Magnesium and Hearing

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Abstract

The last several decades have revealed clinical and experimental data regarding the importance of magnesium (Mg) in hearing. Increased susceptibility to noise damage, ototoxicity, and auditory hyperexcitibility are linked to states of Mg deficiency. Evidence for these processes has come slowly and direct effects have remained elusive because plasma Mg levels do not always correlate with its deficiency. Despite the major progress in the understanding of cochlear mechanical and auditory nerve function, the neurochemical and pharmacologic role of Mg is not clear. The putative mechanism suggests that Mg deficiency may contribute to a metabolic cellular cascade of events. Mg deficiency leads to an increased permeability of the calcium channel in the hair cells with a consequent over influx of calcium, an increased release of glutamate via exocytosis, and over stimulation of NMDA receptors on the auditory nerve. This paper provides a current overview of relevant Mg metabolism and deficiency and its influence on hearing.

Key Words: magnesium deficiency, hearing, L-type calcium channel, NMDA, nitric oxide, cochlea, noise, gentamicin, salicylate, outer hair cells, distortion product otoacoustic emissions, transient evoked otoacoustic emissions, cisplatin chemotherapy

Abbreviations: ABR = auditory brainstem response; ATP = adenosine triphosphate; Ca = calcium; CSF = cerebral spinal fluid; DPOAE = distortion product otoacoustic emissions; Ca++ = ionized calcium; Mg++ = ionized magnesium; Mg = magnesium; Na/K - sodium/potassium; NMDA = N-methyl-D-aspartate; OHCs = outer hair cells; RDA = Recommended Dietary Allowance; TEOAE = transient otoacoustic emissions.

Sumario:

En las últimas décadas se ha revelado información clínica y experimental en relación a la importancia del magnesio (Mg) en la audición. El incremento en la susceptibilidad al daño causado por el ruido, la ototoxicidad y la hiperexcitabilidad auditiva están relacionadas con estados de deficiencia de Mg. La evidencia de dichos procesos se ha acumulado lentamente y la demostración de los efectos directos ha sido esquiva, porque los niveles plasmáticos de Mg no siempre correlacionan con su deficiencia. A pesar de los progresos realizados para entender la mecánica coclear y la función del nervio auditivo, el papel neuroquímico y farmacológico del Mg no está claro. El mecanismo supuesto sugiere que la deficiencia de Mg puede contribuir a una cascada celular metabólica de eventos. La deficiencia de Mg conduce a un aumento en la permeabilidad del canal de calcio en la célula ciliada, con un consecuente flujo incrementado de calcio, una liberación aumentada de glutamato

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por exocitosis, y una sobre-estimulación de los receptores de NMDA en el nervio auditivo. Este artículo aporta una revisión actual del metabolismo y la deficiencia del Mg, así como su influencia en la audición.

Palabras Clave: deficiencia de magnesio, audición, canal de calcio tipo L, NDMA, óxido nítrico, cóclea, ruido, Gentamicina, salicilato, células ciliadas externas, emisiones otoacústicas por productos de distorsión, emisiones otoacústicas evocadas por transientes, cisplatino, quimioterapia.

Abreviaturas: ABR = respuesta evocadas de tallo cerebral; ATP = adenosin trifosfato; Ca = Calcio; CSF = líquido céfaloraquideo; DPOAE = emisiones otoacústicas por productos de distorsión; Ca++ = calcio ionizado; Mg++ = magnesio ionizado; Mg = magnesio; Na/K = sodio/potasio; NMDA = N-metil-D-aspartato; OHCs = células ciliadas externas; RDA = Ración dietética recomendada; TEOAE = emisiones otoacústicas evocadas por transientes.

