

## Neuropathy

## ABSTRACTS

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**Acupuncture for the treatment of chronic painful peripheral diabetic neuropathy: a long-term study.**

Abuایشا BB, Costanzi JB, Boulton AJ. Department of Medicine, Manchester Royal Infirmary, University of Manchester, UK.

Diabetes Res Clin Pract. 1998 Feb;39(2):115-21.

Forty-six diabetic patients with chronic painful peripheral neuropathy were treated with acupuncture analgesia to determine its efficacy and long-term effectiveness. Twenty-nine (63%) patients were already on standard medical treatment for painful neuropathy. Patients initially received up to six courses of classical acupuncture analgesia over a period of 10 weeks, using traditional Chinese Medicine acupuncture points. Forty-four patients completed the study with 34 (77%) showing significant improvement in their primary and/or secondary symptoms ( $P < 0.01$ ). These patients were followed up for a period of 18-52 weeks with 67% were able to stop or reduce their medications significantly. During the follow-up period only eight (24%) patients required further acupuncture treatment. Although 34 (77%) patients noted significant improvement in their symptoms, only seven (21%) noted that their symptoms cleared completely. All the patients but one finished the full course of acupuncture treatment without reported or observed side effects. There were no significant changes either in the peripheral neurological examination scores, VPT or in HbA1c during the course of treatment. These data suggest that acupuncture is a safe and effective therapy for the long-term management of painful diabetic neuropathy, although its mechanism of action remains speculative.

**Monograph:Alpha-Lipoic Acid.**

Anon.

Altern Med Rev 1998 Aug;3(4):308-11

Alpha-Lipoic acid is a potent antioxidant in both fat- and water-soluble mediums. Furthermore, its antioxidant activity extends to both the oxidized form and its reduced form. DHLA is capable of regenerating ascorbic acid from dehydroascorbic acid, directly regenerating vitamin C and indirectly regenerating vitamin E. Researchers have found lipoic acid to increase intracellular glutathione levels as well as Coenzyme Q10. Clinically, it appears lipoic acid has the potential to prevent diabetes, influence glucose control,

and prevent chronic hyperglycemia associated complications such as neuropathy and cataracts. Lipoic acid may also be useful in the treatment of glaucoma, ischemia-reperfusion injury, amanita mushroom poisoning, and cellular oxidative damage.

### **Effects of a static magnetic field on haemoglobin structure and function.**

Atef MM et al.

Int J Biol Macromol 1995; 17: 105-11.

Abstract coming soon.

### **Use of anticonvulsants for treatment of neuropathic pain.**

Backonja MM. Department of Neurology, University of Wisconsin Hospital and Clinics, Room H6/574, 600 Highland Avenue, Madison, WI 53792-5132, USA. backonja@neurology.wisc.edu

Neurology. 2002 Sep 10;59(5 Suppl 2):S14-7.

Emerging evidence from animal models of neuropathic pain suggests that many pathophysiologic and biochemical changes occur in the peripheral and central nervous system. Similarities between the pathophysiologic phenomena observed in some epilepsy models and in neuropathic pain models justify the use of anticonvulsants in the symptomatic management of neuropathic pain. Positive results from laboratory and clinical trials further support such use. Carbamazepine was the first of this class of drugs to be studied in clinical trials and has been longest in use for treatment of neuropathic pain. Clinical trial data support its use in treating trigeminal neuralgia, but data for treatment of painful diabetic neuropathy are less convincing. Use of newer anticonvulsants has marked a new era in the treatment of neuropathic pain. Gabapentin has demonstrated efficacy, specifically in painful diabetic neuropathy and postherpetic neuralgia. Lamotrigine has been reported to be effective in relieving pain from trigeminal neuralgia refractory to other treatments, HIV neuropathy, and central post-stroke pain. Results from clinical trials of phenytoin are equivocal. Zonisamide's mechanisms of action suggest that it would be effective in controlling neuropathic pain symptoms. Other anticonvulsants, including lorazepam, valproate, topiramate, and tiagabine, have also been under investigation. Anecdotal experience provides support for studies with oxcarbazepine and levetiracetam for treating neuropathic pain. Evidence supporting the efficacy of anticonvulsants in treatment of such pain is evolving. Additional clinical trials should provide information that will better define their role in neuropathic pain.

### **Interaction between oxidative stress and gamma-linolenic acid in impaired neurovascular function of diabetic rats.**

Cameron NE, Cotter MA. Department of Biomedical Sciences, University of Aberdeen, Scotland, United Kingdom.

Am J Physiol 1996 Sep;271(3 Pt 1):E471-6

Nerve conduction and perfusion deficits in diabetic rats depend on increased oxidative stress and impaired n-6 essential fatty acid metabolism, which are corrected by free radical scavenger and gamma-linolenic acid (GLA)-rich oil treatments, respectively. We investigated the interaction between these mechanisms on conduction velocity and endoneurial blood flow by use of low-dose antioxidant (BM15.0639) and GLA treatments, alone and in combination. After 8 wk of streptozotocin-induced diabetes, sciatic motor conduction velocity was 20.9% reduced. Treatment with GLA or BM15.0639 for the final 2 wk corrected this deficit by 18.5 and 20.0%, respectively; however, joint treatment caused 71.5% improvement, corresponding to a 7.5-fold amplification of individual drug effects. A 48.3% deficit in sciatic nutritive endoneurial blood flow was corrected by 34.8 and 24.8% with GLA and BM15.0639 treatments, respectively. With joint treatment, the flow improvement of 72.5% was greater than expected from individual drug effects, indicating a facilitatory interaction. Thus the synergistic effect of combined antioxidant and n-6 essential fatty acid treatment could potentially provide increased therapeutic power against diabetic neuropathy.

### **Metabolic and vascular factors in the pathogenesis of diabetic neuropathy.**

Cameron NE, Cotter MA. Department of Biomedical Sciences, University of Aberdeen, Scotland, U.K.

Diabetes 1997 Sep;46 Suppl 2:S31-7

Reduced nerve perfusion is an important factor in the etiology of diabetic neuropathy. Studies in streptozotocin-induced diabetic rats show that nerve conduction velocity (NCV) and blood flow deficits are corrected by treatment with vasodilator drugs, with angiotensin II and endothelin-1 antagonists being particularly important. The AT1 antagonist ZD7155 also prevents diabetic deficits in regeneration following nerve damage, indicating that hypoperfusion is an important limitation for nerve repair. Metabolic changes include high polyol pathway flux, increased advanced glycosylation, elevated oxidative stress, and impaired omega-6 essential fatty

acid metabolism. Aldose reductase inhibitors (ARIs) restore NCV via their effects on perfusion. ARI action probably depends on blocking the conversion of glucose to sorbitol, thus preventing depletion of vasa nervorum glutathione, an important endogenous free radical scavenger. Free radicals cause vascular endothelium damage and reduced nitric oxide vasodilation. Inhibition of advanced glycosylation and autoxidation (autoxidative glycosylation), major sources of free radicals, by aminoguanidine or transition metal chelators, corrects neurovascular dysfunction. Evening primrose oil supplies gamma-linolenic acid (GLA) to improve vasodilator eicosanoid synthesis in diabetes, correcting nerve blood flow and NCV deficits. Interactions between some of these mechanisms have therapeutic implications. Thus, combined ARI and evening primrose oil treatment produced a 10-fold amplification of NCV and blood flow responses. Similarly, GLA effects are markedly enhanced when given in combination with ascorbate as ascorbyl-GLA. Thus, metabolic abnormalities combine to produce deleterious changes in nerve perfusion that make a major contribution to the etiology of diabetic neuropathy. The potential importance of multi-action therapy is stressed.

### **Chronic inorganic mercury induced peripheral neuropathy.**

Chu CC, Huang CC, Ryu SJ, Wu TN. Department of Neurology, Chang Gung Memorial Hospital and Chang Gung University, Taipei, Taiwan.

Acta Neurol Scand. 1998 Dec;98(6):461-5.

We report the clinical features, electrophysiological studies, and morphometric analysis of sural nerve pathology in a patient with polyneuropathy due to inorganic mercury intoxication. He developed slowly progressive generalized paralysis of all limbs after 3 months ingestion of herb drugs which contained mercuric sulfate. Electrophysiologic studies revealed axonal polyneuropathy involving both motor and sensory fibers. Sural nerve biopsy demonstrated axonal degeneration with demyelination and a predominant loss of large myelinated fibers. His muscle strength showed only mild improvement after 2 years' follow-up. We concluded that inorganic mercury exposure may induce severe axonal sensorimotor polyneuropathy in humans and that neurological deficits may persist in severe cases.

