

Hearing Loss

ABSTRACTS

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Noise-induced hypertension and magnesium in rats: relationship to microcirculation and calcium.

Altura BM, Altura BT, Gebrewold A, Ising H, Gunther T. Department of Physiology, State University of New York, Brooklyn 11203.

J Appl Physiol 1992 Jan;72(1):194-202

It has been demonstrated that audiogenic stress (AS) can induce elevation of arterial blood pressure (ABP) in animals and humans and that noise-induced hearing loss may be associated with alterations in Mg metabolism. Experiments were designed to determine whether 1) there is a causal relationship among environmental noise stress, serum and vascular tissue (aortas and portal veins) Mg contents, and development of hypertension and 2) such noise-induced hypertension has a microcirculatory basis and what the mechanism may be. Rats maintained on normal Mg-containing diets for 12 wk (plasma [Mg] = 0.96 +/- 0.02 mM) and subjected to AS (85 dB(A), 12 h/day for 8 wk; 95 dB(A), 16 h/day for 4 wk) demonstrated significant elevation in systolic and diastolic ABP; plasma [Mg] showed a 15% deficit, whereas aortic and portal vein muscle exhibited slight reductions in Mg content and elevation in Ca. Moderate and more severely Mg-deficient animals not subjected to AS also exhibited significant elevations in systolic and diastolic ABP; vascular tissue Mg content decreased, whereas Ca content rose. Animals subjected to combined Mg deficiency and AS for 12 wk exhibited the greatest deficits in plasma and vascular muscle Mg and the greatest elevations in systolic and diastolic ABP; vascular tissue Ca contents also showed the greatest increases. In situ measurements of mesenteric arterioles, venules, and precapillary sphincters in the various subgroups revealed that the lower the plasma [Mg], the more constricted the microvessels, and the higher the ABP, the lower the plasma [Mg]. Capillary blood flow velocities were decreased in relation to the degree of plasma Mg deficit.(ABSTRACT TRUNCATED AT 250 WORDS)

NG-methyl-L-arginine protects the guinea pig cochlea from the cytotoxic effects of pneumolysin.

Amaee FR, Comis SD, Osborne MP. Department of Physiology, Medical School, University of Birmingham, England.

Acta Otolaryngol 1995 May;115(3):386-91

Sensorineural hearing loss is a major sequela of the bacterial meningitis associated in particular with Streptococcus pneumoniae. Recent studies have shown pneumolysin, a toxin elaborated by S. pneumoniae, to be cytotoxic to the guinea pig cochlea. The mechanisms of this cytotoxicity are, however, not fully understood. In the present study this deleterious action of pneumolysin has been shown to be blocked by pretreating the cochlea with NG-methyl-L-arginine, a known inhibitor of nitric oxide synthesis. Furthermore, pretreatment of the cochlea with MK-801, an NMDA receptor antagonist, was also found to confer marked protection from the action of pneumolysin. This latter finding is consistent with previous reports that excess stimulation of NMDA receptors within the cochlea, an event known to lead to excess nitric oxide release, have similar effects on the cochlea as pneumolysin perfusion. It would therefore appear that nitric oxide may represent a significant link in the chain of events leading to the deafness of bacterial meningitis.

The consequences of untreated hearing loss in older persons.

Anon.

ORL Head Neck Nurs. 2000 Winter; 18(1): 12-6.

No abstract available.

Vitamin E and lipoic acid, but not vitamin C improve blood oxygenation after high-energy IMPULSE noise (BLAST) exposure.

Biochem Biophys Res Commun 1998 Dec 9;253(1):114-8

Exposure to high energy impulse noise (BLAST) caused by explosions, result in structural and functional damage to the hollow organs, especially to the respiratory and auditory systems. Lung damage includes alveolar wall rupture, edema and hemorrhage, and may be fatal. Previous observations at the molecular level using the rat model, suggested that secondary free radical-mediated oxidative stress occurs post exposure resulting in antioxidant depletion and hemoglobin (Hb) oxidation. This study examined whether a short period of pre-exposure supplementation with antioxidants would protect Hb from the effects of BLAST exposure. Six groups of male Sprague-Dawley rats (8/group) were gavaged with 800 IU vitamin E (VE) in 2 ml corn oil, 1000 mg vitamin C (VC) in 2 ml distilled water or 25 mg or (-lipoic acid (LA) in 2 ml corn oil for 3 days. Matched control groups were gavaged with the respective vehicles. On day 4, rats were deeply anesthetized and exposed to a simulated BLAST wave with an average peak pressure of 62 +/- 2 kPa. Rats were euthanized one hour post exposure and blood samples were obtained by cardiac puncture and analyzed using a hemoximeter. Post exposure oxygenation states (HbO₂, O₂ saturation, and O₂ content) were markedly decreased, while reduced-Hb was increased. Supplementation with VE and LA reversed the trend and increased Hb oxygenation, but VC did not. This suggests that a brief dietary loading with pharmacological doses of VE or LA, but not VC shortly before BLAST exposure may be beneficial. Moreover, measurement of blood oxygenation may function as a simple semi-invasive biomarker of BLAST-induced injury applicable to humans.

Oral magnesium intake reduces permanent hearing loss induced by noise exposure.

Attias J, Weisz G, Almog S, Shahar A, Wiener M, Joachims Z, Netzer A, Ising H, Rebentisch E, Guenther T. Institute of Noise Hazards Research, I.D.F. Medical Corps, Haifa, Israel.

Am J Otolaryngol 1994 Jan-Feb;15(1):26-32

INTRODUCTION: Following animal experiments where correlations were observed between serum magnesium level and noise-induced permanent hearing threshold shifts (NIPTS), we tested the prophylactic effect of magnesium in human subjects exposed to hazardous noise. **METHODS:** Subjects were 300 young, healthy, and normal-hearing recruits who underwent 2 months of basic military training. This training necessarily included repeated exposures to high levels of impulse noises while using ear plugs. During this placebo-controlled, double-blind study, each subject received daily an additional drink containing either 6.7 mmol (167 mg) magnesium aspartate or a similar quantity of placebo (Na-aspartate). **RESULTS:** NIPTS was significantly more frequent and more severe in the placebo group than in the magnesium group, especially in bilateral damages. NIPTS was negatively correlated to the magnesium content of blood red cells but especially to the magnesium mononuclear cells. Long-term additional intake of a small dose of oral magnesium was not accompanied by any notable side effect. **CONCLUSION:** This study may introduce a significant natural agent for the reduction of hearing damages in noise-exposed population.

Hearing loss.

Bertoni, J.M. et al.

In Professional Guide to Signs & Symptoms, Third Edition 2001, pp. 286, 370-5. Springhouse, PA: Springhouse.

[Vitamin A and the ear. Review of the literature.] [Article in German]

Biesalski HK.

Z Ernährungswiss 1984 Jun;23(2):104-12

Since the first characterization and description of vitamin A this is used in otolaryngologic therapy for different forms of hearing disorders, and its relation to the inner ear is subject of investigation. Animal experiments and clinical studies were done to clarify the significance of vitamin A for the function of hearing. Besides this there were a lot of observations describing correlations between vitamin A metabolism and hearing loss. Recent investigations showed that vitamin A is present in high concentrations in the inner ear and stored there. Morphological experiments revealed different and in some way contradictory results, but they showed that vitamin A seems to be essential for inner-ear morphogenesis.

Vitamin A deficiency increases noise susceptibility in guinea pigs.

Biesalski HK, Wellner U, Weiser H. Department of Physiological Chemistry, University of Mainz, West Germany.

The effect of vitamin A deficiency in guinea pigs on noise-induced temporary threshold shift (TTS) was evaluated after short (15 min) acoustic overstimulation with a moderate (90 dB) broad-band white noise. Some guinea pigs were fed ad libitum a purified diet deficient in vitamin A (VAD group) until biochemical signs of deficiency occurred. A second, control group (VA group) received the same diet as well as 100 IU vitamin A daily by pharyngeal tube. Cochlear potentials were recorded by special computerized equipment using implanted electrodes. Before acoustic stimulation, a baseline value was determined with a test stimulus [90 dBA (A-filter according to usual DIN instructions)] corresponding to that for TTS measurements. Noise-induced changes were determined by calculating the changes in latency and amplitude of the N1-signal of the compound action potential (CAP) at various times (1, 3, 5, 7, 11 min) after termination of acoustic stimulation in comparison with baseline values. Statistical analysis of the CAP data showed that the VAD group had significantly smaller amplitudes and increased latency of the N1-potential after acoustic stimulation and that the VA group did not show a significant change in amplitude or latency. The reduction in N1-amplitude and N1-latency in the VAD group reflects changes in inner ear hair cell activity. We conclude that vitamin A deficiency increases the sensitivity of the inner ear to noise and that this increased sensitivity increases the probability of noise-induced hearing loss.

Effect of ascorbic acid on the numerical hair cell loss in noise exposed guinea pigs.

Branis M, Burda H. Institute of Experimental Medicine, Czechoslovak Academy of Sciences, Prague.

Hear Res 1988 May;33(2):137-40

Two groups of guinea pigs were exposed to 1/3 octave band noise centered at 4 kHz, 113-118 dB SPL, for 2 h. The animals of the first group were treated with ascorbic acid (AA), 0.5 mg per 1 g of body mass injected intraperitoneally before noise exposure. The second group (control) was exposed without being treated. By means of the surface specimen method and consequent assessment of numerical atrophy of cochlear hair cells it was found that application of ascorbic acid before the noise exposure resulted in a lower or no loss of hair cells especially within the respective frequency segment of the basilar membrane. Possible protective effect of AA and/or the negative effect of hypovitaminosis "C" are discussed.

Biotin-responsive encephalopathy with myoclonus, ataxia, and seizures.

Bressman S, Fahn S, Eisenberg M, Brin M, Maltese W.

Adv Neurol 1986;43:119-25

Prominent neurological abnormalities, including myoclonus, seizures, ataxia, and hearing loss, have been noted in juvenile-onset biotin-responsive MCD. The underlying defect in many of these patients, who generally present in the first year of life, appears to be a deficiency of biotinidase. We have presented a young woman with adult-onset myoclonus, ataxia, hearing loss, seizures, hemianopia, and hemiparesis who responded to pharmacologic dosages of biotin. Although she displayed many of the clinical and biochemical features of juvenile-onset MCD, she did not have a biotinidase deficiency, and the underlying defect remains to be determined. Because of her response to biotin, we have advocated that other patients with unexplained myoclonus syndromes be evaluated for biotin-dependent carboxylase deficiencies and undergo a therapeutic trial with biotin.

Vitamin D deficiency--a new cause of cochlear deafness.

Brookes GB.

J Laryngol Otol 1983 May;97(5):405-20

Ten patients are reported with bilateral cochlear deafness which was associated with vitamin D deficiency. The features of these cases are discussed following an overview of the clinical aspects and diagnosis of vitamin D deficiency. The most likely pathogenesis is localized demineralization of the cochlea resulting in secondary morphological changes. Replacement therapy resulted in unilateral hearing improvement in two of the four patients in whom the response to treatment could be assessed. This suggests a previously unrecognized causal correlation between vitamin D deficiency and cochlear deafness. Impaired vitamin D activity may be important in the aetiology of otosclerosis, presbycusis and the deafness associated with chronic renal failure. Vitamin D deficiency should be considered in the differential diagnosis of unexplained bilateral cochlear deafness. It is important, as this 'new' metabolic type of sensorineural deafness may be reversible, and may also lead to the diagnosis of early osteomalacia before more serious generalized skeletal symptoms can occur.

Vitamin D deficiency and deafness: 1984 update.

Brookes GB.

Am J Otol 1985 Jan;6(1):102-7

Vitamin D deficiency has been diagnosed in 27 patients with bilateral deafness in a period of just over 3 years. It should be considered in the differential diagnosis of unexplained bilateral cochlear deafness and may be important in the origin of some cases of otosclerosis, presbycusis, and the deafness associated with chronic renal failure. Treatment should prevent progressive hearing loss, which may occasionally be partly reversible, and the development of clinical osteomalacia with more generalized skeletal symptoms.

Vitamin D deficiency and otosclerosis.

Brookes GB.

Otolaryngol Head Neck Surg 1985 Jun;93(3):313-21

A prospective study of 47 patients with otosclerosis was undertaken to investigate the possible etiologic role of vitamin D undernutrition. The population comprised 27 women and 20 men, with a mean age of 46.4 years (range 21 to 79). The disease was bilateral in 43 patients, and cochlear involvement was present in 84.4%. The mean duration of symptoms was 17.1 years. Vitamin D status was evaluated by measuring the plasma 25-hydroxy vitamin D3 (25-OHD), which is the main storage metabolite. Abnormally low 25-OHD levels were found in 10 patients (21.7%) and borderline low levels in another two. Raised serum alkaline phosphatase levels were present in 32.6%, calcium in 6.5%, and inorganic phosphate in 4.3%. Calcium and vitamin D replacement therapy resulted in significant hearing improvement in 3 of 16 patients; these data support a causal correlation. Vitamin D deficiency is probably a factor in the etiology of some cases of otosclerosis and is important, since the deafness resulting from cochlear involvement may be reversible.

D-methionine provides excellent protection from cisplatin ototoxicity in the rat.

Campbell KC, Rybak LP, Meech RP, Hughes L. Department of Surgery, SIU School of Medicine, Springfield, IL 62794-1618, USA.

Hear Res 1996 Dec 1;102(1-2):90-8

Cisplatin (CDDP) is a widely used chemotherapeutic agent. Unfortunately, CDDP is highly ototoxic. We tested D-methionine (D-Met), a sulfur containing compound, as an otoprotectant in male Wistar rats. Complete data sets were obtained for five groups of five animals each, including a treated control group (16 mg/kg CDDP), an untreated control group (administered an equivalent volume of saline) and three groups that received either 75, 150, or 300 mg/kg D-Met 30 min prior to the 16 mg/kg CDDP dosing. Auditory brainstem response (ABR) thresholds were obtained in response to clicks, and 1 kHz, 4 kHz, 8 kHz, and 14 kHz toneburst stimuli, before and 3 days after drug administration. Scanning electron microscopy (SEM) was used to examine the outer hair cells of the apical, middle and basal turns of the cochlea. Animal weight was measured on the first and final day. D-Met provided excellent otoprotection even at the lowest level with complete otoprotection obtained for the 300 mg/kg dosing as measured by both ABR and SEM. D-Met also markedly reduced weight loss and mortality. All animals receiving D-Met (15/15) survived to the end of the study period as opposed to only 5/10 of the treated controls.

