: one in which they took L-Theanine at the start of an

experimental procedure, one in which they took L-Theanine midway, and two control trials in which they either took a placebo or nothing. The experimental sessions were performed by double-blind, and the order of them was counterbalanced. The results showed that L-Theanine intake resulted in a reduction in the heart rate (HR) and salivary immunoglobulin A (s-IgA) responses to an acute stress task relative to the placebo control condition. Moreover, analyses of heart rate variability indicated that the reductions in HR and s-IgA were likely attributable to an attenuation of sympathetic nervous activation. Thus, it was suggested that the oral intake of L-Theanine could cause anti-stress effects via the inhibition of cortical neuron excitation.

Biol Psychol. 2007 Jan;74(1):39-45

### **THE DEPLOYMENT OF INTERSENSORY SELECTIVE ATTENTION: A HIGH-DENSITY ELECTRICAL MAPPING STUDY OF THE EFFECTS OF THEANINE.**

**OBJECTIVE:** Ingestion of the nonproteinic amino acid theanine (5-N-ethylglutamine) has been shown to increase oscillatory brain activity in the so-called alpha band (8-14 Hz) during resting electroencephalographic recordings in humans. Independently, alpha band activity has been shown to be a key component in selective attentional processes. Here, we set out to assess whether theanine would cause modulation of anticipatory alpha activity during selective attentional deployments to stimuli in different sensory modalities, a paradigm in which robust alpha attention effects have previously been established. **METHODS:** Electrophysiological data from 168 scalp electrode channels were recorded while participants performed a standard intersensory attentional cuing task. **RESULTS:** As in previous studies, significantly greater alpha band activity was measured over parieto-occipital scalp for attentional deployments to the auditory modality than to the visual modality. Theanine ingestion resulted in a substantial overall decrease in background alpha levels relative to placebo while subjects were actively performing this demanding attention task. Despite this decrease in background alpha activity, attention-related alpha effects were significantly greater for the theanine condition. **CONCLUSION:** This increase of attention-related anticipatory alpha over the right parieto-occipital scalp suggests that theanine may have a specific effect on the brain's attention circuitry. We conclude that theanine has clear psychoactive properties, and that it represents a potentially interesting, naturally occurring compound for further study, as it relates to the brain's attentional system.

Clin Neuropharmacol. 2007 Jan-Feb;30(1):25-38

### **MODULATION OF GAMMA AND ALPHA ACTIVITY DURING A WORKING MEMORY TASK ENGAGING THE DORSAL OR VENTRAL STREAM.**

Despite extensive experimental work in both animals and humans, the actual role of oscillatory brain activity for working memory maintenance remains elusive. Gamma band activity (30-100 Hz) has been hypothesized to reflect either the maintenance of neuronal representations or changing demands in attention. Regarding posterior alpha activity (8-13 Hz), it is under debate whether it reflects functional inhibition or neuronal processing required for the task. The aim of the present study was to further elucidate the role of oscillatory brain activity in humans using a working memory task engaging either the dorsal or ventral visual stream. We recorded brain activity using magnetoencephalography from subjects performing a delayed-match-to-sample task. Subjects were instructed to remember either the identity or the spatial orientation of shortly presented faces. The analysis revealed stronger alpha power around the parieto-occipital sulcus during retention of face identities (ventral stream) compared with the retention of face orientations (dorsal stream). In contrast, successful retention of face orientations was associated with an increase in gamma power in the occipital lobe relative to the face identity condition. We propose that gamma activity reflects the actual neuronal maintenance of visual representations, whereas the alpha increase is a result of functional inhibition.

