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## ABSTRACTS

### Protection via Methylcobalamin

Life Extension magazine republishes abstracts on health and longevity topics in each issue, drawn from research papers originally published in science and medical journals throughout the world.

***Protective effects of a vitamin B12 analogue, methylcobalamin, against glutamate cytotoxicity in cultured cortical neurons***

*Akaike A Tamura Y Sato Y Yokota T, Eur J Pharmacol (1993 Sep 7) 241(1):1-6*

The effects of methylcobalamin, a vitamin B12 analogue, on glutamate-induced neurotoxicity were examined using cultured rat cortical neurons. Cell viability was markedly reduced by a brief exposure to glutamate followed by incubation with glutamate-free medium for 1 h. Glutamate cytotoxicity was prevented when the cultures were maintained in methylcobalamin-containing medium. Glutamate cytotoxicity was also prevented by chronic exposure to S-adenosylmethionine, which is formed in the metabolic pathway of methylcobalamin. Chronic exposure to methylcobalamin and S-adenosylmethionine also inhibited the cytotoxicity induced by methyl-D-aspartate or sodium nitroprusside that releases nitric oxide. In cultures maintained in a standard medium, glutamate cytotoxicity was not affected by adding methylcobalamin to the glutamate-containing medium. In contrast, acute exposure to MK-801, a NMDA receptor antagonist, prevented glutamate cytotoxicity. These results indicate that chronic exposure to methylcobalamin protects cortical neurons against NMDA receptor-mediated glutamate cytotoxicity.

## Methylcobalamin and Diabetic Neuropathy

### ***Clinical usefulness of intrathecal injection of methylcobalamin in patients with diabetic neuropathy***

*Ide H Fujiya S Asanuma Y Tsuji M Sakai H Agishi Y, Clin Ther (1987) 9(2):183-92*

Seven men and four women with symptomatic diabetic neuropathy were treated with methylcobalamin (2,500 micrograms in 10 ml of saline) injected intrathecally. Treatment was begun when patients had good metabolic control, as determined by measurements of plasma glucose and hemoglobin, and was repeated several times with a one-month interval between injections. Three patients were re-treated one year after the last intrathecal injection. Symptoms in the legs, such as paresthesia, burning pains, and heaviness, dramatically improved. The effect appeared within a few hours to one week and lasted from several months to four years. The mean peroneal motor-nerve conduction velocity did not change significantly. The mean (+/- SD) concentration of methylcobalamin in spinal fluid was 114 +/- 32 pg/ml before intrathecal injection (n = 5) and 4,752 +/- 2,504 pg/ml one month after intrathecal methylcobalamin treatment (n = 11). Methylcobalamin caused no side effects with respect to subjective symptoms or characteristics of spinal fluid. These findings suggest that a high concentration of methylcobalamin in spinal fluid is highly effective and safe for treating the symptoms of diabetic neuropathy.

## Nerve Regeneration with Methylcobalamin

### ***Ultra-high dose methylcobalamin promotes nerve regeneration in experimental acrylamide neuropathy.***

*Watanabe T Kaji R Oka N Bara W Kimura J, J Neurol Sci (1994 Apr) 122(2):140-3*

Despite intensive searches for therapeutic agents, few substances have been convincingly shown to enhance nerve regeneration in patients with peripheral neuropathies. Recent biochemical evidence suggests that an ultra-high dose of methylcobalamin (methyl-B12) may up-regulate gene transcription and thereby protein synthesis. We examined the effects of ultra-high dose of methyl-B12 on the rate of nerve regeneration in rats with acrylamide neuropathy, using the amplitudes of compound muscle action potentials (CMAPs) after tibial nerve stimulation as an index of the number of regenerating motor fibers. After intoxication with acrylamide, all the rats showed equally decreased CMAP amplitudes. The animals were then divided into 3 groups; rats treated with ultra-high (500 micrograms/kg body weight, intraperitoneally) and low (50 micrograms/kg) doses of methyl-B12, and saline-treated control rats. Those treated with ultra-high dose showed significantly faster CMAP recovery than saline-treated control rats, whereas the low-dose group showed no difference from the control. Morphometric analysis revealed a similar difference in fiber density between these groups. Ultra-high doses of methyl-B12 may be of clinical use for patients with peripheral neuropathies.