Influence of dietary magnesium on the amplitude of wave V of the auditory brainstem response.

Cevette MJ, Franz KB, Brey RH, Robinette MS. Mayo Clinic-Scottsdale, Brigham Young University, Scottsdale, AZ 85259.

Otolaryngol Head Neck Surg 1989 Nov;101(5):537-41

Thirty-six weanling guinea pigs were fed either a low (600 ppm) or normal (3000 ppm) diet of magnesium for 8 weeks. One half of each diet group received intramuscular injections of magnesium-depleting drugs, furosemide and gentamicin. The other half were controls and received equal intramuscular injections of saline. Auditory brainstem responses were obtained from all animals before and after 8 weeks of treatment of diet and drugs to examine the effects of treatment upon hearing and auditory brainstem function. A three-way analysis of variance of dietary magnesium, by drug and by sex, showed no significant differences in auditory brainstem wave V thresholds, wave V latencies, or interpeak wave I-V latencies between the control and experimental groups. The low magnesium diet group, which received drugs, had significantly greater wave V auditory brainstem response amplitudes. Results can be explained on the basis of magnesium influencing the uptake of calcium into both the hair cells and associated brainstem pathways.

The role of taurine in infant nutrition.

Adv Exp Med Biol 1998;442:463-76

The importance of taurine in the diet of pre-term and term infants has not always been clearly understood and is a topic of interest to students of infant nutrition. Recent evidence indicates that it should be considered one of the "conditionally essential" amino acids in infant nutrition. Plasma values for taurine will fall if infants are fed a taurine-free formula or do not have taurine provided in the TPN solution. Urine taurine values also fall, which is indicative of an attempt by the kidney to conserve taurine. The very-low-birth-weight infant, for a variety of reasons involving the maturation of tubular transport function, cannot maximally conserve taurine by enhancing renal reabsorption and, hence, is potentially at greater risk for taurine depletion than larger pre-term or term infants, and certainly more than older children who have taurine in their diet. Taurine has an important role in fat absorption in pre-term and possibly term infants and in children with cystic fibrosis. Because taurine-conjugated bile acids are better emulsifiers of fat than glycine-conjugated bile acids, the dietary (or TPN) intake has a direct influence on absorption of lipids. Taurine supplementation of formulas or TPN solutions could potentially serve to minimize the brain phospholipid fatty acid composition differences between formula-fed and human milk-fed infants. Taurine appears to have a role in infants, children, and even adults receiving most (> 75%) of their calories from TPN solutions in the prevention of granulation of the retina and electroencephalographic changes. Taurine has also been reported to improve maturation of auditory-evoked responses in pre-term infants, although this point is not fully established. Clearly, taurine is an important osmolyte in the brain and the renal medulla. At these locations, it is a primary factor in the cell volume regulatory process, in which brain or renal cells swell or shrink in response to osmolar changes, but return to their previous volume according to the uptake or release of taurine. While there is a dearth of clinical studies in man concerning this volume regulatory response, studies in cats, rats, and dog kidney cells indicate the protective role of taurine in hyperosmolar stress. The infant depleted of taurine may not be able to respond to hyper- or hyponatremic stress without massive changes in neuronal volume, which has obvious clinical significance. The fact that the brain content of taurine is very high at birth and falls with maturation may be a protective feature, or compensation for renal immaturity. Defining an amino acid as "conditionally essential" requires that deficiency result in a clinical consequence or consequences which can be reversed by supplementation. In pre-term and term infants, taurine insufficiency results in impaired fat absorption, bile acid secretion, retinal function, and hepatic function, all of which can be reversed by taurine supplementation. Therefore, this small beta-amino acid, taurine, is indeed conditionally essential.

Experimental studies on the role of vitamin A in the inner ear.

Chole RA.

Otolaryngology 1978 Jul-Aug;86(4 Pt 1):ORL-595-620

With the sole exception of the hair cells of the inner ear, where information is lacking, all special somatic afferent receptor cells have been shown to be dependent upon vitamin A for normal function. In view of the paucity of information on the role of vitamin A in the inner ear, three experiments were performed to examine this relationship. Temporal bone histopathology was studied in rats deprived of vitamin A. In a second experiment, vitamin A-deficient rats were maintained with vitamin A acid and the histopathology was studied under the light microscope. In the third experiment, a microfluorometric estimate of the content of vitamin A in the guinea pig cochlea was performed. A fluorescent compound with the exact spectral characteristics of vitamin A was found in the guinea pig cochlea at a concentration of 21.2 micrograms/gm, which is ten times the vitamin A concentration found in most other tissues.

Temporal bone histopathology in experimental hypovitaminosis A.

Chole RA, Quick CA.

Laryngoscope 1976 Mar;86(3):445-53

Twenty-five years ago hearing loss was observed in some subjects during a comprehensive study of the effects of hypovitaminosis A on human volunteers. Experimental studies documenting histopathological changes in the temporal bone due to hypovitaminosis A are conflicting. Even the recent textbooks of otolaryngology and physiology make no mention of a role of vitamin A in the ear. To explore the role of vitamin A in the ear adult and weanling rats maintained on a diet totally lacking vitamin A were sacrificed at intervals. Their temporal bones were examined with the light microscope. After six weeks on a vitamin A free diet weanling rats showed hypertrophy of the periosteal portions of the otic capsule. At 16 weeks a narrowing of the internal auditory canal due to bony exostoses was present. The neuroepithelia of the cochlea and the vestibular apparatus were histologically normal even in the longest surviving animals. Adult rats maintained on a vitamin A free diet showed minimal thickening of the bone adjacent to the internal auditory meatus. The cochlea and the vestibular apparatus in these animals remained normal throughout the 28-week experiment. Although we have demonstrated marked abnormalities of the otic capsule in hypovitaminosis A, our results do not support those of some earlier investigators who reported that atrophy of the cochlear and vestibular neuroepithelium occurred in the

absence of dietary vitamin A.

Hearing aids.

Clayman, C.B.

In The American Medical Association Encyclopedia of Medicine 1989, p. 511.

New York: Random House.

Attenuation of neomycin ototoxicity by iron chelation.

Conlon BJ, Perry BP, Smith DW. Division of Otolaryngology-Head and Neck Surgery, Duke University Medical Center, Durham, North Carolina 27710, USA.

Laryngoscope 1998 Feb;108(2):284-7

Increasing evidence suggests that aminoglycoside ototoxicity is mediated by the formation of an aminoglycoside-iron complex and that the creation of this complex is a preliminary step in generation of free radical species and subsequent hair cell death. In this study we have assessed the ability of the iron chelator deferoxamine to attenuate the hearing loss induced by an ototoxic dose of the aminoglycoside neomycin (100 mg/kg per day for 14 days). Experiments were carried out on pigmented guinea pigs weighing 250 to 300 g. Changes in auditory sensitivity were characterized by monitoring shifts in compound action potential (CAP) thresholds, recorded through indwelling electrodes implanted at the round window, vertex, and contralateral mastoid. Results show that animals receiving neomycin alone suffered a mean threshold shift exceeding 35 dB at all test frequencies (2.0, 4.0, and 8.0 kHz) 30 days after initiation of treatment. In comparison, all animals receiving cotherapy of neomycin and deferoxamine (150 mg/kg twice daily for 14 days) maintained their CAP threshold, suggesting significant protection from neomycin ototoxicity. A statistical comparison of treatment groups showed that in the animals receiving cotherapy with neomycin and deferoxamine, deferoxamine produced a significant protective effect against neomycin-induced ototoxicity ($P < 0.001$). These results provide further evidence of the intrinsic role of iron in aminoglycoside ototoxicity and suggest that deferoxamine may have a therapeutic role in attenuating the cytotoxic action of aminoglycoside antibiotics.

Attenuation of aminoglycoside-induced cochlear damage with the metabolic antioxidant alpha-lipoic acid.

Conlon BJ; Aran JM; Erre JP; Smith DW The Hearing Research Laboratories, Division of Otolaryngology-Head and Neck Surgery, Duke University Medical Center, Durham, NC 27710, USA.

Hear Res (Netherlands) Feb 1999, 128 (1-2) p40-4

Free radical generation is increasingly implicated in a variety of pathological processes, including drug toxicity. Recently, a number of studies have demonstrated the ability of gentamicin to facilitate the generation of radical species both in vivo and in vitro, which suggests that this process plays an important role in aminoglycoside-induced ototoxicity. Free radical scavengers are compounds capable of inactivating free radicals, thereby attenuating their tissue damaging capacity. In this study we have determined the ability of the powerful free radical scavenger alpha-lipoic acid (100 mg/kg/day) to attenuate the cochlear damage induced by a highly ototoxic regimen of the aminoglycoside amikacin (450 mg/kg/day, i.m.). Experiments were carried out on pigmented guinea pigs initially weighing 200-250 g. Changes in cochlear function were characterized as shifts in compound action potential (CAP) thresholds, estimated every 5 days, by use of chronic indwelling electrodes implanted at the round window, vertex, and contralateral mastoid. Results showed that animals receiving alpha-lipoic acid in combination with amikacin demonstrated a significantly less severe elevation in CAP thresholds compared with animals receiving amikacin alone ($P < 0.001$; t-test). These results provide further evidence of the recently reported intrinsic role of free radical generation in aminoglycoside ototoxicity, and highlight a potential clinical therapeutic use of alpha-lipoic acid in the management of patients undergoing aminoglycoside treatment.

Iodine deficiency disorders in Europe.

Delange F, Burgi H.

Bull World Health Organ 1989;67(3):317-25

Recent data on iodine excretion in the urine of adults, adolescents and newborns and on the iodine content of breast milk indicate a high prevalence of iodine deficiency (moderate in many cases and severe in a few) in many European countries. These cases may manifest as subclinical hypothyroidism in neonates and as goitre in adolescents and adults. Lack of iodine causes not only goitre, but also mental deficiency, hearing loss and other neurological impairments, and short stature due to thyroid insufficiency during

fetal development and childhood. Although iodinated salt is available theoretically in most countries where it is needed, its quality and share of the market are often unsatisfactory. In many countries where only household salt is iodinated the iodine content has been set too low owing to an overestimation of household salt consumption. Governments are therefore urged to pass legislation and provide means for efficient iodination of salt wherever this is necessary.

Effects of nutrition on brain development in humans.

DeLong GR. Division of Pediatric Neurology, Duke University Medical Center, Durham, NC 27710.

Am J Clin Nutr 1993 Feb;57(2 Suppl):286S-290S

Brain development in humans is remarkably resistant to permanent damage from protein-energy malnutrition. However, specific nutrients have crucial roles. Iodine deficiency is the most important and widespread nutrient deficiency; it causes endemic cretinism, associated with deaf-mutism and cerebral palsy. Iodine deficiency during pregnancy causes both maternal and fetal hypothyroxinemia, resulting in irreversible impairment of brain development at a critical stage. Neuropathological data place this after 14 wk, perhaps continuing through the third trimester. Gross brain structure, including the gyral pattern of the cerebral cortex, develops normally; the insult affects neuron and dendrite growth. Recent magnetic-resonance-imaging (MRI) images of neurological cretin brains show remarkably normal appearance except for gliotic lesions of the globus pallidus, correlating with the proximal motor rigidity seen clinically. Myxedematous cretinism is paradoxical in showing more severe hypothyroidism and growth failure, yet better intellectual, motor, and hearing function; these observations implicate a second independent factor in its pathogenesis.

Effects of dietary taurine on auditory function in full-term infants.

Dhillon SK, Davies WE, Hopkins PC, Rose SJ. Hearing Services Centre City Hospital, Birmingham, England.

Adv Exp Med Biol 1998;442:507-14

Three groups of neonates fed taurine supplemented infant formula, non-supplemented infant formula or breast milk, respectively, were studied from birth to 12 weeks of age. In addition to the measurement of whole blood taurine content, auditory function was monitored using auditory brainstem responses (ABRs) and transient evoked otoacoustic emissions (TEOAEs). The results showed a significant reduction in whole blood taurine concentration in the non-supplemented formula group. In addition, there was a significant drop in whole blood taurine levels in all 3 groups over the first four weeks of life. ABR wave latencies were significantly shorter in the non-supplemented group, with wave V showing the greatest reductions. Falling taurine levels after full-term birth may aid synaptic maturation/efficiency within the auditory system. TEOAE responses were significantly larger over the low to mid frequencies in the breast fed group suggesting improved middle ear function.

[Therapeutic trial in acute cochlear deafness. A comparative study of Ginkgo biloba extract and nicergoline]

Dubreuil C

Presse Med (France) Sep 25 1986, 15 (31) p1559-61

Ischemia and the metabolic disorder it entails would seem to be the pathogenic mechanism behind acute cochlear deafness, irrespective of the triggering process. The prognosis is entirely dependent on the rapid initiation of an effective treatment. At the end of a double-blind therapeutic trial comparing Ginkgo biloba extract and a standard alpha blocker (nicergoline), a significant recovery was observed in both therapeutic groups, but improvement was distinctly better in the Ginkgo biloba group.

Effect of copper-deficient diet on metabolism in rat auditory structures.

Farms WB, Godfrey DA, Askari A. Department of Otolaryngology, Medical College of Ohio, Toledo 43699-0008.