### **Epidemic optic neuropathy in Cuba--clinical characterization and risk factors. The Cuba Neuropathy Field Investigation Team.**

CNFIT.

N Engl J Med 1995 Nov 2;333(18):1176-82

**BACKGROUND.** From 1991 to 1993, epidemic optic and peripheral neuropathy affected more than 50,000 people in Cuba. The number of new cases decreased after the initiation of vitamin supplementation in the population. In September 1993, Cuban and U.S. investigators conducted a study to characterize and identify risk factors for the optic form of the syndrome. **METHODS.** We conducted ophthalmologic and neurologic examinations, assessed exposure to potential toxins, administered a semiquantitative food-frequency questionnaire, and assessed serum measures of nutritional status in 123 patients with severe optic neuropathy, matched for sex and age to randomly chosen normal subjects. **RESULTS.** In the case patients, prominent clinical features were subacute loss of visual acuity with field defects, diminished color vision, optic-nerve pallor, and decreased sensitivity to vibration and temperature in the legs. Tobacco use, particularly cigar smoking, was associated with an increased risk of optic neuropathy. The risk was reduced among subjects with higher dietary intakes of methionine, vitamin B12, riboflavin, and niacin and higher serum concentrations of antioxidant carotenoids. The risk was also reduced among subjects who raised chickens at home or had relatives living overseas--factors that may be indirect measures of increased food availability. **CONCLUSIONS.** The epidemic of optic and peripheral neuropathy in Cuba between 1991 and 1993 appears to be linked to reduced nutrient intake caused by the country's deteriorating economic situation and the high prevalence of tobacco use.

### **Antiplatelet effect of pentoxifylline in human whole blood.**

de la Cruz JP, Romero MM, Sanchez P, Sanchez de la Cuesta F. Department of Pharmacology and Therapeutics, School of Medicine, University of Malaga, Spain.

Gen Pharmacol 1993 May;24(3):605-9

1. Pentoxifylline inhibits platelet aggregation in whole blood more than in platelet-rich plasma. 2. An inhibition of the erythrocyte uptake of adenosine contributes to the antiaggregatory effect of pentoxifylline.

### **Effectiveness of natural oils as sources of gamma-linolenic acid to correct peripheral nerve conduction velocity abnormalities in diabetic rats: modulation by thromboxane A2 inhibition.**

Dines KC, Cotter MA, Cameron NE. Department of Biomedical Sciences, University of Aberdeen, Marischal College, Scotland, UK.

Reduced nerve conduction velocity (NCV) in experimental diabetes can be prevented by evening primrose oil (EP), which is rich in gamma-linolenic acid (GLA). This study examined the efficacy of natural GLA sources, blackcurrant (BC), borage (BO) and fungal (FU) oils, compared with EP, in correcting motor and sensory NCV deficits in streptozotocin-diabetic rats, and any potential contribution of thromboxane (TX) A<sub>2</sub> synthesis using the TX antagonist, ZD1542, alone and jointly with GLA-rich oils. Sciatic motor NCV, 20% reduced by 8 weeks of diabetes, was partially (16%) corrected by 2 weeks ZD1542 treatment. 1% BC, BO, FU and EP dietary supplementation caused 11%, 32%, 41% and 53% NCV ameliorations, respectively. A 2% EP diet, more closely matching the GLA intake from the other oils, caused 67% correction. Joint oil/ZD1542 treatment produced further motor NCV improvements for BC and, particularly, BO. A 13% sensory saphenous NCV deficit in diabetic rats was ameliorated by 31%, 24%, 49%, 81%, 70% and 94% for ZD1542, BC, BO, FU, EP and 2% EP, respectively. Joint ZD1542-oil treatment further improved NCV, particularly for BO. Therefore, efficacy against experimental diabetic neuropathy is not predictable from the GLA content of natural oils, EP consistently outperforming BC, BO and FU. Increased TXA<sub>2</sub> with diabetes made a minor contribution to NCV deficits, but blockade improved the response to BO.

**Expression of constitutive cyclo-oxygenase (COX-1) in rats with streptozotocin-induced diabetes; effects of treatment with evening primrose oil or an aldose reductase inhibitor on COX-1 mRNA levels.**

Fang C, Jiang Z, Tomlinson DR. Department of Pharmacology, St. Bartholomew's, London, UK.

Altered prostanoid metabolism participates in the pathogenesis of diabetic complications. The rate-limiting enzyme in the control of prostanoid metabolism is constitutive cyclo-oxygenase (COX-1). This study examined the possibility that altered prostanoid metabolism derives from altered COX-1 expression in those tissues from diabetic rats, with characteristic changes in prostanoid production and related haemodynamics. This account also describes a procedure for estimation of minute amounts of COX-1 mRNA by reverse transcription and competitive polymerase chain reaction (RT-cPCR) amplification. In streptozotocin-diabetic rats (STZ-D, 55 mg/kg body weight), compared with age-matched controls, the level of COX-1 mRNA (in attomoles/micrograms tRNA +/- 1SD) was significantly decreased in sciatic nerve (0.50 +/- 0.26 versus 0.89 +/- 0.32 in controls; P < 0.05) and thoracic aorta (3.99 +/- 1.67 versus 8.80 +/- 2.37 in controls; P < 0.05). There were no differences in COX-1 mRNA in diabetic and control rat kidney and retina, though there was a trend towards increased expression with diabetes in the latter. Evening primrose oil (EPO) treatment increased COX-1 mRNA in nerve and retina to levels in diabetic rats that were higher than those of non-diabetic controls (1.21 +/- 0.28 for nerve and 0.065 +/- 0.017 for retina, where control retinae gave 0.031 +/- 0.020-see above for nerve). Treatment of diabetic rats with an aldose reductase inhibitor was without effect on COX-1 mRNA levels in the tissues examined. This study demonstrates that the changes in COX-1 mRNA levels in diabetic rats are organ specific and suggests that altered prostanoid metabolism can, in part, be explained by altered COX-1 expression. Apart from providing arachidonate as substrate for COX, EPO stimulates COX-1 expression in some tissues.

**Pentoxifylline effects on nerve conduction velocity and blood flow in diabetic rats.**

Flint H, Cotter MA, Cameron NE. Department of Biomedical Sciences, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Scotland, UK.

Pentoxifylline has several actions that improve blood rheology and tissue perfusion and may therefore potentially be applicable to diabetic neuropathy. The aims of this study were to ascertain whether 2 weeks of treatment with pentoxifylline could correct nerve conduction velocity and blood flow deficits in 6-week streptozotocin-diabetic rats and to examine whether the effects were blocked by co-treatment with the cyclooxygenase inhibitor, flurbiprofen, or the nitric oxide synthase inhibitor, NG-nitro-L-arginine. Diabetic deficits in sciatic motor and saphenous sensory nerve conduction velocity were 56.5% and 69.8% corrected, respectively, with pentoxifylline treatment. Sciatic endoneurial blood flow was approximately halved by diabetes and this deficit was 50.4% corrected by pentoxifylline. Flurbiprofen co-treatment markedly attenuated these actions of pentoxifylline on nerve conduction and blood flow whereas NG-nitro-L-arginine was without effect. Thus, pentoxifylline treatment confers neurovascular benefits in experimental diabetic neuropathy, which are linked at least in part to cyclooxygenase-mediated metabolism.

**The effects of treatment with alpha-lipoic acid or evening primrose oil on vascular hemostatic and lipid risk factors, blood flow, and peripheral nerve conduction in the streptozotocin-diabetic rat.**

Ford I, Cotter MA, Cameron NE, Greaves M. Departments of Medicine & Therapeutics, University of Aberdeen, Aberdeen, Scotland.