Permanent and temporary changes in auditory function have been linked to nutritional deficiencies of magnesium (Mg). Mg deficiency has resulted in increased susceptibility to noise-induced hearing loss (Ising et al.1982; Joachim et al.1983; Joachim et al. 1987; Scheib et al. 2000a), ototoxicity (Vormann and Günther, 1993), and hyperexcitability (Kruse et al, 1932; Cevette et al 1989; Bac et al, 1994) of the auditory system. The alterations to hearing may be acute or gradual depending on the degree of deficiency present and magnitude of noise exposure or dosage of drug. Careful measurements of pure tone thresholds, OAEs and auditory evoked potentials demonstrate changes at the level of the cochlea, auditory nerve and brainstem (Günther et al, 1988; Cevette et al, 1989; Attias et al. 1994; Cevette et al 2000). Dietary-induced Mg deficiency in rats correlates with compromised cerebral function illustrated by audiogenic seizures that often prove fatal (Kruse et al. 1932; Bac et al, 1994). The relationship between a deficiency of Mg and the auditory perceptions of tinnitus and hyperacusis remains unclear.

Certainly, a cascade of metabolic processes is involved in Mg deficiency that ultimately results in the compromise of auditory function. This is understandable given the complexity of cochlear neurochemistry and neuropharmacology, the influence of Mg deficiency on cell function, on microcirculation and the formation of reactive oxygen species. Understanding the subtle effects of Mg deficiency are an important issue in the development of future research aimed at the prevention of Mg related auditory dysfunction. The following is an overview of Mg deficiency and hearing, including the related neurochemistry.

MAGNESIUM METABOLISM

Mg is the divalent cation most abundant in cells. About 21-28 gm of Mg is found in the body with about half associated with bone and the remaining half in tissues and blood (Rude 1998; Saris et al. 2000). The surface of the bone crystal is considered to be the buffer that helps to maintain plasma Mg levels. In the body, Mg functions both as a macromineral and also as a trace mineral. It is required by hundreds of enzymes in the body, including any reaction with adenylate cyclase, ATP, Na/K-ATPase, and phospholipase C. In addition, Mg has a role in the transport of calcium (Ca), potassium, and sodium across the plasma membrane of cells. Mg modulates Ca uptake at the cell membrane (Seelig, 1994).

Most causes of Mg deficiency can be placed into two categories: 1. decreased uptake from low dietary intake of Mg or from decreased intestinal absorption, and 2. enhanced losses of Mg through the gastrointestinal tract or kidneys (Whang 1984). Dietary surveys indicated that self-selected diets provide marginal or inadequate Mg levels for a significant percentage of adults

based on the recommended dietary allowances (Morgan et al. 1985). The current RDA for Mg is 320 mg for women and 420 mg for men, but dietary intakes are about 100 mg less than the RDA (Institute of Medicine 1997).

Plasma Mg levels may or may not reflect Mg nutritional status. Insulin appears to be needed to move both glucose and Mg into many tissues (Hua et al. 1995; Barbagallo et al. 2001). In insulin resistance and type 2 diabetes, Mg uptake into tissues is impaired so that plasma Mg may be within the normal range with intracellular Mg being decreased .

Plasma Mg may be increased (Henrotte et al. 1985; Porta et al. 1994; Mocci et al. 2001) or decreased (Cernak et al. 2000; Laires et al. 1993; Weissberg et al. 1991; Whyte et al. 1987) as part of stress reactions. Mild physical or psychological stress appears to increase plasma Mg, while prolonged severe or chronic stress decreases plasma Mg. Genetic differences may also occur at intracellular and extracellular Mg levels with increased stress sensitivity being associated with the lower Mg levels (Henrotte et al. 1985, 1991, 1999). Within cells or extracellular fluids, Mg will be bound to membranes or in a free, ionic state. It is the free, ionic form (Mg++) that is metabolically active.

It was in 1932 when Kruse et al. reported the first severe Mg deficiency with rats. These young weanling rats became very irritable and excitable, particularly when exposed to noises. Within two to three weeks of beginning the diet, a sudden sound was found to provoke seizures, which often were fatal. The sound of running water was sufficient to produce convulsions in these severely Mg deficient rats. The mechanism for these sound induced seizures is still not completely understood.