Hear Res 1993 May;67(1-2):45-50

Copper is a trace element known to be critical for normal brain function, and abnormal copper metabolism has been associated with some disorders involving the auditory system. We examined effects of copper deficiency on metabolism in major structures of the auditory system. Homogenates of cochlea, cochlear nucleus and inferior colliculus of rats, as well as whole brain, were assayed for activities of enzymes of oxidative and glycolytic energy metabolism--malate and lactate dehydrogenase, enzymes of acetylcholine metabolism--choline acetyltransferase and acetylcholinesterase, and concentrations of amino acids. Whole brain was also assayed for activity of superoxide dismutase, a copper-containing enzyme, and concentrations of minerals. For these chemicals and tissues, the only significant differences between copper-deficient and copper-adequate rats were: (1) decreased copper and magnesium and increased potassium concentrations in whole brain of copper-deficient rats and (2) an elevation of glutamine concentration in inferior

colliculus and whole brain of copper-deficient rats. The elevated glutamine could not be related to any change in activity of glutamine synthetase or glutaminase, major enzymes of glutamine metabolism. It is speculated that the increase in glutamine might result from a net increase in ammonia accumulation in the brains of copper-deficient rats.

Sudden hypoacusis treated with hyperbaric oxygen therapy: a controlled study.

Fattori B, Berrettini S, Casani A, Nacci A, De Vito A, De Iaco G. ENT Clinic, Department of Neurosciences, University of Pisa, Via Savi no. 10, 56100 Pisa, Italy. bfattori@ent.med.unipi.it

Ear Nose Throat J. 2001b Sep;80(9):655-60.

The term sudden hypoacusis describes a hearing loss of rapid onset and unknown origin that can progress to severe deafness. Of the many therapeutic protocols that have been proposed for treating sudden hypoacusis, hyperbaric oxygen therapy (HOT) plays a leading role. We studied 50 patients who had been referred to our ENT unit within 48 hours of the onset of sudden hypoacusis. We randomly assigned 30 of these patients to undergo once-daily administration of HOT for 10 days; the other 20 patients were treated for 10 days with an intravenous vasodilator. Response to therapy in all patients was evaluated by calculating the mean hearing threshold at frequencies between 500 and 4,000 Hz and by assessing liminal tonal audiometry results recorded at baseline and 10 days after the cessation of treatment. These results, plus the findings of other audiologic and otoneurologic examinations, revealed that the patients in the HOT group experienced a significantly greater response to treatment than did those in the vasodilator group, regardless of age and sex variables. Significantly more patients in the HOT group experienced a good or significant response. In both groups, patients with pantonal hypoacusis responded significantly better than did those with a milder condition. Based on our findings, coupled with the fact that oxygen therapy is well tolerated and produces no side effects, we conclude that HOT should be considered the preferred treatment for patients with sudden hypoacusis.

[Oxygen therapy in the long term treatment of Meniere's disease] [Article in Italian]

Fattori B, Nacci A, Casani A, Donati C, De Iaco G. Dipartimento di Neuroscienze, Clinica ORL, Università di Pisa.

Acta Otorhinolaryngol Ital. 2001a Feb;21(1):1-9.

Endolymphatic hydrops is the histopathological substrate characteristic of Meniere's disease. Besides the classical treatment with diuretics and/or osmotic drugs for some time, now treatment in a "pressure chamber" (OTI) has also been applied. The oxygen administered in the hyperbaric chamber can reduce the hydrops both by increasing the hydrostatic pressure and by mechanically stimulating the flow of endolymph toward the duct and endolymphatic sac. In addition, an increase is seen in the amount of O₂ dissolved in the labyrinthine fluids and this contributes to recovering cell metabolism and restoring normal cochlear electrophysiological functions. Between 1992 and 1996 40 patients with monolateral Meniere's disease were studied: 15 underwent oxygen therapy at a constant pressure (2.2 ATA) (HOT), 25 with a continuous variation in pressure (from 1.7 to 2.2 ATA) (Alternobaric therapy, AOT). During the acute phase the patients underwent daily OTI treatment for 15 days in a row. The maintenance treatment called for one treatment cycle (one session a day for 5 days in a row) a month for 1 year, followed by for one treatment cycle (one session a day for 5 days in a row) every three months during the 2nd, 3rd and 4th years. The controls consisted of a group of 18 patients treated with 10% glycerol i.v. (during the acute phase) and betahistine (8 mg x 3/die) between episodes. A comparison was made of the average hearing threshold for the frequencies 500-3000 Hz (PTA), how frequently episodes of dizziness arose and extent of hearing loss in the three groups after the initial 15 days of treatment and at the end of the 4-year follow-up, in compliance with the criteria laid down by the Committee on Hearing and Equilibrium in 1995. At the end of the first 15 days of treatment, there were no statistically significant differences between the three groups. At the end of the follow-up, on the other hand, hyperbaric treatment, and in particular alternobaric therapy, enabled a significant reduction in the episodes of dizziness as compared to the control group. PTA and deafness also improved significantly in the patients who had undergone hyperbaric treatment. The results of the present work show that HOT, and in particular AOT, offer a valid alternative to drugs in the treatment of Meniere's disease.

Protection of both auditory hair cells and auditory neurons from cisplatin induced damage.

Gabaizadeh R, Staecker H, Liu W, Kopke R, Malgrange B, Lefebvre PP, Van de Water TR. Department of Otolaryngology, Albert Einstein College of Medicine Bronx, New York, USA.

Acta Otolaryngol 1997 Mar;117(2):232-8

Cisplatin is an effective anti-neoplastic agent used in the treatment of squamous cell cancer of the head and neck, but with serious side effects. One serious side effect is damage to both the auditory hair cells and the auditory neurons. The damage to the neurons has been shown to be a direct effect and not due to the loss of the neurotrophic support provided by the hair cells. Several neurotrophins have been shown to lessen the extent of cisplatin induced damage of auditory neurons in vitro, but these neurotrophins have had no effect on the extent of damage to the hair cells. D-methionine (D-met) has been demonstrated to provide

protection against cisplatin's nephrotoxicity in vivo and ototoxicity in vitro. In this study the combination of brain derived neurotrophic factor (BDNF) with D-met has shown that both auditory neurons and auditory hair cells can be protected from cisplatin induced damage in vitro. These results demonstrate that this type of combination therapy (i.e. a neurotrophin combined with a free radical scavenger) can provide more complete protection for the auditory receptor against cisplatin toxicity than either of these agents alone. Because both BDNF and D-met have been shown to have trophic activity in vitro we proposed that the combination of these agents will also provide effective protection against cisplatin induced ototoxicity and neurotoxicity of the auditory receptor in vivo.

Taurine in pediatric nutrition: review and update.

Gaull GE. Department of Pediatrics, Northwestern University School of Medicine, Chicago.

Pediatrics 1989 Mar;83(3):433-42

Taurine was long considered an end product of the metabolism of the sulfur-containing amino acids, methionine and cyst(e)ine. Its only clearly recognized biochemical role had been as a substrate in the conjugation of bile acids. Taurine is found free in millimolar concentrations in animal tissues, particularly those that are excitable, rich in membranes, and generate oxidants. Various lines of evidence suggest one major nutritional role as protecting cell membranes by attenuating toxic substances and/or by acting as an osmoregulator. The totality of evidence suggests that taurine is nonessential in the rodent, it is an essential amino acid in the cat, and it is conditionally essential in man and monkey. Absence from the diet of a conditionally essential nutrient does not produce immediate deficiency disease but, in the long term, can cause problems. Taurine is now added to many infant formulas as a measure of prudence to provide improved nourishment with the same margin of safety for its newly identified physiologic functions as that found in human milk. Such supplementation can be justified by the finding of improved fat absorption in preterm infants and in children with cystic fibrosis, as well as by salutary effects on auditory brainstem-evoked responses in preterm infants. Experimental findings in animal models and in human cell models provide further justification for taurine supplementation of infant formulas.

Biochemical mechanisms affecting susceptibility to noise-induced hearing loss.

Gunther T, Ising H, Joachims Z. Institut fur Molekularbiologie und Biochemie, Freie Universitat Berlin, West Germany.

Am J Otol 1989 Jan;10(1):36-41

In magnesium (Mg)-deficient rats and guinea pigs, noise-induced hearing loss (NIHL) was found to be correlated to the decrease of Mg in serum and perilymph. Also, in noise-exposed humans, NIHL increased with decreasing serum Mg. During the process of mechano-electrical transduction within the hair cells in the inner ear, membrane permeability of K⁺ and Ca²⁺ will transiently increase. Mg deficiency may additionally increase membrane permeability and, therefore, energy-dependent K⁺ and Ca²⁺ turnover. The increased release of catecholamines in Mg deficiency may affect the hair cells, either directly by increasing the intracellular concentration of free Ca²⁺ and/or indirectly by reducing the blood flow. Also, thromboxane A₂, which is increased in Mg deficiency, may reduce the blood flow in the inner ear. By these mechanisms, Mg deficiency may cause energy depletion and irreversible damage to the hair cells.

[Mitochondrial neurogastrointestinal encephalomyopathy presenting with protein-losing gastroenteropathy and serum copper deficiency: a case report.] [Article in Japanese]

Hamano H, Ohta T, Takekawa Y, Kouda K, Shinohara Y. Department of Neurology, Tokai University School of Medicine.

Rinsho Shinkeigaku 1997 Oct;37(10):917-22

We report a 56-year old female with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), presenting with protein-losing gastroenteropathy and serum copper deficiency. There was no neuromuscular disease in her family members. Three years prior to admission, she developed severe gastrointestinal symptoms including diarrhea, nausea, vomiting and ascites, and was diagnosed as having protein-losing gastroenteropathy based on alpha(1)-antitrypsin clearance and other tests. She was referred to our department when neurological symptoms were apparent. Neurological examinations revealed bilateral ptosis, ophthalmoplegia, hearing loss, facial and limb muscle weakness, mild sensory deficit of vibration on her feet and hypoactive deep tendon reflexes. Pigmentary retinopathy, cerebellar ataxia and heart block were not seen. Serum copper level was decreased to 45 micrograms/dl (normal: 83-155). Chronic intestinal pseudo-obstruction was proven by X-ray studies, and diffuse leukoencephalopathy demonstrated on brain MRI. On EMG, motor nerve conduction velocities were prolonged with temporal dispersion. Her muscle biopsy from biceps brachii muscle showed both neuropathic and myopathic changes, scattered ragged-red fibers and focal cytochrome c oxidase deficiency. Southern blot and polymerase chain reaction analysis on mitochondrial DNA showed no deletions nor point mutations. The clinical and pathologic findings of the present patient fulfilled the diagnostic criteria of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) proposed by Hirano et al. There are few reported patients with MNGIE in Japan, but none presented with protein-losing gastroenteropathy and serum copper deficiency. Since the copper is a cofactor of cytochrome c oxidase,

decreased serum copper level may aggravate the respiratory chain enzyme metabolism in mitochondria. Therefore, treatment for gastrointestinal tract disturbance and copper administration may be necessary to prevent disease progression.

[Ginkgo extract EGb 761 (tenobin)/HAES versus naftidrofuryl A randomized study of therapy of sudden deafness]

Hoffmann F; Beck C; Schutz A; Offermann P Universitäts-HNO-Klinik Freiburg im Breisgau.

Laryngorhinootologie (Germany) Mar 1994, 73 (3) p149-52

80 patients with idiopathic sudden hearing loss existing no longer than 10 days were included in a randomised reference-controlled study. The therapeutic value of Ginkgo EGb 761 (Tebonin) + HAES was compared to that of Naftidrofuryl (Dusodril)+HAES. The main mechanisms of action of EGb 761 are a vasoregulating activity (increased blood flow), the platelet activating factor antagonism and a prevention of membrane damage caused by free radicals. Naftidrofuryl has antiserotonergic and therefore vasodilatory properties. The statistical analysis of the audiometric data was performed in measuring the relative hearing gain as described by Eibach 1979. After one week of observation, 40% of the patients in each group showed a complete remission of hearing loss. This was also observed by other authors who had compared other drugs. Therefore, in these cases, it is most likely that spontaneous recovery is the most important factor. After two and three weeks of observation, measuring the relative hearing gain, there was a significant borderline benefit of EGb 761 ($p = 0.06$) without any side effects. Some patients of the reference group developed side effects such as orthostatic dysregulation or headache or sleep disturbances. Minimising side effects should be one of the most important goals in therapy of sudden hearing loss until the efficiency of infusion therapy is proved.

[Ginkgo special extract EGb 761 in tinnitus therapy. An overview of results of completed clinical trials]. [Article in German]

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Fortschr Med 2001 Jan 11;118(4):157-64

In a systematic search of the literature 19 clinical trials investigating the effects of tinnitus treatment with Ginkgo biloba special extract EGb 761 were identified and evaluated. The results of eight controlled studies on tinnitus due to cerebrovascular insufficiency or labyrinthine disorders of varying genesis for the most part show a statistically significant superiority of treatment with the Ginkgo biloba special extract EGb 761 as compared with placebo or reference drugs applied of periods of one to three months. Open studies, too, some involving large numbers of patients, revealed appreciable improvements under ginkgo treatment. Therapeutic success was not directly correlated with either the genesis or the duration of tinnitus. However, investigations of prognostic factors revealed that short-standing disorders have a better prognosis, so that better results can be expected from early-onset treatment. The tolerability of Ginkgo biloba special extract EGb 761 was excellent, and in this respect the controlled clinical trials revealed little difference between drug-treated and control groups.

Age-related hearing loss, vitamin B-12, and folate in elderly women.

Houston DK, Johnson MA, Nozza RJ, Gunter EW, Shea KJ, Cutler GM, Edmonds JT. Department of Foods and Nutrition, The University of Georgia, Athens 30602, USA.