Oxidative stress and defective fatty acid metabolism in diabetes may lead to impaired nerve perfusion and contribute to the development of peripheral neuropathy. We studied the effects of 2-week treatments with evening primrose oil (EPO; n = 16) or the antioxidant alpha-lipoic acid (ALA; n = 16) on endoneurial blood flow, nerve conduction parameters, lipids, coagulation, and endothelial factors, in rats with streptozotocin-induced diabetes. Compared with their nondiabetic littermates, untreated diabetic rats had impaired sciatic motor and saphenous sensory nerve-conduction velocity (NCV;  $P < .001$ ), reduced endoneurial blood flow ( $P < .001$ ), and increased serum triglycerides ( $P < .01$ ), cholesterol ( $P < 0.01$ ), plasma factor VII ( $P < .0001$ ), and von Willebrand factor (vWF;  $P < .0001$ ). Plasma fibrinogen and serum high-density lipoprotein concentrations were not significantly different. Treatment with either ALA or EPO effectively corrected the deficits in NCV and endoneurial blood flow. ALA was associated with marked and statistically significant decreases in fibrinogen, factor VII, vWF, and triglycerides ( $P < .01$ , paired t tests before v after treatment). In contrast, EPO was associated with significant ( $P < .05$ ) increases in fibrinogen, factor VII, vWF, triglycerides, and cholesterol and a significant decrease in high-density lipoprotein. Changes in levels of coagulation factors and lipids, qualitatively similar to those found with EPO, were obtained with a diet containing sunflower oil (to control for calorific and lipid content) or with a normal diet alone. Blood glucose and hematocrit levels were not significantly altered by treatments. These data suggest that although both ALA and EPO improve blood flow and nerve function, their actions on vascular factors differ. The marked effects of ALA in lowering lipid and hemostatic risk factors for cardiovascular disease indicate potential antithrombotic and antiatherosclerotic actions that could be of benefit in human diabetes and merit further study. Copyright 2001 by W.B. Saunders Company

### **Plasma and platelet taurine are reduced in subjects with insulin-dependent diabetes mellitus: effects of taurine supplementation.**

Franconi F, Bennardini F, Mattana A, Miceli M, Ciuti M, Mian M, Gironi A, Anichini R, Seghieri G. Institute of Biochemistry, University of Sassari, Italy.

Am J Clin Nutr 1995 May;61(5):1115-9

Plasma and platelet taurine concentrations were assayed in 39 patients with insulin-dependent diabetes mellitus (IDDM) and in 34 control subjects matched for age, sex, and both total and protein-derived daily energy intake. Platelet aggregation induced by arachidonic acid in vitro at baseline and after oral taurine supplementation (1.5 g/d) for 90 d was also studied. Plasma and platelet taurine concentrations (mean  $\pm$  SEM) were lower in diabetic patients (65.6  $\pm$  3.1  $\mu$ mol/L, or 0.66  $\pm$  0.07 mol/g protein) than in control subjects (93.3  $\pm$  6.3  $\mu$ mol/L, or 0.99  $\pm$  0.16 mol/g protein,  $P < 0.01$ ). After oral supplementation, both plasma and platelet taurine concentrations increased significantly in the diabetic patients, reaching the mean values of healthy control subjects. The effective dose (mean  $\pm$  SEM) of arachidonic acid required for platelets to aggregate was significantly lower in diabetic patients than in control subjects (0.44  $\pm$  0.07 mmol compared with 0.77  $\pm$  0.02 mmol,  $P < 0.001$ , whereas after taurine supplementation it equaled the mean value for healthy control subjects (0.72  $\pm$  0.04 mmol). In in vitro experiments, taurine reduced platelet aggregation in diabetic patients in a dose-dependent manner, whereas 10 mmol taurine/L did not modify aggregation in healthy subjects.

### **Use of noninvasive electroacupuncture for the treatment of HIV-related peripheral neuropathy: a pilot study.**

Galantino ML, Eke-Okoro ST, Findley TW, Condoluci D. Neuromusculoskeletal Institute, Department of Physical Medicine and Rehabilitation, School of Osteopathic Medicine, University of Medicine and Dentistry of New Jersey, Stratford 08084, USA. galantinoml@stockton.edu

J Altern Complement Med. 1999 Apr;5(2):135-42.

**OBJECTIVES:** The main objective of this study was to test the hypothesis that low-voltage non-invasive electroacupuncture will improve the condition of neuropathic human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) patients.

**DESIGN:** A prospective study using HIV/AIDS patients who had antiretroviral drug-induced neuropathy. Eleven patients were enrolled, but complete data was obtained from only 7. Non-invasive skin electrodes were placed on leg acupuncture points BL60, ST36, K1, LIV3, and low-voltage current passed for 20 minutes every day for 30 days. Patients were assessed preintervention and postintervention with MOS-HIV 30-item instrument questionnaire and tibial H-reflex was similarly recorded from the right calf muscle.

**RESULTS:** There was improvement in the condition of all 7 patients. They felt much better and reported feelings of increased physical strength. Outcomes on MOS-HIV 30-item instrument showed significant overall improvement in functional activities (pre 33 $\pm$ 10, post 38.4 $\pm$ 9.6,  $p = 0.02$  MANOVA). This was confirmed by postintervention H-reflex parameters; H-max and direct muscle response (M-response) amplitudes were potentiated in relation to pretreatment values (H-max: pre = 1.19 $\pm$ 1.2, post = 2.68 $\pm$ 1.9,  $p < 0.05$ ; M-response: pre = 0.93 $\pm$ 1.1, post = 2.34 $\pm$ 1.8,  $p < 0.05$ ); M-response latency decreased in relation to pretreatment value (pre = 9.7 $\pm$ 1.8, post = 7.8 $\pm$ 1.9,  $p < 0.01$ ).

**CONCLUSION:** The results support the hypothesis that low-voltage electroacupuncture will improve the condition of the neuropathic

HIV/AIDS patient.

**[The effect of pentoxifylline and nicergoline on the systemic and cerebral hemodynamics and on the blood rheological properties in patients with an ischemic stroke and atherosclerotic lesions of the major cerebral arteries]** [Article in Russian]

Gara II.

Zh Nevropatol Psikhiatr Im S S Korsakova 1993;93(3):28-32

Pentoxifylline versus nicergoline therapy has been studied in 56 patients with atherosclerosis of major cerebral arteries who had ischemic apoplexy. Pentoxifylline enhances circulation primarily in the stenotic vessels, while nicergoline in the intact cerebral arteries. The former is more potent in inducing antiaggregation inhibiting spontaneous platelet and red cell aggregation and reducing blood viscosity. The results of the study suggest better response in case of pentoxifylline treatment of patients with hypo- and eukinetic circulation, while in nicergoline treatment hyperkinetic hemodynamics patients benefit more in view of the drug cardiodepressive activity.

**Effect of anti-platelet therapy (aspirin + pentoxiphylline) on plasma lipids in patients of ischaemic stroke.**

Gaur SP, Garg RK, Kar AM, Srimal RC. Department of Pharmacology and Clinical & Experimental Medicine Central Drug Research Institute, Lucknow.

Indian J Physiol Pharmacol 1993 Apr;37(2):158-60

Twenty-one patients of ischaemic stroke were put on prolonged administration of antiplatelet drugs (aspirin 320 mg once daily with pentoxiphylline 400 mg thrice daily). The serum lipids along with other biochemical parameters were estimated before starting the treatment and after completion of 2 months of therapy. No significant changes were observed in any of the biochemical parameters including lipid profile except in serum high density lipoprotein (HDL) which increased significantly ( $< 0.05$ ) after 2 months therapy. It is concluded that 2 months antiplatelet therapy has no adverse metabolic effect in patients of ischaemic stroke and the raised serum HDL may contribute to cerebral protective effect.

**Oral zinc therapy in diabetic neuropathy.**

Gupta R, Garg VK, Mathur DK, Goyal RK. Dept. of Medicine, JLN Medical College and Associated Group of Hospital, Ajmer, Rajasthan-305 001.

J Assoc Physicians India. 1998 Nov;46(11):939-42.

The present double blind randomized study was conducted on 50 subjects; 20 age and sex matched healthy controls (Group--I); 15 patients of diabetes mellitus with neuropathy who received placebo for 6 weeks (Group--IIA); and 15 patients of diabetes mellitus with neuropathy who were given supplemental zinc sulphate (660 mg) for 6 weeks (Group--IIB). Serum zinc level, fasting blood sugar (FBS) and post prandial blood sugar (PPBS) levels and motor nerve conduction velocity (MNCV) were estimated on day 0 and after 6 weeks in all subjects. Serum zinc levels were significantly low ( $p < 0.001$ ) in group IIA and IIB as compared to healthy controls (Group--I) at baseline. After 6 weeks the change in pre and post therapy values of FBS, PPBS and MNCV (median and common peroneal nerve) were highly significant ( $P = < 0.001$ ) for group IIB alone with insignificant change ( $P = > 0.05$ ) in group IIA. No improvement ( $P = > 0.05$ ) in autonomic dysfunction was observed in either groups. Therefore, oral zinc supplementation helps in achieving better glycemic control and improvement in severity of peripheral neuropathy as assessed by MNCV.