J Neurosci. 2007 Mar 21;27(12):3244-51

### **OPTIMAL SUSTAINED ATTENTION IS LINKED TO THE SPECTRAL CONTENT OF BACKGROUND EEG ACTIVITY: GREATER ONGOING TONIC ALPHA (APPROXIMATELY 10 HZ) POWER SUPPORTS SUCCESSFUL PHASIC GOAL ACTIVATION.**

Efficient executive control frequently requires the timely activation or re-activation of a task-goal to enable purposeful behaviour. Additionally, more generalized factors such as alertness or neurological health will influence the efficiency with which control can be implemented. Goal-directed processes have been investigated by examining event-related potentials (ERPs), but much less is known about the involvement of background or 'tonic' processes reflected in the ongoing electroencephalogram (EEG), and how these affect the phasic processes expressed in the broad-band ERP. Here, we investigate the relationship between a key attention-sensitive tonic process--the alpha rhythm--and relevant phasic processes observed during a sustained attention paradigm in neurologically healthy subjects. We report that subjects with relatively higher tonic alpha power (approximately 10 Hz) show a larger-amplitude late positive ERP component that is thought to index goal activation and has been found to predict good sustained attention performance as defined by correct response patterns. Source localization results suggest that the neural generators responsible for oscillatory alpha activity, which are found primarily in the parietal and occipital lobes, are distinct from those giving rise to the late positive component. The results are discussed in terms of increased alpha synchrony facilitating goal-directed behaviour.

### **INDUCTION OF NEUTRAL ENDOPEPTIDASE (NEP) ACTIVITY OF SK-N-SH CELLS BY NATURAL COMPOUNDS FROM GREEN TEA.**

Deposition of amyloid beta-peptide as senile plaques in the brain is one of the neuropathological hallmarks of Alzheimer's disease, which is the most prevalent progressive neurodegenerative disease leading to dementia. Neutral endopeptidase is one of the major beta-amyloid-degrading enzymes in the brain. To examine the influence of different polyphenols and other natural products from green tea extract (from *Camellia sinensis*, Theaceae), we used the neuroblastoma cell line SK-N-SH and studied the changes in the specific cellular neutral endopeptidase activity after long-term treatment with these substances. We have shown that caffeine leads to an increase in specific cellular neutral endopeptidase activity more than theophylline, theobromine or theanine. We have also shown that the combination of epicatechin, epigallocatechin and epigallocatechingallate with caffeine, theobromine or theophylline induced cellular neutral endopeptidase activity. It is suggested that the enhancement of cellular neutral endopeptidase activity by green tea extract and its natural products might be correlated with an elevated level of intracellular cyclic adenosine monophosphate.

J Pharm Pharmacol. 2006 Apr;58(4):495-501

### **THEANINE AND GLUTAMATE TRANSPORTER INHIBITORS ENHANCE THE ANTITUMOR EFFICACY OF CHEMOTHERAPEUTIC AGENTS.**

Biochemical modulation has played an important role in the development of cancer chemotherapy. The combined effects of theanine, a specific amino acid in green tea, and glutamate transporter inhibitors on the antitumor activity of doxorubicin (DOX), were investigated and we clarified the biochemical mechanisms of action of these modulators. In M5076 ovarian sarcoma-bearing mice, theanine significantly enhanced the inhibitory effect of DOX on tumor growth and increased the DOX concentration in the tumor, compared to DOX-alone group. Furthermore, the oral administration of theanine or green tea similarly enhanced the antitumor activity of DOX. Moreover, the combination of theanine with DOX suppressed the hepatic metastasis of ovarian sarcoma. In contrast, an increase in DOX concentration was not observed in normal tissues, such as liver and heart. Namely, theanine did not enhance, rather it tended to normalize the increase of lipid peroxide (LPO) levels and reduction of glutathione peroxidase activity as indicators of the DOX-induced side toxicity. On the other hand, in vitro experiments proved that theanine inhibited the efflux of DOX from tumor cells, supporting a theanine-induced increase in the DOX concentration in tumors in vivo. Moreover, theanine significantly inhibited the glutamate uptake by M5076 cells similar to specific inhibitors. Two astrocytic high-affinity glutamate transporters, GLAST and GLT-1, were expressed in M5076 cells. These results suggested that the inhibition of DOX efflux was induced by theanine-mediated inhibition of glutamate transporters. The reduction in the concentration of glutamate in tumor cells caused by theanine induced decreases in the intracellular glutathione (GSH) and GS-DOX conjugate levels. As the expression of MRP5 in M5076 cells was confirmed, it is suggested that the GS-DOX conjugate was transported extracellularly via the MRP5/GS-X pump in M5076 cells and that theanine affected this route. Namely, theanine increases the concentration of DOX in a tumor in vivo through inhibition of the glutamate transporter via the GS-X pump. Similarly, dihydrokainate (DHK) and L-serine-O-sulfate (SOS), specific glutamate transporter inhibitors, indicated the enhancement of the DOX antitumor activity via inhibition of glutamate uptake. Therefore, we revealed the novel mechanism of enhancement of antitumor efficacy of DOX via the inhibition of glutamate transporters. Similarly, theanine enhanced the antitumor activities of other anthracyclines, cisplatin and irinotecan. Consequently, the modulating effect of theanine on the efficacy of antitumor agents is expected to be applicable in clinical cancer chemotherapy.