More recent work has confirmed that low Mg increases epileptiform activity in rat hippocampal slices by increasing the excitotoxicity of the N-methyl-D-aspartate (NMDA) receptors (Nakamura et al. 1994; Zhang et al. 1994). Both glutamate (Milani et al. 1991) and Mg (Dubray et al. 1997) modulate the activity of the NMDA receptor. If glutamate is increased or if Mg is low, the receptor activity is increased. If Mg is high and glutamate is low, NMDA activity is decreased. Activation of the NMDA receptor opens a channel for ionized Ca (Ca++) to enter the cell.

The function of L-type Ca channels is also integral to hearing. The slow motile response of the outer hair cells (OHCs) is both Ca and ATP dependent (Zenner,1986; Ulfendah, 1987). Evidence exists that the L-type Ca channels are directly involved in the operation of the organ of Corti (Bobbin et al. 1990). Cochlear perfusion of nimodipine, an L-type Ca channel antagonist, resulted in a dose-related suppression of the cochlear microphonic, negative summating potential and compound action potential (Bobbin et al, 1990). Since OHCs produce much of the summating potential, Ca antagonists decrease the summating potential (Bobbin et al, 1990). Antithetically, the loss of the Ca antagonists affects an increase of the summating potential. When Mg is low, more Ca++ passes through the L-type Ca channel. In addition, L-type Ca channels are associated with muscle contraction in smooth muscle (Zakharov et al. 1999), where action is modulated by Mg++ (Altura et al. 2001).

Ca++ within cells acts as a second messenger and initiates specific functions that are unique to that cell. When Ca++ begins to increase in cells inappropriately, cells act to decrease the ionized Ca++ by binding it to membranes within the cell, pumping it out of the cells, and as the last resort, pumping it into the mitochondria using energy. If too much Ca++ is pumped into the mitochondria, there may not be enough energy left to carry out cellular functions, and the processes resulting in necrotic cellular death begin (Zhu et al. 2000). This process extends to hair cell function within the cochlea.

Nitric oxide synthesis is also modulated by Mg (Howard et al. 1995; Rock et al. 1995): low Mg results in increased nitric oxide synthesis and high Mg decreases nitric oxide synthesis. These effects of Mg on the NMDA receptor and nitric oxide synthesis may be applicable in hearing.

HOW DO THESE PROCESSES WORK IN THE EAR?

When sound reaches OHCs in the cochlea, the hair cells are displaced. The displacement of sterocilia results in hair cell depolarization via potassium influx through mechanosensitive channels. The depolarization of the OHCs then activates voltage sensitive Ca++ channels across the plasma membrane resulting in Ca++ influx (Hudspeth,1985). Increased intracellular Ca++ causes mobilization of synaptic vesicles and exocytotic release of

glutamate at the base of the hair cells. This Ca channel is an L-type channel (Chen et al. 1995; Zhang et al. 1999). The movement of the ions sets up electrical currents that result in proportionate amounts of glutamate being released at the afferent nerve terminal (Kataoka and Ohmori 1994), which then binds to both N-methyl-D-aspartate (NMDA) and non-NMDA receptors on the spiral ganglion neurons of the auditory nerve (Puel 1995; Nordang et al. 2000). With glutamate activating NMDA and non-NMDA (AMPA and kainate) receptors, Ca++ enters the nerve cells and message of sound has been carried from the hair cells to the auditory nerve. The concentration of Mg++ in the surrounding fluid modulates these processes and affects the central nervous system's processing of sound, the health of the hair cells themselves, and the spiral ganglion neurons.

If Mg++ were low, too much Ca++ would enter the hair cells. In turn, more glutamate would then be produced in response to the increased electrical currents being generated by the Ca++. Increased glutamate, in turn, would greatly increase the activity of the NMDA receptor, which also is operating with low Mg. With the double insult of high glutamate and low Mg, a flood of Ca++ would go through the NMDA channel into the nerve cell. If the Ca++ were too much, the energy system of the cell may be compromised and necrosis processes would be initiated. Low Mg++ would also have a direct effect on decreasing the activity of the mitochondria. Excessive nitric oxide production could increase oxidative stress of the inner ear. Over time, low Mg++ in the inner ear could compromise many critical processes required for hearing and contribute to sensorineural hearing loss. Noise would intensify the processes initiated by low Mg++. Over-stimulation of the NMDA receptors by excessive Ca++ has been implicated in hearing loss (Duan et al. 2000), and a block of this receptor helps to protect against noise-induced hearing loss.