## Methylcobalamin, Bell's Palsy

### ***Methylcobalamin treatment of Bell's Palsy***

*Jalaludin MA, Methods Find Exp Clin Pharmacol (1995 Oct) 17(8):539-44*

Bell's palsy patients were assigned into three treatment groups: steroid (group 1), methylcobalamin (group 2) and methylcobalamin + steroid (group 3). Comparison between the three groups was based on the number of days needed to attain full recovery, facial nerve scores, and improvement of concomitant symptoms. The time required for complete recovery of facial nerve function was significantly shorter in the methylcobalamin and methylcobalamin plus steroid groups than in the steroid group. The facial nerve score after 1-3 weeks of treatment was significantly more severe ( $p < 0.001$ ) in the steroid group compared to the methylcobalamin and methylcobalamin plus steroid groups. The improvement of concomitant symptoms was better in the methylcobalamin treated groups than the group treated with steroid alone.

## Nerve Terminal Regeneration

### ***Methylcobalamin (methyl-B12) promotes regeneration of motor nerve terminals degenerating in anterior gracile muscle of gracile axonal dystrophy (GAD) mutant mouse.***

*Yamazaki K Oda K Endo C Kikuchi T Wakabayashi T, Neurosci Lett (1994 Mar 28) 170(1):195-7*

We examined the effects of methylcobalamin (methyl-B12, mecobalamin) on degeneration of motor nerve terminals in the anterior gracile muscle of gracile axonal dystrophy (GAD) mutant mice. GAD mice received orally methyl-B12 (1 mg/kg body wt/day) from the 40th day after birth for 25 days. In the distal endplate zone of the muscle, although most terminals were degenerated in both the untreated and methyl-B12-treated GAD mice, sprouts were more frequently observed in the latter. In the proximal endplate zone, where few degenerated terminals were seen in both groups of the mice, the perimeter of the terminals was increased and the area of the terminals was decreased significantly in the methyl-B12-treated GAD mice. These findings indicate that methyl-B12 promotes regeneration of degenerating nerve terminals in GAD mice.

## Fighting Neurotoxicity

### ***Protective effects of methylcobalamin, a vitamin B12 analogue, against glutamate-induced neurotoxicity in retinal cell culture.***

*Kikuchi M Kashii S Honda Y Tamura Y Kaneda K Akaike, Invest Ophthalmol Vis Sci (1997 Apr) 38(5):848-54*

**Purpose:** To examine the effects of methylcobalamin on glutamate- induced neurotoxicity in the cultured retinal neurons. **Methods:** Primary cultures obtained from the fetal rat retina (gestation days 16 to 19) were used for the experiment. The neurotoxicity was assessed quantitatively using the trypan blue exclusion method. **Results:** Glutamate neurotoxicity was prevented by chronic exposure to methylcobalamin and S-adenosylmethionine (SAME), which is formed in the metabolic pathway of methylcobalamin. Chronic exposure to methylcobalamin and SAME also inhibited the neurotoxicity induced by sodium nitroprusside that release nitric oxide. By contrast, acute exposure to methylcobalamin did not protect retinal neurons against glutamate neurotoxicity. **Conclusions:** Chronic administration of methylcobalamin protects cultured retinal neurons against N-methyl-D- aspartate-receptor-mediated glutamate neurotoxicity, probably by altering the membrane properties through SAME-mediated methylation.

## Methyl Donor Effects

### ***Effect of cobalamin derivatives on in vitro enzymatic DNA methylation: methylcobalamin can act as a methyl donor.***

*Leszkowicz A Keith G Dirheimer G, Biochemistry (1991 Aug 13) 30(32):8045-51*

Methylcytosine synthesis in DNA involves the transfer of methyl groups from S-adenosylmethionine to the 5'-position of cytosine through the action of DNA (cytosine-5)-methyltransferase. The rate of this reaction has been found to be enhanced by cobalt ions. We therefore analyzed the influence of vitamin B12 and related compounds containing cobalt on DNA methylation. Vitamin B12, methylcobalamin, and coenzyme B12 (methylcobalamin) were found to enhance significantly the de novo DNA methylation in the presence of S-adenosylmethionine for concentrations up to 1 microM, but at higher concentrations these compounds were found to inhibit DNA methylation. Methylcobalamin behaves as a competitive inhibitor of the enzymatic methylation reaction ( $K_i = 15$  microM), the  $K_m$  for S-adenosylmethionine being 8 microM. In addition, the use of radioactive methylcobalamin shows that it can be used as a methyl donor in the de novo and maintenance DNA methylation reactions. Thus, two DNA methylation pathways could exist: one involving methylation from S-adenosylmethionine and a second one involving methylation from methylcobalamin.