Biochim Biophys Acta. 2003 Dec 5;1653(2):47-59

### **NEUROPROTECTIVE EFFECT OF GAMMA-GLUTAMYLETHYLAMIDE (THEANINE) ON CEREBRAL INFARCTION IN MICE.**

In the present study, we examined the neuroprotective effect of gamma-glutamylethylamide (theanine) on the ischemic brain damage in a middle cerebral artery occlusion model in mice. Theanine was injected i.p. 3 h after the occlusion or immediately before and 3 h after the occlusion. Theanine (1 mg/kg) significantly decreased the size of the cerebral infarcts 1 day after the occlusion. In contrast, theanine did not affect the cerebral blood flow, brain temperature and physiological variables (pH, pCO<sub>2</sub>, pO<sub>2</sub> and hematocrit) in this model. These results suggest that theanine directly provides neuroprotection against focal cerebral ischemia and may be clinically useful for preventing cerebral infarction.

Neurosci Lett. 2004 Jun 3;363(1):58-61

### **EFFECTS OF THEANINE, R-GLUTAMYLETHYLAMIDE, ON NEUROTRANSMITTER RELEASE AND ITS RELATIONSHIP WITH GLUTAMIC ACID NEUROTRANSMISSION.**

Theanine, *r*-glutamylethylamide, is one of the major amino acid components in green tea and many researchers have compared theanine's effects with glutamic acid because the chemical structure is similar. In the previous study, we demonstrated that theanine can pass brain-blood barrier and may play as an agonist or an antagonist of some receptors. In this study, we investigated the effects of theanine on neurotransmitter release in the rat brain striatum by *in vivo* brain microdialysis and examined whether theanine affected glutamate transporters by comparing it with a glutamate transporter blocker, L-trans-Pyrrolidine-2,4-dicarboxylic acid (L-trans-2,4-PDC). Because we investigated whether the effects of theanine is similar to L-trans-2,4-PDC on the brain neurotransmission, we measured dopamine release and some amino acids release which are known as excitatory or inhibitory neurotransmitters from neurons by theanine or L-trans-2,4-PDC perfusion into the rat brain striatum. L-trans-2,4-PDC or theanine perfusion into the brain striatum caused dopamine release from dopaminergic neurons. In addition, L-trans-2,4-PDC perfusion increased glutamic acid, aspartic acid and, whereas theanine perfusion prevented aspartic acid release and increased glycine release. These results suggested that the mechanism of dopamine release caused by theanine is different from glutamate transporter blockers or glutamic acid. Further, L-trans-2,4-PDC cause excitatory neurotransmission, whereas theanine may inhibit excitatory neurotransmission and cause inhibitory neurotransmission via glycine receptors.