WHAT IS THE EVIDENCE THAT THESE PROCESSES ARE AFFECTED BY MG IN ANIMALS OR PEOPLE?

The picture is still not complete, but several pieces of evidence are compelling. Perilymph Mg affects Ca++ uptake into hair cells (Siegel and Relkin 1987). In guinea pigs, the concentrations of Mg in perilymph (0.80 mmol/l) and cerebral spinal fluid (CSF) (0.87 mmol/l) are lower than plasma Mg (1.24 mmol/l) when the animals are on a high Mg diet (Scheibe et al. 1999). On a low Mg diet, the CSF Mg (0.79 mmol/l) is higher than the plasma Mg level (0.68 mmol/l), which shows an ability of the blood brain barrier to concentrate Mg taken up from plasma. However, the perilymph Mg concentration (0.58 mmol/l) was lower than the plasma Mg (0.68 mmol/l), which suggests an inability of the blood-perilymph barrier to concentrate plasma Mg in its transport into the perilymph. These results showed that both dietary and plasma Mg affect perilymph Mg. The perilymph Mg concentrations in these guinea pigs correlated well with their plasma Mg levels.

Mg in Noise Induced Hearing Loss

After being exposed to noise for years, a certain percentage of exposed persons develop a permanent hearing threshold shift. Although the relationship between noise and damage of hair cells is well established, additional conditioning factors must be involved, as not all people exposed to noise develop hearing damage to the same degree.

In humans and laboratory animals, noise induced an elevation of serum Mg concentrations and an increased urinary excretion of Mg. This was mainly explained by increased stress reactions (Ising, 1981). In humans a negative correlation between noise sensitivity and erythrocyte Mg concentration was found ($r = -0.27$, $p < 0.05$) (Ising et al., 1981). In addition to the known neuromuscular and vascular hyperexcitability in Mg deficiency, the question arose whether a changed Mg status might explain the different susceptibility to noise. Various animal experiments showed that Mg is significantly involved in noise induced hearing loss.

When guinea pigs were fed a Mg deficient diet and supplemented with either 4.5, 2.5, or 0.5 mmol Mg/L in their drinking water, noise exposure with 95 dB for 16 h a day over a period of 4 weeks led to permanent hearing threshold shifts of 16.8, 22.7 and 34.2 dB (Ising et al., 1982). The lower the Mg intake, the higher the noise-induced threshold shift (Figure 1). No correlation between hearing loss and myocardial or erythrocyte

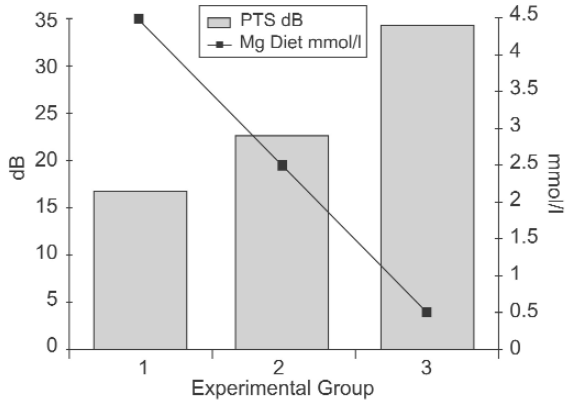

Figure 1. Permanent noise-induced threshold shifts by Mg content of diet (after Ising et al, 1982)