## Horse Chestnut, Compression

### ***Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency.***

*Diehm C Trampisch HJ Lange S Schmidt C, Lancet (1996 Feb 3) 347(8997):292-4*

**Background:** Diseases of the venous system are widespread disorders sometimes associated with modern civilization and are among the major concerns of social and occupational medicine. This study was carried out to compare the efficacy (edema reduction) and safety of compression stockings class II and dried horse chestnut seed extract (HCSE, 50 mg escin, twice daily).

**Methods:** Equivalence of both therapies was examined in a novel hierarchical statistical design in 240 patients with chronic venous insufficiency. Patients were treated over a period of 12 weeks in a randomized, partially blinded, placebo- controlled, parallel study design. **Findings:** Lower leg volume of the more severely affected limb decreased on average by 43.8 mL (n = 95) with HCSE and 46.7 mL (n = 99) with compression therapy, while it increased by 9.8 mL with placebo (n = 46) after 12 weeks therapy for the intention-to-treat group (95% CI: HCSE: 21.1-66.4; compression: 30.4-63.0; placebo: 40.0-20.4). Significant edema reductions were achieved by HCSE ( $p = 0.005$ ) and compression ( $p = 0.002$ ) compared to placebo, and the two therapies were shown to be equivalent ( $p = 0.001$ ); in this design, however, compression could not be proven as standard with regard to edema reduction in the statistical test procedure. **Interpretation:** These results indicate that compression stocking therapy and HCSE therapy are alternative therapies for the effective treatment of patients with edema resulting from chronic venous insufficiency.

## Horse Chestnut, Inflammation

### ***Effects of escins Ia, Ib, IIa, and IIb from horse chestnut, the seeds of Aesculus hippocastanum L., on acute inflammation in animals.***

*Matsuda H Li Y Murakami T Ninomiya K Yamahara J Yoshikawa M, Biol Pharm Bull (1997 Oct) 20(10):1092-5*

We investigated the effects of escins Ia, Ib, and IIb isolated from horse chestnut, the seeds of *Aesculus hippocastanum* L., and desacylescins I and II obtained by alkaline hydrolysis of escins on acute inflammation in animals (p.o.). Escins Ia, Ib, IIa, and IIb (50- 200 mg/kg) inhibited the increase of vascular permeability induced by both acetic acid in mice and histamine in rats. Escins Ib, IIa, and IIb (50-200 mg/kg) also inhibited that induced by serotonin in rats, but escin Ia didn't. Escins Ia, Ib, IIa, and IIb (200 mg/kg) inhibited the hind paw edema induced by carrageenin at the first phase in rats. Escin Ia (200 mg/kg) and escins Ib, IIa, and IIb (50-200 mg/kg) inhibited the scratching behavior induced by compound 48/80 in mice, but escin Ia was weakest. Desacylescins I and II (200 mg/kg) showed no effect. With regard to the relationship between their chemical structures and activities, the acyl groups in escins were essential. Escins Ib, IIa, and IIb with either the 21-angeloyl group or the 2'-O-xylopyranosyl moiety showed more potent activities than escin Ia which had both the 21-tigloyl group and the 2'-O- glucopyranosyl moiety.

## Chronic Venous Insufficiency

### ***[Effects of horse-chestnut seed extract on transcapillary filtration in chronic venous insufficiency] (Published in German)***

*Bisler H Pfeifer R Kluken N Pauschinger P, Dtsch Med Wochenschr (1986 Aug 29) 111(35):1321-9*

The effect of horse-chestnut seed extract (standardized on escin; Venostasin retard) was assessed in a randomized placebo-controlled crossover double-blind trial of 22 patients with proven chronic venous insufficiency by measuring the capillary filtration coefficient and the intravascular volume of the lower leg by venous-occlusion plethysmography. Three hours after taking two capsules of Venostasin (600 mg; each capsule containing 50 mg escin) the capillary filtration coefficient had decreased by 22%, whereas after administration of an identical-looking placebo capsule it rose but slightly over three hours. The difference in the effect of Venostasin and placebo is statistically significant ( $P = 0.006$ ). The intravascular volume was reduced 5% more after Venostasin than the placebo, but this is not statistically significant. It is concluded that Venostasin has an inhibitory effect on edema formation via a decrease in transcapillary filtration and thus improves edema-related symptoms in venous diseases of the legs.