Nutr Neurosci. 2005 Aug;8(4):219-26

**INTENSIVE LIPID LOWERING WITH ATORVASTATIN IN PATIENTS WITH STABLE CORONARY DISEASE.**

**BACKGROUND:** Previous trials have demonstrated that lowering low-density lipoprotein (LDL) cholesterol levels below currently recommended levels is beneficial in patients with acute coronary syndromes. We prospectively assessed the efficacy and safety of lowering LDL cholesterol levels below 100 mg per deciliter (2.6 mmol per liter) in patients with stable coronary heart disease (CHD). **METHODS:** A total of 10,001 patients with clinically evident CHD and LDL cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) were randomly assigned to double-blind therapy and received either 10 mg or 80 mg of atorvastatin per day. Patients were followed for a median of 4.9 years. The primary end point was the occurrence of a first major cardiovascular event, defined as death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke. **RESULTS:** The mean LDL cholesterol levels were 77 mg per deciliter (2.0 mmol per liter) during treatment with 80 mg of atorvastatin and 101 mg per deciliter (2.6 mmol per liter) during treatment with 10 mg of atorvastatin. The incidence of persistent elevations in liver aminotransferase levels was 0.2 percent in the group given 10 mg of atorvastatin and 1.2 percent in the group given 80 mg of atorvastatin ( $P<0.001$ ). A primary event occurred in 434 patients (8.7%) receiving 80 mg of atorvastatin, as compared with 548 patients (10.9%) receiving 10 mg of atorvastatin, representing an absolute reduction in the rate of major cardiovascular events of 2.2% and a 22% relative reduction in risk (hazard ratio, 0.78; 95% confidence interval, 0.69 to 0.89;  $P<0.001$ ). There was no difference between the two treatment groups in overall mortality. **CONCLUSIONS:** Intensive lipid-lowering therapy with 80 mg of atorvastatin per day in patients with stable CHD provides significant clinical benefit beyond that afforded by treatment with 10 mg of atorvastatin per day. This occurred with a greater incidence of elevated aminotransferase levels.

N Engl J Med. 2005 Apr 7;352(14):1425-35

**HIGH-DOSE ATORVASTATIN AFTER STROKE OR TRANSIENT ISCHEMIC ATTACK.**

**BACKGROUND:** Statins reduce the incidence of strokes among patients at increased risk for cardiovascular disease; whether they reduce the risk of stroke after a recent stroke or transient ischemic attack (TIA) remains to be established. **METHODS:** We randomly assigned 4,731 patients who had had a stroke or TIA within one to six months before study entry, had low-density lipoprotein (LDL) cholesterol levels of 100 to 190 mg per deciliter (2.6 to 4.9 mmol per liter), and had no known coronary heart disease to double-blind treatment with 80 mg of atorvastatin per day or placebo. The primary end point was a first nonfatal or fatal stroke. **RESULTS:** The mean LDL cholesterol level during the trial was 73 mg per deciliter (1.9 mmol per liter) among patients receiving atorvastatin and 129 mg per deciliter (3.3 mmol per liter) among patients receiving placebo. During a median follow-up of 4.9 years, 265 patients (11.2%) receiving atorvastatin and 311 patients (13.1%) receiving placebo had a fatal or nonfatal stroke (5-year absolute reduction in risk, 2.2%; adjusted hazard ratio, 0.84; 95% confidence interval, 0.71 to 0.99;  $P=0.03$ ; unadjusted  $P=0.05$ ). The atorvastatin group had 218 ischemic strokes and 55 hemorrhagic strokes, whereas the placebo group had 274 ischemic strokes and 33 hemorrhagic strokes. The five-year absolute reduction in the risk of major cardiovascular events was 3.5 percent (hazard ratio, 0.80; 95% confidence interval, 0.69 to 0.92;  $P=0.002$ ). The overall mortality rate was similar, with 216 deaths in the atorvastatin group and 211 deaths in the placebo group ( $P=0.98$ ), as were the rates of serious adverse events. Elevated liver enzyme values were more common in patients taking atorvastatin. **CONCLUSIONS:** In patients with recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin per day reduced the overall incidence of strokes and of cardiovascular events, despite a small increase in the incidence of hemorrhagic stroke.