**The role of taurine in diabetes and the development of diabetic complications.**

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Diabetes Metab Res Rev 2001 Sep-Oct;17(5):330-46

The ubiquitously found beta-amino acid taurine has several physiological functions, e.g. in bile acid formation, as an osmolyte by cell volume regulation, in the heart, in the retina, in the formation of N-chlorotaurine by reaction with hypochlorous acid in leucocytes, and possibly for intracellular scavenging of carbonyl groups. Some animals, such as the cat and the C57BL/6 mouse, have disturbances in taurine homeostasis. The C57BL/6 mouse strain is widely used in diabetic and atherosclerotic animal models. In diabetes, the high extracellular levels of glucose disturb the cellular osmoregulation and sorbitol is formed intracellularly due to the intracellular polyol pathway, which is suspected to be one of the key processes in the development of diabetic late complications and associated cellular dysfunctions. Intracellular accumulation of sorbitol is most likely to cause depletion of other

intracellular compounds including osmolytes such as myo-inositol and taurine. When considering the clinical complications in diabetes, several links can be established between altered taurine metabolism and the development of cellular dysfunctions in diabetes which cause the clinical complications observed in diabetes, e.g. retinopathy, neuropathy, nephropathy, cardiomyopathy, platelet aggregation, endothelial dysfunction and atherosclerosis. Possible therapeutic perspectives could be a supplementation with taurine and other osmolytes and low-molecular compounds, perhaps in a combinational therapy with aldose reductase inhibitors. Copyright 2001 John Wiley & Sons, Ltd.

**[Aldose reductase inhibitor SNK-860]** [Article in Japanese]

Hibi C.

Sanwa Kagaku Kenkyusho Co., Ltd., Research and Development Section.

Nippon Rinsho 1997 Nov;55 Suppl:212-5

No abstract available.

**Pluripotent protective effects of carnosine, a naturally occurring dipeptide.**

Hipkiss AR, Preston JE, Himsworth DT, Worthington VC, Keown M, Michaelis J, Lawrence J, Mateen A, Allende L, Eagles PA, Abbott NJ. Molecular Biology and Biophysics Group, King's College London, Strand, United Kingdom. alan.hipkiss@kcl.ac.uk

Ann N Y Acad Sci 1998 Nov 20;854:37-53

Carnosine is a naturally occurring dipeptide (beta-alanyl-L-histidine) found in brain, innervated tissues, and the lens at concentrations up to 20 mM in humans. In 1994 it was shown that carnosine could delay senescence of cultured human fibroblasts. Evidence will be presented to suggest that carnosine, in addition to antioxidant and oxygen free-radical scavenging activities, also reacts with deleterious aldehydes to protect susceptible macromolecules. Our studies show that, in vitro, carnosine inhibits nonenzymic glycosylation and cross-linking of proteins induced by reactive aldehydes (aldose and ketose sugars, certain triose glycolytic intermediates and malondialdehyde (MDA), a lipid peroxidation product). Additionally we show that carnosine inhibits formation of MDA-induced protein-associated advanced glycosylation end products (AGEs) and formation of DNA-protein cross-links induced by acetaldehyde and formaldehyde. At the cellular level 20 mM carnosine protected cultured human fibroblasts and lymphocytes, CHO cells, and cultured rat brain endothelial cells against the toxic effects of formaldehyde, acetaldehyde and MDA, and AGEs formed by a lysine/deoxyribose mixture. Interestingly, carnosine protected cultured rat brain endothelial cells against amyloid peptide toxicity. We propose that carnosine (which is remarkably nontoxic) or related structures should be explored for possible intervention in pathologies that involve deleterious aldehydes, for example, secondary diabetic complications, inflammatory phenomena, alcoholic liver disease, and possibly Alzheimer's disease.

**Current progress in clinical trials of aldose reductase inhibitors in Japan.**

Hotta N, Kakuta H, Ando F, Sakamoto N. Third Department of Internal Medicine, Nagoya University School of Medicine, Japan.

Exp Eye Res 1990 Jun;50(6):625-8

In addition to the results of our clinical trial of epalrestat in diabetic retinopathy (the open study), the current progress in the clinical trials of aldose reductase inhibitors for the 'triopathy' of complications (neuropathy, retinopathy and nephropathy) in Japan is reported. No data from the placebo-controlled double-blind studies in Japan are shown because a detailed analysis of the effects of epalrestat on diabetic neuropathy and retinopathy is now under way. However, it must be stressed that in the phase III placebo-controlled double-blind studies in neuropathy and retinopathy, epalrestat was effective.

**Lipoic acid decreases lipid peroxidation and protein glycosylation and increases (Na<sup>+</sup> + K<sup>+</sup>)- and Ca<sup>++</sup>-ATPase activities in high glucose-treated human erythrocytes.**

Jain SK, Lim G. Department of Pediatrics, Louisiana State University Health Sciences Center, Shreveport, LA 71130, USA. sjain@lsuhsc.edu

Free Radic Biol Med. 2000 Dec;29(11):1122-8.

Lipoic acid supplementation has been found to be beneficial in preventing neurovascular abnormalities in diabetic neuropathy. Insufficient (Na<sup>+</sup> + K<sup>+</sup>)-ATPase activity has been suggested as a contributing factor in the development of diabetic neuropathy. This study was undertaken to test the hypothesis that lipoic acid reduces lipid peroxidation and glycosylation and can increase the

(Na(+)+K(+))- and Ca(++)-ATPase activities in high glucose-exposed red blood cells (RBC). Washed normal human RBC were treated with normal (6 mM) and high glucose concentrations (45 mM) with 0-0.2 mM lipoic acid (mixture of S and R stereoisomers) in a shaking water bath at 37 degrees C for 24 h. There was a significant stimulation of glucose consumption by RBC in the presence of lipoic acid both in normal and high glucose-treated RBC. Lipoic acid significantly lowered the level of glycosylated hemoglobin (GHb) and lipid peroxidation in RBC exposed to high glucose concentrations. High glucose treatment significantly lowered the activities of (Na(+)+K(+))- and Ca(++)-ATPases of RBC membranes. Lipoic acid addition significantly blocked the reduction in activities of (Na(+)+K(+))- and Ca(++)-ATPases in high glucose-treated RBC. There were no differences in lipid peroxidation, GHb and (Na(+)+K(+))- and Ca(++)-ATPase activity levels in normal glucose-treated RBC with and without lipoic acid. Thus, lipoic acid can lower lipid peroxidation and protein glycosylation, and increase (Na(+)+K(+))- and Ca(++)-ATPase activities in high-glucose exposed RBC, which provides a potential mechanism by which lipoic acid may delay or inhibit the development of neuropathy in diabetes.

### **Intravenous methylcobalamin treatment for uremic and diabetic neuropathy in chronic hemodialysis patients.**

Kuwabara S, Nakazawa R, Azuma N, Suzuki M, Miyajima K, Fukutake T, Hattori T. Department of Neurology, Chiba University School of Medicine.

Intern Med 1999 Jun;38(6):472-5

**OBJECT:** To study the effects of the intravenous administration of methylcobalamin, an analogue of vitamin B12, for uremic or uremic-diabetic polyneuropathy in patients who are receiving maintenance hemodialysis. An ultra-high dose of vitamin B12 has been reported to promote peripheral nerve regeneration in experimental neuropathy.

**METHODS:** Nine patients received a 500 microg methylcobalamin injection 3 times a week for 6 months. The effects were evaluated using neuropathic pain grading and a nerve conduction study.

**RESULTS:** Serum concentrations of vitamin B12 were ultra-high during treatment due to the lack of urinary excretion. After 6 months of treatment, the patients' pain or paresthesia had lessened, and the ulnar motor and median sensory nerve conduction velocities showed significant improvement. There were no side effects.

**CONCLUSION:** Intravenous methylcobalamin treatment is a safe and potentially beneficial therapy for neuropathy in chronic hemodialysis patients.

### **Can diabetic neuropathy be prevented by angiotensin-converting enzyme inhibitors?**

Malik RA.