Am J Clin Nutr 1999 Mar;69(3):564-71

BACKGROUND: Hearing impairment is 1 of the 4 most prevalent chronic conditions in the elderly. However, the biological basis of age-related hearing loss is unknown. **OBJECTIVE:** The objective was to test the hypothesis that age-related hearing loss may be associated with poor vitamin B-12 and folate status. **DESIGN:** A thorough audiometric assessment was conducted in 55 healthy women aged 60-71 y. Hearing function was determined by the average of pure-tone air conduction thresholds at 0.5, 1, 2, and 4 kHz and was categorized into 2 groups for logistic regression analyses: normal hearing (<20 dB hearing level; $n = 44$) and impaired hearing (≥ 20 dB hearing level; $n = 11$). **RESULTS:** Mean age was the same (65 y) for the normal hearing and impaired hearing groups. Pure-tone averages were inversely correlated with serum vitamin B-12 ($r = -0.58$, $P = 0.0001$) and red cell folate ($r = -0.37$, $P = 0.01$). Women with impaired hearing had 38% lower serum vitamin B-12 (236 compared with 380 pmol/L, respectively, $P = 0.008$) and 31% lower red cell folate (425 compared with 619 nmol/L, respectively, $P = 0.02$) than women with normal hearing. Among participants who did not take supplements containing vitamin B-12 or folate, women with impaired hearing had 48% lower serum vitamin B-12 (156 compared with 302 pmol/L, respectively, $P = 0.0007$) and 43% lower red cell folate (288 compared with 502 nmol/L, respectively, $P = 0.001$) than women with normal hearing. **CONCLUSION:** Poor vitamin B-12 and folate status may be associated with age-related auditory dysfunction.

Evaluation of vitamin D metabolism in patients with bilateral sensorineural hearing loss.

Ikeda K, Kobayashi T, Itoh Z, Kusakari J, Takasaka T. Department of Otolaryngology, Tohoku University School of Medicine, Sendai, Japan.

Am J Otol 1989 Jan;10(1):11-3

The possible role of vitamin D in hearing impairment was investigated by the measurement of three metabolites of vitamin D in 28 patients with bilateral sensorineural hearing loss (BSNHL). Twenty-three of 28 patients showed a significantly decreased level of 1,25-dihydroxyvitamin D₃, with a normal value of 25-hydroxyvitamin D₃. In addition to experimental and clinical reports regarding vitamin D deficiency, the present study suggests that vitamin D deficiency is one of the etiologies of BSNHL, through the calcium metabolism and microcirculation in the cochlea.

Increased noise trauma in guinea pigs through magnesium deficiency.

Ising H, Handrock M, Gunther T, Fischer R, Dombrowski M.

Arch Otorhinolaryngol 1982;236(2):139-46

Mg-deficient guinea pigs developed significantly increased hearing loss during 4 weeks of noise exposure [95 dB(A)] as compared to animals fed a Mg-rich diet. The hearing loss was negatively correlated to the Mg content of the perilymph ($r = -0.86$). Besides this auditory effect, there was a decrease of intracellular Mg and an increase of collagen in the myocardium, both of which were correlated to the hearing loss and caused by Mg deficiency and noise stress.

[Hydergine in pathology of the inner ear] [Article in Spanish]

Jimenez-Cervantes Nicolas J; Amoros Rodriguez LM

An Otorrinolaringol Ibero Am (Spain) 1990, 17 (1) p85-98

There have been treated a total of 20 patients with troubles on the cochlear compartment and/or vestibular level which have been clinically expressed by a perceptive hypoacusia, tinnitus and rotatory vertigo. The final evaluation is referred to 17 patients, since three patients do not appear for control. All patients were treated only with Hydergine, on doses of 30 drops thrice daily, which is the equivalent to 4.5 mg/day of active substance. This treatment remained unaltered till the end of the last control. Controls have been effected after 30, 60 and 90 days of starting the treatment. In each control there was evaluated the subjective improvement of vertigo, tinnitus and hypoacusia when effecting to all patients by means of liminar- supraliminar- and automaticaudiometry, impedancimetry, T one-decay-test and electrooculonistagmography. The most meliorated symptomatology was vertigo, with a global improvement of 93.7 per cent on the treated patients. Tinnitus improve by 57.1 per cent and hypoacusia by 20 per cent. There is a total correspondence between the subjective data furnished by the patients and the objective tests carried out in the successive controls.

[Prevention of noise-induced hearing loss.] [Article in Hebrew]

Joachims HZ, Ising H, Gunther T. Otolaryngology Dept., Rambam Medical Center, Haifa.

Harefuah 1989 Sep;117(5-6):133-5

Noise-induced hearing loss appears to result from energy depletion in the hair cells. Cell membrane permeability is increased in hypomagnesemia, causing Na⁺ and Ca⁺⁺ influx, with subsequent increase in energy-dependent ion-pumping. Energy exhaustion is further enhanced by hypomagnesemia-induced vasoconstriction. Dietary supplementation with magnesium was shown to lessen hearing loss in noise-exposed rats. It is postulated that the same mechanisms may act in man and the possible benefit of magnesium supplementation for noise-exposed workers should be investigated.

Dependence of noise-induced hearing loss upon perilymph magnesium concentration.

Joachims Z, Babisch W, Ising H, Gunther T, Handrock M.

J Acoust Soc Am 1983 Jul;74(1):104-8

Noise-induced hearing loss (NIHL) is significantly greater in rats fed a magnesium-deficient diet than in rats on a magnesium-rich diet. The hearing loss was found to be negatively correlated with the magnesium concentration of the perilymph. It is suggested that also in man, the magnesium concentration in the perilymph may be of importance in determining susceptibility to NIHL.

Oral magnesium supplementation as prophylaxis for noise-induced hearing loss: results of a double blind field study. (Article in German).

Joachims Z, Netzer A, Ising H, Rebentisch E, Attias J, Weisz G, Gunther T.

Schriftenr Ver Wasser Boden Lufthyg 1993;88:503-16

The effect of oral Mg-supplementation as prophylaxis against noise-induced hearing loss was tested in a placebo-controlled double blind study involving 320 voluntary subjects during a 2-month period of military training. The hearing thresholds of all subjects were checked and only persons with normal hearing were accepted. Before and after the 2-month training, blood samples were collected and Mg was analysed in serum, erythrocytes and lymphocytes. Seven days after the last exposure to firearm noise, the audiograms of all test subjects were checked and permanent threshold shifts (PTS) were determined. The total group received a drink containing either 4g Mg granulate verum (6.7 mmol Mg aspartate) or placebo every working day during the 2-month training period. The primary source of noise exposure were firearms: 420 shots per person, mean peak level 164 dB(A). The recruits used ear plugs with a mean insertion loss of 25 dB. In both groups Mg-concentration in serum and in erythrocytes increased with time. Lymphocyte Mg increased in the Mg group only. In the placebo group the percentages of ears with PTS > 25 dB at 4 kHz/6 kHz and/or 8 kHz after exposure to firearm noise were twice as high as in the Mg group.

Effects of Ginkgo biloba extract on the cochlear damage induced by local gentamicin installation in guinea pigs.

Jung HW; Chang SO; Kim CS; Rhee CS; Lim DH Department of Otorhinolaryngology - Head & Neck Surgery, Seoul National University College of Medicine, Korea.

J Korean Med Sci (Korea) Oct 1998, 13 (5) p525-8

Investigations evaluating the protective effect of Ginkgo biloba extract (EGb) on gentamicin (GM) ototoxicity were undertaken. Guinea pigs treated with 5 mg/kg gentamicin sulfate on the round window niche (RWN) showed acute changes on electrocochleogram and hair cell or microvilli damage on scanning electron microscopy (SEM). There was accumulation of GM in the whole cochlea, especially in the organ of Corti, stria vascularis, and type III fibrocyte on immunohistochemical study. However, the guinea pigs pretreated with local or systemic EGb revealed no significant changes by local GM installation. From these results, we concluded that EGb has a protective effect on the development of GM ototoxicity in the cochlea.

Glutathione protection against gentamicin ototoxicity depends on nutritional status.

Lautermann J, McLaren J, Schacht J. Kresge Hearing Research Institute, Department of Otolaryngology, University of Michigan, Ann Arbor 48109-0506, USA.

Hear Res 1995 Jun;86(1-2):15-24

This study demonstrates that gentamicin ototoxicity depends on dietary factors and correlates with tissue glutathione levels. After 15 days of gentamicin injections (100 mg/kg/day s.c.) guinea pigs on a regular protein diet (18.5% protein) had an average hearing loss of 9 dB at 3 kHz, 31 dB at 8 kHz and 42 dB at 18 kHz. Guinea pigs on a 7% protein diet showed an increased hearing loss of 52 dB at 3 kHz, 63 dB at 8 kHz and 74 dB at 18 kHz. Supplementing the low protein diet with either essential or sulfur-containing amino acids did not protect against gentamicin ototoxicity. Glutathione levels in the cochlear sensory epithelium were decreased in animals on a low protein diet and could be restored to normal by oral administration of glutathione monoethyl ester (1.2 g/kg/day) in combination with vitamin C (100 mg/kg/day). Glutathione supplementation significantly reduced the magnitude of hearing loss in the low protein diet group at all frequencies (43 dB reduction at 3 kHz, 27 dB reduction at 8 kHz and 21 dB reduction at 18 kHz). In animals on a full protein diet, dietary glutathione neither increased cochlear glutathione levels nor attenuated hearing loss. Serum gentamicin levels did not differ between animals on the various diets with or without glutathione supplement. These results suggest that gentamicin toxicity and detoxifying mechanisms are affected by the metabolic state of the animal and the glutathione content of the tissue. Thus, compounds that could potentially protect against gentamicin ototoxicity may be more correctly assessed in animal models of deficient nutritional states in which endogenous detoxifying mechanisms are compromised. This animal model might also be more realistically related to the clinical situation of a critically ill patient receiving gentamicin treatment.

The influence of chronic vitamin A deficiency on human and animal ears.

Lohle E.

Arch Otorhinolaryngol 1982;234(2):167-73

After feeding young rats a diet deficient in vitamin A, we examined the inner ear with the electron microscope. There were changes

in the cuticle of the outer and inner hair cells. Furthermore, there were changes in the reticular system of the intermediate zone and massive degenerative changes in the ganglion cells of the VIII nerve. In a second experiment with older animals we found no significant changes in the sensory cells, though there was new bone formation in Rosenthal's canal and damage to the ganglion cells, of a lesser extent than was evident in the first experiment, however. In a further clinical study, we carefully chose human subjects suffering from alcoholic liver disease who also had a negative history of ear infection, noise exposure, head injury and use of streptomycin. Normal auditory function in the family was also a criterion. A decreased auditory function associated with low vitamin A levels was found in these patients. Those with liver disease showed not only a significant auditory dysfunction in the higher frequencies, but as well a poorer performance in the tone decay test. They were compared to a control group with normal hepatic, renal and thyroid status.

Age-related cochlear hair cell loss is enhanced in mice lacking copper/zinc superoxide dismutase.

McFadden SL, Ding D, Reaume AG, Flood DG, Salvi RJ. Center for Hearing and Deafness, State University of New York at Buffalo, 14214, USA. mcfadden@acsu.buffalo.edu

Neurobiol Aging 1999 Jan-Feb;20(1):1-8

Age-related hearing loss in humans and many strains of mice is associated with a base-to-apex gradient of cochlear hair cell loss. To determine if copper/zinc superoxide dismutase (Cu/Zn SOD) deficiency influences age-related cochlear pathology, we compared hair cell losses in cochleas obtained from 2-, 7-, and 17- to 19-month-old wild type (WT) mice with normal levels of Cu/Zn SOD and mutant knockout (KO) mice with a targeted deletion of *Sod1*, the gene that codes for Cu/Zn SOD. WT and KO mice exhibited similar patterns of hair cell loss with age, i.e., a base-apical progression of hair cell loss, with greater loss of outer hair cells than inner hair cells. Within each age group, the magnitude of loss was much greater in KO mice compared to WT mice. The results indicate that Cu/Zn SOD deficiency potentiates cochlear hair cell degeneration, presumably through metabolic pathways involving the superoxide radical.

Cu/Zn SOD deficiency potentiates hearing loss and cochlear pathology in aged 129,CD-1 mice.

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J Comp Neurol 1999 Oct 11;413(1):101-12

Copper/zinc superoxide dismutase (Cu/Zn SOD) is a first-line defense against free radical damage in the cochlea and other tissues. To determine whether deficiencies in Cu/Zn SOD increase age-related hearing loss and cochlear pathology, we collected auditory brainstem responses (ABRs) and determined cochlear hair cell loss in 13-month-old 129/CD-1 mice with (a) no measurable Cu/Zn SOD activity (homozygous knockout mice), (b) 50% reduction of Cu/Zn SOD (heterozygous knockout mice), and (c) normal levels of Cu/Zn SOD (wild-type mice). ABRs were obtained by using 4-, 8-, 16-, and 32-kHz tone bursts. Cochleas were harvested immediately after testing, and separate counts were made of inner and outer hair cells. Compared with wild-type mice, homozygous and heterozygous knockout mice exhibited significant threshold elevations and greater hair cell loss. Phenotypic variability was higher among heterozygous knockout mice than among wild-type or homozygous knockout mice. Separate groups of wild-type and homozygous knockout mice were examined for loss of spiral ganglion cells and eighth nerve fibers. At 13 months of age, both wild-type and knockout mice had significantly fewer nerve fibers than did 2-month-old wild-type mice, with significantly greater loss in aged knockout mice than in aged wild-type mice. Thirteen-month-old knockout mice also had a significant loss of spiral ganglion cells compared with 2-month-old wild-type mice. The results indicate that Cu/Zn SOD deficiencies increase the vulnerability of the cochlea to damage associated with normal aging, presumably through metabolic pathways involving the superoxide radical. Copyright 1999 Wiley-Liss, Inc.

Hypothyroidism and the ear: electrophysiological, morphological, and chemical considerations.

Meyerhoff WL.