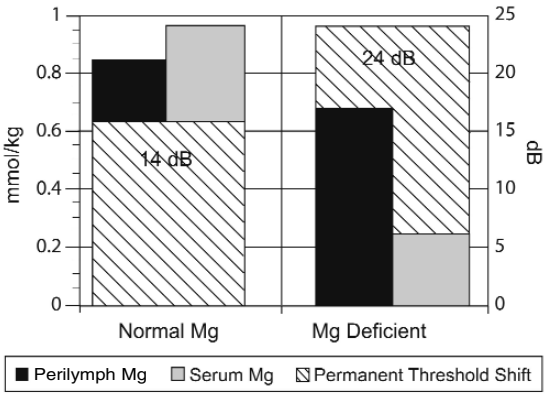

Figure 2. Permanent noise-induced threshold shifts for rats fed different Mg intakes and the respective relationships to perilymph Mg and serum Mg (after Joachims et al, 1983).

Mg content could be detected. Perilymph Mg concentrations were measured in guinea pigs, fed with different Mg intakes, that were noise exposed for 10 days with 95 dB, 16 hours per day (Ising et al., 1982). Noise-induced hearing loss increased significantly with decreasing perilymph Mg concentration. These results were repeated (Meyer et al. 1996) and significantly increased hearing losses occurred in the Mg-deficient guinea pigs compared to those with adequate Mg.

Similar results were obtained when normotensive and spontaneously hypertensive rats were fed a normal or a Mg deficient diet over a period of three months, with or without 105 dB of noise for16 h a day (Joachims et al. 1983). Generally, permanent hearing threshold shifts were detected in all noise-stressed animals at the end of the experimental period, but in the Mg deficient rats, this effect was more significant than in rats on a high Mg diet (Figure 2). As with guinea pigs (Ising et al. 1982), rats had a significant negative correlation between hearing loss and perilymph Mg concentrations. Up to 75% of the variance of hearing loss in a group of identically treated guinea pigs or rats could be explained by the levels of perilymph Mg (Vormann and Günther 1993).

These animal experiments, described above, were performed with animals subjected to more severe Mg deficient conditions than are usually found in humans. In addition, the animals were exposed to intense noise over prolonged periods of time. Only recently has it been shown, with guinea pigs, that a less severe Mg deficiency in combination with acute high-intensity impulse noise exposure was able to increase temporary or permanent hearing loss (Scheibe et al. 2000a). The noise was comparable to that occurring in an industrial or military environment. A weak negative correlation ($r = -0.442$, $p = 0.039$) was found between perilymph or plasma ($r = -0.474$, $p = 0.04$) Mg concentrations and threshold shifts.

No human data about perilymph Mg concentrations and noise induced hearing loss are available. However, as serum Mg concentrations are in proportion with perilymph Mg concentrations, serum Mg concentrations could be considered a surrogate for perilymph Mg and compared with hearing loss in humans. Serum Mg concentrations were compared with hearing loss in 24 air force pilots, a group that is exposed to much noise (Joachims et al. 1987). Their serum Mg concentrations varied between 0.63 and 0.92 mmol/L. Those pilots with the lowest serum Mg concentrations had significantly more hearing loss than those with the higher levels ($r = -0.61$, $p < 0.001$). No correlation between erythrocyte Mg content and hearing loss was found.

If low Mg concentrations in the perilymph aggravate noise-induced hearing loss, then upper normal levels should provide protection from noise trauma. This was investigated in a double-blind study (Attias et al. 1994) in military recruits who consumed daily 167 mg of Mg or a placebo during their training. These young, healthy and normal-hearing

recruits underwent two months of basic military training during which they were exposed repeatedly to high levels of impulse noises due to shooting training. On average, every recruit fired 420 shots with high impulse noise during that period. A noise-induced permanent hearing threshold shift was significantly more common with greater severity in the placebo group than in the Mg group. From 130 subjects in the placebo group 37 (28.5%) developed permanent threshold shift of greater than 25dB hearing loss for at least one frequency in the range of 2 to 8 kHz. In the Mg group, hearing loss was detected in only 14 of 125 subjects (11.2%). A negative relationship between the Mg content of mononuclear cells and permanent threshold shift was also shown ($r = -0.15$, $p < 0.04$). The higher the mononuclear Mg content, the lower the incidence of hearing loss. No correlation between serum Mg concentration and hearing loss was detected.