Ann Med 2000 Feb;32(1):1-5

The incidence of diabetes and its complications is increasing to staggering proportions. Presently the WHO estimates an overall prevalence of 130 million, but by 2025 there will be 300 million individuals with diabetes mellitus. The incidence of diabetic neuropathy approaches 50% in most diabetic populations; there is no treatment, and its consequences in the form of foot ulceration and amputation are financially punishing for health care providers. Attempts to develop treatments have faltered for want of an understanding of the aetiology of diabetic neuropathy. As a consequence, 1999 saw the demise of two further compounds: recombinant growth factor by Roche-Genentech and the aldose reductase inhibitor zopolrestat, by Pfizer, both had reached phase III clinical trials. They joined an impressive list of at least 30 other compounds which have reached phase III clinical trials and failed to establish efficacy. The need to establish a viable treatment for human diabetic neuropathy is absolutely paramount. To provide a rational answer as to whether angiotensin-converting enzyme (ACE) inhibitors can prevent human diabetic neuropathy, two major issues need addressing: 1) Does vascular dysfunction cause human diabetic neuropathy? 2) Can ACE inhibitors ameliorate diabetic vascular dysfunction and hence neuropathy? Epidemiological studies support a strong association between neuropathy, retinopathy and nephropathy. Microangiopathy is deemed as the root cause of both nephropathy, and retinopathy and mounting evidence provides support for a vascular basis of diabetic neuropathy. ACE inhibitors appear to correct many of the abnormalities associated with the vascular dysfunction found in diabetes. Thus effective ACE inhibition impacts very positively on cardiovascular outcomes in patients with ischaemic heart disease, particularly in diabetic patients. ACE inhibition also prevents the development and progression of incipient and established diabetic nephropathy and delays progression of background retinopathy. Quinapril improves measures of diabetic autonomic neuropathy. Our recent study has demonstrated a significant improvement in peripheral neuropathy following 12 months of treatment with the ACE inhibitor trandolapril.

### **Chronic administration of pharmacologic doses of vitamin E improves the cardiac autonomic nervous system in patients with type 2 diabetes.**

Manzella D, Barbieri M, Ragno E, Paolisso G. Department of Geriatric Medicine and Metabolic Diseases, Second University of Naples, Italy.

Am J Clin Nutr 2001 Jun;73(6):1052-7

**BACKGROUND:** Type 2 diabetes is associated with elevated oxidative stress and declines in antioxidant defense. The disease is also characterized by an imbalance in the ratio of cardiac sympathetic to parasympathetic tone. Antioxidants, vitamin E in particular, may have beneficial effects on the cardiac autonomic nervous system through a decline in oxidative stress.

**OBJECTIVE:** We investigated the possible effects of vitamin E on the cardiac autonomic nervous system, as assessed by analysis of heart rate variability, in patients with type 2 diabetes and cardiac autonomic neuropathy.

**DESIGN:** In a double-blind randomized controlled trial, 50 patients with type 2 diabetes were assigned to treatment with vitamin E (600 mg/d) or placebo for 4 mo.

**RESULTS:** The anthropometric characteristics of the patients remained unchanged throughout the study. Chronic vitamin E administration was associated with decreases in concentrations of glycated hemoglobin ( $P < 0.05$ ), plasma insulin ( $P < 0.05$ ), norepinephrine ( $P < 0.03$ ), and epinephrine ( $P < 0.02$ ); a lower homeostasis model assessment index ( $P < 0.05$ ); and improved indexes of oxidative stress. Furthermore, vitamin E administration was associated with increases in the R-R interval ( $P < 0.05$ ), total power ( $P < 0.05$ ), and the high-frequency component of heart rate variability (HF;  $P < 0.05$ ) and decreases in the low-frequency component (LF;  $P < 0.05$ ) and the ratio of LF to HF ( $P < 0.05$ ). Finally, change in the plasma vitamin E concentration was correlated with change in the LF-HF ratio ( $r = -0.43$ ,  $P < 0.04$ ) independently of changes in the homeostasis model assessment index and plasma catecholamines concentrations.

**CONCLUSIONS:** Chronic vitamin E administration improves the ratio of cardiac sympathetic to parasympathetic tone in patients with type 2 diabetes. Such an effect might be mediated by a decline in oxidative stress.

### **Supplemental therapy in isolated vitamin E deficiency improves the peripheral neuropathy and prevents the progression of ataxia.**

Martinello F, Fardin P, Ottina M, Ricchieri GL, Koenig M, Cavalier L, Trevisan CP. Department of Neurological and Psychiatric Sciences, University of Padua, Italy.

J Neurol Sci 1998 Apr 1;156(2):177-9

A 24-year-old male, who suffered since childhood from a progressive form of ataxia associated with peripheral neuropathy, was found severely deficient in serum vitamin E. He walked with bilateral aid and presented severe dysmetria of the limbs and dysarthric speech; muscular strength and trophism were slightly diminished in the distal muscles of four limbs and there was hypotonia of the arms; he presented absent deep tendon reflexes, bilateral Babinski's sign, reduced proprioception at four limbs, pes cavus and fasciculations of the tongue. Intestinal fat malabsorption and other gastrointestinal or haematological conditions associated with deficiency of this vitamin were ruled out. In this patient, after 2 years of a daily supplement of high doses of vitamin E, a further progression of the disease was not observed and, moreover, the neurophysiological characteristics of his neuropathy appeared clearly improved. A longitudinal evaluation of serum vitamin E levels showed values in the normal range after 13 months of therapy. The patient had molecular genetic analysis of chromosome 8 and was found homozygous for the unusual mutation 513insTT in the alpha-tocopherol transfer protein gene.

### **Gabapentin for neuropathic pain: systematic review of controlled and uncontrolled literature.**

Mellegers MA, Furlan AD, Mailis A. University of Maastricht, The Netherlands.

Clin J Pain. 2001 Dec;17(4):284-95.

**OBJECTIVE:** To assess the efficacy/effectiveness and side effects of gabapentin for the treatment of neuropathic pain. **DESIGN:** Systematic review of the literature. **METHODS:** Extensive search of several electronic databases located both controlled and uncontrolled studies. Efficacy was assessed through meta-analysis of randomized controlled trials (RCTs), whereas the effectiveness of gabapentin in uncontrolled studies was assessed via a novel system of dichotomous classification of "bad" versus "good" results.

**FINDINGS:** Thirty-five papers involving 727 patients with multiple neuropathic pain conditions met the inclusion criteria. The meta-analysis of the 2 high-quality, placebo-controlled RCTs showed positive effect of gabapentin in diabetic neuropathy and post-herpetic neuralgia. The addition of 2 low-quality, placebo-controlled RCTs did not alter the magnitude or direction of observed effect. The

uncontrolled studies demonstrated positive effect on pain in different neuropathic syndromes, as well as benefit on different types of neuropathic pain; highest dose administered and rate-of-dose escalation showed wide variability between prescribers. Fewer and less severe side effects were reported in the uncontrolled studies.

**CONCLUSIONS:** Gabapentin seems to be effective in multiple painful neuropathic conditions. The variable prescribing patterns of the uncontrolled studies raise the suspicion that effectiveness may be reduced if one limits administration of the drug to very low doses, whereas rapid dose escalation may be associated with increased central nervous system side effects. Well-designed controlled trials may provide insight into differential symptom sensitivity to the drug.

**[Mechanism of the effect of methylcobalamin on the recovery of neuromuscular functions in mechanical and toxin denervation]** [Article in Russian]

Mikhailov VV, Mikhailov VV, Avakumov VM.

Farmakol Toksikol 1983 Nov-Dec;46(6):9-12

It has been shown in experiments on rats that daily administration of methylcobalamine in a dose of 50 micrograms/100 g bw produces marked activation of the regeneration of mechanically damaged axons of motoneurons. Systematic administration of the drug has a protective action on the development of neuromuscular transmission blockade induced by botulinum toxoid.

**Polyol pathway hyperactivity is closely related to carnitine deficiency in the pathogenesis of diabetic neuropathy of streptozotocin-diabetic rats.**

Nakamura J, Koh N, Sakakibara F, Hamada Y, Hara T, Sasaki H, Chaya S, Komori T, Nakashima E, Naruse K, Kato K, Takeuchi N, Kasuya Y, Hotta N. The Third Department of Internal Medicine, Nagoya University School of Medicine, Nagoya, Japan.

J Pharmacol Exp Ther 1998 Dec;287(3):897-902

To investigate the relationship between polyol pathway hyperactivity and altered carnitine metabolism in the pathogenesis of diabetic neuropathy, the effects of an aldose reductase inhibitor, [5-(3-thienyl) tetrazol-1-yl]acetic acid (TAT), and a carnitine analog, acetyl-L-carnitine (ALC), on neural functions and biochemistry and hemodynamic factors were compared in streptozotocin-diabetic rats. Significantly delayed motor nerve conduction velocity, decreased R-R interval variation, reduced sciatic nerve blood flow and decreased erythrocyte 2, 3-diphosphoglycerate concentrations in diabetic rats were all ameliorated by treatment with TAT (administered with rat chow containing 0.05% TAT, approximately 50 mg/kg/day) or ALC (by gavage, 300 mg/kg/day) for 4 weeks. Platelet hyperaggregation activity in diabetic rats was diminished by TAT but not by ALC. TAT decreased sorbitol accumulation and prevented not only myo-inositol depletion but also free-carnitine deficiency in diabetic nerves. On the other hand, ALC also increased the myo-inositol as well as the free-carnitine content without affecting the sorbitol content. These observations suggest that there is a close relationship between increased polyol pathway activity and carnitine deficiency in the development of diabetic neuropathy and that an aldose reductase inhibitor, TAT, and a carnitine analog, ALC, have therapeutic potential for the treatment of diabetic neuropathy.