Laryngoscope 1979 Oct;89(10 Pt 2 Suppl 19):1-25

There is both clinical and laboratory evidence that hearing loss can result from congenital and acquired hypothyroidism. The reversibility of this process, however, and its incidence and pathophysiology are not universally agreed upon. Laboratory animals rendered hypothyroid with radioactive iodine 131 or propylthiouracil demonstrated normal perilymph sodium and potassium levels but increased auditory thresholds for N1N2 response and brain stem evoked audiometry as well as a crystallized consistency of the bone of the bullae and cochleae, ossicular abnormalities, obliteration of the oval and round window, large dark staining lipid accumulations in Hensen's cells, large intercellular spaces in the stria vascularis with degeneration of the marginal and intermediate cells, inner and outer hair cell degeneration, debris in the cochlear duct, and tectorial membrane irregularity. Otic capsule biochemical alterations were identified which may account for the osseous changes observed morphologically. The morphological,

biochemical, and electrophysiological findings in this study support the hypothesis that the cochlea is a site of lesion for sensorineural hearing loss in hypothyroidism. Middle ear changes identified could be responsible for the conductive component.

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Evaluation of tinnitus patients by peroral multi-drug treatment.

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Auris Nasus Larynx 1998 May;25(2):149-54

To evaluate patients complaining of subjective tinnitus, this study examined their response to peroral betahistine mesilate, vitamin B complex and diazepam in combination. Because three drugs were used together, it remains to be seen whether a single drug or a combination of drugs was effective. We issued questionnaires to 67 patients with tinnitus associated with sensorineural hearing loss of unknown etiology or tinnitus, despite normal hearing in pure tone audiometry and lack of distinct systemic disorders. Our original questionnaire contained seven items and allotted points for each item to facilitate evaluation. After prescribing the above drugs and observing patients' progress for 5 weeks, 50 of the 67 subjects were evaluated again by the same questionnaire. The present study evaluates tinnitus of patients as an example of clinical applications; this was not a controlled double blind study. It was found that, after patients took the prescribed medication, the total number of points were significantly reduced (paired t-test, $P < 0.001$). After medication, cases of bilateral tinnitus were significantly reduced from 27 to 14, and cases of two types of tinnitus sound, were significantly decreased from 22 to 11 (chi 2-test, $P < 0.05$). After 5 weeks of administration, 54% of patients felt treatment had been effective. Preliminary results suggest this peroral multi-drug treatment may provide relief for some patients with subjective tinnitus. However, long-term efficacy of the treatment was not investigated.

Pediatric and Geriatric Tinnitus.

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Int Tinnitus J 1997;3(2):101-103

The subject of tinnitus in the population extremes-children and the elderly-is ignored by the literature, probably because children do not complain of tinnitus spontaneously, whereas it is only one challenge among other major health problems in the elderly. A short review of the literature on this subject is presented. Presbytinnitus, defined as tinnitus that accompanies the progressive hearing loss of presbycusis is classified as: type 1 (normal aging affecting the cochlea), and type II (preexistent sensorineural hearing loss accompanied by multiple systemic complaints, especially of sensory ones). The incidence of tinnitus in presbycusis is 11%. Like in other age groups, there is no significant gender predilection in the prevalence of tinnitus, but a correlation was demonstrated between the severity of tinnitus and exposure to noise. Hypertension was associated with a lower incidence of tinnitus, as compared to normotension and hypotension. Several treatment modalities of geriatric tinnitus are reviewed: the superiority of the band-noise masker in patients with presbycusis, as compared to electrical promontory stimulation; amino-oxyacetic in presbycusis and Meniere's disease; zinc supplementation in marginally zinc-deficient elderly patients in improving sensorineural hearing loss and tinnitus; aeration of the middle ear in presbycusis caused by secretory otitis media. Pediatric tinnitus has an incidence of 13% in children who passed an audiometric screening test, and 23-60% in those with hearing loss, 44% in secretory otitis media, but only 3% complain spontaneously because that the child considers tinnitus to be a normal event. There is no significant difference between children with tinnitus and those without in terms of hearing level, age, gender, or etiology of the deafness. Despite the fact that often children do not mention it, tinnitus may incite behavioral problems.

Auditory startle response is diminished in rats after recovery from perinatal copper deficiency.

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J Nutr 1996 Mar;126(3):618-27

Recovery from perinatal copper deficiency was studied in female and male Sprague Dawley rats for 6 mo. Month-old offspring reared by dams on copper-deficient treatment starting d 7 of pregnancy had up to 80% reductions in regional brain copper concentrations compared with offspring from copper-supplemented dams. Liver copper concentrations and plasma ceruloplasmin diamine oxidase activities of copper-deficient rats were restored to control levels within 1 mo of nutritional repletion with dietary copper. However,

brain copper concentrations, with the exception of the hypothalamus and medulla, remain lower than in controls even after 5 mo of treatment. Rats were screened for startle responses and foot splay after 1, 3 and 5 mo of depletion. Diminished auditory startle was evident in rats of both sexes at all depletion times tested, whereas tactile startle and prepulse inhibition of tactile startle were not influenced by prior copper deficiency, suggesting auditory sensory perception abnormalities. In a separate study, postweaning male rats deprived of dietary copper for 5 wk exhibited clear signs of copper deficiency but normal acoustic startle responses and foot splay. Long-term neurochemical and behavioral abnormalities persist in rats after perinatal copper deficiency.

L- and D- methionine provide equivalent long term protection against CDDP-induced ototoxicity in vivo, with partial in vitro and in vivo retention of antineoplastic activity.

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Neurotoxicology 1999 Oct;20(5):731-48

Treatment of metastatic tumors with ionic platinum compounds is hampered by the potent nephrotoxic, ototoxic and neurotoxic properties of these drugs. Recent studies have shown that sulfur-containing antioxidants relieve the dose limiting side effects of cis-diamminedichloroplatinum (CDDP), the most commonly used ionic platinum therapy. Here we report that both isomers of the sulfur-containing antioxidant methionine (MET) completely block the in vivo ototoxic and nephrotoxic effects of CDDP, and the duration of MET otoprotection is longer than has been previously reported. Rats treated with either L- or D-MET in addition to CDDP exhibited no signs of auditory system damage after 7 days, as evaluated by the auditory brainstem response and scanning electron microscopic examination of the organ of Corti, while CDDP-treated rats exhibited pronounced evidence of ototoxic damage after only 3 days. Microscopic examination of kidney tissue revealed moderate to severe nephrotoxic damage to CDDP-treated rats after 5 days, while rats co-treated with either MET isomer showed no evidence of kidney damage. Mortality among CDDP-treated subjects increased steadily over the period of the study, while all of the MET-protected rats survived. Finally, the efficacy of CDDP in the presence of L- or D-MET was evaluated in vitro using cultures of MTLN-3 breast tumor cell lines, and in vivo using implanted MTLN-3 tumors. Both L- and D-MET reduced the ability of CDDP to kill tumor cells in vitro and in vivo, however, our data suggest that a higher proportion of the antineoplastic activity of CDDP is retained in the presence of L- MET.

An epidemic in Cuba of optic neuropathy, sensorineural deafness, peripheral sensory neuropathy and dorsolateral myeloneuropathy.

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J Neurol Sci 1994 Dec 1;127(1):11-28

An epidemic outbreak of peripheral neuropathy affected Cuba in 1992-93 resulting in 50,862 cases (national cumulative incidence rate (CIR) 461.4 per 100,000). Clinical forms included retrobulbar optic neuropathy, sensory and dysautonomic peripheral neuropathy, dorsolateral myeloneuropathy, sensorineural deafness, dysphonia and dysphagia, spastic paraparesis, and mixed forms. For epidemiological purposes, cases were classified as optic forms (CIR 242.39) or peripheral forms (CIR 219.25). Increased risk was found among smokers (odds ratio (OR) 4.9), those with history of missing meals (OR 4.7) resulting in lower intake of animal protein, fat, and foods that contain B-vitamins, combined drinking and smoking (OR 3.5), weight loss (OR 2.8), excessive sugar consumption (OR 2.7) and heavy drinking (OR 2.3). Optic neuropathy was characterized by decreased vision, bilateral and symmetric central or cecocentral scotomata, and loss of color vision due to selective lesion of the maculopapillary bundles. Peripheral neuropathy was a distal axonopathy lesion affecting predominantly large myelinated axons. Deafness produced selective high frequency (4-8 kHz) hearing loss. Myelopathy lesions combined dorsal column deficits and pyramidal involvement of lower limbs with spastic bladder. Clinical features were those of Strachan syndrome and beriberi. Intensive search for neurotoxic agents, in particular organophosphorus esters, chronic cyanide, and trichloroethylene intoxication, yielded negative results. Treatment of patients with B-group vitamins and folate produced rewarding results. Most patients improved significantly and less than 0.1% of them remained with sequelae; there were no fatal cases. Supplementation of multivitamins to the entire Cuban population resulted in curbing of the epidemic. Overt malnutrition was not present, but a deficit of micronutrients, in particular thiamine, cobalamin, folate and sulfur amino acids appears to have been a primary determinant of this epidemic.

The therapeutic effect of vitamins A and E in neurosensory hearing loss.

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Acta Vitaminol Enzymol 1985;7 Suppl:85-92

After an anatomical and physiological outline of the organ of Corti, the pathology of the cochlea related to the sensorineural

deafness is described. The role of Vitamin A on cochlear function and the effects of Vitamin E in man are then emphasized, on the base of some experimental results. Clinical and therapeutic efficacy of the combination of Vitamin A + E is shown by a number of papers, pointing out a 5-15 decibel improvement of the pure-tone threshold in patients with sensorineural hearing-loss particularly when the auditory troubles are due to presbycusis.

Chemical anatomy of excitatory endings in the dorsal cochlear nucleus of the rat: differential synaptic distribution of aspartate aminotransferase, glutamate, and vesicular zinc.

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J Comp Neurol 1998 Sep 28;399(3):341-58

In order to identify cytochemical traits relevant to understanding excitatory neurotransmission in brainstem auditory nuclei, we have analyzed in the dorsal cochlear nucleus the synaptic distribution of aspartate aminotransferase, glutamate, and vesicular zinc, three molecules probably involved in different steps of excitatory glutamatergic signaling. High levels of glutamate immunolabeling were found in three classes of synaptic endings in the dorsal cochlear nucleus, as determined by quantitation of immunogold labeling. The first type included auditory nerve endings, the second were granule cell endings in the molecular layer, and the third very large endings, better described as "mossy." This finding points to a neurotransmitter role for glutamate in at least three synaptic populations in the dorsal cochlear nucleus. The same three types of endings enriched in glutamate immunoreactivity also contained histochemically detectable levels of aspartate aminotransferase activity, suggesting that this enzyme may be involved in the synaptic handling of glutamate in excitatory endings in the dorsal cochlear nucleus. There was also extrasynaptic localization of the enzyme. Zinc ions were localized exclusively in granule cell endings, as determined by a Danscher-selenite method, suggesting that this ion is involved in the operation of granule cell synapses in the dorsal cochlear nucleus.

Dose dependent protection by lipoic acid against cisplatin-induced ototoxicity in rats: antioxidant defense system.

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Toxicol Sci. 1999 Feb;47(2):195-202.

This study investigated the alterations that occur in auditory brainstem-evoked responses (ABRs) concurrent with changes in cochlear concentrations of glutathione (GSH), lipid peroxidation, and antioxidant enzyme activity in cisplatin-induced ototoxicity and in dose-dependent otoprotection by an antioxidant lipoate. Male Wistar rats were divided into different groups and were treated as follows, with: (1) vehicle (saline) control; (2) cisplatin (16 mg/kg, i.p.); (3) lipoate (100 mg/kg, i.p.) plus saline; (4) cisplatin plus lipoate (25 mg/kg); (5) cisplatin plus lipoate (50 mg/kg), and (6) cisplatin plus lipoate (100 mg/kg). Post-treatment ABRs were evaluated after three days, the rats were sacrificed, and cochleae were harvested and analyzed. The cisplatin-injected rats showed ABR threshold elevations above the pre-treatment thresholds. Rats treated with lipoate plus cisplatin did not show significant elevation of hearing thresholds. Cisplatin administration resulted in a depletion of cochlear GSH concentration (69% of control), whereas, cisplatin-plus-lipoate treatment increased GSH concentration close to control value. Cisplatin-treated rats showed a decrease in cochlear superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), and glutathione reductase (GR) activities (57, 78, 59, and 58% of control, respectively), and an increase in malondialdehyde (MDA) concentration (196% of control). Cochlear SOD, CAT, GSH-Px, and GR activities and MDA concentrations were restored in the rats injected with cisplatin plus graded doses of lipoate than those with cisplatin alone. It is concluded that cisplatin-induced ototoxicity is related to impairment of the cochlear antioxidant defense system, and the dose-dependent otoprotection conferred by an antioxidant lipoate against cisplatin ototoxicity is associated with sparing of the cochlear antioxidant defense system.

Application of antioxidants and other agents to prevent cisplatin ototoxicity.

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Laryngoscope. 1999 Nov;109(11):1740-4.

OBJECTIVE/HYPOTHESIS: To review the recent data from experiments performed in this laboratory to test the hypothesis that cisplatin ototoxicity is related to depletion of glutathione and antioxidant enzymes in the cochlea and that the use of antioxidants or protective agents would protect the cochlea against cisplatin damage and prevent hearing loss.

STUDY DESIGN/METHODS: Data were reviewed from experiments performed in this laboratory. Control rats were treated intraperitoneally with cisplatin 16 mg/kg. Experimental rats were given cisplatin in combination with one of the following protective agents: diethyldithiocarbamate, 4-methylthiobenzoic acid, ebselen, or lipoic acid. Animals in each group underwent auditory brainstem response (ABR) threshold testing before and 3 days after treatment. Cochleae were removed after final ABR testing and analyzed for glutathione and activities of the enzymes superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and malondialdehyde.

RESULTS: Rats in the control group receiving cisplatin were found to have significant ABR threshold shifts. This was accompanied by a reduction of glutathione and the activity of antioxidant enzymes (superoxide dismutase, glutathione peroxidase, catalase, and glutathione reductase) and an elevation of malondialdehyde. Experimental animals had preservation of ABR thresholds and levels of glutathione, antioxidant enzyme activity, and malondialdehyde that were similar to untreated animals.