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## SAMe and Liver Cancer

### ***Chemoprevention of rat liver carcinogenesis by S-adenosyl-L- methionine: a long-term study.***

*Pascale RM Marras V Simile MM Daino L Pinna G Bennati S Carta M Seddaiu MA Massarelli G Feo F, Cancer Res (1992 Sep 15) 52(18):4979-86*

Previous work has shown a consistent fall in S-adenosyl-L-methionine (SAMe) in the liver of diethylnitrosamine-initiated rats, during the development of preneoplastic lesions, in persistent nodules (PNs), and hepatocellular carcinomas. The injection of SAM into rats causes the reconstitution of the SAMe pool, coupled with growth restraint, remodeling, and apoptosis of preneoplastic cells, and inhibits the development of PNs and hepatocellular carcinomas. To evaluate if SAMe treatment causes a long-term prevention of preneoplastic and neoplastic liver lesions or merely causes a delay in their development, we evaluated the effect of a relatively short SAMe treatment on the development of preneoplastic and neoplastic lesions in a long-term study. Male Wistar rats were subjected to initiation with diethylnitrosamine, followed by selection and then by the administration of phenobarbital for 16 weeks. After selection, the rats were given i.m. injections of a purified SAMe preparation (384 micromol/kg/day) for 24 weeks. In SAMe-treated rats, a decrease in the incidence of PNs was found 6, 14, and 24-28 months after initiation. Nodule diameter started to increase rapidly again only 8 months after arresting SAMe treatment, when complete recovery of DNA synthesis in nodular cells occurred. The majority of nodules present in the liver 6-28 months after initiation belonged to the clear and acidophilic cell types, with lower percentages of mixed cell and basophilic cell types. A decrease in basophilic nodules occurred in SAMe-treated rats. Fourteen and 24-28 months after initiation hepatocellular carcinoma incidence was 11 of 12 and 10 of 10 in control rats, respectively, and only 1 of 12 and 3 of 11 in SAMe-treated rats. At the 24th-28th month all control rats had tumors identified as 2 poorly differentiated carcinomas, 6 trabecular carcinomas, or 3 adenocarcinomas, while only 2 relatively small trabecular carcinomas and 1 small glandular tumor developed in SAMe-treated rats. In 3 of 11 SAMe-treated rats, but in none of the control rats, leukemic infiltration of liver occurred 24-28 months after initiation. Leukemic infiltration of the spleen occurred in 5 and 3 control and SAMe-treated rats, respectively.

## Hyperhomocysteinemia

### ***Hyperhomocysteinemia as a risk factor for deep-vein thrombosis***

*den Heijer M Koster T Blom HJ Bos GM Briet E Reitsma PH Vandenbroucke JP Rosendaal FR, N Engl J Med (1996 Mar 21) 334 (12):759-62*

Previous studies have suggested that hyperhomocysteinemia may be a risk factor for venous thrombosis. To assess the risk of venous thrombosis associated with hyperhomocysteinemia, we studied plasma homocysteine levels in patients with a first episode of deep- vein thrombosis and in normal control subjects. We measured plasma homocysteine levels in 269 patients with a first, objectively diagnosed episode of deep-vein thrombosis and in 269 healthy controls matched to the patients according to age and sex. Hyperhomocysteinemia was defined as a plasma homocysteine level above the 95th percentile in the control group (18.5 micromol per liter). Of the 269 patients, 28 had plasma homocysteine levels above the 95th percentile for the controls, as compared with 13 of the controls (matched odds ratio, 2.5; 95 percent confidence interval, 1.2 to 5.2). The association between elevated homocysteine levels and venous thrombosis was stronger among women than among men and increased with age. High plasma homocysteine levels are a risk factor for deep-vein thrombosis in the general population.

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