**Acute effects of static magnetic fields on cutaneous microcirculation in rabbits.**

Ohkubo C, Xu S.

In Vivo 1997; 11: 221-6.

Abstract coming soon.

**Diabetes Mellitus.**

Powers AC.

Principles of Internal Medicine 15th Ed. 2001; p. 2109-37. New York: McGraw-Hill.

Abstract coming soon.

**Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (alpha-lipoic acid): a two year multicenter randomized double-blind placebo-controlled trial (ALADIN II). Alpha Lipoic Acid in Diabetic Neuropathy.**

Free Radic Res. 1999 Sep;31(3):171-9.

Short-term trials with the antioxidant thioctic acid (TA) appear to improve neuropathic symptoms in diabetic patients, but the long-term response remains to be established. Therefore, Type 1 and Type 2 diabetic patients with symptomatic polyneuropathy were randomly assigned to three treatment regimens: (1) 2 x 600(mg of TA (TA 1200), (2) 600)mg of TA plus placebo (PLA) (TA 600) or (3) placebo and placebo (PLA). A trometamol salt solution of TA of 1200 or 600 mg or PLA was intravenously administered once daily for five consecutive days before enrolling the patients in the oral treatment phase. The study was prospective, PLA-controlled, randomized, double-blind and conducted for two years. Severity of diabetic neuropathy was assessed by the Neuropathy Disability Score (NDS) and electrophysiological attributes of the sural (sensory nerve conduction velocity (SNCV), sensory nerve action potential (SNAP)) and the tibial (motor nerve conduction velocity (MNCV), motor nerve distal latency (MNDL)) nerve. Statistical analysis was performed after independent reviewers excluded all patients with highly variable data allowing a final analysis of 65 patients (TA 1200: n = 18, TA 600: n = 27; PLA: n = 20). At baseline no significant differences were noted between the groups regarding the demographic variables and peripheral nerve function parameters for these 65 patients. Statistically significant changes after 24 months between TA and PLA were observed (mean +/- SD) for sural SNCV: +3.8 +/- 4.2 m/s in TA 1200, +3.0 +/- 3.0 m/s in TA 600, -0.1 +/- 4.8 m/s in PLA (p < 0.05 for TA 1200 and TA 600 vs. PLA); sural SNAP: +0.6 +/- 2.5 microV in TA 1200, +0.3 +/- 1.4 microV in TA 600, -0.7 +/- 1.5 microV in PLA (p = 0.076 for TA 1200 vs. PLA and p < 0.05 for TA 600 vs. PLA), and in tibial MNCV: +/- 1.2 +/- 3.8 m/s in TA 1200, -0.3 +/- 5.2 m/s in TA 600, 1.5 +/- 2.9 m/s in PLA (p < 0.05 for TA 1200 vs. PLA). No significant differences between the groups after 24 months were noted regarding the tibial MNDL and the NDS. We conclude that in a subgroup of patients after exclusion of patients with excessive test variability throughout the trial, TA appeared to have a beneficial effect on several attributes of nerve conduction.

### **The case history of an elite ultra-endurance cyclist who developed chronic fatigue syndrome.**

Rowbottom DG, Keast D, Green S, Kakulas B, Morton AR. Department of Human Movement, University of Western Australia, Nedlands, Australia.

Med Sci Sports Exerc. 1998 Sep;30(9):1345-8.

An elite ultra-endurance athlete, who had previously undergone physiological and performance testing, developed chronic fatigue syndrome (CFS). An incremental cycling exercise test conducted while he was suffering from CFS indicated decreases in maximum workload achieved (Wmax; -11.3%), the maximum oxygen uptake (VO2max; -12.5%), and the anaerobic threshold (AT; -14.3%) compared to pre-CFS data. A third test conducted after the athlete had shown indications of significant improvement in his clinical condition revealed further decreases in Wmax (-7.9%), VO2max (-10.2%) and AT (-8.3%). These data, along with submaximal exercise data and muscle biopsy electron microscopic analyses, suggest that the performance decrements were the result of detraining, rather than an impairment of aerobic metabolism due to CFS per se. These data may be indicative of central, possibly neurological, factors influencing fatigue perception in CFS sufferers.

### **Inhibition of development of peripheral neuropathy in streptozotocin-induced diabetic rats with N-acetylcysteine.**

Sagara M, Satoh J, Wada R, Yagihashi S, Takahashi K, Fukuzawa M, Muto G, Muto Y, Toyota T. Third Department of Internal Medicine, Tohoku University School of Medicine, Sendai, Japan.

Diabetologia 1996 Mar;39(3):263-9

N-acetylcysteine (NAC) is a precursor of glutathione (GSH) synthesis, a free radical scavenger and an inhibitor of tumour necrosis factor alpha (TNF). Because these functions might be beneficial in diabetic complications, in this study we examined whether NAC inhibits peripheral neuropathy. Motor nerve conduction velocity (MNCV) was significantly decreased in streptozotocin-induced-diabetic Wistar rats compared to control rats. Oral administration of NAC reduced the decline of MNCV in diabetic rats. Structural analysis of the sural nerve disclosed significant reduction of fibres undergoing myelin wrinkling and inhibition of myelinated fibre atrophy in NAC-treated diabetic rats. NAC treatment had no effect on blood glucose levels or on the nerve glucose, sorbitol and cAMP contents, whereas it corrected the decreased GSH levels in erythrocytes, the increased lipid peroxide levels in plasma and the increased lipopolysaccharide-induced TNF activity in sera of diabetic rats. Thus, NAC inhibited the development of functional and structural abnormalities of the peripheral nerve in streptozotocin-induced diabetic rats.

### **Effect of acetyl-L-carnitine in the treatment of painful peripheral neuropathies in HIV+ patients.**

Scarpini E, Sacilotto G, Baron P, Cusini M, Scarlato G. Department of Clinical Neurology, IRCCS-Ospedale Maggiore Policlinico, University of Milano, Italy.

We studied the effects of acetyl-L-carnitine on pain in 16 HIV+ patients affected by painful distal symmetrical neuropathy. Patients were treated with 0.5-1 gr per day of acetyl-L-carnitine either i.m. or i.v. for 3 weeks. Pain intensity was measured before and after the treatment by the Huskisson's analogic scale. Ten patients (62.5%) reported an improvement of symptoms, five patients (31.25%) were unchanged, one patient worsened. The results of this open study show that acetyl-L-carnitine can have a role in the treatment of pain in distal symmetrical polyneuropathy related to HIV infection. However, further double-blind, placebo-controlled studies are needed to confirm these preliminary results.

#### **Molecular mechanisms of thiamine utilization.**

Singleton CK, Martin PR. Department of Biological Science, Vanderbilt University, Nashville, TN 37235, USA.  
Charles.K.Singleton@Vanderbilt.edu

Curr Mol Med 2001 May;1(2):197-207

Thiamine is required for all tissues and is found in high concentrations in skeletal muscle, heart, liver, kidneys and brain. A state of severe depletion is seen in patients on a strict thiamine-deficient diet in 18 days, but the most common cause of thiamine deficiency in affluent countries is alcoholism. Thiamine diphosphate is the active form of thiamine, and it serves as a cofactor for several enzymes involved primarily in carbohydrate catabolism. The enzymes are important in the biosynthesis of a number of cell constituents, including neurotransmitters, and for the production of reducing equivalents used in oxidant stress defenses and in biosyntheses and for synthesis of pentoses used as nucleic acid precursors. Because of the latter fact, thiamine utilization is increased in tumor cells. Thiamine uptake by the small intestines and by cells within various organs is mediated by a saturable, high affinity transport system. Alcohol affects thiamine uptake and other aspects of thiamine utilization, and these effects may contribute to the prevalence of thiamine deficiency in alcoholics. The major manifestations of thiamine deficiency in humans involve the cardiovascular (wet beriberi) and nervous (dry beriberi, or neuropathy and/or Wernicke-Korsakoff syndrome) systems. A number of inborn errors of metabolism have been described in which clinical improvements can be documented following administration of pharmacological doses of thiamine, such as thiamine-responsive megaloblastic anemia. Substantial efforts are being made to understand the genetic and biochemical determinants of inter-individual differences in susceptibility to development of thiamine deficiency-related disorders and of the differential vulnerabilities of tissues and cell types to thiamine deficiency.