CONCLUSION: Cisplatin ototoxicity appears to be initiated by free-radical production, which causes depletion of glutathione and antioxidant enzymes in the cochlea, and lipid peroxidation, manifested by an increase in malondialdehyde. These effects were blocked by each of a series of antioxidant compounds given in combination with cisplatin. A mechanism for cisplatin ototoxicity is elaborated with a proposed plan of chemoprevention using agents with different mechanisms of action. These substances could be used alone or in combination to reduce the severity of cisplatin ototoxicity in patients.

Ototoxicity. Amelioration by protective agents.

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Ann N Y Acad Sci. 1999 Nov 28;884:143-51.

The findings of studies from this laboratory are summarized to compare the efficacy of four chemoprotective agents against the effects of cisplatin-induced hearing loss and biochemical damage in the rat cochlea. A number of studies have shown that cisplatin is ototoxic, resulting in hearing loss, morphologic damage, and biochemical changes in the cochlea. These studies used Wistar rats, which underwent pre- and posttreatment ABR testing using clicks and tonebursts stimuli at 8, 16, and 32 kHz. Controls received i.p. saline injection. Cisplatin-treated rats were given 16 mg/kg cisplatin i.p. Animals received protective agents in the following dosage: DDTC protected rats received 600 mg/kg subcutaneously an hour after cisplatin. MTBA-protected animals were given 250 mg/kg i.p. 30 minutes before cisplatin. Animals protected with ebselen received 16 mg/kg i.p. an hour before cisplatin. One hundred mg/kg of alpha-lipoic acid was injected i.p. 30 minutes before cisplatin. Rats were sacrificed three days after treatment and the cochleae were harvested and frozen in liquid nitrogen and stored at -80 degrees C until analysis of glutathione (GSH), the activity of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase) and malondialdehyde was performed. Cisplatin-treated rats were found to have ABR threshold shifts of 27-40 dB, and rats treated with chemoprotective agents plus cisplatin all had ABR thresholds shifts of less than 10 dB. Significant depletion of glutathione and decrease of the activities of the antioxidant enzymes were observed in cisplatin-treated rats. These changes were accompanied by a marked elevation of malondialdehyde. These changes were almost completely prevented by the use of the chemoprotective agents. These findings suggest that cisplatin ototoxicity is related to lipid peroxidation and that the use of protective agents prevents hearing loss and lipid peroxidation by sparing the antioxidant defense system in the cochlea.

[Hearing recovery in sudden deafness with profound hearing loss.] [Article in Japanese]

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Nippon Jibiinkoka Gakkai Kaiho 1998 Jun;101(6):836-40

We investigated the hearing recovery in 51 patients with sudden deafness with the initial averaged five-frequency hearing levels worse than or equal to 100 dB. Twenty-two patients were treated in an outpatient setting with a peri-oral steroid, vasodilator, metabolic activator, and vitamin B. The remaining 29 patients were treated in the hospital with additional hyperbaric oxygenation therapy and/or Satellite ganglion block. The results were as follows. 1) The ultimate averaged five-frequency hearing levels were mainly distributed from 55 to 80 dB. Only seven patients showed ultimate hearing levels worse than 100 dB. Two patients achieved complete recovery better than 20 dB. 2) There was no significant difference in the hearing recovery between the patients treated in an outpatient setting and in the hospital. 3) The time interval until the hearing recovery began was distributed broadly between 2 and 28 days from the onset. While most of the patients who began to recover within 14 days from the onset showed ultimate hearing levels better than 80 dB, the patients who recovered after 14 days had worse hearing levels.

Pharmacokinetics of coenzyme Q10 in recovery of acute sensorineural hearing loss due to hypoxia.

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Acta Otolaryngol Suppl 1988;458:95-102

Coenzyme Q10 (CoQ10) has already been favorably evaluated in the clinical treatment of heart disease. In the otolaryngological field, it has been reported that CoQ10 is effective in promoting recovery from acute sudden deafness. However, the pharmacokinetics of CoQ10 in the inner ear is not yet clarified. The present study focuses upon the pharmacokinetics of CoQ10 using guinea pigs with acute sensorineural hearing loss artificially induced by hypoxia conditions. The respiration of the animals was controlled in an artificial respirator while the ABR, ECG and blood pressure were monitored. Repeated hypoxia caused a gradual disappearance of the ABR. After the experiments, the animals were sacrificed and brain and inner ear were examined by histological and histochemical methods as well as by SEM and TEM. The results indicated that CoQ10 is effective in promoting recovery from damage in auditory hairs as well as preventing respiratory metabolic impairment of hair cell due to hypoxia.

Preventive effect of magnesium supplement on noise-induced hearing loss in the guinea pig.

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Eur Arch Otorhinolaryngol 2000;257(1):10-6

The effect of magnesium (Mg) on noise-induced hearing loss was investigated in two groups of adult pigmented guinea pigs maintained either on optimal or suboptimal (physiologically high or low) Mg produced by different diets. The total Mg concentrations of the perilymph (PL), cerebrospinal fluid, blood plasma and red blood cells were measured by atomic absorption spectrometry and were found to differ significantly between the two groups ($P < 0.01$). One ear of each animal was exposed to either a single shooting impulse at a peak pressure level of 187 dB or two impulse noise series at a rate of 1/s and peak pressure levels of 150 dB (1,000 impulses) and 167 dB (2,280 impulses), respectively. Temporary (TTS) and permanent (PTS) hearing threshold shifts in anesthetized animals were measured 2 h and 1 week after the noise exposure, using auditory brain stem response (ABR) audiometry at a frequency range from 3.75 to 30 kHz. Exposure to the single noise impulse resulted in a mean TTS that was significantly lower in the high Mg group than that in the low Mg group ($P < 0.05$), although no substantial PTS was observed in either group. In the animals exposed to 150 dB noise, the TTS showed a tendency towards an Mg-related reduction at the higher frequencies. A small difference in PTS was found between the low Mg and high Mg groups, but was not significant. Exposure to the 167-dB noise series caused a considerable TTS, which was significantly lower in the high Mg group at 7.5 and 15 kHz than in the low Mg group ($P < 0.05$). The mean PTS showed a significant difference between the two Mg groups over the whole frequency range ($P < 0.05$) and was found to correlate negatively with the total Mg concentrations of both PL and plasma ($P < 0.05$). Moreover, the high Mg group showed a faster recovery from the hearing threshold shift than the low Mg group. The present findings show that preventive oral Mg supplements can significantly reduce the rate of acoustic trauma caused by high-level impulse noise exposure in the guinea pig.

Preventive magnesium supplement reduces ischemia-induced hearing loss and blood viscosity in the guinea pig.

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Eur Arch Otorhinolaryngol 2000;257(7):355-61

The effect of magnesium (Mg) on ischemia-induced hearing loss was investigated in two groups of adult pigmented guinea pigs of either an optimal or suboptimal (physiologically high or low) Mg status maintained by different diets. Total Mg concentrations of the perilymph, cerebrospinal fluid, blood plasma and red blood cells were found to differ significantly between the two groups, as tested in a previous study. Local vascular impairment was produced by unilateral ferromagnetic thrombosis of cochlear blood vessels. Cochlear blood flow (CBF) and hearing function were measured using laser Doppler flowmetry and auditory brain-stem response audiometry, respectively. Ferromagnetic thrombosis resulted in significant reductions of the mean apical CBF in both experimental groups and of the mean basal CBF in the low Mg group compared to the contralateral ears. In the high Mg group, the basal CBF was not decreased. However, the laser Doppler signals revealed considerable interindividual variations and the differences found between the two experimental groups were not significant. In contrast, the hearing loss in the low Mg group was significantly higher than that in the high Mg group. A correlation was found to exist between the vascular impairment and the hearing threshold shift. In a separate series, we also tested the effect of Mg on hemorheology and found both the blood viscosity and blood viscoelasticity to be significantly lower in the high Mg group than in the low Mg group, depending on the shear rates tested. The present findings show that a preventive oral Mg supplement can significantly reduce the rate of ischemia-induced hearing loss and improve blood viscosity in the guinea pig.

Biologic activity of mitochondrial metabolites on aging and age-related hearing loss.

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Am J Otol. 2000 Mar;21(2):161-7.

HYPOTHESIS: Compounds that upregulate mitochondrial function in an aging model will improve hearing and reduce some of the effects of aging.

BACKGROUND: Reactive oxygen metabolites (ROM) are known products of oxidative metabolism and are continuously generated in vivo. More than 100 human clinical conditions have been associated with ROM, including atherosclerosis, arthritis, autoimmune diseases, cancers, heart disease, cerebrovascular accidents, and aging. The ROM are extremely reactive and cause extensive DNA, cellular, and tissue damage. Specific deletions within the mitochondrial DNA (mtDNA) occur with increasing frequency in age and presbycusis. These deletions are the result of chronic exposure to ROM. When enough mtDNA damage accrues, the cell becomes bioenergetically deficient. This mechanism is the basis of the mitochondrial clock theory of aging, also known as the membrane hypothesis of aging. Nutritional compounds have been identified that enhance mitochondrial function and reverse several age-related processes. It is the purpose of this article to describe the effects of two mitochondrial metabolites, alpha-lipoic acid and acetyl L-carnitine, on the preservation of age-related hearing loss.

METHODS: Twenty-one Fischer rats, aged 24 months, were divided into three groups: acetyl-1-carnitine, alpha-lipoic acid, and control. The subjects were orally supplemented with either a placebo or one of the two nutritional compounds for 6 weeks. Auditory brainstem response testing was used to obtain baseline and posttreatment hearing thresholds. Cochlear, brain, and skeletal muscle tissues were obtained to assess for mtDNA mutations.

RESULTS: The control group demonstrated an expected age-associated threshold deterioration of 3 to 7 dB in the 6-week study. The treated subjects experienced a delay in progression of hearing loss. Acetyl-1-carnitine improved auditory thresholds during the same time period ($p < 0.05$). The mtDNA deletions associated with aging and presbycusis were reduced in the treated groups in comparison with controls.

CONCLUSIONS: These results indicate that in the proposed decline in mitochondrial function with age, senescence may be delayed by treatment with mitochondrial metabolites. Acetyl-1-carnitine and alpha-lipoic acid reduce age-associated deterioration in auditory sensitivity and improve cochlear function. This effect appears to be related to the mitochondrial metabolite ability to protect and repair age-induced cochlear mtDNA damage, thereby upregulating mitochondrial function and improving energy-producing capabilities.

Salicylate attenuates gentamicin-induced ototoxicity.

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Lab Invest 1999 Jul;79(7):807-13

Aminoglycosides, primarily gentamicin, are the most commonly used antibiotics worldwide despite their toxicity to the kidney and the inner ear. A preventive therapy against these side effects should combine safety and efficacy with low cost because aminoglycoside-induced deafness is most prevalent in developing countries. We have previously shown that aminoglycosides catalyze the formation of free radicals in an iron-dependent reaction and have delineated the structure of an iron-gentamicin complex. Here we demonstrate that 2-hydroxybenzoate (salicylate), which can act as an iron chelator and antioxidant, effectively protects against gentamicin-induced hearing loss in guinea pigs. Co-therapy with salicylate reduced a profound gentamicin-induced auditory threshold shift of more than 60 dB to less than 20 dB. Morphological assessment of the inner ear confirmed protection of auditory sensory cells. Salicylate altered neither serum levels of gentamicin nor its antibacterial efficacy. Because the required salicylate levels correspond to anti-inflammatory levels in humans, this treatment holds promise for clinical application.

Antioxidants attenuate gentamicin-induced free radical formation in vitro and ototoxicity in vivo: D-methionine is a potential protectant.

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We have recently suggested antioxidant therapy against aminoglycoside-induced hearing loss based on the hypothesis of a redox-active aminoglycoside-iron complex causing ototoxicity. The present study compares seven antioxidants and iron chelators for their ability to attenuate gentamicin-induced free radical generation in vitro and ototoxicity in guinea pig in vivo. Free radical formation by gentamicin was measured by chemiluminescence detection both in a non-enzymatic system in vitro and in cell culture. Deferoxamine, 2,3-dihydroxybenzoate, or salicylic acid suppressed gentamicin-induced luminescence in both tests. This indicated the usefulness of the assay as a screen for potential protectants since these agents had previously been shown to attenuate gentamicin-induced ototoxicity in vivo. Histidine and D-methionine, amino acids with chelating and antioxidant properties, also suppressed gentamicin-mediated luminosity both in vitro and in cell culture. In contrast, the metal chelators succimer (2, 3-dimercaptosuccinic acid (DMSA)) and trientine (N, N'-bis[2-aminoethyl]-1,2 ethanediamine) promoted free radical formation and were excluded from further studies. Histidine and D-methionine were then administered to guinea pigs receiving concurrent treatment with gentamicin (120 mg/kgx19 days). Threshold shifts induced by gentamicin were significantly attenuated by twice-daily injections of D-methionine. Once-daily injections of histidine or D-methionine were less effective, pointing to the importance of pharmacokinetics in antioxidant protection in vivo. The study presents a simple screening system for agents with the potential to attenuate gentamicin-induced hearing loss. It also supports the hypothesis of free radical formation as an underlying cause of gentamicin ototoxicity.

Zinc: the neglected nutrient.

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Am J Otol 1989 Mar;10(2):156-60

Zinc was first recognized as essential for animals at the University of Illinois School of Agriculture in 1916, when it was found that zinc-deficient baby pigs were runty, developed dermatitis on their legs, and were sterile. Zinc deficiency was first recognized in man by Dr. Ananda Prasad of Detroit 26 years ago when he measured serum and hair zinc levels in young male Egyptian dwarfs who had failed to mature and were small in stature. By simply adding zinc to their regular diet, they grew in height and became sexually mature. It is now recognized that dwarfism in males is frequent around the Mediterranean, where wheat is the staple of life and has been grown for 4,000 years on the same soil, thereby resulting in the depletion of zinc. Professor Robert Henkin first suggested that zinc deficiency might cause hearing-nerve impairment. Assay of the soft tissues of the cochlea and vestibule revealed a zinc level higher than that of any other part of the body. Previously, the eye was considered to have the highest level of zinc of any organ. To diagnose zinc deficiency clinically, we use serum zinc assays made at the Mayo Clinic Trace Element Laboratory. With zinc supplementation in patients who are marginally zinc deficient, there has been improvement in tinnitus and sensorineural hearing loss in about one-third of elderly adults. We believe zinc deficiency is one causation of presbycusis; by recognizing and correcting it, a progressive hearing loss can be arrested.