Generally one has to keep in mind that perilymph and serum Mg concentrations equilibrate only slowly, while acute changes in serum Mg do not influence perilymph Mg concentrations profoundly. Only long term changes in serum Mg concentrations result in significantly changed perilymph Mg concentrations. Therefore, not only the actual value of serum Mg should be correlated to hearing loss, but it is also important to know how long a low serum Mg concentration has persisted.

Ototoxicity and Mg

Not only noise but also various pharmaceuticals are known to impair the auditory system. The best known groups of substances in this respect are the aminoglycoside antibiotics and cisplatin. However, salicylates in high doses of more than 3 grams per day produce temporary hearing threshold shifts in humans. As with noise there is a great inter-individual variability in the onset and repair of these ototoxic events that might be due to the varied Mg nutritional status found in individuals. Animal experiments have investigated whether Mg deficiency might induce or aggravate the ototoxic effects of the aminoglycoside antibiotic gentamicin and of salicylic acid (Vormann and Günther 1991). Generally, Mg deficiency was induced by feeding a Mg deficient diet (3 mmol Mg/kg diet) to growing rats for one month. Mg-deficient or control rats were either treated once with 700 mg/kg salicylic acid or 5 times with 100 mg/kg gentamicin injections. Hearing thresholds were measured one day and 7 days after the last drug treatment. All animals received the control diet following the last drug treatment. Mg deficiency alone did not induce hearing loss. Also administration of salicylate or gentamicin to control animals induced small increases in hearing thresholds. However, the same dose of drugs given to the Mg-deficient animals induced pronounced increases in hearing thresholds. In 9 of 25 Mg-deficient rats receiving gentamicin, an almost complete, irreversible hearing loss occurred. Also salicylic acid induced a severe, but temporary hearing loss in Mg-deficient animals one day after treatment. In contrast to gentamicin, there was complete repair of the ototoxic effects of salicylate 6 days later.

Administration of gentamicin to Mg deficient pregnant rats from day 16-20 of gestation also produced ototoxicity. Three weeks after birth, permanent hearing threshold shifts could be detected in the maternal rats as well as in their offspring (Vormann and Günther 1991).

Together these data suggest that Mg deficiency is a relevant predisposing risk factor for the development of otoacoustic toxicity induced by various causes (Günther et al. 1989).

However, there are other mechanisms that might contribute to the increased ototoxicity in Mg deficiency. It has been shown that microcirculation is reduced in Mg deficiency (Altura et al. 1984). In Mg deficient noise-stressed rats, capillary blood flow velocities were decreased in relation to the degree of Mg deficit, as well as a reduction in the number of mesenteric capillaries was observed. The reactivity of terminal arterioles to constrictor agents was increased by Mg deficiency and noise stress as was the tissue Ca content (Altura et al. 1992). Furthermore, local vascular impairment of the cochlear blood vessels was correlated to the hearing threshold shifts in guinea pigs on a high or a low Mg diet after unilateral ferromagnetic occlusion of the cochlear blood flow (Scheibe et al. 2000b). In these experiments it was also shown that a higher Mg concentration in serum reduced blood viscosity and the viscous component of viscoelasticity,