#### **Biochemical pathogenesis of subacute combined degeneration of the spinal cord and brain.**

Surtees R. Institute of Child Health, London, UK.

J Inherit Metab Dis 1993;16(4):762-70

In humans, subacute combined degeneration of the spinal cord and brain, a primary demyelinating disease, is caused by cobalamin or methyltetrahydrofolate deficiency. Experimental studies into its pathogenesis suggest that dysfunction of the methyl-transfer pathway may be the cause. Compelling evidence for this comes from the study of inborn errors of cobalamin metabolism where deficiency of methylcobalamin, but not deoxyadenosylcobalamin, is associated with demyelination. Recent studies have focused upon inborn errors of the methyl-transfer pathway. Cerebrospinal fluid concentrations of metabolites of the methyl-transfer pathway have been measured in humans with sequential errors of the pathway and correlated with demyelination demonstrated on magnetic resonance imaging of the brain. This has provided new data suggesting that deficiency of S-adenosylmethionine is critical to the development of demyelination in cobalamin deficiency.

#### **Effects of propionyl-L-carnitine on cardiac dysfunction in streptozotocin-diabetic rats.**

Terada R, Matsubara T, Koh N, Nakamura J, Hotta N. Third Department of Internal Medicine, Nagoya University School of Medicine, Japan.

Eur J Pharmacol. 1998 Sep 18;357(2-3):185-91

The effects of orally administered propionyl-L-carnitine on cardiac dysfunction in rats with streptozotocin-induced diabetes were investigated. Wistar male rats were divided into four groups: untreated normal, propionyl-L-carnitine (daily for 4 weeks with 3 g/kg orally) -treated normal, untreated diabetic, propionyl-L-carnitine-treated diabetic. Four weeks after streptozotocin administration, plasma lipid levels were increased and myocardial carnitine content was decreased in untreated diabetic rats. These changes were significantly reversed by the propionyl-L-carnitine treatment. Assessment of cardiac function with isolated perfused working hearts revealed a depression of left ventricular developed pressure as well as both maximum positive and negative dP/dt in untreated diabetic as compared with that in normal hearts. Cardiac function at the higher left atrial filling pressures in the propionyl-L-carnitine-treated diabetic rats was improved significantly compared to that in untreated hearts. The data thus suggest that oral administration

of propionyl-L-carnitine can reduce abnormalities of cardiac function, correlated with a significant increase in myocardial carnitine content and improved lipid metabolism in terms of lowered plasma lipids.

**A new mechanism of neurodegeneration: a proinflammatory cytokine inhibits receptor signaling by a survival peptide.**

Venters HD, Tang Q, Liu Q, VanHoy RW, Dantzer R, Kelley KW. Laboratory of Immunophysiology, Department of Animal Sciences, University of Illinois, Urbana, IL 61801, USA.

Proc Natl Acad Sci U S A 1999 Aug 17;96(17):9879-84

Heightened expression of both a proinflammatory cytokine, tumor necrosis factor alpha (TNF-alpha), and a survival peptide, insulin-like growth factor I (IGF-I), occurs in diverse diseases of the central nervous system, including Alzheimer's disease, multiple sclerosis, the AIDS-dementia complex, and cerebral ischemia. Conventional roles for these two proteins are neuroprotection by IGF-I and neurotoxicity by TNF-alpha. Although the mechanisms of action for IGF-I and TNF-alpha in the central nervous system originally were established as disparate and unrelated, we hypothesized that the signaling pathways of these two cytokines may interact during neurodegeneration. Here we show that concentrations of TNF-alpha as low as 10 pg/ml markedly reduce the capacity of IGF-I to promote survival of primary murine cerebellar granule neurons. TNF-alpha suppresses IGF-I-induced tyrosine phosphorylation of insulin receptor substrate 2 (IRS-2) and inhibits IRS-2-precipitable phosphatidylinositol 3'-kinase activity. These experiments indicate that TNF-alpha promotes IGF-I receptor resistance in neurons and inhibits the ability of the IGF-I receptor to tyrosine-phosphorylate the IRS-2 docking molecule and to subsequently activate the critical downstream enzyme phosphatidylinositol 3'-kinase. This intracellular crosstalk between discrete cytokine receptors reveals a novel pathway that leads to neuronal degeneration whereby a proinflammatory cytokine inhibits receptor signaling by a survival peptide.

**Static magnetic field therapy for symptomatic diabetic neuropathy: a randomized, double-blind, placebo-controlled trial.**

Weintraub MI, Wolfe GI, Barohn RA, Cole SP, Parry GJ, Hayat G, Cohen JA, Page JC, Bromberg MB, Schwartz SL.

Arch Phys Med Rehabil 2003; 84: 736-46.

**OBJECTIVE:** To determine if constant wearing of multipolar, static magnetic (450G) shoe insoles can reduce neuropathic pain and quality of life (QOL) scores in symptomatic diabetic peripheral neuropathy (DPN). **DESIGN:** Randomized, placebo-control, parallel study. **SETTING:** Forty-eight centers in 27 states. **PARTICIPANTS:** Three hundred seventy-five subjects with DPN stage II or III were randomly assigned to wear constantly magnetized insoles for 4 months; the placebo group wore similar, unmagnetized device. **INTERVENTION:** Nerve conduction and/or quantified sensory testing were performed serially. **MAIN OUTCOME MEASURES:** Daily visual analog scale scores for numbness or tingling and burning and QOL issues were tabulated over 4 months. Secondary measures included nerve conduction changes, role of placebo, and safety issues. Analysis of variance (ANOVA), analysis of covariance (ANCOVA), and chi-square analysis were performed. **RESULTS:** There were statistically significant reductions during the third and fourth months in burning (mean change for magnet treatment, -12%; for sham, -3%;  $P < .05$ , ANCOVA), numbness and tingling (magnet, -10%; sham, +1%;  $P < .05$ , ANCOVA), and exercise-induced foot pain (magnet, -12%; sham, -4%;  $P < .05$ , ANCOVA). For a subset of patients with baseline severe pain, statistically significant reductions occurred from baseline through the fourth month in numbness and tingling (magnet, -32%; sham, -14%;  $P < .01$ , ANOVA) and foot pain (magnet, -41%; sham, -21%;  $P < .01$ , ANOVA). **CONCLUSIONS:** Static magnetic fields can penetrate up to 20mm and appear to target the ectopic firing nociceptors in the epidermis and dermis. Analgesic benefits were achieved over time.

**Chronic submaximal magnetic stimulation in peripheral neuropathy: is there a beneficial therapeutic relationship?**

Weintraub MI.

Am J Pain Management 1998; 8: 12-6.

Abstract coming soon.

**[Pharmacological studies on degeneration and regeneration of the peripheral nerves. (2) Effects of methylcobalamin on mitosis of Schwann cells and incorporation of labeled amino acid into protein fractions of crushed sciatic nerve in rats] [Article in Japanese]**

Yamatsu K, Yamanishi Y, Kaneko T, Ohkawa I.

Nippon Yakurigaku Zasshi 1976 Mar;72(2):269-78

Male Wistar rats (140 to 150 g) in which the unilateral sciatic nerve had been crushed were treated consecutively with methylcobalamin (5, 50 and 500 µg/kg/day i.p.) or saline immediately after the nerve-crush. Thereafter, they were periodically sacrificed for biochemical and histological examinations. At different intervals after the nerve-crush, L-leucine-4,5-T (20 µCi/100g, specific activity 15 mCi/m mole) or L-leucine -14C(U) (15 µCi/100g, specific activity 270 mCi/m mole) was given i.p. to some rats of each group and 3 hr later they were sacrificed to determine the rate of leucine incorporation into protein fractions of the crushed nerve and the denervated muscles. The nerve and muscles of the contralateral side served as control. Longitudinal sections of proximal and distal stumps of the sciatic nerve were prepared and stained with hematoxylin and eosin. As compared with saline group, repeated injections of 5, 50 and 500 µg/kg/day of methyl-cobalamin caused a significant increase of the in vivo incorporation of radioactive leucine into the protein fraction of the crushed sciatic nerve 5 to 7 days after the crush. In contrast, a recovery of the increased incorporation of leucine into the crushed nerve was more rapid in methylcobalamin groups than in the saline group. On the other hand, methylcobalamin (5 approximately 500 µg/kg/day i.p.) had no significant effect on the leucine incorporation into the denervated muscles (m. gastrocnemius, m. tibialis anterior and m. soleus). In addition, consecutive injections of methylcobalamin (5 approximately 500 µg/kg/day) did not affect the mitosis of Schwann cells during the period of Wallerian degeneration of the crushed sciatic nerve. These results suggest that methylcobalamin possesses a stimulating effect on proteosynthesis in Schwann cells at the initial stage of axon regeneration and it may facilitate neural regeneration.