Vitamin B12 deficiency in patients with chronic-tinnitus and noise-induced hearing loss.

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Am J Otolaryngol 1993 Mar-Apr;14(2):94-9

INTRODUCTION: This study examines the incidence of vitamin B12 deficiency in three groups of noise-exposed subjects: patients with chronic tinnitus and noise-induced hearing loss (NIHL), patients with NIHL only, and subjects demonstrating normal hearing. **MATERIALS AND METHODS:** A group of 113 army personnel exposed to military noise was studied. The mean age was 39 years. Chronic tinnitus and NIHL existed in 57 subjects. NIHL alone was observed in 29 subjects, and 27 subjects had normal audiograms. All subjects were queried about noise exposure and dietary habits. Vitamin B12 serum levels were measured. **RESULTS:** Patients with tinnitus and NIHL exhibited vitamin B12 deficiency in 47% of cases (blood levels < or = 250 pg/mL). This was significantly more ($P < .023$) compared with NIHL and normal subjects who exhibited vitamin B12 deficiency in 27% and 19%, respectively. **CONCLUSION:** These observations suggest a relationship between vitamin B12 deficiency and dysfunction of the auditory pathway. Some improvement in tinnitus and associated complaints were observed in 12 patients following vitamin B12 replacement therapy. The authors recommend that routine vitamin B12 serum levels be determined when evaluating patients for chronic tinnitus.

Delayed auditory brainstem response in thiamin-deficient rats.

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Department of Pediatrics, Fukui Medical School, Japan.

J Nutr Sci Vitaminol (Tokyo) 1990 Jun;36(3):209-15

We recorded the auditory brainstem responses of rats fed a thiamin-deficient diet. The interpeak latencies between waves I and III, as well as those between waves I and IV, were significantly prolonged from day 24, while the latency of wave I was prolonged on day 26 of the thiamin-deficient diet. These delayed responses were corrected in 2 to 4 days after the initiation of daily intraperitoneal thiamin injections from day 32. The rats that were fed the thiamin-deficient diet, and then sacrificed on day 32, showed a decrease of total thiamin levels in the brain (26% of the level in control rat brains). Based on these results, we emphasize the value of the auditory brainstem response to detect thiamin deficiency.

Clinical improvement of memory and other cognitive functions by Ginkgo biloba: review of relevant literature.

Soholm B.
Sano-Pharm A/S, Vedbaek, Denmark.

Adv Ther 1998 Jan-Feb;15(1):54-65

Ginkgo biloba is a plant extract used to alleviate symptoms associated with cognitive deficits, e.g., decreased memory performance, lack of concentration, decreased alertness, tinnitus, and dizziness. Pharmacologic studies have shown that the therapeutic effect of ginkgo is based on several active constituents with vasoactive and free radical-scavenging properties. The use of ginkgo extract in either dementias of the Alzheimer or multi-infarct type or in the case of cerebral insufficiency, a symptom complex related to age-dependent impairment of cerebral circulation, is based mainly on positive results from good-quality placebo-controlled studies that enrolled approximately 1,200 patients with criteria established by International Classification of Diseases (9th and 10th revisions, ICD-9 and ICD-10) or the 3rd revision of the Diagnostic and Statistical Manual (DSM-III-R) (uncomplicated dementia). Effect on cognitive symptoms was within the range of a 25% reduction. Memory, concentration, and alertness were the first symptoms to be relieved, with tinnitus and dizziness improving somewhat later. A minimum of 4 to 6 weeks were needed before a pronounced effect could be expected. The pharmacologic advantage of ginkgo seems to be a very tolerable side-effect profile, with a side-effect frequency at the placebo level.

Protection from gentamicin ototoxicity by iron chelators in guinea pig in vivo.

Song BB, Anderson DJ, Schacht J.
Kresge Hearing Research Institute, University of Michigan, Ann Arbor 48109-0506, USA.

J Pharmacol Exp Ther 1997 Jul;282(1):369-77

This study details the prevention of gentamicin-induced hearing loss in guinea pig in vivo. The approach is based on our recent demonstrations of a redox-active gentamicin-iron complex in vitro and partial attenuation of gentamicin-induced hearing loss by the iron chelators deferoxamine and 2,3-dihydroxybenzoate. In our study, guinea pigs receiving injections of gentamicin (120 mg/kg body weight daily x 19 days) developed a progressive threshold shift reaching 50 to 70 dB at 18 kHz. Concurrent treatment with different doses of 2,3-dihydroxybenzoate (30-300 mg/kg/day) reduced the threshold shift to 25 to 15 dB. Coinjection of gentamicin with dihydroxybenzoate (100 mg/kg/day) plus mannitol (15 mg/kg/day) yielded complete functional and morphological protection from gentamicin ototoxicity although partial protection was observed with combinations of dihydroxybenzoate and deferoxamine. Dihydroxybenzoate also attenuated gentamicin-induced vestibular toxicity. The iron chelators and radical scavengers affected neither serum levels nor the antimicrobial efficacy of gentamicin against *Escherichia coli*. These results confirm that iron and free radicals play a crucial role in the toxic side effects of gentamicin. Furthermore, they suggest that iron chelators, which are well-established drugs in clinical therapy, may be promising therapeutic agents to reduce aminoglycoside ototoxicity.

Variable efficacy of radical scavengers and iron chelators to attenuate gentamicin ototoxicity in guinea pig in vivo.

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Hear Res 1996 May;94(1-2):87-93

Recent studies from our laboratory have suggested that the ototoxic side effects of gentamicin are caused by a metabolized or 'activated' form of the drug. Furthermore, we have postulated that the activation proceeds via the formation of an iron-gentamicin complex and that this complex produces free radicals. The present study assessed the protection effects of free radical scavengers and iron chelators on gentamicin-induced ototoxicity in guinea pigs in vivo. Gentamicin (120 mg/kg per day for 19 days) caused progressive threshold shifts reaching 50-65 dB at 18 kHz. Co-therapy with different radical scavengers yielded results ranging from no protection (with allopurinol, dimethyl sulfoxide, benzoate, lazaroid U74389G) to a moderate attenuation of hearing loss (with mannitol, 4-methylthiobenzoate, WR-2721). This finding agrees well with previous reports of inconsistent effects of scavengers on aminoglycoside-induced ototoxicity although it should be cautioned that only a single dose and route of application was tested. Two

iron chelators, deferoxamine and 2,3-dihydroxybenzoate, significantly reduced the gentamicin-induced threshold shifts to about 10 dB or less. Iron chelators markedly decreased total serum iron levels while gentamicin treatment alone had no influence. There were no differences in serum gentamicin levels among all treated groups. This study confirms that iron plays a critical role in gentamicin ototoxicity and suggests that iron chelators, which are well-established drugs in clinical therapy, may be promising therapeutic agents to reduce aminoglycoside ototoxicity.

Iron chelators protect from aminoglycoside-induced cochleo- and vestibulo-toxicity.

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Free Radic Biol Med 1998 Jul 15;25(2):189-95

The attenuation of gentamicin-induced hearing loss by iron chelators and radical scavengers has recently been demonstrated in guinea pig in vivo. The present study investigated whether this protective treatment is effective against hearing loss and vestibular damage caused by other aminoglycosides. In a direct comparison, dihydroxybenzoate was chosen over deferoxamine because of its more effective action against gentamicin-induced hearing loss. Guinea pigs received daily injections of kanamycin (250 mg/kg/d) or streptomycin (300 mg/kg/d) for 23 d to induce severe cochlear or vestibular toxicity, respectively. Kanamycin injections resulted in a progressive threshold shift of 60 to 80 dB at 18 kHz, while streptomycin injections induced only a small threshold shift. In contrast, streptomycin abolished almost all vestibular responses. Coinjection of aminoglycosides with a mixture of dihydroxybenzoate (100 mg/kg/d) and mannitol (30 mg/kg/d) significantly attenuated kanamycin-induced hearing loss and protected against streptomycin-induced vestibulotoxicity. DHB/mannitol did not affect serum levels or the antibacterial efficacy of either aminoglycoside. This study supports the idea that iron and free radicals play a critical role in the toxic side effects of aminoglycoside antibiotics. Furthermore, the previously proposed therapeutic protection is not limited to gentamicin but applicable to other aminoglycosides as well.

[The effect of polikatan on the ototoxic action of kanamycin.] [Article in Russian]

Spasov AA, Lobzov MS, Sanzharovskaia NK, Kozhevnikova EV, Kuzubova EA.

Volgograd State Medical Academy, Russia.

Eksp Klin Farmakol 1999 Jul-Aug;62(4):65-6

Experiments on guinea pigs demonstrated that preliminary injection of polycatan (standardized magnesium solution containing the mineral bischofite) into the parotid region by means of electrophoresis reduces the ototoxic effect of the aminoglycoside antibiotic kanamycin. Polycatan prevents kanamycin-induced degenerative changes of the hair cells found in the labyrinth of the internal ear and improves the local blood flow.

[Noise from a car airbag as a cause of acute acoustic trauma] [Article in Polish]

Stankiewicz C, Przewozny T, Kozłowski J.

Katedra i Klinika Chorob Uszu, Nosa, Gardla i Krtani AM w Gdansk.

Otolaryngol Pol. 2000;54(6):775-81.

A case of acute acoustic trauma in 32 year male, caused by a noise from car airbag, was described. The symptoms occurring directly after the airbag shot were tinnitus and hearing loss in right ear. Patient was admitted to ENT Clinic in Gdansk just after 5 months after an accident. Treatment--vasodilators and oxygen hyperbaric therapy--was ineffective. Review of literature, concerning the side effects of car airbag shot, was made. A mechanism of airbag action was presented as a source of short time noise.

Iron deficiency and hearing loss. Experimental study in growing rats.

Sun AH, Xiao SZ, Li BS, Li ZJ, Wang TY, Zhang YS.

ORL J Otorhinolaryngol Relat Spec 1987;49(3):118-22

Cochlear changes were studied in 141 growing rats raised on a basic iron-deficient diet for 7-100 days; 130 rats served as normal or chronic anemia controls. Electrophysiological findings showed that the incidence of an auditory threshold elevation of more than 15 dB was 31.85% in the iron-deficient rats, but it was unchanged in all the control animals. The main cochlear histopathological changes induced by iron deficiency were stria atrophy and reduction of spiral ganglion cells. It is concluded that the observed anomalies may be attributed solely to iron deficiency of the cochlear tissue.

Changes in the cochlear iron enzymes and adenosine triphosphatase in experimental iron deficiency.

Sun AH, Li JY, Xiao SZ, Li ZJ, Wang TY.

Otolaryngological Laboratories, Changhai Hospital, Shanghai, People's Republic of China.

Ann Otol Rhinol Laryngol 1990 Dec;99(12):988-92

The influences of iron deficiency on the cochlear iron enzymes and adenosine triphosphatase were studied in 68 iron-deficient rats and 68 control rats (normal and with chronic anemia). A disorderly or topographic distribution and reduction or disappearance of the cochlear succinic dehydrogenase and peroxidase reaction products were found in 37.8% of the rats fed on a basic iron-deficient diet for 14 to 100 days. The activity of cochlear sodium-potassium-dependent adenosine triphosphatase in iron-deficient rats was slightly increased, compared to that in normal controls. These results suggest that iron deficiency would produce significant abnormalities of succinic dehydrogenase and peroxidase activity, which in turn would disturb cell respiration and initiate peroxidative damage to the inner ear cells, result in sensorineural hearing loss, or provide a pathologic basis for cochlear deafness.

Noise-induced hearing loss in iron-deficient rats.

Sun AH, Wang ZM, Xiao SZ, Li ZJ, Lin DY, Liang ZF, Hu ZY, Wang GY, Ye XT.

Otolaryngological Laboratories, Changhai Hospital, Shanghai, China.

Acta Otolaryngol 1991;111(4):684-90

The role of iron deficiency in noise-induced hearing loss (NIHL) was evaluated in 64 rats of four different experimental groups. Iron-deficient rats (ID-rats) and normal rats (N-rats) were simultaneously exposed to a steady state white noise (20-10,000 Hz) at 110 dB SPL for 30 min. Unexposed ID- and N-rats served as controls. In N-rats the temporary threshold shifts (TTS) would have completely disappeared if the animals were allowed to survive for 72 h. No permanent threshold shift (PTS) was seen in any of the N-rats. The ultrastructural correlates in N-rats are stereocilia disarray and mitochondria swelling in outer hair cells (OHCs). The TTS in ID-rats were larger than those in the N-rats, and most ID-rats with larger threshold shifts showed varying degrees of PTSs at 11 days post-exposure. The ultrastructural correlates of NIHL in ID-rats are obvious pathology of the stereocilia, such as segmental coalescence of stereocilia of many continuous OHCs and fusion of the tips of stereocilia of OHCs, and a significant reduction of mitochondria as well as slight degeneration of nucleus in the OHCs. It is concluded that iron deficiency can provide a pathological basis for NIHL.

The effects of coenzyme Q10 treatment on maternally inherited diabetes mellitus and deafness, and mitochondrial DNA 3243 (A to G) mutation.

Suzuki S, Hinokio Y, Ohtomo M, Hirai M, Hirai A, Chiba M, Kasuga S, Satoh Y, Akai H, Toyota T.

Third Department of Internal Medicine, Tohoku University School of Medicine, Sendai, Japan.