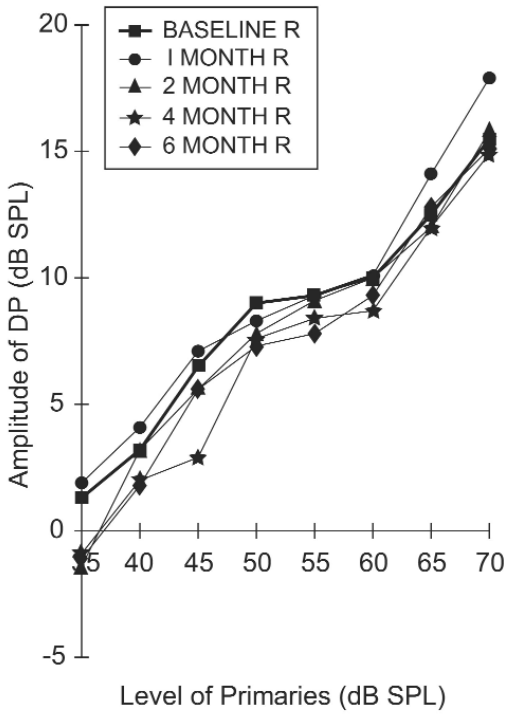

Figure 3. DPOAE growth functions at 5000 Hz for a subject with normal hearing over a 6-month period of time, who received daily Mg supplementation after baseline testing (with permission, JAAA 11: 323-329, 2000).

indicating a lower erythrocyte aggregation under pulsatile shear conditions.

Other factors possibly involved in the blood supply to the cochlea may be involved in Mg deficiency. It has been shown that vasoactive substances, such as catecholamines (Günther et al. 1978) and thromboxane B2 (Nigam et al. 1986) are increased in Mg-deficient animals.

A further effect of Mg deficiency is increased oxidative stress (Calviello et al. 1994). In Mg deficient animals an intracellular accumulation of iron can be observed which is associated with increased lipid peroxidation (Vormann et al. 1998). Glutathione and superoxide dismutase, which are important for antioxidant defense systems, are decreased in Mg deficiency (Calviello et al. 1994). It is also known that oxidative stress is involved in noise-induced hearing loss (Jacono et al. 1998), aging and drug-induced ototoxic effects (Lautermann et al. 1995). Lautermann et al (1997) showed that the antioxidant system was sensitive towards environmental influences as seen for age and cisplatin. For gentamicin and noise trauma, whole tissue glutathione and enzyme levels did not correlate with functional damage.

Cisplatin. Cisplatin is ototoxic (Waters et al. 1991) and nephrotoxic (Dickerson and Brown 1985; Lam and Adelstein 1986). The paired sites of damage are the OHCs within the cochlea and the renal proximal tubule cells within the thick ascending loop of Henle in the kidney. Although cisplatin blocks metabolism in OHCs, there is no evidence of intracellular cisplatin in the OHCs (Saito and Aran 1994). Rather, there are increased significant levels of intracellular Ca in the OHCs after cisplatin administration (Comis et al. 1986). Likewise, there are no defects in the renal handling of electrolytes other than Mg following the related nephrotoxicity seen with the administration of cisplatin (Lam and Adelstein 1986). Since Mg is an antagonist to Ca at the cell membrane the hearing loss associated with cisplatin therapy may be influenced by a Mg-related factor.

In a prospective study, 47% of 32 patients receiving cisplatin developed a sensorineural hearing loss of 15 dB or greater after receiving a mean cumulatives dose of 203 mg/m2 (Reddel et al. 1982). This hearing loss is usually irreversible and high frequency, accompanied by transient or persistent tinnitus. Case studies have shown continued deterioration of hearing loss after cessation of cisplatin administration (Aguilar-Markulis et al. 1981; Fausti et al. 1984; Sweetow and Will 1993). Moreover, otoacoustic emissions (OAEs) change prior to behavioral pure tone thresholds for both transient and distortion production (Plinkert and Krober 1991).

Amplitude increases of both transient evoked otoacoustic emissions (TEOAEs) and DPOAEs during and after ototoxic amikacin treatment in an animal (chinchilla) model has been shown (Kakigi et al. 1998). The investigators noted that as a basal cochlear lesion progresses apically, there is often a transient increase in a frequency-specific OAE before it decreases or is lost. Their findings suggest that the increase in OAE amplitudes precedes the expression of detectable cochlear pathology. In addition, localized damage to the apical or middle turn may be accompanied by an increase in OAE measured from the adjacent apparently normal cochlea (Raveh et al. 1998). Wave V amplitudes of the ABR were shown to increase in guinea pigs fed a Mg deficient diet (600 ppm) compared to animals on a Mg rich diet