### **Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant alpha-lipoic acid. A 3-week multicentre randomized controlled trial (ALADIN Study).**

Ziegler D, Hanefeld M, Ruhnau KJ, Meissner HP, Lobisch M, Schutte K, Gries FA. Diabetes-Forschungsinstitut an der Heinrich-Heine-Universität, Dusseldorf, Germany.

Diabetologia. 1995 Dec;38(12):1425-33.

Anti-oxidant treatment has been shown to prevent nerve dysfunction in experimental diabetes mellitus, thus providing a rationale of potential therapeutic value for diabetic patients. The effects of the anti-oxidant alpha-lipoic acid (thioctic acid) were studied in a 3-week multicentre, randomized, double-blind placebo-controlled trial (Alpha-Lipoic Acid in Diabetic Neuropathy; ALADIN) in 328 non-insulin-dependent diabetic patients with symptomatic peripheral neuropathy who were randomly assigned to treatment with intravenous infusion of alpha-lipoic acid using three doses (1200, 600, or 100 mg ALA) or placebo (PLAC). Neuropathic symptoms (pain, burning, paraesthesiae, and numbness) were scored at baseline and at each visit (days 2-5, 8-12, and 15-19) prior to infusion. In addition, the Hamburg Pain Adjective List, a multidimensional specific pain questionnaire, and the Neuropathy Symptom and Disability Scores were assessed at baseline and day 19. According to the protocol 260 (65/63/66/66) patients completed the study. The total symptom score in the feet decreased from baseline to day 19 by -4.5 +/- 3.7 (-58.6%) points (mean +/- SD) in ALA 1200, -5.0 +/- 4.1 (-63.5%) points in ALA 600, -3.3 +/- 2.8 (-43.2%) points in ALA 100, and -2.6 +/- 3.2 (-38.4%) points in PLAC (ALA 1200 vs PLAC:  $p = 0.003$ ; ALA 600 vs PLAC:  $p < 0.001$ ). The response rates after 19 days, defined as an improvement in the total symptom score of at least 30%, were 70.8% in ALA 1200, 82.5% in ALA 600, 65.2% in ALA 100, and 57.6% in PLAC (ALA 600 vs PLAC;  $p = 0.002$ ). The total scale of the Pain Adjective List was significantly reduced in ALA 1200 and ALA 600 as compared with PLAC after 19 days (both  $p < 0.01$ ). The rates of adverse events were 32.6% in ALA 1200, 18.2% in ALA 600, 13.6% in ALA 100, and 20.7% in PLAC. These findings substantiate that intravenous treatment with alpha-lipoic acid using a dose of 600 mg/day over 3 weeks is superior to placebo in reducing symptoms of diabetic peripheral neuropathy, without causing significant adverse reactions.

### **Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy.**

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**OBJECTIVE:** To evaluate the efficacy and safety of alpha-lipoic acid given intravenously, followed by oral treatment in type 2 diabetic patients with symptomatic polyneuropathy.

**RESEARCH DESIGN AND METHODS:** In a multicenter randomized double-blind placebo-controlled trial (Alpha-Lipoic Acid in Diabetic Neuropathy [ALADIN] III Study), 509 outpatients were randomly assigned to sequential treatment with 600 mg alpha-lipoic acid once daily intravenously for 3 weeks, followed by 600 mg alpha-lipoic acid three times a day orally for 6 months (A-A;  $n = 167$ ); 600 mg alpha-lipoic acid once daily intravenously for 3 weeks, followed by placebo three times a day orally for 6 months (A-P;  $n = 174$ ); and placebo once daily intravenously for 3 weeks, followed by placebo three times a day orally for 6 months (P-P;  $n = 168$ ). Outcome measures included the Total Symptom Score (TSS) for neuropathic symptoms (pain, burning, paresthesias, and numbness) in the feet, and the Neuropathy Impairment Score (NIS). Data analysis was based on the intention to treat.

**RESULTS:** No significant differences between the groups were noted for the demographic variables and the nerve function parameters at baseline. The TSS in the feet decreased from baseline to day 19 (median [range]) by -3.7 (-12.6 to 5.0) points in the

group given alpha-lipoic acid intravenously and by -3.0 (-12.3 to 8.0) points in the placebo group ( $P = 0.447$ ), but the area under curve on a daily basis was significantly smaller in the active as compared with the placebo group (85.6 [0-219] vs. 95.9 [5.5-220]);  $P = 0.033$ ). After 7 months, the changes in the TSS from baseline were not significantly different between the three groups studied, which could be due to increasing intercenter variability in the TSS during the trial. The NIS decreased after 19 days by  $-4.34 \pm 0.35$  points (mean  $\pm$  SEM) in A-A and A-P and  $-3.49 \pm 0.58$  points in P-P ( $P = 0.02$  for alpha-lipoic acid versus placebo) and after 7 months by  $-5.82 \pm 0.73$  points in A-A,  $-5.76 \pm 0.69$  points in A-P, and  $-4.37 \pm 0.83$  points in P-P ( $P = 0.09$  for A-A vs. P-P). The rates of adverse events were not different between the groups throughout the study.

**CONCLUSIONS:** These findings indicate that a 3-week intravenous treatment with alpha-lipoic acid, followed by a 6-month oral treatment, had no effect on neuropathic symptoms distinguishable from placebo to a clinically meaningful degree, possibly due to increasing intercenter variability in symptom scoring during the study. However, this treatment was associated with a favorable effect on neuropathic deficits without causing significant adverse reactions. Long-term trials that focus on neuropathic deficits rather than symptoms as the primary criterion of efficacy are needed to see whether oral treatment with alpha-lipoic acid over several years may slow or reverse the progression of diabetic neuropathy.

### **Alpha-lipoic acid in the treatment of diabetic polyneuropathy in Germany: current evidence from clinical trials.**

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Diabetic neuropathy represents a major health problem, as it is responsible for substantial morbidity, increased mortality, and impaired quality of life. Near-normoglycaemia is now generally accepted as the primary approach to prevention of diabetic neuropathy, but is not achievable in a considerable number of patients. In the past two decades several medical treatments that exert their effects despite hyperglycaemia have been derived from the experimental pathogenetic concepts of diabetic neuropathy. Such compounds have been designed to improve or slow the progression of the neuropathic process and are being evaluated in clinical trials, but with the exception of alpha-lipoic acid (thioctic acid) which is available in Germany, none of these drugs is currently available in clinical practice. Here we review the current evidence from the clinical trials that assessed the therapeutic efficacy and safety of thioctic acid in diabetic polyneuropathy. Thus far, 15 clinical trials have been completed using different study designs, durations of treatment, doses, sample sizes, and patient populations. Within this variety of clinical trials, those with beneficial effects of thioctic acid on either neuropathic symptoms and deficits due to polyneuropathy or reduced heart rate variability resulting from cardiac autonomic neuropathy used doses of at least 600 mg per day. The following conclusions can be drawn from the recent controlled clinical trials.

- 1.) Short-term treatment for 3 weeks using 600 mg of thioctic acid i.v. per day appears to reduce the chief symptoms of diabetic polyneuropathy. A 3-week pilot study of 1800 mg per day given orally indicates that the therapeutic effect may be independent of the route of administration, but this needs to be confirmed in a larger sample size.
- 2.) The effect on symptoms is accompanied by an improvement of neuropathic deficits.
- 3.) Oral treatment for 4-7 months tends to reduce neuropathic deficits and improves cardiac autonomic neuropathy.
- 4.) Preliminary data over 2 years indicate possible long-term improvement in motor and sensory nerve conduction in the lower limbs.
- 5.) Clinical and postmarketing surveillance studies have revealed a highly favourable safety profile of the drug. Based on these findings, a pivotal long-term multicenter trial of oral treatment with thioctic acid (NATHAN I Study) is being conducted in North America and Europe aimed at slowing the progression of diabetic polyneuropathy using a clinically meaningful and reliable primary outcome measure that combines clinical and neurophysiological assessment.

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