N Engl J Med. 2006 Aug 10;355(6):549-59

**STATIN SAFETY: A SYSTEMATIC REVIEW.**

A systematic review of cohort studies, randomized trials, voluntary notifications to national regulatory authorities, and published case reports was undertaken to assess the incidence and characteristics of adverse effects in patients treated with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins. For statins other than cerivastatin, the incidence of rhabdomyolysis in 2 cohort studies was 3.4 (1.6 to 6.5) per 100,000 person-years, an estimate supported by data from 20 randomized controlled trials. Case fatality was 10%. Incidence was about 10 times greater when gemfibrozil was used in combination with statins. Incidence was higher (4.2 per 100,000 person-years) with lovastatin, simvastatin, or atorvastatin (which are oxidized by cytochrome P450 3A4 [CYP3A4], which is inhibited by many drugs) than pravastatin or fluvastatin (which are not oxidized by CYP3A4). In persons taking simvastatin, lovastatin, or atorvastatin, 60% of cases involved drugs known to inhibit

CYP3A4 (especially erythromycin and azole antifungals), and 19% involved fibrates, principally gemfibrozil. The incidence of myopathy in patients treated with statins, estimated from cohort studies supported by randomized trials, was 11 per 100,000 person-years. For liver disease, randomized trials reported fewer hepatobiliary disorders in patients allocated statins than in those allocated placebo. The notification rate of liver failure to regulatory authorities was about 1 per million person-years of statin use. Randomized trials show no excess of renal disease or proteinuria in statin-allocated participants, and the decline in glomerular filtration rate was smaller with statins than with placebo. Evidence from 4 cohort studies and case reports suggests that statins cause peripheral neuropathy, but the attributable risk is small (12 per 100,000 person-years). No change in cognitive function was found in randomized trials of statins in elderly patients.

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### **EFFECT OF COENZYME Q10 ON MYOPATHIC SYMPTOMS IN PATIENTS TREATED WITH STATINS.**

Treatment of hypercholesterolemia with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) is effective in the primary and secondary prevention of cardiovascular disease. However, statin use is often associated with a variety of muscle-related symptoms or myopathies. Myopathy may be related in part to statin inhibition of the endogenous synthesis of coenzyme Q10, an essential cofactor for mitochondrial energy production. The aim of this study is to determine whether coenzyme Q10 supplementation would reduce the degree of muscle pain associated with statin treatment. Patients with myopathic symptoms were randomly assigned in a double-blinded protocol to treatment with coenzyme Q10 (100 mg/day, n = 18) or vitamin E (400 IU/day, n = 14) for 30 days. Muscle pain and pain interference with daily activities were assessed before and after treatment. After a 30-day intervention, pain severity decreased by 40% ( $p < 0.001$ ) and pain interference with daily activities decreased by 38% ( $p < 0.02$ ) in the group treated with coenzyme Q10. In contrast, no changes in pain severity (+9%,  $p = \text{NS}$ ) or pain interference with daily activities (-11%,  $p = \text{NS}$ ) was observed in the group treated with vitamin E. In conclusion, results suggest that coenzyme Q10 supplementation may decrease muscle pain associated with statin treatment. Thus, coenzyme Q10 supplementation may offer an alternative to stopping treatment with these vital drugs.

Am J Cardiol. 2007 May 15;99(10):1409-12

### **STATINS PROVOKING MELAS SYNDROME. A CASE REPORT.**

**BACKGROUND:** Statins inhibit the production of 2,3-dimethoxy,5-methyl,6-polyisoprene parabenzoquinone also known as ubiquinone or coenzyme Q10 (CoQ10), which is required for mitochondrial electron transport. Idiopathic or primary CoQ10 deficiencies have been known to cause mitochondrial encephalomyopathy. **METHODS:** We present the case of a patient with mitochondrial syndrome, consisting of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), whose symptoms were temporally related to statin therapy. **CONCLUSION:** Statins may provoke symptoms related to MELAS in susceptible individuals.