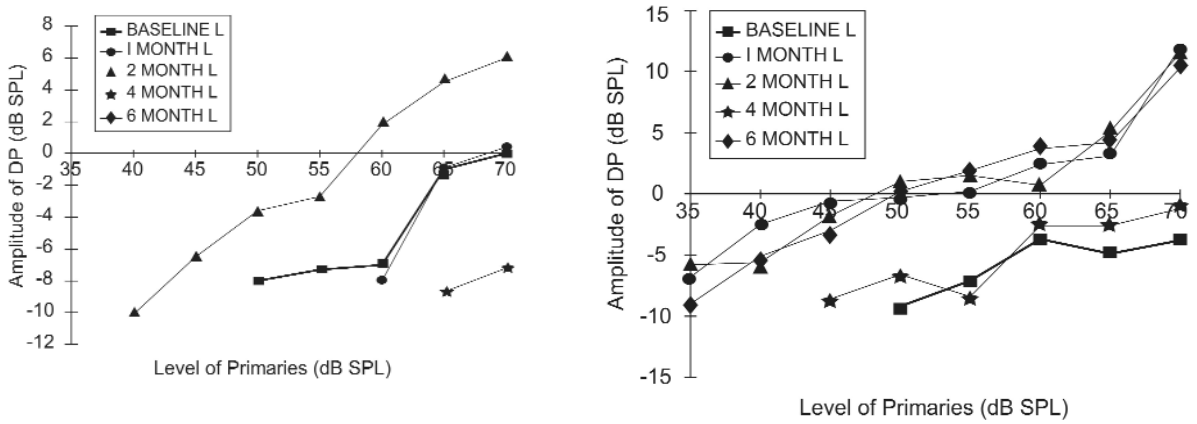

Figure 4. A, right ear; B, left ear. DPOAE growth functions at 5000 Hz over six months for a patient who was treated with cisplatin chemotherapy (with permission, JAAA 11: 323-329, 2000).

(3000 ppm) when both groups were receiving the Mg depleting drugs of gentamicin and furosemide (Cevette et al, 1989).

Various investigators have demonstrated that DPOAE amplitudes are relatively stable over time periods of four to six weeks (Franklin et al. 1992;Roede et al. 1993). Figure 3 demonstrates the consistency of amplitudes over a six-month period of time in a normal hearing individual (Cevette et al, 2000).

Figure 4 (A and B) illustrates DPOAE amplitudes that fluctuated over a six-month period for a patient who received cisplatin chemotherapy (Cevette et al, 2000). The largest change was seen in the left ear from baseline to 1 month showing a 15.8 dB increase in amplitude. In addition, there was a significant decrease in amplitude of 12.7 dB from 2-month to 4-month test dates. This was followed again by an increase of the DPOAE of 11.5 dB at the 6-month test. Significant increases in DPOAE amplitudes are also seen in the right ear. The largest increase in amplitude (5.6 dB) occurred from 1-month to 2-month testing, followed by a significant decrease in amplitude (13.2 dB) from 2 to 4 months. At 6 months there were no measurable DPOAEs for the right ear.

The pathobiochemical mechanisms leading to ototoxicity are similarly affected by Mg deficiency, noise, and ototoxic drugs. If a subject is exposed to one of these negative impacts alone, damage might possibly be overcome. In combination, however, overt hearing loss might be induced.

SUMMARY

The intent of this paper was to provide an overview of the relevant research related to Mg metabolism and hearing. Mg deficiencies are associated with susceptibility of noise-induced hearing loss, ototoxicity, and auditory hyperexcitability. Although the exact mechanisms are unknown, the consequent effects on the handling of Ca by the cell, increased production of glutamate, and over stimulation of the NMDA receptors on the auditory nerve appear to be relevant. The reduced microcirculation induced by Mg deficiency, as well as the formation of free radicals with subsequent increased lipid peroxidation contribute as other factors with implications to hearing loss. Perhaps future studies will clarify the underlying mechanisms related to pathological effects of the auditory system created by deficiencies of this important cation.

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