Diabetologia 1998 May;41(5):584-8

The characteristic clinical features of diabetes mellitus with mitochondrial DNA (mtDNA) 3243(A-G) mutation are progressive insulin secretory defect, neurosensory deafness and maternal inheritance, referred to as maternally inherited diabetes mellitus and deafness (MIDD). A treatment for MIDD to improve insulin secretory defects and reduce deafness has not been established. The effects of coenzyme Q10 (CoQ10) treatment on insulin secretory response, hearing capacity and clinical symptoms of MIDD were investigated. 28 MIDD patients (CoQ10-DM), 7 mutant subjects with impaired glucose tolerance (IGT), and 15 mutant subjects with normal glucose tolerance (NGT) were treated daily with oral administration of 150 mg of CoQ10 for 3 years. Insulin secretory response, blood lactate after exercise, hearing capacity and other laboratory examinations were investigated every year. In the same way we evaluated 16 MIDD patients (control-DM), 5 mutant IGT and 5 mutant NGT subjects in yearly examinations. The insulin secretory response assessed by glucagon-induced C-peptide secretion and 24 h urinary C-peptide excretion after 3 years in the CoQ10-DM group was significantly higher than that in the control-DM group. CoQ10 therapy prevented progressive hearing loss and improved blood lactate after exercise in the MIDD patients. CoQ10 treatment did not affect the diabetic complications or other clinical symptoms of MIDD patients. CoQ10 treatment did not affect the insulin secretory capacity of the mutant IGT and NGT subjects. There were no side effects during therapy. This is the first report demonstrating the therapeutic usefulness of CoQ10 on MIDD.

Long-term auditory and visual complications of biotinidase deficiency.

Taitz LS, Leonard JV, Bartlett K.

Early Hum Dev 1985 Sep;11(3-4):325-31

The biochemical, dermatological and neurological motor disorders of biotinidase deficiency (multiple carboxylase deficiency) show a dramatic response to pharmacological doses of biotin. This condition is characterised by the accumulation of biocytin and depletion of biotin. Neuromuscular function returns to normal with the reversal of the characteristic organic acidaemia. It would appear that the optic and auditory nerves or their related neurological structures may suffer damage from the excess biocytin and deficient biotin. Despite reversal of the dermatological and psychomotor abnormalities children are likely to be left with auditory and/or visual handicaps if diagnosis and treatment is delayed beyond the first year of life. Treatment with biotin was commenced 6, 18, and 13 months after onset of symptoms. Two children subsequently were found to have visual impairment (acquired retinal dysplasia) and two had sensori-neural deafness. In one patient both defects were present.

Randomized trial of taurine supplementation for infants less than or equal to 1,300-gram birth weight: effect on auditory brainstem-evoked responses.

Tyson JE, Lasky R, Flood D, Mize C, Picone T, Paule CL.
Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas 75235.

Pediatrics 1989 Mar;83(3):406-15

Taurine may be important to the developing eye and brain of the small preterm infant. A blinded randomized trial was conducted to determine whether taurine supplementation of healthy infants of less than or equal to 1,300 g birth weight until their discharge from the hospital increases their growth rate, neurobehavioral development, electroretinographic development, or maturation of auditory brainstem-evoked responses. Infants were fed with Similac Special Care as desired, which was prepared to contain less than 5 mg/L of taurine or 45 mg/L of taurine, a concentration similar to that of human milk. Infants who did not receive taurine supplementation (n = 19) and those who did (n = 18) were similar with respect to condition at study entry, caloric intake, and growth rates throughout the study, and electroretinographic findings and scores on the Brazelton Behavioral Assessment Scale at 37 weeks' postmenstrual age. Infants who received taurine supplementation had greater overall plasma taurine concentrations. The group receiving taurine supplementation also had more mature auditory-evoked responses at 37 weeks' postmenstrual age with a modest (0.2 to 0.5 ms) but consistent reduction (P less than .05) in the interval between stimulus and response at two different stimulation rates. Although further study is needed, taurine intake appears to influence auditory system maturation of preterm infants.

Iodine intakes assessed by urinary iodine concentrations in healthy children aged ten months, two years, and four years.

Valeix P, Preziosi P, Rossignol C, Farnier MA, Hercberg S.
Institut Scientifique et Technique de la Nutrition et de l'Alimentation, CNAM, Paris.

Biol Trace Elem Res 1992 Jan-Mar;32:259-66

Urinary iodine excretion was assessed in 642 healthy children aged 10 mo (n = 243), 2 yr (n = 183), and 4 yr (n = 216) living in the Paris area and originating from continental France (60.3%), North Africa (13.8%), the West Indies (9.1%), West Africa (8.3%), Southeast Asia (4.8%), and southern Europe (3.8%). Mild impairment of neurological (reflexes, tone, audiometry) and intellectual development (Brunet-Lezine scale) was assessed in relation to iodine status. Iodine excretions (median values) were 18.4, 11.9, and 10.9 micrograms/100 mL at 10 mo, 2 yr, and 4 yr, respectively, and risk of mild iodine deficiency (5-10 micrograms/100 mL) was 18.1%, 34.8%, and 38.3% for the same age groups. No relationship was found between anthropometry, global development quotient, and iodine status. High hearing thresholds were more commonly associated with lower iodine excretion, suggesting mild hearing defects. In spite of iodine prophylaxis, the risk of mild to moderate iodine deficiency still exists in France and in a number of European countries. Evaluation of neurological sequels of borderline iodine status is a major public health problem in European communities.

Relationship between urinary iodine concentration and hearing capacity in children.

Valeix P, Preziosi P, Rossignol C, Farnier MA, Hercberg S.
Institut Scientifique et Technique de la Nutrition et de l'Alimentation, CNAM, France.

Eur J Clin Nutr 1994 Jan;48(1):54-9

Urinary iodine excretion was assessed in 1222 healthy children aged 10 months (n = 456), 2 years (n = 368) and 4 years (n = 398) living in the Paris area and originating from continental France (55.2%), North Africa (15.7%), the West Indies (9.7%), West Africa (8.2%), Southeast Asia (5.5%), and southern Europe (5.7%). Iodine excretions (median values) were, respectively, 18.1, 13.4 and 11.6 micrograms/100 ml at 10 months, 2 years and 4 years, and risk of mild to moderate iodine deficiency (< 10 micrograms/100 ml) was 18.0%, 32.3% and 37.2% for the same age groups. Urinary iodine excretion was highest among Southeast Asian children,

and lowest among West Africans. Hearing acuity was measured either by conventional mono-aural pure-tone audiometry or by binaural free field testing depending on the child's age. Hearing loss at 4000 Hz and average hearing impairment at speech frequencies (500, 1000 and 2000 Hz) were more severe among children at risk of mild to moderate iodine deficiency (less than 10 micrograms/100 ml) compared with those with urinary excretion above 10 micrograms/100 ml.

Comparison of the developmental changes of the brainstem auditory evoked response (BAER) in taurine-supplemented and taurine-deficient kittens.

Vallecalle-Sandoval MH, Heaney G, Sersen E, Sturman JA.

Department of Developmental Biochemistry, Institute for Basic Research in Developmental Disabilities, Staten Island, NY 10314.

Int J Dev Neurosci 1991;9(6):571-9

A similar development of the brainstem auditory evoked response is present in taurine-supplemented and taurine-deficient kittens between the second postnatal week and the third month of life. Between birth and the second postnatal week kittens from mothers fed the 1% taurine diet showed earlier maturation of the brainstem auditory evoked response as indicated by lower threshold, shorter P1 latency and shorter central conduction time when compared to the kittens from mothers fed the 0.05% taurine diet. These results suggest an important role of taurine in the anatomical and functional development of the auditory system.

Biotinidase deficiency: presymptomatic treatment.

Wallace SJ.

Arch Dis Child. 1985 Jun;60(6):574-5.

Biotinidase deficiency presents with clinical signs of biotin deficiency at the age of 3 months, or soon after. In an infant in whom the diagnosis was made on cord blood, vision and hearing were normal before presymptomatic treatment with biotin. Physical and mental development are good at 14 months.

Improvement in hearing among otherwise normal schoolchildren in iodine-deficient areas of Guizhou, China, following use of iodized salt.

Wang YY, Yang SH.

Lancet 1985 Sep 7;2(8454):518-20

According to a survey in Guizhou province of China, the average hearing level of otherwise normal schoolchildren in an area of endemic iodine-deficient goitre and cretinism was significantly poorer than in a non-endemic control area. After iodine prophylaxis for three years, audiometric tests showed that the average hearing level had improved and approached that of the non-endemic controls. In addition, mean values for thyroid function tests were restored to within the normal range. It is suggested that the most likely cause of the poorer hearing level among the ostensibly normal schoolchildren in endemic areas is subclinical hypothyroidism due to prolonged severe iodine deficiency.

Biotinidase deficiency: a survey of 10 cases.

Wastell HJ, Bartlett K, Dale G, Shein A.

Department of Clinical Biochemistry, Newcastle General Hospital, Newcastle upon Tyne.

Arch Dis Child 1988 Oct;63(10):1244-9

Ten patients with biotinidase deficiency were studied. Clinical findings at presentation varied with dermatological signs (dermatitis and alopecia), neurological abnormalities (fits, hypotonia, and ataxia), and recurrent infections being the most common features, although none of these occurred in every case. Biochemically the disease is characterised by metabolic acidosis and organic aciduria. Treatment with biotin results in pronounced, rapid, clinical and biochemical improvement, but some patients have residual neurological damage comprising neurosensory hearing loss, visual pathway defects, ataxia, and mental retardation. The cause of this permanent damage remains obscure and it is not clear if the early introduction of treatment will prevent it.

[Results of multistep oxygen therapy in the treatment of sudden hearing loss.] [Article in German]

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Oxygen multistep therapy (von Ardenne) was applied in 28 patients suffering from an idiopathic sudden hearing loss. The oxygen therapy consisted of a multistep short procedure, each of which lasted for 15 minutes. The results of our study were evaluated by means of standardised statistics confirming the effectiveness and even the superiority of the oxygen multistep therapy in comparison with any other treatment, and also in view of the spontaneous remission rate in cases of sudden hearing loss.

Role of glutathione in protection against noise-induced hearing loss.

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Kresge Hearing Research Institute, The University of Michigan, 1301 East Ann Street, Ann Arbor, MI 48109-0506, USA.

Brain Res 1998 Feb 16;784(1-2):82-90

A potential mechanism of hearing loss due to acoustic overstimulation is the generation of reactive oxygen species (ROS). ROS not removed by antioxidant defenses could be expected to cause significant damage to the sensory cells of the cochlea. We studied the influence of the antioxidant glutathione (GSH) on noise-induced hearing loss by using L-buthionine-[S,R]-sulfoximine (BSO), an inhibitor of GSH synthesis, and 2-oxothiazolidine-4-carboxylate (OTC), a cysteine prodrug, which promotes rapid restoration of GSH when GSH is acutely depleted. Pigmented female guinea pigs were exposed to broadband noise (102 dB SPL, 3 h/day, 5 days) while receiving daily injections of BSO, OTC, or saline. By weeks 2 and 3 after noise exposure, BSO-treated animals showed significantly greater threshold shifts above 12 kHz than saline-treated subjects, whereas OTC-treated animals showed significantly smaller threshold shifts at 12 kHz than controls. Histologically assessed noise-induced damage to the organ of Corti, predominantly basal turn row 1 outer hair cells, was most pronounced in BSO-treated animals. High performance liquid chromatographic analysis showed that OTC significantly increased cysteine levels, but not GSH levels, in the cochlea. These findings show that GSH inhibition increases the susceptibility of the cochlea to noise-induced damage and that replenishing GSH, presumably by enhancing availability of cysteine, attenuates noise-induced cochlear damage. Copyright 1997 Elsevier Science B.V.

Influence of intense sound exposure on glutathione synthesis in the cochlea.

Yamasoba T, Harris C, Shoji F, Lee RJ, Nuttall AL, Miller JM.

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Brain Res 1998 Aug 31;804(1):72-8

Previous studies have shown that depletion of endogenous glutathione (GSH) potentiates noise-induced hearing loss (NIHL), whereas replenishment of GSH attenuates NIHL (Yamasoba et al., Brain Res. 784 (1998) 82-90). Since these findings indicate an important role of GSH in protection from NIHL, we assessed the influence of intense sound exposure (broadband noise, 105 dB SPL, 5 h) on GSH and cysteine levels in the guinea pig cochlea using high performance liquid chromatography. GSH levels were significantly increased in the lateral wall 2 and 4 h post-exposure and returned to normal 6 h post-exposure. GSH levels in the sensory epithelium and modiolus did not show significant changes following noise. Cysteine levels were unchanged in any of the cochlear segments. For the cochlea as a whole, intense sound exposure did not significantly change GSH or cysteine levels throughout the 6-h measurement period post-exposure. These results indicate that GSH synthesis is markedly upregulated selectively in the lateral wall by noise exposure, presumably in response to the robust consumption of GSH, as it is utilized in scavenging reactive oxygen species. Copyright 1998 Elsevier Science B.V.

L-carnitine treatment improves brain stem auditory evoked potentials in diabetic rats.

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Department of Pharmacology, Gulhane School of Medicine, Ankara, Turkey.

Neuroreport 1996 Nov 25;7(18):2957-9

The effect of L-carnitine (LC) on brain stem auditory evoked potentials (BAEP), was examined in alloxan-diabetic rats. LC (200 mg kg⁻¹, i.p., once daily) was given to diabetic rats starting from the third week after the induction of diabetes, lasting for 4 weeks. Age-matched non-diabetic rats served as controls. The latency of wave I and interpeak latency I-IV were measured once weekly. Diabetes-induced deficits in BAEP latencies ($p < 0.05$, diabetics vs non-diabetic controls) were improved after LC treatment ($p < 0.05$, LC-treated diabetic rats vs non-diabetic controls). Weight and glucose levels were not influenced by LC treatment. Our results suggest that LC had beneficial effects on diabetic central neuropathy but these effects are not associated with the regulation of glycaemia in alloxan-diabetic rats.

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