Eur Neurol. 2007;57(4):232-5

### **THE CLINICAL USE OF HMG COA-REDUCTASE INHIBITORS AND THE ASSOCIATED DEPLETION OF COENZYME Q10. A REVIEW OF ANIMAL AND HUMAN PUBLICATIONS.**

The depletion of the essential nutrient CoQ10 by the increasingly popular cholesterol lowering drugs, HMG CoA reductase inhibitors (statins), has grown from a level of concern to one of alarm. With ever higher statin potencies and dosages, and with a steadily shrinking target LDL cholesterol, the prevalence and severity of CoQ10 deficiency is increasing noticeably. An estimated 36 million Americans are now candidates for statin drug therapy. Statin-induced CoQ10 depletion is well documented in animal and human studies with detrimental cardiac consequences in both animal models and human trials. This drug-induced nutrient deficiency is dose related and more notable in settings of pre-existing CoQ10 deficiency such as in the elderly and in heart failure. Statin-induced CoQ10 deficiency is completely preventable with supplemental CoQ10 with no adverse impact on the cholesterol lowering or anti-inflammatory properties of the statin drugs. We are currently in the midst of a congestive heart failure epidemic in the United States, the cause or causes of which are unclear. As physicians, it is our duty to be absolutely certain that we are not inadvertently doing harm to our patients by creating a wide-spread deficiency of a nutrient critically important for normal heart function.

Biofactors. 2003;18(1-4):101-11

### **TREATMENT OF STATIN ADVERSE EFFECTS WITH SUPPLEMENTAL COENZYME Q10 AND STATIN DRUG DISCONTINUATION.**

Fifty consecutive new cardiology clinic patients who were on statin drug therapy (for an average of 28 months) on their initial visit were evaluated for possible adverse statin effects (myalgia, fatigue, dyspnea, memory loss, and peripheral neuropathy). All patients discontinued statin therapy due to side effects and began supplemental CoQ(10) at an average of 240 mg/day upon

initial visit. Patients have been followed for an average of 22 months with 84% of the patients followed now for more than 12 months. The prevalence of patient symptoms on initial visit and on most recent follow-up demonstrated a decrease in fatigue from 84% to 16%, myalgia from 64% to 6%, dyspnea from 58% to 12%, memory loss from 8% to 4% and peripheral neuropathy from 10% to 2%. There were two deaths from lung cancer and one death from aortic stenosis with no strokes or myocardial infarctions. Measurements of heart function either improved or remained stable in the majority of patients. We conclude that statin-related side effects, including statin cardiomyopathy, are far more common than previously published and are reversible with the combination of statin discontinuation and supplemental CoQ(10). We saw no adverse consequences from statin discontinuation.

Biofactors. 2005;25(1-4):147-52

### **EFFECT OF DIFFERENT ANTILIPIDEMIC AGENTS AND DIETS ON MORTALITY: A SYSTEMATIC REVIEW.**

**BACKGROUND:** Guidelines for the prevention and treatment of hyperlipidemia are often based on trials using combined clinical end points. Mortality data are the most reliable data to assess efficacy of interventions. We aimed to assess efficacy and safety of different lipid-lowering interventions based on mortality data. **METHODS:** We conducted a systematic search of randomized controlled trials published up to June 2003, comparing any lipid-lowering intervention with placebo or usual diet with respect to mortality. Outcome measures were mortality from all, cardiac, and noncardiovascular causes. **RESULTS:** A total of 97 studies met eligibility criteria, with 137,140 individuals in intervention and 138,976 individuals in control groups. Compared with control groups, risk ratios for overall mortality were 0.87 for statins (95% confidence interval [CI], 0.81-0.94), 1.00 for fibrates (95% CI, 0.91-1.11), 0.84 for resins (95% CI, 0.66-1.08), 0.96 for niacin (95% CI, 0.86-1.08), 0.77 for n-3 fatty acids (95% CI, 0.63-0.94), and 0.97 for diet (95% CI, 0.91-1.04). Compared with control groups, risk ratios for cardiac mortality indicated benefit from statins (0.78; 95% CI, 0.72-0.84), resins (0.70; 95% CI, 0.50-0.99) and n-3 fatty acids (0.68; 95% CI, 0.52-0.90). Risk ratios for noncardiovascular mortality of any intervention indicated no association when compared with control groups, with the exception of fibrates (risk ratio, 1.13; 95% CI, 1.01-1.27). **CONCLUSIONS:** Statins and n-3 fatty acids are the most favorable lipid-lowering interventions with reduced risks of overall and cardiac mortality. Any potential reduction in cardiac mortality from fibrates is offset by an increased risk of death from noncardiovascular causes.

Arch Intern Med. 2005 Apr 11;165(7):725-30

### **REDUCTION OF SERUM UBIQUINOL-10 AND UBIQUINONE-10 LEVELS BY ATORVASTATIN IN HYPERCHOLESTEROLEMIC PATIENTS.**

Reduction of serum cholesterol levels with statin therapy decreases the risk of coronary heart disease. Inhibition of HMG-CoA reductase by statin results in decreased synthesis of cholesterol and other products downstream of mevalonate, which may produce adverse effects in statin therapy. We studied the reductions of serum ubiquinol-10 and ubiquinone-10 levels in hypercholesterolemic patients treated with atorvastatin. Fourteen patients were treated with 10 mg/day of atorvastatin, and serum lipid, ubiquinol-10 and ubiquinone-10 levels were measured before and after 8 weeks of treatment. Serum total cholesterol and LDL-cholesterol levels decreased significantly. All patients showed definite reductions of serum ubiquinol-10 and ubiquinone-10 levels, and mean levels of serum ubiquinol-10 and ubiquinone-10 levels decreased significantly from 0.81 +/- 0.21 to 0.46 +/- 0.10 microg/ml ( $p < 0.0001$ ), and from 0.10 +/- 0.06 to 0.06 +/- 0.02 microg/ml ( $p = 0.0008$ ), respectively. Percent reductions of ubiquinol-10 and those of total cholesterol showed a positive correlation ( $r = 0.627$ ,  $p = 0.0165$ ). As atorvastatin reduces serum ubiquinol-10 as well as serum cholesterol levels in all patients, it is imperative that physicians are forewarned about the risks associated with ubiquinol-10 depletion.

J Atheroscler Thromb. 2005;12(2):111-9

### **PRESCRIPTION OF STATINS TO DYSLIPIDEMIC PATIENTS AFFECTED BY LIVER DISEASES: A SUBTLE BALANCE BETWEEN RISKS AND BENEFITS.**

**AIM:** Statins reduce cardiovascular morbidity and mortality in the general population with an excellent risk-benefit profile. The most frequent adverse events are myopathy and increase in hepatic aminotransferases. In this review, we consider the role of liver in metabolism of statins, their potential hepatic toxicity and the guidelines for their prescription in patients affected by different liver diseases. **DATA SYNTHESIS:** Statin-induced hepatic toxicity: i) occurs in 1-3% of patients; ii) is characterized by increased aminotransferase levels; iii) is dose-related; iv) is frequently asymptomatic; v) usually reverts after dosage reduction or treatment withdrawal. Finally, after recovery, a rechallenge with the same or other statins may not result in increased aminotransferases. **CONCLUSIONS:** Caution is needed when prescribing statins to patients with liver disease, and liver toxicity should always be monitored during statin treatment. In particular, i) the potential hepatic toxicity requires frequent control of biochemical parameters related to hepatic cytolysis and cholestasis in all patients on statins; ii) administration of statins is counterindicated in patients with advanced or end-stage parenchymal liver disease due to the relevant impairment of their metabolism; iii) cholestatic disorders with secondary dyslipidemia do not require statin treatment even if relevant alterations of the lipid pattern are detected; iv) patients with acute liver disease of viral or alcoholic etiology should not receive statins until

normalization of cytolysis enzymes; v) chronic hepatitis patients may be treated by statins if their cardiovascular risk is elevated and provided that careful follow-up is carried out to rapidly recognize the onset of further liver damage; vi) liver transplantation recipients affected by dyslipidemia induced by immunosuppressive therapy can be treated with statins under careful clinical control; vii) the benefits of statins should likely overcome the risks in the large majority of dyslipidemic patients affected by non-alcoholic hepatosteatosis, a disease frequently diagnosed in insulin-resistant subjects.

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